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Foreword

In writing the Foreword for this much-needed textbook, I thought it appropriate to relate some of the history leading up to the multi-disciplinary involvement that currently exists in the chemotherapeutic treatment of gynecologic malignancies. In the 1960s, very few chemotherapeutic agents existed and had been successfully utilized in the management of solid tumors including ovarian epithelial carcinoma. Management of ascites was particularly troublesome to physicians burdened with the management of these patients when the use of alkylating agents was shown to be definitely advantageous. Medical oncology was, at that time, an embryonic field emerging from the well-established subspecialty of Hematology Oncology. In the United States and elsewhere, gynecologists, particularly interested in the treatment of malignancies of the genital track, made a conscious decision to embrace the evolving field of chemotherapeutic agents for solid tumors and thereby permit much, if not all, of the therapy of these afflicted women to rest in the hands of one physician. These were the early gynecologic oncologists who felt that the philosophy of one lead physician would be in the best interest of the patients' physical and emotional health. Now, there are multiple disciplines involved in the chemotherapy of gynecologic malignant neoplasms, and this text by Angioli et al. will be helpful to all.

The editors begin with a discussion of the *Basic Principles of Chemotherapy* which includes some investigative areas such as mechanisms of chemotherapy resistance, gene therapy, and high dose chemotherapy. Under the *Clinical Aspects of Chemotherapy* section, the editors have a potpourri of subjects ranging from the role of hormone replacement therapy in so-called "estrogen sensitive" malignancies to the use of chemotherapy in the pregnant patient. This section is rather unique in that it is focused in on problems that may be of special complexity in the patient with a gynecologic cancer.

The editors then turn to discussing chemotherapy of particular malignancies grouped by organ site starting with ovarian cancer and going on to fallopian tube carcinoma, corpus carcinoma, cervical carcinoma, vulvo-vaginal carcinoma, and gestational trophoblastic disease.

The authors, for each and every chapter, have selected from a list of world authorities. The resulting text is a one-of-a-kind resource which I believe every individual treating or caring for patients with gynecologic malignancies should have in their library. It is well-written, it is current, and it is, indeed, comprehensive.

Philip J. DiSaia, M.D.
Professor, Department of Obstetrics and Gynecology
Director, Division of Gynecologic Oncology
University of California, Irvine

Preface

The idea of a work entirely dedicated to the chemotherapeutic management of gynecological malignancies evolved from the recognized advances in this field throughout the last few years in addition to the lack of a well-structured book discussing this topic.

Gynecologists, general surgeons and medical oncologists were typically involved in the management of these patients with a mandatory tight collaboration among specialties. In the last 40 years, however, the subspecialty of gynecologic oncology has rapidly grown. This subspecialty is quite unique because it includes various classical specialties such as abdominal/pelvis surgery, chemotherapy, radiotherapy, and molecular biology; moreover, the field of chemotherapy for patients affected by gynecologic tumors is becoming highly specialized. Gynecologic oncologists, as well as medical oncologists, are now regularly involved in the decision and administration of chemotherapy to these patients. The need for a systematic discussion of the use of chemotherapy for gynecologic malignancies was obvious. One of our main goals was to include standard therapies, major ongoing trials, and future directions in a very practical book.

The first section includes the basic principles of chemotherapy, with particular emphasis to the mechanism of action of the various drugs, their interaction in vitro as well as in vivo with other drugs, and interaction with the host. Immunotherapy, gene therapy, and pharmacogenomics are also discussed.

In the second part of the book, general clinical aspects of chemotherapy are described. This section begins with a description of how to write a clinical protocol and then continues to focus on concepts applicable to any patient receiving chemotherapy (i.e. supportive treatments, management complications, psychological support, pain management, etc.)

The final sections describe, in detail, the recommended chemotherapeutic management of cancer for each site organ of the lower female genital tract (ovary, fallopian tube, uterus, vulva, and vagina).

The various chapters have been written by highly specialized physicians and scientists entirely dedicated to the topic described. A panel of international experts in this field was chosen as authors of the various chapters. The close collaboration among different working groups has allowed this endeavor to be developed using a standardized method.

This book is directed to basic scientists in training and involved in research; it is dedicated to cancer treatment researchers, medical oncologists, as well as gynecologic oncologists in training and in practice. We find this book useful for both training and everyday clinical management. We also find this book useful for current management and future approaches for any physician and paramedic dealing with gynecologic cancer patients.

Roberto Angioli
Pierluigi Benedetti Panici
John J. Kavanagh
Sergio Pecorelli
Manuel Penalver

Contents

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Antineoplastic Agents: Classification and Mechanisms of Action

Rui Aoki and John J. Kavanagh
The University of Texas M. D. Anderson Cancer Center, Houston, Texas, U.S.A.

There has been a remarkable increase in the number of newly developed antineoplastic agents in the last few years. In this chapter, discussions of mechanisms of action are focused on the major antitumor agents that have been used for the treatment of gynecologic cancer.

CLASSIFICATION BY MECHANISM OF ACTION

The gynecologic antitumor agents can be classified into four major groups according to their mechanisms of action in relation to the cell-cycle phases affected (Table 1). Each of the agents listed in the table is discussed below (Table 2).

Alkylating Agents

Alkylating agents act through the covalent bonding of alkyl groups to cellular macromolecules, especially DNA. Highly reactive intermediates of the alkylating agents mainly attack DNA by producing DNA interstrand cross-links, resulting in cessation of DNA synthesis essential to cell replication. The alkylating agents are cell-cycle nonspecific, with their lethal effects depending upon subsequent cell division.

Classic Alkylating Agents

Cyclophosphamide Cyclophosphamide is activated to alkylating metabolites by the mixed-function oxidases in hepatic microsomes (1). 4-Hydroxycyclophosphamide and aldophosphamide are the intermediate metabolites serving as a transport form to deliver phosphoramide mustard that plays a significant role in the cytotoxicity of this drug.

The cytotoxic effects of cyclophosphamide correlate with the amount of cross-linking between 1) two opposite strands of DNA (interstrand cross-link), 2) two sites on the same strand (intrastrand cross-link), and 3) DNA and histone proteins (2).

Table 1 Classification of Gynecologic Antitumor Agents

Classification	Phase arrested	Antitumor agents
Alkylating agents	G1, G2	cyclophosphamide ifosfamide melphalan hexamethylmelamine cisplatin carboplatin dactinomycin mitomycin bleomycin
Antimetabolites	G1/S	methotrexate 5-fluorouracil gemcitabine
Antimicrotubule agents	M	vincristine vinblastine vinorelbine paclitaxel docetaxel
Topoisomerase inhibitors	S	topotecan irinotecan etoposide doxorubicin

The cross-linking of DNA results in inactivation of DNA template followed by cessation of DNA synthesis, thus leading to cell death.

Ifosfamide Ifosfamide is chemically similar to cyclophosphamide. It becomes activated to highly reactive intermediates through P450 enzymatic reactions in the microsomes in the liver (3,4). Isophosphoramide mustard is the final active alkylating moiety that attacks DNA.

The resultant metabolites, especially 4-hydroxyifosfamide, decompose in plasma and peripheral tissues to yield acrolein and its alkylating metabolite (5). It is to be noted that the acrolein metabolite accumulates in the urinary bladder to result in dose-limiting urotoxicity (6).

The activation of ifosfamide occurs at a lower speed than that of cyclophosphamide, leading to a longer plasma half-life for the parent compound (7).

Like cyclophosphamide, the metabolites bind to DNA and proteins to generate cross-links, leading to DNA chain scission and inhibition of thymidine uptake.

Melphalan Melphalan is a bifunctional alkylating agent derived from nitrogen mustard. The cytotoxicity of this agent is related to the extent of its interstrand cross-linking with DNA. The cross-linking by melphalan has been assumed to occur between the N-7 positions of deoxyguanylic acid residues in complementary DNA strands, as is the case of other bis(chloroethyl) amines such as cyclophosphamide and ifosfamide (8,9).

This drug requires active transport systems for entry into cells; one is a sodium-independent transfer system for leucine, and the other is a cation-dependent system (10).

Table 2 Plasma Terminal Half-Life and Pharmacokinetic Features of Major Gynecologic Antitumor Drugs

D	Plasma terminal t1/2 (hr)	Features
Cyclophosphamide	4–6.5	prolonged half-life in renal failure cases
Ifosfamide	7–15	prolonged half-life in renal failure cases
Hexamethylmelamine	5–13	higher concentration in small metastatic tumors
Doxorubicin	30–50	longer half-life for pegylated liposomal doxorubicin
Dactinomycin	36	fast distribution, long plasma terminal half-life
Mitomycin	0.4–1.5	not affected by impaired hepatic or renal function
Bleomycin	2–4	intracavitary administration effective
Cisplatin	24	AUC nearly equals plasma concentration at 24 hr
Carboplatin	22–40	AUC = dose/(creatinine clearance + 25)
Methotrexate	8–10	Monitor plasma concentration for high-dose therapy
5-Fluorouracil	2–5	decrease in clearance with increasing doses
Gemcitabine	1.4	not protein bound, rapidly distributes into tissues
Vincristine (VCR)	23–85	clearance rate lower than VBL and VRL
Vinblastine (VBL)	20–64	clearance rate higher than VCR and VRL
Vinorelbine (VRL)	18–49	tissue distribution greater than VCR and VBL
Paclitaxel	11–19	nonlinear pharmacokinetics
Docetaxel	11–14	pharmacokinetics similar to paclitaxel
Topotecan	2.6 (lactone), 3.3 (total)	AUC correlates with platelet count
Irinotecan	7.0 (lactone), 10.5 (total)	longer t1/2 and higher plasma concentration than topotecan
Etoposide	6–8	marked schedule dependency

Nonclassic Alkylating Agent

Hexamethylmelamine Although the mechanism of action of hexamethylmelamine has not been completely clarified yet, it is generally considered that this drug acts like an alkylating agent by generating DNA–protein cross-links.

It is suggested that hexamethylmelamine enters cells by a mechanism of simple diffusion, and some tumor cells (11) can convert the parent drug to reactive methyl intermediates that are covalently bound to nucleic acids and protein molecules (12). Metabolic activation of hexamethylmelamine in the tumor cells is necessary for its cytotoxic activity (13).

Antitumor Antibiotics

Dactinomycin (Actinomycin-D) Dactinomycin (Actinomycin-D) binds to DNA molecules by intercalation preferentially with G–C sequences on one DNA strand and the complementary sequence on the other strand (14,15).

This drug inhibits DNA-dependent ribosomal RNA synthesis as well as de novo RNA synthesis. The elongation of RNA chains is more seriously impaired than the initiation, termination, or release of RNA (16). Inhibition of RNA synthesis leads to secondary inhibition of protein synthesis. The cytotoxic action is cell-cycle nonspecific, although the maximal cytotoxicity is found in the G_1 phase.

The cellular response to dactinomycin depends on the ability of the cells to retain this agent at a cytotoxic concentration after intracellular accumulation by passive diffusion (17). In addition to the inhibitory actions on RNA and protein synthesis by dactinomycin, in vitro studies using a T-cell hybridoma cell line suggest dactinomycin-induced apoptosis (18).

Mitomycin Mitomycin is an alkylating agent that intercalates DNA molecules to inhibit DNA synthesis. Both mono-, bi-, and even possibly trifunctional alkylations are thought to result in DNA cross-linking (19). Like the other alkylating agents, the action of mitomycin is cell-cycle nonspecific.

Activation of this agent is required for its alkylating effect that results in cytotoxicity. Either chemical or enzymatic activation occurs in reductive environments where the reduced quinones are produced (20). It was also reported that mitomycin was activated selectively by hypoxic cells. This may be suggestive of its application to hypoxic tumors (21).

Bleomycin Bleomycin has its antitumor activity of DNA damage by producing single- and double-strand cleavage with a ratio of 10:1.

This drug is not activated when it exists as a Cu(II)–bleomycin complex in the extracellular space. As it moves to the intracellular space, it becomes transformed to an activated Fe(II)–bleomycin–O_2 complex that is competent to break DNA. Oxygen-free radicals produce the DNA strand breaks as the Fe(II)–bleomycin complex functions catalytically as an oxidase (22).

DNA at the G_2–M and G_1 phases of the cell cycle is more sensitive to DNA cleavage than DNA at the S phase. The cytotoxicity of this agent is maximal in the G_2 phase, although cell death also occurs during G_1 (23). Bleomycin is cell-cycle dependent for the G_2 phase.

Platinum Compounds

Platinum(II) compounds, whose oxidation state of the platinum is $+2$, can cause displacement reactions in which one or both ligands are displaced by a competing nucleophile. The displacement reactions cause the platinum to become stably bound to DNA, RNA, and proteins, in analogy to the reactions of alkylating agents.

Although the antitumor cytotoxic mechanisms of the platinum compounds have not been completely elucidated, formation of 1) interstrand cross-links and 2) intrastrand adducts appears to be the major pharmacologic behaviors relevant to cell killing.

The platinum compounds are cell-cycle nonspecific, although the cytotoxic effects can be maximized in the S phase.

Cisplatin The major cytotoxic target of cisplatin is DNA. Cisplatin binds to DNA to form interstrand cross-links (24) and intrastrand bidentate N-7adducts at

d(GpG) and d(ApG) (25). Guanine-rich sequences appear to be targeted preferentially by cisplatin (26).

The antitumor effect of this drug has been mainly attributed to the intrastrand adducts that cause conformational alterations in DNA, thus inhibiting DNA replication.

DNA damage by cisplatin also leads to apoptosis in platinum-sensitive cell lines (27). Cell survival or death may be influenced by the intactness of the apoptotic pathways in the cell.

Cisplatin can inhibit enzymatic activities of DNA polymerase 1 (28), RNA polymerase (29), restriction enzymes (30), and S1 nuclease, which is an endonuclease specific for single-stranded DNA (31). This drug also suppresses Na^+, K^+-ATPase activity in kidney tissue (32), mitochondrial respiration (33), and microtubule assembly (34).

Carboplatin Carboplatin has a mechanism of action similar to that of cisplatin. It forms intrastrand DNA cross-links and DNA adducts. However, the cross-linking occurs 6 to 12 hr later for carboplatin than for cisplatin, and adduct formation is also slower for carboplatin (35). Additionally, DNA damages generated by carboplatin are recognized by the same antibodies that react with adducts formed by cisplatin (36).

Like cisplatin, this agent binds not only to DNA but also to RNA and proteins. Other than DNA damage, the cytotoxic effects of carboplatin may be partially attributable to its inhibition of various enzymes essential for both DNA and RNA synthesis. Phosphorylation of nuclear proteins subsequent to carboplatin treatment may also be relevant to the cytotoxicity (37).

Antimetabolites

Targeting the metabolites essential for DNA and RNA syntheses has been one of the most crucial strategies against cancer cells. The major antimetabolites used in the present gynecologic oncology are methotrexate, 5-fluorouracil and its derivatives, and gemcitabine.

Antifolate

Methotrexate Methotrexate acts as an inhibitor of dihydrofolate reductase (38), leading to an accumulation of folates in the inactive dihydrofolate form, with variable depletion of reduced folates (39). Inhibition of this enzyme also results in the accumulation of 10-formyldihydrofolate polyglutamates (40). These metabolites and polyglutamated derivatives of methotrexate that occur inside the cell directly inhibit the folate-dependent enzymes of purine and thymidylate biosynthesis (41).

Thus methotrexate causes partial depletion of reduced folates and inhibition of the de novo purine and thymidylate biosynthesis, eventually leading to its cytotoxic mechanism of arresting DNA, RNA, and protein synthesis (42).

Fluoropyrimidine

5-Fluorouracil (5-FU) 5-Fluorouracil (5-FU) is a false pyrimidine, with a fluorine atom substituted at the carbon 5 (C-5) position of its pyrimidine ring in place of hydrogen. This agent is cell-cycle specific, with cytotoxic effects being maximal in the S phase.

5-FU undergoes multistep activation to become a fraudulent nucleotide, fluorouridine triphosphate (FUTP), which is incorporated into RNA to interfere with RNA synthesis (43).

Another mechanism of action is inhibition of thymidylate synthase (TS) by an active metabolite of 5-FU named 5-fluoro-21-deoxyuridine-5′-monophosphate (FdUMP) (44). The inhibition of TS leads to depletion of dTMP and dTTP, and accumulation of dUMP and dUTP. Additionally, incorporation of FdUMP may affect DNA stability (45).

Cytidine Analogue

Gemcitabine Gemcitabine is a fluorine-substituted nucleoside analogue whose structure is highly homologous to cytosine arabinoside (ara-C).

Conversion from gemcitabine as a prodrug to its activated forms depends on deoxycytidine kinase, by which gemcitabine undergoes multiple intracellular phosphorylation reactions to form di- and triphosphate metabolites. The triphosphate is subsequently incorporated into DNA as a fraudulent base pair to interfere with DNA chain elongation by preventing exonucleases from excising the fraudulent base pair (46). The diphosphate and the triphosphate inhibit ribonucleotide reductase and DNA polymerases, respectively, which results in the inhibition of DNA synthesis and repair (47).

Antimicrotubule Agents

In addition to the conventional Vinca alkaloids that inhibit microtubule assembly, so-called microtubule stabilizers (paclitaxel and docetaxel) have contributed to the remarkable improvement in the clinical results of gynecologic chemotherapy.

Inhibitors of Microtubule Assembly

Vincristine, Vinblastine, and Vinorelbine Vincristine and vinblastine are the Vinca alkaloids, while vinorelbine is a semisynthetic derivative of vinblastine. These alkaloids bind to tubulin molecules that are essential components of microtubules in dividing cells, leading to the inhibition of microtubule assembly. As a result, the mitotic spindle formation is impaired and cell division or mitosis is arrested (48). All of the three drugs are cell-cycle specific for the M phase, in which their cytotoxic effects are expressed.

The Vinca alkaloids also affect the microtubules involved in intracellular transport of secretory granules in neural cells, platelet structural integrity, membrane trafficking, and signal transduction (49,50).

Microtubule Stabilizers

Paclitaxel and Docetaxel Paclitaxel and docetaxel belong to the taxanes that inhibit mitosis of the cell. They have high-affinity binding ability to microtubules to shift the dynamic equilibrium between tubulin dimers, which are essential components of the microtubules, toward microtubule assembly, leading to stabilization of the microtubules against depolymerization (51–53).

The stabilization of the microtubules halts cell division in the M phase of the cell cycle, thus resulting in inhibition of cell proliferation (54). The sustained mitotic block induced by these drugs is at the metaphase–anaphase boundary.

It is to be noted that paclitaxel and docetaxel promote the microtubule assembly instead of preventing it as done by the Vinka alkaloids such as vincristine, vinblastine, and vinorelbine (55).

Paclitaxel has also been reported to affect locomotion and shape changes of the cell as well as intracellular transportation, all of which may be relevant to the invasiveness and metastatic potential of tumor cells (56).

Docetaxel shares the same tubulin-binding site (N-terminal 31 amino acids of the β-tubulin subunit). However, the affinity for the site is 1.9-fold more effective than that of paclitaxel (67). The microtubules treated with docetaxel are more slowly reversible than that with paclitaxel.

Both paclitaxel and docetaxel may trigger apoptosis similar to many other antitumor agents (57).

Topoisomerase Inhibitors

DNA topoisomerases catalyze the unlinking of the DNA strands by making transient DNA strand breaks, allowing the DNA to rotate or traverse through the breaks. These enzymes play an important role in releasing torsional strain in DNA as well as in DNA condensation (58).

Topoisomerase I links to the 3′-terminus of a single-strand break, whereas topoisomerase II becomes linked to the 5′-terminus of a double-strand break. Agents that prevent the catalytic activities of these DNA unwinding enzymes can inhibit DNA replication and RNA transcription (59).

Topoisomerase I Inhibitors

Topotecan and Irinotecan Topotecan and irinotecan are camptothecin analogues that inhibit DNA topoisomerase I (TOPO-I) (60). This enzyme relaxes a torsional strain in the DNA resulting from supercoiling of the double-stranded helix, which shares common functional similarities with DNA topoisomerase II (TOPO-II) (61).

Both topotecan and irinotecan interact noncovalently with DNA–TOPO-I cleavable complexes to inhibit the religation step of the reaction. As a consequence, the cleavable complexes become stabilized and accumulate, leading to cell-cycle arrest in the G_2 phase (62). The stabilized DNA–TOPO-I complex interacts with a DNA replication fork, resulting in the formation of a complete double-stranded DNA break and subsequent lethality of the cell (63).

Topoisomerase II Inhibitors

Etoposide (VP-16) Etoposide is a DNA topoisomerase II (TOPO-II) inhibitor (64). TOPO-II is an enzyme that binds to DNA to form a complex, mediating the DNA double-strand passage in the G_2 phase. The enzyme separates chromatin loops by catalyzing DNA swiveling and relaxation, and the resultant condensation of DNA is required for chromosome assembly (65).

Etoposide stabilizes a transition form of the DNA–TOPO-II complex and blocks the religation of DNA to cause DNA double-strand breaks (66). The cytotoxicity of this drug is maximal in the G2 phase on which the TOPO-II is dependent for its activities. Thus the cell cycle in treated cells becomes halted in the G_2 phase (67).

Doxorubicin Doxorubicin (Adriamycin) is an anthracycline antibiotic, whose major mechanisms of action are not only 1) to inhibit DNA topoisomerase II catalytic activity, but also 2) to intercalate DNA, 3) to generate reactive oxygen intermediates, and 4) to induce apoptosis. Doxorubicin is not cell-cycle-phase specific, although its cytotoxic effects are maximized in the S phase (68).

Doxorubicin inhibits the catalytic activity of TOPO-II by trapping DNA strand passage intermediates to stabilize the initial enzyme–DNA complexes (69). This drug produces topoisomerase-related DNA cleavage in specific regions of the DNA, suggesting that the action is gene specific (70).

In addition to the inhibition of TOPO-II, it has been reported that a portion of the anthracycline in Doxorubicin intercalates the double helix of DNA, and 5'-TCA is the consensus sequence for the highest affinity (71). Like the alkylating agents, DNA intercalation by doxorubicin eventually inhibits DNA synthesis.

Doxorubicin can enhance the formation of reactive oxygen intermediates, or oxygen free-radicals (72). However, the role of oxygen radical formation in tumor cell kill might well be reserved, because solid tumors to which doxorubicin demonstrates to be effective have hypoxic microenvironments therein (73).

It is also possible that the redox reactions of doxorubicin may play an important role in programmed cell death or apoptosis, which is modulated by the interplay between *bcl*-2 and *p*53 genes after exposure of tumor cells to the agent (74).

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Mechanisms of Chemosensitivity and Resistance

Shilpa Gajarawala and Bernd-Uwe Sevin
Division of Medical and Surgical Gynecology, Mayo Clinic, Jacksonville, Florida, U.S.A.

INTRODUCTION

Resistance to chemotherapy is a major concern and often an obstacle to successful treatment of malignancies. Chemotherapy kills cancer cells through the induction of necrosis or apoptosis. Necrosis is an adenosine triphosphate (ATP)-independent process, which involves cellular death via lysis and eventual phagocytosis after massive cellular insult (1). Necrosis is considered a passive catabolic process, and is characterized by early plasma membrane rupture (2). Apoptosis is an energy-dependent cellular programmed death, activated by cellular damage or physiological injury, including death receptor ligation or withdrawal of survival signals (3–5). Apoptosis involves Ca^{2+} influx into the cytoplasm, endonuclease activation, formation of cross-links between proteins, microtubule disruption, changes in cell membrane lipid composition, cytoplasmic condensation, chromatin fragmentation, and nuclear compaction (6). Compared to necrotic cell death, apoptosis is induced by lower doses of cytotoxins. Apoptosis is regulated by multiple interconnected signaling pathways. These pathways regulate not only apoptosis, but also survival, proliferation, and differentiation (4). The p53 gene is important in the activation of apoptosis. In an effort to survive, cancer cells have developed mechanisms to escape apoptosis. Drug resistance can occur when cells with drug-mediated damage fail to undergo apoptosis.

Tumor growth, for most solid malignancies, follows a Gompertzian growth pattern: as tumor size increases, the growth rate slows, the growth fraction decreases, and tumor volume and growth eventually start to plateau. Large tumors that have reached the plateau stage will have decreased drug sensitivity because of unfavorable cytokinetics (7). Tumor growth relies on several dependent factors including: (1) the total number of cells in a specific tumor population; (2) cell cycle time (the average time for a cell to cycle from G1 through mitosis); (3) growth fraction (percentage of cells actively dividing); and (4) the intrinsic cell death rate of tumor cells (8). These four factors impact not only tumor growth but also chemosensitivity and resistance.

The unique microenvironment of solid tumors may contribute to drug resistance (9). Solid tumors consist of proliferating, nonproliferating, and necrotic cells (10).

Rate of cell proliferation decreases with increasing distance of cells from the blood vessels. When tumor cells grow faster than vascular endothelial cells, stress conditions result from reduced blood flow; in short, the tumor outgrows its blood supply. Stress conditions, such as glucose starvation, hypoxia, and low pH, have been shown to cause an in vitro glucose regulated stress response in cancer cells. This can lead to cell cycle arrest at G1, decreased Topo II expression, gene amplification, and altered protein expression (11).

In addition, large tumors experience impaired drug delivery, secondary to decreased blood supply and hypoxia at the center of a tumor (farthest from the blood supply) (9). This resistance is partly attributable to the fact that most chemotherapeutic drugs work on actively proliferating cells; however, it will reverse when the "oxidative stress" is removed (12,13). In contrast, antiangiogenic agents are currently being investigated to prevent new blood vessel formation to cause tumor cell starvation and cell necrosis (14).

Genomic instability is an important characteristic of cancer cells. As a tumor grows, there is an increased tendency for spontaneous mutations. The heterogeneous tumor population is likely to contain cells that have mutated to a drug-resistant phenotype. Chemotherapy eliminates chemosensitive cells, but the mutated resistant cells will survive and continue to grow. It is also important to note that many cytotoxic agents are mutagenic, increasing the likelihood of producing more drug-resistant cells during chemotherapy (7). As the number of chemoresistant cells increases, the overall chemosensitivity of the tumor decreases. According to the log cell kill model, tumor growth is exponential with first-order kinetics, which states that specific chemotherapy dose will kill a constant percentage, but not a constant number of tumor cells. Therefore, maximum benefit to chemotherapy occurs when the tumor is small in size and before it has the opportunity to develop drug-resistant cells.

Both normal and malignant cells exhibit a dose-response effect when exposed to cytotoxic agents. At lower concentrations, cell kill is not seen. As drug concentration increases, cell kill proportionately increases. At high concentrations, a plateau is reached and cell kill tapers off. Therapeutic index refers to the difference in tumor and normal tissue response (7).

A proper understanding of cytokinetics is necessary to fully appreciate the nature of chemosensitivity and resistance. Progression through the cell cycle is a highly regulated orderly process of both normal and neoplastic cells (Figure 1). The cell cycle is divided into cell division (S, G2, and M phases) and interphase (G0 and G1 phases). In solid tumors, most cells reside in G0, a quiescent or dormant phase. During cell division, cells proceed from G0 or G1 (GAP 1 phase) to S phase (synthesis phase), G2 (GAP 2), and M phase. During G1 and G2, RNA and protein synthesis occur, while DNA content remains stable. DNA synthesis/duplication occurs during the S phase. The duplicate strands of DNA are separated in M phase and both subunits will enter either G1 or G0 phase.

Cell-cycle progression involves positive and negative controls that rely on cyclin-dependent kinases (CDKs) (Figure 1). Kinases are proteins that activate/deactivate other proteins by phosphorylation. CDKs function at specific cell cycle checkpoints. Checkpoints are biochemically defined points in the cell cycle that, when activated, prevent transition to the next cell cycle phase (15). As a general rule, one phase must be completed before the cell can enter the next phase. Major checkpoints are present between G1 to S and G2 to M phases. The most important checkpoint is at the G1–S

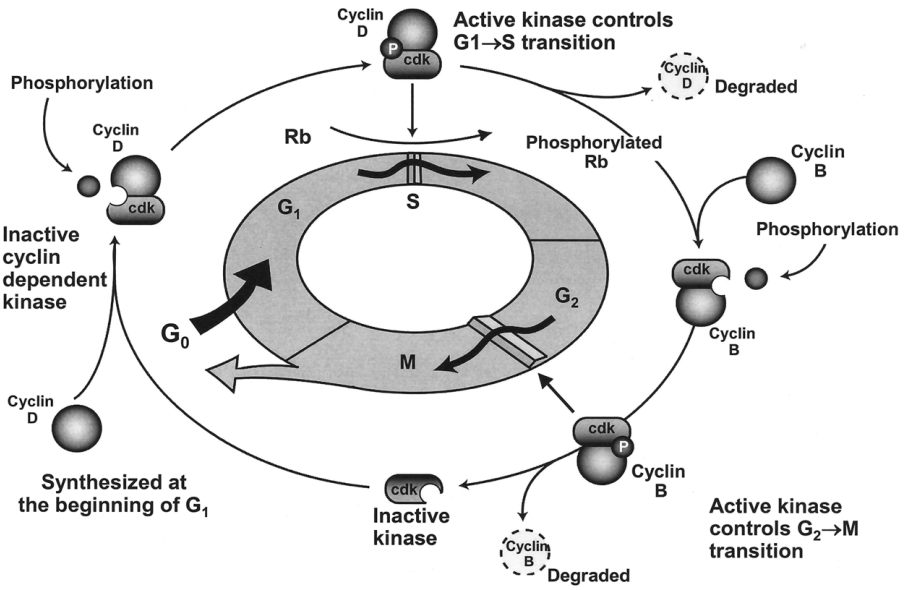

Figure 1 Cell cycle regulation—schematic illustration of the cell cycle and key mechanisms involved in DNA synthesis.

transition. If a cell does not progress beyond G1, it may enter G0 or undergo apoptosis. Cell cycle checkpoints can be activated by both intracellular and extracellular factors such as nutrient deprivation, environmental stress (temperature or pH changes, hypoxia), nucleotide depletion, or DNA damage. The tumor suppressor gene p53 plays an important role in cell cycle control, especially at the G1–S checkpoint (15).

Cell cycle progression and intracellular activity are also influenced by growth factors (cytokines). Cytokines are insoluble proteins that mediate cellular communication. Binding of growth factors to specific receptors initiates a cascade of biochemical processes that can induce or repress specific genes involved with cell proliferation, differentiation, and survival. Continued growth factor exposure is needed for a cell to progress past the G1 check point (15).

Chemosensitivity refers to the overall chemotherapy response of malignancies in patients. Patient response to chemotherapy can be influenced by several factors such as age, nutritional status, and immunocompetence. For example, as age increases, total body water decreases, total body fat increases, and concentration of plasma protein decreases, which results in higher peak plasma levels and shorter half-lives for water-soluble drugs and the opposite effect for lipid-soluble drugs (16).

Treatment variables such as drug type, dose, frequency, and route of drug application, strongly influence peak plasma concentrations and tissue levels. Drug tissue levels depend on both drug concentration and exposure time, as well as tumor size, location, and degree of vascularization (17). Limitations to increasing treatment intensity are defined by the toxicity to normal tissues of the host (therapeutic index).

The primary goal of chemotherapy drugs is to inhibit cell division and cause cell death. The major classes of chemotherapeutic agents can be divided into alkylating

agents, antimetabolites, natural products, and a group of miscellaneous drugs. The drugs can also be categorized in relation to the cell cycle. Cell cycle-nonspecific drugs are those affecting resting or active cells (i.e., mechlorethamine). Cell cycle nonphase-specific drugs work on dividing cells (not in G0), regardless of the specific phase (i.e., cyclophosphamide, melphalan, cisplatin, carboplatin, doxorubicin). Cell cycle phase-specific drugs are only effective during a specific cell cycle (vincristine, paclitaxel, etoposide).

Alkylating agents interact with precursors of DNA, RNA, and protein. They inhibit DNA replication with resultant cell death or mutation. The majority of these agents are nonphase-specific; however, some are also cell cycle nonspecific. This class includes the nitrogen mustards (chlorambucil, cyclophosphamide, and melphalan) and the metal salts (i.e., cisplatin and carboplatin) (8).

Antimetabolites act as false substrates and inhibit nucleic acid synthesis by acting as nucleoside analogues. They eventually are incorporated into DNA and RNA and interfere with DNA or RNA production and/or function. Some antimetabolites interfere with the production of enzymes needed for nucleotide synthesis (7). They are S-phase-specific. Some examples of antimetabolites are cytarabine, gemcitabine, methotrexate, and hydroxyurea. Cytarabine (ARA-C) and gemcitabine prevent replication by acting as DNA-chain terminators. Gemcitabine also inhibits the enzyme ribonucleotide reductase, preventing RNA synthesis. Methotrexate is an antifolate that inhibits the enzyme dihydrofolate reductase, which eventually prevents synthesis of purine nucleotides and thymidylate. Hydroxyurea inhibits the enzyme ribonucleotide reductase, which converts ribonucleotides to deoxyribonucleotides (8).

Natural products include mitotic inhibitors, microtubular polymer stabilizers, podophyllum derivatives, and antibiotics. The mitotic inhibitors (i.e., vincristine, vinblastine) interfere with the mitotic spindle and result in cell cycle arrest (during M phase) and inhibition of mitosis. These agents are cell cycle phase specific. Paclitaxel and docetaxel are microtubular polymer stabilizers and also interfere with mitotic spindle function. Topoisomerase inhibitors interfere with topoisomerase 1 (Topo 1) and topoisomerase 2 (Topo 2). These enzymes repair single- and double-stranded DNA breaks secondary to transcription and replication of DNA. Topo 1 inhibitors (topotecan and irinotecan) and Topo 2 inhibitors (etoposide) produce DNA strand breakage and cell cycle arrest either in late S or G2 phase. The antibiotics are produced by the *Streptomyces* species. Dactinomycin and the anthracyclines cause DNA cleavage, while bleomycin and mitomycin impair DNA replication.

Drug resistance appears to be multifactorial, and has been attributed to modifications in drug transport, metabolism, and cell repair (18). Resistance can be intrinsic or acquired. Intrinsic resistance describes cancer cells that are unresponsive to chemotherapy drugs without prior exposure to these drugs (19). Acquired resistance refers to tumors that recur after initially responding to a chemotherapeutic agent (20). Clinicians measure drug resistance by evaluating the response rate to chemotherapy, the duration of response, and the cancer-related death rate despite treatment. Basic scientists view drug resistance as a molecular phenomenon.

Advancements in molecular genetics have greatly increased our understanding of molecular mechanisms involved in drug resistance (21). It is obvious that coexisting multiple pathways are involved. Deciphering the relative qualitative and quantitative contribution of each resistance mechanism is needed in order to better understand and effectively deal with chemoresistance (21). At the cellular level, chemotherapy resist-

ance can occur through a variety of mechanisms including alterations in cell membrane drug influx or efflux, changes in intracellular metabolic activation or catabolism of drugs, alterations in the drug's intended targets, genetic changes affecting DNA synthesis, changes and repair of DNA (22), and failure to trigger apoptosis (23).

For didactic reasons, we structured the discussion of molecular mechanisms involved in chemosensitivity and resistance in a functional-anatomic fashion. We will discuss currently known and investigated mechanisms that may contribute to chemoresistance by somewhat arbitrarily compartmentalizing groups based on location in the cell structure: cell membrane, cytoplasm, nuclear membrane, and nucleus (Figure 2). It has to be understood, however, that many of these functions involve several of these components.

(A) Multidrug resistance (MDR), focusing on transmembrane and cytoplasmatic transport mechanisms
(B) Cytoplasmatic drug detoxification and sequestration
(C) DNA synthesis and repair
(D) Oncogenes and tumor suppressor genes
(E) Intracellular signaling pathways

Multidrug Resistance (MDR)

Multidrug resistance (MDR) was initially described as a transmembrane drug transport system and thought to be one of the major causes of drug resistance. MDR describes in vitro drug resistance in a tumor cell population against numerous drugs differing in chemical structure and mechanism that develops after exposure to a single

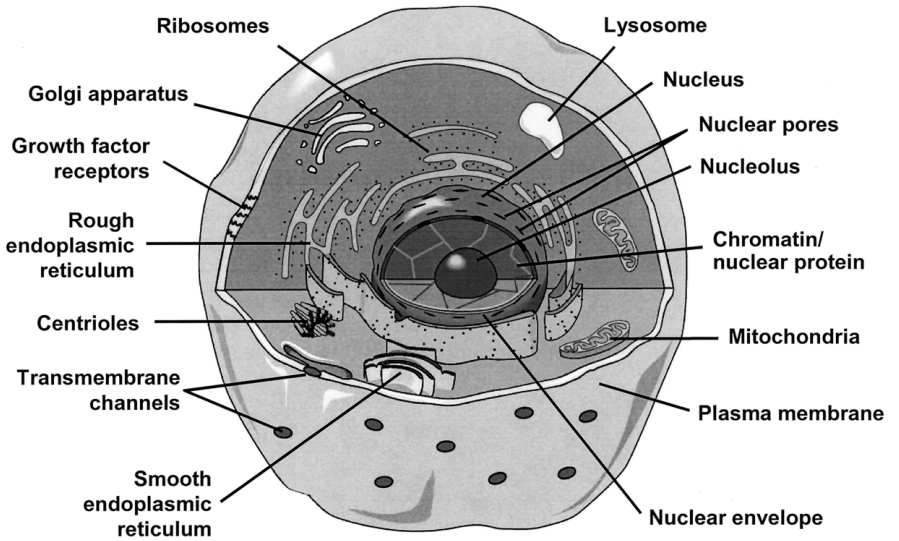

Figure 2 Anatomy of the cell—schematic illustration of the cellular structures involved in drug transport, reproduction, DNA synthesis, and intracellular signaling pathways.

agent (24). It is one of the major defense systems that limit drugs to reach their target in the cell nucleus via drug transport systems.

The molecular mechanisms of MDR are not only numerous but also operate at different levels of the cytotoxic pathways. These mechanisms include:

1. Activation of the transmembrane EFFLUX pumps (i.e., P-glycoprotein),
2. Activation of the enzymatic detoxification system,
3. Changes in intracellular drug transport and drug sequestration,
4. Alteration of genes and proteins involved in apoptosis (i.e., p53, bcl-2).

The plasma membrane is the site of several transporter proteins involved with drug resistance (Figure 2). Mechanisms of drug resistance involve members of the ATP-binding cassette (ABC) superfamily of transporter proteins such as P-glycoprotein (Pgp) and multidrug resistance-associated protein (MRP). The ABC family of transporter proteins actively extrudes drugs from cells against a concentration gradient reducing intracellular drug amounts to sublethal levels (25–27). Several other proteins have been described, including TAP (transporter associated with antigen processing), ARA (anthracycline resistance-associated protein), BRCP (breast cancer resistance protein), DRP (drug resistance-associated protein), and ABCP (adenosine triphosphate-binding cassette protein). Cytotoxic damage is also reduced by increased glutathione-*S* transferase (GST)-mediated cellular export of drugs that have been conjoined with reduced glutathione (25,28).

P-glycoprotein (Pgp)

Pgp is a 170-kDa-membrane transport protein product of the MDR1 gene that resides in the plasma membrane (4,24,29). It is involved with ATP-dependent drug export of natural product lipophilic xenobiotics (i.e., anthracyclines, vinca-alkaloids, and epipodophyllotoxins). Overexpression of Pgp/MDR1 gene was found to correlate with poor treatment outcome in patients with cancer, and was also associated with a higher incidence of lymph node metastases (30). Pgp may be a marker for more aggressive tumor behavior and poor treatment outcome independent of its effect on chemosensitivity (31). Solid tumors, such as colon cancer, renal cell carcinoma, nonsmall cell lung cancer, that are drug-resistant at the time of diagnosis express high levels of Pgp (32,33). Other cancers such as ovarian and breast cancer, that do not usually express Pgp at the time of diagnosis, were found to have elevated Pgp levels after treatment (34–37). Pgp may also play a role in drug redistribution within the cytoplasm, which reduces the accessibility of drugs to their targets in the nucleus (38).

Multidrug-Resistant Protein (MRP)

MRP is also an ATP-dependent drug efflux pump that has been identified in resistant non-Pgp overexpressing cells, such as fibrosarcoma, breast, cervical, and bladder cancers. MRP is also involved in intracellular and cytoplasmic drug sequestration, and thus prevents drugs from reaching their targets (24). MRP covers a similar spectrum of resistance as Pgp, except that it includes taxanes and mitoxantrones (39). MRP transport is GSH-dependent; that is, neutral drug substrates are transported by MRP as GSH conjugates or cotransported with GSH (39).

MRP and its seven member genes make up the family of multispecific organic anion transporters (MOAT) (40–45). As additional MRP genes were identified, the original MRP was designated MRP1 (24). Its gene is located on chromosome 16p13.1. MRP1 is a 190-kDa protein located in the plasma membrane and in cytoplasmatic

membranes such as the endoplasmic reticulum and Golgi apparatus (Figure 2) (39). MRP1 can be blocked by ATP and glutathione depletion.

Studies with the seven homologs of MRP have yielded the following results. MRP1 transfection does not cause resistance to cisplatin, vinca alkaloids, and anthracyclines (28,46). MRP2 transfection leads to cisplatin, anthracycline, etoposide, and methotrexate resistance (47–49). MRP3 transfection leads to resistance to vinca alkaloids, etoposide, and methotrexate. MRP4 overexpression is associated with high levels of resistance to nucleoside analogues (50). MRP5 overexpression is associated with low levels of resistance to thiopurines (i.e., 6-mercaptopurine) (51) and also appears to be a nucleotide analogue pump. The physiological function of MRP5-7 is not fully understood.

Lung Resistance-Related Protein (LRP)

LRP was first identified in an MDR lung cancer cell line (52,53). The LRP gene codes for a 10-kDa vault protein (54). It belongs to the vault family of ribonucleoproteins and is the major human vault protein (MVP), accounting for greater than 70% of the mass of vault particles (55). Vaults are organelles that are localized in cytoplasmic vesicles and the nuclear membrane. They constitute the transporter core of the nuclear pore complex (56).

The main function of LRP is associated with the efflux and influx of drugs into and out of the nucleus (57,58). Like Pgp and MRP, LRP functions in the detoxification process in normal tissues. Although LRP may be involved in transmembrane drug transport, it is not an ABC transporter protein (38,56). Vaults are present in many cells, but have been found to be upregulated in some cancer cells that overexpress LRP. The overexpression of intracellular vaults results in drug sequestration in the vaults, and thus prevents the drug from reaching its intracellular and nuclear target (24). LRP may confer resistance to anthracyclines, vincristine, platinum derivatives, and alkylating agents, as well as natural products, including mitoxantrone, vincristine, and etoposide (59,60). LRP overexpression has been reported to be an adverse prognostic factor in ovarian cancer (61).

LRP expression can be measured by LRP-56 antibody and has been used as an in vitro marker of resistance to doxorubicin, vincristine (MDR-related drugs), cisplatin, carboplatin, melphalan, and nonclassical MDR drugs (29). LRP's role in drug resistance is supported by the finding of LRP overexpression in Pgp-negative, drug-selected MDR breast cancer cell lines (61–63). Interestingly, studies found that the forced expression of LRP in drug-sensitive cells does not cause drug resistance (64).

Transporter Associated with Antigen Processing (TAP)

TAP is a membrane-associated drug transport protein that has been identified in non-Pgp MDR tumor cell lines. TAP heterodimer is composed of TAP1 and TAP2 proteins. TAP mediates peptide translocation from the cytoplasm to the endoplasmic reticulum, where the peptides are coupled with class I molecules of the major histocompatibility complex and then transported to the cell membrane for presentation to cytotoxic T lymphocytes (65). Transfection of TAP1 and TAP2 genes into TAP-deficient cells has resulted in resistance to doxorubicin (66).

Breast Cancer Resistance Protein (BRCP)

BRCP was first identified from MDR breast cancer cells (67). BRCP is a 72.6-kDa transporter protein that is half the size of full transporters (Pgp or MRP) (24). BRCP

confers resistance to anthracyclines and mitoxantrone and is also called mitoxantrone resistance gene (MXR1) or human placental ABC transporter (ABC-P) (68,69). It is inhibited by noncytotoxic levels of fumitremorgin C, which is considered a chemosensitizer for mitoxantrone-resistant cells (29).

Drug Resistance Associated Protein (DRP)

Drug resistance associated protein (DRP) overexpression has been found in drug-resistant breast cancer and leukemia cell lines. It is an intracellular 50-kDa protein that has sites for ATP binding, ceasin kinase and protein kinase C phosphorylation, *N*-myristoylation, and plasma membrane attachment. DRP transfection into drug-sensitive cells confers a clinical level increase (9–10× in doxorubicin resistance when compared to the chemosensitive parental cell line) (29). The expression and mechanism of DRP is still under investigation.

Modulators of MDR

MDR can be partially overcome by modulators and/or modifiers (55,70,71). Modulators include noncytotoxic compounds that competitively inhibit Pgp and other MDR-protein mediated drug transport (55). Efflux blockers include calcium channel blockers (verapamil, nifedipine), antipsychotic agents (phenothiazines), hormones (megestrol, tamoxifen), immunosuppressants (cyclosporin A), antiarrhythmic agents (quinolone), steroids, detergents, and indole alkaloids (55,72–76).

Unfortunately, the use of modulators has not significantly changed clinical drug resistance in solid tumors (33). The efficacy of Pgp modulators is low because of the presence and coexpression of other drug resistance mechanisms (55). The success of modulators is also limited because a clinically tolerable dose may not be sufficient to reverse MDR. With the current advances in molecular science, MDR may be reversed by the use of antisense oligonucleotides and antibodies (77,78). MDR1/Pgp drug resistance reversal has been induced by downregulating MDR1 expression using MDR1-specific antisense oligonucleotides, as well as protein-C kinase inhibitors (55).

Cytoplasmic Drug Detoxification and Sequestration

Thiol-containing molecules such as glutathione-*S* transferase, glutathione (GSH), and metallothionein (MT) may also be responsible for chemoresistance through multiple pathways. They bind to DNA adducts, prevent DNA cross-linking, facilitate DNA repair, and function as cofactors for a variety of DNA polymerases (79). MT may also be involved in the intracellular inactivation of metal-containing chemotherapeutic agents such as cisplatin.

Glutathione (GSH)

GSH is the most abundant cellular nonprotein thiol (80). Multiple pathways are involved in resistance conferred by thiol-containing molecules such as GSH. These pathways involve drug turnover, drug inactivation, inhibition of DNA adduct formation, and increased DNA repair (81). GSH has also been associated in buffering apoptosis related oxidative stress (82). GSH may alter the active sites of MRP or modify other factors involved in drug transport.

Studies involving ovarian cancer cell lines have found a relationship between increased intracellular levels of GSH and GSH-type enzymes and resistance to alkylating agents and cisplatin (23,83,84). The cisplatin resistance is thought to be

attributable to C-jun-mediated overexpression of the enzyme γ-glutamylcysteine synthetase (85). GSH binds to and inactivates drugs such as cisplatin (86). GSH depletion, inhibition of GSH production, and inhibition of GSH activity were all shown to increase the antitumor activity of platinum and alkylating agents (87). High levels of heterogenicity of cellular GSH exist between individual cells within the same ovarian tumor (88). The role GSH plays in resistance to platinum and other alkylating drugs in ovarian cancer is still not fully understood.

Glutathione-S Transferase (GST)

GST is part of a multigene family of enzymes that inactivates a wide range of electrophilic compounds by conjugation to GSH. GST also plays an important role as an intracellular antioxidant (89). GST includes five multifunction isoenzymes, three of which—GSTχ, GSTμ, and GSTπ—mediate cellular detoxification and are related to chemoresistance. GST function includes:

1. Conjugation of GSH to drugs resulting in increased water solubility and drug export;
2. Elimination of drug-generated toxic-free radicals;
3. Binding and sequestering of drugs, thus decreasing their bioavailability (89–91).

GSTπ may play a role in platinum and anthracycline resistance in various malignancies (92–94). Low cellular levels of GSTπ lead to sensitivity to platinum, whereas high cellular levels of GSTπ lead to chemoresistance to platinum (95). Some studies have also found a significant association between increased GSTπ and resistance to combination therapy with cyclophosphamide and cisplatin, as well as to drugs such as doxorubicin (96,97).

Coexpression of Pgp and GSTπ has been observed in cells, which suggests that the Pgp gene (MDR1) and GSTπ gene may share a common regulatory mechanism such as a transcription factor or regulatory protein (21,98).

Metallothionine (MT)

MT is a 6- to 7-kDa intracellular protein that has the ability to bind heavy metal ions such as zinc and platinum (21). MT is present in most mammalian tissues, but levels can vary by tissue type. MT has also been detected in ovarian tumors, testicular germ cell tumors, and colorectal tumors (21,99–101). Cytokines, growth factors, tumor promoters, chemicals, and stressors, such as heat, cold, and starvation, can induce MT synthesis (102).

MT functions as a heavy metal detoxifier and regulates intracellular levels of heavy metals (103). Resistance to cisplatin, melphalan, and doxorubicin has been found in transfected lines overexpressing MT (104). Experiments have found that resistance to alkylating agents and cisplatin in ovarian cell lines has been related to intracellular levels of MT and GSH (83).

DNA Synthesis and Repair

Cellular response to DNA damage includes cell cycle arrest (G1, G2 phase), or delayed progress through S phase, increased DNA repair, and apoptosis (5,105,106). DNA repair mechanisms include direct repair, nucleotide excision repair, and mismatch

repair (MMR) (107–109). Chemotherapeutic agents, such as the platinum drugs, and nitrogen mustards form DNA adducts, which impair DNA repair and cause cell death. Any relevant increase in the cell's capability to repair damaged DNA can result in chemoresistance (110).

Direct DNA repair is a complex process involving many enzymes. An increased rate of repair of intracellular DNA adducts is associated with resistance to cisplatin and alkylating agents. Upregulation of DNA repair mechanisms has been observed in cisplatin-resistant ovarian cancer cells (111–114). Inhibitors of DNA synthesis and/or repair (i.e., Ara C, thiotepa, hydroxyurea, and novobiocin) were found to increase cisplatin cytotoxicity (115). DNA repair is compromised by aphidocolin via inhibition of DNA polymerase (α and γ). Experimentally, aphidocolin was found to reverse cisplatin and alkylating agent resistance (116).

The nucleoside excision repair (NER) system is considered one of the major DNA repair systems capable of repairing a wide range of DNA damage such as ultraviolet lesions and chemical-induced adducts (117). NER is upregulated in platinum-resistant tumors. NER genes are grouped as the xeroderma pigmentosa (XP) complementation group. ERCC1 (X-ray cross-complementing gene) is a critical NER gene, but not a member of the XP group (118). Mutations in the XP genes and ERCC1 have been used as markers for NER deficiency and treatment resistance (119).

Mismatch repair (MMR) refers to the identification and removal of a DNA mismatched base by a specific mechanism (120). In tumors treated with DNA damaging agents (i.e., platinum), cell death does not occur after MMR correction of the error. A faulty MMR causes the DNA error/mismatch to be bypassed during replication and may result in a drug-resistant phenotype (121–123).

Topoisomerases

Topoisomerases (Topo I and Topo II) are nuclear enzymes that are vital in establishing and maintaining the normal three-dimensional structure of DNA during replication and RNA synthesis. They allow DNA to uncoil and permit complementing RNA and DNA synthesis to occur (124).

Topo II is expressed during the S/G2 phase and degraded during M/G1 transition (9). It also plays a role in chromatid segregation during mitosis (125). The two genes for Topo II code for two 170-kDa protein isoforms cotermed α and β.

Topoisomerases have been the target for many chemotherapy drugs such as anthracyclines and epipodophyllotoxins (126,127). These drugs stabilize the cleavable complex formed between topoisomerases and DNA, resulting in increased DNA excision of "detectable" single/double DNA strand breaks (9,21). The cytotoxic effect of anthracyclines depends on the number of cleavable complexes stabilized and the inability of the cell to repair the DNA lesions (128).

Qualitative and quantitative changes in Topo II have been implicated in the development of resistance to the above drugs (129,130). Studies of cancer cells resistant to Topo II poisons found decreased expression of Topo II α activity (131,132).

Drug resistance to topo inhibitors is most likely multifactorial, including disturbances in the cell cycle, DNA damage, and downstream events caused by topo inhibitors that influence regulation of cell death and survival. Stress-mediated resistance can be partially explained by a decrease in Topo II α expression (6). Stress leads to cell cycle arrest at G1, which leads to decreased levels of Topo II α secondary to increased degradation during G1 phase (9).

Thymidylate Synthase (TS)

Thymidylate synthase (TS) is an enzyme involved with DNA synthesis and associated with cell division and proliferation (133). TS is the target for chemotherapeutic drugs such as 5-fluorouracil and methotrexate (134). Alterations in cell cycle regulatory genes may result in increased levels of transcription factors, which can result in increased TS transcription (22). Upregulation of TS has been associated with 5FU resistance (135). Cisplatin- and doxorubicin-resistant tumor cells have also been found to increase levels of TS (113,136). TS may also play a role in regulating other genes, as suggested by the evidence that TS protein binds to c-*myc* mRNA (137). c-*myc* is an oncogene coding for a nuclear protein that functions as a transcription regulator (6).

Dihydrofolate Reductase (DHFR)

DHFR is a key intracellular enzyme for folate metabolism and regenerates tetrahydrofolate from dihydrofolate, a product of thymidylate synthetase (138). Methotrexate is a DHFR inhibitor. DHFR inhibition leads to decreased intracellular levels of tetrahydrofolate coenzymes, lower purine, and DNA biosynthesis (139). Methotrexate (MTX) resistance can be caused by a variety of cellular mechanisms including:

1. Impaired transport and decreased drug accumulation;
2. Lowered retention secondary to lack of polyglutamate formation;
3. DHFR gene amplification;
4. Altered and/or mutated DHFR that lowers the binding affinity of methotrexate;
5. Increased levels of lysosomal enzyme γ-glutamyl/hydrolase that hydrolyses methotrexate polyglutamate (140).

Heat Shock Proteins (HSP)

This is a family of proteins that protects cells from toxic external stimuli (21). HSP production is stimulated by a variety of environmental and pathophysiological conditions (141). The development of transient chemoresistance has been linked to increased HSP production (142–144). Doxorubicin resistance in breast cancer cells has been linked to HSP27 and HSP70 (145). Transinfection studies using HSP27 in MDA-MB-231 breast cancer cells increased doxorubicin resistance threefold (146). MCF7 breast cancer cells with an increased endogenous HSP27 are highly resistant to doxorubicin. Unfortunately, results have been inconsistent (21). Schardt et al. (147) compared HSP levels in human tumor cell lines with acquired resistance to doxorubicin and cisplatin and parental cell lines and found no difference in mRNA expression of HSP27 and HSP60.

Nuclear Factor κB (NF-κB)

NF-κB is a transcription factor and may be a major determinant of chemoresistance. NF-κB is involved in the regulation of prometastatic, proangiogenic multidrug resistance and antiapoptotic genes (148). NF-κB has the ability to act as a convergence point for a variety of stimuli (4). NF-κB can mediate cell cycle arrest which would provide enough time for cellular assessment of incoming signals before determining which pathway to follow (4).

As an antiapoptotic factor, it protects against TNFα, ionizing radiation, and cytotoxic drugs by transcription of cytokines/growth factors (IL-2, IL-6, G-CSF, and GM-CSF) (149–151). NF-κB has a protective effect following serum starvation similar

to Bcl-2 overexpression (see below). Following DNA damage, NF-κB is needed for Fas ligand upregulation (152). NF-κB is also involved in the transcription of the cell cycle regulators p53 and c-*myc*, both of which have been implicated in apoptosis (150,152).

The inactive form of NF-κB is normally found in the cytoplasm bound to IκB (inhibitor of NF-κB) proteins. When cells are stressed with cytotoxic drugs, IκB is phosphorylated and releases the NF-κB. The free NF-κB translocates to the nucleus where it activates target genes that will protect the cancer cells against apoptosis (148). NF-κB also induces expression of prometastatic genes, interleukin-6, urokinase plasminogen activator, and matrix metalloproteinase-9, as well as proangiogenic interleukin-8 and antiapoptotic genes (c-IAP1, c-IAP2, TRAF1, TRAF2, Gfl-1/A1, Bcl-X_1, and MnSOD) (153).

Telomerases

Telomerases are ribonucleoproteins that add specific DNA sequences to chromosome telomeres and facilitate the cell's ability to proliferate. Loss of telomeres during DNA replication will limit a cell's ability to proliferate/replicate (154–156). Telomerases have been implicated in anthracycline resistance. The exact role telomerases play in anthracycline resistance is still not understood (128).

Cytokeratin

Cytokeratin is an intermediate filament-type protein. The combination of cytokeratin 8 and 18 is a major cytoplasmic component of epithelial-derived tumors. Studies have shown that the intrinsic MDR drug resistance phenotype is partially attributable to the expression of cytokeratin 8 and 18.

Mitoxantrone has been shown to modify cytokeratin. Cytokeratin-dependent drug resistance (C-MDR), however, is not associated with the cell's ability to assemble the cytokeratin monomers into intermediate filament networks. The exact mechanism of C-MDR is not known. It is hypothesized that the interaction of the cytotoxic drug with cytokeratin may signal pathways favoring cell survival.

Oncogenes/Tumor Suppressor Genes

Most tumors develop and advance secondary to genetic alterations. Cancer cells can acquire mutations in genes that result in abnormal cell cycle control mechanisms (increased oncogene activity) or decreased inhibition of cell cycle progression (loss of tumor suppressor gene activity). An oncogene is a gene whose product contributes to malignant transformation, while a tumor suppressor gene is one that leads to cell growth control and differentiation. Oncogenes abnormally activate growth factors, growth factor receptors (i.e., HER2/neu), intracellular signaling molecules (i.e., RAS and c-raf), or nuclear transcription factors (i.e., c-*myc*).

Tumor suppressor genes are expressed in normal cells, but when mutated or inhibited lead to malignant transformation. Examples are the p53 gene, BRCA1, BRCA2, and the retinoblastoma (RB) gene. p53 is involved in the G1 cell cycle checkpoint and can cause either G1 arrest or apoptosis after DNA damage (15). RB expression inhibits the cell cycle progression by blocking the transcription of genes needed for the entry into S-phase. Figure 3 illustrates the multiple interactions of these genetic factors involved in DNA repair mechanisms.

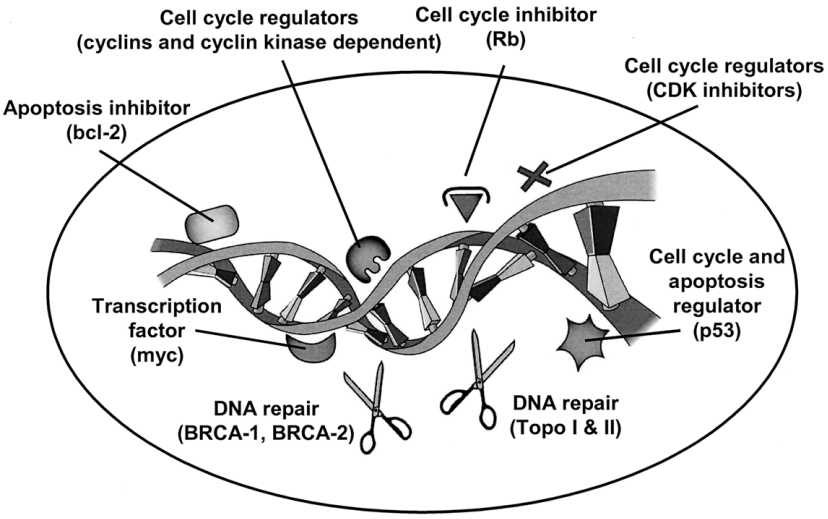

Figure 3 DNA repair—schematic illustration of mechanisms involved in DNA repair.

p53

Normal (wild-type) p53 is a multifunctional tumor suppressor gene playing a central role in cell cycle regulation, apoptosis induction, and maintenance of genetic stability by controlling differentiation (157–159). After cytotoxic damage or DNA malfunction, p53 stops the cell cycle and provides an opportunity for any damage to be repaired. If the damage is substantial and cannot be repaired, p53 will trigger apoptosis (2). The cell's decision to stop the cell cycle and allow for DNA repair or to induce apoptosis depends on the amount of DNA damage and the cell cycle stage when the damage occurred (160).

p53 mediates control over a group of cell cycle proteins that inhibit cycle-dependent kinases (CDK) (see below) (160). p53-mediated inhibition of CDKs not only causes G1 cell cycle arrest, but also prevents E2F (see "Retinoblastoma Gene (RB)" section for details)-dependent production of gene products needed for cell growth. In the presence of DNA-damaging drugs, wild-type p53 triggers an increased production of key gene products sufficient enough to block Rb phosphorylation by CDK, thus the expression of gene products needed for DNA synthesis is prevented and the cell cycle is halted.

Normal p53 function can also cause apoptotic cell death. High-dose chemotherapy leads to necrotic cell death (nonapoptotic death). A cell treated with an intermediate dose of chemotherapy, with intact p53 function, may be able to circumvent cell cycle arrest and result in p53-dependent apoptosis. p53-dependent apoptosis involves upregulation of bax and bcl-xc (tumor suppressor genes) and downregulation of bcl-2, bcl-xl and mcl-1 (survival genes) (81,161,162). Bax and bcl-2 are positive and negative targets of p53. The bax/bcl-2 ratio is important to p53-mediated apoptosis (163).

Because wild-type p53 assures genetic stability by either cell cycle inhibition or apoptosis, abnormal p53 function can lead to a variety of pathologic events. Normal p53 function can be modified by mutations, post-translational inactivation, inactiva-

tion by inhibitors [e.g., murine double minute chromosome (MDM)], or p53 degradation (e.g., by E6 protein of Human Papilloma virus [HPV]) (160). Wild-type p53 related pathways would prevent the transfer of faulty genetic material and maintain genetic fidelity. If p53 function is abnormal, apoptosis may be prevented and mutations may be passed on to subsequent cell populations. This would increase the chances of subpopulations to become more chemoresistant (Goldie–Coldman hypothesis) (160).

Cell death and drug resistance involve collaboration of many complicated alternative pathways. p53 mutations are believed to play a major role in oncogenesis and chemoresistance (2). p53 mutations can be somatic or germline mutations. Cellular p53 expression within individual tumors is quite variable (6). This would account for the variable impact of p53 mutations on chemosensitivity (164). Disregulation of the p53 pathway leads to abnormal rapid cell growth and overproduction of gene products responsible for entry in the S phase of cell cycle. Wild-type p53 suppresses the promoter of the MDR1 gene, whereas the mutant p53 protein may actually stimulate the promoter (165,166). Stimulation of MDR1 promoter by p53 may cause resistance to natural product chemotherapy agents (160). Cells with p53 mutations have decreased apoptosis induction by cisplatin, carboplatin, and melphalan (167).

p53 may enhance chemosensitivity by:

1. Promoting apoptosis via a transcription independent pathway,
2. Transcriptional activation of proapoptotic genes (i.e., bax),
3. Repression of antiapoptotic genes (i.e., bcl2).

p53 may reduce chemosensitivity by:

1. Promoting p21 dependent and independent growth arrest,
2. Increasing DNA repair,
3. Increased transcription of bcl-x (antiapoptotic gene) (168).

Evidence suggests p53 mutations in colorectal, breast, prostate, and ovarian carcinoma are associated with poor prognosis (169). Elevated levels of mutated p53 have been found in human breast cancer (26%, 431 of 1640 samples) (2). p53 mutations were associated with de novo resistance to doxorubicin in breast cancer patients. Breast cancer patients with wild-type p53 genes responded better to adjuvant therapy when compared to patients with p53 gene alterations (170).

Ovarian cancer has a monoclonal origin (171). The variability of p53 alterations found in ovarian cancer suggests that loss of p53 function is a late event. Unlike BRCA1 and BRCA2, germ line mutations of p53 have not been found in ovarian cancer cells (172–174). Somatic p53 mutations have been found in 30–70% of ovarian cancers (175).

p53 mutations were found in paclitaxel-resistant human ovarian carcinoma clones. These cells were also found to have β tubulin mutations. Cells with tubulin mutations and a restored wild-type p53 did not regain their drug sensitivity (176). Cisplatin resistance in some ovarian cancer cell lines was associated with failure of p53 upregulation or abnormal p53 expression (177). It is interesting to note that wild-type p53 tumors are responsive to cisplatin. Disrupting endogenous wild-type p53 leads to cisplatin resistance in ovarian cancers (178,179).

Breast Cancer–Related Tumor Suppressor Genes (BRCA1, BRCA2)

BRCA1 and BRCA2 are tumor suppressor genes that are involved with DNA damage repair and transcriptional regulation. Studies have shown that individuals with germ-

line mutations of BRCA1 and BRCA2 are predisposed to breast and ovarian cancer. BRCA1 mutation is associated with an 80% lifetime risk of breast cancer. BRCA2 mutations convey a similar risk, but are associated with a later age of disease onset (180). In addition to breast cancer, individuals with BRCA mutations also have an increased risk for ovarian cancer (180).

Cells without a normal BRCA1 or BRCA2 accumulate chromosomal abnormalities (chromosomal breaks, aneuploidy, and centromere amplification). Chromosomal instability secondary to mutant BRCA1 or BRCA2 may be the pathologic basis for the development of breast cancer (180). Most cells with somatic or germline inactivating mutations of BRCA1 or BRCA2 will not be able to repair damaged DNA and will die. Some of the DNA damage may involve cell cycle checkpoint genes (i.e., p53). Checkpoint gene mutations would permit a cell to evade apoptosis and proliferate with a potential for invasive growth (180). Studies have shown that tumors with BRCA1 or BRCA2 germline mutations may also have somatic mutations of p53.

NF-κB has been the only protein found to regulate BRCA2 expression. NF-κB regulates the expression of genes critical to apoptosis, tumorigenesis, and inflammation. Studies have found that NF-κB stimulates cell cycle progression in estrogen receptor negative breast cancer cells. This pathway may be responsible for sporadic breast tumors that are overexpressing BRCA2 (180).

BRCA1 has been shown to affect apoptosis via p53, p21, the JNK pathway, H-Ras, fas/fas ligand, and caspase 8 and 9 interaction (181). With such an extensive network, it is not surprising that BRCA1 and BRCA2 have been linked to chemoresistance. In experiments, BRCA1 inhibition caused resistance to mitotic-spindle poisons (Taxol) (181). After treatment with microtubule-interfering drugs, BRCA1 activates apoptosis via the JNK pathway.

Retinoblastoma Gene (Rb)

Rb is a tumor suppressor gene that codes for a 105-kDa nuclear phosphoprotein. Rb is a substrate for cyclin-dependent kinases (21,138). During G1, the functionally active hypophosphorylated Rb is bound to E2F. Hyperphosphorylated Rb releases E2F when the cell traverses from G0 to S1. Elevated levels of E2F increase the transcription of genes involved in DNA replication (i.e., DHFR) and cell cycle progression (50). As an example, increased DHFR expression and enzyme activity cause methotrexate and antimetabolite resistance (50,138). Therefore, any process that decreases Rb expression or function can theoretically increase drug resistance by increasing E2F levels and DHFR activity. Overexpression of cyclins, however, can overcome Rb-mediated growth suppression (21).

Cyclin-Dependent Kinase Inhibitors (CDK Inhibitors)

p21 and p27 are universal CDK inhibitors that bind to cyclin/CDK complexes of the cell cycle and arrest cell growth. p21 plays a rather complex role in cellular mechanics (182). p21 is involved with ErB2-dependent oncogenicity (183). $p21^{waf1}$ is a central mediator of ErB2's antiapoptotic mechanism.

It is interesting to note that members of the p21–CDK family can function in an inhibitory or activating capacity. Lower-order complexes of cyclin–CDK–$p21^{waf1}$ in a 1:1:1 ratio usually function as activators. However, in some instances, with the addition of more $p21^{waf1}$, function changes to inhibition (184).

p27 gene codes for a CDK inhibitor in a variety of cancers. Cell cycle progression from G1 to S phase is regulated in part by p27. High levels of nuclear p27 have been found in normal epithelial tissues such as ovarian, breast, and prostate. Primary regulation of p27 happens at the post-transcriptional level by altered proteolytic activity (185). Loss of p27 has been shown to be associated with aggressive tumor type and poor prognosis in breast, prostate, and ovarian carcinoma (185–187). Low levels of epithelial p27 have been found in ovarian cancer and have been associated with chemoresistance (64,188).

Levels of p27 were associated with chemoresistance to doxorubicin, etoposide, and cisplatin (189). p27 immunocytochemistry staining is easily done and reliable, and its levels may prove to be markers for chemosensitivity and resistance (185).

Bcl-2 Gene

Bcl-2 gene codes for an antiapoptotic protein that promotes cellular survival, rather than proliferation. It protects against almost all apoptosis-inducing stimuli, including drugs, growth factor withdrawal, radiation, heat, and death receptor activation (190–195). There are 17 mammalian homologs of Bcl-2 protein. Some are antiapoptotic (Bcl-XL, Mcl-1, A1, Bcl-W, B00), and others are proapoptotic (Bax, Bak, Bok, Bik, Blk, Hrk, BNIP-3, Bim, Bad, Bid, Bcl-Xs, and Diva).

Approximately half of all human cancers have increased levels of Bcl-2, including non-Hodgkin's lymphoma, acute leukemias, and breast cancer. Transfection of Bcl-2 or Bcl-XL into cells was found to greatly increase resistance to cytotoxic drug-induced apoptosis (190,191,196). An increase in Bax (proapoptotic protein) or Bcl-Xs (Bcl-2 antagonists) and Bcl-2 inhibition using antisense oligonucleotides was found to reverse chemoresistance (C 174–177). Bcl-2 family interactions with targets such as Apaf-1 (antiapoptotic factor) may be regulated by PKC-meditated phosphorylation.

HER2-neu Oncogene

HER2-neu is also called erbB2. HER2-neu/ErbB2 oncogene is a member of the epidermal growth factor receptor family (EGF). HER2-neu/ErbB2 belongs to the membrane-spanning type I receptor tyrosine kinase family. Resistance to cytotoxic drugs and radiation has been found in cancer cells overexpressing HER2-neu/ErbB2 (197–199).

HER2-neu overexpression renders cancer cells resistant to chemotherapy by altering the balance between cell survival and death signals. It seems to act as an antiapoptotic cell survival factor (200,201). HER2-neu/ErbB2 overexpression hyperactivates the cell cycle machinery. Elevated levels of HER2-neu have been linked to Bcl-2 and Fas ligand, two key regulators of apoptosis (202). HER2-neu overexpression may also facilitate DNA repair mechanisms (203,204).

The exact mechanism by which HER2-neu/ErbB2 overexpression stimulates tumor growth and/or makes cells chemoresistant is not completely understood (205). The HER2-neu/ErbB2 protein product is p185 HER2/neu, and is seen in approximately 30% of carcinomas of the breast, as well as a large percentage of ovarian carcinomas (206). Overexpression of HER2-neu is not only associated with increased chemoresistance but also with poor prognosis after surgical therapy (201,207–209). Chemoresistance to paclitaxel has been associated with HER2-neu overexpression in breast cancer (199,210).

HER2-neu oncogene may prove to be a very useful target in treating breast cancer (207,208,211,212). Downregulation of HER2-neu may decrease DNA repair and/or enhance apoptotic cell mechanisms (211). HER2-neu downregulation can be achieved via any of the following:

1. Antisense oligonucleotides,
2. Monoclonal antibodies (limited to work at the cell surface and not intracellularly),
3. Inhibition of $P184^{HER2}$ neu tyrosine kinase activity,
4. Target HER2-neu promotor (i.e., EIA, SU40 large T antigen) (205,213).

All of these mechanisms are being investigated for therapeutic interventions.

Ras Oncogene

Ras gene codes for a G protein located in the plasma membrane that plays a pivotal role in multiple pathways involved with amplification of abnormal signals. Oncogenic Ras cycles between an active (GTP-bound) and inactive (GDP-bound) form in response to growth factors or interaction with cell surface receptors. Receptor-activated Ras relays extracellular signals through signal transduction pathways mediating multiple intracellular responses including growth, survival, apoptosis, and immune response (4).

Ras upregulates Bcl-2 and Bcl-XL, members of a family of apoptotic regulators that protect cells from proapoptotic factors (214). Overexpression of Bcl-2 or Bcl -XL correlates with disease aggression, chemoresistance, and decreased patient survival (215,216).

Oncogenic Ras activation causes an increase in tumor proliferation and suppression of apoptosis. Patients with N-Ras mutations have a decreased chemotherapy response and lower rates of remission (217). Ras can be directly activated by Bcr-Abl (an oncogene) (218). Bcr-Abl positive cancers are aggressive, drug-resistant, usually growth factor-independent, and resistant to apoptotic stimuli (219–221). Bcr-Abl not only activates Ras but also activates P13 kinase, a downstream effector of Ras (222).

Abnormal Ras activity can result from the following:

1. Deregulation of guanine nucleotide exchange factors (GEFs) or GTPase-activating proteins (223);
2. Overexpression of growth factor receptors (224);
3. Autonomous cytokine production (i.e., interleukins) (225,226);
4. Ras promoter mutations (227);
5. Activation of co-oncogenes (i.e., Bcr-Abl) (218).

Because Ras plays such a pivotal role in multiple cellular pathways, it has led to the development of drugs targeting Ras. Ras is synthesized as an inactive precursor molecule. The development of Ras into an active mature protein requires multiple post-translational modifications. Most importantly, Ras modification involves the enzyme farnesyl transferase. Inhibition of farnesyl transferase prevents post-translational modification of Ras in a very specific manner. Farnesyl transferase inhibitors (FTI) block Ras modification signaling and transformation, without overt toxicity (228,229). Anti-Ras neutralizing antibodies have been found to promote apoptosis and tumor regression.

Intracellular Signaling Pathways

Multiple interconnecting signaling pathways (i.e., P13-kinase/PKB, PKC, the stress-activated protein kinases [SAPK] or c-jun N-terminal kinases [JNK], caspases, and Fas/CD95) are involved with regulation of apoptosis, cell survival, and proliferation (4). Exploitation of survival pathways significantly contributes to drug resistance. Antiapoptotic mechanisms are recruited to equip the cell with an increased survival capacity in order to facilitate disease progression and evade drug-induced apoptosis (4). Survival signals are unique in protecting cells by preventing the conversion of cytotoxin-induced injury into death signals (4). Survival signals increase the capacity of a cell to survive insult by allowing time for damage repair, thus promoting disease aggression and chemoresistance. These pathways will be briefly reviewed.

P13 Kinase

P13 kinase mediates survival signals and protects against apoptosis-inducing stimuli (i.e., growth factor withdrawal) (230,231). It is activated by the binding of growth or survival factors to cell surface receptors. p13 kinase may also be stimulated by interaction with activated Ras. p13 kinase binding to activated Ras in turn leads to increased levels of activated Ras (232,233). Active p13-kinase binds with protein kinase B (PKB) and the activated PKB phophorylates BAD (proapoptotic Bcl-2 homolog). Phosphorylated BAD is then sequestered by the cytoplasmic protein 14-3-3 and apoptosis is inhibited.

Protein Kinase B (PKB)

PKB (also called Akt) is an antiapoptotic survival-promoting molecule. PKB inhibition leads to BAD dephosphorylation and release of BAD by the antiapoptotic protein 14-3-3. Free BAD will bind and neutralize antiapoptotic Bcl-2 family members (Bcl-2, Bcl-XL) and lead to apoptosis (234). Relationships between PKB, BAD, and survival are cytokine and cell-type specific (235,236).

PKB's role in cell survival is emphasized by the fact that it is cleaved and inactivated by caspases (proapoptotic proteases). Procaspase-9 (an initiator caspase) is also a target for PKB phosphorylation and subsequent inactivation. This emphasizes the role of PKB in cell survival (4).

PKB also inactivates glycogen synthase kinase 3 (GSK3). GSK3 is involved in the regulation of many substrates, metabolic enzymes, and transcription factors including c-*myc*, AP1 (the regulatory subunit of cyclic AMP-dependent protein kinase), and elF-2B (a translation factor) (237–240). The exact role played by GSK3 and chemoresistance is not yet fully understood (241,242).

Protein Kinase C (PKC)

Protein kinase C (PKC) is a family of serine/threonine protein kinases made up of 11 isoenzymes, including a calcium-dependent group, a non-calcium-dependent group, and an atypical group (243). PKC's role in oncogenesis is often contradictory (4). PKC plays a diverse role, mediating intracellular effects of many extracellular signals (i.e., growth factors, hormones, drugs). PKC influences mitogenesis, differentiation, survival, and apoptosis (244–246).

The exact role of PKC in disease progression is still not fully understood. Overexpression of the isoenzymes PKCα and PKCβ is associated with a less aggressive type

of breast cancer (247). Inhibition of PKCα has been found to reverse the neoplastic properties of human lung cancer (248).

There is a definite relationship between PKC, MDR, Bcl-2, and the many signaling molecules/pathways. PKC-mediated phosphorylation may influence interactions between Bcl-2 family members and targets such as the apoptosis-activating factor (Apaf1). It has been hypothesized that Bcl-2 and Apaf1 inhibit procaspase 9 processing, thus inhibiting apoptosis (249). PKCε has been found to induce Bcl-2 expression and has been associated with chemoresistance, disease aggression, and poor clinical outcome (215,216).

Ras and PKC enhance antiapoptotic functions by increasing Bcl-2 expression (250,251). Active PKC plus functional Ras promotes cell proliferation; however, if PKC is inhibited, Ras promotes apoptosis.

MDR phenotype is also observed to have elevated PKC activity (252). Pgp phosphorylation via increased activity and expression of PKCα has been associated with MDR (253). Pgp is phosphorylated by PKC, as is glutathione-*S* transferase and topoisomerase II (254).

c-Jun N-terminal Kinases (JNK)

Stress-activated protein kinases (SAPK) or c-Jun N-terminal kinases (JNK), a subgroup of the mitogen-activating protein kinase family (MAP), mediate cellular response to physiological stressors, inflammatory cytokines, DNA damage, and heat shock (255,256). JNK, like many other signaling molecules, exerts a wide, varied, and sometimes contrasting range of function (i.e., transformation, growth, development, death, and survival) (255,256).

JNK may determine sensitivity and/or response to drug therapy. In some sensitive cells, JNK triggers the caspase cascade that leads to drug-induced apoptosis. Cells lacking JNK activity are resistant to cytotoxic drug-induced apoptosis (257,258).

The JNK-mediated cellular response depends on cell type, external stimulus/stressors, and activation/deactivation of multiple signaling pathways (4). The balance between JNK and extracellular signal-related kinases (ERK) determines if the survival or apoptosis/death pathway is chosen (259–261). JNK and c-Jun are considered essential for the apoptotic cascade (4). Stress-activated JNK activates c-Jun (a member of the transcription factor AP-1). Deregulated AP-1 can initiate malignant transformation and also contribute to chemoresistance) (262). Depending on the cell type and situation, c-*jun* may inhibit apoptosis and contribute to cell proliferation and/or differentiation (255,256). JNK is also critical for Fas-mediated apoptosis (263–265). Cell type and inducing stimuli determine if JNK activation is a causal or secondary event in apoptosis (266). The final outcome mediated by JNK activity appears dependent on the activation and deactivation of various signaling pathways within a cell (4).

Caspases

Caspases are a family of cysteine proteases activated by apoptotic insult (267). They destroy and inactivate multiple survival mediators including PKB, Raf-1, Ras-Ras-GTPase activating protein (GAP), DNA repair enzymes, and cytoskeleton components (i.e., actin, lamin) (268,269). Caspases amplify the apoptotic cascade by activating downstream procaspase zymogens into active caspases (270). They also cleave Bcl-2, converting Bcl-2 from an antiapoptotic protein to a proapoptotic protein (269). Defects in caspase activation have been associated with chemoresistance (271).

Procaspase 9 is another target for PKB activity (272). PKB inhibition of procaspase 9 can result in drug resistance secondary to suppression of apoptosis. There is a potential to overcome resistance or increase chemotoxicity by combining chemotherapy with PKB inhibition. This combination would synergistically activate the caspase cascade and induce apoptosis (273).

Fas

Fas, also referred to as APO1 and CD95, is a member of the extended tumor necrosis factor (TNF) superfamily of death receptors (274). Activation of the Fas receptor by specific death ligands (i.e., Fas antibody) triggers apoptotic signals. The exact role of Fas/Fas ligand (Fas l) in chemotherapeutic drug-induced apoptosis is not fully understood.

Multiple signaling pathways and antiapoptotic molecules play a role in determining the sensitivity of Fas-induced cell death (275–278). Activation of Fas recruits signaling molecules including Fas-associated death domain (FADD) and procaspase 8, which begins the caspase cascade-initiated cell death via both mitochondrial and nonmitochondrial pathways (261).

Chemotherapeutic drugs have been found to upregulate Fas ligand expression in leukemic cells (279). Unfortunately, expression of Fas l by tumor cells is often accompanied by the loss of the death receptor Fas, decreasing the possibility of self-induced apoptosis (280). In some studies, chemotherapeutic drugs have been found to induce apoptosis via Fas receptor activation and interaction with FADD, but in a Fas l-independent manner.

Fas/Fas l upregulation may rely on the presence of functional p53 (281). Inhibition of PKC increases sensitivity of Fas-mediated apoptosis (250). Oncogenic Ras downregulates Fas, thus suppressing Fas-mediated apoptosis (282). P13 kinase (in a PKB-dependent path) counteracts Fas-induced apoptosis (283).

CONCLUSION

In this chapter, we have given an overview of current data on the complex cellular mechanisms involved in chemotherapy response and resistance. This is a rapidly evolving field of intense research. Malignant tumors show enormous heterogeneity, not only in regard to their morphology, but even more so in their genetic and functional make-up. Research is usually carried out on established "pure" cell lines, often derived from very different but select stem cells (i.e., ovary, breast, colon, lung), making comparisons of molecular systems difficult. Genetic instability of malignant tumors and clonal selection as a result of chemotherapy make the analysis of the complex, extensively interwoven molecular systems even more difficult. The continuous effort in understanding these complex biological mechanisms allows us to better correlate the biological behavior with clinical characteristics in terms of growth and response to therapy.

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3

In Vitro Testing for Drug Sensitivity/Resistance

Bernd-Uwe Sevin
Division of Medical and Surgical Gynecology, Mayo Clinic, Jacksonville, Florida, U.S.A.

INTRODUCTION

Every living cell is designed to assure survival and reproductive capability despite the many environmental toxins it may be exposed to. This is particularly true for cancer cells. The preceding discussion demonstrates the multiple interrelated, complex, and adaptive cellular mechanisms assuring cell survival and procreation. These multifaceted escape mechanisms are also the basis for tumor drug resistance. Because of the multitude of escape mechanisms, it is unlikely that any one molecular substance or gene will be able to serve as a drug-resistance marker. While genomics and proteinomics in combination with microarray technologies have the promise to identify markers of drug resistance, only direct drug testing on fresh tumor tissue makes it possible at this time to provide information regarding chemotherapy response of individual tumors (1).

History of In Vitro Drug Testing

For the last 30 years, many attempts have been made to develop an in vitro system, similar to bacteriology assays for infectious diseases, that will allow the clinician to preselect drugs that have the highest probability of achieving maximal tumor cell kill. The first problem encountered was the difficulty to grow tumor cells in vitro, without allowing the nonmalignant cells (e.g., fibroblasts) or infections (bacteria, yeast) to contaminate or even overgrow the tumor cells in vitro. The second problem was the selection of the most appropriate measurable endpoint that best reflects the drug effect on the tumor cell population. One of the first clinically applicable assays was the human tumor clonogenic assay (HTCA), publicized by Hamburger and Salmon (2). Solid tumors were disaggregated into a single cell suspension. The cells were washed, exposed to a chemotherapeutic agent for 1 hr, washed again, and plated in soft agar enhanced with growth media. Cells that remained viable were allowed to grow and form colonies, which were then counted after an average of 3 to 4 weeks. The soft agar

with growth media created a favorable environment to permit tumor cell growth, while simultaneously inhibiting nonmalignant cell proliferation.

This assay was the first and laid the ground for assays developed later. Second-generation assays include the radiolabeled DNA precursor assays (3), the methyl thiol-diphenyl-tetrazolium (MMT) bromide assay and differential staining cytotoxicity (DiSC) assay, ATP-cell viability assay (ATP-CVA), the ChemoFx assay, and the Fluoroscent Cytoprint Assay (FCA). These assays differ in several ways (4–6).

The Human Tumor Clonogenic Assay

The human tumor clonogenic assay (HTCA) described above is the most well-studied chemosensitivity assay (2,7–9). Several retrospective studies have shown good correlation between test prediction and clinical response (9–11). However, the colony-forming assay has several problems making it impractical for routine clinical use (10–12). One major drawback of the HTCA is its low percentage of approximately 40% to 70% of successful assays (7,9,13). This low evaluability rate was due to poor tumor growth and the large number of cells required for the assay. Von Hoff (11) reported on 13,932 specimens tested, of which 5098 specimens were from the female reproductive tract; of these, only 35.2% of control plates formed >20 colonies. The evaluability rate proved to be the most important parameter limiting the clinical usefulness of this in vitro testing system.

Radiolabeled DNA Precursor Uptake Methods

Two different methods of in vitro assays using DNA precursors have been described (Volm/Kern Test) (14,15). A tumor suspension is plated in liquid media over an agar underlayer and incubated with the drug for 3–4 days, followed by additional incubation of 18–24 hr with ^{3}H-thymidine. Uptake of the radiolabeled DNA precursor by tumor cells and untreated controls is then measured with a liquid scintillation counter (16). Testing suprapharmacological drug concentrations, this method primarily evaluates extreme drug resistance (EDR) (17). Evaluability rates are reported to be around 80%.

Radiolabeling measures the effect of cytotoxic drugs only in those cells that are actively synthesizing DNA. Solid tumors in vivo have a relatively small fraction of cells undergoing DNA synthesis of 5–10% (18). Therefore these tests evaluate only a select small tumor population and provide no information regarding the effects of a drug on tumor cells in the G_0/G_1 phase of the cell cycle.

Differential Staining Cytotoxicity Assay

Weisenthal and Lippman (18) originally developed this system for hematological malignancies. It is based on the ability of most viable cells to exclude dyes in vitro. Tumor cell suspensions are incubated in liquid medium for 4 to 6 days in polypropylene-coated culture tubes, which reportedly prevent attachment and growth of normal cells. Fast green stain, which penetrates incompetent cell membranes, is used to identify dead or dying cells and hematoxylin-eosin or Wright–Giemsa stain to identify living cells. Fixed duck red blood cells (DRBCs) are used as an internal standard. The ratio of living tumor cells or DRBCs and dead tumor cells, counted under the

microscope, is used as a measure of drug-related cytotoxicity. The DiSC assay has a reported evaluability rate of about 77% (19,20).

Fluorescent Cytoprint Assay

Another method to overcome some of the limitations of the HTCA was developed by Rotman et al. (21). To improve plating efficiency, this method uses small tumor tissue fragments of about 50 or more cells called "microorgans," instead of a single cell suspension, for plating. These microorgans are immobilized in a cellulose–collagen matrix and plated at the liquid/gas interface on a stainless-steel grid in conventional tissue culture plates. Viable cells with intact cell membranes incorporate fluorescein–monoacetate and through hydrolysis produce fluorescein, which renders the cell brightly fluorescent. Within 2 hours fluorescein diffuses out of the cells. After short exposures to fluorescein, microorgans are repeatedly photographed to assess cell viability. Cytotoxicity is measured by comparing photographs of fluorescent cytoprints before, during, and after drug exposure. Assay results are available in 5–10 days. Average evaluability rates of 80% have been reported (22). The reported advantage of this assay is that microorgans maintain cell-to-cell contact, postulated to result in a more normal response to chemotherapeutic agents. There are, however, no separate untreated controls as the cytoprint prior to drug exposure is used as "internal control." It is therefore difficult to determine if the tumor cells are dying in response to the drug treatment or because they are unable to maintain viability in culture.

The MTT Dye Reduction Assay

The MTT dye reduction assay uses a single cell suspension and depends on cellular reductive capacity to metabolize the MTT dye to a highly colored formazan product, and makes the assumption that the cell's reductive capacity remains constant throughout the test (23,24). Advantages of this test are less labor intensive than the HTCA, performed in a few days and suited to automation. The disadvantages include limited experience with fresh solid human tumors and that the assay may be susceptible to changes in enzymatic activity, pH, cellular-ion concentrations, and cell-cycle variation (25,26). In addition, the MTT formazan dye begins to lose color within hours and is affected by the grade of DMSO that is required to solubilize the formazan crystals. The evaluability rate of this assay is around 70%.

The ChemoFx Assay

To overcome the problem of limited viable cells to be exposed to chemotherapeutic agents in vitro, the ChemoFx assay developed by Kornblith et al. (27) focused on improving in vitro growth conditions for human tumor cells (6). After mincing tumor cells into small pieces, cells are grown in vitro until sufficiently large numbers are available to test several drugs and drug combinations in multiple replicates (28). Cells are transferred into microtiter plates, incubated for 24 hr, and then exposed for 2 hr to 4–6 drug concentrations, depending on the pharmacology of each drug tested. Afterward, cells are washed and incubated for 72 hr and evaluated for cell death by operator-assisted microscopy. The assay has an evaluability rate of over 90%.

ATP-Cell Viability Assay

The ATP-CVA, also called ATP-chemosensitivity assay (ATP-CSA) or ATP-tumor chemosensitivity assay (ATP-TCA), was developed for clinical use by Sevin et al. (29). It has been applied to studies in the in vitro response of cell lines and fresh gynecological human tumors and breast cancers against a variety of antineoplastic agents including chemotherapeutic agents, hormones, and biological response modifiers (29–34). Fresh tumor tissue is minced and gently disaggregated to obtain a uniform suspension of cell aggregates of up to 50 cells. These are then plated in media and agar underlayer, including drugs at five concentrations and untreated controls, and are incubated for 6 days. This assay measured ATP-dependent light production with a luminometer as cellular ATP interacts with the luciferin–luciferase complex.

Quantification of the light produced has been shown to directly correspond with the number of viable cells (4,29). Survival fractions can be accurately determined by calculating the ATP ratios of treated to untreated samples. The assay is reproducible, reliable, and has a success rate in fresh tumor of over 90% (4,29).

Discussion of In Vitro Assays

The years of developing in vitro chemosensitivity/resistance assays were filled with heated discussions centering around the following issues: tissue preparation, in vitro drug concentration, exposure times, and assay endpoints. The HTCA requires a single cell suspension, as do the Volm, EDR, MMT, and DiSC assays. To disaggregate solid tumor tissue into a single cell suspension requires extensive mechanical and enzymatic disaggregation techniques, which damage and kill many tumor cells, leaving only a small viable tumor cell population to be tested. Low viability at the time of plating limits the number of assays that can be set up and reduces the probability of obtaining evaluable assay result. Two assays avoid this problem by using only limited disaggregation techniques, the FCA and ATP-CVA, plating out small tissue aggregates of up to 50 cells, thus increasing the number of viable cells for plating. The ChemoFx assay does this too, but in addition allows cells to grow in vitro until sufficient viable cells are available to set up an assay.

The HTCA and many other second-generation assays tested only one or two drug concentrations. However, for quality control and to obtain reliable assay results, dose–response curves need to be produced, testing each drug at four to five concentrations. To set up triplicate assays for each drug and drug combination as well as for untreated controls requires large amounts of viable cells. This will also provide information on sensitivity (low concentration) and resistance (high concentration). The most commonly used reference value for in vitro drug testing is the published peak plasma concentration (PPC) for each drug. In vitro drug concentrations tested ranged from 0.1 to $5.0 \times$ PPC.

The time from the moment tumor is harvested to the moment in vitro assay results are reported back to the clinician is another important issue of controversy and practicality. The HTCA requires 3–4 weeks, as does the ChemoFx assay, because both rely on prolonged cell proliferation in vitro. Most other assays are considered short-term assays, requiring 4 to 10 days to obtain assay results. Besides the benefit of providing the clinician with results quickly, there is a major biological issue involved, that of testing drugs on selected vs. unselected tumor cell populations. Growing cells in

the artificial environment of the in vitro system leads to selection of cells which may not be representative of the original in vivo tumor tissue. While it is well accepted that any in vitro system represents an artificial environment, the shorter the in vitro exposure, the less likely is the selection and adaptation process. At least this is a major argument posed by short-term assay proponents against long-term assays. The need for triplicate assays for each drug and drug combination, each at three to six concentration, obviates the need to develop an assay that maximizes tumor viability in the in vitro test system, especially as more and more new drugs and drug combinations that should be tested are made available to the clinician.

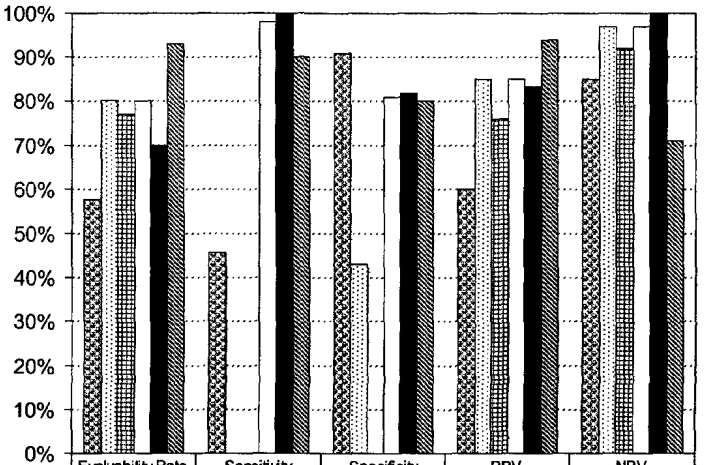
Another important variable in the different assay systems is the endpoint by which the effect of drug is measured. In the HTCA, cell colonies are counted under the microscope, a rather subjective and labor-intense process. The ChemoFx counts cells but with the aid of an operator-assisted computer microscope. The Volm and Kern tests measure the incorporation of radiolabeled DNA precursors with a scintillation counter. As most chemotherapeutic agents interfere with cell proliferation, this method tests the inhibitory effect of drugs on DNA replication. However, cell cycle perturbations are common after drug exposure, but because of repair mechanisms, these are not necessarily resulting in cell death. The EDR assay exposes tumor cells to suprahigh doses of drugs, thus only testing for drug resistance to nonphysiological high drug concentrations that cannot be achieved in vivo. The FCA and DiSC assays use fluorescent and fast green dyes, respectively. The former measures intact and the latter incompetent cell membrane function as surrogates for cell viability. The MMT relies on the viable cell's reductive capacity to metabolize the MMT dye to produce a blue color that is measured by spectrophotometry. In contrast, the ATP-CVA measures intracellular ATP, the universal energy source for all living cells. The light generated when ATP interacts with the luciferin–luciferase complex is measured with a luminometer and corresponds directly with the number of viable cells in the assay. As few as 50–100 cells are needed to obtain measurable assay results, making it possible to test many drugs and drug concentrations even on small amounts of tumor tissue (29).

Clinical Correlation

Several excellent reviews have been published summarizing data on clinical correlation for the different in vitro systems (4,5,35,36).

However, many variables influence the overall chemotherapy response in patients, such as host factors (age, nutritional status, immunocompetence), treatment variables (dose, frequency, route of drug application, peak plasma concentration), as well as tumor variables (size, localization, degree of vascularization). These variables between the "endorgan" drug response at the cellular level which is evaluated with the in vitro test system, and the overall clinical chemotherapy response in the patient, define the limitations of information that can be obtained even with the best method of chemosensitivity testing. It becomes rather obvious that the best one can expect from an in vitro chemosensitivity test is an increase in probability for the prediction of clinical response, or lack of response, of a particular drug or drug combination.

Most described chemosensitivity assays are quite good in predicting lack of response with reported negative predictive values above the 90% rate. However, the clinicians really want information about drug sensitivity so they can select the most



	Evaluability Rate	Sensitivity	Specificity	PPV	NPV
Human tumor cloning assay	57.60%	45.60%	91.00%	60%	85%
Kern assay	80%	NA	43%	85%	97%
Differential staining cytotoxicity assay	77%	NA	NA	76%	92%
Fluorescent cytoprint assay	80%	98%	81%	85%	97%
MTT assay	70%	100%	81.80%	83.30%	100%
APT-CVA	93%	90%	80%	94%	71%

PPV=Positive Predictive Value, NPV=Negative Predictive Value
Source: From Ref. 36

active ones for treatment of a specific patient. It is of interest to see that most of the methods described emphasize the benefit of their method to determine drug resistance (NPV). Predicting lack of response is more likely to be successful with in vitro testing than is prediction of clinical response (PPV), because if the endorgan does not respond, the other biological and pharmacological variables affecting overall response lose significance.

Studies to establish the validity of an in vitro testing system have been done by either correlating in vitro assay results with in vivo patient response data or using in vitro assay results to select drug therapy for individual patients. Most data in the past have been collected through retrospective and only very few through prospective studies. Prospective studies correlating in vitro assay results with in vivo patient response data have been limited in the past by evaluability rates and the fact that patients are not always treated with drugs tested in vitro (37). Patients were also frequently treated with drug combinations, while in vitro assays tested only single drugs, complicating the correlation of data even further. To bypass the issue of direct correlation between assay results and treatment response of individual patients, many authors have used published clinical response rates of individual drugs in comparable neoplasms (e.g., the effect of cisplatin in ovarian cancer) as a correlative for the in vitro response rates observed in their assay system. As pointed out by Weisenthal and Kern (38), the expected likelihood of a certain drug to be active in vivo will define the probability of positive in vitro test results. This relationship is described by the principles of the Bayesian theorem and applicable to chemosensitivity testing (4). For example, the response probability of primary ovarian carcinoma to a platinum-

containing regimen is over 70%. In contrast, the probability for recurrent ovarian carcinoma to respond to any chemotherapy is around 30%. Comparing the expected with the observed response rates will define the benefit that can be obtained if the patient is treated with tumor-sensitive drugs. An increase of only 20% in the probability of drug response would translate into response rates of 90% and 50% for primary and recurrent ovarian cancer, respectively.

Alberts et al. (7) observed a survival advantage in recurrent ovarian cancer patients treated with in vitro-selected drug treatment (10.5 months) compared to clinician-selected drugs (3.0 months). Von Hoff (11) observed improvement in clinical response rates (348 trials) in patients with recurrent ovarian cancer treated with single agents selected by in vitro tests of 25%, compared to 11% in those selected by clinicians. In a prospective study by the Southwest Oncology Group (39), a response rate of 28% was observed when patients with refractory ovarian cancer were treated according to HTCA results, compared to 11% in patients treated according to clinician's choice. However, there was no significant difference in survival between the two groups (6.25 vs. 7.0 months). Cortazar and Johnson (40) reviewed 12 prospective clinical studies evaluating the benefit of in vitro assays. They identified 506 patients treated based on in vitro assay results with an overall response rate of 27%, compared to 17% of those treated based on physician's choice.

O'Meara and Sevin (36) did a very detailed analysis of 161 patients with advanced ovarian cancer (75% primary, 25% recurrent), who were treated with combination chemotherapy, including cisplatin, Taxol, or cyclophosphamide. Tumors from these patients were all tested for single drugs and drug combinations with the ATP assay. The overall clinical chemotherapy response rate was 65%. Patients showing in vitro sensitivity had a clinical in vivo response of 83% compared to only 43% for patients with in vitro resistance. The risk ratio for clinical response for sensitive in vitro tumor results was 1.91 (95% CI 1.34–2.57, $P = 0.00004$).

CONCLUSION

This chapter, as well as the one on mechanisms of chemotherapy and resistance, has illustrated how complex the mechanisms of chemosensitivity, chemoresistance, and prediction of tumor response are. The prediction of in vivo response using in vitro testing is complicated by several factors, including in vitro tumor growth, lack of vascularization and modification of environment with absence of many cytokines and other important molecular components.

Tumor heterogeneity in regard to in vitro drug response, even in a select organ system such as ovarian cancer, has been illustrated by a study of 100 consecutive primary ovarian cancers (41). Dose–response curves for four single drugs and two drug combinations ranging from 0.1 to $5.0 \times$ PPC were done on all tumors using the ATP-CVA. Dose–response curves for each drug and drug combination were quite variable for illustrating the enormous heterogeneity of drug response in these tumor specimens. However, more impressive was the enormous range of variability in the survival fractions for similar drugs such as cisplatin and carboplatin with *r*-values ranging between 0.344 and 0.462 for all except the highest drug concentration of $5.0 \times$ PPC, when cell kill is almost complete for both drugs. Similar results were observed for drug combinations.

Tumor heterogeneity and chemotherapy resistance, primary and acquired, will continue to be the biggest obstacle to cancer chemotherapy. The cell's ability to escape toxic influences to assure survival and procreation will continue to challenge cancer therapists, irrespective of which treatment modality will be applied. The future will add more and more powerful treatment modalities to the armamentarium in the arena of cancer therapy, but "Mother Nature" also has a powerful, and still poorly understood, arsenal of weapons to respond.

Clinicians have learned that primary treatment offers the best chance to cure cancer. Studying each patient's tumor tissue with the most sophisticated tools available, including genetic and molecular markers, will hopefully provide the clinician, and with that the patient, a competitive advantage. Currently, in vitro drug testing, and using that information in clinical practice, should be part of the clinician's armamentarium, because it offers a tool to increase the probability of selecting the most active drugs for treatment before the tumor can turn on its own drug-resistance mechanisms.

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4

Basic Principles of Dose Intensity and High-Dose Chemotherapy

M. Untch and N. Ditsch
University of Munich, Munich, Germany

P. Wimberger and R. Kimmig
University of Essen, Essen, Germany

V. Möbus
Stadtische Kliniken, Frankfurt, Germany

In the United States, more than 25,000 women are diagnosed each year with epithelial ovarian cancer (1). Seventy to eighty percent of patients have advanced disease at diagnosis which often is not completely resectable (2), with 20–30% five-year survival after conventional therapy. The most important factor for curative treatment is a radical adequate surgery. Standard surgery includes abdominal hysterectomy, bilateral salpingoophorectomy, omentectomy, appendectomy, intraabdominal debulking, if possible radical pelvine and paraaortic lymphonodectomy, and, if necessary, surgery of gut.

A R0-resection has the most favorable prognosis, compared to patients with a residual tumor of less than 1 cm, respectively 1–2 cm, or "bulky disease" (3,4).

Systemic therapy is the second very important factor for outcome.

The combination paclitaxel/cisplatin compared to cyclophosphamide/cisplatin prolonged the median progression-free survival from 13 to 18 months and the median overall survival from 24 to 38 months (5). Carboplatin is equieffective compared to cisplatin, but with less nephrotoxicity, gastrointestinal, neuro- and ototoxicity. Carboplatin can be individualized according to the area under the curve (AUC) with regard to glomerular filtration rate and carboplatin-clearance (6).

The standard treatment after initial surgery for these patients is platinum- and paclitaxel-based chemotherapy.

The results of the GOG-111 study (5) and its confirmation by a European–Canadian study group (EORTC-GCCG) defined a new standard for conventional first-line chemotherapy, namely, the use of paclitaxel/platinum.

Ovarian cancer might be subject to high-dose chemotherapy because of the following (7):

- It is one of the most chemotherapy-sensitive tumors with about 75% response rate.
- Dose–effectiveness relationship does exist (in vitro and probably also in vivo).
- Chemotherapy can lead to long-term survival (15% of patients with advanced cancer).
- The development of resistance occurs in about 30% very quickly.
- Lack of cure after second-line therapy.
- Dose intensification of active substances is possible.

A moderate dose intensification without stem cell transplant could not show an improvement. Most of the studies used a dose intensification of about 1.7 times. Dose intensifications about two times were only possible with support of stem cell transplant. A supportive therapy with stem cells makes a dose of carboplatin up to 30 mg/ml × min (absolute dose) possible (8).

High-dose chemotherapy is possible in two settings:

- Second-line chemotherapy
- Consolidation therapy in patients who responded to a conventional first-line therapy

RESULTS

The first data about high-dose chemotherapy were available from U.S. transplantation centers in 1992.

In 146 out of 153 patients, the response to high-dose chemotherapy with stem-cell transplantation was 85%, with 34% complete response (CR).

Thirty-seven patients were platinum-sensitive and had a response rate of 87% with a CR of 73%. These data showed a dose–effectiveness relationship above the conventional dose (9).

Further information is given in the statistics of "Autologous Bone Marrow Transplant Registry" (ABMTR) (10). In 1997, data of 422 patients were available. Most of these patients (87%) were treated with high-dose chemotherapy from 1989 to 1996 in 57 centers. The median age was 48 years. Eighty-eight percent of the patients had an ovarian cancer FIGO III or IV, 63% had at least two chemotherapy regimes, 38% were platinum-resistant, 50% had incomplete remission at the time of high-dose chemotherapy.

The complete remission rate was 42%. The transplantation-associated mortality was 7% and 14% after 2 years. The 2-year survival was 39% and the progression-free survival 12%.

In 79 patients treated with high-dose chemotherapy at first complete or partial remission, the corresponding 2-year DFS and OS is 60% and 20%, respectively.

The following negative relative risk factors for progression or death were found:

Age >47 years (RR 1.35)
Karnofsky-Index <90% (RR 1.7)
Histology of a clear cell tumor (RR 1.77)

Resistance to platinum (RR 1.77)

After 2 years, 7% of the patients with platinum resistant tumors were alive without progression.

High-Dose Consolidation

Legros et al. (11) studied retrospectively a series of 53 patients with poor-prognosis chemosensitive epithelial ovarian cancer for toxicity and long-term survival, treated with high-dose chemotherapy followed by hematopoetic rescue.

After surgery, patients were treated by cisplatin combination chemotherapy. After second-look operation, high-dose chemotherapy was administered in patients who were divided into two groups according to initial response, one with no macroscopic tumor and the other with tumor at second-look surgery. Group A received consolidation therapy, group B salvage therapy. High-dose chemotherapy with melphalan or carboplatin/cyclophosphamide was administered (Table 1).

Group A included 31 patients in complete clinical remission (19 patients were in complete pathological response at second-look operation, 7 patients had microscopical residual disease, and 5 patients had complete clinical response but refused second-look operation). For this group, HDC was given as a consolidation treatment to prevent progression because these patients had strong prognostic factors of recurrence.

Group B included 22 patients with macroscopic disease at second-look operation. Eighteen were optimally secondary debulked during second-look operation (residual tumor <2 cm in diameter) and four patients had residual disease after second-look operation. For this group, HDC was given as a salvage treatment. Between 1984 and 1989, 23 patients received melphalan (140 mg/m^2 d1). Since 1989,

Table 1 Description of the Two Groups of Patients According to Initial Chemotherapy Response

	Group A (n = 31)	Group B (n = 22)
SLO results[a]		
Pathologic complete response	19	
Microscopically residual disease	7	
No SLO but clinical CR[b]	5	
Redebulking complete or optimal		18
Macroscopic residual disease		4
Stage at diagnosis		
IIa	0	1
IIIc	20	16
IV	11	5
Initial surgery		
Complete	8	3
Optimal	12	8
Suboptimal	9	8
Biopsies only	2	3

[a] SLO: Second-look operation.
[b] CR: Clinical response.
Source: From Ref. 11.

30 patients received a combination of carboplatin (400 mg/m^2 d1 + 4) and cyclophosphamide (1.6 g/m^2 d1 + 4). Autologous stem-cell transplantation was performed.

The median follow-up was 81 months. The 5-year survival rate was 60% and 5-year disease-free survival was 24%. Twenty-four patients (45.3%) were alive, 12 with no evidence of disease, and 12 with recurrent disease.

A pathologically complete response was reached in 19 patients (74% five-year OS, 33% five-year DFS). The toxicity was acceptable, one patient died with cardiac failure after high-dose chemotherapy.

High-Dose Chemotherapy in Patients with Relapse

From 1989 to 1996, Stiff et al. (12) transplanted 100 ovarian cancer patients with autologous stem cells following chemotherapy with high-dose carboplatin, mitoxantrone, and cyclophosphamide with or without cyclosporine ($n = 70$). Twenty-five patients had melphalan and mitoxantrone with or without paclitaxel and five had other regimens. Median age was 48 years, 70% had papillary serous histology, 72% grade III tumors, 66% were platinum resistant and 61% had tumor >1 cm after surgery. The median number of prior regimens was two (range 1–6). Uni- and multivariate analysis were performed. Age, residual tumors, and sensitivity to platinum are the most important factors for the result of the high-dose chemotherapy.

In platinum refractory relapses the remission rate was 81%, the median remission time 5–6 months, and median survival 1 year. These results were worse than the expected results with conventional therapy.

Better results were seen in platinum-sensitive relapses. Median remission time and overall survival were 12 and 23 months, respectively.

The median PFS and OS were 7 and 13 months, respectively. In the Cox hazard model, tumor bulk ($p = 0.0001$) and cisplatin sensitivity ($p = 0.0249$) were the best predictors of PFS. Age ($p = 0.0017$), tumor rest ($p = 0.0175$), and platinum sensitivity ($p = 0.0330$) provided the best prediction of OS. The median PFS and OS in the 20 patients with platinum sensitive and <1 cm disease were 19 and 30 months, respectively. No differences in OS were seen when chemotherapy or surgery was used to achieve a minimal disease state. One has to be careful with the interpretation because these patients were selected. For patients with platinum refractory relapses, high-dose chemotherapies are contraindicated as a conclusion of this study.

Schilder and Shea (13) published their 1998 data where the use of colony-stimulating factors and peripheral blood progenitor cells significantly decreased the morbidity and mortality of such treatment compared with traditional autologous bone marrow transplantation. These innovations allow the use of multiple cycles of high-dose chemotherapy as consolidation after achieving the best response to conventional chemotherapy or as initial treatment.

High-Dose Chemotherapy as Primary Therapy

High-dose chemotherapy as primary therapy is interesting to overcome the fast development of resistance. The disadvantage is the treatment of platinum-resistant patients.

In primary therapy, three studies have been published. Aghajanian et al. (14) used a single cycle of mobilization, primed with cyclophosphamide (CPA)/paclitaxel

(TxL) and filgrastim (G-CSF), followed by three cycles of high-dose carboplatin (CBDCA)/TxL and one cycle of high-dose melphalan (MEL), each followed by stem-cell support.

Twenty-one patients were enrolled, 98 high-dose cycles were performed without treatment-related deaths, 34 complicated by hospitalization, 76% developed grade 3 to 4 GI toxicity, and 62% grade 2 to 3 neuropathy.

In 5/15 (33%) at second-look surgery, a pathologically complete response was seen. In the overall analysis, 56 patients were reviewed, 44 had a second-look operation, 15/44 (34%) had a pathologically verified complete remission.

The basis of this therapy was the Norton–Simon hypothesis (15). In patients with FIGO I–III and tumor (<1 cm) after surgery, the histologically complete remission was 55%. In patients with FIGO IV or FIGO III and residual tumor (>1 cm) there was no benefit.

Shinozuka et al. (16) presented long-term results in 105 patients. A platinum-based chemotherapy was given to optimize and/or mobilize peripheral blood stem cells. After surgery, high-dose chemotherapy with stem-cell support was given.

Regimen A: cyclophosphamide, doxorubicin, cisplatin (58 patients)
Regimen B: cyclophosphamide + carboplatin (47 patients)

OS and DFS were better in regimen A in stages III and IV with residual tumor <0.5 cm.

Experiences of the German Phase I/II Study in First-Line

We performed a multicenter phase I/II study initiated in 1996 and closed in 1998 in Germany.

The effectiveness of a high-dose chemotherapy was tested in 49 patients. After stem-cell mobilization, three cycles of high dose chemotherapy followed. Carboplatin was increased to AUC 18–22. In the first two cycles of high-dose chemotherapy it was combined with paclitaxel 250 mg/m^2 and in the last cycle with melphalan and etoposide. The dose of carboplatin was escalated from AUC 18 to AUC 22. An intermediate analysis of the first 36 patients was published by Frickhofen et al. in 1999. The toxicity was evaluated. The hematological toxicity was equal to other known high-dose protocols. The nonhematological toxicities were esophagitis, diarrhoea, dysfunction of motility, ileus, and abdominal pain. The experience from this phase I/II study showed the practicability of three sequential high-dose chemotherapy cycles immediately after primary surgery as "front-line" therapy of advanced ovarian cancer. After the omission of etoposide in the last high-dose cycle, we found a reduction of stomatitis. Neurotoxicity and ototoxicity were minimal.

Patients with progression who received conventional second-line chemotherapy after high-dose chemotherapy tolerate the second-line therapy similar to patients with a previous conventional first-line chemotherapy. Response rates were dependent on the length of therapy-free interval (> or <1 year). The results of the phase I/II study showed that sequential high-dose chemotherapy was practicable, safe, and effective in patients with ovarian cancer after radical surgery. The CCR and NED were seen in ≥80%. In case of recurrence, second-line chemotherapy was efficient. The clinical outcome has to be investigated in a phase III study.

PHASE III HD-OVAR-2

In 1998 the randomization for the phase III HD-OVAR-2 was started.

Design of Study

The multicenter sequential, prospective randomized, high-dose study for advanced ovarian cancer with autologous blood stem-cell transplantation (HD-OVAR-2) of the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) and Arbeitsgemeinschaft Internistische Onkologie (AIO) is a phase III study with first-line chemotherapy in ovarian cancer. Carboplatin was given at AUC 20 without etoposide in the third cycle of high-dose chemotherapy. The standard arm is according to the AGO "OVAR-7":

A: carboplatin AUC5 + paclitaxel 175 mg/m^2 (6xq3w)→4x topotecan 1.25 mg/m^2 (4xq3w)
B: carboplatin AUC5 + paclitaxel 175 mg/m^2 (6xq3w, standard)

Inclusion criteria are:

- Epithelial ovarian (with the exception of clear cell carcinoma) or fallopian tube cancer.
- Stage FIGO IIB to FIGO IV.
- Age ≤60 years.
- Standard operation with at least hysterectomy and bilateral salpingoophorectomy and omentectomy.
- Karnofsky score of ≥70% or performance status 0-1 (ECOG).
- No previous chemotherapy, radiation, or experimental drugs.
- Adequate hematological, renal, and hepatic function.
- Chemotherapy starts within 4 weeks after surgery.
- Written consent.

The HD-OVAR-2 study compares a sequential high-dose chemotherapy with autologous blood stem-cell transplantation with a conventional standard dose of chemotherapy. The high-dose chemotherapy starts with two induction cycles with cyclophosphamide 3 g/m^2 and paclitaxel 250 mg/m^2 in a 2-week interval, with

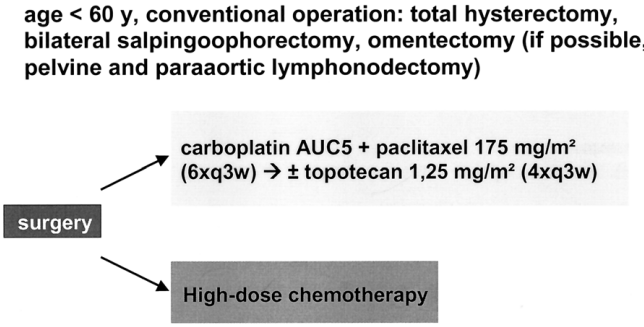

Figure 1 AGO/AIO Phase III Study: primary high-dose chemotherapy vs. conventional therapy (FIGO IIb–IV).

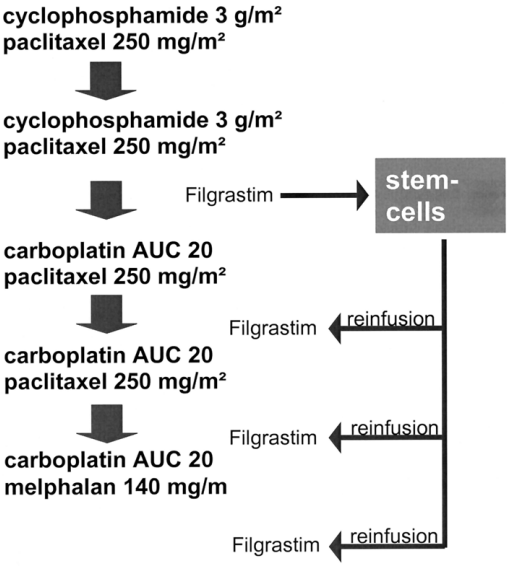

Figure 2 AGO high-dose trial.

filgrastim support. About 8 to 10 days after the second induction cycle, blood stem-cell collection is performed. Two weeks after the second induction cycle the first of three 3-week high-dose cycles with carboplatin AUC20 and paclitaxel 250 mg/m^2 is given followed by the second high-dose cycle. The last high-dose cycle with carboplatin AUC20 is combined with melphalan 140 mg/m^2. Between the chemotherapy cycles filgrastim is given. After each high-dose cycle autologous stem cells are reinfused (Figures 1 and 2).

RATIONALE OF THE STUDY

The response rate of 60–80%, with a platinum-based chemotherapy, is provided by the high primary chemosensitivity in ovarian cancer. With autologous stem-cell transplantation a dose escalation of 4 to 5 times for carboplatin and 10 times for alkylating substances is practicable. The dose escalation for carboplatin is 1500 to 1800 mg/m^2 or AUC 20 to 24 mg/ml $\times$ min.

The primary aim of the study is the investigation of progression-free survival 2 years after sequential high-dose chemotherapy or conventional chemotherapy.

The secondary aim of the study is the progression-free survival after 5 years, the overall survival after 2 and 5 years, evaluation of toxicity of both regimens, evaluation of life quality under and after therapy.

SUMMARY

The role of dose intensity in the chemotherapy of advanced epithelial ovarian cancer is controversial. No significant benefit has been achieved by escalating doses in the

range applicable without cellular support. The high-dose chemotherapy seems to be suitable only in patients with platinum sensitive tumors or in primary therapy. Recent phase I/II trials show a benefit in patients with residual tumor <1 cm rather than in bulky disease.

Although in some studies higher remission rates were achieved in the higher-dose arm, this did not translate into meaningful prolongation of median overall survival, while toxicity was clearly dose-related. At present, no definitive conclusions can be drawn in patients with ovarian cancer except that high-dose chemotherapy should be administered only in the context of a trial allowing the clear assessment of benefits and risks.

The high-dose chemotherapy (prospective phase III trial of the AGO) in patients with ovarian cancer will give a first evidence-based result.

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Immunotherapy in Gynecologic Malignancies

Pedro T. Ramirez and Ralph S. Freedman
The University of Texas M.D. Anderson Cancer Center, Houston, Texas, U.S.A.

INTRODUCTION

The management of gynecologic malignancies has been expanded in recent years to encompass not only a spectrum of surgical and cytotoxic therapies, but also treatments that target in a more specific manner the genetic, phenotypic, and microenvironmental differences between cancer and the "normal" tissue compartment. Immunotherapy has already shown credible evidence of clinical responses in human malignancies, including malignant melanoma, renal cancer, lymphoma, and epithelial ovarian cancer (EOC). Widespread application of recombinant DNA technology, which includes production of cytokines, other activating molecules, and reengineered human antibodies, is providing a broad and comprehensive array of immunotherapeutic tools. In addition, there is a rapidly expanding knowledge base on tumor immunology and the role of the microenvironment in cancer, which is providing the resources for hypothesis-driven clinical trials.

Immunology Overview

An important function of the immune system is to recognize any antigen that is not derived from self. In addition, the immune system should recognize antigens that are derived from self that are poorly expressed, antigenically altered, or not ordinarily encountered by the immune system (1). The immune system has two major components, the innate and the adaptive. The innate immune system is programmed to recognize the patterns of certain microbial substances encoded in the germ line. It is considered more primitive phylogenetically and develops rapidly (2). Cells involved in innate immunity include certain macrophages, natural killer cells (NK), and T cells, primarily T-cell receptor gamma delta (TCR $\gamma\delta$), which recognize a variety of viral or microbial components. There is recent evidence that certain cells of the innate system also recognize and are activated by "stress proteins" that are variably expressed on the surface of tumor cells (3). Some of these proteins have been identified on ovarian cancer tissues. The adaptive immune system involves complex interactions between antigen-presenting cells (APCs), which include dendritic cells (DCs) and

macrophages, and cells of the T- and B-cell lineages. Tissue specific or mutated antigens may be overexpressed in tumor cells and could provide the stimulus for a T-cell response.

Antigens of exogenous or endogenous origin are taken up by antigen-presenting cells and processed to produce peptides that are presented at the cell surface in an associated state with the major histocompatibility complex (MHC) (4). The MHC–peptide complexes may activate one of two helper cell pathways: TH1-type $CD3^+CD4^+TCRab^+$ cells that facilitate pro-inflammatory or T-cell-mediated immunity, or TH2-type $CD3^+CD4^+TCRab^+$ cells that facilitate anti-inflammatory or humoral (antibody) responses. The TH system is better understood in murine models than in humans. Immunogenic antigens of endogenous origin are enzymatically split by the proteosomes into peptides that are approximately eight amino acids in length and coassemble by attachment at specific sites (motifs) with the polypeptide chains comprising the MHC. T cells recognize the peptide in the context of the APC's MHC and become activated, a process that involves helper cytokine production by TH1 T cells and conversion of the precytotoxic T cells to cytotoxic T cells, and the cross-primed $CD3^+CD8^+TCRab^+$ will lyse or inhibit the growth (by cytokine action, e.g., IFNγ or TNF) of any tumor cell that also has the naturally expressed antigen. Exogenous antigens are processed by lysozomes and presentation of the epitopes involves the MHC class II complex.

The cells of the immune system communicate with each other through proteins known as cytokines, or chemokines, which are usually smaller and have a major role in trafficking of immune cells apart from other important functions. TH1-type helper cells secrete interferon gamma (IFNγ), tumor necrosis factor (TNF), interleukin-2 (IL-2), and granulocyte–macrophage colony-stimulating factor (GM-CSF), which are all important in different phases of development of the activated $CD8^+$ T cells. In vivo, these cells take part in delayed-type hypersensitivity reactions that also include other populations such as neutrophils, NK cells, $CD8^+$ T cells, DC, and macrophages. $CD8^+$ T cells that are specifically activated so that they can recognize a tumor-associated epitope may have the capacity to kill or inhibit the growth of tumor cells in vivo that express the same epitope. TH2-type helper cells secrete IL-4, IL-5, IL-6, and IL-10. Some of these cytokines, such as IL-10 and IL-6, may be suppressive to cell-mediated immunity functions and have therefore been designated as anti-inflammatory. IL-4, IL-5 and IL-6 are important in the differentiation and activation of antibody-producing B cells (5,6).

Presentation of antigen as peptide requires, in addition to appropriate processing of the antigen, the maturation of the DC with coexpression of costimulatory antigens (7), including CD80, CD83, and CD83 surface glycoproteins, and production of IL-12. IL-12 stimulates and activates NK cells and $CD4^+$ T cells, which produce IFNγ (Fig. 1). IFNγ is also produced by $CD8^+$ cytotoxic T cells and is therefore a pivotal cytokine for both adaptive and innate immunity against tumors. The number of $CD4^+$ T helper cells present is also important for tumor rejection (8). Human DCs do not have a specific marker and are generally identified as a small population of cells in the blood that do not carry markers for the common lineages of T cells, B cells, and NK cells, and are DR antigen positive, hence Lin^-DR^+. These cells are composed of two main populations, $CD11c^+$ and $CD123^-$, and $CD11c^-$ and $CD123^+$. To summarize, tumor-specific rejection is primarily dependent on an early inflammatory response whereby antigens from the tumor are processed by antigen-presenting cells,

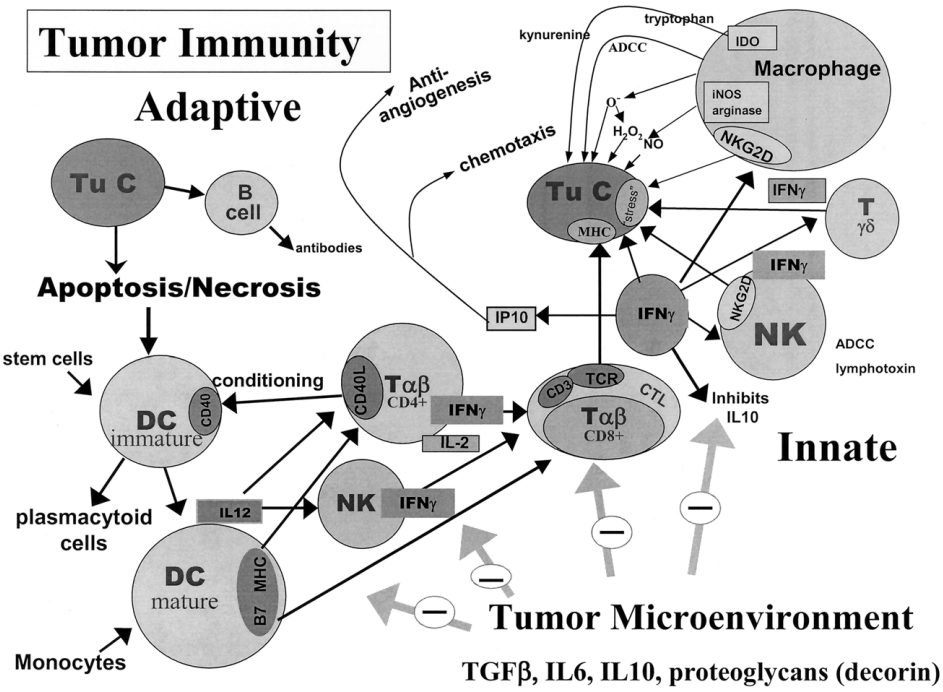

Figure 1 Active cellular immunity and antitumor activity.

inducing T helper cells and finally leading to proliferation and cytokine production. Through appropriate activation of cytokines, cytotoxic T cells are activated and destroy the tumor cell by direct target killing, cytokine secretion, and macrophage recruitment (8,9).

Immune dysfunction in tumor bearing animals can be identified by depletion of specific lymphocyte populations or with assays that demonstrate failure of the cells to recognize the tumor. Failure of T cells to recognize the tumor may be due to immunologic tolerance which is easier to demonstrate in animal models (10), down-regulation of the MHC or tumor-associated antigens (TAA) or their genetic deletion (11), interference with peptide transport mechanisms (12), and secreted inhibitory factors, including prostaglandins, insulin-like growth factors, shedding of intercellular adhesion molecules and gangliosides, and inhibitory cytokines such as IL-10, IL-6, TGFβ isotypes (13–17). IL-10 may downregulate the MHC and costimulatory antigens, and both IL-10 and TGFβ can interfere with T-cell activation at different levels. IL-10 may also specifically block IFNγ production (18). The immunosuppressive effects of tumor-associated or -produced cytokines may possibly be overcome by reducing the tumor burden through surgical debulking or with conventional or standard dose chemotherapy (8).

Active immunotherapy includes active specific immunotherapy in which a cellular immune response is induced by immunizing a patient either with tumor antigens or with peptides. Tumor antigens used for vaccination include purified antigens (single or multiple), intact, usually autologous, irradiated tumor cells (which

may require gene transfer of costimulatory antigens), and lysates (which require some type of adjuvant). Peptide motifs need to be matched to the HLA type of the individual. There is also a requirement for an adjuvant and for maturation of the DC for peptide loading. The peptide should be capable of eliciting cytotoxicity by the effector cells (usually $CD8^+$ T cells) at reasonable effector-to-target ratios against the naturally expressed tumor antigen peptide epitope. Autologous tumor cells may have the advantage of including a broader array of antigens although some could certainly be tolerogenic. We have largely moved away from using allogeneic tumor cell lines primarily for reasons of safety. "Cross presentation" would allow the antigens from these cells to be processed and represented by APCs, but there is also the concern based on results of microarray studies that many established tumor cell lines may have antigens that do not closely resemble the antigen profile of the parent tumor. An immune response can be induced against virally or chemically modified tumor cells, thereby also inducing cross-reactivity against nonmodified tumor cells (19,20). In another interesting approach, murine monoclonal antibodies have been used as vaccines. The immune response is generated not only against the conserved part of the antibody but also against the hypervariable or complimentary determinant region. Immunization may result in an anti-idiotypic response that matches to the antigen that binds to the monoclonal antibody. The antibodies generated in the patient may contribute to antibody-dependent or complement-dependent cytotoxicity of the tumor. Recently, however, inhibitors of complement activity have been identified on tumor cells. T-cell responses may also be detected post immunization (19). Passive specific immunotherapy involves the use of monoclonal antibodies that target cell surface membrane molecules to deliver radionuclides, natural toxins, cytotoxic drugs, or prodrugs to the tumor (19,21). Adoptive specific immunotherapy uses tumor-infiltrating lymphocytes that have been expanded ex vivo into lines or T-cell clones that have demonstrated specific antigen-dependent activity; either killing of cells in an MHC restricted fashion, or specific production of cytokines such as IFNγ and GM-CSF. This approach was developed by Dr. Steve Rosenberg at the NCI for treatment of malignant melanoma and is currently being used with systemic rIL-2 and peptide-specific vaccines. Lymphokine activated killer (LAK) cells, which are $CD3^-$ cells, are rarely used nowadays, as their antitumor effects are considered substantially inferior to TIL-derived T-cell lines or clones (22).

In the remaining segments of this chapter, we will focus on how our knowledge of tumor immunity is being applied to the prophylaxis and treatment of epithelial ovarian and uterine cervical carcinomas.

IMMUNOTHERAPY IN OVARIAN CANCER

Over the past several years, the survival rates in ovarian cancer have improved modestly owing to improvements in diagnostic techniques, aggressive surgical approaches, and development of effective cytotoxic chemotherapies. Unfortunately, ovarian cancer remains the second most common gynecologic malignancy in the United States, with an estimated 25,000 patients diagnosed each year and nearly 16,000 patients dying of this disease within the same time period (23). At this time, the most effective drugs for first-line treatment of ovarian epithelial cancer are platinum-based compounds, cisplatin, or carboplatin (24). Several randomized trials have

confirmed the efficacy of adding taxanes to platinum compounds, and this has become the standard therapy for ovarian cancer (25).

Although nearly 70% of ovarian cancers will respond to the combination of platinum and taxanes, the majority of patients will suffer recurrence of their disease within 2 years of completion of initial therapy. In the setting of recurrent disease, no treatment is clearly effective in curing the disease or even prolonging life. Patients with recurrent disease will gain the most benefit from innovative therapeutic modalities.

Immunotherapeutic approaches may be considered as having either prophylactic (preventive) or therapeutic (treatment of an established cancer) intent. Prophylactic approaches for ovarian cancer will have to await a better understanding of the cognate antigens in this disease. Progress in the identification of genetically predisposed individuals will hopefully encourage more research in this area. Therapeutic approaches may be divided broadly into active and passive therapies. Active therapies include vaccines, cytokines, growth factors, adoptive therapies [tumor infiltrating lymphocytes (TIL), DC, and activated monocytes], and various molecules that can activate T cells (e.g., anti-CTLA4 mAb, CD40L, anti-CD28mAb) (Table 1). Passive approaches employ mAbs as immunoconjugates. Many of these approaches have been dealt with in extensive reviews, including also a discussion of the role of the microenvironment (26).

Monoclonal Antibodies

Kohler and Milstein were the first to describe the concept of immortalizing B cells for the production of antibodies with monoclonal specificity in 1975 (27), and for which they received the Nobel Prize. They created genetically identical antibodies by fusing nonimmortal splenic B cells from immunized mice with myeloma cells to produce an immortalized antibody-secreting hybrid cell line. Monoclonal antibodies that recognize molecules of both physiological and pathological importance have been generated by this method, and are being extensively used in molecular biology, as diagnostic agents and now as therapeutic agents. The goal of in vivo approaches that employ monoclonal antibodies is to target a tumor with the highest possible specificity and targeting properties.

In ovarian cancer, one of the promising areas of research is the use of monoclonal antibodies to target the growth-regulatory factor HER2/neu. Significant efforts have been devoted to understanding the function and impact of HER2/neu because it

Table 1 Immunotherapeutics in Cancer

Cytokines	Leukocyte IFN, IFN-α, IFN-β, IFN-γ, IL-2, IL-1-α, IL-12, TNF-α, CD40-L(ST), GM-CSF, FLT3-L
Cell therapies[a]	LAK, TIL, TIL (specific targeted), DC (peptide/RNA pulsed)
Antibodies	Target surface Ags: Immunoconjugates (radio, chemo, toxins) T-cell activation: α-CDTLA4, α-CD28, α-TGF-β, α-IL-10, α-IL-10Rc
Vaccines[a]	Autologous tumor (costimulation), peptides, CHO-Ags, e.g., O-linked mucin glycans-sTn, sTn(c)

[a] May require combination with cytokines or growth factors.

is an excellent therapeutic target for the immune system. HER2/neu is a growth factor receptor transmembrane protein with an extracellular domain that functions in ligand binding and an intracellular cytoplasmic domain involved in cell signaling. The ligand is unknown. Amplification of the gene and overexpression of the HER2/neu protein have been identified in several malignancies, including 20–30% of ovarian cancers (28), although recent data from the Gyncecologic Oncology Group (GOG) suggest that overexpression occurs in less than 20% of patients. Patients whose tumors overexpress HER2/neu typically have a poorer prognosis than those whose tumors do not (29). The GOG is currently conducting a phase II trial of recombinant anti-HER2/neu (Herceptin) in patients with recurrent ovarian cancer and overexpression of antigen detected by immunohistochemical studies. At the University of Texas M.D. Anderson Cancer Center (UT MDACC), we are conducting a trial evaluating the effects of herceptin in combination with first-line chemotherapy in patients who have undergone suboptimal tumor reductive surgery. Herceptin (Genentech, Inc., So. San Francisco, CA) may also mediate ADCC. In Figs. 2 and 3, we show that GM-CSF-primed monocytes show enhanced cytotoxicity of a surrogate tumor cell target MCF7-HER^+ cell line but not the HER^- parent line after treatment of the cultured tumor cells with herceptin. It is hoped that development of new monoclonal antibodies (especially human) will carry a broader range of reactivity than HER2/neu. Monoclonal antibodies have also been used to target other receptors in ovarian cancer tissue such as the membrane folate receptor, which is over expressed in 70–90% of epithelial ovarian tumors. Molthoff et al. used Mov18 immunoglobulin G (IgG), which is a monoclonal antibody against the folate receptor, in a phase I trial and found that it was well tolerated and that it had reduced immunogenicity (30). In another interesting approach, Hwu et al. have developed a recombinant bifunctional antibody that recognizes the folate receptor and is fused to T-cell signaling chains (31). The construct is being tested in patients with ovarian cancer in an ongoing trial. Other similar approaches have been reported (32,33). Wagner reported the use of anti-idiotypic antibodies imitating CA-125 (34). He found that patients who received this immunotherapy historically have a significantly higher survival rate than controls who did not receive the immunotherapy. In that study, 58 patients with advanced ovarian carcinomas received 131-I-labeled-F $(Ab)_2$-fragments of the OC125 mAb against the tumor-associated antigen CA125. The investigators showed that despite the same surgical and chemotherapeutic regimes, the survival of patients receiving the mAb OC125 was significantly longer. This finding has added to the motivation for large ongoing randomized trials to determine if the antibody could be useful as a vaccine. In a different study to evaluate the utility of a murine monoclonal antibody with high affinity to CA-125, Ehlen et al. studied 345 patients with stage III–IV epithelial ovarian cancer who were randomized to MAb-B43.13 (OV) or placebo in a double blind study to determine immune response and clinical outcomes. They found a statistically significant difference in the OV-treated patients in the generation of Ab2 or HAMA responses. This was associated with a greater than twofold prolongation of median time to relapse compared with patients without the immune response (35).

Several problems associated with the use of monoclonal antibodies need to be addressed. These include nonspecific binding resulting in damage to normal tissues, decreased uptake by the tumor because of more rapid clearance, limited utility with large tumors because of inability to penetrate the mass (32), and generation of human antimurine antibodies which may limit the future use of even humanized monoclonal

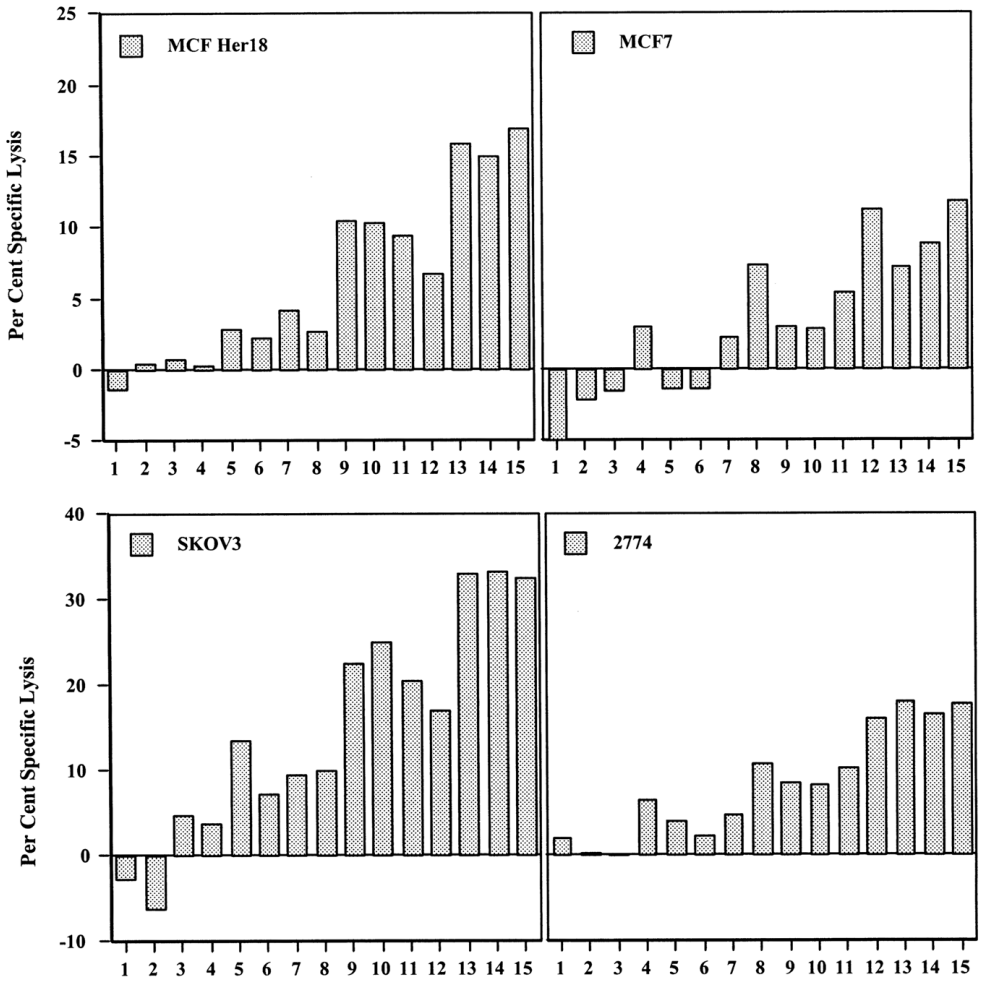

Figure 2 1. Target cells (TC) + Herceptin 1 mg/ml. 2. TC + Herceptin 5 mg/ml 3. TC and Herceptin 10 mg/ml. 4. TC + monocytes (MO 10:1) 5. TC + Herceptin 1mg/ml + MO(10 :1). 6. TC + Herceptin 5 mg/ml + MO(10:1). 7. TC + Herceptin 10 mg/ml + MO(10:1). 8. TC + MO (20:1). 9. TC + Herceptin 1 mg/ml + MO(20:1). 10. TC + Herceptin 5 mg/ml + MO(20:1). 11. TC + Herceptin 10 mg/ml + MO(20:1). 12. TC + MO (40:1). 13. TC + Herceptin 1 mg/ml + MO(40:1). 14. TC + Herceptin 5 mg/ml + MO(40:1). 15. TC + Herceptin 10 mg/ml + MO(40:1).

antibodies. To circumvent these problems, murine antibodies are being replaced with humanized and human antibodies. At the UT MDACC, we are conducting a clinical trial to estimate the antitumor activity of the combination of paclitaxel, carboplatin, and herceptin in patients with untreated advanced ovarian cancer, peritoneal cancer, or fallopian tube cancer. The study is currently ongoing and no results are yet available (36,37).

Another approach has been to develop systems in which the monoclonal antibodies are not sensitive to antigen heterogeneity in tumor cells. Radioimmuno-

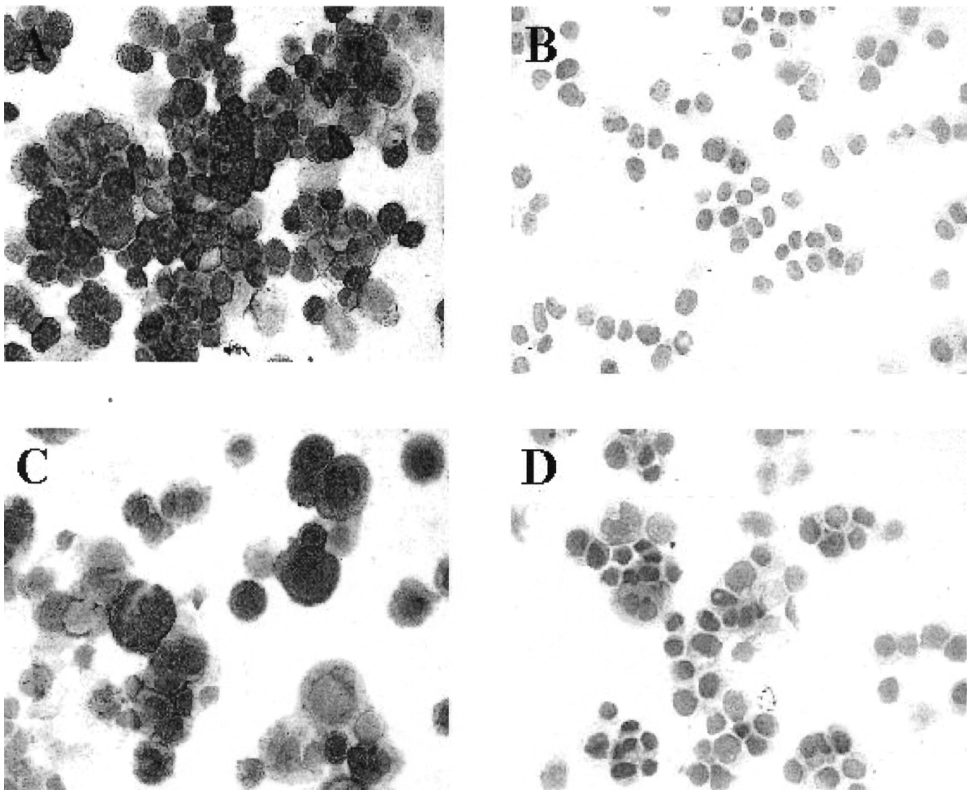

Figure 3 Staining of $SKOV_3$ (A) and MCF7/HER transfected (C) with α HER2/neu (c-erbB2) primary monoclonal antibody (Neomarker) at 1:100 dilution. Stain developed with DAB chromogen. Weak staining of 2774 (B) and MCF7 (HERneg) (D).

therapy (RIT) is a modality that can deliver radiation to tumor cells at levels 5–30 times higher than to the normal tissue (38). When labeled with a suitable radionuclide, monoclonal antibodies can deliver a lethal dose of radiation to cancer cells over a distance ranging from a fraction of a millimeter to several millimeters (39). Several factors affect the total amount and rate of energy deposition in tumors. These include the stability of the immunoconjugate, physical behavior of the emitted particles, the immunoreactivity of the selected monoclonal antibody that should also be cell surface binding, and finally the characteristics of each individual tumor and the kinetics and biodistribution of the administered radiolabelled immunoreagent (39,40). Two human tumor-cell surface reacting monoclonal antibodies have been developed in laboratories, one of which recognizes cell surface antigens on EOC, and the other on uterine cervix cancer (36,37). Yttrium-90 labeled AC6C3 and CR4E8 antibodies have shown activity in preclinical animal studies (41,42) and efforts are ongoing to introduce them into clinical trials.

Nicholson et al. performed an analytic comparison of RIT after chemotherapy and chemotherapy alone in patients with ovarian cancer (43). The group used ^{90}Y-labeled murine IgG_1 monoclonal antibody HMFG1, which reacts with an epithelial

mucin. The mucin is a product of the *MUC-1* gene, which is expressed at elevated levels in an abnormally glycosylated form on the cell surfaces of over 90% of ovarian cancers. In total, 25 patients with epithelial ovarian cancer received RIT intraperitoneally after completion of conventional chemotherapy. The authors found that the survival rate at 5 years after treatment was 80% for the RIT group and 55% for the matched control group. This difference was statistically significant. Alvarez et al. published promising results on a phase I trial in patients with small volume disease (44). They used escalating doses of intraperitoneal lutetium-177-CC49 in 27 patients with recurrent ovarian cancer. The dose-limiting toxicity in this trial was transient bone marrow suppression. Responses were observed in 1 of 13 patients with gross disease, while several patients with microscopic or small-volume disease had an extended disease-free interval (45).

Another area of research interest in the use of monoclonal antibodies has focused on the conjugation of cytotoxic chemotherapeutic agents. After the antibody binds to the cell surface antigens, the immunotoxins are internalized by endocytosis and subsequently subjected to lysosomal catabolism. It should be noted that immunotoxins would destroy only those cancer cells with the relevant target antigen. This may have a disadvantage in not targeting any antigen-negative bystander cells (46). In preclinical investigations, Hasan et al. found that photodynamic therapy utilizing a photoimmunoconjugate in combination with cisplatin resulted in increased cytotoxicity in three ovarian cancer cell lines and 12 primary ovarian cancer cell lines obtained from patient tumor or ascites samples (47). In the past, this form of therapy was hampered by significant toxicity to healthy tissue, and consideration has to be given to the fact that the tumor cells may already be resistant to the chemotherapeutic agent used. It may also be difficult to link cytotoxic agents to the monoclonal antibody in sufficient number and reversible form, and with the ability to achieve therapeutic drug concentrations in the tumor cell (32).

Research with immunotherapy using monoclonal antibodies is developing more rapidly now that a variety of reengineered antibodies is being created. This remains an exciting area of investigation and may ultimately benefit ovarian cancer patients.

Cytokines

Cytokines or chemokines (smaller molecules) are glycoproteins that are produced by virtually all types of cells and that are able to stimulate or inhibit cell growth, regulate cell differentiation, induce cell chemotaxis, and modulate expression of other cytokines (48). They are physiologically designed to work at close range. Certain cytokines have an important role in the progression of ovarian cancer, serving to promote unregulated growth of tumor cells and metastasis, possibly by increasing cell adhesiveness and/or enhancing tumor angiogenesis. Other cytokines may be produced as an epiphenomenon and have little or no effect on disease progression. It is also possible that certain cytokines produced in the tumor microenvironment, such as IL-10, IL-6, and the TGFβ isotypes, may interfere with recognition and activation of antitumor immunity (48).

In the tumor microenvironment of patients with EOC, the following cytokines are expressed either at the transcript level or as detectable intracellular or secreted proteins: IL-1, IL-2, IL-6, IL-8, IL-10, TNF-α, transforming growth factor (TGF)-β, and various myeloid colony-stimulating factors.

Certain cytokines, which can be detected in the EOC environment, have nevertheless shown utility in the treatment of patients. Granulocyte colony-stimulating factor (G-CSF) and to a lesser extent GM-CSF are currently used for treating and preventing the neutropenia induced by chemotherapy (49–51). In addition, recombinant human IL-3, IL-6, IL-11, and thrombopoietin (TPO) have been shown to be effective in the treatment of thrombocytopenia in patients with ovarian cancer (52–55).

Hwu and Freedman have reviewed the results of published studies of cytokines and other forms of immunotherapy that have shown antitumor activity against ovarian cancer (26). The majority of the reported studies on cytokines in EOC have utilized the intraperitoneal (IP) route, emphasizing potential pharmacological and pharmacodynamical advantages. In preclinical experiments, administration of intraperitoneal cisplatin plus rIL-2 was effective in reducing ovarian tumors producing a 60% response rate in mice with cisplatin-resistant tumors (56). A clinical trial of two schedules of intraperitoneal rIL-2 showed that a 24-hr infusion had more acceptable toxicity than the 7-day infusion, and 9 of 35 patients had a surgical response, including 5 who were platinum sensitive (57). In 1998, Edwards et al. reported results of a GOG phase II trial of ip IL-2. Twenty patients with persistent ovarian cancer limited to less than 2 cm in size were treated for 16 weeks with 18% response in eligible patients (58). Three patients had grade 3 abdominal pain and three patients developed catheter-related infections.

Berek, following earlier dose finding studies (59), reported the results of a phase II trial of ip alpha-2b-recombinant interferon (rIFNα2b) in EOC patients with minimal residual disease, defined as < 0.5 cm. Patients were subdivided into two groups: favorable (platinum-sensitive and/or relapsed 6 months or longer after completing treatment) or unfavorable (platinum-resistant and/or relapsed less than 6 months after completing treatment). Patients were treated for 12 cycles. In 80 evaluable patients who received 50×10^6 U weekly ip, the response rate was 32% in the favorable group of patients and 0% in the unfavorable group (60). Results from this and another study in which ip IFNα2b (25×106 U) was combined with cisplatinum, 60 mg/M^2 (61) indicated that only platinum-sensitive individuals appeared to benefit from either ip rIFNα2b alone or with platinum. Grade 3 neurotoxicity occurred in 14% of the combination patients indicating that the systemic effects of ip delivery need to be considered. Not all cytokine studies have employed the ip route. Five responses including two CRs were reported following subcutaneous administration of lymphoblastoid interferon which contains a number of interferon-α species (62), and a phase II trial of IV recombinant interferon gamma (rIFNγ) had 4 of 14 (29%) responses in patients with recurrent EOC (63). In our study of sc leukocyte interferon, we observed 1 of 14 responses (64). Another very interesting trial was conducted by Pujade-Lauraine et al. using ip rIFNγ (65). They treated 98 evaluable patients with residual disease following chemotherapy with 20×10^6 U/M^2 twice weekly and observed 23% CRs. Interesting features of this trial were that nine of the CRs had more than 0.5 cm residual, that the treatment was well tolerated with relatively few significant events, and few significant adhesions post ip treatment. rIFNγ has shown substantial antitumor activity in preclinical experiments either alone (66) or in combination with cisplatin (67) and a recently reported randomized trial that compared cisplatinum + cyclophosphamide + rIFNγ with cisplatinum + cyclophosphamide alone showed progression free survivals of 48 and 17 m, respectively (68). The trial has spurred a new randomized trial that utilizes the currently employed chemotherapy agents, carboplatin and paclitaxel. Given the strategic importance of IFNγ in immune

mechanisms, its diverse tumor inhibitory properties and both preclinical and clinical evidence of antitumor effects, further research into its clinical usage with other agents and mechanistic studies may be warranted. At the UT MDACC, we have conducted a phase I trial with intraperitoneal r-IL-12 (which is an inducer of IFNγ) in 28 patients with intra-abdominal disease from Müllerian and other carcinomas (69). A safe biologically active weekly dose of 300 ng/kg was determined and a four-institution phase II clinical trial is in progress. rIL-12 is also considered to have antiangiogenic properties, possibly related to IFNγ production. Although rIFNα, rIFNγ, and rIL-12 (as an IFNγ inducer) have some overlapping biological effects there are differences that could influence the clinical outcome in terms of both tumor response and toxicity. Such differences might involve signaling pathways (70) or subtle differences in the molecule structure between the recombinant and natural glycoproteins. These issues should be considered in designing future trials with these agents.

Adoptive Specific Immunotherapy

Adoptive therapy (not to be confused with adaptive) was previously applied by Spiess and others to the therapeutic administration of TIL-derived T cells, which had been expanded with rIL-2 in culture and that exhibited HLA restricted cytotoxicity (22). The implication was that the transfer involved immune cells with activity that was specific to the tumor. Moreover, TIL-derived T-cell lines that demonstrated specificity were at least 50× more effective than LAK cells , which are primarily $CD3^-$. Clinical trials of adoptive immunotherapy and high-dose rIL-2 in melanoma patients demonstrated that 10^{10} cells were considered optimum and that clinical responses were associated with autologous tumor killing, the production of GM-CSF and IFNγ by the T cells, in vitro, which comprised large numbers of $CD8^+$ T cells. Rosenberg and colleagues are currently incorporating TIL into vaccine trials (71,72). The importance of these seminal trials is that they helped to set the standards for adoptive immunotherapy and to identify a number of peptides as immunogens and as target epitopes for vaccine therapies. Based on our earlier preclinical studies demonstrating the presence of specifically activated T cells in ovarian cancer (73–76), we performed a small feasibility trial in patients with ovarian cancer (77). We expanded ovarian TIL to 10^{10} cells; however, the expanded cells comprised large numbers of $CD4^+$ T cells, some of which demonstrated autologous tumor cell cytotoxicity and IFNγ and GM-CSF production. Patients received 4 days of IP TIL on d1 + rIL-2 at 0.6×10^6 IU for 4 days. There were no objective responses. Most of the patients had received extensive chemotherapy and were platinum resistant, and most had substantial tumor burdens. The amount of tumor required to initiate the cultures ranged from 0.2 to 8 g. Furthermore, even with use of a bioreactor the mean time taken to produce large numbers of cells was 47 days. We attempted unsuccessfully to improve on the production of specific $CD8^+$ TIL by using cell selection devices (78) and, subsequently, by priming patients with a sequence of rIFNγ and rIL-2 (79). We concluded that HLA class I and II antigen expressions can be enhanced by treatment of patients with rIFNγ, but the addition of IL-2 was unable to provide costimulation for the production of specifically activated T-cell lines. Moreover, treatment with rIL-2 appeared to be associated with increased IL-10 production in vivo (79,80). We next embarked on a study to use rIFNγ in conjunction with autologous irradiated tumor cells that had been modified to express the B7.1 costimulatory factor. Vaccines that include highly purified tumor cells have been prepared from eight patients.

Several other studies examined the effects of LAK cell (nonspecific) therapy. Stewart et al. reported the results of a phase I trial of intraperitoneal recombinant IL-2/LAK cells (81). The dose-limiting toxicity was abdominal pain. They noted that intraperitoneal infusion of recombinant IL-2 induced durable regional LAK activity. In another study, Steis et al. administered LAK cells and IL-2 therapy intraperitoneally to patients with malignancies limited to the peritoneal space (82). They observed a partial response rate of 20% in patients with ovarian cancer. However, they also noted significant short-term toxicity.

A new approach to adoptive therapy involves the use of DC that have been expanded in vivo with GM-CSF and cross-primed with tumor antigens. The matured DC have been used in immunization strategies (83,84). The DC can be loaded in the immature state with lysates, apoptotic cells, membrane fractions, or tumor cell RNA (85). In the mature state, they can be loaded with peptides. Mach et al. showed that both GM-CSF and Flt3-ligand (Flt3-L) induce the infiltration and maturation of dendritic cells. In their study, these investigators showed that injection of tumor cells expressing either GM-CSF or Flt3-L resulted in a dramatic increase of $CD11c^+$ cells in the spleen and tumor infiltrate. They showed that there are critical differences in the abilities of GM-CSF and Flt3-L to enhance the function of dendritic cells in vivo and that these findings could have important implications in the development of tumor vaccines (86). Treatment of lymphoma patients using this approach has been very promising (84). GM-CSF might also mobilize and prime macrophages with antitumor activity. A new trial has been initiated at UT MDACC for patients with potentially platinum-sensitive EOC, which will employ a chemoimmunotherapy regimen comprising GM-CSF, rIFNγ, and carboplatin. The immunotherapy regimen utilizes the monocyte and DC mobilizing and priming properties of GM-CSF and the antitumor cell macrophage activating properties of rIFNγ.

Vaccine Therapy

The development of suitable vaccines for use in EOC has generally trailed the advances that have been made in other tumors such as melanoma and lymphoma. In part, this is due to the heterogeneity of human EOC. Several antigens have been identified, some of which could have applications in the treatment of EOC (Table 2). Important issues related to peptide vaccines in EOC are expanded in a previous review by Hwu and Freedman (26). Most of the work has been done with HER2/neu that is overexpressed

Table 2 Tumor Antigen Epitopes in Ovarian Cancer

• HER-2 Neu	– Peptides
• Telomerase	– h TERT (protein component)
• Folate binding protein (a-folate receptor)	
• Mesothelin	
• Testis proteins	– NY-ESO ($CD8^+$ and $CD4^+$ T cells) (recognize different epitopes)
	– MAGE, BAGE

in about 10–20% of EOC (74,87,88). These studies demonstrate that HER-2 epitopes generate HLA-2-restricted peptide reactive T cells and produce generous amounts of IFNγ in vitro. Cytotoxicity experiments with T-cell lines or clones using HLA-2^+ HER2/neu$^+$ cell lines as targets show modest killing even at high E/T ratios (89,90). NY-ESO-1 is a member of the testis group of antigens that have also been identified in a variety of tumors including EOC (91). Two HLA-2.1 restricted T-cell epitopes (ESO-1:157-167 or 1:157-165) from within NY-ESO-1 have been shown to generate peptide reactive cytotoxic T-lymphocytes (92). By substituting valine at the c-terminus, activated T cells were generated that recognized HLA-2.1^+ NY-ESO-1^+ tumor cells. Several other peptides have been identified that are derived from tumor-associated antigens that are variously expressed on ovarian tumor cells. It is important that these peptide-activated T cells recognize the naturally expressed peptide on tumor cells from the immunized patients. It is likely that polyvalent preparations will be required to recognize a range of antigen epitopes that are expressed within the tumors of individual patients and between patients. Other issues relate to the quality of in vivo activation, the trafficking efficiency to these tumors and how to deal with hostile factors in the tumor environment. In recognizing the interference role of suppressor T cells, Dudley's group has recently reported that 6 of 13 advanced melanoma patients responded to a nonablative regimen of cyclophosphamide and fludarabine followed by adoptive transfer of selected TIL population and high-dose IL-2 (93). Studies on tumor vaccines have previously focused on the use of the whole tumor cells or extracts as immunizing agents, using either autologous tumor cells or allogeneic tumor cell lines. We had treated a number of EOC patients with extracts of cultured EOC tumor cells that had been infected with the PR8-A strain of influenza virus (94,95). There were 2 of 13 pathologically complete responders to ovarian viral oncolysate after treating patients with minimum residual disease following prior chemotherapy (40). It is entirely conceivable that T cells could be activated by this approach by processing of the cellular antigens by DC or macrophages—a process called cross-priming. There is increasing evidence that peritoneal cavity DC could have the capacity to stimulate T-cell responses (132).

In a different approach, Maclean et al. used a synthetic carbohydrate antigen to induce active response, which was primarily antibody mediated against cryptic surface antigens, in patients with extensive metastatic ovarian disease (96). They noted no toxic effects. In 1995, Bowen-Yacyshyn et al. showed that survival of patients with breast or ovarian cancer who were immunized with these carbohydrate linked antigens correlated with increased levels of the CD69$^+$ and HLA-DR$^+$ activation antigens (97).

Currently, the major limitation to the application of vaccines in EOC is a dismal lack of information about tumor antigen epitopes that have relevance for specific activation and recognition. It is possible that the progress that continues to be made in melanoma vaccinology will eventually translate into advances in other tumors such as ovarian cancer.

IMMUNOTHERAPY IN CERVICAL CANCER

Cervical carcinoma is a major public health problem worldwide; approximately 450,000 new cases are diagnosed and nearly 200,000 deaths are attributed to this disease each year (98). In developing countries, cervical cancer remains a leading cause

of cancer-related death in women. In the United States, screening with Pap smears has contributed to the lowered incidence of new cases of invasive cancer and approximately 4800 deaths per year. However, the cost of this screening in the United States alone has been estimated at nearly $6 billion annually (52).

Immunotherapeutic strategies for cervical cancer have focused primarily on the major target that has been strongly correlated with premalignant and invasive lesions of the cervix, the human papilloma virus (HPV). Epidemiologic and experimental studies have shown that the majority of all grades of premalignant lesions of the cervix can be attributed to oncogenic HPV infections (99). Most high-grade squamous intraepithelial lesions (HGSIL) of the cervix contain high-risk HPV types, and both high- and low-risk HPV types have been found in low-grade squamous intraepithelial lesions (LGSIL) of the cervix (99,100). Moreover, HPV-negative women who tested positive in an enrollment study were 3.8 times more likely to have low-grade SIL subsequently diagnosed, confirming a link between the virus and SIL (101).

Human Papilloma Virus

HPV is a double-stranded circular DNA virus with a size of 8000 kilobases. The HPV genome can be divided into three segments of unequal sizes: a long control region, which represents about 10% of the genome, and the early (E) and late (L) genes, which make up about 50% and 40% of the genome, respectively. Two genes, L1 and L2, code for viral capsid proteins; the E genes encode proteins that have a variety of regulatory functions. Three E genes identified with carcinogenesis are E2, E6, and E7. The E2 protein regulates transcription and replication of the HPV genome by encoding a protein that is involved in the regulation of the viral promoter directing the expression of the E6 and E7 genes. E2 is capable of suppressing growth and arresting the cell cycle, functions that correlate with inhibition of E6 and E7 transcripts (102,103).

Over 100 different types of HPV genotypes have been described, approximately 30 of which infect the lower genital tract, causing anogenital disease ranging from condyloma accuminata to invasive cervical cancer. HPV can be divided into low- and high-risk genital types. The low-risk group includes types 6 and 11, which are commonly associated with condylomata accuminata and LGSIL. The high-risk group includes types 16, 18, 45, and 56. These are commonly found in patients with HGSIL. The difference between the two groups lies in the high binding capacity of high-risk HPV E6 and E7 proteins for the products of tumor suppressor genes. The E6 protein is associated with the p53 gene product, and the E7 protein binds to the retinoblastoma gene product (104,105) and interferes with P53-related growth regulation of cells.

Immune Response Evasion

Nearly 30% of HGSIL lesions progress to invasive cervical carcinoma over a period of 20 years (106). HPV type, viral load, and integration status all may affect the chances of progression and possibly the immunologic response to HPV infection. It has been previously shown that HPV-infected or -transformed cells can evade the immune response. A number of mechanisms have been proposed, including downregulation of HLA class I molecules, production of either inhibitory cytokines or proteins that can inactivate stimulatory cytokines, and downregulation of signaling components of the

CD3 T-cell receptor (107–111). It has also been shown that the HPV may itself subvert the activation of DC (112). Smoking, which could be an important cofactor in this disease, may also contribute to impairment of T-cell responses.

Expression of HLA class I molecules is dependent upon the normal function of the proteosome and transporter-associated antigen processing (TAP). Loss of proteosome low molecular proteins (LMP) or TAP expression prevents the proper assembly of HLA class I molecules and associated peptide epitopes on the cell surface (113–116). Interference with this mechanism could allow the tumor cells to escape recognition by activated cytotoxic T cells. There may also be genetically determined loss of expression of the HLA complex which also would prevent recognition by epitope specific T cells (113).

Vaccine Rationale

Several factors suggest the validity of pursuing a vaccine for the prophylaxis and treatment of HPV infection (Fig. 4). The L1 and L2 structural component vaccines may evoke antibodies that neutralize the virus, and the purpose of E6 and E7 antioncoprotein vaccines is to suppress the oncogenic activity of the virus as well as to provide targets for the destruction of infected cells. The L1 and L2 proteins engage the immune system while preserving their native conformation. The E6 and E7 antigens may induce responses that obliterate viral expression in active infection (117).

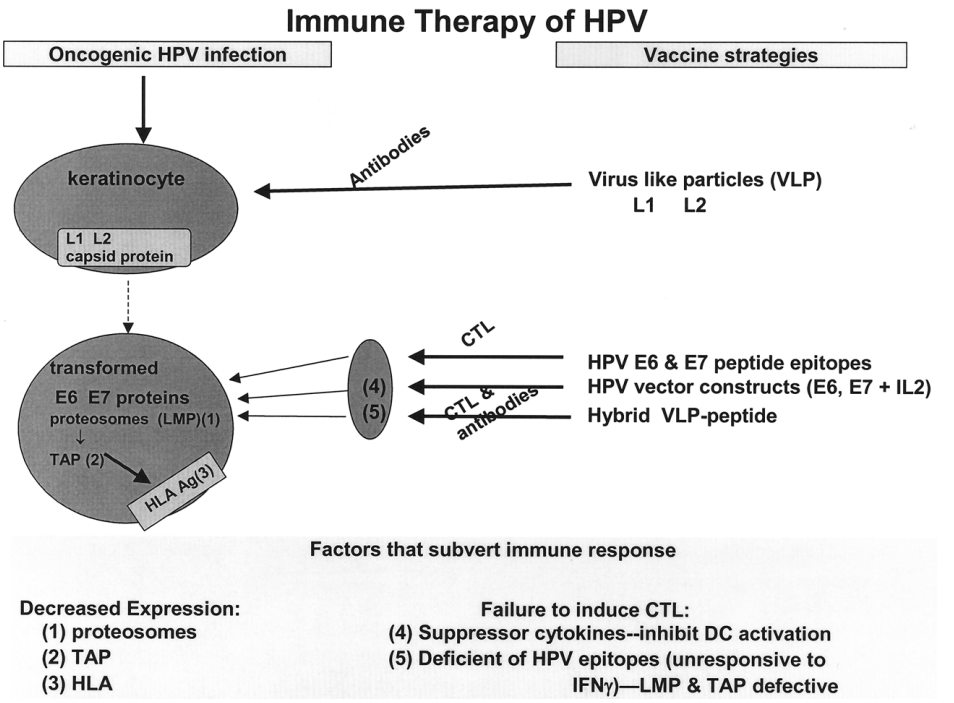

Figure 4 Immune therapy of HPV.

In developing a vaccine for cervical cancer, there are two main approaches. The first, the prophylactic vaccine, has as its aim to induce antiviral neutralizing antibodies before viral infection occurs. The ideal prophylactic HPV vaccine for cervical cancer should be safe, stable, cost-effective, active against all or at least the major oncogenic HPV subtypes, and capable of generating a long-lasting antibody response on genital mucosal surfaces. Prophylactic vaccine development for HPV has focused on recombinant subunit preparations consisting of the L1 and L2 virion structural proteins. Studies dealing with the prevention of HPV infection have focused on the expression of the major capsid protein of HPVs, with and without coexpression of L2, in eukaryotic cells that self-assemble into virus-like particles (VPL) which are indistinguishable from native virions (115). Such empty capsids do not contain potentially oncogenic viral DNA. These capsids induce high-titer, neutralizing antibodies in animal models.

VPLs have been shown to be immunogenic when injected into animals. Several investigators have shown that, in animal models, papilloma virus infection can be prevented by immunization with papilloma virus VPLs followed by experimental challenge with native virus (118,119). It is important to note that capsid proteins of HPV are only expressed during infection of keratinocytes, and not by established cancer cells. Therefore VPLs would be useful for preventing infection but not for treating patients in whom oncogenic transformation had occurred. To overcome this issue, chimeric HPV 16–VLPs have been introduced that include an E7 epitope. These preparations can also efficiently activate DC (120). One of the most difficult obstacles to overcome in the development of an attenuated vaccine has been the fact that there is no known effective culturing medium for propagating HPV.

The second approach is a therapeutic vaccine, which is administered to reduce or eradicate existing disease or infection. The vaccine targets and destroys cells expressing tumor-associated or tumor-specific antigens on their surface. The viral peptides derived from high-risk HPV E6 and E7 oncoproteins that match specific HLA motifs are employed as vaccine epitopes to stimulate specific T-cell responses against tumor cells that have parts of the HPV genome incorporated (115,117,121). Human cytotoxic T cells induced against certain E6 and E7 peptides cause lysis of HPV-positive cervical carcinoma cell lines that have HLA matching motifs (122).

Hines et al. very importantly suggested that the evaluation of efficacy of vaccines for cervical carcinoma, be it for prophylactic or therapeutic purposes, must first identify the endpoints of interest (123). They also reported that the population to be studied is crucial in this process. For example, in studying the prevention of genital warts or dysplasia, an HPV-naive population should be the target of the study and the subunit VPL vaccine should contain predominantly low- and intermediate-risk serotypes. Conversely, if an endpoint of decreasing the incidence of cervical carcinoma is selected, then a multivalent subunit vaccine that includes high-risk HPV types 16, 18, 45, and 56 should theoretically prevent 70–80% of cervical carcinomas.

Vaccine Techniques

Several different techniques have been used to identify the most effective approaches to vaccination. One technique has been adoptive transfer of cytotoxic T-lymphocytes. Adoptive transfer of cytotoxic T-lymphocytes raised against a subdominant HPV 16 E7 cytotoxic T-lymphocyte epitope has been accomplished successfully in mice against

HPV 16-induced tumors, leading to tumor eradication (124). TIL with NK- or LAK-mediated killing potential not restricted to the MHC have also been isolated at cervical carcinoma sites (125). However, development of adoptive transfer of immunized T cells is limited by its technical complexity and cost and the fact that HLA expression may be downregulated in advanced disease. HLA expression is also important for vaccines that induce CTL.

Based on the rationale that vaccination with tumor-specific peptides may activate antigen-specific cytotoxic T-lymphocytes, another technique has used peptide-based vaccines. In vivo studies in mice have shown that successful vaccination with HPV 16 E7-derived, high-affinity MHC class I-binding peptides can induce protection against the growth of HPV 16-transformed syngeneic tumor cells (126,127). One of the limitations of peptide-based vaccines is that the patient's HLA haplotype must be known in order to choose the appropriate peptides compatible with that particular haplotype. Proposals for overcoming this limitation have suggested making use of protein-based vaccines. One could also potentially use multivalent peptides that contain a range of HLA motifs.

A different technique has been proposed that involves using vectors encoding for HPV as vaccines. This method uses a recombinant viral vector that carries genes for HPV 16 E6 and E7 proteins. This leads to the production of a target antigen inside host cells, antigen processing, and ultimately MHC class I-mediated antigen presentation (113). Previous studies using this technique have thus far yielded few or no responses (122,124). Recent improvements have utilized a virus vector that includes a gene cassette that encodes both for mutated gene products, to prevent inactivation of growth regulatory genes and secondly for a cytokine cofactor.

DNA vaccines have been used; this involves injecting DNA that encodes for antigenic proteins, which is capable of inducing both a humoral and cell-mediated immunoresponsiveness against viral proteins (128). This technique offers the advantage of avoiding injection of protein, a live replicating vector, or an attenuated version of the pathogen (113).

Clinical Trials

Investigators have evaluated the intradermal use of a live vaccinia virus HPV 16 and 18 E6/E7 gene construct. Responses were seen in one of three evaluable patients with advanced cervical cancer, in three of 12 volunteers with cervical intraepithelial neoplasia type 3, and in four of 29 patients with early invasive cervical cancer. Studies have shown that this vaccine appears to be safe and has the ability to induce cytotoxic T-lymphocyte class 1-specific HPV response against HPV 16 and 18 in patients with preinvasive or invasive cancer (127,129,130).

The feasibility of peptide vaccination has also been studied. A phase I–II trial was performed involving vaccination with HPV 16 E7 peptides in patients suffering from HPV 16-positive cervical carcinoma that was refractory to conventional treatment. Nineteen patients were included with no adverse effects observed. Two patients showed stable disease for 1 year after vaccination, 15 patients showed progression of disease, and two patients showed tumor regression after chemotherapy following vaccination (102).

One large trial has been published by Herrero et al. studying the prevalence of HPV infection and the risk associated with various HPV types. In screening 9175

women, the investigators found that 73% of LGSILs were HPV positive, with HPV-16 being the predominant type. HPV was also found in 89% of HGSILs and 88% of cancers. They concluded that polyvalent vaccines, including the main cancer-associated HPV types, may be able to prevent most cases of cervical disease (131). Large trials, both randomized and nonrandomized, are in progress or in the planning phase. As the natural history of cervix cancer is long and trials to prevent invasion would be limited by trial duration and large numbers of participants, most of the emphasis in vaccine trials is targeted to prevention of oncogenic virus infection or preinvasive disease.

CONCLUSION

There has been significant progress in our understanding of tumor molecular biology and modulation of immune responses. As we continue to accumulate information about the mechanism of interaction between tumors and the immune system, we will be able to expand our preventive, diagnostic, and therapeutic tools to eradicate tumor cells. Given the limited response to current therapies, new treatment modalities are desperately needed in ovarian cancer. Immunotherapy alone or in combination with chemotherapy will potentially serve as an adjuvant treatment to prolong disease-free interval and survival. As cervical cancer is one of a limited number of tumors that are of viral origin, this is being exploited to develop both preventive and therapeutic vaccine approaches. The successful development of an HPV vaccine would have an enormous impact on health care worldwide and large trials are in progress. Continuing efforts to develop novel immunotherapy applications are expected to lead to additional treatments for patients with gynecologic malignancies.

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6

Gene Therapy of Ovarian Cancer

George Coukos and Christina S. Chu
University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.

INTRODUCTION

Gene therapy is defined as a therapeutic approach that utilizes the introduction of a cloned gene, a gene fragment, or other nucleic material into tumor cells in order to modify the behavior of tumor cells or induce their death (1). As developments in cell and molecular biology have deepened our understanding of the mechanisms of apoptosis and cell cycle control, several genes have been identified which play key roles in maintenance of genomic integrity and regulation of the cell cycle. Alterations in specific genes have been associated with the development of sporadic or hereditary tumors and have been shown to affect tumor cell response to chemotherapy. This growing bulk of information has enabled the design of specific molecular strategies aimed at controlling tumor progression. Three fundamental approaches have been undertaken in cancer gene therapy. First, in the cytotoxic (or suicide) gene approach, the genes encoding enzymes, which transform inactive prodrugs into cytotoxic active drugs, are inserted into cancer cells. Only transfected cells expressing the specific enzyme become susceptible to killing. Second, corrective gene approaches are designed to combat observed alterations of specific genes involved in pathways controlling apoptosis and/or the cell cycle. Specific genes are introduced into tumor cells in order to cause cell cycle arrest, induce programmed cell death, or make tumor cells susceptible to conventional therapeutic agents such as chemotherapy and radiation. Third, immunopotentiating approaches introduce specific genes in tumor cells in order to enhance their recognition by the host immune system. Several approaches have emerged as potentially promising and some have already been tested in epithelial ovarian cancer.

VECTORS

Gene therapy strategies have been designed to target specific gene functions implicated in the development and growth of cancer. Although they have yielded promising results in preclinical in vitro and animal models, their use in clinical practice has been problematic. The optimal method for gene delivery has yet to be determined. While the Recombinant DNA Advisory Committee (RAC) has approved hundreds of protocols

for cancer gene therapy, the majority of trials approved by the RAC involve the use of viruses as gene transfer vectors, although some use DNA–protein complexes, DNA particle ribozymes, or lipid-based vehicles (2). Although several types of vectors have been developed (Table 1) and tested, all are faced with significant limitations related to low efficacy, inability to penetrate deeply in tumor nodules, inactivation by the immune system, and undesired side effects.

Nonviral Vectors

Direct gene delivery of plasmid DNA by relatively inert vehicles presents an alternative to the use of viral vectors. Liposomes currently represent the best vehicle to deliver plasmid DNA into mammalian cells. Liposomes are amphipathic lipids containing both a hydrophobic domain and a hydrophilic domain composed of hydrocarbon chains. While anionic liposomes are unable to package large fragments of DNA because they do not bind DNA directly, positively charged cationic liposomes with amine groups bind DNA with great affinity (3). Nonspecific ionic interactions may facilitate liposome binding to the cell surface. These complexes are thought to cross the cell membrane through endocytosis mechanism, but fusion mechanisms may also be involved (4).

The use of nonviral vectors has several major advantages. Liposomes are not associated with the toxicity of viral vectors. Liposomes are also poorly immunogenic, therefore permitting transgene expression even after multiple administrations (5). Despite their low immunogeniticy, liposomes have been shown to trigger a strong direct cytokine response, even in the absence of a transgene, thereby inducing significant tumor regression (6). Liposomes are easily produced on a large scale and

Table 1 Vectors for Gene Delivery

Nonviral vectors
Cationic lipids
Gene gun
Liposomes (cationic and stealth)
Naked plasmid DNA
Viral Vectors
Adeno-associated virus
Adenovirus
Herpes simplex virus
Lentiviruses
Human immunodeficiency virus
Simian immunodeficiency virus
Feline immunodeficiency virus
Oncoretroviral vectors
Moloney murine leukemia virus
Harvey murine sarcoma virus
Avian spleen neurosis virus
Papilloma simian virus
Polyoma virus
Vaccinia virus

offer the ability to carry large transgenes, up to 50 kb. While in vitro studies have confirmed the ability of cationic liposomes to deliver transgenes to a large variety of malignant cells, a major disadvantage of liposome use relates to their poor in vivo transduction efficiency when compared to viral vectors. In addition, expression of liposome-delivered transgenes is only transient. Another disadvantage relates to the scavenging of cationic liposomes by the reticuloendothelial cell system (7). Stealth technologies may be needed to increase the tumor selectivity of these agents.

In vivo, liposomes have been safely utilized intraperitoneally and intravenously. Intratumoral injections have also been described. In particular, liposomes have been used in gene therapy studies of epithelial ovarian cancer (EOC). Not only have EOC cells been shown to uptake liposomes efficiently (8), but liposome-mediated gene transfer has also been found to be facilitated by cisplatin treatment (9). Current research is directed at improving the transfer efficiency of liposomes as well as their tumor selectivity.

Viral Vectors

Viral vectors offer a high efficiency of gene transfection and still remain the vectors of choice despite their disadvantages. Viruses are a natural choice as a vector for gene therapy, as they have evolved to utilize successful strategies to both introduce their own genome into eukaryotic cells and to employ the host cell biochemical machinery. Wild-type viruses have the ability to infect several cell types, in which they carry out a replicative cycle under permissive circumstances, leading to the death of the host cell.

Replication-Incompetent Viral Vectors

To address safety concerns, viral vectors have been manipulated in order to render them incapable of reproducing. Portions of the genome that are critical for viral replication have been deleted in the replication-incompetent viruses. Therapeutic transgenes are inserted in their place, often under the control of a strong exogenous promoter.

Adenovirus While adenoviruses possess some limitations for use as vectors for gene delivery, their advantages outweigh their disadvantages. In fact, most human gene therapy trials, including cancer gene therapy trials, have utilized adenoviral vectors. These viruses present several advantages: they are stable, can be produced on a large scale, and may be manufactured without contamination by replication-competent adenovirus (RCA) (10). In addition, they may accommodate inserts of up to 7.5-kb transcripts. The virus gains entry into human cells through clathrin-coated vesicles (11) via the vitronectin receptor ($\alpha v\beta 3$ integrin) and a newly identified coxsackie/adenovirus receptor (CAR). Because the viral genome remains extrachromosomal, adenoviruses do not mediate long-term gene expression in dividing cells, leading to vector dilution with each cell division. Adenovirus is also highly immunogenic. While these qualities present barriers for the effective therapy of genetic disorders, these properties may prove to be an advantage for cancer gene therapy (12).

Several replication-incompetent strains have been produced through modification of the viral genome. First-generation vectors were engineered by removing the early (E) genes E1A and E1B, which control viral replication and regulate the expression of late genes, and substituting a designated transgene (13). Replication-incompetent adenovirus must be produced on appropriate packaging cell lines that

supply the missing genes necessary for replication. Because this in vitro manufacturing process incurs a high likelihood of recombination events, these initial first-generation strains produced an unacceptable degree of contamination by replication-competent adenovirus (14). Given the remarkable efficiency with which wild-type virus infects the liver, the in vivo use of these first-generation strains in mice resulted in severe hepatotoxicity. A second-generation virus was next produced by adding an additional mutation in the E2A or E3 regions (10). Replication-competent adenovirus contamination was dramatically decreased, thus improving the toxicity profile of the vectors.

Administration of adenovirus produces an intense inflammatory response which eventually results in immune-mediated vector neutralization through different mechanisms. Activation of the human Toll receptor 2 probably mediates the early innate response: inflammatory cytokines such as interferon gamma (IFN-γ), interleukin (IL)-1, and IL-6 are released, an acute inflammatory cell infiltrate is recruited, and virus-specific neutralizing antibody and T-cell responses are generated (15). Cells transfected by adenovirus express both the transgene and viral genes and trigger specific $CD8^+$ and $CD4^+$ T-cell responses (16). While the generation of an intense inflammatory reaction in the proximity of the tumor may enhance tumor recognition by the host immune system, the potential for immune-mediated vector neutralization poses marked limitations on gene delivery. EOC cells have been shown to be susceptible to infection by adenoviral vectors (17) in vitro. Although epithelial ovarian cancer cells in xenograft murine models are susceptible to infection by adenoviral vectors, patients with ovarian cancer have been shown to display neutralizing antibodies in both serum and peritoneal fluid which significantly decrease the efficacy of adenoviral vectors in vitro. Blackwell et al. (18) investigated inhibitory factors in ascites from ovarian cancer patients and determined that inhibition was primarily due to IgG antibodies directed against the adenoviral fiber protein. In an attempt to circumvent those neutralizing antibodies, they demonstrated that an adenoviral vector with a modified fiber protein could mediate efficient gene transfer in vitro, even in the presence of ascites with high neutralizing antibody titers. While the presence of anti-adenoviral antibody titers did not appear to compromise the efficiency of gene transfer in a phase I trial of adenoviral gene therapy for pleural mesothelioma (19), concern regarding immune-mediated neutralization still exists, particularly when repeated vector administrations are planned. To address these concerns, a third-generation adenoviral vector was produced by deletion of the E1 and E4 genes, with preservation of the E3 region (10), whose protein product inhibits MHC I transport to the cell surface, thereby limiting the immunogenicity of adenovirus-infected cells. Both E1/E4 virus and E1/E3 deleted virus performed similarly in several EOC cell lines.

Adeno-Associated Virus Adeno-associated virus (AAV) is a 4.7-kb virus not associated with any known disease in humans. Adeno-associated virus requires coinfection by a helper virus such as adenovirus or herpes virus to enable replication (20). Replication-incompetent AAV vectors can be constructed by removing the sequences encoding viral structural proteins and generating a backbone with the two inverted terminal repeats (ITRs) surrounding the inserted transgene (21). A packaging cell line is used for vector production. Adeno-associated virus has several major advantages. It is able to infect both dividing and nondividing cells, and thus may prove useful in treating tumors that contain a large low S-phase cell fraction. Adeno-associated virus is highly stable, integrates into the host genome, and produces efficient

transfection. Adeno-associated virus infection is not accompanied by inflammation and does not generate a strong recall immune response (22). Additionally, the presence of a preexisting immune response in the host does not appear to interfere with transfection efficiency. However, AAV can only accommodate relatively small transgenes; while adenoviruses can carry transgenes up to 7.5 kb in size, AAV cannot contain genes greater than 4.5 kb in size. Primary human epithelial ovarian cancer cells have been shown to be susceptible to AAV infection, making AAV a promising vector that awaits further testing (23,24).

Herpes Simplex Virus Herpes simplex virus (HSV) is an enveloped double-stranded 150-kb DNA virus capable of infecting a wide variety of human tissues, entering cells through several identified receptors (25–27). The HSV genome has been used to create several different vectors, including replication-incompetent virus and amplicons (28). Amplicon vectors, derived from plasmids that carry both HSV genes and bacterial genes (29), contain full-length HSV genomes in which various viral genes have been deleted and substituted by transgenes (28). In order for these transgenes to be expressed, amplicon vectors require coinfection with a helper virus or the presence of additional HSV-1 genes. Replication-incompetent HSV vectors have been constructed by disrupting genes in control of viral replication, such as ribonucleotide reductase, thymidine kinase, UL5, and ICP34.5 (30). Herpes simplex virus vectors display several major advantages such as the versatility of the vector system and the ability to produce large-scale quantities of vector. In addition, because the HSV genome contains at least 30 genes that are not necessary for viral replication, multiple genes may be deleted without affecting the ability of the vector to propagate, allowing for insertion of large or multiple transgenes. Moreover, unlike HSV mutants that are prone to undergo latency, replication-incompetent HSV vectors may generate cytotoxicity in infected cells independently of transgene expression through expression of toxic viral proteins such as ICP0, ICP4, ICP22, ICP27, and the UL13 gene products (31).

Herpes simplex virus may be a promising vector for the gene therapy of ovarian cancer. Ovarian cancer cells are highly susceptible to infection by HSV vectors. When an HSV ICP34.5 deleted vector was used in vitro to infect EOC cells, a multiplicity of infection (MOI) of only one was necessary to achieve an infection rate of 75%. In comparison, a replication-incompetent adenovirus required an MOI of 50–500 to achieve a similar rate of infection (32). Wang et al. (33) investigated a replication-defective HSV-1 vector and confirmed this sensitivity of EOC to HSV infection. However, given the prevalence of immunity against HSV-1 (34), the effectiveness of HSV-mediated gene therapy may be hindered. Herpes simplex virus-neutralizing antibodies in serum or peritoneal fluid of patients may decrease the efficacy of any HSV-mediated gene therapy.

Retroviruses Retroviruses are diploid positive-strand RNA viruses which replicate in the host through DNA reverse transcription. After infection, viral DNA is transcribed from the viral RNA template and integrated into the host genome. Next, copies of the RNA virus are produced by the host's own nuclear machinery (35). Different retroviruses have been investigated as potential gene therapy vectors. Oncoretroviruses such as the murine leukemia virus (MLV) require dividing target cells, but lentiviruses, such as recombinant human immunodeficiency virus (HIV), have the ability to target nondividing cells as well. An advantage of retroviruses is their

ability to incorporate into the host genome, thereby providing potential long-term transgene expression (36). Also, because retroviral vectors do not produce significant viral proteins, immune response following administration is minimal, and unlike adenovirus, no prior recall immune responses have been encountered in humans. These properties should facilitate repeated administrations of the virus.

The use of retroviral vectors raises several safety concerns. The first concern with retroviral vectors relates to insertional mutagenesis (35,37). Insertion of viral DNA occurs in a pseudo-random fashion and could potentially disrupt a tumor suppressor gene or modify a growth-promoting gene to result in tumorigenesis. A second concern is related to possible insertion of transgenes into the germ line of the host. While insertion of a suicide gene into the germ line would cause sterility, nonlethal transgenes could potentially be passed down to future progeny. A third concern is that retroviruses may recombine in the host to generate infectious replication-competent viruses, which may be transmitted to other individuals. Despite these concerns, almost 20 years of experience with oncoretroviral vectors has proven their feasibility and safety of administration. However, in response to these concerns, the FDA currently requires that all patients enrolled in retroviral gene therapy trials undergo lifelong annual testing for the presence of replication-competent retrovirus.

Replication-Competent (Oncolytic) Viral Vectors

Direct intratumoral injections of wild-type replication-competent viruses were first studied in the 1950s and 1960s, but were met with limited success and were eventually abandoned. However, when the development of newer molecular technologies made it possible to generate recombinant viruses, interest in virus-based oncolytic tumor therapies was renewed. Multiple viruses have been used experimentally in clinical situations, including influenza virus, vaccinia virus, Newcastle disease virus, vesicular stomatitis virus, herpes simplex virus 1, and adenovirus.

Herpes Simplex Virus Replication-competent HSV-1 mutants are potent oncolytic agents. Two clinical trials focusing on the treatment of malignant gliomas are currently ongoing using intracerebral tumor administration of ICP 34.5 deficient mutants (38,39). The ICP34.5 protein is critical for neurovirulence (40,41) and plays an important role in viral replication (42), viral exit from infected cells (43), and prevention of the premature shutoff of protein synthesis in infected host cells (44). Although initially designed for the treatment of central nervous system (CNS) tumors (45), HSV-1 recombinant strains are also displaying efficacy and tumor selectivity against various extra-CNS malignancies such as prostate cancer (46), mesothelioma (47), metastatic colon carcinoma (48), malignant melanoma (49), breast cancer (50), and head and neck squamous cancer (51). Safety of these viruses has been examined in animal studies of i.p. virus administration: no toxicity was detected, and no spread of the virus could be documented outside the tumors by immunohistochemistry or polymerase chain reaction (PCR) (32,47). Thus, HSV-based oncolytic therapy may provide an attractive approach for the treatment of solid tumors (30).

Herpes simplex virus-1 may prove to be an effective oncolytic agent in the treatment of ovarian cancer. EOC cells are quite susceptible to recombinant HSV-1 infection and express viral antigens after infection. We examined several established ovarian cancer cells 16 hr after exposure to a recombinant ICP34.5-deficient HSV-1 strain and used immunofluorescence and flow cytometry to evaluate HSV antigen expression. Approximately 70% of the cells were infected at only 1 MOI, and

approximately 99% of the cells were infected at only 1.5 MOI (32). Several different ICP34.5-deficient HSV-1 strains were also tested and were all found to exert a potent oncolytic activity on established EOC cell lines. Primary ovarian cancer cell cultures were also tested and found to be even more susceptible to HSV killing than established lines (38,52). In vitro assays showed HSV-1 mediated oncolysis to be equally as effective in both chemotherapy-sensitive and chemotherapy-resistant EOC (53). Furthermore, in vivo experiments testing human EOC xenografts in the severe combined immunodeficient (SCID) mouse provided additional confirmation that ICP34.5-deficient HSV-1 demonstrates a cytotoxic effect against both chemotherapy-sensitive and chemotherapy-resistant EOC (32).

Cell death following infection by recombinant ICP34.5-deficient HSV-1 appears to be mediated through apoptosis. Within 24–48 hr of infection, EOC cells were found to undergo varying degrees of apoptosis as assessed by both cell cycle analysis and in situ DNA fragmentation analysis. Apoptosis was noted to be independent of p53 status, perhaps explaining in part the ability of HSV-1 to induce EOC cell death despite the presence of chemotherapy resistance. Further investigations using HSV-G207, a doubly deleted strain of HSV-1 lacking ICP34.5 and ribonucleotide reductase (RR), a regulator of viral proliferation, revealed lysis in EOC cells in vitro, but sparing of normal human mesothelial cells (52). An increasing bulk of evidence supports the safety of these agents for in vivo oncolytic therapy.

Adenovirus Among the oncolytic therapies under development, ONYX-015 is the agent which has undergone the most extensive clinical testing in nonbrain tumors (54). ONYX-015 is an adenovirus that has been engineered with a defective E1B gene. Normally, the E1B gene serves to inactivate the p53 tumor suppressor gene, an inhibitor of adenoviral replication. Being deficient in E1B, ONYX-015 is theoretically able to replicate only in p53-deficient tumor cells but not in normal host cells possessing wild-type p53. Notably, when ONYX-015 was tested by intratumoral injection into human cervical carcinoma grown in nude mice, complete regression was noted in 60% of the tumors (54). Further reports confirmed that intratumoral or intravenous administration of ONYX-015 had antitumoral efficacy against a variety of human tumor xenografts in nude mice. Furthermore, the virus demonstrated no toxicity to normal human cells. Oncolysis by ONYX-015 demonstrated a synergism with platinum-based chemotherapy. While different authors dispute that intact p53 function and p53-dependent apoptosis are necessary for adenoviral replication (55), clinical trials with ONYX-015 for head and neck cancer and lung cancer are in progress, despite the controversy over mechanism of action and tumor selectivity of the virus. Preliminary results from a phase II study of ONYX-015 plus 5-FU/cisplatin chemotherapy in 30 head and neck cancer patients indicated significantly higher response rate and disease-free interval in patients receiving the virus (56). A randomized phase III trial currently under preparation in head and neck cancer will further clarify the efficacy of ONYX-015. Because EOC often displays mutations in the p53 pathway, ONYX-015 may also represent a useful tool for recurrent/persistent EOC.

Tissue-Specific Targeting of Viral Vectors

Recent investigation has focused on enhanced tissue-specific targeting of adenoviral vectors. Improved targeting of therapy to target cells would theoretically increase gene transfer to relevant cells, decrease host toxicity, and reduce the number of viral particles necessary to achieve a given level of gene transfection. Two primary

approaches have been suggested. The first involves linking the transgene of interest to a tissue-specific promoter that would only have activity in the target tissue. In this method, normal cells as well as tumor cells may be infected by the viral vector, but transgene expression would be limited to target cells possessing the necessary intracellular machinery to drive the promoter. Carcinoembryonic antigen (CEA) is a suitable candidate, particularly in the therapy of gastric and colorectal cancer and potentially for some ovarian cancers. U3 (57) is another example of a promoter with ovarian-specific activity which may prove promising for future therapies.

A second approach to tissue-specific targeting involves directing adenoviral vectors to a particular receptor with increased expression on target cells relative to normal cells, thereby increasing gene delivery. Rancourt et al. (58) have cross-linked adenoviral particles to basic fibroblast growth factor (FGF2), significantly increasing the affinity of adenovirus toward an epithelial ovarian cancer cell line, resulting in a 10-fold enhancement of efficacy in an in vivo mouse model. Kelly et al. (59) used CC49, a monoclonal antibody, to construct a conjugate with a fragment of the neutralizing antiknob antibody in order to target adenoviral binding to tumor cells via the tumor-associated glycoprotein 72 (TAG-72) receptor, which is expressed on most ovarian cancers. This method of gene transfer proved very selective for tumor cells, with adenoviral-mediated gene transfer augmented 2- to 28-fold in ovarian cancer cells vs. untargeted adenovirus. Also, transfer to autologous normal mesothelial cells was decreased 4- to 9-fold.

STRATEGIES

Cytotoxic (Suicide) Gene Therapy

One strategy for the gene therapy of cancer involves the introduction into tumor cells of a transgene encoding an enzyme capable of converting a nontoxic prodrug into a highly toxic drug. Ideally, the transgene would only be expressed in tumor cells, and therefore the production of the toxic drug should be limited to tumor cells. The most frequently utilized system for such cytotoxic, or suicide, gene therapy involves the HSV thymidine kinase (HSVtk). Various vector systems are utilized to introduce the HSVtk transgene into target cells. Next, the prodrug ganciclovir (GCV) is administered to the host. In cells expressing the HSVtk, GCV is phosphorylated into GCV-monophosphate (60), which is subsequently phosphorylated by ubiquitous mammalian kinases into GCV-triphosphate, a potent inhibitor of DNA synthesis. Ganciclovir induces cell death in a cell cycle-dependent manner: incorporation of GCV-triphosphate into DNA during the S phase inhibits DNA polymerase and ultimately leads to DNA fragmentation followed by apoptosis (61), thereby providing a mechanism for partial tumor selectivity of the cytotoxic therapy.

Other combinations of enzyme/prodrugs have been tested, offering different advantages and limitations. For example, the enzyme cytosine deaminase, which converts 5-fluorocytosine (5-FC) into 5-fluoruracil (5-FU) (62), has been approved for human clinical trials. The disadvantage of this system is that treatment is limited to those tumors that are sensitive to 5-FU, such as colorectal carcinoma. Another example is a novel "suicide switch" system, which exploits the dimeric nature of caspases. Caspases are a family of cysteine proteases that function as downstream mediators in the apoptosis pathway. Various caspases, such as caspase-1/interleukin-

1β-converting enzyme (ICE) and caspase-3/YAMA, are able to cross-link to a FK506 analog, a nontoxic lipid-permeable dimer. These complexes are able to trigger rapid apoptosis through binding to FK506-binding proteins (FKBP) (63). This newly developed suicide system is an extremely promising strategy for cancer gene therapy.

Although suicide gene therapy with HSVtk/GCV was expected to affect only transfected tumor cells and to spare nontransfected tumor, studies demonstrated unexpected cell death in neighboring nontransfected cells (64). The term "bystander effect" was given to collectively describe various amplification mechanisms for cell killing. Initial studies demonstrated that transfection of only 5–15% of cells was sufficient to achieve 100% cell killing with the HSVtk/GCV system in vitro. This observation was later confirmed by in vivo experiments. A variety of other cytotoxic systems such as CD/5-FC, cytochrome p450/cyclophosphamide, CPG2/CMDA, XGPRT/6PX, and DOD/MEPDR are also associated with similar amplification cascades (65).

Several mechanisms may contribute to the bystander effect. For example, the spread of toxic metabolites to untransfected cells may be responsible for additional cell killing. Diffusion into neighboring cells of nonlipid-soluble toxic metabolites, such as GCV-triphosphate in the HSVtk/GCV system, occurs through gap junctions (66). Lipid-soluble metabolites, such as those generated by the CD/5-FC and the p450/cyclophosphamide systems, may propagate freely to cells nearby (67). Dying cells may, in turn, release cytotoxic cytokines which induce apoptosis in neighboring cells (68). Additionally, other mediators (such as Fas, FasL, and two downstream apoptosis mediators such as ICE and caspase-3/YAMA) involved in cell cycle arrest and apoptosis pathways may be implicated in the bystander effect induced by HSVtk (69).

Viral-based strategies may serve to trigger an antitumor immune response, amplifying the effects of suicide gene therapy (70). Virus administration may generate an intense inflammatory response in the region of tumor cells, leading to improved tumor antigen presentation and immune recognition. Studies have confirmed that utilization of HSVtk can result in the generation of an antitumor immune response (71). Indeed, HSVtk/GCV therapy has proven more efficacious in immunocompetent than in immunodeficient mice (72), lending further support to the notion that antitumor immune response may potentiate the effects of cytotoxic gene therapy. The mode of cell death affects the immunogenicity of tumor cells, with tumor necrosis being a more potent stimulus for immune response than apoptosis. When HSVtk/GCV therapy induced tumor cell necrosis, a specific CD4+/CD8+ T cell infiltrate was observed (73). The cytokine profile included IL-2, IL-12, IFN-γ, TNF-α, and GM-CSF suggesting a Th1 lymphocyte response (68). Treated cells also demonstrated up-regulation of MHC class I and costimulatory molecules such as B7 and ICAM (73,74).

Various suicide gene therapy systems have been tested on EOC cells in preclinical studies. While cytotoxic systems such as the prodrug CP1954 combined with the *Escherichia coli* nitroreductase gene have been found to be successful, most research has been done with the HSVtk/GCV system. HSVtk has been delivered via viral vectors as well as liposomes (75–77) and has been shown to be able to induce cytotoxicity, reduce tumor burden, and increase survival in both in vitro assays and in vivo in the immunodeficient mouse model (17,78–81). In particular, several different EOC cell lines such as SKOV3, CaOV3, OVCAR3, and A2780 have been shown to be susceptible to killing by HSVtk/GCV (82). In mouse models, a single i.p. administration of 1×10^9 particles of an E1/E3-deleted adenoviral vector delivering HSVtk

with a respiratory syncytial virus (RSV) promoter induced marked tumor regression. Repeated i.p. administrations of the virus increased the antitumor effect (personal observations). Rosenfeld et al. (81) reported that preimmunization of immunocompetent animals did not reduce the therapeutic efficacy of HSVtk/GCV delivered by an adenoviral vector. In a syngeneic mouse model of intraperitoneal ovarian carcinoma, LTKOSN.2VPC cells were first transduced with a retroviral vector carrying HSVtk, and then injected intraperitoneally into immunocompetent mice. These mice demonstrated decreased tumor burden when compared to controls injected with parental tumor cells, further supporting the antitumor effect of the HSVtk system. Al-Hendy et al. (83) used another syngeneic mouse model of EOC, SaskMouse, to demonstrate that multiple intraperitoneal injections of adenovirus-HSVtk followed by treatment with GCV resulted in statistically improved survival when compared to both single injection and untreated controls.

HSVtk/GCV has the potential to enhance the antitumor immune response in ovarian cancer. Freeman et al. (84) injected PA-1 human ovarian teratocarcinoma cells engineered to express HSVtk intraperitoneally into mice with previously established intraperitoneal adenocarcinomas. Subsequent GCV treatment led to the regression of the tumors. Because established tumors did not get directly transduced with HSVtk, one may infer that bystander or immune mechanisms were responsible for tumor regression. Histologic analysis of the adenocarcinoma tumors revealed an intense inflammatory reaction where the PA-1 cells had become adherent to the tumor surface. Generation of inflammation in the area of the tumor may aid in disrupting immune tolerance and help develop an antitumor immune response.

Based on promising in vitro and in vivo studies, patients with advanced or recurrent epithelial ovarian cancer (Table 2) have been treated with HSVtk/GCV gene therapy under various clinical trials (85). At Baylor College of Medicine in Houston,

Table 2 Clinically Tested Gene Therapy Approaches Used in Ovarian Cancer

Target gene	Hypothesis
Adenovirus E1A	The E1A gene product opposes the HER-2 protein (overexpressed by approximately 30% of ovarian cancers), and inhibits tumor growth in cancers overexpressing HER-2/neu.
BRCA1	Overexpression of BRCA1 causes suppression of tumor growth.
HER-2/neu	Expression of a gene encoding an anti-HER-2/neu antibody causes decreased cell surface expression of HER-2 protein, resulting in tumor growth suppression.
HSV-thymidine kinase	After administration of ganciclovir, cancer cells expressing thymidine kinase convert the prodrug to the active form, inducing cell death. Associated toxic metabolites and inflammatory cytokines cause bystander cell death. A cell-mediated immune response may also be triggered against the tumor.
p53	Over half of advanced ovarian cancers show loss of p53. Overexpression of p53 causes cell cycle arrest and increased sensitivity to chemotherapy. Overexpression of p53 may also cause block angiogenesis and encourage bystander cell death.

Texas, 10 patients were treated on a phase I protocol involving HSVtk delivered by an adenoviral vector. Intraperitoneal injection was followed by treatment with acyclovir and topotecan (86). Myelosuppression was the most common toxicity, but three patients developed thrombocytopenia, three had mild elevations in hepatic transaminases, and two had uncomplicated fevers. All side effects resolved. The investigators concluded that adenoviral vector therapy with concomitant topotecan chemotherapy was well tolerated without significant side effects. Although phase I studies of an adenoviral vector carrying HSVtk have demonstrated safety of administration, no significant tumor responses have been noted. Further studies are currently in progress to evaluate possible therapeutic benefit.

In addition to improved targeting which has been discussed previously, several strategies have been investigated in order to improve the therapeutic efficacy of suicide gene therapy. One possible approach is to combine HSVtk/GCV gene therapy with conventional cytotoxic chemotherapeutic drugs, which may increase cell killing in a synergistic fashion (87). Another approach involved choosing an optimal promoter to drive expression of the suicide gene since in vitro data have shown that different promoters affect the transductive efficiency of HSVtk, as well as the cytotoxicity of the treatment (88). Another development which may facilitate i.p. gene therapy delivery involves the use of microspheres constructed of biodegradable polymer such as L-lactide/glycolide copolymer (PLG) (89), which release suspended drugs in a sustained fashion. This material has been previously tested and proven safe for the i.p. delivery of chemotherapy drugs and has also been shown to accommodate both adenoviral vectors (90) and GCV (91). Theoretically, microspheres may be administered shortly after surgery to coat peritoneal surfaces and to provide sustained release of both vector and GCV to areas of tumor which may later be blocked to drug access by postoperative adhesion formation. It is possible that application of this technology may result in optimization of the conditions of intraperitoneal gene therapy.

Corrective Gene Therapy

As molecular defects in cancer have been identified, gene therapy approaches have been developed to target specific genetic alterations. In tumors with loss of a particular gene function, such as p16, p21, p53, and BRCA1, wild-type genes may be delivered to induce normal or high levels of expression of the missing gene in order to produce apoptosis or cell cycle arrest. In tumors with documented overexpression of oncogenes, ablative gene therapies may be carried out to neutralize oncogene function (92).

Several different genetic alterations have been identified in ovarian cancer. Approximately 50–75% of EOCs demonstrate mutations in the p53 tumor suppressor gene. Defective p53 may result in alterations of normal apoptosis or cell cycle control pathways. Loss of p53 may contribute to chemotherapy resistance and represents an independent prognostic factor for poor outcome (93). Another molecular alteration implicated in EOC is HER-2/neu, a protein in the epidermal growth factor receptor family. About 30% of EOC specimens have been shown to overexpress HER-2/neu protein (94), which may lead to malignant transformation and unrestrained tumor growth. Other oncogenes such as K-ras and c-*myc* are overexpressed in ovarian cancer (93). The cyclin inhibitors p21 and p16, which play a role in cell cycle control, may display defects as well. The BRCA-1 and BRCA-2 genes have been noted to be mutated in many patients with hereditary ovarian/breast cancer. Although their

functions have yet to be fully characterized, BRCA-1 appears to act as a tumor suppressor gene involved in the repair of double-stranded DNA breaks.

Gene therapy with tumor suppressor genes and genes involved in the cell cycle control has been tested in EOC and other solid malignancies. Bax, a proapoptotic gene (95), is a protein in the Bcl-2 family. Mutations in bax have been identified in tumors of the breast, colon, and ovary (96–100). Tsuruta et al. (101) used a recombinant adenovirus carrying the bax alpha gene to demonstrate high levels of bax expression in several ovarian cancer cell lines in vitro. Cytotoxic effects were documented in cisplatin-sensitive A2780, cisplatin-resistant A2780, and OVCAR3 cell lines. However, cisplatin-resistant SKOV3 cells only displayed mild cytotoxic susceptibility. The combination of bax therapy with cisplatin or paclitaxel appeared to enhance cytotoxicity in most cell lines tested, indicating the potential for bax treatment in conjunction with traditional chemotherapies. Introduction of the bax gene by adenoviral vectors has also been noted to augment the effect of radiotherapy on ovarian cancer cells in vitro as well as in mouse studies (102).

BRCA-1 has also been used for gene therapy of EOC. The BRCA-1 protein was noted to block cell cycling via p21 (103) and to cause tumor growth inhibition via the Rb gene (104). Given its potential to act as a tumor suppressor gene, studies were conducted using a splice variant of BRCA-1 delivered by a retroviral vector to both EOC cells in vivo, as well as in vivo tumors established in animal models (105). Results showed that overexpression of BRCA-1 could arrest tumor growth. Next, a human phase I trial at Vanderbilt University Cancer Center used a retroviral vector to deliver the splice variant BRCA-1 to patients with sporadic recurrent or persistent ovarian cancer (106). After three intraperitoneal injections, toxicity consisted mainly of self-limiting peritonitis in 25% of patients. Patients had antiretroviral antibody titers documented with high doses of vector, and Southern blot confirmed gene transfer to 5–10% of tumor cells biopsied at later laparoscopy. Of the 12 patients initially treated, 1 demonstrated a partial response, 7 showed stable disease, and 4 demonstrated disease progression.

Most research in corrective gene therapy of cancer has been conducted with the p53 tumor suppressor gene. Preclinical evidence suggests that p53 delivered by viral or liposomal vectors results in increased amount of apoptosis in EOC cells in vitro. Studies of intraperitoneal tumors in mice showed tumor regression as well (107–109). Von Gruenigen et al. (110) tested an adenovirus carrying the p53 gene driven by a cytomegalovirus (CMV) promoter. In vitro studies of OVCAR3 cells demonstrated transient high levels of p53 by Western blot. Cell cycle analysis revealed G1 arrest and apoptosis. In vivo studies examined microscopic intraperitoneal tumor xenografts in nude mice treated with multiple intraperitoneal injections of the virus. Overall survival was prolonged in treated mice when compared to controls. Therapy with p53 may affect tumor sensitivity to chemotherapy. Synergistic effects in EOC in vitro between p53 and platinum as well as paclitaxel have been reported (111,112). Gene therapy with p53 has also been noted to result in decreased expression of vascular endothelial growth factor (VEGF) (113) and increased Fas/FasL (114), indicating that inhibition of tumor angiogenesis or release of toxic metabolites or cytokines from apoptotic cells may be possible mechanisms for tumor response.

Significant clinical experience with the use of p53 gene therapy in human patients has been established in nonsquamous cell lung cancer (NSCLC). An adenoviral vector carrying p53 has been safely administered via bronchoscopic intratumoral injections

in phase I trials. A recently published series describes 52 patients with NSCLC treated with Ad.p53 with or without cisplatin (115). After 6 months of intratumoral administration, 16 of 26 patients receiving the Ad.p53 alone showed either a partial response or stable disease. The addition of cisplatin increased the progression-free survival. Transgene expression was documented in the treated tumor. Recently, adenoviral p53 gene therapy has also been tested in patients with EOC. No significant complications were observed in 37 EOC patients receiving i.p. injections of Ad.p53, and more than half of patients had documented decreases in serum CA125 levels (116).

Neutralization gene therapy strategies target overexpressed oncogenes through several different mechanisms. Some strategies utilize ribozymes, which are catalytic RNA sequences that bind to specific mRNA molecules and mediate their enzymatic cleavage (117). Another strategy uses triplex-forming oligonucleotides to target specific DNA sequences of oncogenes or growth factors (118). Stable triple helix formation results in functional inactivation of DNA due to disruption of transcription factor binding. Antisense oligonucleotides may also be engineered to bind and inactivate mRNA sequences (119). Antibodies targeting overexpressed proteins have also been used. While few oncogenes have been identified in EOC, K-ras, c-*myc*, and HER-2/neu may be suitable target for neutralization strategies (93).

Herceptin™, a monoclonal antibody directed against HER-2/neu, has been recently approved by the FDA for breast cancer and is currently being tested in patients with EOC. One strategy for HER-2/neu neutralization involves administration of a gene designed to encode an anti-HER-2/neu antibody (120). After transfection of EOC cells in vitro, measurable levels of intracytoplasmic antibodies could be detected. Decreased cell surface expression of HER-2/neu was also noted, possibly due to entrapment of newly synthesized proteins within the endoplasmic reticulum. Mouse models of intraperitoneal EOC tumors also demonstrated regression after treatment with the gene (121), and phase I trials in humans are currently underway (122).

Another neutralization strategy for HER-2/neu utilizes the adenoviral E1A gene product. This protein serves to suppress the HER-2/neu promoter, acting as a tumor suppressor gene in cells overexpressing nER-2/neu (123). Transfection of EOC cells with the E1A gene led to a dramatic reduction of the malignant phenotype in vitro and in vivo (124). A replication-incompetent adenoviral vector with intact E1A gene was administered intraperitoneally to immunosuppressed mice bearing EOC tumors, resulting in intratumoral expression of the E1A protein with an associated decrease in HER-2/neu expression and prolonged survival (125). Adenoviral E1A delivered via liposomes has been safely tested in phase I clinical trials at the M.D. Anderson Cancer Center in patients with metastatic breast or ovarian cancer with documented overexpression of HER-2/neu. Several patients experienced disease stabilization. Downregulation of HER-2/neu was observed in two patients, while E1A gene expression was documented in tumors and normal organs such as the kidney, the lungs, and the liver (75).

Immune Gene Therapy

Tumors are often poorly immunogenic and have escaped host recognition by inducing peripheral immune tolerance. Gene therapy for cancer is also beginning to address means of improving host recognition and destruction of tumor cells in preclinical

studies. Cytokine therapy is one promising area of research. Cytokines have been noted to have multiple effects on tumor immune biology. First, cytokines modify the function of antigen-presenting cells, T-lymphocytes, and other effector cells. IL-2, IL-12, tumor necrosis factor-alpha (TNF-α), IFN-γ, and granulocyte-macrophage colony-stimulating factor (GM-CSF) serve to activate the immune system, while IL-6, IL-10, transforming growth factor-beta (TGF-β), and vascular endothelial growth factor (VEGF) suppress dendritic cell (DC) and/or T-cell function (126). Aside from effects on the host immune system, evidence indicates that cytokines may also directly influence tumor cell proliferation and survival. Cytokines such as IL-1, IL-2, IL4-γ, and TGF-β have been shown to directly affect tumor cell growth. The specific effect exerted by these cytokines depends on several factors, including the intrinsic immunogenicity of the individual tumor, the composition of the surrounding extracellular matrix, as well as the types of cytokines and cytokine receptors expressed by the tumor itself. One example is IL-1, which, depending on the tumor, may show either cytocidal effects or promote metastatic spread (127,128).

Tumor immunogenicity may also be modified by exposure to various cytokines. For instance, immune system recognition and elimination of certain tumor cells may be improved through IFN-γ-mediated increased expression of MHC class I (129). The pattern of cytokines and chemokines present within the tumor environment controls leukocyte migration, modifies the type of inflammatory cell infiltrate activated by the tumor, and influences the type of memory mechanisms mediated by T-helper cells (126,130). Activation of a Th_1-type response mediates the delayed-type hypersensitivity reaction which is critical for tumor recognition and eradication, whereas a Th_2-type response, which stimulates allergic reactions, is ineffective against tumors.

Because of the abundance of evidence supporting the antitumor effects of various cytokines, clinical trials involving the systemic administration of interleukins, including IL-1, IL-2, and IL-12, have been initiated (131,132). Partial clinical responses, as well as the occasional complete response, have been noted in patients with melanoma, renal cell (133), colon, and ovarian carcinoma. Specifically in the area of ovarian cancer, several clinical trials using cytokines have been initiated. For example, preclinical evidence has demonstrated the ability of IL-2 to enhance the activation of lymphokine-activated killer (LAK) cells and cytotoxic T cells, thereby promoting the cytotoxic effect of autologous T cells against EOC cells. These findings have led to a phase I/II trial of i.p. IL-2 administration in patients with recurrent of progressive disease. In the 35 patients evaluated, the overall response rate was 25% and included six surgically confirmed complete responses (134). IL-12 is another cytokine under clinical study for use in ovarian cancer. The Gynecologic Oncology Group (GOG) protocol #170-B is currently ongoing in an attempt to evaluate i.v. administration of IL-12 in recurrent or refractory ovarian cancer. Interferon has also been administered to patients with ovarian cancer. While i.v. IFN yielded poor results (135), improved responses were observed with i.p. administration (136). In a recent GOG trial, intraperitoneal IFN-$\alpha_2\beta$ was noted to be well tolerated in patients with minimal disease residual. Although ineffective in platinum-resistant patients, measurable responses were noted in patients with platinum-sensitive disease (28% overall response, including 16% surgically documented complete response) (137). IFN-γ is another cytokine of interest in immunotherapy because of its ability to up-regulate expression of MHC class I molecules. A small phase II study carried out in recurrent ovarian cancer resulted in a clinical response in approximately 25% of patients (138).

A recent European multicenter randomized phase III trial in patients with stage Ic–IV ovarian cancer used subcutaneous systemic IFN-γ as adjuvant therapy to first-line cisplatinum and cyclophosphamide. A 3-fold prolongation of the disease-free interval was seen in the experimental arm compared to the control arm ($P = 0.031$) with similar toxicity profile in each group (139). Although this did not translate into an improved overall survival, the results are promising for the further use of biologic response modifiers as first-line treatment.

Several studies have examined the role of immunostimulatory cytokines in the gene therapy of cancer as well. Animal studies using colon cancer cells transfected with IL-2 for in situ vaccination have demonstrated induction of protective systemic immunity. The IL-2 served to maximize tumor cell immunogeniticity independent of helper T-cell interactions (140). Dranoff et al. (141) studied the effects of 20 different cytokines using a replication-incompetent retroviral vector which was used to transfect B16 cells, an immunologically inactive melanoma cell line, with different cytokine genes. Transfected cells were used for in situ vaccination. Granulocyte-macrophage colony-stimulating factor emerged as the most powerful cytokine. Analysis of the vaccine site showed an intense local inflammatory infiltrate; regional lymph nodes revealed enlarged paracortical T-cell areas, suggesting the presence of dendritic cell interactions with CD4+ and CD8+ T lymphocytes to induce activation and immune protection. Currently, multiple cytokine gene therapy trials for cancer are underway.

To date, work in the gene therapy of ovarian cancer has primarily focused on animal models. Syngeneic murine ovarian cancer has been successfully treated with cisplatin combined with lipofection of the IFN-γ gene into tumor cells (142). Cytotoxicity has been found to be mediated by nitric oxide. Liposomal vectors have been used to deliver IL-2 DNA to murine ovarian teratocarcinoma (MOT) cells in another syngeneic model, resulting in a local increase in IL-2, IFN-γ, and GM-CSF levels, with an associated decrease in ascites volume. A significant antitumor effect has been noted along with prolonged survival (143). Another cytokine, IL-12, has been tested in an ID8 syngeneic murine ovarian cancer model (144). After flank injection of cancer cells, mice treated concurrently with fibroblasts retrovirally transduced to express IL-12 in the opposite flank showed a decrease in tumor burden with no discernible evidence of IL-12-induced toxicity. The authors cited both immune and anti-angiogenic mechanisms for tumor response. Fibroblasts may be a safe and effective vehicle for delivery of IL-12 for antitumor therapy.

Other cytokines have been noted to play an immunosuppressive effect in the development of cancer. Transforming growth factor-beta may inhibit the immunostimulatory effects of IL-2. Transforming growth factor-beta is produced by many human ovarian cancers and has been found to inhibit activation of cytotoxic T lymphocytes. Dorigo et al. (145) engineered MOT cells to express TGF-beta antisense. When administered in vivo to mice in conjunction with fibroblasts retrovirally transduced to express IL-2, animals were protected against intraperitoneal tumor challenge. Both therapy with TGF-beta antisense and IL-2 were necessary for effective antitumor responses, suggesting that tumor cell expression of immunosuppressive factors may inhibit immune therapies of cancer.

Little work has been completed using human ovarian cancer. Hey-A8 human ovarian cancer cells have been tested after transduction with IFN-beta in nude mice (146). When transduced cells were injected intraperitoneally, no tumors developed, whereas wild-type cancer cells produced large tumors. Local IFN-beta production

increased the expression of nitric oxide synthetase in host macrophages, thereby inhibiting the in vivo growth of human ovarian cancer cells.

Optimal methods for inducing cytokine secretion in the tumor microenvironment are being investigated. The use of adenoviral vectors to transfect autologous cancer cells (147) has proven to be a successful strategy, resulting in high local levels of cytokine as well as a local inflammatory infiltrate. Others have engineered replication-competent oncolytic HSV to deliver GM-CSF (148). Granulocyte-macrophage colony-stimulating factor has been used in vitro to induce the differentiation of dendritic cells, the most potent antigen-presenting cells, from immature mononuclear cell precursors. Injection of the vector into tumor nodules also demonstrated local cytokine production and the induction of an antitumor immune response which enhanced oncolysis. Another approach for cytokine delivery has been reported (149). The investigators developed a universal carrier cell line to deliver GM-CSF by engineering MHC negative lymphoma cells which can secrete cytokines at the tumor site without inducing a dominant allogeneic anti-MHC response against the vector. When irradiated carrier cells and autologous tumor were administered together to animals with established tumors, sustained regression of the cancer was noted. This carrier line has also been used in humans to administer GM-CSF and has resulted in some clinical responses.

CONCLUSIONS

While physicians currently rely on cytoreductive surgery and chemotherapy to treat ovarian cancer, the tremendous advances in the fields of molecular biology and genetic engineering may signal the advent of multimodality approaches using gene therapy or immune therapy to complement traditional approaches. Although the field of cancer gene therapy is in a very early stage, additional investigation into the safety, feasibility, and effectiveness of various molecular therapies is desperately needed.

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Basic Concepts of Chemotherapy Sequence and Combinations

Francis Y. Lee
Pharmaceutical Research Institute, Bristol-Myers Squibb, Princeton, New Jersey, U.S.A.

Renzo Canetta
Pharmaceutical Research Institute, Bristol-Myers Squibb, Wallingford, Connecticut, U.S.A.

THE FUNDAMENTAL GOALS OF CANCER CHEMOTHERAPY

The ultimate goal of cancer chemotherapy is to reduce the tumor burden to the lowest possible level without intolerable toxicity. With very few exceptions, most notably choriocarcinoma, chemotherapy utilizing single agents had not been successful in prolonging patient survival, and in this regard, the introduction of combination chemotherapy in the early 1960s marked a major step forward. Combination chemotherapy is now the standard component for the treatment of most advanced cancers. In the following discussion of the fundamental concepts of combination chemotherapy, two major areas will be considered: the first will be the pharmacological rationale for the selection of chemotherapeutic agents to be used in combination, and the second will be the clinical considerations impacting on the administration of combination chemotherapy.

FACTORS INFLUENCING DRUG EFFICACY—THE CONCEPTS OF DIFFERENTIAL SENSITIVITY AND TUMOR HETEROGENEITY

Inherent in the rationale for the practice of modern chemotherapy is the fundamental concept that different cell populations, whether normal or malignant, may be differentially susceptible to the action of a given anticancer agent. The fundamental goal for chemotherapy is therefore to exploit the sensitivity differential between the cells that must be eradicated or controlled (clonogenic tumor cells) and the cells that must necessarily be spared (vital normal cells).

Differential sensitivity is, however, a double-edged sword. Although clonal in origin, tumors are almost always highly heterogeneous in their composition at diagnosis as a result of genetic instability (1). Within a solid tumor, only a fraction

of the tumor cell population would be responsive to a given single agent. Given this diversity, the need to eradicate as great a population of tumor cells as possible is one of the most compelling reason for combination chemotherapy.

Kinetics of Tumor Cell Kill—The Fractional Cell Kill Hypothesis

Most cytotoxic chemotherapeutic agents had been shown to follow the fractional cell kill hypothesis (2) which states that each given dose of a chemotherapeutic agent will kill a constant fraction of a tumor cell population, irrespective of the number of cells present at treatment initiation. For example (Fig. 1A), if a dose D of a given agent A reduces the survival fraction to 0.1 of the initial cell population (90% or 1 log cell kill, LCK), then a second but equal dose of the same agent given immediately after the first will reduce survival by the multiplicity of the survival fraction of the individual dose, i.e., $0.1 \times 0.1 = 0.01$ (99% or 2 LCK). Ideally, the fractional cell kill principle should apply equally to combination chemotherapy (Fig. 1B). Successful treatment regimens have usually combined two (or more) agents, each of which has significant antitumor activity on its own, and the activity of the combination should optimally approach the multiplicity of cell kill of each agent (that is, if Drug A produces 1 LCK and Drug B produces 2 LCK, the combination will produce 3 LCK).

Differential Sensitivity Based on Cell and Tumor Growth Kinetics

The vast majority of current anticancer drugs exert their action by affecting DNA synthesis or function. Consequently, proliferating tumor cells in active division cycle

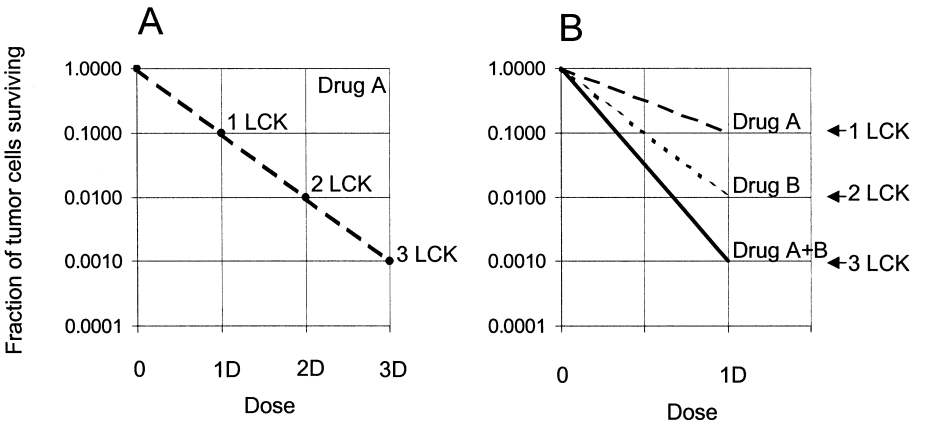

Figure 1 The fractional cell kill hypothesis (log kill rule) states that each equal dose of an agent kills the same fraction of cells irrespective of the initial cell number. (A) If dose D of Drug A kills 90% of initial cells (1 log cell kill), a second treatment with Drug A at the same dose given immediately after the first will kill 90% of the 10% remaining cells resulting in 99% cell kill (2 log cell kill). (B) Application of the log kill rule to combination chemotherapy. If a dose of Drug A produces 1 log cell kill by itself and Drug B produces 2 log cell kill, then an optimal drug combination of Drugs A and B should kill close to 3 log of cells or greater.

(mitotic cycle) are far more susceptible to the antitumor effects of most of the drugs. Resting cells are not killed unless such cells divide soon after exposure to the drug (3). In reality, however, all solid tumors are composed of various proportion of nonproliferating (usually >50%) and proliferating cell populations. The effectiveness of currently available anticancer drugs is therefore determined largely by the drug sensitivity of the proportion of cells that proliferates, termed the growth fraction (4) (see below for further discussion on the nonproliferating cells' role in drug resistance). Moreover, within the proliferating cell subpopulations that comprise the growth fraction, significant differences in drug sensitivity exist among cells in various phases of the cell cycle. As shown in Fig. 2, the mammalian cell cycle can be divided in four distinct phases. At mitosis (M), the cell divides to form two daughter cells. This is followed by a period of apparent inactivity, termed G_1 (or the first "gap"), in which cells are preparing for the next phase of the cycle, the S phase, where the cells actively synthesize DNA. Between S and the next cell division (M), there is another "gap" termed G_2. Seminal work pioneered by Bruce et al. (5) demonstrated that chemotherapeutic agents can be classified by their selectivity against cells in the various proliferative states. Agents that are preferentially active during a particular phase of the cell cycle (e.g., S phase) are referred to as cell cycle stage-specific (or Class I agents). The class of agents that is preferentially toxic against cells in active cycle but independent of the cell cycle phase is termed cell cycle stage-nonspecific (Class II agents) (Table 1). This classification of drugs based on their cell cycle se-

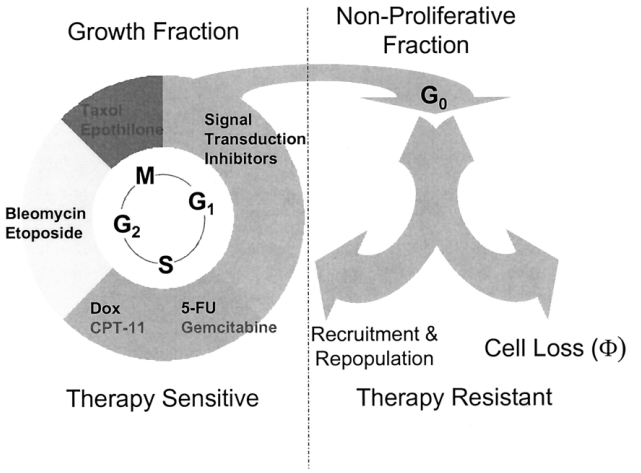

Figure 2 A solid tumor is comprised of proliferating (growth fraction) and nonproliferating cell populations. Cells in the growth fraction are in different stages of the cells cycle: G1, S, G2, or M. Almost all chemotherapeutic agents are preferentially toxic against proliferating cells. In addition, some agents are selectively toxic against cells in a particular stages of the cell division cycle (Class I agents). Other agents are equally toxic to cells in all stages of the cell cycle so long as the cells are cycling during drug exposure or will soon after (Class II). Nonproliferating cells are resistant to standard chemotherapy and may contribute to therapy failure as they may be recruited into the growth fraction following treatment that kills the existing proliferating cells.

Table 1 Anticancer Drugs Classification Based on Cell Cycle Phase Specificity

Class	Examples
Cell cycle phase specific (Class I)	G1: actinomycin D Early S: hydroxyurea, cytarabine, fluorouracil (5-FU), capecitabine, gemcitabine, methotrexate, irinotecan (CPT-11), topotecan Late S: doxorubicin (dox), daunomycin G2: bleomycin, etoposide, teniposide M: paclitaxel (Taxol), docetaxel, vincristine, vinblastine, vinorelbine, epothilone
Cell cycle phase nonspecific, proliferation-dependent (Class II)	Cytotoxic: cisplatin, carboplatin, nitrogen mustard, nitrosoureas Cytostatic: signal transduction inhibitors, anti-angiogenetic agents (see Table 2)

lectivity is a key consideration in the choice of agents for combination regimens, where the goal is to as far as possible allow for independent cell killing by each agent.

In addition to the traditional cytotoxic agents discussed above, emerging new classes of so-called cytostatic agents are playing increasingly important roles in the overall strategy of combination chemotherapy. These new classes of agents consist chiefly of inhibitors of growth signal transduction, some with anti-angiogenetic properties. A number of these are currently in early or advanced clinical development (Table 2). These agents, in general, do not kill cells directly but rather deprive cancer cells of the growth and survival signals that they are uniquely dependent upon. As a result, cell growth is inhibited and affected cells may eventually enter an apoptotic state. Thus, by definition, signal transduction inhibitors may also be classified as cell cycle stage-nonspecific agents (but proliferation-dependent). Because within a solid tumor the dependency on a particular signal for growth is heteroge-

Table 2 Emerging Agents Targeting Growth Signal Transduction

Targets	Examples of agents in development
Ras farnesyltransferase (ras-FT)	BMS-214662 (BMS), Zarnestra, R115777 (Janssen), SCH66336 (Schering)
Epidermal growth factor (EGF, Her1)	Erbitux, Cetuximob, C-225 (ImClone/BMS/Merck KGA); Iressa, ZD-1839 (Astra-Zeneca); Tarceva, erlotinib, OSI-774 (OSI/Genentech)
Her2-neu	Herceptin, trastuzumab (Genentech/Roche)
Bcr-abl	Glivec, imofinib STI-571 (Novartis)
Raf kinase	BAY 43-9006 (Bayer)
Mek kinase	PD 184352 (Pfizer)
Vascular epidermal growth factor (VEGF)	ZD-6474 (Astra-Zeneca), SU-5416 and SU-6668 (Sugen), PTK787 (Novartis)
Platelet-derived growth factor (PDGF)	SU101 (Sugen)

neous, there is currently a general view that cytostatic agents may most effectively be used in combination with traditional cytotoxic drugs. Another consideration is that, typically, cytostatic agents lack the classical normal tissue toxicity (e.g., myelosuppression and gastrointestinal toxicity) associated with traditional cytotoxic drugs and therefore may be optimally combined with cytotoxic agents without the complication of overlapping toxicity.

As alluded to earlier, another type of differential drug sensitivity/resistance arises from the suboptimal population growth kinetics of tumors. Cancer cells in laboratory cell culture systems appear unrestrained in their growth, proliferate as rapidly as they are able to, and are limited only by the intrinsic length of the cell division cycle and the availability of adequate supply of nutrient. In human cancers, however, not all of the cells in a tumor that are capable of dividing would actually proceed through cell division. In fact, at any given time, tumor cell populations in a tumor are composed of proliferating (P) and quiescent (Q) cells. Moreover, in human tumors, there is significant spontaneous cell loss. In effect, tumor growth is a function of net gain of cell proliferation over cell loss and is determined by three principal factors: (1) the cell cycle time (τ) of proliferating cells; (2) the growth fraction (GF) where GF = number of proliferating cells (P)/total number of cells (P + Q); and (3) the extent of cell loss (Φ). Tumor growth is typically measured as the time needed to double the volume (tumor volume doubling time, TVDT) and had been estimated to vary from a few days (6–8 days) to >300 days, with an average of about 60 days for a series of primary and secondary lung tumors. (6) Cell cycle time in culture, however, had been determined to be considerably more brief (range: 15–120 hr, average: 48 hr). The remarkably slower rate of clinical tumor growth is attributable to the fact that the GF in human tumors is much less than 1 (e.g., 0.02–0.29) (7), and the cell loss factor is exceedingly large, ranging from 50% to 96% in each cell cycle (8,9). As illustrated by the mathematical modeling of tumor growth (Fig. 3), a tumor that has a τ of 48 hr, GF = 1, and $\Phi = 0$ will double in volume in just

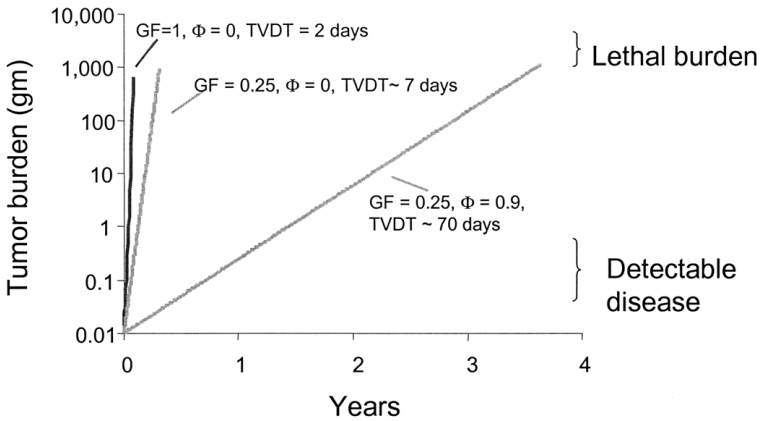

Figure 3 Mathematical modeling of the growth curves of human tumors with a constant cell cycle time of 48 hr but varying growth fraction (GF) and cell loss factor (Φ). These parameters, particular cell loss, clearly impact dramatically on the growth kinetics of human tumors and on the time at which lethal tumor burden is reached.

48 hr. Reducing the GF to 0.25 but keeping $\Phi = 0$ will result in TVDT of ~6 days. However, if $\Phi = 0.9$, the TVDT will become ~60 days. Clearly, both GF and Φ profoundly affect the growth kinetics of tumors. Thus in any consideration of the choice of agents in combination chemotherapy, one must ideally include not only agents that kill or control proliferating cells, but also those that affect the quiescent cell populations and thereby accelerate the rate of cell loss. It has been proposed that the therapy-resistant nonproliferating fraction contributes to treatment failure following chemotherapy and radiotherapy. Currently, there is no approved therapy against dormant or quiescent tumor cells.

Differential Sensitivity Based on Mechanism of Drug Action and Drug Resistance

It is well established that cancer cells can be intrinsically sensitive or resistant to a particular drug based on the drug's mode of action. Largely for this reason, only a fraction of patients of any cancer types respond to initial single-agent therapy. Because tumors are composed of highly heterogeneous populations, even those initially responsive will rapidly "acquire" resistance to a particular agent due to the presence of a small number of preexisting resistant tumor cells. Additionally, initially sensitive tumor cells can also become resistant through changes of their genetic makeup (10). Table 3 is an attempt to classify current and emerging cancer chemotherapeutics based on their mechanism of action. Table 4 summarizes the most frequently reported mechanisms of resistance to currently used cancer drugs. In selecting agents for combination chemotherapy, one of the accepted guidelines is to choose agents that have different mechanism of action and which have nonoverlapping mechanism of resistance.

CLINICAL CONSIDERATIONS IN COMBINATION CHEMOTHERAPY

In addition to the preclinical rationale for combining anticancer agents, based chiefly upon differences in mechanism of action, potential synergism, and the need to over-

Table 3 Major Drug Categories Classified by Mechanism of Action

Mechanism of action	Examples
Antimetabolites	Fluorouracil (5-FU), methotrexate, capecitabine, gemcitabine, cytarabine, mercaptopurine, thioguanine
Alkylating agents	Nitrogen mustard, chlorambucil, melphalan, cyclophosphamide, ifosfamide
Platinum agents	Cisplatin, carboplatin, oxaliplatin
Tubulin disruptive agents	Vincristine, vinblastine, vinorelbine
Tubulin polymerizing agents	Paclitaxel (Taxol), docetaxel, epothilone
Topoisomerase I inhibitors	Irinotecan (CPT-11), topotecan
Topoisomerase II inhibitors	Doxorubicin, daunorubicin, mitoxantrone, etoposide, teniposide

Table 4 Mechanisms of Resistance Applicable to Multiple Agents with Diverse Modes of Action

Mechanism of resistance	Associated agents
Multidrug-resistance (MDR, P-glycoprotein mediated)	Paclitaxel (Taxol), docetaxel, doxorubicin, daunorubicin, mitoxantrone, colchicine, vincristine, vinblastine, etoposide, teniposide, actinomycin D, topotecan, irinotecan (CPT-11)
Multidrug resistance-related protein (MRP)	Cisplatin, doxorubicin, daunorubicin, etoposide, teniposide
Lung resistance-related protein (LRP)	Doxorubicin, cisplatin, melphalan
Topoisomerase II (atypical MDR)	Etoposide, doxorubicin, m-AMSA
Thymidylate synthase	Fluorouracil (5-FU), capecitabine
Glutathione-related	Alkylating agents, platinum agents, ionizing radiation
DNA repair	Alkylating agents, nitrosoureas, platinum agents, ionizing radiation

come tumor resistance (intrinsic and/or acquired), there are also clinical considerations that influence the development of combination chemotherapy regimens.

The Overlapping of Clinical Toxicities

The difficulty in establishing superior combination regimens often arises from the inability to administer full dosages of each component of the regimen due to overlapping clinical toxicity. Because of this, the development of combination regimens has increased in complexity as the number of drugs available for combination has increased. The statisticians from the U.S. National Cancer Institute (NCI) have attempted to provide mathematical insights into the issue by graphically modeling the toxicity interactions that would guide the selection of promising combination regimens (Fig. 4) (11). For anticancer drugs that possess single-agent antitumor efficacy, the organ-specific maximum tolerated dose (MTD) has been identified (Table 5). This information is necessary in order to develop tolerable dose diagrams for two-drug combination regimens that would attempt to assess the interplay of different dose-limiting toxicities and, potentially, suggest margins of improvement if a specific organ-protecting agent (e.g., cytokines, antiemetics, renal protectants, antimucositis) was to be utilized. Examples of this evaluation, involving paclitaxel (TAXOL®, Bristol-Myers Squibb) and platinum agents, are offered in Fig. 5. The NCI model addresses mostly acute overlapping toxicities, and the development of combination regimens is further complicated when cumulative, long-term toxicities emerge from the combination of multiple agents (12,13). Doublets (two-drug regimens) involving classes with no or little overlapping toxicity have demonstrated significant superiority in at least two prospectively randomized trials in gynecological malignancies as in the case of taxanes and platinums in ovarian (14–18) and cervix (19) cancer, platinum and fluoropyrimidines in cervix cancer, (20,21), and doxorubicin and platinum in endometrial cancer (22,23). These doublets have had more

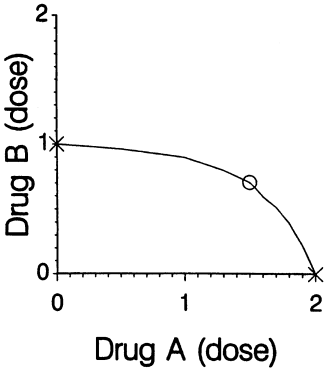

Figure 4 Tolerable-dose diagram for two hypothetical drugs. Points on or below the line represent dose combinations with tolerable toxicity. Circled point represents one particular MTD combination, 1.5 units of drug A and 0.7 units of drug B. (From Ref. 11.)

success than other combinations because of the possibility to administer full or near-full doses of each component (Table 6). Triplets have been more difficult to develop, and, although a meta-analysis of advanced ovarian cancer randomized trials suggests superiority of results when an anthracycline is added to an alkylator/platinum combination (24), results are less convincing when a platinum/taxane regimen constitutes the comparator (25).

Cell Resistance and Drug/Regimen Sequencing

Based on the development of mathematical models, Goldie and Coldman (10,26) have advanced the hypothesis that the emergence of resistant clones through cell

Table 5 Approximate Organ-Specific MTDs (mg/m^2)

	Drug				
Toxicity	Cisplatin	Carboplatin	Paclitaxel	Fluorouracil	Doxorubicin
Leukopenia	180	500 [a]	175 [b]	2,400	75
Thrombocytopenia	360	500	500	19,200	300
Mucositis	–	–	315	4,800	225
Cardiac	–	–	400	–	105[c]
Neurotoxicity	160	2,000	300	19,200	–
Renal	140 [d]	2,000	–	–	–
Emesis	240	1,600	500	9,600	225
Hepatic	–	2,000	–	–	–

Numbers in box represent the standard MTD.
Doses refer to single-dose, intermittent regimens (except for fluorouracil, daily × 5 days).
[a] Equivalent to area under the time–concentration curve (AUC) of 6 mg/mL, for a patient with adequate glomerular filtration function.
[b] Equivalent to 210 mg/m^2 when paclitaxel is administered over 3 hr infusion.
[c] Based on cumulative allowable dose of 525 mg/m^2 divided by 5 courses.
[d] A dose of 120 mg/m^2 is usually not exceeded.
Source: Ref. 11.

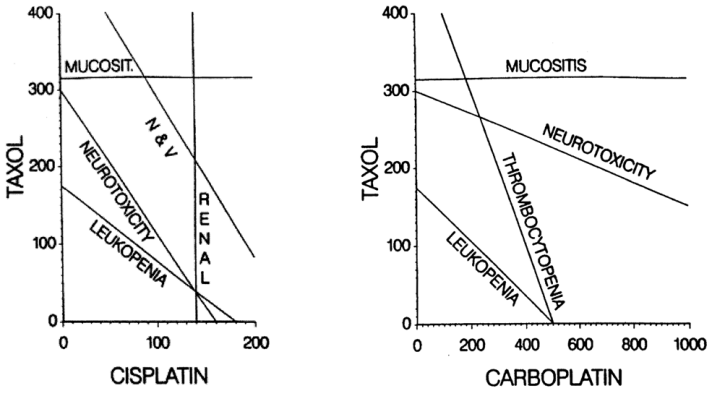

Figure 5 Tolerable-dose diagrams of paclitaxel (TAXOL®) and cisplatin or carboplatin. Dosages are expressed in mg/m^2. (From Ref. 11.)

mutations would be avoided by alternating active agents. However, this theory has been challenged by Norton and Simon (27), who suggested that a sequential approach would be more effective in reducing the tumor burden (Fig. 6). This hypothesis has renewed the interest on combination chemotherapy approaches that have utilized sequential cycles of full doses of each component of the regimen rather than concomitant administrations, either as sequential single agents (28) or as sequential doublets (29). This approach might prove valuable in avoiding overlapping toxicities, but it has not yet undergone a rigorous, prospective clinical evaluation in gynecological malignancies. In fact, the only clinical results that would suggest the validity of this approach come from indirect evidence from trials in advanced ovarian cancer that have not been originally designed to test this hypothesis (30,31). Effective sequential administration of individually active agents at full doses might also evolve into what has been referred to as a "dose-dense"

Table 6 Percent of Single-Agent MTDs Administered in Standard Regimens for the Treatment of Gynecological Malignancies

Combination		Dosage administered (mg/m^2)		Percent of MTD		
Drug A	Drug B	Drug A	Drug B	Drug A	Drug B	Ref.
Paclitaxel (24 hr)	Cisplatin	135	75	77%	54%	14,19
Paclitaxel (3 hr)	Cisplatin	175	75	83%	54%	15
Paclitaxel (3 hr)	Carboplatin	175	AUC 5	83%	83%	16
		175	AUC 7.5	83%	125%	17
		185	AUC 6	88%	100%	18
Fluorouracil[a]	Cisplatin[a]	1000 (×4)	75	33%	54%	20
		1000 (×4)	50	33%	36%	21
Doxorubicin	Cisplatin	60	50	80%	36%	22,23

See Table 5 for single-agent MTDs.
[a] Regimen associated with pelvic irradiation.

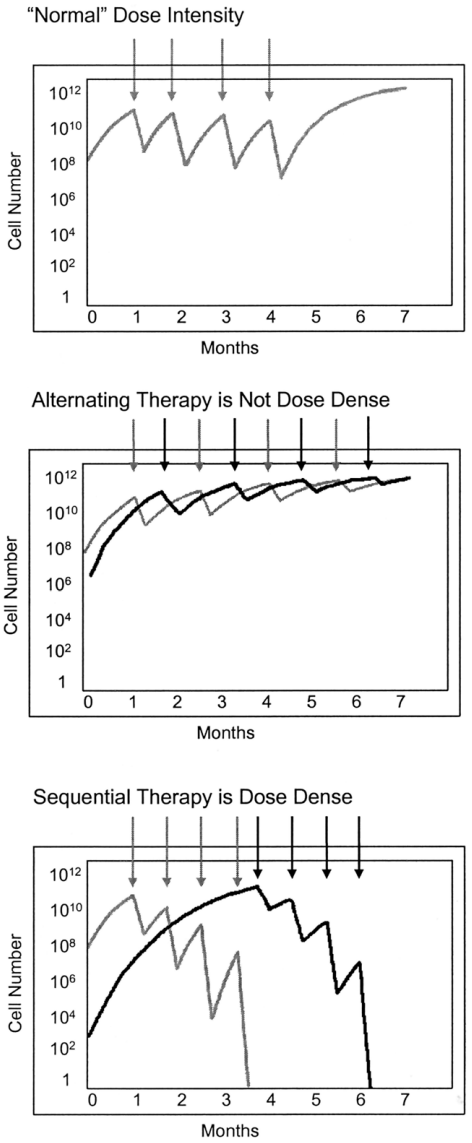

Figure 6 Cell kinetic models for alternating and sequential therapy. (Courtesy of Dr. Larry Norton.)

approach, in the attempt to reduce the tumor recovery and its possibility to develop resistance after the administration of full doses of each single active agent (Fig. 7). This approach requires intensive support with bone marrow growth factors and is currently being tested in several clinical trials in solid tumors, but not in gynecological malignancies (32). Another development has been the continuation of the attempts to establish high-dose chemotherapy regimens. Despite some success in hematologic malignancies, high-dose chemotherapy has failed to improve the clinical

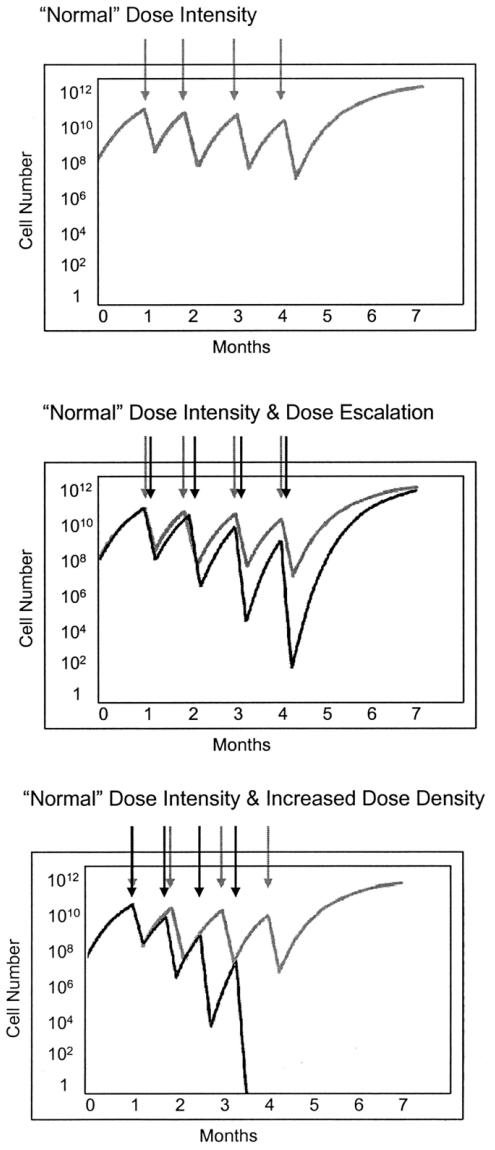

Figure 7 Cell kinetic models for high-dose and dose-dense therapy. (Courtesy of Dr. Larry Norton.)

results in solid tumors, particularly in breast cancer. Indeed, several randomized trials investigating the effectiveness of increasing the dosage of platinum-containing regimens have failed to improve the results in advanced ovarian cancer, as predicted by kinetic models (Fig. 7) and clinical experience (33,34). Randomized studies of high-dose chemotherapy in minimal residual disease, after standard induction chemotherapy is given to "chemically debulk" the primary tumor, are still ongoing in ovarian cancer (35).

Pharmacologic Interactions and Immediate Sequencing

In designing combination regimens, another important consideration must be kept in mind: the sequence by which the different components of the combination are administered has, in certain circumstances, proven critical for obtaining optimal results. In the context of this section of the chapter, we refer to the word "sequence" as the immediate temporal relationship between the administration of two (or more) drugs as components of the same regimen or course of therapy. A typical case is represented by the combination of prolonged infusions (24 hr) of paclitaxel and of cisplatin. Rowinsky et al. (36) have demonstrated, through elegant preclinical experiments in murine tumors followed by a clinical trial of different sequences of the combination, that there can be different outcomes, both in efficacy and in toxicity, if the sequence of administration of the two drugs is reversed (Table 7) (37). With this doublet, the sequence of paclitaxel followed by cisplatin yielded optimal results, both preclinically and clinically, and in terms of both efficacy (antitumor cytotoxicity in

Table 7 Sequence-Dependent Interactions

Drugs (infusion time) and sequence		Toxicity	Pharmacology	Ref.
Paclitaxel (24 hr)	→ Cisplatin (2 hr)[a]	–	–	37
Cisplatin (2 hr)	→ Paclitaxel (24 hr)	Neutropenia ↑	Paclitaxel clearance ↓ 33%	
Paclitaxel (24 hr)	→ Doxorubicin (48 hr)	Mucositis ↑	Doxorubicin clearance ↓ 33%, peak concentration and AUC ↑	38
Doxorubicin (48 hr)	→ Paclitaxel (24 hr)	–	–	
Paclitaxel (24 hr)	→ Cyclophosphamide (1 hr)	Neutropenia ↑ Thrombocytopenia ↑	Similar clearance in both cohorts for paclitaxel and cyclophosphamide	39
Cyclophosphamide (1 hr)	→ Paclitaxel (24 hr)	–		
Paclitaxel (3 hr)	→ Carboplatin (0.5 hr)	Similar effects in both groups	Similar in both groups for paclitaxel and carboplatin	40
Carboplatin (0.5 hr)	→ Paclitaxel (3 hr)			
Paclitaxel (3 hr)	→ Doxorubicin (bolus)	Similar effects in both groups	Doxorubicin peak concentration ↑	41
Doxorubicin (bolus)	→ Paclitaxel (3 hr)			

[a] This sequence produced better cytotoxicity in L1210 murine leukemia cells in vitro (36).

vitro) and safety (neutropenia in patients). Of interest, an observation of sequence dependency has been made for prolonged infusions of paclitaxel and doxorubicin or cyclophosphamide, but in these cases, the results were better in terms of toxicity, when paclitaxel was administered second (38,39). The reason for these results most likely resides in modifications of the metabolism of the selected drugs. This is indirectly confirmed by the observation that when short infusions (3 hr) of paclitaxel are utilized, no clinically significant sequence-dependent interaction for toxicity is observed for combinations with carboplatin (40) or with doxorubicin (41) (Table 7).

Potential interactions should always be evaluated whenever hepatic or renal metabolism interference is anticipated. Reduced organ clearance induced by interactions at the level of cytochrome P450 liver enzyme complex is a phenomenon that has been well described (42) and that can be anticipated, as in the case of the taxanes and of the anthracyclines. The same concept holds true when an agent is eliminated by the kidneys (43), as in the case of the platinums. It is important to keep in mind that these considerations might apply not only to the anticancer agents selected for the combination regimen, but also to frequently utilized supportive care or premedication drugs.

A different aspect of combination therapy involves combined modality approaches, when chemotherapy is associated together with radiation therapy in the attempt to increase DNA damage and/or affect DNA repair mechanism. This approach has proven particularly important in the treatment of cervix cancer, a disease for which the neo-adjuvant or concomitant administration of chemotherapy has produced results superior to those obtained by radiotherapy alone (20,44,45). In this situation, drugs that lend themselves to concomitant, continuous administration during the period of irradiation would present an obvious theoretical advantage.

Newer Combinations

Protectant Agents

A number of supportive care treatments have become available or are being investigated whose aim is to reduce certain therapy-induced toxicities. Besides the already mentioned bone marrow growth factors for the protection from myelotoxicity (leukopoietins and erythropoietins), potent antiemetics, renal protectants, antidiarrheals, cardioprotectants, antimucositis, and bone-resorption inhibitors have added to the possibility to develop multidrug combinations that would be less affected by certain dose-limiting toxicities. Unfortunately, no effective protectant of neurologic toxicity has yet been approved for general use (Table 8). It is very important that the possibility of drug–drug interactions be always kept in mind, especially when multiple agents are simultaneously administered.

Newer Agents

Whereas the investigation of novel classes of cytotoxic agents with novel mechanisms of action is still being actively pursued, the recent years have witnessed the discovery and the development of new classes of therapeutic agents, commonly (and sometimes improperly) referred to as cytostatics.

The avenues of research that have been most vigorously investigated involve signal transduction inhibitors, compounds able to interfere with biomolecular pathways of cell proliferation and/or apoptosis, and the anti-angiogenesis agents, compounds able to interfere with the process of metastasization and neovascular

Table 8 Drugs Specifically Approved in the United States as Adjuncts to Antineoplastic Therapy

Compound	Indication
Allopurinol	Hyperuricemia
Amifostine	Nephrotoxicity, xerostomia
Dexrazoxane	Cardiomyopathy
Dolasetron	Emesis
Dronabinol	Emesis
Epoetin	Anemia
Filgrastim	Neutropenia
Fluconazole	Candidiasis
Granisetron	Emesis
Levamisole	Adjuvant to fluorouracil
Levothyroxine	Hypothyroidism
Mesna	Cystitis
Octreotide	Diarrhea
Ondansetron	Emesis
Pamidronate	Hypercalcemia
Pilocarpine	Xerostomia
Sargramostim	Neutropenia

Source: Physicians' Desk Reference, 2001 (Edition 55), Medical Economics Company.

formation. None of these agents, as of yet, has been definitively proven to have a role in the management of gynecological malignancies. However, the extent of ongoing preclinical and clinical research as well as early results of these investigations promise that, sooner or later, these therapeutic modalities will be added to the current oncologic armamentarium of gynecological oncologists.

For signal transduction inhibitors, inhibitors of the ras-farneslytransferase (ras-FT) pathway and of the epidermal-growth factor (EGF) pathway seem to hold most promise. The interest of ras-FT inhibitors, several of which have currently entered clinical development, resides not only in their novel mechanism of antitumor action, but also in their high potential for enhancing the effect of standard (46,47) and of newer experimental chemotherapeutic agents (48). Moreover, the selective effect of some of these compounds on nonproliferating, quiescent tumor cell subpopulations offers great promise for combination regimens aimed at the whole tumor cell population (49). The EGF inhibitors also offer promising potential, both as single agents or as enhancers of standard chemotherapy (50–52). In addition, they present the potential for enhancing radiation therapy (53), and they could provide a selectively targeted approach to certain gynecological malignancies, such as ovarian and cervix cancer, that frequently carry overexpression of the EGF receptor. Finally, cell cycle inhibitors such as flavopiridol (54) or newer, more specific agents (55) could also prove to be of value. For the proper incorporation of these molecularly targeted therapeutics in standard regimens, several of the considerations expressed before in this chapter could be repeated, particularly for the immediate sequencing-related aspects of compounds that target different phases of the cell cycle. As a final consideration concerning the broad category of signal transduction inhibitors, combining

several molecularly targeted agents is a promising future development, provided their inhibitor effect is played on alternative cellular pathways.

For agents directed at affecting the neo-formation of vasculature and/or the seeding of metastatic foci, similar mechanistic considerations also apply. Whether their effect will be best in sequential use after initial "pharmacological debulking" or in concomitant use with other more traditional treatment modalities still remains, at this point, to be seen. Of interest, some preliminary results obtained with matrix metalloproteinase inhibitors seem to suggest a better effect in patients without established distant metastatic disease (56).

PHARMACOGENOMICS

One of the most recent developments in cancer research has been the advent of genomics. The expression of certain genetic characteristics can be assessed today through evaluation of nucleic acid microarrays in tumor specimens. Whereas, in the past, broad correlations of this information have been made mostly with overall historical disease outcomes, it is now possible to more specifically correlate certain genetic characteristics with resistance or with responsiveness to specific antitumor agents, whereby the term pharmacogenomics or oncopharmacogenomics was born. Investigation of these genetic expressions and prospective validation of their prognostic value could make possible the development of combination therapy regimens "custom-tailored" to the specific characteristics of individual tumors and of individual patients.

Although several retrospective correlation studies have been undertaken, a prospective clinical trial addressing this issue in gynecological malignancies has not yet been launched, at this time. However, accumulating the information that would render these kind of clinical trials possible represents one of the most exciting activities in current translational research.

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8

Pharmacoeconomic Applications in Gynecologic Oncology

Judith A. Smith
The University of Texas M. D. Anderson Cancer Center, Houston, Texas, U.S.A.

INTRODUCTION

Background

In today's healthcare system, there is an overriding theme to provide cost-effective medical care. The similarity between healthcare services and other economic goods and services was first describe in the 1960s in the seminal article by Kenneth Arrow. Since this time, health economists have worked to develop appropriate analytical methods to compare the cost of medical treatments against the clinical benefits. The process is most commonly referred to as pharmacoeconomics in medical practice because of the strong motivation from pharmaceutical companies to demonstrate that new treatments are cost-effective (1).

In pharmacoeconomics, the goal is to provide the optimal medical care with the resources of a given budget. Demonstrating that a treatment alternative is effective is no longer sufficient because another treatment may achieve the same outcome for a lower cost. Thus pharmacoeconomic methodologies provide a formal scientific approach to justify allocating resources for the preferred treatment pathways to obtain the desired clinical outcomes. Economists depend heavily on the judgment of healthcare providers to help place a value on the desired clinical outcomes (1). It is assumed when conducting pharmacoeconomic analysis that the treatment alternative that will provide a given population with more benefit per dollar is the preferred choice. However, due to unavoidable healthcare budget constraints, issues of equity sometimes arise because of the ethical issues associated with these assumptions (2). Nevertheless, cost-effective analysis operates under this basic assumption to maximize the total benefit using the available resources, even if, in some cases, this will translate to only providing a treatment alternative for a selected portion of the population.

Pharmacoeconomic Model

A pharmacoeconomic evaluation is a continual process used to provide decision makers with the necessary relevant information to use for selecting treatment options. Reassessment of a given analysis should be a continual process as new treatment

alternatives are put forth. Thus pharmacoeconomics is a circle of reoccurring steps (3). This includes the initial development of treatment protocol, pharmacoeconomic analysis methods, interventions to be compared, and the assessment of the economic cost for each intervention than a critical data analysis to provide adequate feedback to the decision makers to continually revise and improve the treatment protocol or guidelines.

Decision Rules

Decision rules are implemented to provide some guidance to aid in the selection of the optimal cost-effective treatment. Decision rules usually are based upon the budget constraints or medical necessity. Budget decision rules will define the amount of resources that will be spent for treating a certain patient population or to gain a unit of clinical benefit (4). Medical necessity defines the treatment intervention that should be offered or whether or not a treatment intervention should be provided for a specific person or situation (5). As a decision rule, medical necessity will define the tradeoff of providing a treatment as an option for all patients that may benefit while restricting it from those less likely to benefit. Again, issues of equity become an ethical concern when employing this method in pharmacoeconomic analysis.

METHODOLOGIES

Cost-Effectiveness Analysis

The traditional approach used in pharmacoeconomic analyses is the cost-effectiveness analysis (CEA). In CEA, the clinical effects of alternative treatments are compared to the net costs of each treatment. There are four fundamental stages for developing a CEA to evaluate new treatment alternatives: identification of the costs, measurement of costs, valuation of the cost data, and identifying whose perspective will be used for the CEA (6,7).

When designing a CEA, the identification of the costs for each treatment is the first crucial step. The cost for treatment may be broken down to four categories including medical direct costs, nonmedical direct costs, indirect costs, and intangibles (8–10). Medical direct cost would include the cost of hospitalization, drug costs, health professional time fees, laboratory test costs, rehabilitation services, and long-term care costs. On the other hand, nonmedical direct costs would include the cost of childcare, transportation, lost time from work, and costs to meet special dietary needs. Similarly, indirect costs generally include those items that the patient has to "pay out of pocket" such as loss of income, caretaker loss time from work, insurance co-pays, premature death reducing lifetime earning potential, and decreased productivity (3,6). Finally, intangible costs include those things that are very difficult to determine a value, such as quality of life, pain and suffering, or treatment adverse effects. In traditional CEA, indirect and intangible costs are not included and the focus is more on direct costs. However, other methodologies that are discussed in this section will include these costs in the identification of costs.

After all costs are identified, the next important step is to determine a method for measuring the cost in comparable natural units, i.e., life years saved. A cost-effectiveness ratio (CER), which represents the cost per unit of health effect, is often the

measurement unit used for CEA (11). In this ratio, the numerator is the cost of the treatment and the denominator would be the clinical effect under consideration, i.e., progression-free survival. Cost-effectiveness ratios for different treatments are then ranked and compared in league tables that will assist in the clinical decision process and in justifying resource allocations (9).

Another component that will contribute to the decision process is the valuation of the costs. The valuation phase is achieved by determining the comparable local cost for goods and services based on market prices, computing the cost for time lost from work, using disability and rehabilitation payments to estimate lost of productivity, and reviewing input from the policymakers that will influence the healthcare costs (6). Negotiations between healthcare administrators, government, and private insurance companies often determine the cost for the goods and services provided. One controversial component of the valuation process of CEA is the practice of discounting. In this practice, future costs and gains are discounted by a fixed annual percentage, typically 3% to 5% (12,13). Discounting has been implemented in many CEA to account for time preference and society consumption. Although it has been well accepted that future monetary costs or savings should be discounted, the discounting of health benefits such as life years saved has not been looked upon as favorable. For instance, a patient may appreciate saving $500 today by using a less-expensive treatment alternative rather than waiting 5 years to receive that $500. Health benefits are more difficult to ascertain because an immediate health benefit may seem more attractive in the present day, but perhaps not as attractive when the future arrives. Discounting nonmonetary health cost and benefits calls for some degree of speculation.

The perspective that is used for a CEA will influence valuation of the cost considerably. The different perspectives that can be utilized are society, patient, insurance company, hospital, or pharmaceutical industry (7,13). From a societal perspective, all costs and all benefits are included in the CEA regardless of who incurs the costs or receives the benefits from the treatment. When evaluating a treatment from patients' perspective, the CEA would focus more on "out-of-pocket" expenses and other indirect costs to the patient. If the CEA is going to use the insurance companies' perspective, the valuation of cost would be based on what charges the insurance companies will allow. However, the hospital or institutional perspective would want to use the actual cost for services and resources associated with providing a new treatment alternative. The industry perspective would focus on the financial benefit to the company, and this perspective is not applicable to the healthcare decision process and rarely used for making clinical decisions. When comparing different CEA studies, it is important to consider and compare the perspective used for the CEA.

Cost Minimization Analysis

Cost minimization analysis (CMA) is one of the basic, straightforward cost analyses used in pharmacoeconomics (12). The monetary costs of alternative treatments are compared, and the least costly alternative is selected as the preferred treatment. Only the direct cost of the treatment such as drug cost is included in this approach. Often, institutions that are working with a limited budget and making formulary decisions will use the CMA approach for making clinical decisions regarding what drugs or

devices will be provided. The limitation associated with the approach for pharmacoeconomic analysis is the assumption made that all the treatment alternatives are equally efficacious (1,7).

Cost Benefit Analysis

Cost benefit analysis (CBA) will provide a comparison of alternative treatments in monetary terms. Thus the first step for CBA requires a monetary value be assigned to the clinical benefits of a particular treatment so that both the numerator and denominator of the CER are in the same units (6). To accomplish this objective, CBA uses individual spending decisions to estimate the monetary value of a clinical benefit. One of the limitations of the use of CBA is that many healthcare providers are hesitant to assign a monetary value to a year of life, and this is required for identifying the costs for a CBA. The most common approach for determining the value of the intervention is the "willingness to pay" (WTP). Again, there are different perspectives to consider when determining WTP, a healthy volunteer (ex ant insurance), a patient (ex post user), family member of a patient, or healthcare provider (12,14). Often, a survey is used to ascertain the WTP from all these different perspectives. For example, a patient that has a specific disease or ailment would be given all the relevant information regarding a new treatment such as adverse effects and potential clinical benefits and then would be asked what their WTP is for the new treatment. At the same time, a healthy volunteer would also be presented with the same information and then asked what would be their WTP for the new treatment. By gathering the WTP information from all perspectives, the monetary value can be estimated more accurately for the CBA.

Cost Utility Analysis

Cost utility analysis (CUA) is intended to measure the utility of the clinical effects gained from a treatment alternative. Utility is the inclination of an individual or society toward a particular desired set of health outcomes (8). This approach will allow for different health outcomes, including morbidity and mortality, to be compared (15). Utility assessment can be measured by the gamble (What is the patient willing to risk to return to perfect health?), time tradeoff (What life expectancy the patient is to lose to return to perfect health now?), or rating scale approach [evaluating the quality of life (QOL) desired] (7). By evaluating the individual preferences for different health conditions and adjusting the monetary values of the interventions needed to achieve those conditions until they are unable to choose between these options measures the utility of a treatment or intervention. The final ratio of cost of treatment and health condition or clinical benefit defines the utility of the treatment option.

The common unit of measurement used in CUA is the quality-adjusted life year (QALY), or health year equivalents (HYE), to capture both the quality and quantity of life gained (7). A matrix that classifies health states in regards to disability and levels of distress is used to determine quality of life scale and then multiplied by the number of years spent in this state will determine the QALY. An advantage of CUA is that the QALY of various treatments can be compared to assist in the clinical decision process.

Assessing Treatment Benefits

It is probably apparent at this point that the determination of value of treatment interventions is a critical component of pharmacoeconomic analyses. The *Markov model* is a process to estimate the outcome of a clinical situation in which the patient is repetitively exposed to a specific risk. The objective is to define the pertinent health conditions and transitions and the likelihood of each outcome. This information can be useful for decision analysis and determining costs of treatment.

Another instrument used is the *Gompertz model* to determine the survival benefit between two or more treatment groups (16). The survival curve is extrapolated out to infinity but does not take quality of life into account. On the other hand, the Q-TWIST method will evaluate survival benefits with respect to duration and QOL. There are three cohorts to stratify patients for the Q-TWIST assessment. The first cohort includes the survival of those patients that are symptom-free and with toxicity that is used to define the TWIST (time without symptoms and toxicity). The second cohort includes the survival of patients with treatment-associated toxicity that is used to define the TOX (time spent with toxicity). The last cohort includes the survival after patients relapse (REL). The Q-TWIST method cannot be used for lifetime analysis because it does not account for life expectancy or discounted survival values. However, the Gompertz model and Q-TWIST method have been successfully combined for conducting lifetime CUA (16).

EVALUATION OF PHARMACOECONOMIC ANALYSES

Important Components of Pharmacoeconomic Analysis

Before implementing the recommendations of any pharmacoeconomic analysis, the analysis design and methodology should be critically evaluated (9,17). First and foremost, the study question should be clearly stated. Each analysis should define the costs being evaluated including direct costs, indirect costs, and intangible costs. Consider if the measurement and valuation of the cost seem suitable and accurate. In addition, determine if future cost was discounted and if the fixed rate was appropriate. Also, the perspective that was used for conducting the pharmacoeconomic analysis should be identified for the reader. Moreover, determine if the perspective used is relevant to your practice. Finally, the type of pharmacoeconomic analysis method that was used for comparing the treatment options should be included. Based on your clinical experience, consider if the study question, costs, perspective, and methods are reasonable and acceptable.

Sensitivity Analysis

Upon completing a pharmacoeconomic analysis, a sensitivity analysis can be used to identify the assumptions that acutely influence the results and the sensitivity of the results to deviations in the initial assumptions (1,7). This is often used to demonstrate the range of economic outcomes that could result from the analysis itself. In other words, the sensitivity analysis will demonstrate the uncertainty of the results. To complete a simple sensitivity analysis of the data, an important component of the calculation is substituted with a wide range of conceivable values and the CER is

recalculated, providing the range of results. The sensitivity analysis reveals the strength of the conclusions from the pharmacoeconomic analysis.

APPLICATIONS OF PHARMACOECONOMIC ANALYSIS IN GYNECOLOGIC ONCOLOGY

With a growing aging population and shrinking healthcare budgets, pharmacoeconomics is a relevant concern to consider in creating treatment options for gynecologic malignancies. Providing healthcare at the end of life is associated with higher costs than at any other time, and unfortunately, most patients with cancer will eventually die from it (18). Previously, most economic analyses in the oncology area have focused on the economic burden to society for the treatment of cancer or one specific cancer (19,20). Most recently, CBA have demonstrated that palliative care, despite its modest benefit, is cost-effective based on patients' expectations and WTP (15,18). Currently, the trend in economic analyses in the oncology arena is moving to measurements of QOL (i.e., QALY) and prolonging life (i.e., overall survival, progression-free survival, and response rate) as the primary clinical benefits when evaluating new chemotherapy treatment options (8,21). New treatment options should be compared against the standard treatment defined as those regimens being used in clinical practice.

The paclitaxel plus platinum regimen is the current accepted standard of care for first-line treatment of advanced ovarian cancer (22–24). In 1996, when paclitaxel was first being evaluated for first-line treatment, the significant cost of this plant-derived agent was evaluated. Cowens et al. (25) completed a CEA from a providers' perspective of the paclitaxel and cisplatin regimen. This study concluded that paclitaxel added a benefit and could be considered for first-line treatment of advanced ovarian cancer. In a CUA pharmacoeconomic analysis of amifostine conducted in the United States, the analysis determined that amifostine had both a clinical and cost benefit compared to other medical therapies (8). A CBA completed in Canada also supported that amifostine would be a cost-saving addition to cisplatin regimens (8). In another CBA by Rose and Lappas (26), it was demonstrated that addition of cisplatin to the standard radiation for the treatment of advanced cervical cancer provided a substantial benefit at an acceptable cost compared to radiation alone. These are just a few examples of how pharmacoeconomic analyses have been employed to justify the addition of new agents to standard of care for the treatment of gynecologic malignancies. As the allocation of resources for healthcare costs becomes more and more regulated, the appropriate use of pharmacoeconomic analyses will assist in the clinical decision analysis of which therapies are beneficial and cost-effective for the optimal treatment of gynecologic cancers.

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9

Guidelines to Writing a Clinical Protocol

Edward L. Trimble
National Cancer Institute, Bethesda, Maryland, U.S.A.

Writing a clinical protocol initially appears to be a daunting task. By taking advantage of templates that are available electronically, however, you can draft a protocol relatively easily. Protocol templates for phase I and II clinical trials are available on a website of the Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI) [http://ctep.cancer.gov/guidelines/templates.html]. These templates are used commonly by investigators developing studies through the Gynecologic Oncology Group or NCI-designated Cancer Centers. The major goal in writing a protocol must be clarity. You want the doctors, nurses, and pharmacists who read your protocol to understand exactly what to do at each step of the process.

The title page should include the title of the protocol and the lead investigators, including the statistician and nurse. Physicians and nurses who are caring for patients on this study need to be able to contact the doctor and nurse conducting this study for questions.

TITLE: A Phase 2 Study of *Study Agent* in *Study Disease*

Use MedRA terminology for study disease. Please refer to the CTEP home page (http://ctep.cancer.gov/guidelines/codes.html) *for a complete list of IMT disease terms.*

Coordinating Center:	*Name of Organization* *(If this is a multi-institution study, only one organization/institution can be the coordinating center.)*
***Principal Investigator:**	*Name* *Address* *Address* *Telephone* *e-mail address*

Co-Investigators:	*Name* *Address* *Address* *Telephone* *e-mail address* *Name* *Address* *Address* *Telephone* *e-mail address*

*A study can have only one Principal Investigator. The Principal Investigator must be a physician and is responsible for all study conduct. Please refer to the Investigator's Handbook on the CTEP home page for a typical description of the Principal Investigator's responsibilities (http://ctep.cancer.gov/handbook/index.html).

If the study is to be conduced in the United States, using a drug sponsored by the NCI, then the Principal Investigator and all physicians responsible for patient care must have a current FDA form 1572 and CV on file with the NCI. Failure to register all appropriate individuals could delay protocol approval. If you are unsure of an investigator's status, please contact the Pharmaceutical Management Branch, CTEP, at (301) 496-5725.

If this is a multi-institution study, the protocol title page should include the name of each participating institution, the investigator responsible for the study at that institution, and his/her phone number. (This requirement does not apply to Cooperative Group studies.)

Statistician: *(if applicable)*	*Name* *Address* *Address* *Telephone* *e-mail address*
Responsible Research Nurse:	*Name* *Address* *Address* *Telephone* *Fax* *e-mail address*
Responsible Data Manager:	*Name* *Address* *Address* *Telephone* *Fax* *e-mail address*
NCI-Supplied Agent:	*Study Agent (NSC #; IND #)*

SCHEMA

Please provide a schema for the study. If preferred, a summary or synopsis may be provided. This section should outline the design of the study in one page or less, so that readers can quickly learn about the study.

The next page should be a table of contents. This permits anyone reading the protocol to find a specific section quickly.

TABLE OF CONTENTS

1. OBJECTIVES

This section should be brief, with no more than 1–2 sentences for each objective

1.1 Please insert primary protocol objectives, such as response rate or time to progression of disease.
1.2 Please insert secondary protocol objectives, if pertinent. These might include survival and/or correlative studies.

2. BACKGROUND

This section should be more detailed, possibly as long as 2–4 pages.

2.1 Study Disease

Please provide background information on the study disease.

2.2 Study agent

Please provide background information on the investigational study agent, including information to support safety issues and the rationale for the starting dose chosen. The pharmaceutical company who developed the drug or the NCI should be able to supply you with this information.

2.3 Rationale

Please provide the background rationale for evaluating this therapy in this disease. Why do you want to study this drug? Does the biology of this particular cancer suggest that the new agent will be effective? Were responses seen in phase I studies of this agent?

3. PATIENT SELECTION

In this section, you need to spell out exactly what patients should be recruited for your study.

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed *Study Disease*. Please specify eligible disease(s)/stage(s) using International Medical Terminology (IMT) terms (http://ctep.info.nih.gov/code sand.htm).

3.1.2 Please insert appropriate criteria for the particular patient population. Note: lesions are either measurable or nonmeasurable using the criteria provided in Section 9. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy. Suggested text is provided below.

Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm with conventional techniques or as $\geq$10 mm with spiral CT scan. See Section 9.2 for the evaluation of measurable disease.

3.1.3 Please state allowable type and amount of prior therapy. Define as appropriate any limitations on prior therapy and the time from last prior regimen (e.g., no more than six cycles of an alkylating agent; no more than 450 mg/m^2 doxorubicin for agents with expected cumulative cardiotoxicity). Include separate definitions for duration as needed (e.g., at least 4 weeks since prior chemotherapy or radiation therapy, 6 weeks if the last regimen included BCNU or mitomycin C). Include site/total dose for prior radiation exposure as needed (e.g., no more than 3000 cGy to fields including substantial marrow).

3.1.4 Age < / > # years. Please state reason for age restriction. If applicable, the following text can be used.

Because no dosing or adverse event data are currently available on the use of *Study Agent* in patients < 18 years of age, children are excluded from this study but will be eligible for future pediatric single-agent trials, if applicable.

3.1.5 Life expectancy of greater than [#weeks or months].

3.1.6 ECOG performance status $\leq$2 (Karnofsky $\geq$ 60%; see Appendix B).

3.1.7 Based on the known toxicity of the study agent, you may need to modify the requirements for normal organ and marrow function. Standard requirements are as follows: Patients must have normal organ and marrow function as defined below:

• leukocytes	$\leq$3000/μL
• absolute neutrophil count	$\leq$1500/μL
• platelets	$\leq$100,000/μL
• total bilirubin	within normal institutional limits
• AST(SGOT)/ALT(SGPT)	$\leq$2.5 X institutional upper limit of normal

• creatinine	within normal institutional limits
OR	
creatinine clearance	≤60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

3.1.8 Please insert other appropriate eligibility criteria.

3.1.9 Please use or modify the following paragraph as appropriate.

The effects of *Study Agent* on the developing human fetus at the recommended therapeutic dose are unknown. For this reason and because *Agent Class* is known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.10 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

You must make clear who should not be in your study.

3.2.1 Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

3.2.2 Patients may not be receiving any other investigational agents.

3.2.3 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to *Study Agent*.

3.2.5 *Please insert appropriate agent-specific exclusion criteria.*

3.2.6 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.7 *The Investigator(s) must state a medical or scientific reason if pregnant or nursing patients or patients who are HIV-positive will be excluded from the study. The full text of the Policies, Guidelines, and Procedures pertinent to this requirement is available on the CTEP home page (http://ctep.cancer.gov/guidelines).*

Pregnant women are excluded from this study because *Study Agent* is *a/an Agent Class* agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse

events in nursing infants secondary to treatment of the mother with *Study Agent*, breastfeeding should be discontinued if the mother is treated with *Study Agent*.

Because patients with immune deficiency are at increased risk of lethal infections when treated with marrow-suppressive therapy, HIV-positive patients receiving combination antiretroviral therapy are excluded from the study because of possible pharmacokinetic interactions with *Study Agent*. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.3 Inclusion of Women and Minorities

Both men and women and members of all ethnic groups are eligible for this trial. The proposed study population is illustrated in the table below. *[Use prior phase 2 data from your institution.]*

	Race/Ethnicity					
Gender	White, not of Hispanic Origin	Black, not of Hispanic Origin	Hispanic	Asian or Pacific Islander	Unknown	Total
Male						
Female						
Total						

Full text of the Policies, Guidelines, and Procedures pertinent to this section is available on the CTEP home page (http://ctep.cancer.gov/guidelines).

4. TREATMENT PLAN

4.1 Agent Administration

Treatment will be administered on an *inpatient/outpatient* basis. Expected adverse events and appropriate dose modifications for *Study Agent* are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Refer to the CTEP home page (http://ctep.cancer.gov/guidelines/nomenclature.html) for Guidelines for Treatment Regimen Expression and Nomenclature.

Please describe the regimen and state any special precautions or warnings relevant for study agent administration (e.g., incompatibility of the agent with commonly used intravenous solutions, necessity of administering agent with food, premedications, etc.).

4.2 Supportive Care Guidelines

Please state guidelines for use of appropriate supportive care medications or treatments.

4.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for *[# cycles]* or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5. EXPECTED ADVERSE EVENTS/DOSE MODIFICATIONS

5.1 Expected Adverse Events Associated with *Study Agent*

Please describe the expected adverse events associated with the study agent, identifying dose-limiting adverse events with bold or underlined type. A list of the expected adverse events for investigational study agent(s) supplied by CTEP is provided as an attachment to the approved Letter of Intent (LOI) response.

5.2 Dosing Delays/Dose Modifications

Treatment plans should explicitly identify when treatment (typically dosage) modifications are appropriate. Treatment modifications and the factors predicating treatment modification should be explicit and clear. If dose modifications are anticipated, please provide a dose de-escalation schema with treatment modifications expressed as a specific dose or amount rather than as a percentage of the starting or previous dose.

6. AGENT FORMULATION AND PROCUREMENT

Study Agent (NSC #)

Note: An extensive description of the expected adverse events associated with *Study Agent* is provided in Section 5.1 *and should not be repeated here.*

Pharmaceutical information for investigational study agents supplied by CTEP will be provided as an attachment to the approved Letter of Intent (LOI) response and should be inserted here.

Availability

Study Agent is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

If the study agent is provided by NCI under a Cooperative Research and Development Agreement (CRADA) or Clinical Trials Agreement (CTA) with the manufacturer, the following text must be included in the protocol. Information on the study agent's CRADA/CTA status will be provided in the approved LOI response.

Study Agent is provided to the NCI under a Cooperative Research and Development Agreement (CRADA) or Clinical Trials Agreement (CTA) between *Agent Manufacturer* and the DCTD, NCI (see Section 10.4).

Agent Ordering

NCI-supplied agents may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that the agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). Completed Clinical Drug Requests (NIH-986) should be submitted to the PMB by fax (301) 480-4612 or mailed to the Pharmaceutical Management Branch, CTEP, DCTD, NCI, 9000 Rockville Pike, EPN Rm. 707, Bethesda, MD 20892.

Agent Accountability

The Investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form. *See the CTEP home page for Policy and Guidelines for Accountability and Storage of Investigational Drugs (http://ctep.cancer.gov/requisition/storage.html).*

7. CORRELATIVE/SPECIAL STUDIES

Please describe all planned correlative studies. Materials and methods should be described here. Please provide information on endpoint validation including background, description of the assay(s) used, and assay validation. If samples will be shipped to a central laboratory for processing and analysis, handling procedures, responsible parties, and contact information should be provided.

A correlative study code should be provided for each planned correlative study using the Protocol Submission Worksheet found on the CTEP home page (http://ctep.cancer.gov/forms/index.html). This code is necessary for electronic study results reporting.

8. STUDY CALENDAR

Schedules shown in the Study Calendar below are provided as an example and should be modified as appropriate.

Baseline evaluations are to be conducted within 1 week prior to administration of study agent. Scans and x-rays must be done $\leq$4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hr prior to initiation of the next cycle of therapy.

9. MEASUREMENT OF EFFECT

Please provide response criteria. If the criteria for solid tumors below are not applicable, the investigator(s) should provide disease-appropriate criteria (e.g., for specific hematologic malignancies) with references, and all solid tumor criteria should be deleted.

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Off Study[d]
Study Agent[a]		X		X		X		X		X		X		
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X	—	—	—	—	—	—	—	—	—	—	X	
Physical exam	X	X		X		X		X		X		X		X
Vital signs	X	X		X		X		X		X		X		X
Height	X													
Weight	X	X		X		X		X		X		X		X
Performance status	X	X		X		X		X		X		X		X
CBC w/diff, plts	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EKG (as indicated)	X													
Adverse event evaluation	X	—	—	—	—	—	—	—	—	—	—	—	X	X
Tumor measurements	X	Tumor measurements are repeated every *[# weeks]* weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X[d]
Radiologic evaluation	X	Radiologic measurements should be performed every *[# weeks]* weeks.												X[d]
B-HCG	X[c]													
Other tests, as appropriate														
Other correlative studies														

[a] *Study Agent*: Dose as assigned; route/schedule.

[b] Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.

[c] Serum pregnancy test (women of childbearing potential).

[d] Off-study evaluation. Two consecutive measurements taken 4 weeks apart must be used to document progressive disease if the patient is removed from study for this reason.

For the purposes of this study, patients should be reevaluated for response every *[# of weeks]* weeks. In addition to a baseline scan, confirmatory scans should also be obtained *[# of weeks](not less than 4)* weeks following initial documentation of objective response.

9.1 Definitions

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205–216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or nonmeasurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

9.1.1 Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm with conventional techniques (PET, CT, MRI, x-ray) or as $\geq$10 mm with spiral CT scan. All tumor measurements must be recorded in *millimeters* (or decimal fractions of centimeters).

9.1.2 Nonmeasurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter $<$20 mm with conventional techniques or $<$10 mm using spiral CT scan), are considered nonmeasurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all nonmeasurable.

9.1.3 Target Lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

9.1.4 Nontarget Lesions

All other lesions (or sites of disease) should be identified as nontarget lesions and should also be recorded at baseline. Nontarget lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as nonmeasurable lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout the follow-up.

9.2 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the

beginning of treatment and never more than 4 weeks before the beginning of the treatment.

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.*

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound (US). When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific additional criteria for standardized usage of prostate-specific antigen (PSA) and CA-125 response in support of clinical trials are being developed.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

9.3 Response Criteria

9.3.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

9.3.2 Evaluation of Nontarget Lesions

Complete Response (CR):	Disappearance of all nontarget lesions and normalization of tumor marker level
Incomplete Response/ Stable Disease (SD):	Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions

Although a clear progression of "nontarget" lesions only is exceptional, in such circumstances the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the review panel (or study chair).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

9.3.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see Section 9.3.1).

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note:

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of treatment.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

9.4 Confirmatory Measurement/Duration of Response

9.4.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed *[# weeks, no less than 4]* after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of *[# weeks, not less than 6–8 weeks]* (see Section 9.3.3).

9.4.2 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

9.4.3 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

9.5 Progression-Free Survival

Include this section if time to progression or progression-free survival (PFS) is to be used.

Uncontrolled trials using PFS as a primary endpoint should be considered on a case-by-case basis. The methodology to be applied should be thoroughly described in the protocol.

9.6 Response Review

For trials where the response rate is the primary endpoint, it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

Note: When a review of the radiological images is to take place, it is also recommended that images be free of marks that might obscure the lesions or bias the evaluation of the reviewer(s).

10. REGULATORY AND REPORTING REQUIREMENTS

Adverse events (AE) will use the descriptions and grading scales found in the revised NCI Common Toxicity Criteria (CTC). This study will utilize the CTC version 3.0 for adverse event reporting. All appropriate treatment areas should have access to a copy of the CTC version 2.0. A table showing the expected adverse events associated with *Study Agent* and the related IMT terms can be found in Appendix A. *A list of the expected adverse events for investigational study agent(s) supplied by CTEP is provided as an attachment to the approved Letter of Intent (LOI) response. A copy of the CTC version 3.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov/reporting/ctc.html).*

10.1 Expedited Adverse Event Reporting

(AE; formerly known as Adverse Drug Reaction.)

10.1.1 Expedited Reporting Guidelines—Phase 2 Studies with Investigational Agents

Unexpected Event		Expected Event	
Grades 2–3 Attribution of Possible, Probable, or Definite	Grades 4 and 5 Regardless of Attribution	Grades 1–3	Grades 4 and 5 Regardless of Attribution
Expedited report within 10 working days.	Report by phone to IDB within 24 hr. Expedited report to follow within 10 working days.	Adverse Event Expedited Reporting NOT required.	Expedited report, including Grade 5 Aplasia in leukemia patients, within 10 working days.

Unexpected Event		Expected Event	
Grades 2–3 Attribution of Possible, Probable, or Definite	Grades 4 and 5 Regardless of Attribution	Grades 1–3	Grades 4 and 5 Regardless of Attribution
(Grade 1 Adverse Event Expedited Reporting NOT required.)			Grade 4 Myelosuppression not to be reported, but should be submitted as part of study results. Other Grade 4 events that do not require expedited reporting would be specified in the protocol.

- Telephone reports to the Investigational Drug Branch at 301-230-2330 available 24 hr daily (recorder between 5 P.M. and 9 A.M. EST).
- Expedited reports are to be sent to: Investigational Drug Branch, P.O. Box 30012, Bethesda, Maryland 20824 or by fax to 301-230-0159.
- A list of agent-specific expected adverse events can be found in Appendix A.
- Use the NCI Protocol Number on all reports.

10.1.2 Forms

Forms for this phase 2 study are listed below.

Investigational Agent(s) Obtained form the NCI:

*DCTD Form for Reporting AEs Occurring with Investigational Agents.*This form can be downloaded from the CTEP home page (http://ctep.cancer.gov/reporting).

10.1.3 Secondary Malignancies

Investigators are required to report secondary malignancies occurring on or following treatment on NCI-sponsored protocols using the form noted above. Exception: Cases of secondary AML/MDS are to be reported using the *NCI/CTEP Secondary AML/MDS Report Form*.

10.2 Data Reporting

This study will be monitored by the Clinical Data Update System (CDUS) version 2.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31. *Instructions for submitting data using the CDUS can be found on the CTEP home page (http://ctep.cancer.gov/reporting/cdus.html).*

10.3 CTEP Multicenter Guidelines

This section should be marked "N/A" if this study is being performed within a single institution. A copy of the CTEP Multicenter Guidelines is provided in Appendix C *and should be inserted here for multi-institutional trials.*

10.4 Cooperative Research and Development Agreement (CRADA)/ Clinical Trials Agreement (CTA)

If the study agent is provided by CTEP under a Cooperative Research and Development Agreement (CRADA) or Clinical Trials Agreement (CTA) with the manufacturer, this section must be included in the protocol. If neither a CRADA nor CTA applies to the study agent, this section should be marked "N/A" and the text below deleted. Information on the study agent's CRADA/CTA status will be provided in the approved LOI response.

The agent(s), *Study Agent(s)*, used in this protocol is/are provided to the NCI under a Clinical Trials Agreement (CTA) or a Cooperative Research and Development Agreement (CRADA) between *Agent Manufacturer(s)* [hereinafter referred to as ACollaborator(s)@] and the NCI Division of Cancer Treatment and Diagnosis. Therefore the following obligations/guidelines, in addition to the provisions in the AIntellectual Property Option to Collaborator@ terms of award modifications, apply to the use of *Study Agent(s)* in this study:

1. *Study Agent(s)* may not be used for any purpose outside the scope of this protocol, nor can *Study Agent(s)* be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for *Study Agent(s)* are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators.
2. For a clinical protocol where there is an investigational agent used in combination with (an)other investigational agent(s), each the subject of different CTAs or CRADAs , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data".):
    a. NCI must provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit the use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval, or commercialize its own investigational agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational agent.

3. Clinical Trial Data and Results and Raw Data developed under a CTA or CRADA will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial should be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts should be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Copies of any manuscript and/or abstract should be sent to:

   Regulatory Affairs Branch, CTEP, DCTD, NCI
   Executive Plaza North, Room 718
   Bethesda, Maryland 20892
   FAX 301-402-1584

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript, or other form of public disclosure shall contain any of Collaborator's confidential/proprietary information.

11. STATISTICAL CONSIDERATIONS

11.1 Study Design/Endpoints

Please specify the study design and primary endpoints. The design should provide for early termination for sufficiently discouraging results (e.g., by use of a two-stage design). For the primary endpoint, indicate the range of values sufficiently promising to justify further testing of the agent (e.g., response rate of at least 20%) and the probability of a positive result, given that the true value falls within that range. Likewise, indicate a range of values sufficiently discouraging to justify no further testing of the agent (e.g., response rate no greater than 5%) and the probability of a negative result, given that the true value falls within that range, along with the probability of early negative termination.

11.2 Sample Size/Accrual Rate

Please specify the planned sample size and accrual rate (e.g., patients/month).

11.3 Stratification Factors

Please specify any planned patient stratification factors. Indicate whether interim monitoring and efficacy determination will be done for each stratum individually.

11.4 Analysis of Secondary Endpoints

If secondary endpoints are included in this study, please specify how they will be analyzed. In particular, brief descriptions should be given of analyses of pharmacokinetic and biologic endpoints.

11.5 Reporting and Exclusions

11.5.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with *[Study Agent]*.

11.5.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 8) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4–9 should be considered as failing to respond to treatment (disease progression). Thus an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4–9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

REFERENCES

Please provide the citations for all publications referenced in the text.

MODEL INFORMED CONSENT FORM

NOTE:
*Model text is in **bold**.
*Instructions are in [*italics*].
*_____Indicates that the investigator should fill in the appropriate information.

STUDY TITLE

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family.

[*Attach NCI booklet* "Taking Part in Clinical Trials: What Cancer Patients Need To Know."]

You are being asked to take part in this study because you have TYPE OF cancer.

[*Reference and attach information about the type of cancer (and eligibility requirements, if desired).*]

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to

[*Applicable text:*] **Find out what effects (good and bad) STUDY AGENT has on you and your TYPE OF cancer.**

This research is being done because

[*Explain in one or two sentences. Examples are*: "**Currently, there is no effective treatment for this type of cancer,**" or "**We do not know which of these two commonly used treatments is better.**"]

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

[*If appropriate:*]

About ____ people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

[*Provide simplified schema and/or calendar.*]

[*For nonrandomized and randomized studies:*]

If you take part in this study, you will have the following tests and procedures:

[*List procedures and their frequency under the categories below. If blood will be drawn, indicate the total amount drawn in each procedure or test. Include whether a patient will be at home, in the hospital, or in an outpatient setting. If objectives include a comparison of interventions, list all procedures, even those considered standard.*]

- Procedures that are part of regular cancer care and may be done even if you do not join the study.
- Standard procedures being done because you are in this study.
- Procedures that are being tested in this study.

HOW LONG WILL I BE IN THE STUDY?

We think you will be in the study for MONTHS/WEEKS, UNTIL A CERTAIN EVENT. [*Where appropriate, state that the study will involve long-term follow-up.*]

The researcher may decide to take you off this study if [*List circumstances, such as in the participant's medical best interest, funding is stopped, supply of agent(s) is insufficient, patient's condition worsens, new information becomes available.*]

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first. [*Describe any serious consequences of sudden withdrawal from the study.*]

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other agents will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after STUDY AGENT **is stopped, but in some cases side effects can be serious or long-lasting or permanent.** [*List by regimen the physical and nonphysical risks of participating in the study in categories of "very likely" and "less likely but serious." Nonphysical risks may include such things as the inability to work. Do not describe risks in a narrative fashion. Highlight or otherwise identify side effects that may be irreversible or long-term or life-threatening. If insufficient data are available to complete the table, the table may be deleted and appropriate text inserted.]*

STUDY AGENT

	Common Happens to 21–100 patients out of every 100	**Occasional** Happens to 5–20 patients out of every 100	**Rare** Happens to 1–4 patients out of every 100
Immediate: Within 1–2 days of receiving *Study Agent*			
Prompt: Within 2–3 weeks, prior to next course			
Delayed: Any time during therapy, excluding the above conditions			
Late: Any time after completion of therapy			
Unknown timing and frequency: .			

Risks and side effects related to the PROCEDURES, AGENTS, OR DEVICES we are studying include: [*List risks related to the investigational aspects of the trial. Specifically identify those that may not be reversible.*]

Reproductive Risks: Because the agents used in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. You should not nurse your baby while on this study. Ask about counseling and more information about preventing pregnancy. [*Include a statement about possible sterility when appropriate.*] [*Attach additional information about contraception, etc.*]

For more information about risks and side effects, ask the researcher or contact. [*Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks.*]

WHAT ARE THE BENEFITS OF TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with TYPE OF cancer in the future.

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you have these options: [*List alternatives including commonly used therapy and* "**No therapy at this time, except care to help you feel more comfortable.**"] [*If appropriate (for noninvestigational treatments):*] **You may get STUDY TREATMENTS/AGENTS AT THIS CENTER AND OTHER CENTERS even if you do not take part in the study.**

Please talk to your regular doctor about these and other options. [*Reference and attach information about alternatives.*]

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

Certain organizations, including qualified representatives of the National Cancer Institute, Food and Drug Administration, and AGENT MANUFACTURER, may inspect and/or copy your research records for quality assurance and data analysis.

WHAT ARE THE COSTS?

The Division of Cancer Treatment and Diagnosis, NCI, will provide you with *STUDY AGENT* free of charge while you are being treated on this study. [*If appropriate:*]

Should *STUDY AGENT* become commercially available or approved for this indication during the course of this study, you may be asked to purchase subsequent doses of the agent needed to complete the study in the event that the company no longer provides the agent to the NCI.

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be billed for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay on this study. [*Or when a Data Safety and Monitoring Board exists:*]

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about new information from this board or other studies that may affect your health, welfare, or willingness to stay on this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the researcher NAME(S) **at** TELEPHONE NUMBER.

For questions about your rights as a research participant, contact the *NAME OF CENTER* Institutional Review Board (which is a group of people who review the research to protect your rights) at *TELEPHONE NUMBER*. [*And, if available, list patient representative (or other individual who is not on the research team or IRB).*]

WHERE CAN I GET MORE INFORMATION?

You may call the **Cancer Information Service** at: **1-800-4-CANCER (1-800-422-6237)** or **TTY: 1-800-332-8615**

Visit the NCI's Web Sites. **cancerTrials**: comprehensive clinical trials information http://cancer.gov/clinical_trials/ **CancerNet**: accurate cancer information including PDQ http://cancer.gov/cancer_information/.

You will get a copy of this form. You can also request a copy of the protocol (full study plan). [*Attach information materials and checklist of attachments. Signature page should be at the end of package.*]

SIGNATURES

I agree to take part in this study.

Participant _____ **Date**

Physician _____ **Date**

Witness _____ **Date**

ADDENDUM TO MODEL INFORMED CONSENT FORM

I agree to allow the use of blood samples, other body fluids, and tissues obtained during testing, operative procedures, or other standard medical practices for further research purposes.

a. I agree to the use of my specimens for research and teaching purposes related to *PATIENT'S DISEASE*.
___Yes ___No

b. I agree to be recontacted in the future to discuss whether I will give permission for my specimens to be used for genetic research.
___Yes ___ No

c. I agree to allow my specimens to be used for research unrelated to *PATIENT'S DISEASE*.
___Yes ___ No

SIGNATURES

I agree to take part in this study.

Participant _____ **Date**

Physician _____ **Date**

Witness _____ **Date**

APPENDIX A. EXPECTED ADVERSE EVENTS ASSOCIATED WITH *STUDY AGENT* AND RELATED MedRA TERMS

Category	Adverse Event	IMT Preferred Term

Note: The full list of MedRA terms is available on the CTEP home page *(http://ctep.cancer.gov/guidelines/)*.

APPENDIX B. PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed $<50\%$ of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed $>50\%$ of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX C. CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP-sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Protection from Research Risks (OPRR), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OPRR assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OPRR form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for

having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number, and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.

Drug Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

10

Evaluation of Gynecologic Tumor Response: When and How?

Noah A. Goldman
Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York, U.S.A.

Carolyn D. Runowicz
University of Connecticut, Farmington, Connecticut, U.S.A.

INTRODUCTION

For many women with gynecologic malignancies, surgical intervention is only the beginning of treatment. Many patients require additional therapy. These patients need to be monitored for response to treatment, progression, or recurrence of disease. Monitoring a patient receiving chemotherapy or radiation may be difficult, as the currently available modalities do not have sufficient sensitivity or specificity to accurately predict persistent small-volume disease. How a patient is followed is often at the discretion of the treating physician and usually includes a combination of physical examination, serum tumor markers, imaging studies, and rarely, surgical reexploration. This chapter will discuss the role of tumor markers, imaging studies, and surgery in monitoring patients receiving chemotherapy for gynecologic cancers. Lacking prospective randomized trials, the recommendations put forth for monitoring these patients are largely based on expert opinion, nonrandomized studies, and clinical guidelines (1–3).

Prior to discussing which methods are useful in evaluating the response to chemotherapy, it is important to review the criteria that define response to treatment. Tumor burden can be characterized as "measurable" disease (visible disease either on physical examination, imaging studies, or at surgery) or "evaluable" disease (not visible by imaging study, but by some other means, e.g., tumor marker). In 1979, the World Health Organization (WHO) created a guideline for the reporting of tumor response (4). This was done in an effort to standardize reporting, so that data could be compared between investigators. These guidelines continue to be the basis for reporting response to treatment. The measurement of disease called for bidimensional measurement of disease pretreatment and the measurement of disease during treat-

ment to objectively evaluate response. The WHO definitions are noted in Table 1 and are completely described as follows:

Complete response (CR): the total resolution of all disease, determined by two separate measurements not less than 4 weeks apart.

Partial response (PR): 50% or more decrease in the total tumor burden, determined by two separate measurements not less than 4 weeks apart. If there is a single lesion, the decrease is measured by the multiplication of the vertical diameter by the horizontal diameter. If there are multiple lesions, the decrease is measured by the sums of the products of the two diameters.

Stable disease (SD): the lesions have neither decreased more than 50% nor has there been an increase more than 25% in size in one or more of the lesions.

Progressive disease (PD): an increase in one or more of the lesions by 25% or more or the appearance of new lesions.

Recently, a multicenter trial examined the role of unidimensional measurement as compared to bidimensional measurement for reporting tumor response (5). The theory behind unidimensional measurement is that cells are killed on a logarithmic scale; therefore tumor shrinkage should follow in a linear fashion. The Response Evaluation Criteria in Solid Tumors Group (RECIST) has integrated unidimensional measurement into a new set of measurement guidelines (6). The RECIST criteria define a "best response," where multiple areas of recurrence are evaluated individually, but integrated in the final assessment. For example, a patient may have a complete response at one recurrence site and stable disease at another. By RECIST criteria, that patient has had a partial response to treatment.

Table 1 Definition of Tumor Response Based on Measurable or Evaluable Disease

	Measurable disease		Evaluable disease
Response	WHO criteria (4) (bidimensional)	RECIST criteria (6) (unidimensional)	CA125 criteria (7)
CR	Disappearance of disease, confirmed by a second (4-week) exam	Disappearance of disease, confirmed by a second (4-week) exam	Normal CA125, confirmed by a second (4-week) level
PR	Decline of 50%, confirmed by a second (4-week) interval	Decline of 30%, confirmed by a second (4-week) exam	Decline of 50% after two levels,confirmed by a fourth level OR Serial decline of 75% over three levels
SD	Neither PR nor PD	Neither PR nor PD	Neither PR nor PD
PD	Increase greater than 25%	Increase greater than 20%	100% increase from baseline OR one level increased above normal (>35 U/mL)

OVARIAN CANCER

Most patients diagnosed with ovarian cancer will undergo primary cytoreductive surgery and will require postoperative chemotherapy. Determining response to treatment may be difficult, as there may not be measurable disease. A subset of patients with ovarian cancer will not have disease detected by currently available imaging studies. Disease in these patients is only detectable by elevated serum tumor markers. In an effort to objectively follow women with nonmeasurable disease, three Phase II ovarian cancer chemotherapy trials were reviewed, and serum cancer antigen 125 (CA125) response rates were compared to measurable response rates (7). Partial response was defined in one of two ways:

1. After two samples, there was a 50% decrease of serum CA125 levels, confirmed by a fourth sample.
2. There was a serial decline over three samples greater than 75%. The final sample was drawn 4 weeks after the previous sample.

This study produced new definitions of response and aided in the follow-up of women with ovarian cancer that have nonmeasurable, but evaluable, disease (Table 1).

In patients with ovarian cancer, serum CA125 levels are useful in monitoring patients during and following chemotherapy (8). An increase or decrease in CA125 levels of 100% has been used to define tumor progression or response, respectively (8). More than 80% of patients will have an elevated CA125 level prior to treatment (8). In patients with an elevated serum CA125 level, this marker (and possibly other markers depending on whether these were elevated preoperatively) is monitored every 3–4 weeks during treatment (Fig. 1). If the markers are decreasing or have

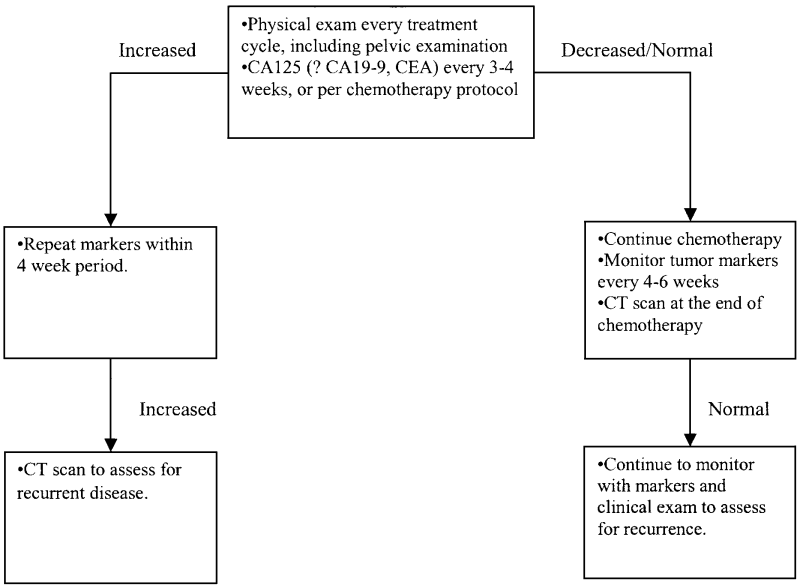

Figure 1 Algorithm for monitoring patients with ovarian cancer during treatment.

reverted to normal (<35 mU/mL), the patient should continue on the current chemotherapy regimen. CA125 may be beneficial in deciding to stop treatment and change therapy, as opposed to continuing with an ineffective, potentially toxic therapy.

Increases or decreases in CA125 have been correlated with tumor progression or regression, respectively (8–15). Vergote et al. (9) evaluated 227 patients and demonstrated that all responders to therapy had a decrease in CA125 levels ranging from 30% to 95%, while none of the patients with stable or progressive disease was noted to have a decrease greater than 30%. The rate at which CA125 levels decline is also a significant predictor of outcome. Those patients who show a rapid decline in the first 3 months of treatment after initial surgery tend to be clinically and surgically free of disease (10). A study evaluating CA125 response in 43 patients receiving chemotherapy demonstrated that those with an 80% or greater reduction of CA125 to baseline in 3 months had longer survival rates (10). Forty-seven percent were declared clinically and surgically free of disease at the end of chemotherapy, and 70% were declared clinically free of disease after chemotherapy, when there was an 80% or greater decline of CA125 from baseline to 3 months. Of note, any patient with less than a 40% reduction at 3 months had clinical evidence of disease at the end of chemotherapy. Redman et al. (11) confirmed the correlation between rapid return to baseline and survival. Patients with serum CA125 levels less than 35 U/mL after two courses of treatment were significantly more likely to achieve complete remission and have a longer median survival period. Normal CA125 levels after two courses of chemotherapy were predictive of survival at 1 year.

Niloff et al. (12) demonstrated a significant relationship between CA125 levels at second-look surgery and subsequent clinical outcome. In their evaluation of 55 patients, an elevated CA125 level (>35 U/mL) at the time of second-look surgery was associated with a 60% chance of having a clinically detectable recurrence within 4 months, whereas a level less than 35 U/mL was associated with only a 5% chance of clinical recurrence within 4 months. The sensitivity and specificity of CA125 levels for predicting clinical recurrence was 94% and 90%, respectively. Several other studies confirm the role of CA125 as a predictor of response or recurrence (14–17). All of these studies note that an elevation in CA125 level (defined as a 100% increase from baseline) was associated with disease progression in 90% to 100% of patients, with a median lead time of approximately 3 months between CA125 increase and clinical recognition of disease. However, a normal CA125 level in a patient following initial therapy is not necessarily reflective of a disease-free state. In a study of 31 patients, 53% of patients with a normal CA125 had persistent disease at the time of second-look surgery (18).

Approximately 80% of patients receiving primary platinum-based chemotherapy will have a complete clinical response; however, up to 75% of patients who respond will have persistent disease or recurrence (19). Physical examination every 3 months, along with monitoring of serum tumor markers, appear warranted. If, at any time, the patient develops symptoms, there are new findings on examination, or there is an increase in the tumor markers, further investigation is necessary. A baseline CT scan following the completion of therapy may be performed, and repeated, if the tumor markers begin to rise (Fig. 2). Since some patients may present with elevated markers prior to measurable recurrent disease, many investigators believe it is important to monitor these tumor markers following chemotherapy, so

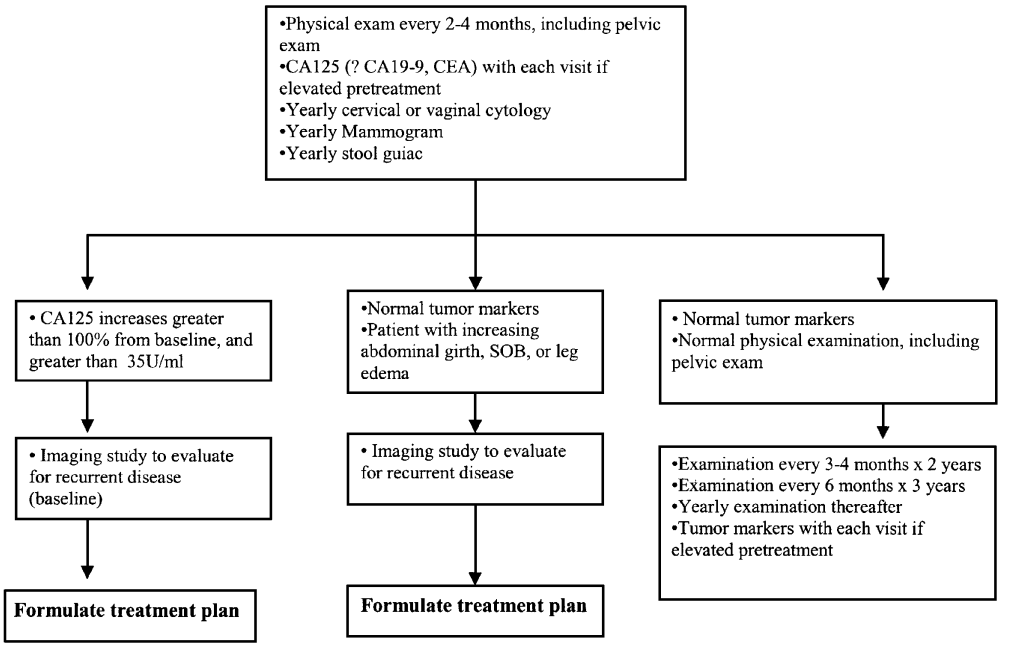

Figure 2 Algorithm for monitoring patients with ovarian cancer, following a complete response to treatment.

that recurrent or persistent disease can be diagnosed early and an alternative treatment plan can be initiated. Since early treatment has not been shown to have an impact on overall survival, other investigators feel that there is little need for such intensive surveillance and wait for patients to present with symptoms.

Although CA125 alone has a high sensitivity and specificity for predicting recurrent disease, investigators have examined other serum tumor markers in combination with CA125 in an attempt to improve the diagnosis of recurrent disease in patients with ovarian cancer. In an effort to improve the correlation of CA125 with tumor progression, Bast et al. (13) examined the concomitant measurement of CA125, carbohydrate antigen 19-9 (CA19-9), and carcinoembryonic antigen (CEA). They demonstrated a correlation with CA125 and change in tumor burden—either regression or progression—in 94% of patients evaluated, but the addition of CA19-9 and CEA was no better than CA125 alone. However, not all ovarian tumors secrete CA125, specifically mucinous and clear cell tumors (20,21). In these tumors, CA19-9 has been detected in approximately 76% of patients (22). Carcinoembryonic antigen has also been found in 62% of benign and malignant mucinous tumors (20). In non-CA125 secreting tumors, there are other markers being investigated that might be useful in detecting disease progression (21,23–26).

The role of computed tomography (CT) scans has been investigated in the follow-up of patients with ovarian cancer. Earlier studies reported that the sensitivity of CT scan in predicting disease was 36% to 100%, with a specificity of 75% to 94%, in patients who had a complete clinical remission after initial chemotherapy (27–31).

The majority of false-positives were secondary to diagnosing unopacified bowel as a tumor mass. These earlier studies missed lesions on the liver dome, diaphragm, paracolic gutters, and pelvic peritoneum (27,32,33). The radiologic diagnosis was often confused by posttreatment peritoneal reaction and scarring. Careful scanning with high-resolution scanners and thinner cuts through the abdomen has improved accuracy (28,34). However, even with newer technology, most false-negatives occur with disease less than 1.5 cm (27,29,31). Although newer technology allows visualization of very small lesions (0.5 cm), data correlating their clinical significance in patients otherwise free of disease, by physical exam and tumor markers, are not available.

Routine CT scan of the chest may not be warranted in the routine follow-up of ovarian cancer patients. In one series, 5/82 (6%) of patients evaluated showed chest recurrence on CT scan (35). Three out of five patients had concomitant abdominal disease, and 2/5 patients with an isolated chest recurrence had elevated serum markers weeks prior to recurrence. These authors suggest that chest CT scans only be performed in those patients with elevated serum tumor markers without evidence of disease in the abdomen or pelvis. The combination of CT scan with CA125 has not been shown to be more advantageous than CA125 and clinical exam in monitoring patients (36,37). The role of CT scan of the abdomen and pelvis should be to investigate clinical suspicion of recurrent disease in symptomatic patients or to serve as a baseline study, prior to starting therapy.

As compared to CT scan, MRI has been found to have a similar sensitivity (44–78% vs. 56–67%) and specificity (94% vs. 94%) (27,29,31). The combination of MRI with CT scan did not improve the diagnosis of recurrent disease (31). Positron-emission tomography (PET) scanning has also been investigated in the management of ovary cancer. Recent data suggest that the sensitivity is similar to CT scan in detecting recurrent disease (38).

Other scanning techniques have been employed as noninvasive methods of evaluating disease status. Surwit et al. (39) investigated the role of ^{111}In–CYT-immunoscintigraphy in following patients with ovarian cancer after treatment. The overall sensitivity was 44%, within the range of CT scanning. Interestingly, six patients who were CA125-negative and CT scan-negative showed evidence of disease using this method. Once injected with the radiolabeled antibody, many patients develop a human anti-murine antibody response (HAMA) (40). These patients can have a prolonged HAMA response, skewing further CA125 testing. However, new methods can account for the HAMA antibody response and provide a corrected CA125.

The original rationale for performing second-look operations was to identify those patients who had achieved a complete clinicopathologic response to primary chemotherapy. In the 1970s and 1980s, second-look surgery was the most sensitive method for determining disease status after treatment. In patients undergoing second-look surgery, who were clinically without evidence of disease, 25% had persistent disease at surgery (41). However, approximately 50% of patients with a negative second-look surgery after platinum-based chemotherapy develop recurrent disease (42,43). Based on the older literature, there is no evidence that survival is affected by the performance of a second-look operation (43,44). It may be time to reassess the role of second-look surgery with the introduction of newer chemotherapeutics and molecular-based therapies. These newer therapies may have an impact on prolongation of disease-free interval or overall survival. A minimally

invasive procedure, such as laparoscopy, may be useful in assessing response. Recent data support using laparoscopy for second-look procedures, as the false-negative rates have been found to be similar to that of laparotomy with less morbidity (45). A randomized controlled clinical trial will be required to reevaluate the role of surgical end-staging or disease assessment.

ENDOMETRIAL CANCER

Endometrial cancer is usually treated surgically, with no need for further treatment. As the majority of patients with endometrial cancer do well after surgical therapy, the intensity of follow-up remains an unresolved issue. Four studies have investigated the best methods for detecting recurrence in endometrial cancer patients (46–49). In these four studies, approximately 14% of patients developed recurrent disease, with 42% presenting without symptoms. In asymptomatic patients, approximately 50% were diagnosed by physical exam.

In a survey of gynecologic oncologists, 84% of physicians performed vaginal cytology with each follow-up visit every 3 months (50). In the surveillance studies, only 7% of patients with recurrent disease were diagnosed with an abnormal cytology. Chest x-rays were obtained by 74% of gynecologic oncologists during the first 2 years of posttherapy surveillance in patients with early endometrial cancer, with a detection rate of recurrent disease of only 14% in the combined studies.

CA125 has been demonstrated immunohistochemically in endometrial glandular tissue, both benign and malignant (51), although solid tumor areas and undifferentiated tumors express low levels of CA125. CA125 may be a useful predictor of disease progression in endometrial cancer in a select group of patients (51,52). If CA125 levels are elevated initially, it might be useful to follow this marker at each surveillance visit (Fig. 3). In a study of 21 women receiving treatment for metastatic or recurrent endometrial cancer, 80% had elevated pretreatment CA125 (52). All patients experiencing a relapse during therapy had a rise in CA125, defined as a 50% increase in marker levels from baseline, simultaneously, or within 1 month of recurrence. In those patients who responded to therapy, 88% had a decline of CA125 to normal within two chemotherapy cycles, and 100% of patients with responding or stable disease become and/or remain tumor-marker-negative. In 12 patients diagnosed with tumor recurrence, 42% had elevated CA125 prior to the clinical detection of disease (51). In a study of 15 patients with uterine papillary serous carcinoma (UPSC), CA125 did not precede or predict tumor recurrence (53). This may be secondary to the fact that these tumors are undifferentiated and do not express CA125. However, there are no studies that demonstrate diagnosing disease earlier with tumor markers results in improved survival.

Investigators have sought to improve the sensitivity of CA125 to predict recurrent disease by evaluating other tumor markers concomitantly with CA125 (54,55). An evaluation of 105 patients with endometrial cancer demonstrated a similar sensitivity for CA125 and CA19-9 in detecting tumor progression, 45.5% and 51.5%, respectively (54).

Since most endometrial cancers recur within the first 2–3 years of treatment, physical examinations every 3–6 months for the first 2–3 years with annual exams thereafter seems indicated (3). Vaginal cytologic smears may be performed annually,

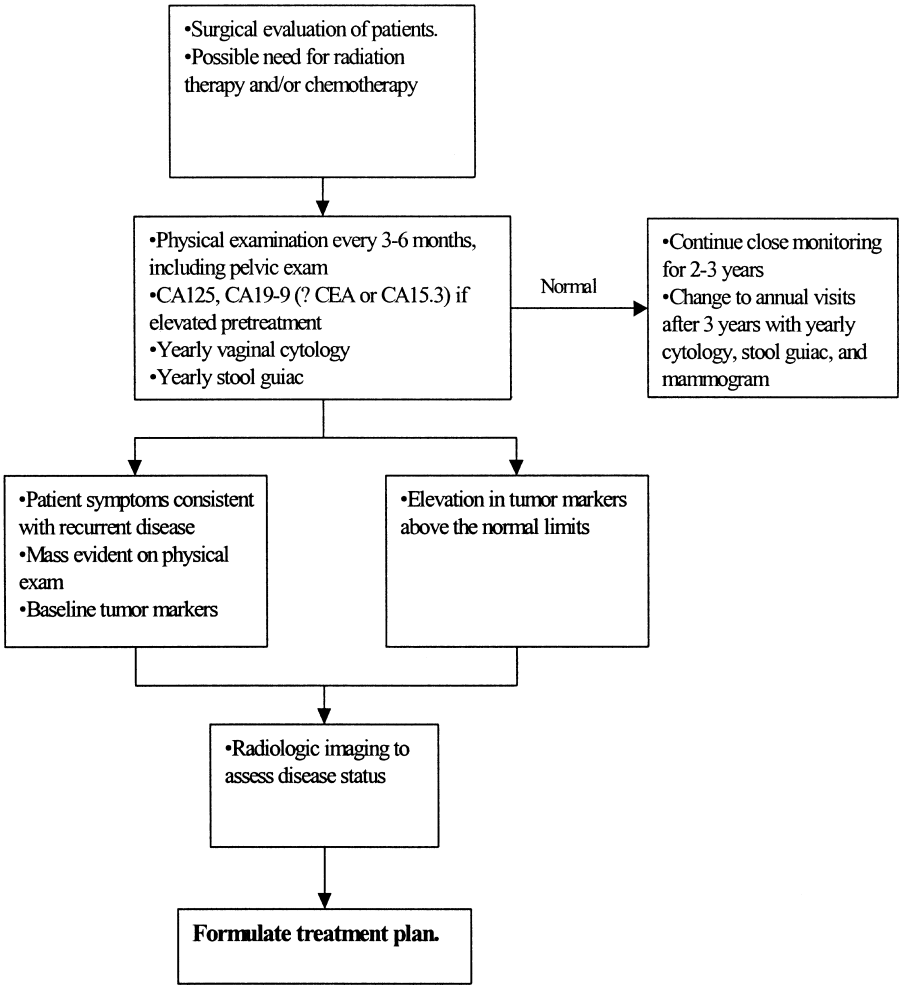

Figure 3 Algorithm for monitoring patients with endometrial cancer after primary therapy.

as the vaginal vault is a frequent site of recurrence. However, there is no evidence that vaginal cytology aids in the early detection of recurrent disease (46–49). If the vaginal cytology is repeatedly negative, the frequency of these examinations can be diminished. Routine chest x-ray or other diagnostic imaging studies are not useful. Studies show that approximately 80% of recurrences will be detected through patient symptoms or physical examination (3,46–49).

CERVICAL CANCER

Most patients with cancer of the cervix are treated with surgery, radiation therapy, or concomitant chemotherapy and radiation therapy (56–60). During initial therapy,

patients are monitored for treatment sequelae. In the surgical patient, this is assessed at routine postoperative visits. When the patient is fully recovered from surgery (approximately 8 weeks), routine surveillance is begun. For the patient receiving radiation therapy alone or concomitant radiation therapy with chemotherapy, weekly visits assess the patient's tolerance to the side effects of treatment. Following completion of radiation therapy, routine surveillance is begun.

Surveillance after primary therapy for invasive carcinoma of the cervix is universally recommended. Approximately 35% of patients will have persistent or recurrent disease. Recurrence or persistent disease is usually diagnosed based on clinical suspicion, with changes secondary to treatment (e.g., radiation fibrosis) acting as confounding variables. Patients are followed by clinical examination, laboratory assessment, and radiologic testing. Few studies have addressed the efficacy of routine surveillance following definitive therapy in asymptomatic and disease-free patients, as opposed to symptom-based reassessment (Fig.4). Surveillance schedules should take into account that recurrence is highest in the first 2 years following treatment (61). It would be beneficial to have a sensitive method of

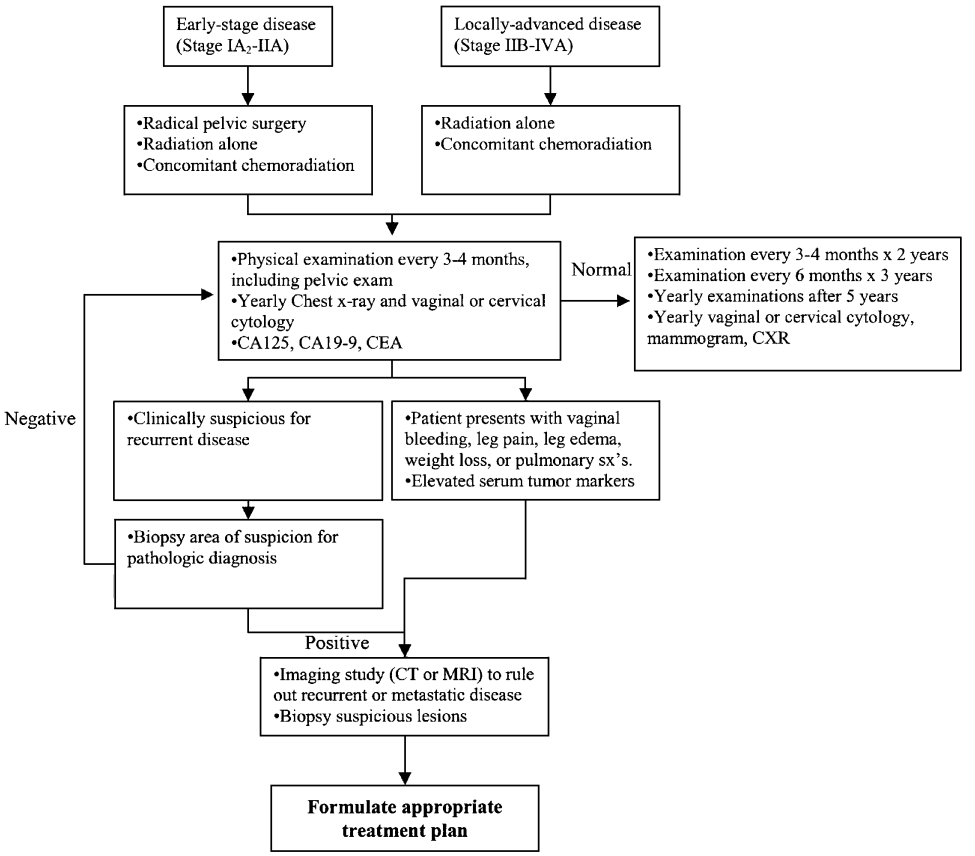

Figure 4 Algorithm for monitoring patients with cervical cancer after initial treatment.

diagnosing recurrence in addition to physical exam so that early, and potentially curative, interventions could be instituted.

Recently, an optimal posttherapy surveillance program was developed for patients who had recurrent disease following therapy for stage IB carcinoma of the cervix (62). Irrespective of the location of the recurrence, those patients who were asymptomatic at the time that the recurrent disease was diagnosed were found to have significantly improved survival rates, as compared to those patients who were symptomatic. The investigators recommend a complete physical examination every 4 months for 2 years, followed by visits every 6 months for 3 years, with yearly visits thereafter. Cervical or vaginal cytology and chest x-ray should be performed yearly, as more frequent examinations have not improved the detection of recurrent disease. Importantly, biopsy of suspicious lesions, local and distant, is the cornerstone for monitoring these patients.

Tumor markers have been investigated in the diagnosis and monitoring of patients with cervical cancer. As a diagnostic tool, tumor markers in cervical cancer have been disappointing. There is some evidence that they may be useful in following patients after treatment (63–67). CA125 is expressed in squamous cell cancer of the cervix and cervical adenocarcinoma in approximately 30–56% of patients at initial diagnosis (63,64). In patients with squamous cell cancer of the cervix, posttreatment elevations in CA125 correspond to persistent or recurrent disease (64). As with ovarian and endometrial cancers, there is a lead time associated with the elevation of CA125 and the appearance of clinical disease. Similar results are seen in patients with cervical adenocarcinoma who have metastatic disease outside of the pelvis (63). However, whether this lead time results in improved survival is unknown.

Carcinoembryonic antigen is not useful in the diagnostic workup, but may correlate with progressive or recurrent disease (66,67). In 65% of patients, CEA has been correlated with recurrence. Carcinoembryonic antigen levels were directly related to tumor stage, correlating with increased tumor burden. In patients with cervical adenocarcinoma, CEA was increased (>2.5 mg/dL) approximately 60% of the time (67). Squamous cell carcinoma antigen (SCC) is an investigational marker. Squamous cell carcinoma antigen was elevated in 65% of patients with squamous cell cancer of the cervix prior to recurrence (68). Posttreatment elevation of SCC antigen occurred more frequently in patients with squamous cell cancer who recurred (69). Persistent elevation of SCC antigen during treatment was a possible sign of treatment failure (70). Squamous cell carcinoma antigen has been used in combination with CA125 and CEA without adding to the positive predictive value for tumor recurrence in patients with cervical adenocarcinoma (63).

Computed tomography scans have been used to accurately detect recurrent disease, with a sensitivity of 90% and a specificity of 95% (71). False-positives are caused by surgical and radiation changes. In one study, CT scans alone failed to predict parametrial spread of cervical cancer with high accuracy (72). Magnetic resonance imaging (MRI) should be more useful than CT as it allows improved visualization of tissue planes using weighted scans. However, in previously treated patients, MRI overestimated tumor size by approximately 30% and was unable to discern parametrial invasion from radiation changes in the majority of patients (73). It does not appear that CT or MRI expedite detection of recurrence after primary therapy and should only be used in the symptomatic patient or in the patient with clinically evident recurrence to document the extent of disease.

SUMMARY

Until recently, the follow-up of patients with gynecologic malignancies was at the discretion of the treating physician. The National Comprehensive Cancer Network has released guidelines for the follow-up of patients with ovarian, endometrial, and cervical cancers (1–3). Because of the lack of data, these guidelines are largely based on expert opinion. Further prospective studies are necessary to evaluate the usefulness of current surveillance strategies.

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11

Practical Guide on How to Deliver Chemotherapy

Antonella Savarese and Francesco Cognetti
Regina Elena National Cancer Institute, Rome, Italy

Alkylating and natural sources-derived agents are the most effective drugs on gynecologic cancers. In this chapter, the principal aspects of therapeutic administration of these compounds will be considered and a brief summary of the standard regimens will be done.

ALKYLATING AND SIMILAR-ALKYLATING AGENTS

The alkylating agents are a diverse group of chemical compounds capable of forming molecular bonds with nucleic acids, proteins, and many molecules of low molecular weight. This alteration results in inhibition or inaccurate replication of DNA, with resultant mutation or cell death. Cyclophospliamide and Ifosfamide have been widely used in the treatment of gynecologic cancer. Actually, metal salts such as cisplatin and carboplatin, working like similar-alkylating agents, represent the most effective drugs and are usually used in combination with other cytotoxic drugs.

Cisplatin

(*cis*-Diamminedichloroplatinum, DDP, CDDP)

Usual Dosage and Schedule

1. 40–120 mg/m^2 i.v. on day 1 as infusion every 3 weeks.
2. 15–20 mg/m^2 i.v. on days 1–5 as infusion every 3–4 weeks.

Special Precautions

Irreversible renal tubular damage may occur if adequate diuresis is not maintained, particularly with doses higher than 40 mg/m^2. For this reason, a vigorous hydration is mandatory and infusion must be avoided if serum creatinine level is more than 1.5

mg/dL. For patients with known or suspected cardiovascular impairment (ejection fraction <45%), a less vigorous rate of hydration can be used, with reduced dose of cisplatin (<60 mg/m^2). An alternative is to give carboplatin.

Administration

1-hr hydration for CDDP <25 mg/m^2

T0–T30: Furosemide 20 mg + 500 mL 5% dextrose + Na 36 mEq + K 6.5 mEq + Cl 30 mEq + HCO_3 10 mEq
T30: CDDP bolus
T30–T60: 500 mL 5% dextrose + Na 36 mEq + K 6.5 mEq + Cl 30 mEq + HCO_3 10 mEq

2-hr hydration for CDDP <75 mg/m^2

T0–T30: Furosemide 40 mg + 500 mL 5% dextrose + Na 36 mEq + K 6.5 mEq + Cl 30 mEq + HCO_3 10 mEq
T30: Mannitol 18% 70 mL + CDDP bolus
T40–120: 1500 mL 5% dextrose + Na 108 mEq + K 13 mEq + Cl 85 mEq + HCO_3 30 mEq

4-hr hydration for CDDP >75 mg/m^2

T0–T30: Furosemide 40 mg + 500 mL 5% dextrose + Na 36 mEq + K 6.5 mEq + Cl 30 mEq + HCO_3 10 mEq
T30: Mannitol 18% 70 mL + CDDP bolus
T40–240: 3500 mL dextrose 5% + Na 108 mEq + K 13 mEq + Cl 85 mEq + HCO_3 30 mEq

Give additional mannitol (12.5–50 g by i.v. push) if necessary to maintain urinary output of 250 mL/hr over the duration of hydration. If signs of congestive heart failure develop, 40 mg of Furosemide may be given.

Carboplatin

(CBDCA, Paraplatin)

Usual Dosage and Schedule

The dosage is assessed by calculating the area under the curve (AUC):

Total dose (mg) = target AUC × (glomerular filtration rate + 25).
The target AUC is usually 5–7, depending on previous therapy and concurrent drugs or radiotherapy.
Area under the curve dose is administered i.v. on day 1 as 60-min infusion every 3 weeks.

Special Precautions

Carboplatin has much less renal toxicity than cisplatin. A reduction to 200 mg/m^2 for clearance of 20–40 mL/min is recommended.

NATURAL PRODUCTS

These drugs are mentioned together not on the basis of activity, but because they are derived from natural sources. The clinically useful drugs are largely employed in gynecologic cancer therapy and can be grouped as follows:

- Mitotic inhibitor (vincristine, vinblastine, vinorelbine)
- Microtubule polymer stabilizer (taxanes)
- Topoisomerase I inhibitors (topotecan, irinotecan)
- Topoisomerase II inhibitors (etoposide, teniposide)
- Antibiotics (doxorubicin, epirubicin, mitoxantrone, bleomycin)

Despite their "natural" origin, special warning for hypersensitivity reactions is recommended only for taxanes and, very occasionally, for anthracyclines.

Paclitaxel

(Taxol)

Usual Dosage and Schedule

1. 135 to 225 mg/m^2 as a 3-hr infusion every 3 weeks
2. 135 to 200 mg/m^2 as a 24-hr infusion every 3 weeks
3. 80 to 100 mg/m^2 as a 1-hr weekly infusion

Special Precautions

Anaphylactoid reactions with dyspnea, hypotension, bronchospasm, and erythematous rashes may occur as a result of the paclitaxel itself or the cremophor vehicle required to make paclitaxel water-soluble. Such reaction is minimized but not totally prevented by pretreatment with antihistamines and corticosteroids and by prolonging the infusion rate (to 24 hr). Paclitaxel must be filtered with a 0.2-μm in-line filter.

Standard Pretreatment Regimen

1. Dexamethasone, 20 mg p.o. 12 and 6 hr before treatment or, in alternative, dexamethasone, 20 mg i.v. 30 to 60 min prior to treatment
2. Cimetidine, 300 mg i.v. 30 to 60 min prior to treatment (or other histamine H2-receptor antagonist)
3. Diphenhydramine, 50 mg i.v. 30 to 60 min prior to treatment

Doxorubicin

(Adriamycin, ADR)

Usual Dosage and Schedule

1. 60–75 mg/m^2 i.v. every 3 weeks (single agent)
2. 30–60 mg/m^2 i.v. every 3 weeks (in combination with other drugs)
3. 15–20 mg/m^2 i.v. weekly

Special Precautions

1. Administer over several minutes into the sidearm of a running i.v. infusion, taking care to avoid extravasation.
2. Do not exceed a lifetime cumulative dose of 550 mg/m^2.
3. Do not give if patient has significantly impaired cardiac function.
4. Reduce dose if patient has impaired liver function, in particular, for bilirubin >2.0 mg/dL.

Doxorubicin, Liposomal

Usual Dosage and Schedule

A 20–50 mg/m^2 i.v. infusion as a 60-min infusion every 3 weeks.

Special Precautions

The drug must be diluted in 250 mL of 5% dextrose.

Epirubicin

(EPI)

Usual Dosage and Schedule

1. 60–120 mg/m^2 i.v. every 3 weeks
2. 25–30 mg/m^2 i.v. weekly

Special Precautions

1. Take care to avoid extravasation.
2. Do not exceed a lifetime cumulative dose of 1000 mg/m^2.

ACUTE REACTIONS OF CHEMOTHERAPY

The side effects of chemotherapy may be acute or chronic, self-limited or permanent, and will be largely discussed in other sections. Some acute reactions depend on route of administration or represent short-term side effects. Management of these reactions is important because they can affect the tolerability and continuation of chemotherapy in addition to overall quality of life (1).

Extravasation

Extravasation is defined as the leakage or infiltration of drug into the subcutaneous tissues. *Vesicant* drugs that extravasate are capable of causing tissue necrosis (i.e., doxorubicin, epirubicin, vinblastine, vincristine, and vinorelbine). Irritant drugs cause inflammation or pain at site of extravasation (i.e., liposomal doxorubicin, taxol, and cisplatin). Management of extravasation is controversial, with some disagreement regarding antidotes. Less than 6% of patients receiving peripheral intravenous chemotherapy experience vesicant extravasation. The most effective management of

extravasation is prevention. A complaint such as burning or pain at the site of vein cannulation should be considered a symptom of extravasation until proven otherwise.

General Procedures

If an extravasation is suspected, the following actions should be taken:

1. Stop administration of the chemotherapy agent.
2. Aspirate any residual drugs in the tubing, the needle, or the extravasation site, then remove the needle.
3. Avoid applying pressure to the site.
4. Inject appropriate antidote drug, if any.
5. Apply warm or cold compresses as appropriate for the specific drugs.
6. Elevate the arm.

Reported in Table 1 are the procedures for specific agents. Little information is available on antidotes for other chemotherapy agents.

Hypersensitivity and Anaphylaxis

Drugs with potential for hypersensitivity with or without an anaphylactic response should be administered under constant supervision, preferably during the daytime hours. An allergic history should be documented but may not predict n allergic reaction to chemotherapy. Drugs for which hypersensitivity reactions may occur include bleomycin, paclitaxel, cisplatin, doxorubicin, or epirubicin. The hypersensitivity reactions experienced by patients receiving cancer chemotherapy are typically type I reactions that usually occur within 1 hr of receiving the drug, but may occur up to 24 hr after exposure. The manifestation of a type I reaction includes urticaria, bronchospasm, and anxiety, but can progress to cardiovascular collapse and shock. Patients may be premedicated prophylactically with corticosteroids and histamine antagonists, as described for paclitaxel administration. A grading scale for anaphylactic symptoms is reported in Table 2.

Table 1 Antidotes for Vesicant or Irritant Drugs

Chemotherapy agent	Pharmacologic antidote	Nonpharmacologic antidote	Methods of administration
Vincristine, vinblastine, vindesine, vinorelbine, etoposide,	Hyaluronidase	Warm compresses, 15–20 min at least four times/day for the first 24–48 hr	Hyaluronidase, 150 U/mL in 1–3 mL saline. Inject through existing i.v. line or s.c. if needle is removed
Doxorubicin, epirubicin, cisplatin, taxol	None	Topical cooling	Apply cold pad or ice pack for 15–20 min at least four times/day for the first 24–48 hr

Table 2 Grading Scale for Anaphylactic Symptoms

Grade	Definition
1	Localized reaction with hives <6 cm
2	Generalized reaction with multiple, widely spread hives each <6 cm or a severe localized reaction with hives measuring >6 cm
3	Severe bronchospasm, difficulty of breathing, chest tightness, cough, vomiting, tachycardia, agitation
4	Anaphylaxis, severe hypotension, shock, or any of the above symptoms plus hypotension and shock

Nausea and Vomiting

With the advent of more effective antiemetic regimens in the past 10 years, many improvements in the prevention and control of nausea and vomiting have led to a better quality of life for patients receiving chemotherapy. The goal is to prevent the three phases of nausea and vomiting: that which occurs before the treatment is administered (anticipatory), that which follows within the first 24 hr after the treatment (acute), and that which occurs more than 24 hr after the treatment (delayed). Factors related to the chemotherapy that can affect the severity of symptoms include the specific agents used, the doses of the drugs, and the schedule of administration. Management of nausea and vomiting will be largely discussed in other sections.

CHEMOTHERAPY IN GYNECOLOGIC CANCERS

Some examples of chemotherapy regimens often used in the treatment of gynecologic cancer are reported in the tables. Doses, schedule, route of administration, dilution, and medications for hypersensitivity or nausea and vomiting related to the treatment are also indicated.

OVARIAN CANCER

CYCLOPHOSPHAMIDE 1100–750 mg/m^2 day 1
Dilute 20 mg/mL on levulose solution

CISPLATIN 110–75 mg/m^2 day 1
Dilute on 20 mL chloride-free solution

Cisplatin hydration:
T0–T30: Furosemide 40 mg + 500 mL 5% dextrose + Na 36 mEq + K 6.5 mEq + Cl 30 mEq + HCO_3 10 mEq
T30: Mannitol 18% 70 mL + CDDP bolus
T40–240: 3500 mL dextrose 5% + Na 108 mEq + K 13 mEq + Cl 85 mEq + HCO_3 30 mEq

Antiemetic therapy:
Dexamethasone 20 mg day 1 e.v.
Dexamethasone 8 mg×2 i.m. days 2, 3
Dexamethasone 4 mg×2 i.m. day 4

Ondansetron 8 mg days 1 e.v., PO days 2, 3, 4
Ranitidine 50 mg days 1 e.v., 300 mg PO days 2, 3, 4

Cycles are administered every 21 days

Swenerton et al., J Clin Oncol 10:718–726, 1992 (2)

ADRIAMYCIN 50 mg/m^2
Dilute 2 mg/mL on chloride-free solution, administered in bolus (maximum dose < 550 mg/m^2)

CYCLOPHOSPHAMIDE 500–750 mg/m^2
Dilute 20 mg/mL of levulose solution

Antiemetic therapy:
Dexamethasone 16 mg day 1 e.v.
Dexamethasone 4 mg days 2, 3 i.m.
Ondansetron 8 mg days 1 e.v.
Ranitidine 50 mg day 1 e.v., 300 mg PO days 2, 3

Cycles are administered every 21 days

CARBOPLATIN AUC: 5–7.5
Reconstructed in chloride-free solutions and administered over 30 min as a rapid intravenous infusion

CYCLOPHOSPHAMIDE 600 mg/m^2
Dilute 20 mg/mL of levulose solution

Antiemetic therapy:
Dexamethasone 12 mg day 1 e.v.
Dexamethasone 4 mg day 2 i.m.
Ondansetron 8 mg day 1
Ranitidine 50 mg days 1, 300 mg PO day 2

Cycles are administered every 21 days

CISPLATIN 75 mg/mq day 2
Dilute on 20 mL chloride-free solution

Cisplatin hydration:
T0–T30: Furosemide 2 fl + 500 mL 5% dextrose + Na 36 mEq + K 6.5 mEq + Cl 30 mEq + HCO_3 10 mEq
T30: Mannitol 18% 70 mL + CDDP bolus
T40–240: 3500 mL dextrose 5% + Na 108 mEq + K 13 mEq + Cl 85 mEq + HCO_3 30 mEq

PACLITAXEL 135–175 mg/m^2 day 1
Dilute on 500 mL glucose 5% solution, infusion on 3 hr
Premedication with:
Dexamethasone 125 mg 12 hr before the PTX/125 mg 6 h before the PTX
Orfenadrin 40 mg i.m. 30 min before the PTX

Antiemetic therapy:
Dexamethasone 20 mg day 1 e.v.
Dexamethasone 8 mg×2 days 2, 3 i.m.
Dexamethasone 4 mg×2 day 4 i.m.
Ondansetron 8 mg days 1e.v., i.m. ×2 days 2, 3, 4
Ranitidine 50 mg days 1 e.v., 300 mg PO days 2, 3, 4

Cycles are administered every 21 days

Rowinsky et al., J Clin Oncol 9:1692–1703, 1991 (3)

CARBOPLATIN AUC: 5–7
Reconstructed in chloride-free solutions and administered over 30 min as a rapid intravenous infusion
PACLITAXEL 175 mg/m^2

Dilute on 500 mL glucose 5% solution, infusion 3 hr
Premedication with:
Dexamethasone 125 mg 12 hr before the PTX/125 mg 6 hr before the PTX
Orfenadrin 40 mg i.m. 30 min before the PTX

Antiemetic therapy:
Dexamethasone 16 mg day 1 e.v.
Dexamethasone 4 mg i.m. days 2, 3
Ondansetron 8 mg day 1 e.v.
Ranitidine 50 mg day 1 e.v., 300 mg PO days 2, 3

Cycles are administered every 21 days

Bookman et al., Proc Am Soc Clin Oncol 14: 271, 1995 (4)

TOPOTECAN 1.5 mg/m^2 on days 1–5
Dilute on 250 mL chloride-free solution in 1-hr infusion

Antiemetic therapy:
Dexamethasone 8 mg days 1, 2, 3, 4, 5 e.v.
Ondansetron 8 mg days 1, 2, 3, 4, 5 e.v.
Ranitidine 50 mg days 1, 2, 3, 4, 5 e.v.

Cycles are administered every 28 days

McGuire et al., J Clin Oncol 18:1062–1067, 2000 (5)

LIPOSOMAL DOXORUBICIN 30–50 mg/mq day 1 (single agent) or 25 mg/mq day 1 (combination regimen)
Dilute on 250 mL glucose 5% and administered on 60 min

Antiemetic therapy:
Dexamethasone 8 mg days 1, 2, e.v./i.m.
Ondansetron 8 mg days 1, 2, 3 e.v/os
Ranitidine 50 mg days 1, 2, 3 e.v/os

Cycles are administered every 21 days

Muggia et al., J Clin Oncol 3:987–993, 1997 (6)

IFOSFAMIDE 1,2–2,4 g/mq/die days 1, 2, 3, 4, 5
Dilute on 500 mL Lacted Ringer's solutions on 30-min infusion

Schedule of Mesna administration, days 1, 2, 3, 4, 5:
T0–T4 Mesna 50% of the ifosfamide dose
T1 ifosfamide bolus
T2 Laevosan 5% 500 mL + Furosemide 1 fl

Antiemetic therapy:
Dexamethasone 8 mg days 1, 2, 3, 4, 5 e.v.
Ondansetron 8 mg days 1, 2, 3, 4, 5 e.v.
Ranitidine 50 mg days 1, 2, 3, 4, 5 e.v.

Cycles are administered every 21 days

Markman et al., J Clin Oncol 10:243–248, 1992 (7)

OVARIAN GERM CELL TUMORS

CISPLATIN 20 mg/m^2 on days 1–5

Cisplatin hydration:
T0 Furosemide 20 mg + 500 mL Levulosio 5% + Na 38 mEq + K 6.5 mEq + Cl 30 mEq + HCO_3 10 mEq
T30 CDDP bolus
T40–45 500 mL Levulosio 5% + Na 38 mEq + K 6.5 mEq + Cl 30 mEq + HCO_3 10 mEq

ETOPOSIDE 100 mg/m^2 on days 1–5
Dilute on 250 mL of physiological sodium chloride solution and administered on 30 min

BLEOMYCIN 20 U/m^2 on days 2, 9, 16
Dilute on 20 mL of physiological sodium chloride solution and administered on bolus

Antiemetic therapy:
Dexamethasone 16 mg day 1 e.v.
Dexamethasone 8 mg days 2, 3, 4, 5
Ondansetron 8 mg days 1, 2, 3, 4, 5
Ranitidine 50 mg days 1, 2, 3, 4, 5

Cycles are administered every 21 days

Williams et al., J Clin Oncol 12:701–706, 1994 (8)

ENDOMETRIAL CANCER

CISPLATIN 50 mg/m^2 day 1

Cisplatin hydration:
T0 Furosemide 40 mg + 500 mL Levulosio 5% + Na 38 mEq + K 6.5 mEq + Cl 30 mEq + HCO_3 10 mEq
T30 Mannitol 18% 70 mL + CDDP bolus
T40–45 1500 mL Levulosio 5% + Na 38 mEq + K 6.5 mEq + Cl 30 mEq + HCO_3 10 mEq

DOXORUBICIN 50 mg/m^2 day 1
CYCLOPHOSPHAMIDE 500 mg/m^2 day 1
Dilute 20 mg/mL of levulose solution

Antiemetic therapy:
Dexamethasone 12 mg day 1 e.v.
Dexamethasone 8 mg days 2, 3
Dexamethasone 4 mg day 4
Ondansetron 8 mg days 1, 2, 3, 4
Ranitidine 50 mg days 1, 2, 3, 4

Cycles are administered every 21 days

Burke et al., Gynecol Oncol 55:47–50, 1994 (9)

PACLITAXEL 175 mg/m^2 day 1
Dilute on 500 mL glucose 5% solution, infusion on 3 hr premedication with:
Dexamethasone 125 mg 12 hr before the PTX/125 mg 6 hr before the PTX
Orfenadrin 40 mg i.m. 30 min before the PTX

EPIRUBICIN 70 mg/m^2 day 1 (dilute on 20 mL of physiological sodium chloride solution and administer on bolus)

CISPLATIN 50 mg/m^2 g1 day 21

Cisplatin hydration:
T0 Furosemide 2 fl + 500 mL Levulosio 5% + Na 38 mEq + K 6.5 mEq + Cl 30 mEq + HCO_3 10 mEq
T30 Mannitol 18% 70 mL + CDDP bolus
T40–45 1500 mL Levulosio 5% + Na 38 mEq + K 6.5 mEq + Cl 30 mEq + HCO_3 10 mEq

Antiemetic therapy:
Dexamethasone 16 mg day 1 e.v.
Dexamethasone 8 mg day 2
Dexamethasone 4 mg days 3, 4
Ondansetron 8 mg days 1, 2, 3, 4
Ranitidine 50 mg days 1, 2, 3, 4

Cycles are administered every 21 days

Lissoni et al., Ann Oncol 8:969–72, 1997 (10)

CERVICAL CARCINOMA

BLEOMICINA 30 mg 24-hr infusion day 1
Dilute on 20 mL of physiological sodium chloride solution

CISPLATIN 50 mg/m^2 day 2

Cisplatin hydration:
T0 Furosemide 2 fl + 500 mL Levulosio 5% + Na 38 mEq + K 6.5 mEq + Cl 30 mEq + HCO_3 10 mEq
T30 Mannitol 18% 70 mL + CDDP bolus

T40–45 1500 mL Levulosio 5% + Na 38 mEq + K 6.5 mEq + Cl 30 mEq + HCO_3 10 mEq

IFOSFAMIDE 5 g/m^2 24-hr infusion day 2
MESNA 6 g/mq 36-hr infusion day 2 q21
Antiemetic therapy:
Dexamethasone 16 mg day 1 e.v.
Dexamethasone 8 mg days 2
Dexamethasone 4 mg days 3, 4
Ondansetron 8 mg days 1, 2, 3, 4
Ranitidine 50 mg days 1, 2, 3, 4

Cycles are administered every 21 days

Buxton et al., J Natl Cancer Inst. 81:359–361, 1989 (11)

MESNA 2500 mg/m^2 T0–T4 days 1, 2

Schedule of Mesna administration:
T0–T4 Mesna 50% of the ifosfamide dose
T1 ifosfamide bolus
T2 Laevosan 5% 500 mL + Furosemide 20 mg days1, 2

IFOSFAMIDE 2500 mg/m^2 dilute on 500 mL Lacted Ringer's solutions on 30-min infusion days 1, 2

CISPLATIN 50 mg/m^2 day 1
Cisplatin hydration:
T0 Furosemide 40 mg + 500 mL Levulosio 5% + Na 38 mEq + K 6.5 mEq + Cl 30 mEq + HCO_3 10 mEq
T30 Mannitol 18% 70 mL + CDDP bolus
T40–45 1500 mL Levulosio 5% + Na 38 mEq + K 6.5 mEq + Cl 30 mEq + HCO_3 10 mEq

PACLITAXEL 175 mg/m^2 day 1
Dilute on 500 mL glucose 5% solution, infusion on 3 hr premedication with:
Dexamethasone 125 mg 12 h before the PTX/125 mg 6 hr before the PTX
Orfenadrin 40 mg i.m. 30 min before the PTX

Antiemetic therapy:
Dexamethasone 16 mg day 1 e.v.
Dexamethasone 8 mg days 2, 3, 4
Ondansetron 8 mg days 1, 2, 3, 4
Ranitidine 50 mg days 1, 2, 3, 4

Cycles are administered every 21 days

Zanetta et al., Ann Oned 9:977–980, 1998(modified)(12)

CISPLATIN 100 mg/m^2 day 1

Cisplatin hydration:
T0 Furosemide 2 fl + 500 mL Levulosio 5% + Na 38 mEq + K 6.5 mEq + Cl 30 mEq + HCO_3 10 mEq

T30 Mannitol 18% 70 mL + CDDP bolus
T40–45 3500 mL Levulosio 5% + Na 38 mEq + K 6.5 mEq + Cl 30 mEq + HCO_3 10 mEq

VINORELBINE 30 mg/m^2 days 1, 8
Dilute on 250 mL of physiological sodium chloride solution and administer on 30-min infusion

Antiemetic therapy:
Dexamethasone 20 mg day 1 e.v.
Dexamethasone 16 mg days 2, 3
Dexamethasone 8 mg day 4
Ondansetron 8 mg X 2 days 1, 2, 3, 4
Ranitidine 50 mg days 1, 2, 3, 4

Cycles repeated every 21 days

Pignata et al., J Clin Oncol 17:756–760, 1999 (13)

CISPLATIN 100 mg/m^2 d1

Cisplatin hydration:
T0 Furosemide 40 mg + 500 mL Levulosio 5% + Na 38 mEq + K 6.5 mEq + Cl 30 mEq + HCO_3 10 mEq
T30 Mannitol 18% 70 mL + CDDP bolus
T40–45 3500 mL Levulosio 5% + Na 38 mEq + K 6.5 mEq + Cl 30 mEq + HCO_3 10 mEq

BLEOMYCIN 15 mg/m^2 day 1
Dilute on 20 mL of physiological sodium chloride solution and administer on bolus

Antiemetic therapy:
Dexamethasone 20 mg day 1 e.v.
Dexamethasone 16 mg days 2, 3
Dexamethasone 8 mg day 4
Ondansetron 8 mg×2 days 1, 2, 3, 4
Ranitidine 50 mg days 1, 2, 3, 4

Cycles repeated every 21 days

Tana et al., Eur J Gynaecol Oncol 20:198–201, 1999 (14)

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Evaluation of the Patient for Chemotherapy

Groesbeck P. Parham and Mia Cowens
University of Alabama School of Medicine, Birmingham, Alabama, U.S.A.

Michael Hicks
Henry Ford Hospital, Detroit, Michigan, U.S.A.

Alessandro D. Santin
University of Arkansas for Medical Sciences, Little Rock, Arkansas, U.S.A.

Raleigh Butler
Princess Margaret Hospital, Nassau, Bahamas

INTRODUCTION

Several important issues must be addressed when any gynecologic cancer patient is being assessed for chemotherapy (see Table 1). The most important question is whether she is a chemotherapy candidate or not. This question is best answered by first considering the global health status of the patient, i.e., her physical, psychological, emotional, and quality-of-life status. Next in line for consideration is the therapeutic aim of the proposed treatment. The answers to these questions should be used to weigh the benefits and risks of chemotherapy and whether in fact it should be given. If cure is the therapeutic aim, then considerable short-term toxicity, as produced by intensive combination chemotherapy, is likely to be acceptable. Where short-term palliation is the aim, few, if any, side effects are acceptable. It must also be remembered that what is achievable can change as the disease evolves. Initial therapy may be aimed at obtaining a cure, but for most gynecologic malignancies, if relapse occurs, cure is not possible, although further chemotherapy may achieve temporary remission and may be indicated. Similarly, second-line chemotherapy may achieve a worthwhile remission in a patient who has had a long remission following first-line therapy. In general, however, when gynecologic cancer patients prove resistant to first-line chemotherapy, they are unlikely to respond to second-line therapy. In such a setting, second-line chemotherapy should therefore be considered experimental, with major toxicity being unacceptable.

Table 1 Issues to be Considered Before Using Chemotherapy

1. Natural history the malignancy
   a. Rate of disease progression
   b. Extent of disease spread
   c. Intrinsic chemoresistance
2. Patient's global status and history
   a. Age, general health, nutritional status, underlying medical conditions
   b. Extent and type(s) of prior cancer therapy
   c. Emotional, psychological, and quality-of-life status
   d. Karnofsky, WHO/(ECOG) Performance Status
3. Likelihood of achieving a beneficial response
   a. Cancers in which chemotherapy is curative in some patients, e.g., germ cell tumors
   b. Cancers in which chemotherapy has demonstrated improvement in survival but does not restore a normal life expectancy, e.g., lower-stage cervical cancers treated primarily with radiation and concomitant chemotherapy
   c. Cancers that respond to treatment but in which improved long-term survival has not been clearly demonstrated, e.g., uterine sarcomas, advanced malignant epithelial ovarian cancers
   d. Cancers with marginal or no response to chemotherapy, e.g., melanomas, small cell neuroendocrine tumors

General Guidelines for Doctor–Patient Discussion

Most individuals recently diagnosed with cancer are frightened and anxious. The clinician should initiate discussions informing patients about the diagnosis, treatment options, and prognosis, encouraging questions from patients and family. Special effort is often necessary to insure understanding of complex treatment schemes and parameters, choice of drugs, minor invasive procedures associated with venous access, potential drug-related side effects and agents used to lessen their severity, symptoms associated with the disease or the treatment, and most important of all, prognosis. Most patients want to know what effect cancer will have on their life expectancy. In answer to this question, it is easy for the physician to quote the published statistical survival information, but this means very little to the patient. The reason being that none of that data takes into consideration many of the factors that are known to have prognostic significance, i.e., the immune status of the patient, the rate of growth of her particular malignancy, inherent tumor chemoresistance, tumor chemosensitivity, her attitude, or how much chemotherapy she will be able to tolerate. On the other hand, patients must be made aware of the present limitations of scientific knowledge and, as such, the real inability of the physician to render an accurate prediction of survival. However, although the clinician cannot accurately predict the length of a patient's life, one can use published data to help her understand whether it is reasonable to establish a goal of palliation or cure, short- or long-term disease-free survival, etc. Patients should know that some chemotherapy treatments remove visible tumor and prolong survival time, while others diminish the visible cancer but do not change expected survival time. Compassionate and honest but optimistic disclosure is the key, in words

Table 2 Test and Observations Prior to Chemotherapy

History and physical examination
Review of systems
Previous medical history
LAB:
CBC with differential
Platelets
Serum Creatinine/BUN
Bilirubin, SGOT, alkaline phosphatase
$Na/K/Cl/HCO_3$
$CA/PO_4/Mg$
Serum albumin
Chest x-ray
EKG
Urinalysis
Audiogram (history of hearing loss and patient to receive neurotoxic agents, e.g., cisplatin)
MUGA or ECHO (if clinically indicated and patient to receive anthracycline-based drugs)
Pulmonary function tests (if patient to receive drugs with pulmonary oxicity, e.g., Bleomycin)

that can be understood by the patient and her family. Doctors should also respect the patient's prerogative to decline information, as well as treatment.

GENERAL ASSESSMENT OF THE PATIENT FOR CHEMOTHERAPY

History, Physical Examination, and Laboratory Tests

Prior to the administration of chemotherapy, it is necessary to subject each patient to a meticulous and thorough history and physical examination. While close attention should be paid to the overall physical health of the patient, the clinician should focus on those organ systems at particular high risk for toxic damage by the chosen chemotherapeutic agents. Specific laboratory tests should be selected to aid in the assessment. After all data have been collected, appropriate dosing determinations and adjustments can be made or alternative drugs can be utilized (see Table 2).

Performance Status

Performance status rating is a rough measure of a patient's physical functional status. There are two widely accepted scales used to describe the functional status of cancer patients. They are the Karnofsky Scale of symptoms and disability (1) (see Table 3) and the WHO/Eastern Cooperative Oncology Group (ECOG) scale of functional status (see Table 4). The latter is a simplification of the former and is based on the scale developed by Zubrod et al. (2). Both are fairly crude indicators of therapy/disease impact.

Table 3 Karnofsky Performance Scale

Karnofsky scale	Performance
90 and 100	Fully active
70 and 80	Restricted in physically strenuous activities, but ambulatory
50 and 60	Ambulatory; capable of self-care; unable to work; up 50% of waking hours
30 and 40	Limited self-care; confined to bed or chair 50% of waking hours
10 and 20	Completely disabled; no self-care

The Karnofsky Performance Status (KPS) is the oldest and most widely used quality-of-life measurement. It was initially designed to monitor the benefits of nitrogen mustards in the treatment of inoperable carcinomas (1). Prior to its development in 1948, the three criteria used to evaluate the usefulness of chemotherapeutic agents in the control of cancer were the following: (1) length of remission and prolongation of life; (2) objective improvement; and (3) subjective improvement (3). According to the KPS, the performance status of an individual patient is rated on a numerical scale from 0 to 100. The final score is indicative of a patient's ability to perform normal activity, engage in active work, and the need for assistance. Since the initial description and publication of the scale, it has been widely accepted and used for making clinical decisions regarding the initiation, continuation, or discontinuation of chemotherapy. It is also used to evaluate response to treatment, in combination with objective measures, and to evaluate the impact of chemotherapeutic agents on quality of life (4). It is thus an important part of the initial assessment of the patient who is being considered for chemotherapy.

Recently, a report was published of an investigation designed to determine the nature and extent of physical problems and psychological distress experienced by advanced ovarian cancer patients. Several different types of quality-of-life scales were used to assess patients before and after chemotherapy. Significant differences were found in all quality-of-life scales between ovarian cancer patients with KPS scores of ≤ 80 and those with ratings of ≥ 90. It was unexpected that a cutoff rating as high as 80 would be so highly significant, in relation to worsening quality of life, since a score of 80 indicates a level at which normal activity can still be carried out, but only *with effort*.

Table 4 WHO/ECOG Performance Scale

0 = No symptoms
1 = Symptoms
2 = In bed less than 50% of the day, no work, can care for self
3 = In bed more than 50% of the day, not bedridden, minimal self-care
4 = Completely bedridden

It would seem that this modest decline in performance status is the clinically significant moment for patients, making it increasingly difficult for them to psychologically ignore the disease (5). Another study found a performance status of 80 to be a cutoff not only for expected survival, but also for quality-of-life response to whole abdominal radiation of patients with chemoresistant intra-abdominal ovarian cancer (6).

Psychological Distress

The prevalence of psychological distress in ovarian cancer patients is not known; however, the limited available data regarding psychological functioning of ovarian cancer patients indicates a high prevalence of depressive and anxiety symptoms (5,7). Not surprisingly, psychological stress tends to make things worse for cancer patients and there is evidence it can shorten their survival time. More specifically, women who display either a fighting spirit or denial fare better than those who stoically accept their condition or respond with feelings of helplessness or hopelessness. Indeed, in one such study of breast cancer patients, a woman's initial psychological response to the diagnosis of cancer proved a better predictor of survival than the initial size of her tumor (8). Consequently, a serious effort should be made to screen patients for psychological distress prior to beginning chemotherapy in order that they may be referred for proper psychological intervention. The fact that such interventions can be of benefit is borne out by a study of advanced breast cancer patients who survived twice as long when they took part in psychological therapy which improved their environment (9). One such screening instrument is the FACT-O, a quality-of-life questionnaire for patients with ovarian cancer which has four general subscales and a subscale of concerns specific to ovarian cancer patients (10). The four general subscales assess physical, functional, social/family, and emotional well-being. A high score on the FACT-O indicates good quality of life. Ranges for the subscales are: physical, 0–28; social, 0–28; emotional, 0–24; and functional, 0–28. In addition, instruments should be used to assess anxiety and depression levels since it has been shown that they are inversely related to poor performance status (10,11).

PATIENTS WHO ARE NOT CANDIDATES FOR CHEMOTHERAPY

Making an effort to determine who is a poor candidate for chemotherapy is difficult. Attempts have been made to develop prognostic models for overall survival in gynecologic cancer patients using large databases of patients (12). Such instruments are difficult to use in the clinical setting since there is always the possibility of a response, albeit partial and of short-term duration.

In this regard, we can only recommend that each clinician follow the general principles so poignantly stated in a recent editorial:

> The first question to be answered in each case and at each step along the treatment path is: can the disease be cured? If the answer is yes, then the patient is sick, not dying, treat! If the answer is no, then the next question must be asked: can life be prolonged? If the answer is no, then don't treat, for the treatment is futile. Care must then be directed at symptom control, i.e. palliative care only (13).

When the situation is deemed terminal, the gynecologic oncologist must amplify his or her abilities as a technician, exercise the priestly qualities upon which the profession is founded, and support the patient in her courageous approach to her end. At all times, he or she should make liberal use of the skills and knowledge of his colleagues in related fields, i.e., the patient's care should be interdisciplinary in nature.

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Chemotherapy in Pregnancy

Christine H. Holschneider
David Geffen School of Medicine at UCLA, Los Angeles, California, U.S.A.

Robert E. Bristow and F.J. Montz
Johns Hopkins University School of Medicine, Baltimore, Maryland, U.S.A.

The number of patients who require chemotherapy during pregnancy is small. Few individuals or institutions attain sufficient clinical experience with the management of cancer in pregnancy and the use of cytotoxic agents in the gravid patient. Our knowledge and treatment recommendations are based on anecdotal case reports and small retrospective series. There are no large prospective studies that address the use of chemotherapy during pregnancy. The interpretation of the literature is further complicated by the fact that, owing to the low incidence of cancer treated with chemotherapy during pregnancy, many case series include a cohort of patients treated over several decades with quite variable therapeutic regimens, many of which may not be relevant to modern oncologic practice.

In this overview of chemotherapy in pregnancy, we have compiled clinically useful information on general principles for the use of chemotherapy in pregnancy, as well as the role of chemotherapy in the management of specific gynecological malignancies in pregnancy.

CANCER DURING PREGNANCY

Cancer complicating pregnancy is uncommon. In a linkage study of the Swedish Cancer Registry and a nationwide fertility registry of more than 2.7 million births, the reported incidence of cancer diagnosed during pregnancy was 1/6410 life births, which rose to 1/1938 in the puerperium. In this study, less than half of the expected cancer cases were diagnosed during pregnancy, suggesting that diagnosis is frequently delayed to the postpartum period (1).

Malignancies are one of the leading causes of death in women of childbearing age, and 5% of maternal deaths in the United States are cancer-related (2). The most common malignancies diagnosed during pregnancy are, in decreasing order of frequency, cervical and breast cancer, melanoma, ovarian and thyroid cancer, leukemia, lymphoma, and colorectal cancer (Table 1).

A diagnosis of cancer during pregnancy poses numerous emotional and ethical challenges to the patient and her family. Cancer is always a frightening diagnosis.

Table 1 Pregnancy-Associated Malignancies

Pregnancy-associated malignancies in order of decreasing incidence
Cervix
Breast
Melanoma
Ovary
Thyroid
Leukemia
Lymphoma
Colorectal

Source: From Ref. 3.

Receiving this diagnosis during pregnancy is a most extreme juxtaposition of fear of death and the creation of new life. The patient may need to, or perceive she needs to, choose between what is best for her life and what is best for her unborn child. Treatment of the malignancy may be incompatible with continuation of the pregnancy. The cancer treatment, especially of gynecological cancers, may result in the patient's loss of her reproductive capacity. If the patient does receive cytotoxic therapy during pregnancy, there is anxiety about acute and long-term effects on the health of the offspring exposed to chemotherapeutic agents in utero.

The approach to the care of a pregnant patient with cancer similarly poses significant challenges to the patient's physicians. Treatment often requires modification compared to a nonpregnant patient. In addition to the patient's psychosocial needs, specific issues must be taken into consideration, including the following:

1. Making the diagnosis of a malignancy during pregnancy often requires increased vigilance to avoid erroneous attribution of symptoms to the pregnancy per se. When cancer is suspected, workup should be as expeditious as in the nonpregnant patient.
2. Once the diagnosis of cancer is confirmed, the concern arises if there are any adverse effects of the pregnancy on the cancer and reciprocally of the cancer on the pregnancy.
3. In the consideration of possible cancer therapies, their effects on the pregnancy and fetus need to be taken into account, both acute and long term.
4. The physiologic changes of pregnancy may alter the metabolism of chemotherapeutic agents and have implications for drug dosing.
5. The timing of therapy poses numerous questions: When can treatment be delayed until the postpartum period without undue risk to the mother? When is early delivery or termination of pregnancy of likely benefit to the maternal outcome and thus advisable?
6. Specific considerations guide cancer therapy in the puerperium.

A successful outcome depends on a multidisciplinary team approach integrating medical, oncological, obstetrical, and perinatal factors with the patient's moral, ethical, religious, and social background and her wishes in regards to the pregnancy.

PRINCIPLES OF CANCER MANAGEMENT DURING PREGNANCY

Surgery

Surgery may be indicated to obtain tissue diagnosis for staging or treatment. Extra-abdominal procedures and most intra-abdominal operations that do not interfere with the reproductive tract are usually well tolerated by both mother and fetus. Diagnostic and staging operations involving a laparotomy in a patient desirous to continue the pregnancy are ideally performed in the early second trimester, as long as maternal well-being is not acutely threatened by that delay. If indicated, the ovaries may be removed safely after the first trimester, when placental progesterone production is sufficient to maintain the pregnancy. Resection of the ovary that carries the corpus luteum gravidarum prior to that time may cause abortion, which can often be prevented by exogenous progesterone administration.

Imaging Studies

Imaging studies are an integral part of the workup and staging of many malignancies in the nonpregnant patient, but frequently require modifications due to the pregnancy. For reasons outlined below, fetal exposure to ionizing radiation should be kept to a strict minimum. Table 2 summarizes the estimated radiation exposure associated with some of the typical imaging procedures. A chest radiograph or mammogram leads to minimal fetal radiation exposure, and judicious use of these imaging procedures in the pregnant patient is appropriate as long as proper shielding is used. In contrast, a 10-section CT scan of the abdomen is associated with a 1.7–2.6 cGy pelvic radiation dose and is to be avoided. Ultrasound or MRI should be substituted during pregnancy.

It is difficult to establish a definite threshold dose below which radiation exposure in pregnancy is safe. As reported by the National Council on Radiation Protection and Measurements (4), it appears that exposure of the embryo to less than 5 cGy is associated with no measurable increase in the risk of developmental abnormalities or major malformations beyond the 3–4% background incidence. However, exposure doses below 5 cGy have been associated with an increased risk of childhood cancers (5). While the period of organogenesis is the most susceptible to teratogenic effects by radiation, there is no gestational age that is safe. Growth restriction and mental retardation appear associated predominately with second trimester exposure (see below).

Table 2 Estimated Fetal Radiation Exposure with Different Imaging Procedures

Procedure	Absorbed pelvic dose (cGy)
Chest radiograph (2 views)	$2–7\times10^{-5}$
Mammogram (4 views)	$0.7–2\times10^{-2}$
CT head (10 cuts)	0.05
CT chest (10 cuts)	0.1
CT abdomen (10 cuts)	1.7–2.6

Source: From Ref. 4.

Radiation Therapy

Therapeutic radiation may result in substantial exposure of the fetus to ionizing radiation. The extent of radiation exposure to the fetus depends on the tissues being radiated, the location and size of the radiation field, the radiation dose, the shielding used, and the gestational age of the pregnancy.

High-dose radiation exposure leads to characteristic adverse fetal effects including microcephaly, mental retardation, and growth restriction (6). The study of children born to mothers exposed to atomic bomb explosions provides evidence for an association between the radiation dose, gestational age at exposure, and the fetal risk (7). With 10–50 cGy radiation exposure, the observed overall risk of mental retardation was 2.4%, which rose to nearly 18% if the exposure was 50–100 cGy. Mental retardation was most frequently observed with exposure at 8–15 weeks, followed by exposure at 16–25 weeks (Table 3). While the CNS maintains its sensitivity to radiation throughout gestation, the predominate effects vary according to gestational age: with exposure up to 15 weeks gestation, microcephaly is the major adverse outcome (8). The highest risk period for severe mental retardation is from 8 to 25 weeks, corresponding to the time of differentiation of the cerebral cortex. Growth restriction and the oncogenic potential are additional significant fetal sequelae of second and third trimester exposure (6).

Thus there is no gestational age that is considered safe for therapeutic radiation exposure of the pregnancy. Therapeutic abdominopelvic radiation during pregnancy is contraindicated unless termination of the pregnancy is one of its purposes. Even supradiaphragmatic radiation may carry substantial exposure risks for the fetus and is indicated in very select cases only. Radiation for breast cancer, for example, at a dose of 5000 cGy, can still result in significant scatter to the fetus even with the use of appropriate shielding, which has been estimated to be 10–15 cGy in the first trimester and up to 200 cGy in later gestation as the uterus rises out of the pelvis (9).

Table 3 Mental Retardation due to Fetal Radiation Exposure in Relation to Gestational Age and Absorbed Dose

Absorbed fetal dose	Retarded/exposed offspring	Retarded/exposed offspring by gestational age at exposure (weeks)			
(cGy)	*N* (%)	0–7	8–15	16–25	≥26
Background control	9/1085 (0.8%)	1/156 (0.6%)	1/253 (0.4%)	3/324 (0.9%)	4/352 (1.1%)
1–9	4/292 (1.4%)	0/42	2/64 (3.1%)	2/94 (2.1%)	0/92
10–49	4/169 (2.4%)	0/19	3/48 (6.3%)	1/49 (2.0%)	0/53
50–99	6/34 (17.6%)	0/2	4/11 (36.4%)	2/14 (14.3%)	0/7
≥100	7/19 (36.8%)	0/1	5/8 (62.5%)	1/6 (16.7%)	1/4 (25%)

Source: From Ref. 6.

Chemotherapy

Chemotherapy plays an integral part in the management of cancer in pregnancy. It is used not only for the treatment of those tumors where chemotherapy is standard primary therapy in the nonpregnant patient, but also for the management of tumors where surgery or radiation may be primary therapies in the nonpregnant state, but are now contraindicated for the sake of the pregnancy which the patient wishes to continue. The rationale for using neoadjuvant chemotherapy in these patients would be to shrink the tumor, treat metastatic disease, and prevent any further spread, while gaining time to reach fetal maturity prior to definitive radiation therapy or surgery.

THE TIMING OF THERAPY

The ultimate decision to delay or initiate chemotherapy during pregnancy requires individualization, taking into account the specific cancer, its stage and prognosis, the gestational age of the pregnancy, the estimated impact of treatment delay on fetal and maternal well-being, as well as the psychosocial needs of the mother and family.

The Impact of Gestational Age at Delivery on Neonatal and Intact Neonatal Survival

With modern neonatal critical care, the threshold for fetal viability is considered 23–24 weeks. However, morbidity and mortality are considerable with delivery at such a premature gestational age. As is outlined in Table 4, significant fetal benefit can accrue

Table 4 Neonatal Survival and Morbidity Based on Gestational Age at Delivery

EGA (weeks)	Survival (%)	Intact survival (%)	RDS (%)	IVH (%)	NEC (%)	PDA (%)	NICU (%)	No c/o of prematurity (%)
24	33–60	6–28	67	25	8	33	100	
25	60–79	45–47	87	30	17	61	100	
26	70–82	50–63	93	30	11	48	100	0
27	80–85		84	16	10	39	100	0
28	>90		64	4	25	43	100	7
29			53	3	15	44	100	6
30	>95		53	2	15	23	94	9
31			37	2	8	16	96	22
32			28	0.9	6	9	98	28
33			34	0	2	2	84	40
34	>98		14	0	3	2	70	59
35			6	0	0.3	1	41	5
36			3	0	0.9	0.4	24	87
≥37			0.4	0	0	0.3	10	95

EGA = estimated gestational age; RDS = respiratory distress syndrome; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; PDA = patent ductus arteriosus; NICU = neonatal intensive care unit; c/o = complications.
Source: From Ref. 10–12.

from relatively short delays in delivery. For newborns without congenital anomalies admitted to a neonatal intensive care unit, the mortality rate approximates 30% at 25–26 weeks, compared to 2% at 34–35 weeks. With continued improvements in neonatal intensive care, the overall viability threshold is decreasing, as is the gestational age at which an infant can be delivered with acceptable risks of prematurity. Neonatal risks of prematurity must be weighed against management options for the mother to reach a decision regarding the gestational age for delivery and definitive maternal therapy.

The Impact of Treatment Delay on Maternal Outcome

While the significance of gestational age at delivery for neonatal survival and intact neonatal survival is well understood, it is extremely difficult to gauge the impact of treatment delay on the mother's cancer, her ultimate therapy and prognosis, and to estimate an acceptable duration of treatment delay due to the paucity of data. Maternal risks from delay of therapy are primarily related to the possibility of disease progression and dissemination during the observation period. Estimates of these risks will depend on the primary site and stage of disease. For some of the gynecological cancers, published data on the deliberate delay of therapy will be discussed later in this chapter on a disease-specific basis.

Once the decision is made that the pregnancy will be continued and that chemotherapy should be given during pregnancy, the timing of treatment becomes important in relation to:

1. The risk of adverse fetal effects by gestational age
2. The planning of a scheduled delivery

Fetal Risks Based on Gestational Age at the Time of Antineoplastic Drug Therapy

Fetal cells divide and differentiate rapidly during the first trimester, and chemotherapy carries well-recognized risks for the fetus. The effects of chemotherapy on the fetus are influenced by several factors, such as the timing, dose, and frequency of exposure, as well as the ability of the drug to cross the placenta (13,14). Most of our knowledge of the teratogenic and mutagenic effects of antineoplastic agents in pregnancy is derived from animal studies and small human case series or case reports. In the first 2 weeks after fertilization, there is an "all or nothing effect": if the blastocyst is not destroyed by the teratogenic insult, there is no increased probability of adverse effects. The most sensitive time is the period of organogenesis, encompassing weeks 3–8 of development, which correspond to a gestational age of 5–10 weeks. For most tissues, organogenesis is fully completed by 13 weeks gestation and the time thereafter is characterized by maturation and growth. The nervous system, eyes, and bone marrow are exceptions. These organs continue to develop throughout intrauterine life (14). If the insult during organogenesis is severe, spontaneous abortion will ensue. If damage is sublethal, teratogenesis may occur. This is reflected in a reported 10–20% major malformation rate associated with first trimester exposure to chemotherapeutic agents, compared to

a 3–4% major malformation rate in the general population (13,15). In the first 210 cases reported by the Registry of Pregnancies Exposed to Chemotherapeutic Agents, sponsored by the National Cancer Institute, there were 29 births with a total of 52 major malformations. Twenty-seven of the 29 births with abnormal outcomes were associated with first trimester exposure (16).

With second and third trimester exposure to cytotoxic agents, there does not appear to be a significant increase in the risk of major malformations. Although the central nervous system continues to develop during the second and third trimester, there are several small retrospective studies that do not report an increased frequency in neurological or psychological developmental delay associated with second or third trimester exposure to chemotherapeutic agents (17–19). It is important to recognize that the delayed effects of in utero exposure to cytotoxic drugs are even less documented than acute effects. Past experience with clear cell carcinoma of the vagina in women exposed to diethylstilbestrol (DES) in utero serves as a reminder of the necessity for vigilant long-term follow-up (20).

In the second and third trimester, growth restriction and preterm birth become the dominant adverse effects and are probably underreported (3,19,21). Chemotherapy also may result in direct fetal toxicities. Reported examples are acute neonatal cardiac toxicity associated with the second trimester use of the anthracycline idarubicin (22), persistent neonatal hearing loss following in utero exposure to cisplatin (23), or fetal and neonatal myelosuppression (23,24). The Toronto Leukemia Study Group had reported that 5 of 15 infants exposed to myelosuppressive agents in utero within 1 month from delivery were cytopenic at birth (19).

These potentially deleterious effects on the fetus must be weighed against the benefits of therapy to the patient. In summary, chemotherapy should be delayed whenever possible until after the first trimester. For the second and third trimesters, currently available data suggest that if aggressive chemotherapy is likely to improve maternal outcome, physicians should not be reluctant to offer it to the patient. Late in pregnancy, early delivery prior to systemic chemotherapy may be an option.

The Timing of Chemotherapy and Delivery

The timing of chemotherapy in relation to a planned preterm or term delivery requires careful coordination. For the mother, the optimal time for delivery is when the acute toxicities of the preceding chemotherapy cycle have subsided and when her leukocyte and thrombocyte nadirs have recovered to reduce the risk of infectious complications or hemorrhage. These considerations are equally important for the fetus since the placenta may be a significant route of drug clearance, in particular, for the preterm fetus whose immature kidneys and liver may have only limited ability to excrete or metabolize some of the cytotoxic agents. Thus, ideally, myelosuppressive chemotherapy should be avoided for 3 to 4 weeks prior to intended delivery.

Chemotherapy in the Puerperium

Many chemotherapeutic agents are excreted into the breast milk, such as methotrexate (25), doxorubicin (26), cisplatin (27), cyclophosphamide (28), and others. Breastfeeding is therefore generally not recommended in women receiving cytotoxic agents.

PREGNANCY CONSIDERATIONS FOR SELECTION AND DOSING OF CHEMOTHERAPEUTIC AGENTS

Appropriate use of chemotherapeutic agents requires knowledge of the mechanisms of action, effect on cell cycle phase, and toxicity. In pregnancy, there are additional considerations of altered drug metabolism, teratogenicity, and fetal toxicity.

Physiologic Changes of Pregnancy

Physiologic changes associated with pregnancy may directly affect the dosing and toxicity of chemotherapeutic agents. Plasma volume increases by about 50%, which may alter the volume of drug distribution, reduce peak drug concentrations, and prolong an agent's half-life, unless the elimination of the drug is also increased (29). The increase in renal blood flow and glomerular filtration rate may increase the clearance of drugs renally excreted. Amniotic fluid may act as a pharmacological third space and may delay drug clearance, thus enhancing drug toxicity, which has been raised as a concern especially for methotrexate (3,14,29). Decreased serum albumin during pregnancy may result in an increased concentration of the free fraction of protein-bound drugs and a potential enhancement of the pharmacologic effects (13). Alteration in hepatic function may increase or decrease the metabolism and excretion of certain drugs (29). Delayed gastric emptying and reduced intestinal motility may alter the oral bioavailability of certain drugs (13).

Although the physiological changes that accompany pregnancy may significantly alter the narrow therapeutic index of cytotoxic agents, potentially curative chemotherapy is typically administered without dose modification compared to the nonpregnant patient. In order to assure that the appropriate amount of drug is given, physiological parameters such as weight, creatinine clearance, or serum album levels need to be monitored regularly and respective dose adjustments need to be made as the pregnancy progresses. The patient needs to be closely monitored for toxicities from the chemotherapy and assessment of disease response. Close surveillance of the pregnancy and fetal well being is indicated.

The Placenta

In animal studies, virtually all chemotherapeutic agents cross the placenta and most are teratogenic. Placental transfer of maternal substances to the fetus is usually established by the fifth week of life (30). One of the placental characteristics is a preferential transfer from the maternal to the fetal circulation of low molecular weight, nonionized, lipophilic molecules which have a low degree of protein binding (14,29). These characteristics are shared by many of the chemotherapeutic agents. It is important to keep in mind that, reciprocally, for a number of cytotoxic substances, the placenta may facilitate elimination from the fetus since it is the primary route of excretion of fetal waste products.

Teratogenicity, Mutagenicity, and Direct Toxic Effects on the Fetus

Use of many chemotherapeutic regimens in pregnancy has been associated with spontaneous abortions, fetal malformations, fetal growth restriction, or fetal death.

It is important, but at times difficult, to differentiate the teratogenic, mutagenic, or direct toxic effects of the chemotherapeutic agent from adverse fetal effects resulting from a compromised intrauterine environment due to the maternal disease itself, maternal malnutrition, or maternal side effects from the chemotherapy, such as neutropenic fever, thrombocytopenia, and cardiac or pulmonary insufficiency. Adverse fetal effects are determined by the specific medication, the gestational age at first exposure, the dose, duration, and frequency of exposure, and the ability of the drug to cross the placenta. Data for individual agents are at times difficult to interpret as chemotherapy is often given as multiagent combination therapy.

CHEMOTHERAPEUTIC AGENTS—ACUTE EFFECTS

Careful thought should go into the selection of specific antineoplastic drugs for chemotherapy in pregnancy. Following is a summary of salient points regarding different classes of antineoplastic agents. However, a detailed discussion of pregnancy considerations for each chemotherapeutic substance is beyond the scope of this chapter. The practitioner who is confronted with the challenge of treating a patient with single or multiagent chemotherapy in pregnancy is referred to the following resources for a more detailed agent-specific analysis:

1. On-line databases, such as
   a. REPROTOX® (www.reprotox.org)
   b. TERIS® (http://depts.washington.edu/~terisweb/index.html)
   c. Perinatology Network (www.perinatology.com)
2. Printed reference books on fetal and neonatal risks associated with drug use in pregnancy (30)
3. The Registry of Pregnancies Exposed to Chemotherapy Agents, which was founded in 1984 at the Clinical Epidemiology Branch of the National Cancer Institute and is currently at the University of Oklahoma Health Sciences Center [Tel.: (405) 271-3663; fax: (405) 271-8697; e-mail: Johnmulvihill@ouhsc.edu].

Since most chemotherapeutic agents are used in combination and since most of our knowledge is based on small case series, anecdotal data, and individual case reports, it is extremely difficult to ascribe an exact relative risk for teratogenicity to specific antineoplastic drugs. Population incidences cannot be accurately calculated from groups of case reports. However, in examining the literature and various classes of cytotoxic agents, certain patterns emerge. Drugs in pregnancy have been assigned a risk factor category (A, B, C, D, or X; Table 5) according to definitions provided by the Food and Drug Administration (31). Nearly all cytotoxic agents are category D (Table 6), which indicates that there is evidence of fetal risk based on human experience, but that the maternal benefit may justify the potential risk to the fetus.

Antimetabolites

This group of antineoplastic drugs, in particular, the folic acid antagonists, is the agents most commonly associated with fetal anomalies (13). First trimester exposure

Table 5 Classification of Drugs Used During Pregnancy According to Fetal Risk

Risk category	Definition
Category A	Controlled human studies fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of risk in the second or third trimester) and the possibility of fetal harm appears remote.
Category B	Either animal studies have not demonstrated a fetal risk but there are no controlled human studies, or animal studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of risk in later trimesters).
Category C	Either animal studies have demonstrated adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled human studies, or studies in women and animals are not available. These drugs should be given only if the potential benefit justifies the potential risk to the fetus.
Category D	There is positive evidence of human fetal risk but due to the benefits to pregnant women in specific situations, use of these drugs may be acceptable despite the fetal risks (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
Category X	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

Source: From Ref. 30.

has been associated with malformation rates as high as 19–30% (13,32). First trimester exposure to the folic acid antagonist aminopterin leads to a characteristic syndrome of cranial dysostosis, hypertelorism, anomalies of the external ear, micrognathia, and limb deformities (13). Methotrexate, a commonly used folic acid antagonist, is well known as a potent abortifacient. Methotrexate is also a human teratogen. First trimester exposure to methotrexate has been associated with multiple birth defects including cranial defects and malformed extremities (33). First trimester exposure of six embryos to cytosine arabinoside alone or in combination therapy leads to the delivery of four normal infants and two with congenital anomalies (34). Other antimetabolites are associated with birth defects less frequently (13). One isolated case report describes multiple congenital anomalies in a neonate exposed to 5-fluorouracil during the first trimester, but the patient also received radiotherapy (35). For 20 pregnant patients exposed to 6-mercaptopurine alone, no fetal anomalies were documented (13).

Alkylating Agents

Based on a review of 70 women who were treated with alkylating agents, such as cyclophosphamide, busulfan, nitrogen mustard, or chlorambucil during pregnancy, the rate of fetal anomalies with first trimester exposure is 14% (13). The chlorambucil syndrome associated with exposure during organogenesis is characterized by renal

Table 6 Reported Teratogenicity with First Trimester Use of Cytotoxic Agents

Cytotoxic agent	First trimester exposure (*N*)	Fetal malformations (*N*; %)	Pregnancy drug category
Antimetabolites			
Aminopterin	52	10 (19%)	
MTX	10	3 (30%)	X
Ara-C	8	2 (25%)	D
5-FU	14	1 (7%)	D
6-MP	34	0	D
Alkylating agents			
Cyclophosphamide	7	3 (43%)	D
Busulfan	31	6 (19%)	D
Chlorambucil	5	1 (20%)	D
Antibiotics			
Doxorubicin	3	0	D
Daunorubicin	4	0	D
Vinca alkaloids			
Vincristine	9	0	D
Vinblastine	14	1 (7%)	D

MTX = methotrexate; Ara-C = cytosine arabinoside; 5-FU = 5-fluorouracil; 6-MP = 6-mercaptopurine.
Source: From Ref. 13, 29, 30, 32.

aplasia, cleft palate, and skeletal abnormalities. When alkylating agents are administered during the second or third trimesters only, the rate of malformations reduces to background levels at 4% (3,36).

Antibiotics

In small series on human exposure to doxorubicin or daunorubicin during the first trimester of pregnancy, neither of these agents has been associated with an increased incidence of birth defects (29). There are several cases where bleomycin has been successfully used in the second and third trimester of pregnancy, followed by the delivery of normal babies (32). However, there have been distinct fetal and maternal toxicities described in association with the use of these agents in pregnancy. Cardiotoxic fetal effects of idarubicin administered in the second trimester have been reported (22). For patients receiving bleomycin, maternal hyperoxygenation to improve fetal well-being may increase the risk of maternal pulmonary toxicity associated with bleomycin (3).

Vinca Alkaloids

In animals, vincristine and vinblastine are embryocidal and teratogenic (30). The experience with use of these agents in humans is limited. To date, an increase in fetal malformations attributable to these agents has not been described (13,15,30). There

are no data on first trimester use of vinorelbine in humans, but case reports attest to the successful use of vinorelbine in the second and third trimesters (30).

Cisplatin

Cisplatin distributes into most tissues and is teratogenic in several animal species (30). Information regarding the use of cisplatin in human pregnancies is limited and controversial. There are several case reports on the administration of cisplatin during the second and third trimester, which find no significant associated increase in severe adverse neonatal outcomes (30,32). However, myelosuppression has been observed in newborns following in utero exposure to cisplatin. One case of persistent moderate bilateral hearing impairment in an infant has been described who was exposed in utero to both cisplatin and an aminoglycoside (23,30).

Taxanes

To date, there is one report on the use of paclitaxel during the second and third trimester of pregnancy without adverse fetal sequelae (37).

Etoposide

There are few reports regarding the fetal risks of the use of etoposide (VP-16) in the second or third trimesters of pregnancy, in particular, growth restriction and myelosuppression (32). While there have been no reports of pregnant women or newborns developing leukemias as a result of exposure to these agents, the risk of secondary acute myelogenous leukemia in children and adults who receive this drug is well recognized (38) and remains a concern for the in utero exposed offspring.

CHEMOTHERAPEUTIC AGENTS—DELAYED EFFECTS

The delayed effects on the offspring of in utero exposure to chemotherapeutic agents are even less well documented than acute effects. Many studies report no significant adverse long-term outcomes (17–19,39). But chemotherapy-induced second malignancies, impaired growth and development, intellectual impairment, and gonadal dysfunction have been reported and are of concern (40). In addition, subtle abnormalities may go unreported. The past experience with in utero exposure to diethylstilbestrol (DES) and the development of clear cell carcinoma of the vagina in young women (20) is a reminder for the need of a highly vigilant and close long-term follow-up of offspring exposed to cytotoxic agents in utero.

SUPPORTIVE DRUG TREATMENT DURING CYTOTOXIC THERAPY IN PREGNANCY

Like in the nonpregnant patient, the management of symptoms and complications of cancer or cancer therapy in pregnancy rests significantly upon drug therapy. Potential

fetal risks need to be considered for each of these medications. Pregnancy risk categories for some of the more frequently used supportive agents are summarized in Table 7.

Recombinant Erythropoetin (Epoetin Alfa)

In most animal studies, erythropoetin is not teratogenic, but increased fetal wastage and slowed growth are observed. While there are controversial results in animals regarding the ability of recombinant erythropoetin to cross the placenta, it appears that in humans, it does not cross the placenta. Small case series in pregnant women report no evidence of adverse fetal effects attributable to the use of exogenous erythropoetin (30).

Recombinant Granulocyte-Colony Stimulating Factor

Granulocyte-colony stimulating factor (G-CSF) is a glycoprotein cytokine that induces the proliferation and differentiation of granulocyte precursors and activates

Table 7 Risk Category of Commonly Used Drugs for Supportive Treatment During Cytotoxic Therapy

Agent	Pregnancy risk category
Hematopoetic growth factors	
Epoetin alfa	C
G-CSF	C
Antiemetics	
Metoclopramide	B
Prochlorperazine	C
5-HT3 receptor antagonists	B
Antihistamines	
Diphenhydramine	B
Ranitidine	B
Lorazepam	D
Corticosteroids	
Prednisone	C
Dexamethasone	C
Analgesics	
Acetaminophen	B
Ibuprofen	B (D in 3rd trimester)
Oxycodone	C
Hydrocodone	C
Morphine sulfate	C
Hydromorphone	C

G-CSF = granulocyte colony-stimulating factor; NSAIDs = nonsteroidal anti-inflammatory drugs.

mature neutrophils. Granulocyte-colony stimulating factor crosses the placenta freely. There is no evidence of acute adverse fetal effects. Several studies report on the successful use of G-CSF during pregnancy (41–43). There is theoretical concern, however, that prolonged administration of G-CSF may increase the risk of developing leukemia (44).

Antiemetics

Metoclopramide has been used extensively in pregnancy as an antiemetic and to reduce gastric emptying time with no associated adverse fetal effects (30). Regarding the use of prochlorperazine in pregnancy, there are occasional case reports of congenital defects of children exposed to the drug in utero. However, the majority of evidence indicates that prochlorperazine is safe for the treatment of nausea and vomiting in pregnancy (30). The 5-HT3 receptor antagonists, ondansetron and granisetron, are potent antiemetics indicated for the prevention and treatment of chemotherapy-induced nausea and vomiting. Human experience with use during pregnancy is limited, but animal studies show no teratogenic effects (30).

Steroids

Dexamethasone is a very potent drug used to treat a variety of cancer-related symptoms, including the prevention and management of chemotherapy-induced nausea and vomiting. It is synergistic with metoclopramide and the 5-HT3 receptor antagonists. Concerns with corticosteroid therapy in early pregnancy include a higher incidence of orofacial clefts (45). Multiple courses of steroids that cross the placenta have been associated with low birth weight, fetal hypoadrenalism, development of cushingoid features, and masculinization of female fetuses. Maternal glucose intolerance is an additional concern. Dexamethasone crosses the placenta. Long-term follow-up evaluations of children exposed in utero to dexamethasone have shown no significant adverse effects from this exposure. However, because prednisone gets metabolized before it crosses the placenta, it is generally the corticosteroid of choice in pregnancy, unless given for fetal indications (30).

Antihistamines

Animal data and published human experience suggest that diphenhydramine, a first-generation antihistamine, is safe for use in pregnancy (30), with the exception of one isolated case-control study, which reports an increase in oral clefts in association with first trimester exposure (46). Ranitidine, a competitive, reversible H2-receptor inhibitor, is not a teratogen and is safe for use during pregnancy (47). Because it has no antiandrogenic activity, ranitidine is preferred over cimetidine for use in pregnancy (30).

Pain Management

The first step is to determine if the pain is from the cancer, the pregnancy, or an unrelated, coexisting cause. Because of its safety profile, acetaminophen is considered the recommended first-line mild analgesic during pregnancy (30). First trimester exposure to nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated

with spontaneous abortions, but there is no increase in anomalies. Second to early third trimester exposure has not been linked to adverse birth outcomes (48). Use of NSAIDs in more advanced pregnancy or near birth has been linked to certain risks such as decreased amniotic fluid volume and mild constriction of the ductus arteriosus (30). Thus while most NSAIDs are in risk category B or C for the second trimester, they are class D for third trimester use. For moderate pain, oxycodone or hydrocodone, often in combination with acetaminophen, is recommended. For severe pain, there are additional narcotic agents such as morphine sulfate or hydromorphone. Opioids are not teratogenic, but rapidly transferred across the placenta. The main concern is fetal and neonatal withdrawal because of physical dependence. After long-term use, it is imperative to prevent acute opioid withdrawal during pregnancy, as it can be life-threatening to the fetus. The neonatal abstinence syndrome consists among other of apnea, autonomic dysfunction, diarrhea, diaphoresis, lacrimation, irritability, respiratory distress, seizures, tachypnea, and wakefulness. Its treatment is usually paregoric to wean the infant off opioids (49).

THE ROLE OF CHEMOTHERAPY IN THE MANAGEMENT OF GYNECOLOGICAL MALIGNANCIES DURING PREGNANCY

It is estimated that coexisting pregnancy complicates 3% of gynecological cancers (50). As is evident from the above discussion, data on the use of chemotherapeutic agents in pregnancy are all but abundant. Information on the management of specific gynecological malignancies with chemotherapy during pregnancy is even more scant and mostly based on case reports. This limited experience has prevented the development of universally accepted algorithms for the management of these patients, whose cancer diagnosis during pregnancy is accompanied by many complex issues requiring individualization of therapy.

CERVICAL CANCER

Cervical cancer is the most common malignancy encountered in pregnancy. The reported incidence of cervical cancer in pregnancy varies from 1.2 to 10.6 per 10,000 pregnancies (51,52). Pregnancy per se does not affect the prognosis for women with cervical cancer, as has been shown by several studies which confirm no difference in survival between patients diagnosed during pregnancy and nonpregnant women, when matched by age, stage, and year of diagnosis (53–57).

The management of invasive carcinoma of the cervix during pregnancy confronts the patient and physician with many challenges. The primary means of therapy for cervical cancer in the nonpregnant patient, radical hysterectomy or irradiation, are incompatible with continuation of the pregnancy. Thus management is individualized based on clinical stage, lesion size, gestational age, and the patient's wishes for the pregnancy. As outlined earlier, the benefit to the fetus from delay in therapy to achieve maturity is easily measurable and unquestioned. It is significantly more difficult to quantify the risk of delay of therapy for maternal outcome. Careful physician–patient counseling is required to decide issues such as termination of pregnancy, timing of delivery, route of delivery, delay of treatment, or mode of therapy during pregnancy.

Impact of Delay of Therapy on Maternal Outcome

Table 8 summarizes small series that report on the intentional delay of therapy for patients with cervical cancer during pregnancy to optimize fetal maturity. All patients had stage I–II disease and treatment was delayed between 3 and 40 weeks. Of the 77 patients, 72 (97%) were alive without evidence of disease at last follow-up. While these data are encouraging, it is important to recognize that most reports are heavily weighed toward stage IA and small stage IB1 disease. For these patients, the risk of

Table 8 Experience with Deliberate Delay of Therapy for Patients with Invasive Cervical Cancer to Allow for Time for Fetal Maturity

Author, year	*N*	Stage	EGA at diagnosis	EGA at delivery	Delay in treat. (wks)	Dz. progr.	F/U (months; mean/range)	Maternal outcome
Prem et al., 1966	4	I	≥28	35–36	6 (average)	–	All > 60	All NED
Prem et al., 1966	5	I	20–34	34–38	11–17	–	34–64	All NED
Boutselis, 1972	5	IA1	8–24	3rd trimester	–	–	72–180	All NED
Dudan et al., 1973	2	IB	–	–	8–24	2	–	≥1 DOD
Thompson et al., 1975	7	IA	–	3rd trimester	5–28	–	50 (3–120)	All NED
Lee et al., 1981	9	IA–II	≥24	3rd trimester	< 12	no	–	All NED
Nisker and Shubat, 1983	1	IB	–	3rd trimester	24	1	–	DOD
Greer et al., 1989	5	IB	20–24	28–37	6–17	no	23 (13–35)	4 NED, 1 DOD
Monk and Montz, 1992	4	IA2–IB	10–23	3rd trimester	10–23	no	40 (2–228)	All NED
Duggan et al., 1993	8	IA1–IB1	11–31	31–40	8–30	no	33 (3–124)	All NED
Sorosky et al., 1995	8	IB1	0–34[a]	33–38	3–40	no	33 (13–68)	All NED
Sood et al., 1996	11	IA1–IB1	–	3rd trimester	3–32	–	118 (12–360)	All NED
Sorosky et al., 996	4[b]	IB1–IB2	18–32	35–36	4–15	–	51 (12–120)	3NED, 1 DOD
Van Vliet et al., 1998	4	IB	23–32	32–35	3–10	–	67 (16–106)	All NED
Total	77	IA1–II	0–34	3rd trimester	3–40	3	2–360	72 NED, 4 DOD

In some cases, treatment delay was greater than the time difference of diagnosis to delivery as postdelivery irradiation may not have started for several weeks postpartum. EGA = estimated gestational age; Treat = treatment; wks = weeks; Dz = disease; Progr = progression; F/U = follow-up.

[a] One patient was diagnosed in the cycle prior to conception and followed through pregnancy.

[b] Excluded three cases that were doubly reported in Sorosky's (85) and (86) series.

clinically significant progression of disease with delay of treatment appears to be small. Based on the available data, one cannot accurately inform the patient with stage IB2 or more advanced disease regarding the magnitude of danger associated with a planned delay in therapy and an informed patient considering a delay in therapy has to be willing to assume this unknown risk.

For the timing of therapy, the following conclusions can be drawn. If the pregnancy is unwanted and previable, immediate treatment of the mother should be initiated. If fetal maturity has already been reached, immediate delivery, followed by the appropriate surgical or chemoradiation therapy, is indicated. Independent of the gestational age at diagnosis, patients with microinvasive disease who have been fully evaluated by conization can be followed closely until delivery, with further evaluation and treatment postpartum. Delay in therapy until fetal maturation is achieved irrespective of the gestational age at diagnosis is also reasonably arguable in the cases of a desired pregnancy in a patient with far-advanced cervical cancer where the maternal prognosis is poor regardless of therapy. However, any scenario in between these extremes, especially when the cancer is diagnosed at a stage with an excellent chance for cure with therapy, but the pregnancy is desired and remote from maturity, requires at times extraordinarily difficult decisions to be made regarding when to institute treatment. If the patient wishes to delay therapy, she should be examined every 2–3 weeks. If there is any clinical suspicion for disease progression, an abdominopelvic MRI should be obtained. The pregnancy should be followed closely and delivery initiated no later than the time of documented fetal lung maturity. If expert neonatal critical care is available, the decision to intervene at an earlier time may be entertained.

Classic teaching has frequently used 20 weeks as a gestational age, beyond which delay in therapy to allow fetal maturity would be offered to patients who desired to continue their pregnancy, whereas termination and immediate therapy would be suggested to patients with earlier gestations (51). However, with continually improving neonatal intensive care capabilities and with growing experience in the use of neoadjuvant chemotherapy, there is an increasing trend toward therapy in accordance with the patient's wishes for the pregnancy even at an earlier gestational age or with more advanced disease.

Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy has been extensively evaluated in the treatment of nonpregnant patients with locally advanced cervical carcinoma with, at times, dramatic tumor regression and overall response rates as high as 85% for stage I/II and 75% for stage III disease (58). For selected pregnant patient with locally advanced disease who declines pregnancy termination, consideration may be given to the use of neoadjuvant chemotherapy in an effort to prevent disease progression during the time needed to achieve fetal viability. The published experience with neoadjuvant chemotherapy in pregnancy has been limited to four cases, which are summarized in Table 9.

Route of Delivery

No convincing data exist indicating that the route of delivery influences the outcome of patients with microinvasive disease (59). Delivery in women with frankly invasive

Table 9 Reported Experience with Neoadjuvant Chemotherapy in Pregnancy

	Giacalone et al., 1996 (88)	Tewari et al., 1998 (89)	Marana et al., 2001 (90)
N	1	2	1
Stage	IB1	IB2–IIA	IIB
EGA at diagnosis	17	20–21	14
EGA at delivery	32	32–34	38
Delivery delay (wks)	15	11–14	24
Chemotherapy	C×3	CV×4–6	CB×2[a]
Disease response	CR	PR×2	PR
Maternal outcome	NED at 12 months	1 NED at 24 months, 1 rec. dz. at 5 months	DOD at 13 months

EGA = estimated gestational age; C = cisplatin; V = vincristine; B = bleomycin; CR = complete response; PR = partial response; NED = no evidence of disease; rec. dz. = recurrent disease; DOD = died of disease.
[a] Patient was noncompliant with therapy during the second half of pregnancy and declined any treatment postpartum.

cervical cancer should be by cesarean section to avoid potential cervical hemorrhage and possible dissemination of tumor cells during vaginal delivery. Numerous cases have been reported in the literature where cervical cancer recurred in the episiotomy scar following vaginal delivery (60,61). Whether vaginal delivery per se is a poor prognostic variable for patients with frankly invasive cervical cancer is controversial (53,62). A cesarean radical hysterectomy with therapeutic lymphadenectomy offers immediate treatment for stage IA2 to IIA cervical cancer with a demonstrated low associated morbidity (54,63). It is the treatment of choice for early lesions, after fetal lung maturity is established. For patients with stage IIB or more advanced disease, pelvic and paraaortic lymphadenectomy can be performed at the time of cesarean section, and definitive therapy in the form of chemoradiation may be initiated immediately postpartum.

OVARIAN CANCER

Adnexal masses are detected in 1–2% of all pregnancies and are an increasingly more common occurrence with the widespread use of prenatal ultrasound. Most of these are small (< 5 cm) simple cysts, which are incidentally found by ultrasound and resolve spontaneously by the early part of the second trimester. Only 3–6% of all adnexal masses detected during pregnancy are malignant neoplasms (50). Owing to the young age of the pregnant patient population, many of the neoplasms are germ cell tumors. As patient age increases, epithelial ovarian neoplasms become more frequent, primarily tumors of low malignant potential, followed by cystadenocarcinomas. Elevated tumor markers, such as CA-125, AFP, and β-hCG may be misleading because pregnancy itself may cause an increase in their values. Traditional recommendations for surgery have been adnexal masses greater than 6 cm in size that persist into the second trimester. Due to improvements in ultrasound and MRI imaging, this size

cutoff has been challenged for benign appearing masses. There are at least two series, each with more than 100 patients with sonographically benign appearing ovarian lesions, who were followed conservatively throughout pregnancy, that report a low incidence of torsion (1–2%) and no malignancies (64,65). Rapidly growing or complex adnexal masses with an ultrasonographic appearance suggestive of malignancy require surgical exploration, which, if the pregnancy is desired, is ideally done in the early second trimester. If the tumor is discovered in the third trimester, therapy can often be delayed until the time of cesarean section or the postpartum period.

The treatment principles for gestational ovarian cancer do not differ significantly from those for the nonpregnant patient. A vertical midline incision is generally required not only to remove the tumor, but also to explore the abdomen. For apparent stage I disease, unilateral salpingo-oophorectomy and surgical staging are appropriate. For more advanced disease in a patient desirous to continue the pregnancy, removal of as much of the cancer as possible is indicated, while minimizing uterine manipulation. This should be followed by the appropriate chemotherapy. Neoadjuvant chemotherapy may offer an interim treatment for selected patients diagnosed at mid-gestation with disseminated epithelial ovarian cancer to allow for fetal maturity prior to extensive surgical cytoreduction.

If an oophorectomy performed in the first trimester leads to removal of the corpus luteum gravidarum, progesterone supplementation needs to be given for the remainder of the first trimester until placental progesterone production is sufficient.

Ovarian Germ Cell Tumors

Ovarian germ-cell tumors encompass an array of biologically diverse cancers, including dysgerminoma, teratoma, polyembryoma, endodermal sinus tumor, and choriocarcinoma. The most common germ cell tumors associated with pregnancy are dysgerminomas (50), accounting for close to 30% of ovarian malignancies in pregnancy (Table 10). Dysgerminomas tend to be large, solid tumors that are heavy and prone to torsion or incarceration in the cul-de-sac (66). They have a propensity for lymphatic spread. Thus surgical management should include staging with lymphade-

Table 10 Relative Frequency of Ovarian Malignancies Reported in Association with Pregnancy

	Relative frequency in pregnancy (%)
Epithelial tumors	35–40%
Low malignant potential	66%
Adenocarcinoma	34%
Germ cell tumors	30–45%
Dysgerminomas	83%
Immature teratomas	13%
Endodermal sinus tumors	4%
Sex cord-stromal tumors	10–20%
Others (sarcomas, metastatic dz.)	10–13%

Source: From Ref. 50, 91.

nectomy in addition to a unilateral salpingo-oophorectomy if there is a unilateral mass. The rate of overt and covert bilaterality for dysgerminomas is about 10–15%, respectively. For patients with stage Ia disease, no additional therapy is indicated and expected recurrence rates approximate 10–15% in the nonpregnant patient. Most recurrences in early-stage disease are in the residual ovary. Patients with more advanced disease should receive adjuvant chemotherapy. Interpretation of the literature regarding the prognosis of pregnancy-associated dysgerminomas is difficult. The largest series to date of 27 patients reported a 30% recurrence rate in apparent stage Ia disease, but many of those patients had not undergone adequate surgical staging (66).

Endodermal sinus tumor (EST) is one of the most aggressive and rapidly growing neoplasms of the ovary. More than 10 cases have been reported in pregnancy (67). All patients with EST require adjuvant cytotoxic therapy. Close to half of the patients reported with EST diagnosed during pregnancy have died of their disease, 80% of whom did not receive adjuvant chemotherapy (50). Most patients with immature teratomas or endodermal sinus tumors will present with disease limited to one ovary, and a unilateral salpingo-oophorectomy plus staging is the appropriate surgical intervention. Except for stage Ia grade 1 disease, all patients with immature teratomas should receive adjuvant chemotherapy. Cure rates for nonpregnant patients with ovarian germ cell tumors are reported at 95% and 75% for stage I and advanced disease, respectively (68).

Based on the success in testicular cancer and on a series of Gynecologic Oncology Group (GOG) studies of more than 180 women with ovarian germ cell tumors (69), 3–4 cycles of bleomycin, etoposide, and cisplatin (BEP) have become the regimen of choice for both early and advanced-stage ovarian germ cell tumors (70). BEP has demonstrated superior results and has replaced the former standard treatment vincristine, actinomycin, and cyclophosphamide (VAC). While most reports on chemotherapy for germ cell tumors during pregnancy have used VAC (67), more recently, there have been reports on the successful outcomes for both mother and fetus with use of the BEP regimen in pregnancy (71). The toxicities associated with bleomycin can be severe, and omission of this agent from the BEP regimen had been considered and used in the nonpregnant (72) and pregnant patient (73).

Sex Cord-Stromal Tumors

Ovarian sex cord-stromal tumors include granulosa cell tumors, Sertoli–Leydig cell tumors, and arrhenoblastomas. These tumors are generally unilateral and solid. Appropriate surgery during pregnancy includes unilateral oophorectomy and staging. In the largest series of sex cord-stromal tumors in pregnancy, all patients were diagnosed with stage I tumors; 35 of the 36 patients were initially treated with unilateral salpingo-oophorectomy. Only two received postoperative chemotherapy. All patients were alive without evidence of disease at a mean follow-up of 4.7 years (74). In the nonpregnant patient, the value of adjuvant chemotherapy for these tumors is controversial and cisplatin-based combination chemotherapy is generally recommended for metastatic or recurrent disease. Given the generally low-grade biology of granulosa cell tumors and most well-differentiated Sertoli–Leydig tumors, it is uncertain if any significant maternal benefit would be derived from chemotherapy during pregnancy.

Epithelial Ovarian Cancer

Tumors of low malignant potential (borderline tumors) are the most common epithelial ovarian neoplasms associated with pregnancy (Table 10). Most of these tumors will present as stage I disease, and prognosis is excellent as in the nonpregnant patient (75). Adjuvant chemotherapy during pregnancy is not indicated, as there is no established benefit even in advanced-stage disease.

Epithelial ovarian cancers diagnosed during pregnancy appear to have a similar prognosis as in nonpregnant patients. In cases where the disease is far-advanced, the extent of aggressive tumor debulking during pregnancy will be dictated by the extent of disease, the gestational age, and the maternal wishes regarding the pregnancy. Hysterectomy during pregnancy is rarely of therapeutic benefit, unless it contributes significantly to the tumor debulking. Adjuvant chemotherapy is indicated for all invasive ovarian carcinomas with the exception of stage IA grade 1 (or 2) tumors. Standard first-line therapy in the nonpregnant patient is a platinum compound plus paclitaxel. Most of the experience in pregnancy is with cisplatin and cyclophosphamide (67). There are several reports in the literature on the successful surgical management of epithelial ovarian cancer followed by administration of chemotherapy with cisplatin and cyclophosphamide during the second and third trimester with good maternal response to therapy and excellent fetal outcomes (76–78). Recently, the first report on the successful use of paclitaxel and platinum during pregnancy has been published with no apparent adverse fetal effects (37).

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14

Supportive Treatment in Gynecologic Malignancies

G. Marx, S. Yip, C. Steer, and P. Harper
Guy's Hospital, London, England

Cytotoxic chemotherapeutic agents play an integral part in the management of patients with gynecologic malignancies, particularly in those with ovarian cancer. Although there are many potential benefits of treatment, there can also be significant toxicity that may adversely impact on patients' quality of life. Furthermore, toxicity of therapy may result in treatment delays, dose reductions, and even cessation of treatment, which could adversely affect outcome. This chapter describes the role of supportive treatments in the management of gynecologic malignancy, with indications and guidelines for usage of these therapeutic modalities.

The most commonly used supportive treatments are erythropoietin (EPO) and colony stimulating factors (CSFs).

ERYTHROPOIETIN

Anemia

Cancer-related anemia is a significant problem in the management of cancer patients. It may contribute to the comorbidity of the illness. Anemia can potentially compromise the tolerability and efficacy of therapy, as well as reduce the ability to perform normal daily activities, contribute to fatigue and impair overall quality of life.

Erythropoietin is a hematopoietic growth factor produced endogenously in the peritubular interstitial cells of the kidney. Receptors for erythropoietin can be found in the bone marrow, peripheral stem cells, and the brain. It stimulates red blood cell production, in response to tissue hypoxia. Its mechanism of response is to increase the number of cells capable of differentiating into mature erythrocytes, triggering their differentiation and augmenting hemoglobin synthesis in developing erythroblasts. Recombinant human erythropoietin is a 165-amino-acid glycoprotein synthesized by recombinant DNA technology. It has the identical amino acid sequence and similar biologic effects as endogenous erythropoietin.

EPO levels have been demonstrated to be disproportionately low for the degree of anemia in patients with cancer. It was demonstrated that for any given degree of anemia, the serum concentration of immunoreactive EPO was lower in this group of

patients than in a group of control patients with iron-deficiency anemia (1). Furthermore, it was also demonstrated that the response of EPO was blunted even further in patients receiving chemotherapy.

The prevalence of anemia in patients with solid tumors may be related to anemia of chronic disease, bone marrow infiltration, as well as the cytotoxic or radiotherapeutic treatments used. The incidence of grade 3 and grade 4 anemia in phase III trials of combination chemotherapy in patients with ovarian cancer ranges from 2% to 42% with cyclophosphamide/platinum combinations, and from 2% to 8% with paclitaxel/platinum combinations (2). In phase III trials conducted by the South West Oncology Group, patients treated with platinum-based chemotherapy had a blood transfusion rate of 33% (2).

Recombinant EPO has been demonstrated to be effective, and well tolerated, in preventing the decline in hemoglobin of patients undergoing aggressive platinum-based chemotherapy for gynecologic cancers (3). In a randomized controlled trial, ten Bokkel Huinink et al. (4) demonstrated that recombinant EPO reduced the need for blood transfusion and maintained hemoglobin levels in patients with ovarian cancer treated with platinum-based chemotherapy.

Fatigue

Fatigue is a complex and multifactorial disorder that has been associated with a deterioration in the quality of life of patients with cancer. The impact of anemia and fatigue on patients' quality of life is an area that has been poorly understood, poorly researched, and poorly managed. The impact that this has had on patients' quality of life and the significance of fatigue for patients has been underestimated. The Fatigue Coalition, a multidisciplinary group including representatives from oncology, HIV, neurology, psychometrics, psychiatry, and patient advocacy groups, was founded to study the importance of fatigue to cancer patients and their caregivers, and to develop guidelines for the diagnosis and treatment of fatigue syndromes.

An initial survey by Vogelzang et al. demonstrated a divergence in opinion between the oncologist and patient as to the importance of fatigue as a symptom. Oncologists felt that pain adversely affected their patients to a greater degree than fatigue (61% vs. 37%), while patients with cancer felt that fatigue adversely affected their daily lives to a greater degree than pain (61 vs. 19%) (5). This essentially reflected the considerable effort and skill that has developed in pain management.

Kurt then described the results of a patient telephone survey to assess the incidence of fatigue and to assess the emotional, social, physical, and economic impact on cancer patients. Seventy-six percent of patients reported feeling fatigued at least once a month, with 30% of patients reporting fatigue on a daily basis. For patients experiencing fatigue after chemotherapy, a third of them had fatigue symptoms for more than 2 weeks. Fatigue was also the most commonly experienced symptom following treatment, being experienced by 76% of patients, compared with 54% of patients complaining of nausea and 23% of pain. In addition to being the most frequent symptom and lasting the longest, fatigue was also ranked highest among the symptoms that most affected everyday life. Ninety percent of patients agreed it takes away the feeling of being in control. More than 70% felt that fatigue can lead to feelings of hopelessness, laziness, and can make interaction with other people difficult,

leading to loneliness and isolation. Overall, the impact of the fatigue experience on the cancer patient was broadly felt, both in terms of activities of daily living and in personal interactions (6).

Cancer-related fatigue has also been demonstrated to have major economic implications. Seventy-five percent of patients during their experience of fatigue changed their employment status. In addition, 20% of their caregivers took days off or accepted fewer responsibilities, reduced work hours, or used unpaid family and medical leave time to help the patient with fatigue (6).

In the United Kingdom, Stone et al. reported a multicenter patient survey on cancer-related fatigue and identified it as being an important problem for patients with cancer. It affected more patients for more time than any other symptom. Patients regarded it as being more important than either pain or nausea/vomiting. Approximately half of the patients who experienced fatigue in the month prior to the survey did not report this symptom to their physician. The most common reasons for lack of reporting were that it was thought to be inevitable, unimportant, or untreatable (7).

Epo and Fatigue

The impact that fatigue has on our patient population is significant. Addressing the issue of anemia is one mechanism that attempts to deal with this very important problem. A number of studies have been performed in recent years addressing the issues of anemia and fatigue and response to recombinant EPO.

Abels (8) performed a double-blind, randomized placebo controlled study in which patients with chemotherapy-induced anemia were treated with recombinant EPO. Over 400 patients were entered in the study. Patients received placebo or EPO three times weekly for 12 weeks. A response was defined as the achievement of a target hematocrit of >38% or an increase in hematocrit of >6%. Patients randomized to EPO demonstrated a significant improvement in hematocrit, a reduction in transfusion requirements, and an improvement in quality of life and functional capacity. This occurred in all tumor types.

Two further open-label, community-based trials by Glaspy and Demetri et al. (9,10) (Table 1) evaluating over 4500 patients confirmed the observed improvement in hemoglobin levels, transfusion requirements, and quality-of-life end points. Glaspy treated patients by using a subcutaneous dose of 150U/kg, three times a week for up to 4 months. They demonstrated that 54% of patients had a greater than 2 g/dL rise in hemoglobin. Importantly, they also demonstrated, using validated and reliable measures of quality of life, that the magnitude of increase of hemoglobin rise correlated with improvement in quality of life. Demetri et al. reported an initial response rate to 10,000 units of 47.1%, and a 65.8% overall response rate after increasing the dose to 20,000 units in patients who had not shown an initial satisfactory response. In addition to the improvement in hemoglobin levels, the percentage of patients requiring transfusion fell from 16.2% in the first month of the study to 4.9% in the fourth month. Patients treated with EPO demonstrated an improvement in quality of life, with improvement in hemoglobin, independent of tumor type or response. It is noteworthy that in this study, patients who achieved lower degrees of hemoglobin improvement, and were not included in the responder group, also showed an improvement in quality of life end points, as measured by a linear analog scale. In contrast, the

Table 1 Management of Cancer-Related Anemia with EPO Alpha Studies (Adapted from Ref. (26))

Name	No. of pts	Trial type	Tumor type	Chemotherapy	EPO Schedule	QOL Questionnaire	Results
Abels (8)	413	a	nonmyeloid	myelosuppressive chemotherapy (±cisplatin) or no chemotherapy	*No chemotherapy* 100 IU/kg alpha tiw, 12 weeks. *Chemotherapy* 150 IU/kg alpha	LASA	+ *EPO* + *chemotherapy*: signif ↑ in hematocrit, signif ↑ in Hb, ↓ transfusion requirements.
Cleeland (13)	4382	b, c	nonmyeloid	myelosuppressive chemotherapy (including cisplatin)	As per Glaspy et al. study (9) and Demtri et al. study (10)	LASA, FACT-An	Greatest incremental improvement in QOL observed when Hb ↑ from 11–12 g/dL.
Demetri et al. (10)	2289	b, c	nonmyeloid	myelosuppressive chemotherapy (including cisplatin)	10,000 IU alpha, tiw, 16 weeks, (↑ to 20,000 IU after 4 weeks if ↑ in Hb <1 g/dL) be consistent in numbers use 10,000 with a comma	LASA, FACT-An	+ *EPO* + *chemotherapy*: signif ↑ in Hb (2 g/dL), ↓ transfusion requirements, ↓ % patients requiring transfusion, QOL benefit from EPO is independent of disease or response to therapy or tumor type, Patients achieving Hb > 2 g/dL had the greatest ↑ in QOL scores.
Gabrilove et al. (15)	2869	b, c single arm	nonmyeloid	myelosuppressive chemotherapy	40,000 IU alpha qw (↑ to 60,000 IU if Hb <1 g/dL after 4 weeks)	LASA, FACT-An	+ *EPO* + *chemotherapy*: signif ↑ in Hb (2 g/dL), ↓ transfusion requirements, ↓ % patients requiring transfusion, signif ↑ in QOL scores

Glaspy et al. (9)	2030	b, c	nonmyeloid	myelosuppressive chemotherapy	10,000 IU alpha, tiw (↑ to 20,000 IU if inadequate response at 8 weeks)	LASA	+ *EPO + chemotherapy*: signif ↑ in Hb (1.8 g/dL), ↓ transfusion requirements, ↓ % patients requiring transfusion, signif ↑ in QOL scores independent of disease response.
Littlewood et al. (12)	375	a	none excluded	Nonplatinum chemotherapy	150 IU/kg alpha, tiw, 22 weeks	LASA, FACT-G, FAC T-F, FACT-An, SF-36	+ *EPO + chemotherapy*: signif ↑ in Hb (2.2 g/dL), ↓ transfusion requirements, signif ↑ in QOL scores.
Kurz et al. (14)	35	a	gynecologic	polychemotherapy	150 IU/kg tiw,12 weeks	Nonvalidated	+ EPO-reduced transfusion requirement. increased Hb, stable QOL
ten Bokkel Huinink et al. (4)	122	d (open with respect to admin of EPO)	ovarian	myelosuppresive, platinum-based chemotherapy	150 IU beta, tiw or 300 IU, tiw, 24 weeks	none	+ EPO: signif ↑ in Hb, ↓ transfusion requirements, initial dose of 300 IU associated with rapid Hb ↑ in ovarian pts and requiring EPO dose reduction

Trial type: a = double-blind, placebo-controlled; b = open-label nonrandomized; c = community-based; d = open-label, randomized, controlled.
EPO alpha schedule: tiw = three times weekly; qw = twice weekly.
QOL questionnaire(s): LASA = Linear Analogue Self-Assessment scale; FACT-G = Functional Assessment of Cancer Therapy—General; FACT-F = Functional Assessment of Cancer Therapy—Fatigue; FACT-An = Functional Assessment of Cancer Therapy—Anemia; QLQ = Quality of Life Questionnaire (EORTC); SP-36 = a generic health status questionnaire.
pts = patients; signif = significant.

group that showed no improvement in hemoglobin levels also showed no improvement in quality of life scores. Similar changes also were observed using the Functional Assessment of Cancer Therapy—Anemia (FACT-AN) subscale analyses. A retrospective analysis of 297 patients with gynecological malignancies who took part in the community-based study by Demetri (11) confirmed that EPO therapy produced improvements in quality of life in association with rises in hemoglobin in this group of patients (11).

Littlewood et al. (Table 1) recently published further confirmatory results, in patients receiving nonplatinum containing chemotherapy. They included patients with solid tumors or hematologic malignancies. Approximately 5% of this group had gynecologic malignancies. Patients were treated three times weekly at a starting dose of 150 IU/kg and increased to 300 IU/kg at 4 weeks if no significant rise was demonstrated. As expected, there was a significant rise in hemoglobin from baseline. This

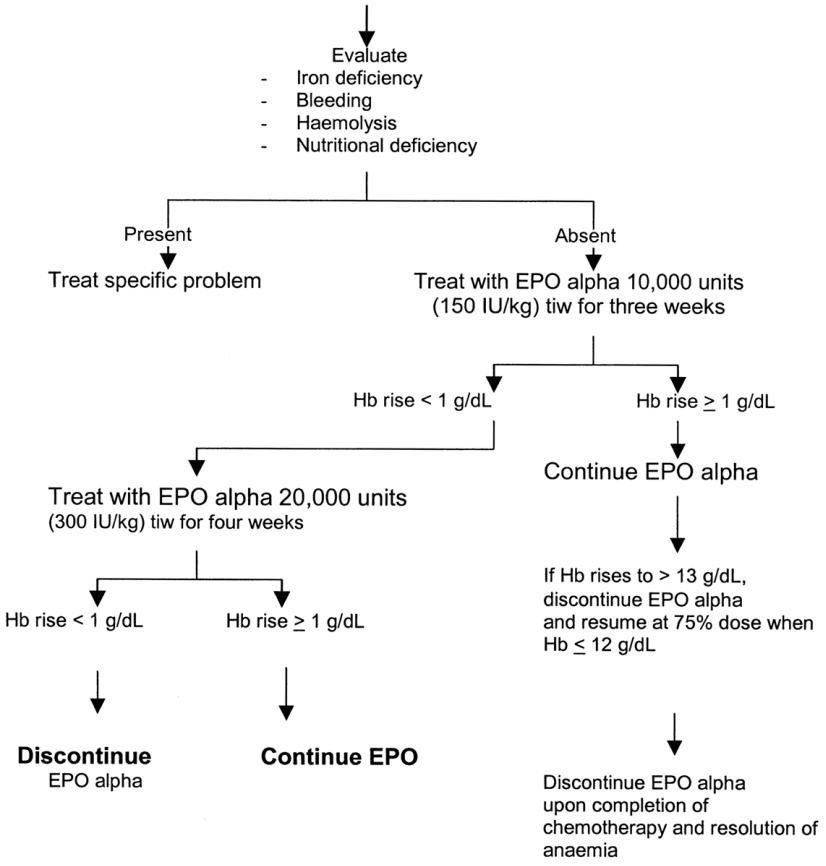

Figure 1 Suggested schedule of EPO alpha treatment for anemia in cancer patients receiving chemotherapy. (From Ref. (9).) [Prior to and during EPO therapy, the patient's iron stores should be evaluated. Virtually all patients will eventually require iron supplementation to adequately support erythropoiesis stimulated by EPO alpha. EPO alpha: epoietin alpha; Hb: haemoglobin; tiw: three times weekly.]

correlated with an improvement in quality of life parameters using linear analog and Functional Assessment of Cancer Therapy scales, including an anemia and fatigue subscale. There was also a significant reduction in transfusion requirements (12).

A nonlinear relationship between hemoglobin level and quality of life has been demonstrated. The combined results of the Glaspy and Demetri studies were analyzed in an attempt to define the hemoglobin level at which the quality of life of patients was optimized. EPO-related increases in hemoglobin were associated with quality of life improvements for the range of hemoglobin from 8 to 14 g/dL. The largest improvement in quality of life for each 1 g/dL change in hemoglobin occurred when the hemoglobin increased from 11 to 12 g/dL. This finding was independently observed in both studies using the respective quality of life measures (13) (Table 1). This has led to a paradigm shift as to the hemoglobin threshold that should be a trigger for treatment. According to the physiologic principles that were used in the development of many transfusion policies in the 1980s, "physiologic hemoglobin of importance" was 8 g/dL. However, as more data on quality of life are becoming available, a "functional" level of hemoglobin that appears to be important is 12 g/dL, as it may be favorably associated with significant improvements in fatigue, compared with that at lower hemoglobin levels. A suggested method for EPO administration for patients undergoing chemotherapy is described in Figure 1.

The results of these studies clearly demonstrate that EPO has an impact on improvement in quality of life as well as an improvement in hemoglobin levels, with an associated reduction in blood transfusion requirements. This impact seemed to be in all tumor groups that were included. Specific studies of the potential for recombinant EPO to impact on these factors in gynecologic malignancies are less common. A randomized double-blind, placebo controlled study has looked at the impact of EPO on these factors in patients treated with polychemotherapy for gynecologic malignancies. They demonstrated that EPO significantly increased hemoglobin levels and decreased transfusion requirements while maintaining quality of life in these patients (14).

Weekly Epo

The three times weekly administration of EPO in these studies was essentially a result of the experience with EPO in patients with renal failure. This was based on the three times weekly dialysis program. Weekly dosing, in patients with cancer, is now being further evaluated with initial data suggesting similar efficacy to the three weekly schedules. This means of administration is obviously far more convenient and beneficial to patients' quality of life (15). The doses used in this study were 40,000 IU weekly and increased to 60,000 IU weekly if the hemoglobin had not increased by 1 g/dL.

Currently, the development of long-acting EPO is underway with the development of the novel erythropoiesis-stimulating protein (NESP). The sialic acid component of the carbohydrate component of human EPO is important for the in vivo activity of this glycoprotein. NESP has five *N*-linked carbohydrate chains, rather than the three carbohydrate chains on EPO. This increases the molecular weight from 30,400 to 37,100 kDa, and the carbohydrate content from 40% to 51%. These alterations occur away from the receptor binding sites of EPO, and principally prolong

the serum half-life of the glycoprotein threefold. Research is ongoing as to the efficacy and optimum dosage schedule for this new agent.

Radiation Therapy

The impact of anemia and transfusion on the response to radiation therapy for cervical cancer has been reported by Grogan et al. (16). In a retrospective study of 605 patients, with a median follow-up of 41 months, the 5-year survival rate was 74% in patients whose average weekly nadir hemoglobin level was >12 g/dL. For patients with hemoglobin levels between 11 and 12 g/dL, the 5-year survival rate was 52% but this figure dropped to 45% in patients with Hb levels of <11 g/dL ($p < 0.0001$). There was no significant difference in the survival rates between those patients who achieved the same level of Hb by transfusion or spontaneously. In addition, both local and distant relapse rates were significantly improved in patients whose Hb level during radiation therapy was >12 g/dL. It seems that maintenance of a mean Hb at these levels is important throughout the treatment period. It is therefore hypothesized that raising and maintaining Hb levels in patients treated with radical radiotherapy may significantly improve outcome. This is now being tested in randomized trials.

The evidence thus far presented highlights some very important management issues in the treatment of patients with cancer-related anemia. First, recombinant EPO results in improved quality of life, improved hemoglobin and reduced transfusion requirements. Second, a paradigm shift of increasing the threshold for the recommendation of intervention of anemia to 12 g/dL will have a major impact on transfusion services resources. This paralleled with the potential risks associated with blood transfusions highlight the importance of considering this supportive treatment option. Further cost analysis and pharmacoeconomic studies need to be performed before definite guidelines or recommendations can be made concerning the use of recombinant EPO in patients with gynecologic malignancies.

COLONY STIMULATING FACTOR (CSF)

The incidence of neutropenia depends on the type and dose of cytotoxic agents used in addition to the condition of the patient. Neutropenia and infection are major dose limiting toxicities of cytotoxic chemotherapies. The risk of infection and subsequent complications are directly related to the depth and duration of neutropenia (17). This is also influenced by various host- and disease-related factors (18,19).

Granulocyte colony stimulating factor (GCSF) is a cytokine that regulates the formation and development of neutrophils within the bone marrow and their release into the peripheral circulation. Endogenous GCSF is only present in small amounts in the circulation. Recombinant forms of GCSF have been developed and administration to patients on treatment results, in an increase in the absolute neutrophil count. GCSF exerts its major effect on neutrophil precursors and has been demonstrated to reduce the duration of neutropenia in patients being treated with chemotherapy (20). GCSF resulted in a greater than 50% reduction in neutropenia (grades 3 and 4) in patients treated for 8–10 days in a randomized double-blind study (17).

The role of colony stimulating factors is limited in the treatment of gynecologic cancers as there has been no definite survival benefit demonstrated with high dose therapy. The use of these factors should therefore be in accordance with their use in the treatment of other malignancies. The American Society of Clinical Oncology (ASCO) has formulated guidelines regarding the prescription of these agents. These were initially formulated in 1994, and subsequently updated in 1996 and 2000 (21). The guidelines recommend the use of CSFs (which include GCSF and GMCSF) in the following circumstances.

Primary Prophylaxis

Primary prophylaxis is defined as the use of CSFs after the completion of the first cycle of treatment and before neutropenia has been documented. The available data recommend the use of GCSF when the incidence of neutropenia is expected to be $> 40\%$. The use of GCSF in this situation reduced hospitalization for the administration of antibiotic therapy. The majority of patients receiving chemotherapy for gynecologic cancers would not be at risk of developing febrile neutropenia in more than 40% of cases. The ASCO guidelines recommend primary administration of CSF only in patients considered to be at high risk due to special circumstances. They suggest that the data on the use of GCSF in this situation are modest with respect to improved clinical outcomes (complications of febrile neutropenia) and economic benefit, and recommended a dose reduction or schedule modification as acceptable alternatives, as there are no data demonstrating an improvement in response or survival (21).

Secondary Prophylaxis

Secondary prophylaxis is defined as the use of CSF in a later cycle after an episode of febrile neutropenia has been documented. This is to maintain dose intensity when a dose reduction is not appropriate. The ASCO guidelines of 2000 suggest that, after an episode of severe neutropenia, dose reduction should be considered as the primary therapeutic option, except in the treatment of curable tumors. There are currently no published data demonstrating disease-free or overall survival benefits when the dose of chemotherapy was maintained with the use of GCSF as secondary prophylaxis in the treatment of gynecologic cancers.

Treatment

This is defined as the use of CSFs at the time of diagnosis of febrile or afebrile neutropenia if the patient is considered to be at high risk of complications from sepsis. The collective results from the trials assessed in the ASCO 2000 guidelines provide strong and consistent evidence that CSF should not be used routinely as adjuvant therapy in the treatment of uncomplicated fever and neutropenia. Although the data have demonstrated a decrease in the duration of neutropenia this has not translated into a clinical benefit (21). Although the use of CSF in this situation have not been proven, it is recommended that these agents be considered for use in those patients

considered to be at high risk of complications from neutropenic sepsis. Such factors that increase the risk of complications include profound neutropenia (absolute neutrophil count <100/μL), uncontrolled primary disease, hypotension, multiorgan dysfunction, invasive fungal infection, and age over 65 years.

THROMBOPOIETIN

Thrombocytopenia is a common toxicity associated with the use of cytotoxic chemotherapy. This is particularly evident with treatments using Carboplatin, which is frequently used in the management of ovarian cancer. The clinical development of thrombopoietic cytokines has been limited because of their modest activity and significant toxicity. Interleukin-11 has been approved as a thrombopoietic cytokine after demonstrating a reduction in platelet transfusions in a randomized trial (22). However, this agent has been associated with significant toxicity including cardiac arrhythmias, fluid retention, and dyspnea.

The discovery of thrombopoietin, the central regulator of megakaryocytopoiesis and thrombopoiesis, gave rise to the hope of a potential method of effectively treating thrombocytopenia without the use of platelet transfusions (23). Two recombinant forms of thrombopoietin have been developed. The first is a pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) and the other is a glycosylated recombinant human thrombopoietin (rHuTPO). These were demonstrated in early studies to be potent stimulators of thrombopoiesis with few adverse effects (24). RHuTPO has been used in the treatment of patients with gynecologic cancer. In a randomized placebo controlled trial, the use of rHuTPO led to a reduction in chemotherapy induced cumulative thrombocytopaenia and platelet transfusion requirements (25). Major bleeding complications are a rare complication of chemotherapy in gynecologic cancer management, and the potential role for these agents in the management of gynecologic cancers is likely to be limited. Particularly as there is no reproducible evidence for a survival benefit with the use of high-dose chemotherapy.

The development of agents used in the supportive treatment of patients undergoing chemotherapy for gynecologic cancers has been an important area of clinical research. The use of these factors is limited at this stage. Although there is minimal data with regard to response and survival benefits with the use of these agents, ongoing research with other important parameters, such as quality of life, utilization of blood products, and pharmacoeconomic data, are important in defining the role of these agents in future patient care.

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15

Hormone Replacement Therapy in Gynecologic Cancer Patients and Survivors

Wendy R. Brewster and Philip J. DiSaia
University of California Irvine Medical Center, Orange, California, U.S.A.

Hormone replacement therapy in women with gynecologic cancers is fraught with theoretical concerns that estrogen might have a deleterious affect upon survival. The disease sites for which this is a concern are breast, uterine corpus, and, to a smaller extent, ovarian malignancies. Ninety percent of U.S. women will live to the climacteric age compared to only 30% just 200 years ago. The average woman can expect to spend at least 40% of her lifetime in the menopausal period. Attrition and aging of ovarian follicles result in the termination of the maturation of granulosa cells which are responsible for estrogen production. The sources of estrogen in the premenopausal woman are many and include the direct production of estradiol by the ovaries in addition to the extraglandular aromatization in adipose cells of androstenedione produced in the adrenal glands and ovary. The hallmark of menopause is the drop in ovarian production of estriol and testosterone. Whereas peripheral aromatization of other steroids is an additional source of estrogen for all postmenopausal women, this source is not sufficient in most women to prevent the symptoms characteristic of estrogen deprivation (Table 1).

Findings from randomized trials such as Women's Health Initiative (WHI) and Heart and Estrogen/progestin Replacement Study (HERS) have provided more information about the actual benefits of estrogen replacement therapy (ERT). The indications for estrogen therapy (including estrogen/progestin combination) are relief from vasomotor instability, genital atrophy, urinary dysfunction, and osteoporosis. Observational data suggest a preventative role of estrogen against colorectal cancer and Alzheimer's disease; however, rigorous randomized trials have yet to clearly specify the degree of effect.

BREAST CANCER

No large, randomized clinical trials published which address the question of safety of estrogen or hormone replacement therapy (HRT) with respect to breast cancer relapse

Table 1 Menopausal Status and Estradiol Levels

Clinical state	Estradiol level (pmol/L)
Postmenopausal	51.4
Postmenopausal on 0.625 mg CEE/day	294–367
Premenopausal, follicular phase	731
Premenopausal, luteal phase	725
Premenopausal	
Follicular phase after 2 months of tamoxifen	1860
Luteal phase after 2 months of tamoxifen	2154

Source: Ref. 2.

(1). However, many healthcare providers have called for a randomized clinical trial of the safety and efficacy of HRT among breast cancer survivors.

The argument against the use of hormone replacement therapy among postmenopausal breast cancer survivors is that (1) they may be at increased risk of a new primary breast cancer given their history of breast cancer and (2) any residual malignant breast cells (particularly if ER +) may be stimulated to grow in an estrogen-rich environment. It is implicit in this argument, without a body of supportive data, that HRT use in this group of women will lead to an overall increase in morbidity and mortality and a decrease in quantity of life.

Cobleigh et al. (2), in a statement made for the Breast Cancer Committee of the Eastern Cooperative Oncology Group, dealt with the arguments relating to HRT use and detection of breast cancer, a second primary cancer, and breast cancer relapse and survival. They concluded that a weighing of the evidence did not support an association between estrogen use and breast cancer incidence, particularly among those on a low dose for less than 10–15 years. They also argued that because tamoxifen reduces the risk of a second primary breast cancer, its use may attenuate any increase in risk of a new primary due to ERT. Cobleigh et al. found no studies relating explicitly to estrogen and recurrence. They noted, however, that if estrogen worked to stimulate dormant tumor cells, then women who are premenopausal when they develop breast cancer should have a worse prognosis than women who are postmenopausal. Rather, the reverse is true (3). While this does not prove the point, it certainly does not provide any support for those who argue that estrogen may be detrimental. Finally, five cohort studies were discussed, none of which supported a decreased survival among estrogen users (4,5,6,7). In fact, the relative risk estimates were all below 1.0, with 3 of the 5 statistically significantly below 1.0. This is a slight indication that survival may be enhanced by estrogen (Table 2).

DiSaia (8) reappraised the role of HRT in breast cancer survivors. He emphasized that the survival and quality of life of women who take HRT, whether or not with a history of breast cancer, should be of utmost concern. He noted that most studies had found HRT to have positive effects on bone mineral density and incidence of bone fractures (9,10,11). There were also indications that HRT may be somewhat protective against colorectal cancer (12,13). He emphasized that most studies could not relate short-term higher levels of estrogen with an increased incidence of breast cancer. Women who have been pregnant within 2 years of their breast cancer diagnosis do not have an increased risk of breast cancer recurrence compared to age-matched women

Table 2 Estrogen Replacement Therapy in Breast Cancer Survivors

Author	Patients (*N*)	ERT duration	Recurrence [*N* (%)]
Blumming	155	30 (1–59)	7 (3)
Eden	90	18 (4–144)	6 (7)
V-Sellin	39	47 (28–80)	1 (3)
DiSaia	238	36 (1–321)	15 (6)
O'Meara	174		17/1000 person years

which were not pregnant within 2 years of their diagnosis (14,15). Interestingly, this is also true of women with a history of breast cancer prior to their pregnancy. Two studies found that women who used oral contraceptives within 2 years of their breast cancer diagnosis do not have diminished survival compared to women who did not use oral contraceptives (16,17). These studies indicate that HRT may not worsen the prognosis of women with breast cancer. Other studies, using different populations and designs, reported similar findings (18–20).

DiSaia et al. (21) identified a cohort of breast cancer patients who had received hormone replacement therapy after diagnosis of breast cancer was identified (cases). Only cases not included in a previously reported matched analysis were selected. Control subjects were identified from the regional cancer registry. Matching criteria included age at diagnosis, stage of breast cancer, and year of diagnosis. Controls were selected only if they were alive at the time of initiation of hormone replacement therapy of the matched case. One hundred twenty-five breast cancer survivors who received HRT after diagnosis of breast cancer met the selection criteria. The mean age of the cases was 51.9 years. The following is the stage distribution of the cases: in situ 13.6%, stage I 41.6%, stage II 21.6%, stage III 8%, stage IV 0.8%, unknown 14.4%. Ninety percent of the cases (123/125) received systemic estrogen; 90/125 (72%) received a progestational agent. The median interval between diagnosis of breast cancer and initiation of HRT was 46 months (range 0–401 months). The median duration of HRT was 22 months (range 1–357 months). These cases were matched with 362 control subjects. Five of the control subjects (1%) had a more favorable stage than their matched case comparison. Survival analysis indicated an advantage for the cohort of subjects who received HRT ($p = 0.003$) (Fig. 1).

The risk of death was lower among the HRT cohort: OR 0.28 (95% CI: 0.11–0.71). Analyses limited only to cases with known breast cancer stage showed the same significant survival trends. Six endometrial cancers were present among the cases, but none were identified in the control group.

Other authors have reported their experience of ERT in breast cancer survivors. Eden et al. (22) reported six recurrences among the 90 women receiving ERT. These ERT users were matched 2:1 with control subjects with no history of sex steroid use after diagnosis of breast cancer. The recurrence rate in the ERT users was 7% and 30% in the non-ERT users. Bluming et al. (23) reported 155 breast cancer patients who received ERT from 1 to 56 months, among whom seven recurrences were identified. The only published prospective randomized trial is being undertaken by Vassilopoulous-Sellin et al. (24). Subjects are randomized to either a placebo or estrogen replacement therapy without a progestational agent. Ninety women have been randomized and 49 have received ERT for a minimum of 2 years. No breast cancer recurrences have been

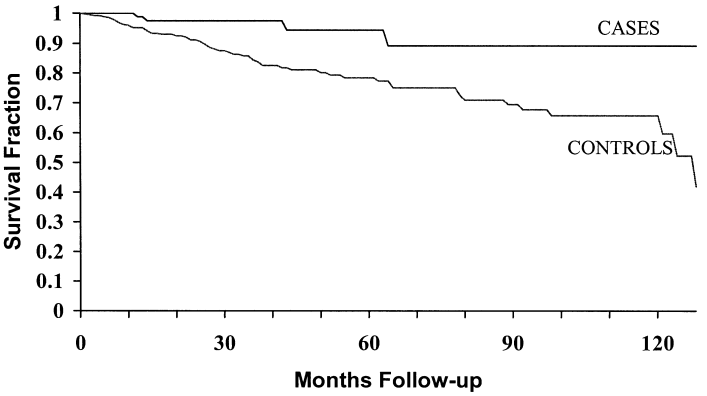

Figure 1 Breast cancer survival and hormone replacement therapy.

observed in the ERT arm. The single recurrence was in the placebo arm. O'Meara et al. (25) assembled 2755 women aged 35–74 years with incident invasive breast cancer enrolled in a large health maintenance organization. Pharmacy records were used to identify 174 users of hormone replacement therapy after the diagnosis who were matched 4:1 with nonusers. The adjusted relative risk of breast cancer recurrence and mortality in users as compared to nonusers was 0.50 (95% confidence interval (CI): 0.3–0.85) and 0.48 (95% confidence interval: 0.29–0.78).

Alterations in quality of life after breast cancer have been linked to pervasive menopausal symptoms. Menopausal symptoms (e.g., hot flashes, vaginal dryness, and stress urinary incontinence) appear to be very common in breast cancer survivors, with a higher prevalence and severity of menopausal symptoms related to lower physical and emotional quality of life (26). In addition, women who are most likely to report a negative impact on sexuality from breast cancer were those who had experienced changes in hormonal status, problems in their relationships, and difficulties with vaginal dryness (27). A study conducted on women undergoing breast cancer treatment indicated that women with hot flashes were significantly younger and significantly more likely to report fatigue, poorer sleep quality, and poorer physical health compared to women without hot flashes (28). Hot flashes during cancer treatment appear to have a negative impact on patient quality of life that may be due, in part, to fatigue and interference with sleep.

The fear that administration of estrogen to women with a history of breast cancer will result in the activation of quiescent metastatic foci and the climate of medical litigation are the bases of much of the reluctance of physicians to prescribe this agent. Currently, the standard of care does not support prophylactic oophorectomy in young women who do not become amenorrheic after cytotoxic therapy. In addition, many women continue to menstruate regularly after treatment and may even complete pregnancies. If castration and pregnancy termination are not routinely recommended, then why should the replacement of estrogen at a much lower dose than is physiological be flatly prohibited?

A guarantee that estrogen replacement therapy will be accompanied with freedom from recurrent breast cancer cannot be provided. Some women will have recurrent disease coincident with renewed hormone exposure. However, can we

continue to prohibit ERT for all patients who have survived breast cancer? We should discuss the theoretical risks, the proven evidence of benefit, and allow the patient to make an informed decision about the consequences *she* will face.

FEMALE GENITAL TRACT MALIGNANCIES

Preservation of fertility is perceived as a priority in the management of premenopausal female genital tract malignancies. Unless uterine involvement is evident or widespread disease is present in the uterine corpus, the uterus and at least one ovary will be preserved. Exceptions are metastatic or persistent trophoblastic neoplasia, advanced stage stromal, germ cell ovarian, cervical, vaginal, and vulvar cancers. For these exceptions, reproductive organs are maintained, without any contraindication for pregnancy and hormonal therapy as is indicated. If cessation of ovarian steroidogenesis is not required for disease management, estrogen supplementation is not prohibited. Controversy exists regarding the safety of estrogen replacement therapy in women with endometrial cancer or uterine sarcoma.

ENDOMETRIAL CANCER

In 1986, Creasman et al. (29) reported 211 patients with clinical stage 1 endometrial cancer retrospectively evaluated. Forty seven of these patients received estrogen after cancer therapy. Patients received at least 3 months of estrogen replacement therapy with a median of 26 months duration. In comparison to the 174 patients who did not receive estrogen replacement therapy, there was an equivalent distribution of risk factors for recurrence. After controlling for risk factors for recurrence, the estrogen

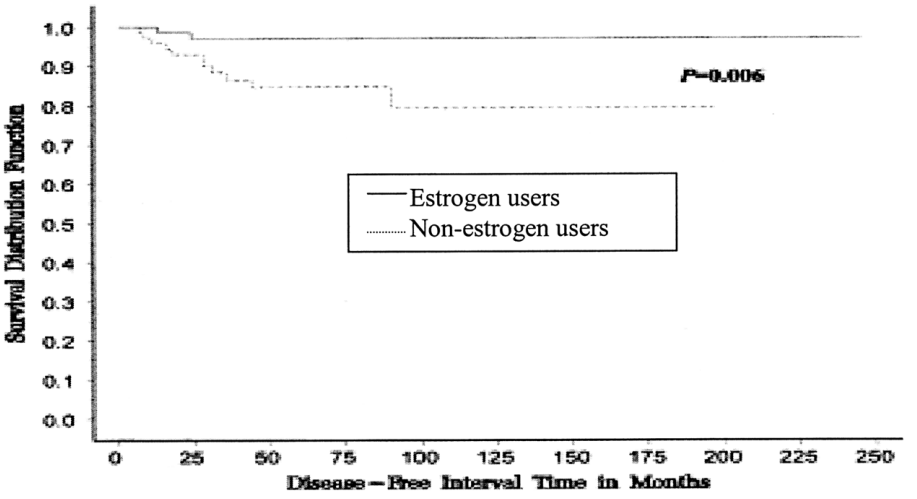

Figure 2 Endometrial cancer and estrogen replacement progression free interval (32).

Table 3 Hormone Replacement Therapy in Endometrial Cancer Survivors

Author	Stage	*N*	Recurrence rate (%)
Creasman et al. (29)	IA–IB	47 ERT	25
		174 no ERT	15
Lee 1989	I	45 ERT	0
		99 no ERT	8
Chapman et al. (31)	I–II	61 HRT/ERT	Overall 6.5
		62 no ERT	
Suriano et al. (32)	I–III	75 ERT/HRT	1
		75 no ERT	14

replacement group had a statistically significant longer survival. Lee et al. (30) presented data on 144 women with clinical stage I endometrial cancer. Forty-four selected women received oral estrogen for a median duration of 64 months. A significant bias existed because the women who received estrogen replacement therapy had low risk factors for recurrence. Nevertheless, when this group of women was compared to other low-risk nonestrogen users, there was a statistically significant lower risk of recurrence among the estrogen users. Chapman et al. (31) identified 123 surgical stages I and II endometrial cancer patients of whom 62 received estrogen replacement therapy. In multivariable analysis, there was no difference in the recurrence rate or disease-free interval between the two groups (Fig. 2).

Suriano et al. (32) performed a matched analysis of 75 with stages I, II, and III endometrial cancer patients matched to 75 nonusers. There was an equivalent recurrence rate; however, the hormone users had a statistically longer disease-free interval than the nonusers. The Gynecologic Oncology Group began a trial of women with early-stage endometrial cancer randomized to estrogen replacement vs. placebo. This trial was closed because of the low incidence of recurrence in either arm.

Clearly, the issue of hormone replacement therapy in this group of cancer survivors will not be easily resolved. The excellent survival of women with early-stage endometrial cancer and the high salvage rate make it difficult to evaluate the effect of estrogen or combination hormone replacement therapy. Nevertheless, the available retrospective data do not demonstrate a deleterious effect (Table 3).

UTERINE SARCOMAS

The safety of estrogen replacement in uterine sarcomas has often been questioned because of the high estrogen and progesterone receptor positivity of these tumors. The expression of estrogen and progesterone receptors in uterine leiomyosarcomas has not been correlated with either survival or progression-free interval (33,34). Furthermore, small case series of fertility sparing surgery in women with uterine leiomyosarcomas have not demonstrated an adverse outcome (35).

Endometrial stromal sarcomas are rare neoplasm more commonly observed in premenopausal women. A higher median receptor expression has been noted for this class of uterine sarcomas in contrast to others, and studies have consistently demon-

strated estrogen receptor expression (36,37). Endometrial stromal sarcomas have demonstrated hormone responsiveness; there is indirect evidence to suggest that unopposed estrogen stimulation may be an etiologic factor in the development of these cancers (38). Further indirect data are evidence that aromatase inhibitors have been reported to induce regression of metastatic endometrial stromal sarcomas (39,40) and the reports of a potential benefit of progesterone therapy in women with low-grade tumors (41).

In summary, endometrial stromal sarcomas are the only subset of uterine sarcomas where there is reasonable evidence that continued estrogen exposure is deleterious.

OVARIAN CANCER

Neoplastic tumors of the ovary may be derived from the coelomic epithelial (epithelial and stromal cancers) or from germ cells. Germ cell cancers are usually diagnosed during the reproductive years, and surgical management is tailored to the preservation of fertility. The chemotherapeutic agents used for the treatment of germ cell cancers do not result in cessation of ovarian function and fertility, and successful pregnancies after treatment are well documented (42). Therefore no contraindication exists for survivors of germ cell tumors who later require estrogen replacement.

The role of hormone replacement therapy on the genesis and malignant progression of development of epithelial ovarian cancer is controversial, as much debate is associated with the discussion of the safety of estrogen replacement therapy in epithelial ovarian cancer survivors. Epidemiological studies on epithelial ovarian cancer and hormone replacement therapy are conflicting. Earlier studies reported either a reduction in risk or no effect (43–45). In the Unites States, a cohort of 44,241 postmenopausal women who participated in the Breast Cancer Demonstration Project was assessed to define the risk of ovarian cancer (46). Three groups were defined: no hormone replacement, estrogen replacement only, and combination therapy. An increased risk of ovarian cancer was noted in the group of women who received estrogen only. However, there was not a statistically significant increase in risk associated with less than 10 years of use of estrogen replacement. Multivariable analysis suggested an elevation of ovarian cancer with increasing duration of use: 10–19 years RR 1.8 (95% confidence interval: 1.1–3.0) >20 years of use RR = 3.2 (95% confidence interval: 1.7–5.7). The risk of ovarian cancer in women using combination therapy was not statistically significant. A case-control study by Sit et al. (47) did not identify any association between epithelial ovarian cancers and hormone replacement therapy formulations. In addition, a large case-control study in Sweden did not identify an increased risk associated with less than 5 years of use of hormone replacement therapy (48), where a nonsignificant elevation in risk was noted among women with 5–10 years of use. There was a twofold increase in risk of epithelial ovarian cancer which was associated to sequential hormone replacement therapy for 10 or more years. No increased risk was noted for women who received continuous combined hormone replacement. Finally, a meta-analysis completed by Garg et al. (49) confirmed a small increased risk associated with ever-use of hormone replacement therapy (OR 1.15, 95% confidence interval: 1.05–1.27); the odds ratio with greater than 10 years of hormone use was 1.27 (95% confidence interval: 1.0–1.61) (Table 4).

Table 4 Estrogen Replacement Therapy in Epithelial Ovarian Cancer Survivors

Author	*N*	Survival
Eeles et al. (52)	78 ERT 295 no ERT	0.73 (0.44–1.20)
Guidozzi and Daponte (55)	59 ERT 66 placebo	44 months 33 months
Ursic-Vrscaj et al. (53)	24 ERT 48 no ERT	0.9 (0.24–5.08)

There is very little data that examine the risk of recurrent epithelial ovarian cancer who elect hormone replacement therapy. The presence of estrogen receptors in epithelial tumors has led many to speculate a harmful or protective role of estrogen replacement (50,51). Physicians may be reluctant to prescribe postoperative estrogen replacement therapy because of the fear that supplementation may lead to ovarian carcinoma relapse; however, three retrospective studies have not identified any significant difference in survival among hormone replacement therapy users and nonusers (52–54). A randomized trial of estrogen replacement therapy in 130 women randomized postoperatively to estrogen replacement therapy or no replacement resulted in similar progression-free interval and overall survival between the two groups (55).

In summary, there is no evidence that estrogen replacement therapy will alter the disease outcome in women with germ cell cancers. The data available to date do not suggest an adverse outcome for women with epithelial ovarian cancer.

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Infections in Patients with Gynecological Malignancies: Prevention and Management

Shivani Singh and Rodger D. MacArthur
Wayne State University, Detroit Medical Center, Detroit, Michigan, U.S.A.

INTRODUCTION

Infections in patients with gynecological malignancies are frequent and a major cause of death and prolonged hospitalization. The patient with cancer is a compromised host and has increased susceptibility to infections due to the tumor itself and also due to therapeutic modalities such as extensive surgical procedures, radiation, and cytotoxic chemotherapy. Infections related to chemotherapy per se are less pronounced than those seen in patients with leukemia, lymphoma, and bone marrow transplantation who have prolonged neutropenia ranging from 1 to 4 weeks. Neutropenia in gynecological malignancy patients lasts approximately for 3 days and therefore infections related to febrile neutropenia are limited. In fact, chemotherapy did not increase the risk of wound complications in this population despite efforts to begin chemotherapy as soon as possible postcytoreductive surgery in one analysis performed in 1992.

EPIDEMIOLOGY

Infection-related morbidity in gynecological oncology has not been investigated extensively. In one retrospective investigation performed at the University of Minnesota in 1987, the highest rate of infection-related morbidity on admission was seen in patients with vulvar cancer and was equal to 21%; the highest infection-related morbidity secondary to surgery occurred in patients with cervical cancer and equaled 22%.

RISK FACTORS

Factors determining the risk of infection in these patients include host factors, tumor-related factors, surgery-related factors, chemotherapy- and radiation-related factors, invasive diagnostic techniques, and supportive procedure-related factors.

Host Factors

1. Normal vaginal and abdominal flora
2. Malignancy-induced alteration in the normal flora
3. Antibiotic use and hospitalization (previous and length of)-induced alteration of the normal flora
4. Altered normal host defense mechanisms such as: mucosal barriers; cellular and humoral immunity; neutrophil, lymphocyte, and macrophage count and function secondary to chemotherapy and radiation therapy
5. Higher morbidity risk in women with malignancy and increased age, poor nutritional status including weight loss and obesity, and comorbidities such as diabetes mellitus, hypertension, and sexually transmitted diseases.

Tumor-Related Factors

1. Disruption of anatomical barriers, which normally prevent invasion of exogenous and endogenous flora
2. Obstruction caused by the tumor
3. Tumor necrosis with manifestation of pre-existing subclinical infections in necrotic malignancy and also superinfection of necrotic malignancy.

Surgery-Related Factors

1. Prolonged surgical procedures with radical dissection of tissue planes and presence of blood and exudates at the site postoperatively
2. Low postoperative albumin
3. Postoperative hemoglobin of 10 g/dL or less
4. Advanced stage of disease
5. Electrocautery use
6. Anesthesia risk.

Invasive Diagnostic Technique-Related Risks

1. Dissemination of pre-existing occult infection at the site of invasive procedure
2. Introduction of nosocomial pathogens.

Supportive Procedure-Related Risks

Nosocomial infections related to the use of central venous catheters (CVC), intraperitoneal catheters, foley catheters, drains, hyperalimentation, ventilatory support, etc.

ETIOLOGY

The major etiological agents of postoperative pelvic infections are the normal vaginal and abdominal flora, thus emphasizing the fact that infection is through the endogenous route. The normal vaginal flora consists of lactobacilli, aerobic gram-negative

Table 1 Pathogens Isolated from Patients with Gynecological Malignancies at the Site of Local Infections

Anaerobes
B. fragilis
Prevotella species
Fusobacterium species
Peptostreptococcus species
Aerobic gram-negative bacilli
E. coli
Klebsiella species
Proteus species
Gardernella vaginalis
Aerobic gram-positive cocci
Viridans streptococci
Group B streptococci
Enterococcus faecalis
S. aureus
Coagulase-negative staphylococci
Mycoplasmas
Mycoplasma hominis
Ureaplasma urealyticum

bacilli, anaerobes, and various species of streptococci. Anaerobes predominate numerically, with a ratio of 10:1. The normal lower abdominal flora consists of the aerobic gram-negative organisms, aerobic gram-positive organisms, and anaerobes including *Bacteroides fragilis*; anaerobes predominate at this site also, with a ratio of 10^4:1. Many factors alter the normal flora and may indirectly predispose the patient to postoperative infection with more virulent, more resistant, and hospital-acquired organisms. Hospitalization and antibiotic use appear to be two such factors and might predispose to infections caused by enterococci, *B. fragilis*, and resistant enteric gram-negative aerobes. The animal model of intra-abdominal infection devised by Weinstein et al. clarified the distinctive roles played by different bacteria in the natural history of pelvic infection. These investigators documented a biphasic response to infection consisting of an early-onset phase with high rates of sepsis and death, in which the enteric gram-negative bacteria predominate (peritonitis stage), and a late-onset phase with abscess formation, in which anaerobes predominate (abscess stage) (Table 1).

PATHOGENESIS

Fever in patients with gynecological malignancies is due predominantly to local infections at the site of the tumor and surgery. Locally operative factors in these patients are: the disruption of anatomical structures that normally prevent the invasion of exogenous and endogenous microorganisms, and obstructive processes secondary to the tumor and tumor necrosis. Dissemination with bacteremia can occur beyond

the site of the tumor especially in the presence of other host factors such as exposure to chemotherapy and irradiation. The causative pathogens infecting the compromised host typically are indigenous microbial flora of the genital tract and the lower gastrointestinal (GI) tract, which are influenced by surgery, irradiation, and chemotherapy. The number of potentially pathogenic aerobic and anaerobic bacterial species is higher in the vaginal vault postoperatively. Polymicrobial mixed infections are frequent.

GENERAL APPORACH TO A PATIENT WITH FEVER

A careful history and physical examination should be performed to identify possible sites of infection. The following sites should be examined carefully:

1. Oral cavity
2. Pharynx
3. Eye (fundoscopical)
4. Lungs
5. Heart
6. Abdomen
7. Perineum including the anus (a digital rectal examination may be relatively contraindicated in a neutropenic patient, unless perirectal abscess is suspected)
8. Skin lesions
9. Bone marrow aspiration sites
10. Vascular and other catheter access sites
11. Tissues around nails.

Two cultures of blood for bacteria and fungi should be obtained in all patients prior to antibiotic administration. If a CVC is in place, blood samples for culture should be obtained from each lumen as well as from a peripheral vein. If a catheter entry site is inflamed or draining, exuding fluid should be examined with Gram staining and culture for bacteria and fungi.

Very little clinically useful information is gained from performing routine cultures of the anterior nares, oropharynx, urine, and rectum when lesions or disease processes are absent. Diarrheal stools should be tested for *Clostridium difficile* toxin and for bacteria (*Salmonella*, *Shigella*, *Campylobacter*, *Aeromonas*, and *Yersinia*), viruses (*Rotavirus* or *Cytomegalovirus*), or protozoa (*Entameba histolytica*, *Giardia*, and *Crytospordium* species). Do not send stool for culture and ova and parasite evaluation when diarrhea develops beyond 3 days of hospitalization due to the low likelihood of these pathogens causing in-hospital diarrhea. Such a patient will benefit from a *C. difficile* toxin evaluation. If at least three such tests are negative and the patient continues to have diarrhea, consider looking for *C. difficile* toxin B. Culture (as opposed to toxin assay) for *C. difficile* is less useful clinically and is therefore discouraged.

Urine cultures are indicated if:

1. Signs or symptoms of urinary tract infection exist
2. A urinary catheter is in place
3. The urine analysis results are abnormal.

Pyuria may be absent in the presence of urinary tract infection in neutropenic patients. Cerebrospinal fluid examination is not routinely recommended, but may be considered if altered mental status exists and central nervous system infection is suspected. Chest radiographs should be obtained whenever any signs or symptoms of respiratory tract abnormality are present. Skin lesions suspected of being infected should be aspirated or biopsied for histological examination, Gram staining, and culture. Complete blood count, electrolytes, and liver function testing are needed to plan supportive care and to monitor the possible occurrence of drug toxicity. Imaging techniques such as ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and radionucleotide imaging may be useful, especially in those individuals with persistent fever and signs of infection.

TYPES OF INFECTIONS

Infections following pelvic surgery, irradiation, and cytotoxic chemotherapy, such as pelvic abscesses, peritonitis, pneumonia, and bacteremia, can be fatal. Urinary tract, wound, and vaginal vault infections occur frequently, but are rarely fatal.

Pelvic Abscess

Pelvic abscess is the most serious late postoperative complication. It occurs many weeks after surgery. A patient with a pelvic abscess may have had no obvious postoperative infection, or may have shown an initial favorable response to antibiotics given for presumptive pelvic cellulitis, only to relapse after discharge. Often, these patients experience a fever spike in the afternoons or evenings and have leukocytosis and/or a palpable mass high in the pelvis. Ultrasonography and CT scans help in diagnosis and determination of whether the mass is loculated, related to an intraperitoneal structure, or drainable percutaneously.

The presence of a postoperative pelvic abscess does not necessarily mandate surgical drainage, especially if it is not readily accessible, as it often responds to antibiotics alone. Antibiotics should include coverage for *B. fragilis* and gram-negative aerobic bacilli. A regimen of clindamycin and gentamicin is frequently employed, although other antibiotic regimens with coverage for aerobic gram-negative organisms and anaerobes should work well. Failure of antibiotic therapy is an indication for intraoperative or percutaneous drainage. Failure of antibiotics is usually not caused by antibiotic resistance but by the unique environment of the abscess that inhibits antibiotic effectiveness. Abscesses usually are drained by the least invasive approach. The abscess cavity should be completely evacuated and a drain should be placed to prevent reaccumulation of fluid. The drain should be left in place until drainage ceases. A patient with a pelvic abscess who does not to respond to antibiotics and is inaccessible by ultrasound or CT needs a laparotomy.

Purulent materials obtained from the abscess, including tissues from the abscess wall itself, should be submitted for culture in an anaerobic transport vial. Materials should be cultured for aerobes, anaerobes, fungi, and mycobacteria.

Parenteral antibiotics should be administered for a minimum 48–72 hr after the resolution of fever, leukocytosis, and signs and symptoms of infection. Controversy exists regarding the need for postdischarge antibiotics. Oral antibiotics such as

amoxicillin/clavulanate or metronidazole are often given for 7 days, especially if the abscess was neither excised nor drained. However, if an adequate course of intravenous antibiotics has been administered during hospitalization, oral postdischarge antibiotics are of little benefit and may contribute to increased side effects. All patients should be evaluated 2 weeks postdischarge to ensure that recurrence or reaccumulation of the abscess has not occurred.

Peritonitis

Operative contamination of the peritoneum, disruption of the surgical anastomosis site, postoperative uterine infection, rupture of a tubo-ovarian abscess, and intraperitoneal catheter infection can all give rise to peritonitis (secondary peritonitis). Most cases of secondary peritonitis are endogenous in origin and are caused by the large number and variety of microorganisms that normally colonize the mucous membranes of the colon and the vagina. The bacteriological characteristics of intra-abdominal infections that complicate female genital tract infections are similar to those of secondary peritonitis from a GI source. Anaerobes are especially frequent (92%) in closed-space infections such as tubo-ovarian and pelvic abscesses. *Bacteroides* species, in particular *B. fragilis*, *Prevotella melaninogenica*, and anaerobic gram-positive cocci, are the most frequently isolated anaerobes. *Escherichia coli* and streptococci are the most frequent facultative anaerobes (aerobic gram-negative enteric bacilli). Relatively antibiotic-resistant organisms such as *Candida* species, *Enterococcus* species, *Enterobacter* species, *Serratia* species, *Acinetobacter* species, and *Pseudomonas aeruginosa* are isolated more frequently from hospitalized patients on broad-spectrum antimicrobial agents.

Secondary peritonitis is usually a mixed infection involving predominantly obligate and facultative anaerobes. The devitalized tissue as a consequence of ischemia, trauma, or neoplastic growth provides the appropriate environment for the growth of these anaerobic organisms. Once the requirements for growth are met, the anaerobic organisms can achieve growth rates similar to those of the aerobic enteric bacilli. The rapidly expanding bacterial and inflammatory cell mass, frequently accompanied by gas production, can interrupt blood supply to immediately surrounding tissues and cause further tissue necrosis. Although the majority of bacteria isolated in mixed infections are probably nonpathogenic by themselves, their presence may be essential for the pathogenicity of the bacterial mixture. Facultatively, anaerobic organisms in mixed infections may provide the reduced environment necessary for the growth of obligate anaerobic organisms. In addition, each component of the pathogenic mixture may contribute in different ways to the clinical picture. In the initial phase, after contamination of the peritoneum, *E. coli* predominates. Bacteremia caused by *E. coli* is common during this phase. Later, indolent intra-abdominal abscesses may develop, in which *B. fragilis* predominates.

The formation and progression of an intraperitoneal abscess are often gradual; the patient who seemed to be recovering from peritonitis or an abdominal operation stops improving, fever returns, and localizing symptoms may develop. Early manifestations of peritonitis involve moderately severe abdominal pain that is aggravated by motion and even respiration. Other symptoms such as anorexia, nausea, and vomiting are also frequently present. Patients manifest fever, chills, decreased urination, inability to pass feces or flatus, and abdominal distention. Other findings include hypothermia, leukocytosis, marked abdominal tenderness to palpation (usually maxi-

mally over the organ in which the process originated), voluntary guarding, and/or hyperresonance due to gaseous intestinal distention. Bowel sounds may initially be hypoactive and then disappear. Rectal or vaginal examination revealing tenderness suggests the diagnosis of a pelvic abscess. Patients with peritonitis characteristically lie quietly in bed, supine, with knees flexed, and with frequent shallow respirations because any motion intensifies the abdominal pain. The patient is alert, restless, and irritable early in the course, but later may become apathetic or delirious.

Tapping ascitic fluid when fluid is present in the abdominal cavity usually confirms the diagnosis. An elevated total white blood cell count of more than or equal to 500 cells/mm^3, or a neutrophil count of more than or equal to 250 cells/mm^3, or a positive Gram stain or culture confirms the diagnosis. Imaging studies of the abdomen (e.g., ultrasound and CT scan) are also useful in determining the source of the peritonitis.

The role of antimicrobial therapy in the outcome of infection caused by anaerobes, or a mixture of anaerobes and aerobes is extremely difficult to assess. Often dramatical response to surgical drainage and débridement alone occurs when there is localized infection. Because these infections are polymicrobial, a broad spectrum of antibiotics is required. Usually combinations of two or three drugs are used. Antibiotics need not be active against every pathogen isolated. Although enterococci are found in about 20% of intra-abdominal infections, the exact role they play in polymicrobial intra-abdominal infection and the need for an antimicrobial regimen specific for these organisms are controversial. A reasonable antimicrobial regimen will provide coverage for both obligate anaerobes and facultative gram-negative enteric organisms. Metronidazole is active against obligate anaerobes such as most *B. fragilis* strains, *Fusobacterium* species, and *Clostridium* species; it also has a unique bactericidal action against *B. fragilis* and *C. perfringens*. It typically is the drug of choice for this disease process. The other agent used to cover the facultative gram-negative rods may be a third-generation cephalosporin. Regimens that substitute a third-generation cephalosporin for an aminoglycoside often do better than a regimen of clindamycin plus an aminoglycoside. Other β-lactams such as imipenem and meropenem have a very broad antimicrobial spectrum with activity against almost all aerobic and anaerobic pathogens. The use of carbapenems should be limited, if possible, due to concerns about antibiotic resistance developing to these very broad-spectrum antibiotics. The duration of antimicrobial therapy after adequate surgery is usually 5–7 days and depends on the severity of infection, clinical response, and normalization of the leukocyte count.

Pneumonia

Pneumonia is responsible for 27–30% of infection-related deaths in hospitalized patients and is the leading cause of infection-related mortality in this group of patients. The risk of developing nosocomial pneumonia may be related to patient risk factors, infection control, in-hospital interventions, or medications. Patient-related risk factors for development of nosocomial pneumonia are: age greater than 70 years, malnutrition, coma, nonambulation, metabolic acidosis, and the presence of comorbid illnesses (chronic obstructive pulmonary disease, alcoholism, azotemia, and central nervous system dysfunction). Infection control-related risk factors include lack of handwashing and the use of contaminated respiratory equipment. Procedures and therapies that invade normal host defenses and expose the host to a large inoculum

of bacteria also contribute to the development of nosocomial pneumonia. The use of ventilatory support is perhaps the greatest risk factor for the development of nosocomial pneumonia, increasing the risk by 20 times over nonventilated patients. Sedatives and narcotics put the patient at risk for aspiration; corticosteroids and cytotoxic agents predispose to infection; and the prolonged use of antibiotics induces resistance and infection with more virulent organisms.

Nosocomial pneumonia may be seen early, occurring within the first 4 days of hospitalization, or late. Early-onset nosocomial pneumonia usually is due to organisms associated with community-acquired pneumonia, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Late-onset nosocomial pneumonia is usually due to enteric gram-negative bacilli (*E. coli, Enterobacter* species, and *Serratia* species), *P. aeruginosa*, and *Staphylococcus aureus* (Table 2).

Nosocomial pneumonia usually presents with nonspecific clinical features. Fever, purulent sputum (especially in intubated patients), elevated white blood cell count, and a changing chest radiograph may be present due to noninfectious causes in a critically ill patient. Therefore, nosocomial pneumonia may be missed in 20–30% of patients. However, the role of more invasive procedures (e.g., bronchoscopy) in diagnosing nosocomial pneumonia, especially ventilator-associated pneumonia, remains controversial.

For early-onset pneumonia, a sputum Gram stain may be the most useful diagnostic test when obtained in association with a chest x-ray. Depending on the sputum Gram stain, the antibiotic of choice could be high-dose intravenous penicillin G or a third-generation cephalosporin (e.g., ceftriaxone), with or without a macrolide (e.g., erythromycin). For aerobic gram-negative rod-associated pneumonia, therapy with a third-generation cephalosporin, such as cefotaxime or ceftriaxone (ceftazidine or cefepime if *P. aeruginosa* is suspected), with or without an aminoglycoside, depending on the severity of illness is reasonable. The addition of a fluoroquinolone or a macrolide is warranted if a *Legionella*, *Mycoplasma*, or *Chlamydia* is suspected.

Pelvic Cellulitis

Symptoms typically develop on the second or third postoperative day, and patients usually complain of increasing lower abdominal and pelvic pain that is more severe on

Table 2 Types and Etiology of Nosocomial Pneumonia

Early-onset nosocomial pneumonia
S. pneumoniae
H. influenzae
M. catarrhalis
Late-onset nosocomial pneumonia
Enteric gram-negative bacilli
E. coli
Enterobacter species
Serratia species
P. aeruginosa
S. aureus

one side. The value of obtaining a culture from the vaginal cuff is controversial. There is inevitable contamination of the cuff with vaginal flora, which often renders such cultures difficult to interpret.

Pelvic cellulitis usually responds to a single parenteral antibiotic agent such as a second-generation cephalosporin (cefotetan or cefoxitin), or to a β-lactam–β-lactamase combination (ampicillin/sulbactam, and ticarcillin/clavulanic acid). Penicillin-allergic patients and those who have failed the initial antibiotic regimen may be treated with a combination of clindamycin and gentamicin. Parenteral therapy is continued until the patient has been afebrile for a minimum of 24–36 hr. Oral outpatient antibiotic therapy after successful parenteral therapy is usually unnecessary.

Cuff Cellulitis

All patients have inflammation around the vaginal cuff postoperatively as a part of the normal healing process, which is not indicative of an infection; this process usually resolves on its own. In a small number of cases, however, cuff cellulitis requires antibiotic therapy. Cuff cellulitis requiring antibiotic therapy usually occurs within 10 days after discharge from the hospital.

Patients complain of increasing central lower abdominal or pelvic pain, increased vaginal discharge, and low-grade fever. There is some suprapubic tenderness on palpation and vaginal surgical margin tenderness on bimanual pelvic examination. However, no masses are palpable. These patients can be successfully treated with oral antibiotics (e.g., amoxicillin/clavulanic acid) as outpatients, but patients should monitor their temperature and reevaluation at 72 hr is warranted.

Cuff Abscess

These patients develop a well-localized collection of fluid just above the vaginal cuff. This process usually manifests with a sense of fullness in the lower abdomen and a fever on the second or third postoperative day. Drainage is usually curative; the drained material should be Gram-stained and cultured for aerobic and anaerobic organisms. Patients should be treated with parenteral antibiotics on the basis of the culture results. Parenteral antibiotics should be continued for a minimum of 24–36 hr after the resolution of fever.

Septic Pelvic Thrombophlebitis

Pelvic vein thrombophlebitis is a rare and unusual cause of fever. It is almost always associated with a diagnosed operative site infection. Certain *Bacteroides* species are capable of degrading heparin, which may explain why septic pelvic vein thrombophlebitis is seen with infections caused by these organisms. Patients usually experience improvement with antibiotics, but the fever, which is usually recurrent, does not resolve. Patients do not appear acutely ill and only manifest a high fever and associated proportional tachycardia. The diagnosis of septic pelvic thrombophlebitis is one of exclusion and is verified by the resolution of fever after therapeutic anticoagulation with heparin.

Osteomyelitis Pubis

Osteomyelitis of the pubis is a rare cause of infection in this group of patients. It usually occurs in patients who have undergone urethral suspension, radical vulvectomy, or pelvic exenteration. Osteomyelitis of the pubis is secondary either to a contiguous spread of infection from a local source, or bacteremic seeding. Patients usually present many weeks after surgery. Symptoms consist of pubic bone pain and tenderness, pain on abduction, difficulty in ambulation, wound drainage, and low-grade fever. Moderate leukocytosis, elevated erythrocyte sedimentation rate, and elevated alkaline phosphatase levels are seen. Blood cultures and cultures of bone biopsy specimens are useful in diagnosis. A radiograph or CT scan of the pubic bone often shows rarefaction, erosion, osteolytic lesions, or irregularities of the bone margins with separation of the symphysis. Radionucleotide scanning techniques may show increased activity.

Antimicrobial therapy should be directed at the isolated organism, or, if none is isolated, should be directed against *S. aureus* and aerobic gram-negative organisms, which are the most common causes of this infection. Antibiotic therapy must be prolonged (approximately 6 weeks) and surgical débridement is usually needed as well.

CVC- AND IMPLANTABLE DEVICE (ID)-RELATED INFECTIONS

The approach to infections of CVC or ID in a cancer patient is usually not straightforward. Some of the concerns making removal of these devices problematical are: thrombocytopenia, difficulty in inserting these devices, and lack of vascular access. The decision to remove a CVC or ID should be based on documented infection of the device, the specific pathogen involved, severity of illness, and device-associated infectious or mechanical complications (Table 3). Even if the catheter is removed, systemic antimicrobial therapy is required. On the other hand, when the catheter is

Table 3 Indications for the Removal of a CVC or ID/Complicated Infections

(a) Tunnel infection or pocket abscess
(b) Specific pathogens such as
P. aeruginosa
Corynebacterium jeikeium
Bacillus species
Fungi
Mycobacteria
(c) Persistent signs of infection despite systemic antimicrobial therapy
(d) Recurrent infection with the same organism
(e) Infectious complications
Septic thrombophlebitis
Endocarditis
Metastatic seeding
(f) Mechanical complications
Poor flow
Venous thrombosis

thought to be salvageable, consideration should be given to antibiotic lock therapy in association with systemic antimicrobial therapy. Antibiotic lock therapy is a comparatively new practice and is included in the guidelines for management of such infections issued by the Infectious Diseases Society of America (IDSA). However, most institutions are currently not familiar with this technique. For more details, refer to suggested readings (no. 2).

Etiology

Although a number of organisms can cause these infections, the ones most commonly isolated are:

1. Coagulase-negative *Staphylococci*
2. *S. aureus*
3. Gram-negative bacilli such as: *E. coli*, *Enterobacter*, *Klebsiella*, *Proteus*, and *Pseudomonas* species
4. *Candida albicans*

Diagnosis

Clinical diagnosis alone is usually not reliable. Fever can be due to a number of causes and, although quite sensitive, is not very specific; on the other hand, discharge at the catheter site, although quite specific, is not commonly seen. When discharge is present, a Gram stain and culture of the discharge should be obtained. Blood cultures are usually most helpful in making the diagnosis. Two sets of blood cultures, ideally drawn from two different peripheral sites, are needed. This approach is especially useful when organisms such as coagulase-negative *Staphylococci* or *Corynebacterium* species are isolated, as these organisms are part of the normal skin flora; if present in both sets, they are probably true pathogens.

Cultures of blood also should be drawn from all the ports of the catheter, together with the peripheral blood cultures. If cultures are positive for the same organism from both the catheter as well as the periphery, it implies true infection as opposed to possible colonization of the catheter (when only the catheter-drawn cultures are positive). Other clues for true catheter infection are the positivity of catheter cultures before peripheral cultures and the isolation of a higher number of organisms from the catheter in comparison to the periphery. For staphylococcal bacteremia, daily blood cultures are recommended until negative cultures are obtained, as duration of therapy is dependent on the duration of bacteremia. A longer duration of bacteremia is an indication for a search for complications such as metastatic seeding, endocarditis, etc. Persistent bacteremia and lack of resolution of fever or leukocytosis with any organism should prompt a search for systemic complications.

Management of CVC- or ID-Related Infections

For complicated infections with tunnel infection or pocket abscess, removal of catheter and drainage of the abscess along with 7–10 days of intravenous antibiotic therapy are recommended. Patients with septic thrombosis or endocarditis require removal of the catheter or device and antibiotic treatment for 4–6 weeks. Patients with

osteomyelitis require the removal of the catheter and antibiotic treatment for 6–8 weeks.

One might try to salvage the CVC or the ID in patients with uncomplicated infections. Two weeks of systemic antibiotic therapy, with or without antibiotic lock therapy, should be used. The duration of treatment for most uncomplicated infections is 7–10 days, except for *S. aureus*-related infections with blood cultures positive for more than 48 hr; 14 days of therapy is recommended in such cases. Reinsertion of tunneled intravascular devices should be postponed until after appropriate antimicrobial therapy (based on susceptibilities of the bloodstream isolate) is begun and negative repeat blood culture results are obtained. If time permits, insertion of a tunneled intravascular catheter or an ID in a stable patient ideally should be performed after a systemic course of antibiotic therapy is completed and repeat blood samples drawn 5–10 days later yield negative results. The choice of antibiotics depends on the pathogen isolated (please refer to Table 4 for some suggestions).

Table 4 Common Pathogens Causing CVC-Related and ID-Related Infections and Treatment

Pathogen	Treatment
Methicillin-susceptible *S. aureus*	Nafcillin, 2 g, q 4 hr
Methicillin-resistant *S. aureus*	Vancomycin, 1 g, q 12 hr
Vancomycin-resistant *S. aureus*	Linezolid, 600 mg, q 12 hr Quinapristin/dalfopristin, 7.5 mg/kg, q 8 hr
Methicillin-susceptible coagulase-negative *Staphylococcus*	Nafcillin, 2 g, q 4 hr
Methicillin-resistant coagulase-negative *Staphylococcus*	Vancomycin, 1 g, q 12 hr
Ampicillin-susceptible *Enterococcus*	Ampicillin, 2 g, q 4–6 hr Ampicillin + gentamicin, 1 mg/kg, q 8 hr
Ampicillin-resistant *Enterococcus*	Vancomycin, 1 g, q 12 hr Vancomycin + gentamicin, 1 mg/kg, q 8 hr
Vancomycin-resistant *Enterococcus*	Linezolid, 600 mg, q 12 hr Quinapristin/dalfopristin, 7.5 mg/kg, q 8 hr
E. coli and *Klebsiella* species	Ceftriaxone, 1–2 gm, qd
Enterobacter species and *Serratia marcescens*	Cefepime, 2 g, q 12 hr; imipenem, 500 mg, q 6 hr
Acinetobacter species	Ampicillin/sulbactam, 3 g, q 6 hr Imipenem, 500 mg, q 6 hr
Stenotrophomonas maltophilia	TMP–SMZ, 3–5 mg/kg, q 8 hr
P. aeruginosa	Ceftazidine, 2 g, q 8 hr; cefepime, 2 g, q 12 hr
C. albicans or other *Candida* species	Fluconazole, 400–600 mg, qd Amphotericin B, 0.5–1 mg/kg/day
C. glabrata	Fluconazole, 600–800 mg, qd
C. krusei	Amphotericin B, 0.5–1 mg/kg/day
C. jeikeium	Vancomycin, 1 g, q 12 hr

INTRAPERITONEAL CATHETER-RELATED INFECTIONS

Most intraperitoneal catheter-related infections are due to the contamination of the catheter by organisms composing the normal skin flora. Alteration of the skin flora may lead to peritoneal contamination with enteric pathogens. Pathogens may contaminate the peritoneum not only from the skin and exit site, but also from an infected subcutaneous tunnel, transient bacteremia, and/or contaminated infusate. Enteric bacteria may gain access to the peritoneal cavity by transmural migration through an intact intestinal wall after the introduction of hypertonic solutions into the peritoneum. Polymicrobial infection with fecal organisms suggests perforation of the bowel as a complication of catheter placement or other abdominal surgical procedures.

Gram-positive cocci comprise 60–80% of the isolates. The most common pathogen is *S. epidermidis*, followed by *S. aureus*, *Streptococcus* species, and diphtheroids. The coagulase-negative staphylococci are known to grow on polymer surfaces and produce a slime or biofilm that protects these bacteria from host defenses. Gram-negative organisms are obtained from 15% to 30% of isolates. *E. coli* is the most common, followed by *Klebsiella*, *Enterobacter*, *Proteus*, and *Pseudomonas* species. Less frequent pathogens include *Acinetobacter* species, *C. albicans*, and anaerobic bacteria. Rarely, other fungi or mycobacteria may be isolated.

Clinical findings include abdominal pain, tenderness, nausea and vomiting, fever, and diarrhea. The peritoneal fluid reveals a leukocyte count greater than 500 cells/mm^3 with a predominance of neutrophils. A preponderance of eosinophils in the peritoneal fluid is seen in a self-limited condition, known as eosinophilic peritonitis, which may represent allergy to the tubing. Peritoneal eosinophilia is also seen in fungal peritonitis. Gram staining of the fluid reveals organisms in only 9–50% of cases, but cultures of the peritoneal fluid are often positive. Peripheral leukocytosis is a poor indicator of peritonitis in these patients. Blood cultures are rarely positive, in contrast to the 30–50% positive rate in other types of intra-abdominal infections. The prognosis is generally favorable. The duration of illness and resolution of positive peritoneal fluid cultures after institution of antimicrobial therapy usually take 1–4 days. However, some infections, especially those caused by *S. aureus*, *P. aeruginosa*, or a fungus, resolve more slowly and may cause relapse more frequently.

One may choose the systemic or the intraperitoneal route for the administration of antibiotics. The goal is to maintain a drug concentration in the peritoneal fluid that is greater than the minimum inhibitory concentration of the pathogen for most of, if not the entire, dosing intervals. After cultures are obtained, initial antimicrobial therapy should be based on the results of Gram staining, or on the most likely pathogen if the Gram stain is not helpful. A reasonable initial empiric regimen would be vancomycin in combination with an aminoglycoside. Vancomycin is preferable to a cephalosporin because of the frequency of β-lactam resistance (i.e., methicillin resistance) in staphylococci, which predicts resistance to cephalosporins as well. Initial antibiotic choices should be modified, if necessary, after culture results are obtained. Because *P. aeruginosa* peritonitis is associated with high failure rates and relapses, it is best treated with a combination of agents active against the infecting strain, in addition to catheter removal. In most cases, clinical improvement occurs within 48–96 hr of initiation of antimicrobial therapy. If the signs and symptoms of peritonitis persist after 96 hr of therapy, reevaluation is warranted, with consideration given to the possibilities of resistant pathogens, unusual organisms (e.g., mycobacterial, fungal), or

Table 5 Indications for Removal of Intraperitoneal Catheters

Persistent skin exit site or tunnel infection
Fungal, fecal, mycobacterial peritonitis
P. aeruginosa peritonitis
Persistent peritonitis
Recurrent peritonitis with the same organisms
Catheter malfunction (e.g., poor flow)
Intraperitoneal abscess

other intra-abdominal processes. Fungal peritonitis caused by *C. albicans* or other fungi should be treated with amphotericin B. However, most patients with fungal peritonitis fail to respond unless the catheter is removed. Removal of the catheter is necessary in 10–20% of patients. The indications for removal of the catheter are given in Table 5.

COLONY-STIMULATING FACTORS

The American Society of Clinical Oncology has published guidelines for the use of these agents with cancer chemotherapy. The routine use of hematopoietic colony-stimulating factors as adjuvant therapy for neutropenic patients with unexplained fevers is not recommended. The likelihood of a good outcome for typical febrile neutropenic episodes is very high with standard antibiotic therapy, especially when the neutropenia is of short duration, as it typically is in patients with solid organ malignancies.

Therapy with colony-stimulating factors may be considered in patients who remain severely neutropenic and who have documented infections that fail to respond to antibiotics. If used, a colony-stimulating factor should be withdrawn once the neutrophil count is stabilized at greater than 500–1000 cells/mm^3.

FEBRILE NEUTROPENIA

Febrile neutropenia is defined as a fever greater than or equal to 38.0°C (100.4°F), with an absolute neutrophil count of less than 500/mm^3 or less than 1000/mm^3 and with a predicted decline to less than or equal to 500/mm^3. In addition to the number of circulating neutrophils, the rate of decline and the duration of neutropenia are important determinants of infection. Solid organ malignancy patients do not have severe and prolonged neutropenia. Therefore, febrile neutropenia is not commonly seen in this group. However, a brief review is presented below.

The evaluation of a patient with febrile neutropenia requires a meticulous history and physical examination, as the signs and symptoms may not be pronounced due to a muted inflammatory response secondary to the decreased number of neutrophils. The evaluation is otherwise similar to that described in general approach to a patient with fever.

Because of the high risk of life-threatening bacterial infections in febrile neutropenic patients, broad-spectrum bactericidal antibiotics should be promptly

given by the intravenous route and in maximal therapeutic dosages. Afebrile patients who are neutropenic (neutrophil count less than 500 cells/mm^3) but with signs or symptoms compatible with an infection should receive empirical broad-spectrum antibiotics as well.

Treatment

Several randomized studies have shown that there are no striking differences between monotherapy and multiantibiotic combinations in the treatment of uncomplicated episodes of fever in neutropenic patients before the etiology of the infection is known. Thus, appropriate monotherapy can be considered a standard of therapy. Cefepime, ceftazidine, or imipenem/cilastatin may be used as monotherapy in most cases. For seriously ill or unstable patients, a two-drug regimen may be chosen with addition of an aminoglycoside to one of the above-mentioned drugs. If a local pelvic infection is suspected, metronidazole should be added (except to imipenem/cilastatin, which provides excellent anaerobic coverage by itself). For suspected pelvic infection-related fever, piperacillin/tazobactam may be used alone. The indications for the addition of vancomycin are listed in Table 6.

At institutions in which fulminant gram-positive bacterial infections are common, vancomycin may be incorporated into the initial therapeutic regimens for some high-risk patients, but vancomycin therapy should be discontinued 3–4 days later if no such infection is identified.

If the patient continues to be febrile in spite of antibiotics and the resolution of the neutropenia is not imminent, amphotericin B may be added on days 5–7. Prolonged neutropenia usually does not occur in patients with solid organ malignancies and nonbone marrow transplant patients. Therefore, if such a situation arises, an infectious diseases specialist should be consulted.

Duration of Therapy

The duration of antibiotic therapy depends on the duration of neutropenia, duration of signs and symptoms including fever, and the isolation of a specific pathogen. If a specific pathogen is isolated, antibiotic therapy should be directed toward it and the likely source. However, if a specific pathogen or site is not isolated and the patient is afebrile by the third day with a neutrophil count greater than 500/mm^3 by the seventh day, antibiotics may be stopped. If the fever has resolved but the neutropenia has not,

Table 6 Selection Criteria for Inclusion of Vancomycin in the Initial Regimen

(a) Patients with clinically obvious, serious catheter-related infections
(b) A blood culture positive for gram-positive bacteria before final identification and susceptibility testing
(c) Hypotension or other evidence of cardiovascular impairment
(d) Intensive chemotherapy that produces substantial mucosal damage (i.e., high-dose cytarabine, which increases the risk for penicillin-resistant streptococcal infections, particularly those due to viridans streptococci)
(e) Prophylaxis with quinolones before the onset of the febrile episode (usually applicable only to bone marrow transplant patients)

and the patient looks clinically well, antibiotics may be stopped. On the other hand, even if the fever has resolved but the patient continues to be unstable or severely neutropenic (absolute neutrophil count less than $100/mm^3$), antibiotics should be continued. In the event of persistent fever and neutropenia, antibiotics should be continued for 14 days with reassessment at the end of antibiotic therapy. If fever persists but the neutropenia has resolved, the antibiotics may be stopped at 5 days with reassessment.

ANTIMICROBIAL PROPHYLAXIS

The efficacy of perioperative prophylaxis in preventing wound infection after many surgical procedures is unquestioned. Nevertheless, issues regarding the optimal choice, frequency, and duration of perioperative antibiotic prophylaxis are unresolved.

There are no studies in gynecology malignancy patients that are large enough to support one approach vs. another. However, most surgeons use perioperative antibiotic prophylaxis in these patients, and there has been an associated decrease in postsurgical infections in general. Although there is a dearth of literature addressing the use of prophylactic perisurgical prophylaxis in gynecological malignancy patients, most clinical studies on perisurgical/presurgical prophylaxis in clean-contaminated surgical procedures (such as in gynecology malignancy patients) support cefazolin as the drug of choice. There is general agreement that the initial dose of systemically administered antibiotics need not be given until the onset of the procedure. The induction of anesthesia represents a convenient point for initiating antibiotic prophylaxis in major surgical procedures. Whether and for how long antibiotics should be given postoperatively is a subject of considerable disagreement; however, short course therapy for 18–24 hr generally is used.

Marked variations in the spectrum of infecting pathogens and in the degree of antimicrobial resistance exist among hospitals. Physicians and individual health care institutions must tailor routine prophylactic regimens based on carefully collected epidemiological data regarding surgical wound infection. Early reexplorations for postoperative bleeding, a history of penicillin or cephalosporin allergy, trauma and other emergency surgery, and existing preoperative infections of nonwound sites (e.g., urinary tract infections and decubitus ulcers) are important variables that may influence the choice and duration of perioperative prophylaxis.

Adverse effects for the patient include allergic reactions ranging in severity from minor skin rashes to anaphylaxis. Antibiotic use, specifically prophylactic antibiotic use, will favor the selection of antibiotic-resistant bacteria in hospitalized patients.

In view of the improvement in overall surgical wound infection rates over recent decades, the consensus is that the benefits of prophylactic antibiotics outweigh the risk. For instance, the 6-month mortality rate of patients who develop a deep wound infection is 2.5-fold that of patients without a deep wound infection.

CONCLUSION

Infections in gynecological malignancy patients are usually seen after surgical procedures and may be complicated by chemotherapy and radiotherapy. Lack of

randomized, controlled trials limits the ability to make clear recommendations. However, most of the infections originate from the local site of surgery. The most common pathogens involved are the enteric gram-negatives and anaerobes; therefore, therapy should be directed against them.

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Pharmacologic Pain Management in Gynecologic Oncology

Wilberto Nieves-Neira

Roberto Angioli
University of Rome Campus Bio-Medico, Rome, Italy

Manuel Penalver
University of Miami School of Medicine, Miami, Florida, U.S.A.

INTRODUCTION

An estimated 1,334,100 new cancer cases have been diagnosed in 2003 in the United States, and approximately an estimated 556,500 cancer-related deaths occurred (1). Cancer patients often struggle with several conditions throughout the course of their disease process even in the absence of premorbid illnesses. These conditions result in significant physical, emotional, psychological, spiritual, and social distress. Physical pain with its different manifestations and perceptions is a common symptom. From the patient's point of view or that of a family member or caregiver, pain is perhaps one of the most feared consequences associated with a diagnosis of cancer (2). Moreover, advances in the treatment of cancer generate another consideration concerning pain management since extension of overall survival may result in a number of patients experiencing cancer-related pain for a prolonged period of time: in general, 50% of patients with cancer experience pain throughout their disease process (3) and up to 75% of patients with advanced or end-stage disease report pain, which is described as severe or excruciating in close to one-third of the cases (4).

On the other hand, several barriers to effective pain control have been identified. These barriers include problems related to the physician and health-care providers, the patients, and the health-care delivery system. Health-care providers may have inadequate knowledge of pain management. Traditionally, pain management has not been an integral part of medical school curriculums. Fear of promoting patient's addiction or side effects may lead to suboptimal pain control.

More recently, however, concerns about disciplinary actions by state medical boards and government agencies have become a reality. In 1999, the Oregon Board of Medical Examiners became the first state medical board to discipline a doctor for undertreatment of pain; in addition, the U.S. Drug Enforcement Administration has

been investigating physicians for what it considers overprescribing practices (5). Patient-related problems include reluctance to report pain and fear that she might be considered a "difficult" patient. Fear of becoming addicted to pain medications is a strong and quite common barrier (6). The health-care delivery system may have a grave impact on pain management as access or availability of the most appropriate treatment may be restricted.

The American Pain Society and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) advocate assessment of pain as the fifth vital sign (7–10). The concept of pain as the "fifth vital sign" has facilitated the recognition of pain being as important as any other physiological variable. It also promotes a proactive attitude toward pain.

The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) announced in December 2000 pain management standards that were developed over 2 years in conjunction with the University of Wisconsin, Madison School of Medicine. The standards indicate that it is the patients' right to have appropriate assessment and management of their pain (7,10). Organizations have a responsibility to develop processes that support improvements in pain assessment and management.

In conclusion, the cancer pain problem has gained recognition as an integral part of the cancer patient care and treatment. Advances in the pharmacology of analgesics, medical management, and surgical treatments make it possible to effectively control pain in most patients (11). The incorporation of alternative or complementary techniques (acupuncture, music therapy, and meditation, among others) may improve pain control and contribute to a sense of well-being. A multidisciplinary approach to treating pain is essential to be successful.

CANCER-RELATED PAIN: CLASSIFICATIONS

Cancer pain is defined as pain that is attributable to cancer or its therapy. It can be classified as acute when it lasts a relatively short time and usually there is an evident cause–effect relationship (i.e., postsurgical pain). On the other hand, pain is defined as chronic when it lasts for long time (i.e., advanced or recurrent cancer-related pain). At last, particular considerations should be done on acute exacerbations of chronic cancer pain.

Cancer pain may be directly related to the tumor itself or be a consequence of the different treatment modalities. The pain may be directly related to the tumor as infiltration or direct pressure of soft tissues, viscera (i.e., carcinomatosis), bone (bone metastasis is a well-recognized cause of severe pain), or nerves (neuropathic-type pain) which produces a painful stimulus. Treatment may also result in painful stimuli. Surgery results in postoperative pain that, in many instances, can be quite severe; also, there is always the possibility of long-term pain problems associated with nerve damage. Postmastectomy pain syndrome occurs in 5–20% of patients undergoing mastectomy (12). Chemotherapy regimens may result in neuropathies that may be perceived as painful sensations: taxol and vincristine are associated with painful peripheral neuropathy. Radiation therapy may have similar consequences: radiation to the lumbar plexus often presents as weakness, but eventually up to half of patients develop pain as part of the syndrome (13); radiation proctitis often presents with rectal pain.

Preexisting pain syndromes may be present in the patient that is diagnosed with cancer. Concomitant nontumor-related pain occurs in about 10% of patients, and it represents a diagnostic and therapeutic challenge (14).

Foley (15) recommended classifying cancer patients with pain into 5 groups: (1) patients with acute cancer-related pain; (2) patients with chronic cancer-related pain caused by either progression of disease or its therapy; (3) patients with preexisting chronic noncancer-related pain as well as cancer-related pain; (4) patients with a history of chemical dependence and cancer-related pain; and (5) actively dying patients who require comfort measures. In gynecologic oncology, another group would include the pregnant patient with cancer pain. This classification addresses pain according to the type of patient rather than a single dimension of pain and allows for a psychosocial approach to management.

CLINICAL PAIN ASSESSMENT

The International Association for the Study of Pain has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (16). This definition recognizes the complexity of the patient's perception of pain and its interpretation. Physiologic processes as well as psychological, emotional, behavioral, and cultural aspects are important in the perception of pain.

A thorough assessment of the pain characteristics is essential to establish the type of pain the patient is experiencing. Proper identification of the nature of pain will guide the physician in selecting the optimal pharmacological intervention. Pain assessment has been identified in large multicentered studies as the major impediment to adequate pain management (17,18). A complete history including psychosocial components and a physical examination are obtained at the initial evaluation. Assessment should continue on a routine basis and more frequently whenever a new treatment is initiated to establish its efficacy.

The thorough history should assess the characteristics of pain (quality, duration, intensity, location, radiation, associated factors, timing, and meaning) and should be obtained preferably from the patient.

Quality

The patient may have difficulty finding the proper description of the pain. It is useful to offer the patient a list of adjectives. Pain that is described as sharp, stabbing, aching, constant, throbbing, or a feeling of pressure is typical of somatic pain. It arises from injury to skin, mucosa, muscle, or bone and usually can be localized. Somatic pain may increase with movement, which is typical of bone lesions. Visceral pain can be deep, lancinating, gnawing, or colicky. It arises from distention, inflammation, obstruction, compression, or ischemia of visceral organs, mesentery, or peritoneum and pleura. Usually, it is diffuse and poorly localized. Neuropathic pain results from damage to the peripheral or central nervous system either from a primary lesion or an induced dysfunction (19). The most common presentation of neuropathic pain is an alteration of sensation. It is typically described as tingling, burning, shooting, shocklike (electrical), or "pins and needles." The skin surrounding

the pain area may be abnormally sensitive to normal touch (allodynia) or just numb. Repeated stimulation with the same stimulus causes a progressive increase in pain intensity (hyperpathia), or the pain may persist after the stimulus is withdrawn (after-reaction).

Duration

Acute pain has a well-defined onset in time and a limited duration.

The patient is usually able to identify what caused the pain. Conventionally, acute pain is defined as pain with less than 30 days duration. Acute pain is useful because it has a protective purpose. It signals an injury, and therefore it is regarded as a symptom. There is an expected physiological response with increased sympathetic tone resulting in vasoconstriction of the cutaneous and splanchnic vessels, increased stroke volume and heart rate, increased blood pressure, metabolic rate, and oxygen consumption. Stimulation of the respiratory center results in hyperventilation. There is pain-related behavior like immobility, grimacing, and moaning, but mild or no associated psychological disturbance (20). Postoperative pain is perhaps the most common example of acute pain in gynecologic oncology. Unrelieved acute pain, including postoperative pain, may be associated with significantly harmful physiologic or psychological effects. These adverse effects may result in significant morbidity (21). Recurrent acute pain has a pattern of isolated episodes of pain over an extended period of time. Chronic pain has a duration of more than 3 months, usually with ill-defined onset and a fluctuating pattern. Chronic pain has no protective quality as it usually persists despite normalization after an injury or disease. In the cancer patient, this definition has some limitations as the patient may experience long-term pain related to persistent disease in the context of recurrence. Some authors consider chronic pain a disease process unto itself (20). Physiologic hyperactivity of the sympathetic system may be absent and pain-related behavior may not be obvious. Chronic pain has a significant effect on quality of life and frequently presents with psychological disturbances like depression or anger. By the time the pain becomes chronic, full resolution of the pain syndrome is unlikely. Patients generally do not feel fully restored or comfortable, even when they recover the majority of lost function (22). Management of chronic pain requires a multidisciplinary effort including physical therapy, rehabilitation, and psychological assessment and intervention (23).

Intensity

The severity of the pain should be quantified. Pain rating scales have been developed and validated for the assessment of cancer pain. The scales help the patient to communicate the intensity of their pain. They also allow monitoring of the pain once therapy has been initiated and provide a reference point to assess the effectiveness of changes in treatment.

Location Topographically, pain can be localized, multifocal, or generalized (22). Asking the patient to mark on a body outline to demonstrate the location of the pain will facilitate her description and allow for future comparisons. Well-localized pain with no radiation is usually somatic in nature and may be indicative of metastasis to the bone. Poorly localized, deep pain is visceral in nature. Pain that follows a dermatomal distribution may be neuropathic in nature. It may be difficult to link the pain to a specific injury particularly at the beginning of the evaluation of the patient. Ongoing reassessment is important as unsuspected new lesions can be identified by analysis of changing pain patterns in over half of cancer patients (24).

Radiation

The area to which the pain spreads or travels provides insight into the type of pain. As already indicated, dermatomal distribution is typical of neuropathic pain. Postherpetic neuralgia is one of the most common and devastating pain syndromes in patients both with and without cancer (25). It is important to differentiate localized pain from referred pain, which has different manifestations (20).

Pain referred along the course of the injured peripheral nerve
Radicular pain: pain referred along the course of a damaged nerve root
Funicular pain: pain referred to nondermatomal parts of the body from lesions involving the spinal cord or central pathways
Pain referred in a nondermatomal fashion from a visceral source (Kerr's sign: shoulder pain from diaphragmatic irritation)

Aggravating/Relieving Factors

Factors that make the pain better or worse can give clues as to the etiology of the pain and may aid in the management of the patient's symptoms. Pain that increases with movement of an extremity may indicate an osseous metastasis. Pain that increases when lying down may indicate involvement of the spine. These factors may also assist in the choice of nonpharmacologic interventions. Heat or cold application may mitigate the intensity of pain.

Timing

The time interval between a specific action and the onset of pain may help to identify a noxious stimulus. Abdominal pain occurring within 1 or 2 hr after a meal (usually with bloating) may be an indication of an early partial small bowel obstruction in ovarian cancer patients. Rectal pain or "discomfort" during defecation, with or without tenesmus, is common in radiation proctitis. Pain developing or intensifying at a specific time of the day may indicate that the medication dosage or schedule is inadequate. Increasing the dose or changing to longer-acting medications are alternatives to manage this situation.

Meaning of the Pain

This area helps the practitioner understand the psychological aspects of pain in the particular patient. The psychological and emotional toll including depression or anxiety can be ascertained. Coping mechanisms can be identified and strengthened. Pain may be a constant reminder of the incurable nature of the disease (26). Patients commonly interpret an increase in pain as a sign of disease progression. Feelings of despair and hopelessness may be avoided by early intervention and reassurance that the pain can be controlled. Understanding the effect of pain in quality of life may help to develop specific interventions or rehabilitation strategies. Insomnia is common in cancer patients with pain and should be addressed as a separate problem. Improving sleep will not only have a positive effect in the sense of well-being of the patient, but also is likely to help with pain management. In terms of rehabilitation strategies, an athletic patient that may not continue to practice high impact sports may benefit from water-based activities.

Measurement of Pain

Pain measurement is based on the patient's self-report and is inherently subjective. The most common and simplest measurement of pain is based on assessing pain intensity.

Intensity is assessed by visual analog scales, categorical verbal scales, and categorical numerical or linear scales (Fig. 1). The most commonly used is the numeric rating scale. Pain is rated on a scale of 0–10 (27). Descriptors are used with 8–10 being severe pain or the worst pain ever experienced, 4–7 being moderate pain, and 1–3 being mild pain (28). Numeric rating scales are efficient, easily understood by most patients, and have adequate sensitivity for clinical practice (29–31). They are good for the initial pain evaluation as well as reassessment once therapy has been started. This approach also allows the patient to objectively evaluate herself the efficacy of initial therapy. A numeric scale can be modified to assess the affective component of pain. Descriptors are changed to reflect "unpleasantness" rather than severity. The anchor for the scale would be 0 = "not bad at all" to 10 = "most unpleasant feeling possible" (29). Scales that use verbal descriptors alone are not as sensitive and are difficult to use by patients with limited language. Analog scales are sensitive and are less likely to be affected by remembering a previous score, but some patients have difficulty understanding the use of the entire range of the scale (29).

More complex pain assessments involve multidimensional reporting using pain questionnaires. The McGill Pain Questionnaire was designed to assess different pain qualities by presenting patients with 78 adjectives or descriptors (32). A shorter form of the McGill Pain Questionnaire has been developed by Melzack (33). Only 15 pain descriptors are used and patients are asked to rate them in a four-point scale ranging from none to severe. This questionnaire has been validated in the evaluation of cancer pain (34), but it has rarely been applied to answer clinical research questions in this field. The Brief Pain Inventory (BPI) was originally developed and standardized on cancer patients (28). It is brief (16 questions) but comprehensive and can be used with both hospitalized and clinic patients. The BPI includes numeric ratings of pain severity at its worst, least, current, and average and a figure drawing for

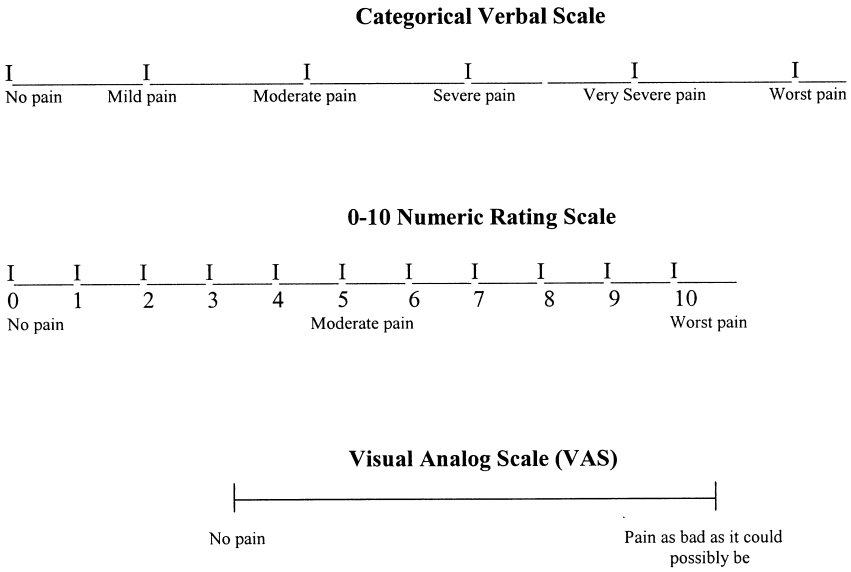


Figure 1 Commonly used scales for pain intensity assessment.

patients to locate the pain. It also provides information about the impact of pain on life activity and emotional functioning like ability to work, sleep, and mood (35). The ease of administration and patient's compliance in advanced cancer patients undergoing palliative care have been questioned (36). A useful approach to assess pain location is to present the patient with a drawing of the front and back of the body and ask her to mark the location of the pain. Drawings are simple and easy to complete and allow for comparisons during the course of the patient's care (29). Patients presenting with complex pain syndromes or chronic pain may need psychometric testing as part of their evaluation. Patients that indicate high levels of emotional distress either on self-report or observation may benefit from evaluation by a psychologist or psychiatrist. Commonly used tools are the Minnesota Multiphasic Personality Inventory, the Beck Depression Inventory, and the Wisconsin Brief Pain Inventory (28).

These scales are valid and have characteristics that should be considered before they are applied to clinical practice or clinical trials. The concept of pain relief needs further study in long-term assessment (37). Three aspects of cancer pain assessment still have significant limitations (38):

1. Which pain should be measured? It is not known which pain should be measured in repeated administration of the scales to have a realistic assessment of the "true pain" experience. The average of multiple measures over time increases the validity of pain intensity assessment in chronic noncancer pain patients (39).
2. What is the sensitivity to treatment effect? The ability to detect changes induced by treatment is considered an important factor when evaluating the validity of a pain scale (40). In short-term evaluation of analgesics, a categorical verbal scale is the most sensitive tool. Numerical rating scales also have good sensitivity. However, their sensitivity for the evaluation of overall cancer pain treatment remains largely unstudied.
3. What is a clinically significant pain change? Changes on the score of a particular scale need to correlate with clinical relief of pain. Farrar et al. studied the use of breakthrough medication as an endpoint to assess the pain intensity that prompted the patients to use the medication. A reduction of less than 33% in pain intensity or less than 2 points on a 0–10 numerical rating scale predicted the use of additional breakthrough medication doses with an accuracy of 72% and 68%, respectively (41).

PAIN MANAGEMENT

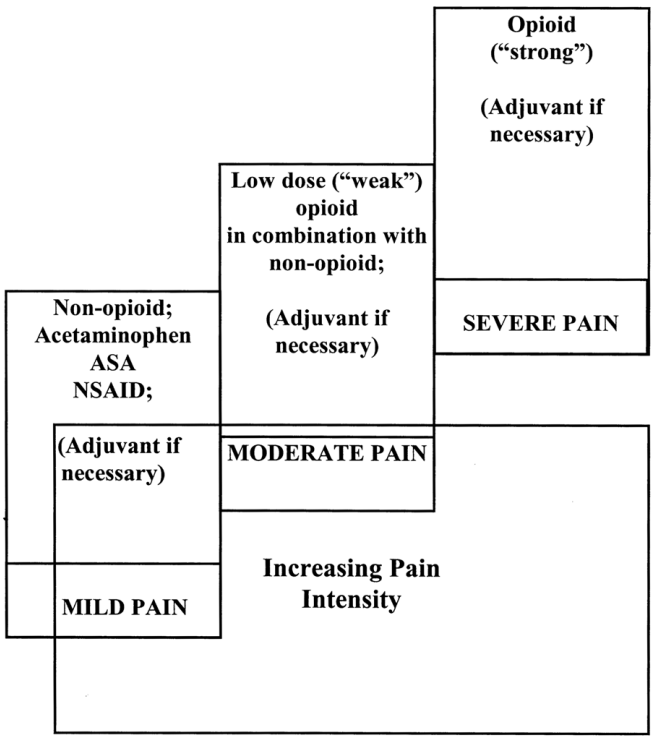
The cornerstone of cancer pain management is drug therapy which can provide satisfactory pain relief for most patients (42). Pain therapy should be individualized taking into account the stage of the disease, characteristics of the pain, medical comorbidities, and psychological and cultural aspects of the patient. The simplest dosage schedule and the least invasive route of administration should be used. The three major categories of drugs used alone or in combination are the nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, the opiate analgesics, and the adjuvant analgesics.

The World Health Organization published in 1986 guidelines for the treatment of cancer pain (43). The guidelines are based on a three-step ladder construct that serves as an algorithm for a sequential pharmacological approach according to the intensity of pain referred by the patient (Fig. 2). According to the analgesic ladder, mild pain should be treated with acetaminophen or an NSAID. Opiates are used in steps two and three. They are classified according to their ability to control mild to moderate pain (i.e., codeine, dextropropoxyphene, and tramadol) and moderate to severe pain (i.e., morphine, oxycodone, hydromorphone, fentanyl, buprenorphine, diamorphine, and methadone) (44). The WHO expert committee introduced morphine as a major pain-relieving medication and has strongly advocated the need to make it available worldwide.

At all levels, certain adjuvant analgesics may be used for specific indications.

Non-opioid Analgesics

Non-opioid analgesics include aspirin, acetaminophen, and NSAIDs (Table 1). As single agents, they are used to treat mild pain (ladder step 1). They provide additive analgesic effects when combined with opioid drugs such as codeine, oxycodone, and hydrocodone (ladder step 2), so they are effective for moderate pain. Non-opioid



Abbreviations: ASA, aspirin, NSAID, non-steroidal anti-inflammatory drug

Figure 2 World Health Organization analgesic ladder.

Table 1 Usual Dosing for Acetaminophen (APAP) and NSAIDs

Drug	Usual dose for adults and children 50 kg body weight
Acetaminophen and over-the-counter NSAIDs	
Acetaminophen	650 mg q 4 hr 1300 mg q 8 hr (extended release caplets)
Aspirin	650 mg q 4 hr 975 mg q 4 hr (enteric-coated)
Ibuprofen (Motrin, Advil, others)	400–600 mg q 6 hr
Prescription NSAIDs	
Choline magnesium trisalicylate (Trilisate)	1000–1500 mg tid
Diflunisal (Dolobid)	500 mg q 12 hr
Etodolac (Lodine)	200–400 mg q 8–12 hr
Fenoprofen calcium (Nalfon)	300–600 mg q 6 hr
Ketoprofen (Orudis)	25–75 mg q 6–8 hr
Ketorolac tromethamine (Toradol)	10 mg q 4–6 hr maximum 40 mg/day = ×5 days 30 mg IV q 6 hr (24–48 hr only)
Meclofenamate sodium (Meclomen)	50–100 mg q 6 hr
Mefenamic acid (Ponstel)	250 mg q 6 hr
Naproxen (Naprosyn)	250–275 mg q 12 hr
Naproxen sodium (Anaprox)	275 mg q 12 hr OTC tabs = 200 mg q 12 hr (Aleve)
Piroxicam (Feldene)	20 mg q day
Sulindac (Clinoril)	150–200 mg q 12 hr
Tolmetin (Tolectin)	200–600 mg q 8 hr

Abbreviations: IV—intravenous; OTC—over-the-counter.

analgesics have a "ceiling" effect for analgesia. They are not associated with tolerance or physical dependence.

Acetaminophen

Acetaminophen has the analgesic potency of aspirin, but the anti-inflammatory potency is minimal. It has antipyretic activity. A central mechanism of action appears to predominate in acetaminophen-mediated analgesia (45). The maximum daily dose is 4000 mg. It is associated with hepatotoxicity, so it needs to be used cautiously in patients with liver function compromised by alcohol abuse, hepatitis, or metastatic disease (46).

Nonsteroidal Anti-Inflammatory drugs

No oral NSAID has clearly demonstrated analgesic superiority. Selection is based on individual preference, dosing schedule, toxicity profile, and cost. Lack of efficacy with one NSAID does not preclude success with another. Sequential trials of different NSAIDs may lead to identification of an agent with a favorable analgesic effect. The only parenteral nonsteroidal analgesic available in the United States is ketorolac. It is a potent agent and is frequently used in the postoperative period. Use of ketorolac for

more than 5 days is not recommended due to gastrointestinal toxicity (47). The common mechanism of action of NSAIDs is inhibition of central and peripheral cyclooxygenase enzyme activity. This inhibition blocks synthesis of prostaglandins, which are known to sensitize peripheral nociceptors (48). COX-1 and COX-2 are the main cyclooxygenase isoenzymes. COX-1 is linked to gastrointestinal ulcerations. The available NSAIDs vary from being COX-1-selective (flurbiprofen, ketoprofen) to COX-2-selective (mefenamic acid, diclofenac) or nonselective (ibuprofen, naproxen). Recent development of COX-2-specific agents like celecoxib and rofecoxib is leading to important progress in analgesic therapy. These agents, named coxibs, provide the analgesic and anti-inflammatory properties of traditional NSAIDs, while avoiding the gastrointestinal complications associated with COX-1 inhibition (49). It is becoming common practice to replace NSAIDs with coxib therapy in cancer patients because of the improved safety profile, but their use and efficacy in cancer pain remain to be established (50).

Nonsteroidal anti-inflammatory drugs have a wide spectrum of toxicity including bleeding diathesis due to inhibition of platelet aggregation, gastritis and peptic ulcer disease, nephrotoxicity, and exacerbation of bronchospasm (51). Elderly patients are at higher risk for developing these complications. Other risk factors include use of high doses, concomitant administration of corticosteroids, and a history of either peptic ulcer or previous gastrointestinal complications from NSAIDs (52,53). The choice of NSAID continues to be dependent on gastrointestinal toxicity and associated risk factors of individual patients (54). The nonacetylated salicylates, including choline magnesium trisalicylate and salsalate, have less effect on platelet aggregation and do not affect the bleeding time (55). They would be preferred in patients undergoing chemotherapy or with a tendency to gastrointestinal toxicity. Data from randomized trials support the use of omeprazole, misoprostol, or famotidine for prophylaxis against NSAID-related peptic ulceration (56–58). Renal function monitoring is essential due to the risk of renal failure secondary to renal prostaglandin synthesis inhibition. The risk of developing NSAID-associated agranulocytosis is greater in cancer patients undergoing chemotherapy when they become pancytopenic. Naproxen may result in the development of pulmonary infiltrates. Ibuprofen, sulindac, and tolmetin may result in aseptic meningitis.

Tramadol

Tramadol represents a newer class of analgesic. It is both a weak mu-1 receptor agonist and an inhibitor of serotonin and norepinephrine reuptake. It is approved in the United States for the treatment of moderate pain (WHO ladder step 2). A 50-mg dose has the analgesic potency of 60 mg of codeine. It can be combined with acetaminophen in patients with contraindications for the use of NSAIDs, and it is highly accepted among patients who want to avoid the use of opioids (59). Tramadol has been associated with seizures at doses over 400 mg per day and may increase sedation if used in combination with opioids (Ultram package insert).

Opioid Analgesics

Opioid analgesics are used for moderate and severe pain (WHO ladder steps 2 and 3) and are the mainstay of pain control in advanced disease. Opioid compounds are classified according to their interaction with the various receptor subtypes. The three general classes are agonist, agonist–antagonist, and antagonist. The pure agonists are

the compounds used in the management of cancer pain. Morphine is considered the "gold standard" in palliative care because it is effective, inexpensive, easy to titrate, and can be administered by different routes including oral, rectal, subcutaneous, and parenteral. Agonists do not have a ceiling effect. As the dose is increased, the analgesic effect increases in a semilog-linear function (55). In clinical practice, dose limitation is dictated by the development of side effects like nausea, vomiting, confusion, sedation, myoclonus, or respiratory depression (60). When there is a favorable balance between analgesia and side effects, the pain is said to be responsive to the drug and route of administration (61). Relative analgesic potency is the ratio of the dose of two analgesics required to produce the same analgesic effect. Equianalgesic doses are presented in Table 2 and they are used as a guideline for dose selection when the compound or

Table 2 Dose Equivalents for Opioid Analgesics in Opioid-Naive Adults

	Approximate equianalgesic dose		Usual starting dose for moderate to severe pain
Drug	Oral	Parenteral	Oral
Morphine	30 mg q 3–4 hr (repeat around the clock dosing)	10 mg q 3–4 hr	30 mg q 3–4 hr
Morphine, CR (MS Contin, Oramorph)	90–120 mg q 12 hr	N/A	90–120 mg q 12 hr
Morphine, SR (Kadian)	90–120 mg q day	N/A	90–120 mg q day
Hydromorphone (Dilaudid)	7.5 mg q 3–4 hr	1.5 mg q 3–4 hr	2–4 mg q 3–4 hr
Oxycodone	20 mg	N/A	5–10 mg q 4 hr
Oxycodone CR (OxyContin)	20 mg q 12 hr	N/A	10–20 mg q 12 hr
Levorphanol (Levo-Duromoran)	4 mg q 6–8 hr	2 mg q 6–8 hr	4 mg q 6–8 hr
Meperidine (Demerol)	300 mg q 2–3 hr	100 mg q 3 hr	N/R
Methadone (Dolophine, other)	20 mg q 6–8 hr	10 mg q 6–8 hr	20 mg q 6–8 hr
Oxymorphone (Numorphan)	N/A	1 mg q 3–4 hr	N/A
Combination opioid/ NSAID preparations			
Codeine (with aspirin or acetaminophen)	180–200 mg q 3–4 hr	130 mg q 3–4 hr	30–60 mg q 3–4 hr
Hydrocodone (in Lorcet, Lortab, Vicodin, others)	30 mg q 3–4 hr	N/A	5–10 mg q 3–4 hr
Fentanyl TS (Duragesic)	Empirically 100 mg/hr is equianalgesic to morphine 4 mg/hr IV		25 μg/hr q 72 hr

Abbreviations: CR—controlled-release; IV—intravenous; SR—sustained-release; TS—transdermal system.

the route of administration is changed. By convention, relative potency is based on comparison with 10 mg of parenteral morphine.

Codeine, dihydrocodeine, hydrocodone, oxycodone, and propoxyphene are most commonly used in combination with acetaminophen or aspirin for the treatment of moderate pain. The use of these combinations may be limited by the amount of acetaminophen or aspirin being ingested by the patient in the course of 24 hr. Use of controlled release single-agent oxycodone allows for the continued use of this agent in higher doses even for the treatment of severe pain.

Codeine

Codeine is the most commonly used opioid for the management of mild to moderate pain in a combination formulation with aspirin or acetaminophen. The analgesic effect of codeine is partly dependent on its conversion to morphine by the genetic polymorphism CYP2D6 (sparteine oxygenase) of cytochrome P−450. Approximately 7% of Caucasians lack CYP2D6 activity (poor metabolizers), and these people have a diminished analgesic effect with codeine (62). Cytochrome P−450 inhibitors like quinidine, cimetidine, and fluoxidine may also diminish its analgesic efficacy. At higher doses, codeine is poorly tolerated due to significant nausea.

Hydrocodone

The analgesic potency of hydrocodone is about half that of oral morphine. It is available in a combination preparation of 10 mg hydrocodone and 1000 mg of acetaminophen (63). Like codeine, it is metabolized by cytochrome P-450 CYP2D6. Therefore poor metabolizers experience decreased analgesic effect.

Oxycodone

Oxycodone has a high bioavailability of 60%. Its analgesic potency is 25% to 50% that of morphine (63). Combination preparations containing 5 mg of oxycodone and 325 mg of acetaminophen are commonly used for postoperative pain as well as management of moderate cancer pain. It is available in single-agent tablets and syrup formulations, which allows titration of the doses to treat severe pain. Controlled-release formulations have a 12-hr duration of action, which is convenient to treat severe pain (64,65). It has been shown to be effective in the control of cancer pain (65,66). The use of controlled-release oxycodone is safe and effective because of the short half-life of oxycodone itself, long duration of action of the preparation, predictable pharmacokinetics, absence of clinically active metabolites, easy titration, and minimal associated stigma (67).

Propoxyphene (Dextropropoxyphene)

Propoxyphene is a congener of methadone. It is metabolized to norpropoxyphene, which has a long half-life, and is associated with tremors and seizures. These excitatory effects are dose-related, but are not a common clinical problem at the usual doses of 50 to 100 mg every 4 hr (68).

Morphine

Morphine is still considered the "gold standard" for the treatment of severe cancer pain. The use of morphine has remarkable versatility due to the different routes of administration and the wide range of formulations which is unique among pure opioid agonists. Formulations include injectable solutions, immediate- and controlled-

release tablets, immediate- and controlled-release suppositories, immediate-release syrup, and controlled-release suspension.

Parenteral preparations are available for intravenous, intramuscular, subcutaneous, and intrathecal administration. Oral bioavailability of morphine varies from 35% to 75%. The plasma half-life is 2 to 3 hr with analgesic effect lasting between 4 and 6 hr.

Morphine is metabolized by hepatic glucuronidation to morphine-3-glucuronide (M-3-G, 55%) and morphine-6-glucuronide (M-6-G, 15%), both of which are excreted by the kidneys (69). Morphine-6-glucuronide binds to opioid receptors and has analgesic effects in animal studies during intrathecal or ventricular injection (70,71). There is no conclusive data to support the role of M-6-G in clinical analgesia, although it is suggested in a recent study (72,73). Accumulation of both M-3-G and M-6-G has been associated with side effects including myoclonus and chronic nausea (74,75). Renal insufficiency results in accumulation of M-3-G and M-6-G (76). Therefore morphine doses should be adjusted with caution in patients with renal insufficiency.

Hydromorphone

Hydromorphone (Dilaudid) is a strong opioid and a useful alternative to morphine. A double-blind study comparing morphine and hydromorphone patient-controlled analgesia (PCA) found no differences with respect to analgesia or side effects (77). Patients receiving hydromorphone had a somewhat poorer cognitive performance, but reported a better mood compared with patients who received morphine. Hydromorphone is the drug of choice for chronic subcutaneous administration due to its water solubility, excellent bioavailability of 87%, and a high concentration formulation (10 mg/mL) (78). Other formulations allow for oral, rectal, and intraspinal administration.

Meperidine

Meperidine is a strong opioid agonist with a short half-life. The adverse effects profile of meperidine limits its clinical utility and, in fact, its use in cancer patients is not recommended. Meperidine is demethylated to normeperidine, an active metabolite with convulsant potential. Normeperidine has a long half-life of 12 to 16 hr and accumulates after repetitive dosing. Central nervous system toxicity is characterized by adverse mood effects, tremulousness, multifocal myoclonus, and, occasionally, seizures (79,80). These effects are more likely to occur in elderly patients or those with renal insufficiency, but have also been observed in young patients.

Fentanyl

Fentanyl is a semisynthetic opioid with a short half-life following bolus administration. Fentanyl is 20 to 30 times more potent than morphine and is available in formulations for intravenous, subcutaneous infusion, transdermal, and oral transmucosal administration. Pharmacokinetic studies show linear drug concentration increases with repeated dosing. Subcutaneous fentanyl infusion is a good alternative for patients with intolerance to morphine (81). The transmucosal formulation in the form of a "lollypop" is useful in the management of "breakthrough" pain (82).

The lipophylic nature of the compound makes it suitable for a transdermal formulation in the form of a skin patch that is changed every 72 hr. This is a relatively recent development that has gained acceptance and has broadened the clinical utility of fentanyl in the treatment of cancer pain (83). Advantages of the patch include the

following: (1) it is highly acceptable to patients; 2) it is easy to apply; 3) there is improved compliance; and 4) long duration of action results in continuous analgesia (84). Transdermal fentanyl is effective in the treatment of cancer pain and is equivalent to sustained-release morphine in terms of pain control (85,86). Fentanyl is reported to have less gastrointestinal side effects than other opioids. This is thought to be related to lack of an oral first-pass effect. Therefore it may be useful in patients with severe morphine-induced nausea, vomiting, or severe constipation (87). Also, patients using the transdermal fentanyl tend to express better satisfaction with the medication compared to those who receive sustained-release morphine (85,88,89).

Fentanyl diffuses to the dermis via the rate-controlling membrane in contact with the skin. A reservoir is created in the dermis. Analgesia develops 6 to 8 hr after application, but it takes 12 to 24 hr to achieve steady-state levels. The patch should be changed every 72 hr, although in some patients, it may need to be changed every 48 hr. The slow equilibration of blood levels makes it unsuitable for short-term use or when rapid dose readjustment is required. Pain should be stabilized by titration with short-acting opioids. The 24-hr opioid requirements are calculated and converted to the patch dose equivalent. There is considerable and sometimes unpredictable variability in establishing the morphine equivalent dose for a particular patient. A ratio of 25 μg/hr transdermal fentanyl to 90 mg/24 hr of oral morphine is generally accepted in the United States (83).

Methadone

Methadone is a synthetic opioid that is increasingly being used in palliative care (90). Better understanding of the pharmacologic and pharmacokinetic properties of methadone has led to an increased use as a second-line drug for treatment of cancer pain. Advantages of methadone include the following: (1) 85% bioavailability with oral or rectal use; (2) no known active metabolites; (3) long half-life allows for increased intervals between doses from 12 to 24 hr; (4) low cost; and (5) improved patient compliance (91). Plasma half-life averages 24 hr (range 13 to more than 100 hr), but analgesic effect may only be 4 to 8 hr (92). Plasma concentrations increase during the accumulation period of 5 to 10 days. Careful monitoring is needed as the appearance of side effects may be delayed including sedation, confusion, and even death.

Recent data from crossover studies with morphine or hydromorphone and methadone indicate that methadone is more potent than previously reported. The equianalgesic dose ratio correlates with total opioid used before switching to methadone (93). The equianalgesic ratio for oral methadone to oral morphine is 1:4 in patients receiving low doses of oral morphine (less than 90 mg/day), 1:8 for patients receiving moderate doses (90 to 300 mg/day), and 1:12 in patients receiving high doses (more than 300 mg/day) (94).

SPECIAL CONSIDERATIONS

Breakthrough Pain

Breakthrough pain has been described as a transient increase in pain to moderate or severe intensity in the presence of a baseline pain that is well controlled (94). The prevalence of breakthrough pain has been reported to be between 40% and 80% (94–96). The presence of breakthrough pain is an indicator of a more severe pain syndrome and is associated with significant functional impairment and psychological distress like

anxiety (96). Although the negative influence of breakthrough pain on quality of life has been recognized, there is lack of studies addressing the efficacy of different drugs, route of administration, or modalities of administration (97).

A rescue dose of an opioid is the most common approach to treating breakthrough pain in patients already stabilized on a baseline opioid regimen. The rescue dose consists of an immediate release preparation that is usually the same opioid being administered on an around-the-clock schedule. The dose suggested is equivalent to 5% to 10% of the total opioid amount given every 2 hr (94). Rectal administration offers the potential for bypassing first-pass metabolism when the drug is absorbed in the distal rectum. Rectal morphine absorption into the systemic circulation is similar to that of oral morphine (98,99). Oral transmucosal fentanyl citrate (OTFC) preparations are a recent and valuable option for the treatment of cancer-related breakthrough pain (82). Oral transmucosal fentanyl citrate has been shown to be effective and safe in comparison to other agents used for breakthrough pain (100). Pain relief can be achieved within 5 min (82). Fentanyl Actiq is available in a wide range of doses (200 to 1600 μg) for the treatment of breakthrough pain in opioid-tolerant adults. Patients with acute decompensation of their pain or presenting with irregular or rapidly accelerating pain requiring immediate treatment are candidates for patient-controlled analgesia (PCA) by intravenous or subcutaneous routes (101). The PCA device should be set to deliver a continuous infusion until the pain has been stabilized. Bolus doses are set to 25% of the hourly dose. Interval lockouts increase the safety of this approach. The doses should be adjusted to provide supplementary analgesia with minimal side effects (102).

Opioid Rotation

Opioid rotation refers to the change of one strong opioid to another when pain management is requiring an accelerated dose escalation or side effects are limiting further use of the opioid. The purpose of opioid rotation is to achieve better pain control and/or to avoid toxicity related to high doses of a drug (103). The concept is based on the clinical observation that there is intraindividual variation in response to different opioids (104). Sequential opioid trial is now widely accepted as a strategy for addressing poorly responsive pain (61). Equianalgesic tables offer a guideline for switching between the strong opioids (Table 2). The most recent development in the application of opioid rotation relates to the expanding role of methadone. The properties of methadone and the general equianalgesic approach have been discussed already. Tolerance is expected to occur in long-term use of opioids and is an important reason for loss of opioid responsiveness. Opioid rotation is a relevant strategy for managing tolerance.

Neuropathic Pain

Neuropathic pain is a complex problem. The clinical characteristics indicative of neuropathic pain have been described already. Traditionally, neuropathic pain has been considered unresponsive to opioids, but more recent studies question this notion (105). Nevertheless, clinical experience suggests that patients with neuropathic pain do benefit from the additional use of adjuvant analgesics (106). Antidepressants are widely accepted as useful in the treatment of neuropathic pain, but there are no randomized trials evaluating their use in the cancer population. Amitriptyline (tertiary

amine) is the best-studied drug. Side effects like tiredness, dry mouth, and constipation compromise its clinical use (107). Secondary amines like desipramine and nortriptyline are better tolerated (108). Selective serotonin reuptake inhibitors like paroxetine have been shown to be effective in diabetic neuropathy (109).

Several studies have shown the effectiveness of anticonvulsants like carbamazepine and gabapentin in nonmalignant neuropathic pain syndromes like postherpetic neuralgia, trigeminal neuralgia, and diabetic neuropathy (110). Gabapentin has been reported to decrease pain intensity and frequency in cancer patients with neuropathic pain (111). It has an acceptable adverse effect profile with no known drug interactions. Treatment usually starts at 100 to 300 mg/day, and dose titration continues until a benefit is achieved or side effects develop. Side effects like somnolence may supervene at high doses beyond 3000 mg/day.

Corticosteroids are effective in pain associated with inflammation. Refractory neuropathic pain is an indication for steroid trial in cancer patients. Oral local anesthetics have been found to be effective in the treatment of neuropathic cancer pain (112). Mexiletine is the preferred agent in the United States, and treatment is started at a low dose of 150 mg/day. Many studies are indicating an analgesic benefit when NMDA-receptor antagonists are used as adjuvant agents. These include drugs like ketamine, dextromethorphan, and amantadine. Methadone has NMDA-receptor blocking activity, and it has been hypothesized that it could be effective in treating cancer-related neuropathic pain (61).

PRACTICAL APPROACH

The WHO analgesic ladder continues to be the clinical model for pain management. This approach matches the patient's reported pain intensity with the potency of analgesic to be prescribed. Several studies regardless of settings of care, social, and cultural environments have confirmed the effectiveness of this approach (42,113,69). In clinical practice, application of the WHO guidelines results in pain relief for up to 90% of patients (43).

For cancer chronic pain, practically:

- Step 1: Begin with a non-opioid drug for mild pain.
- Step 2: For moderate pain that is not controlled by a non-opioid alone, a weak opioid is administered in addition to the non-opioid drug.
- Step 3: For severe pain that is not relieved by weak opioids, a strong opioid is used, either alone or in combination with a non-opioid drug.

A non-opioid drug (i.e., NSAID) could be used in moderate and severe pain just in surgery-related pain. A good option for these patients can be an opioid drug with short-acting effect (meperidine, hydromorphine, and morphine) or an association non-opioid/opioid.

Other pain management concepts advocated by the WHO expert committee include the following:

Oral administration: Administration by mouth is the preferred method to deliver medications. Oral administration is effective, easy to titrate, and inexpensive.

Around the clock: Continuous pain relief can be achieved when patients receive their medications throughout the day or by using sustained release preparations. This approach allows prevention of pain rather than just reacting to pain.

Follow the ladder: Intervention should be guided by the WHO stepwise approach to maximize pain relief.

Individual basis of treatment: Individualized interventions will result in good symptom relief. Patients may require different dosages or interventions.

Follow-up care and reevaluation: Patients need to be reevaluated to assess the effectiveness of the interventions and to ascertain the appearance of side effects.

SUMMARY

Pain is a significant and frequent problem in the cancer patient. Complex pain syndromes develop in cancer patients. A basic understanding of these syndromes will guide the practitioner in the choice of treatment. A comprehensive evaluation with detailed history and physical exam will allow identification of most pain syndromes. Pain rating scales are useful to ascertain the degree of pain the patient is experiencing. Many barriers compromise effective pain control. These barriers include factors directly associated with the practitioners, the patients or their relatives, and the health-care environment. New efforts are directed at resolving these barriers. Most patients can attain adequate pain control with a favorable balance between analgesia and side effects. Individualized treatment and constant reevaluation are paramount for successful pain management. The WHO analgesic ladder continues to be an effective guiding principle for managing cancer-related pain. At the present time, new options of medications and approaches are available and have a great potential to improve analgesic outcomes. Nevertheless, extensive research and clinical trials are needed to better define the role of the multiple new alternatives available to the practitioner.

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Blood Transfusion During Chemotherapy: Risks and Benefits

Alessandro D. Santin
University of Arkansas for Medical Sciences, Little Rock, Arkansas, U.S.A.

Sergio Pecorelli
University of Brescia, Brescia, Italy

INTRODUCTION

Cancer patients frequently experience clinically significant anemia, which is often exacerbated by surgery and myelosuppressive chemotherapy. Although consistent with the anemia of chronic disease, several factors, including the type of tumor, blood loss, nutritional deficiencies, hemolysis, bone marrow infiltration by malignant cells, low serum erythropoietin (Epo) levels, and a decrease in bone marrow responsiveness to recombinant human Epo, may contribute to cancer-induced anemia and significantly influence the percentage of patients needing blood transfusion during chemotherapy. Recently, the traditional belief that blood transfusion is an effective and safe therapy has been challenged by an increased awareness of the infectious and immunologic risks associated with allogeneic blood transfusion. In cancer patients transfusion-induced immunomodulation may have the potential to significantly increase postoperative infections and cancer recurrence, so it seems reasonable to minimize allogeneic blood exposure. During chemotherapy, patients treated with platinum-based regimens more often develop anemia and require transfusions. In this group of patients, the cumulative dose of platinum, as well as advanced age, loss of body weight before treatment, advanced disease stage, and a low primary level of Hb (11 g/dL) or a decrease in Hb level (1–2 g/dL) after the first cycle of chemotherapy, represent important risk factors for increased frequency of transfusions.

INDICATIONS FOR TRANSFUSION

The consequences of anemia, namely, fatigue and cardiovascular symptoms, can adversely affect patients' quality of life and may even alter their response to cancer

treatment. However, clinical symptoms of anemia vary according to an individual's capacity to respond to blood loss or reduced red cell production. It is therefore unlikely that any level of Hb can be used as a universal threshold for transfusion. Guidelines for blood transfusion have been issued by several organizations including a National Institutes of Health consensus conference on perioperative transfusion of red cells (1), the American College of Physicians (2), and the Canadian Medical Association (3). These organizations recommend that blood transfusion should be based on the clinical status of the patient rather than based on Hb value alone. The patient's oxygen consumption and delivery should be examined before making a decision to transfuse. A higher Hb level may be needed for hypermetabolic states (e.g., infections) or poor oxygen delivery state (e.g., heart failure). Chronicity and etiology of anemia should also be considered. Finally, the earlier concept of transfusion trigger to keep Hb at 10 or above to improve wound healing or "well being" should be disregarded (4). Animal studies and observation in postoperative patients indicate that tissue repair is not adversely affected unless the Hb level drops to 5 or less (5).

BLOOD COMPONENTS

The blood components used in transfusion therapy include packed red blood cells (PRBC), whole blood, leukocyte-depleted red blood cells, frozen RBC, albumin, platelets, fresh-frozen plasma (FFP), and cryoprecipitate. Each component has different indications and risks.

PRBCs are prepared by removing the plasma to attain a hematocrit of 75% to 80% and have a shelf life of approximately 35 to 42 days (6). One unit of PRBC is >200 cc and increases the Htc by 0.7–0.8 points. The main indications for PRBC transfusion are blood loss replacement and improvement of oxygen-carrying capacity. Unlike whole blood, PRBCs are associated with reduced volume burden, electrolyte disturbances, allergic reactions, febrile reactions, and exposure to foreign antigens. However, their high viscosity makes rapid transfusion difficult. As a general rule, a single unit of PRBC should not be transfused. If a single unit is sufficient, most likely no units are needed.

Whole blood is prepared by mixing 450 mL of donor blood with 70 mL anticoagulant resulting in a hematocrit of 37%. Massive bleeding may be the only indication for whole blood transfusion. However, PRBC and balanced saline may serve the same purpose. Numerous drawbacks limit today the use of whole blood therapy, including a higher infection risk, volume overload, immune suppression, and electrolyte imbalances.

Depletion of leukocytes by filtration of blood components with third generation filters ($<3 \times 10^6$ white cells per unit) has recently become a standard procedure in the United States because of its beneficial effect in reducing alloimmunization, transfusion reactions, platelet refractoriness, infection, and immunosuppression (7).

Frozen RBCs, which can be preserved up to 10 years in glycerol, are indicated for IgA-deficient patients (there is a possibility of anaphylactic reaction if regular PRBCs are used) and for patients with rare antibodies against PRBC.

Albumin does not carry infectious risk because its preparation includes heat treatment. Some gynecologic oncologists infuse albumin in a continuous fashion in the

early postoperative care to minimize fluctuation in blood pressure and fluid shift in patients treated with radical tumor debulking (8). However, the use of albumin has drastically decreased in the last few years because of its limited benefit and high cost.

Platelets are concentrated from fresh whole blood and stored at 20°C to 24°C, with constant agitation for up to 5 days. One unit of platelets raises the count by 5000 to 10,000/m^2 of body surface area up to 24 hr posttransfusion. Prophylactic platelet transfusions are recommended for nonsurgical patients with a platelet count of less than 20×10^9/L. For patients who have undergone trauma or require surgery, a minimum count of 50–100 $\times$ 10^9/L is considered necessary to maintain adequate hemostasis (9). Platelets are commonly used for the thrombocytopenia that often accompanies the use of myelosuppressive chemotherapy regimens (e.g., carboplatin and Taxol). A single unit of platelets should never be given, the smallest single dose of clinical value being 4 to 6 units. The risk of infection in platelet transfusion is multiplied because the patient requires multiple units, and each unit of platelet carries the same infectious risk as a unit of PRBC.

FFP is prepared by anticoagulating plasma from a single unit of blood that is separated and frozen within 6 hr of the donation to reach a volume of about 250 mL. Each unit of FFP raises clotting factors by 2% to 3% in adults. FFP contains all the coagulation factors as well as naturally occurring inhibitors. Coagulation factor deficiencies, massive blood transfusion, antithrombin III deficiency, and the need to quickly reverse the effect of warfarin are the main indications for FFP (9). In obstetrics and gynecology the most common clinical indication for the use of FFP is acute disseminated intravascular coagulation (CID). Although commonplace, the practice of ordering FFP for patients who have experienced massive bleeding (i.e., 1 unit FFP for every 3 units of PRBC transfused) is not recommended unless a factor deficiency is identified that results in coagulopathy. Pathologic hemorrhage in the patients receiving massive transfusions is caused more frequently by thrombocytopenia than by depletion of coagulation factors (10).

Cryoprecipitate, the cold precipitable protein fraction derived from thawed FFP, contains significant levels of factor VIII, von Willebrand factor, and fibrinogen (average 100–350 mg of fibrinogen in each cryoprecipitate unit). It is mainly indicated for von Willebrand's disease and in patients with a normal blood volume who require factor replacement (9,11). However, as cryoprecipitate is the only concentrated fibrinogen product available, it is the component of choice for the treatment of hypofibrinogenemia that is congenital or acquired through CID. To treat a bleeding patient whose fibrinogen is <100 mg/dL (to guarantee good coagulation, fibrinogen concentration should be 100 mg/dL or above), cryoprecipitate is preferred over FFP because its volume is smaller than that of FFP (11) (Tables 1–3).

RISKS OF TRANSFUSION THERAPY

Although allogeneic blood transfusion remains essential for many types of medical and surgical therapy of cancer patients, transfusion therapy, as with any medical procedure, poses some risks to our patients. The complications of blood transfusion have been generally grouped into three broad categories including infectious, noninfectious, and those of immunologic etiology. Although these risks are actually

Table 1 Example of Order for Transfusion

1—Tylenol II tabs
2—Benadryl 50 mg
3—Transfusion 2 units
4—Each unit 1 hr
5—Furosemide 10–20 mg between first and second unit of PRBC
6—Check Hct/Hb 1 hr after transfusion

decreasing steadily as universal leukodepletion and newer screening tests are introduced, and better antiviral processing and storage capabilities evolve, nevertheless they should be weighed carefully for each patient when making the decision to transfuse.

INFECTIOUS COMPLICATIONS

Donated blood is routinely tested for ABO group, Rh type, RBC antibody screen, HIV I and II antibody, alanine aminotransferase (ALT), syphilis antibody, antibody to hepatitis B core (Anti-Hbc), hepatitis B surface antigen (HbsAg), human T-cell lymphotrophic viruses-I (HTLV-I) and HTLV-II, and hepatitis C virus (HCV) antibody.

HIV has been the major fear among the public about blood transfusion. The risk of transmission of HIV is today down to 1: 493,000 per unit of blood transfused (Table 4) (12,13). Although hepatitis C (HCV) remains the most frequently transmitted infection through blood transfusion, second-generation tests, including EIA and RIBA, which incorporate recombinant viral antigen, have markedly reduced the risk of HCV infection. In the United States the estimated risk of transfusion-transmitted HCV from blood that is negative for HCV antibodies is now 1 in 103,000 transfusions (12,13). However, if one considers the possibility of a chronic, immunologically silent state of infection, the risk of HCV may be as high as 1 in 30,000 (12,13). Fifty percent of patients with post-transfusion HCV will develop chronic liver disease and, of these, up to 20% will subsequently develop chronic active hepatitis or cirrhosis (12,13). Posttransfusion hepatitis B accounts for less than 1% of all posttransfusion hepatitis with current screening (1 in 63,000) (12,13). Contamination of donated blood is very rare. Septicemia causes only 8 to 10 deaths per 10 million blood transfusions (14).

Table 2 Example of Order for Transfusion in Case of Mild Allergy

1—Stop transfusion
2—Benadryl 50 mg IV
3—Tylenol II tabs
4—Hydration
5—Start transfusion again

Table 3 Example of Order for Transfusion in Case of Severe Allergy

1—Stop transfusion
2—Benadryl 50 mg IV
3—Steroids
4—Close monitoring of patient
5—Hydration
6—Send patient's blood and residual PRBC to lab for analysis

NONINFECTIOUS COMPLICATIONS

The most common noninfectious and nonimmunological complications of blood transfusions are those caused by transfusion error (i.e., human error) and circulatory overload. A transfusion error occurs in 1 out of 12,000 transfusions performed and a fatal transfusion error occurs in 1 out of 600,000 transfusions (15). The most common transfusion errors are failure to correctly identify the patient and/or issuing the wrong blood type.

Circulatory overload occurs more commonly in elderly patients, and in patients transfused with whole blood rather than specific components or packed RBCs. The presenting symptoms are consistent with left ventricular failure. The treatment includes stopping the transfusion and treating congestive heart failure. Less common noninfectious complications are adult respiratory distress syndrome (16). Treatment is generally supportive.

IMMUNOLOGIC COMPLICATIONS

Immunologic complications of blood transfusion include allergic, febrile nonhemolytic, hemolytic, and graft-vs.-host reactions, and immunosuppression. Allergic reaction ranges from common urticaria to rare anaphylaxis. Febrile nonhemolytic complication occurs at a rate of 0.5% to 4%. Typical symptoms are fever up to 38°C, with or without rigors occurring generally at the end of the transfusion. Hemolytic reaction occurs in 1 of 6000 to 12,000 transfusions. In decreasing severity, the three types of hemolytic reaction are immediate intravascular hemolysis, delayed hemolysis, and delayed sensitization. Immediate intravascular hemolysis is severe, and the rapid destruction of RBC may cause bleeding and shock. Patients complain of chills, fever,

Table 4 Estimates of Transfusion-Associated Risk per Unit of Blood

HIV	1:493,000
Hepatitis B	1:63,000
Hepatitis C	1:30,000 to 103,000
Human T-lymphotropic virus	1:50,000

back pain, and red or dark urine. Complications of immediate intravascular hemolysis are acute renal failure in up to 15% of cases and disseminated intravascular coagulation in up to 8% of cases (15). In delayed hemolytic reaction, destruction of RBC is less extensive and occurs within 1 to 2 weeks, resulting in no or mild symptoms, mild jaundice, and anemia. Delayed sensitization occurs within 6 weeks, but the patient is often asymptomatic. Management of transfusion hemolysis involves stopping transfusion while maintaining intravenous hydration, treating hypotension, administering furosemide and/or mannitol to keep urine output greater than 1 mL/kg/hr, and identifying the cause by identifying the patient and the transfused unit (Tables 2 and 3).

Graft-vs.-host reaction in transfused patients has been reported after chemotherapeutic treatment of several malignancies (17). If the recipient is immunologically suppressed, engraftment of cells from the donor blood can occur. Although its incidence is low, the illness is often fatal as treatment is largely ineffective. Prevention consists of irradiating all blood products with at least 1500 cGy prior to administration.

The best characterized clinical effect of transfusion-induced modulation is improved survival of renal allografts in previously transfused patients. In 1973, the seminal work by Opelz et al. (18) provided strong clinical evidence that, contrary to the conventional wisdom, allogeneic blood transfusions have a significant immunosuppressive role in renal transplant. Transfusion of allogeneic whole blood products to nonsurgical patients has subsequently been shown to induce alterations in certain immune functions, such as reduced natural killer (NK) activity and T-lymphocyte blastogenesis, and increased suppressor T-lymphocyte activity, which may be of vital significance for host resistance to infection and dissemination of malignant cells (19–21). Consistent with this view, several studies reported a significantly increased incidence of postoperative infections after allogeneic blood transfusion (22,23). Furthermore, the majority of reports evaluating the effect of blood transfusion in cancer patients suggest that allogeneic blood affects prognosis adversely in a variety of tumors (24). Although the mechanism of immunosuppression induced by blood transfusions is still largely unknown, Blajchman et al. demonstrated convincingly in two animal models that white cell depletion of allogeneic transfusions reduces their metastasis-promoting effect (25). However, plasma components may also be of importance, because increased cancer recurrence rates are found in patients receiving perioperative plasma transfusion compared with untransfused patients (26). In the light of these findings, and based on the sum of evidence, immunomodulation seems likely to be added to the list of the unintended effects of allogeneic blood transfusion (27,28). Nevertheless, the role of perioperative blood transfusion in the recurrence of surgically excised tumors and in the survival rates of cancer patients remains controversial (27,28).

AUTOLOGOUS BLOOD TRANSFUSION

Apart from decreasing the risk of infectious disease transmission, autologous blood transfusion reduces exposure to foreign antigens and avoids blood incompatibility reactions. The main requirement for donation is a minimum hemoglobin of 11 gm/dL. Theoretically, the use of autologous blood in gynecologic oncology patients may

obviate the potential for immunosuppression otherwise imposed by allogeneic blood. However, two separate reports of patients undergoing curative resection of colorectal carcinoma failed to demonstrate a difference in relapse-free survival between patients who were randomly assigned to allogeneic transfusion and those assigned to transfusion of autologous blood (29,30). These data suggest that immunomodulatory factors released from leukocytes into the plasma during storage may be of major importance (31–33). Such factors may enhance overall immunosuppression independent of the blood transfusion product. The concern of potential metastases from autologous transfusion was addressed by studies in gynecologic and urologic oncology patients. These studies suggested that there was no increased risk of metastasis when autologous blood was used (34,35).

RECOMBINANT HEMATOPOIETIC GROWTH FACTORS

Please read the chapter on "Supportive Treatment in Gynecologic Malignancies."

CONCLUSION

Blood transfusion remains the mainstay of treatment of cancer and chemotherapy-related anemia, despite the persistence of several concerns related to the safety of blood products, including the transmission of blood-born pathogens, the well-established immunomodulation mediated by allogeneic transfusion, and the potential for severe allergic reactions. Although several of the risks involved with the use of allogeneic blood are decreasing steadily as universal leukodepletion and newer screening tests are introduced, both anesthetists and surgeons should continue to aim for reduced intraoperative blood loss and so avoid unnecessary blood transfusions. Indications for blood transfusions should rely on factors known to be important, such as oxygen tension and hemodynamics, and the decision to transfuse should continue to depend upon that risk–benefit calculus known as clinical judgment. In the last few years, numerous recombinant growth factors including rhEPO, G-CSF, GM-CSF, IL-11, and TPO have seen a wider clinical application. These safer alternatives to allogeneic blood may reduce the need for blood transfusion in cancer-related anemia and may prevent and/or effectively treat chemotherapy-induced anemia, leukopenia, and thrombocytopenia. Nevertheless, economic analyses, including consideration of the costs associated with medical care as well as consequences, will be essential in evaluating the full potential of these recombinant growth factors in treating the myelosuppression associated with cancer chemotherapy.

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Role of Tumor Markers in Gynecologic Oncology

Andrew Li and Jonathan S. Berek
David Geffen School of Medicine at UCLA, Los Angeles, California, U.S.A.

INTRODUCTION

Tumor markers are a loosely defined term that describes characteristics which may indicate the presence of cancer. Ideally, tumor markers should be specific, detect premalignant or early disease, and quantitatively reflect tumor burden. While markers may reflect cytologic, molecular, and genetic events, as well as architectural abnormalities and vascular changes, the term most commonly refers to biochemical substances produced by or in response to tumor tissue (1). These may be broadly classified into tumor-specific and tumor-associated antigens. The latter are more commonly used in clinical practice and include enzymes, hormones, receptors, growth factors, biologic response modifiers, and glycoconjugates (2).

In gynecologic oncology, a major area of active research is the development of tumor markers to screen for premalignant conditions and early-stage disease. Tumor markers are often utilized as an indicator of response to treatment as well as to determine recurrence and progression of disease. While there are no clinically useful markers for uterine, vaginal, or vulvar cancers, tumor markers have a clinical role in the management of ovarian carcinomas and gestational trophoblastic disease, and some data suggest they may have significance in cervical carcinomas.

EPITHELIAL OVARIAN AND FALLOPIAN TUBE CARCINOMA

Epithelial ovarian carcinoma is the most lethal of all the gynecologic malignancies, in part due to the advanced stage most commonly seen at diagnosis. Numerous serum tumor markers have been investigated, and the search for an effective screening tool for premalignant or early, minimal disease has led to the identification of the circulating tumor antigen CA125. CA125 is an antigen expressed by tissue derived from celomic epithelium, such as the mesothelial cells of the pleura, pericardium, and peritoneum, and as well of the mullerian epithelium, such as tubal, endometrial, and endocervical cells. The surface epithelium of normal ovaries does not express CA125, except in inclusion cysts, areas of metaplasia, and papillary excresences (3).

CA125 was first identified using a murine monoclonal antibody, OC125, raised in response to immunologic challenge with an ovarian cancer cell line (4). CA125 has two antigenic domains: A, the domain binding monoclonal antibody OC125; and B, the domain binding monoclonal antibody M11 (5). Current immunoassays utilize both of these antibodies to report clinical values and to reduce interassay variation.

A serum CA125 value of 35 U/mL is generally considered the upper limit of normal in healthy women, although this cutoff is arbitrary. Some authors have suggested that values of 20 or 26 U/mL may be more appropriate for postmenopausal women (6,7). Early studies indicated that approximately 83% of women with epithelial ovarian cancer had CA125 levels greater than 35 (8,9). Further interest was generated when elevated values were found in 25% of prediagnostic sera (10). A prospective cohort study of 2550 women reported a specificity of 96.6% but a positive predictive value of 4.2% when using CA125 greater than 30 U/mL as a cutoff (11). This is due in part to the elevation of CA125 in other cancers (particularly pancreatic, breast, bladder, liver, and lung) as well as in benign inflammatory disease (such as diverticulitis, uterine leiomyomata, and endometriosis) (12).

CA125 elevation is often seen with papillary serous carcinomas of the ovary and fallopian tube, as well as in primary peritoneal serous carcinomas. However, it is less often elevated in mucinous, clear-cell, and borderline tumors (13–15).

The clinical utility of serum CA125 measurement as a screening tool in epithelial ovarian cancers has not been clearly established. However, some data suggest that combining CA125 determination with transvaginal ultrasonography may improve specificity in detecting early-stage cancers (16,17). There are currently two large randomized control trials of ovarian cancer screening that include serum CA125. Jacobs et al. aim to study 120,000 postmenopausal women, and the National Institute of Health's Prostate, Lung, Colorectal, and Ovarian Cancers study is close to reaching their target of 74,000 women (18,19). When the results of these studies are available the role of CA125, either alone or in multimodality screening, will become more clear.

In women with family histories of ovarian cancer, or those with mutations in the breast and ovarian cancer susceptibility genes *BRCA1* and *BRCA2*, CA125 and transvaginal ultrasonography are often recommended as part of annual or biannual screening. However, the reliability of these modalities in detecting early disease has not been demonstrated in women of higher risk. In a large screening trial, 386 women with one first-degree relative or multiple second-degree relatives with confirmed ovarian carcinoma underwent such screening, and 11% were found to have elevated CA125 greater than 35 U/ml. However, no cases of ovarian cancer were diagnosed (20). In another screening study of 180 high-risk women, CA125 was only elevated in four of nine ovarian cancers, while transvaginal ultrasonography detected seven of nine cancers (21). Furthermore, primary peritoneal carcinomas may be a variant of cancers associated with BRCA mutations, and CA125 is likely less reliable in detecting early disease (22).

The prognostic significance of preoperative CA125 in epithelial ovarian cancers has yet to be established. Many reports do not find elevated serum CA125 to be an independent prognostic factor (23–25). However, other studies indicate that high serum CA125 levels may be significant predictors of survival, either when examined with low albumin levels or in early-stage disease (26,27). Postoperatively, the prognostic significance of CA125 levels has been more clearly demonstrated. A CA125 level greater than 35 U/ml in women without residual disease was found to be an

independent prognostic factor (28). Furthermore, other data indicate that reduction of CA125 levels to less than 35 U/ml 4 weeks after the second course of chemotherapy was another independent prognostic factor (29). Serum CA125 also has prognostic significance with recurrence of disease; patients with normal levels at relapse have an improved prognosis than those with elevated levels (28).

The role of CA125 in monitoring response to treatment is more clearly established. Bast et al. reported on 38 patients with epithelial ovarian carcinoma who were monitored with CA125 during and after treatment; rising or falling levels correlated with progression or regression of disease in 42 of 45 instances (93%) (30). Some data indicate that early regression of elevated CA125 levels during chemotherapy may predict pathologic complete response (31). However, correlation of CA125 regression after two courses of chemotherapy with long-term survival has not yet been well established (32).

Elevation of CA125 often precedes clinical detection of recurrence. In patients whose CA125 level decreases to normal after chemotherapy, a doubling from the upper limit of normal has been shown to predict tumor relapse. In those with persistently elevated levels, doubling of CA125 from its nadir level can accurately indicate progression (33,34).

The lack of specificity in preoperative CA125 in predicting cancer has fueled the investigation of other tumor markers as screening tools. In mucinous epithelial ovarian carcinomas, tumor-associated trypsin inhibitor (TATI), CA19-9, CA72-4, and carcinembryonic antigen (CEA) may also be elevated preoperatively (35). Serum hCG-beta has also been evaluated as a preoperative prognosticator. In 146 women with ovarian cancer, only hCG-beta, stage, and grade were found to correlate with prognosis in multivariate analysis (36). Several cytokines have also been studied; serum macrophage colony-stimulating factor (M-CSF) has been shown to have high specificity for ovarian malignancies, with elevation related to stage and independent of histologic type (37). Adjunctive markers to evaluate disease response to chemotherapy have also been examined. Low serum CYFRA 21-1 levels, reflecting fragments of cytokeratin 19, were found to correlate with a greater rate of pathologic complete response, although no association was found with survival (38). Tissue polypeptide specific antigen (TPS) and cancer-associated serum antigen (CASA) have also been demonstrated to improve preoperative sensitivity and specificity, as well as to detect recurrent disease when combined with CA125 (39).

While these adjunctive makers have suggested a multimarker role in the diagnosis and management of epithelial ovarian cancer, their clinical utility has yet to be established. However, preliminary data suggest that determination of serum lysophosphatidic acid (LPA) may have potential as a more sensitive tumor marker. LPA is a bioactive phospholipid with mitogenic and growth-factor activities involved in cancer cell proliferation, and has been found in the ascites of women with ovarian cancer (40). A recent study examined healthy control women and women with ovarian and other gynecologic malignancies, breast cancer, leukemia, and benign gynecologic diseases, and found that total serum LPA was significantly higher in patients with ovarian cancer. Furthermore, elevated preoperative levels were detected in 9 of 10 patients with stage I disease, all 24 women with advanced stage disease, and all 14 women with recurrent cancer (41). The results of a multicenter trial examining preoperative LPA in women undergoing surgical exploration for pelvic masses is currently anticipated.

OVARIAN GERM CELL AND SEX CORD-STROMAL TUMORS

Primitive malignant germ-cell tumors of the ovary recapitulate normal embryonic and extraembryonic cells and structures, and include dysgerminomas, yolk-sac tumors, endodermal sinus tumors, and immature teratomas. The sex cord-stromal tumors are derived from the intraovarian matrix of sex cord cells and pluripotent mesencymal cells that are the precursors of theca cells, Leydig cells, and fibroblasts. Advances in chemotherapy have improved the survivability of these diseases, and tumor markers play a role in diagnosis, monitoring therapeutic response, and detecting recurrences.

Alfa-fetoprotein (AFP) is an oncofetal glycoprotein produced by the fetal liver, yolk sac, and upper gastrointestinal tract. While elevated serum levels are seen in pregnancy, benign liver disease, and some gastric, pancreatic, and colon cancers, AFP is also raised in malignant germ cell tumors (42). Kawai et al. reported on 135 women with germ cell tumors and found elevated levels of AFP in 100% of yolk sac tumors, 61.9% of immature teratomas, and 11.8% of dysgerminomas (43). AFP was also found to be elevated in endodermal sinus tumors and served as a good indicator for prediction of tumor recurrence (44). Embryonal carcinomas also secrete AFP, and monitoring serum levels is also useful in following response to treatment (45).

Human chorionic gonadotropin (hCG) is a glycoprotein hormone with two noncovalently linked subunits alpha and beta, and is produced by the syncytiotrophoblast during pregnancy. Many germ cell tumors also produce hCG, and elevations are seen in endodermal sinus tumors, choriocarcinomas, embryonal carcinomas, and a small percentage of dysgerminomas (46). Measuring serum hCG is also clinically useful to monitor response to chemotherapy, detect recurrence in patients in remission, and identify patients resistant to therapy (47).

Lactate dehydrogenase (LDH) is a glycolytic enzyme that may also be expressed in germ cell tumors, particularly dysgerminomas and yolk sac tumors (43). Serum LDH levels have been correlated with tumor size and stage of disease, and serial measurements have also been described to monitor therapy and detect recurrence (48, 49). However, its low specificity limits its clinical usefulness (50).

Inhibin is a heterodimeric glycoprotein within the transforming growth factor-beta superfamily and is normally produced by ovarian granulosa cells to modulate pituitary follicle-stimulating hormone secretion. Inhibin is composed of a common alpha subunit and one of two beta subunits (inhibin A and inhibin B); a free alpha subunit also circulates in the serum, which has immunoreactive properties. Elevations in serum inhibin concentrations have been found in women with granulosa cell tumors, with levels reflecting tumor burden (51). Measurement of inhibin has also been shown to correlate with response to chemotherapy and predicting recurrent disease (52). While granulosa cell tumors also produce estrogens, inhibin is more specific than measurement of serum estradiol in diagnosing and following these tumors (53).

The majority of Sertoli–Leydig cell tumors present with signs of virilization, reflecting the predominant secretory activity of Leydig cells in androgen production. Elevated plasma testosterone levels are seen with these tumors, with usually normal plasma androstenedione (54). Surgical excision results in a precipitous drop in androgen levels, with partial to complete resolution of the symptoms related to androgen excess.

GESTATIONAL TROPHOBLASTIC DISEASE

Gestational trophoblastic diseases (GTD) describe a spectrum of interrelated diseases including complete and partial molar pregnancies, invasive moles, placental-site trophoblastic tumors, and choriocarcinomas. Virtually all cases of GTD are associated with elevations in serum human chorionic gonadotropin (hCG), with close correlation between hCG levels and tumor burden (42). Thus hCG functions as an ideal tumor marker and is clinically useful in diagnosis, staging, and clinical management.

hCG is normally synthesized in pregnancy by the syncytiotrophoblast and is a glycoprotein hormone composed of two noncovalently linked subunits alpha and beta. Free subunits of hCG and beta core fragments are readily measured by radioimmunoassays, fluoroimmunoassays, or isoelectric focusing techniques, and determination of these markers is of value in monitoring response to therapy (55). Following evacuation of molar pregnancies, serial measurements of beta-hCG allow for construction of regression curves to predict further trophoblastic disease. Abnormal curves, with plateau or elevation of hCG, suggest a diagnosis of invasive mole or choriocarcinoma (56,57).

hCG does not appear to be a predictor of survival in GTD. In a large series of 454 women with all stages of GTD and in a retrospective analysis of prognostic factors in 55 women with metastatic GTD, pretherapy hCG levels were found to be only of borderline significance (58). While some data indicate that hCG may retain prognostic significance when stratified by high-risk, metastatic disease, larger series demonstrate that initial hCG level and site of metastasis had no significant effect on survival (59,60).

CERVICAL CARCINOMA

Presently, cervical cancer screening utilizes exfoliative cytology via the Papanicolaou smear and newer liquid-based cytologic tests. While tumor markers have no clinical role in diagnosing disease, multiple investigations are assessing a possible role for serologic markers in predicting prognosis, recurrence, and response to therapy.

Squamous cell carcinoma antigen (SCC) is a subfraction of tumor antigen TA-4, purified from cervical squamous cell carcinoma tissue (61). SCC has been found to be elevated in the sera of 57% to 65% of women with this disease (62,63). However, SCC may also be elevated in other squamous cell cancers, including head and neck, esophagus, and lung, as well as adenocarcinomas of the uterus, ovary, and lung, and benign conditions as psoriasis and eczema (64). Pretreatment levels have been correlated with stage, tumor volume, and lymph node metastases, but the prognostic significance of SCC has not been clearly defined (65,66).

Multiple other markers are currently under investigation for cervical cancers. Tissue polypeptide antigen and CYFRA 21-1 levels are elevated in up to 50% of women with squamous cell cervical cancers; while serum levels are related to tumor stage and size, no correlation is seen with overall survival (63,67). CA125, in combination with CA19-9 and CEA, demonstrates sensitivity for cervical adenocarcinomas, and elevation of one of the three markers is associated with disease

progression, recurrence, or metastasis (68). However, only CA125 has been shown to be an independent prognostic factor on multivariate analysis (69).

UTERINE, VULVAR, AND VAGINAL CARCINOMA

There are no established tumor markers for cancers of the uterus, vulva, or vagina. Some data indicate that CA125 and CA15-3 may be elevated in endometrial carcinomas, with higher titers for advanced stage disease and poorer grade tumors (70). CA125 may be clinically useful for preoperative evaluation and postoperative surveillance; titers greater than 20 ng/mL may be suggestive of myometrial invasion and recurrent disease (71). However, false elevations have been demonstrated in patients who underwent adjuvant radiation therapy (72). In uterine papillary serous carcinomas, preoperative CA125 elevation may reflect advanced stage disease, but has limited utility in monitoring the effects of adjuvant therapy and may not predict recurrence in the absence of other clinical findings (73).

In vulvar and vaginal carcinomas, tissue polypeptide-specific antigen (TPS) and SCC have been shown to be elevated in 80% and 100% of women, respectively (74, 75). Elevations in urinary core fragments of beta-hCG have also been correlated with advanced- vs. early-stage disease and may be a predictor of recurrence (76). Unfortunately, the rarity of these cancers precludes large studies to determine the clinical effectiveness of these markers in screening or monitoring disease status.

CONCLUSION

Serum tumor markers have a significant clinical role in epithelial ovarian carcinomas and gestational trophoblastic diseases, but their utility in the other gynecologic malignancies remains investigational. While present markers are limited by their specificity, current studies may reveal novel agents that may play a more significant role in screening for premalignant or early-stage disease, as well as in monitoring response to therapy and predicting recurrence and overall survival.

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Role of Chemoprotectors During Chemotherapy for Gynecologic Neoplasms

Emery M. Salom and Luis E. Mendez
University of Miami School of Medicine, Miami, Florida, U.S.A.

INTRODUCTION

In the past few decades, new chemotherapeutic agents have been developed with greater antitumor activity than their predecessors but all the while limited by the broad ranges of toxicities. The development of newer and more specific chemotherapeutic agents continues to meet the same obstacles, namely, dose-limiting toxicities. The inability of these cytotoxic agents to distinguish between malignant and normal cells results in a lower dose-intensive therapy and, consequently, tumor control as well as impairment of patients' quality of life. Some of the toxicities that plague the alkylating and platinum-based agents now recognized as standard therapy in many gynecologic neoplasms include bone marrow suppression, nephrotoxicity, neurotoxicities, and electrolyte abnormalities (Table 1). Chemotherapy is not unique in this regard; radiotherapy in the treatment of endometrial, cervical, and vulvar cancer also produces a number of unpleasant side effects such as epithelial desquamation, mucositis, and anemia.

Chemoprotectants have been developed in an attempt to increase the existing narrow therapeutic index that limits the delivery of adequate chemotherapy to the tumor cell. Moreover, chemoprotectants can confer a therapeutic advantage at the cellular level by making the cell more sensitive to the chemotherapy thus protecting normal cells and targeting malignant cells. These agents can ameliorate the end-organ toxicities that result in the escalation of healthcare costs and the lifestyle compromise for the individual by decreasing prolonged hospitalization, antibiotic treatment, and additional supportive care.

Various chemoprotectants have been investigated in both preclinical and clinical trials with encouraging results. The first chemoprotectant used in clinical practice was leucovorin for the prevention of methotrexate-induced toxicity. Since that time, several new agents have been introduced with differing mechanisms of action. Currently, many agents are under investigation for their chemoprotective and at times chemopreventive properties, such as certain dietary products (flavonoids, isoflavonoids), dexrazoxane (for cardioprotection in anthracycline regimens), and oltipraz (in

Table 1 Dose-Limiting Toxicities of Common Chemotherapeutic Agents Utilized in Gynecologic Cancers

Chemotherapy	Indication	Dose-limiting adverse reaction
Cisplatin	Cervical	Nephrotoxicity
	Ovarian epithelial tumors	Neurotoxicity
Carboplatin	Ovarian epithelial tumors	Bone marrow suppression
		Neuropenia, thrombocytopenia
		Nephrotoxicity
Paclitaxel	Ovarian epithelial tumors	Bone marrow suppression
		Neutrotoxicity
Cyclophosphamide	Ovarian epithelial tumors	Hemorrhagic cystitis
		Bone marrow suppression
Vincristine		
Methotrexate	Molar pregnancy	
5-Fluorouracil	Vulvar and cervical	
Bleomycin	Cervical	Pulmonary fibrosis
	Ovarian germ cell tumors	

hepatocellular carcinoma), among many others. However, these studies are mostly preclinical or have not produced sufficient clinical data to consider broader use. Therefore, in this chapter, we will review the biological principles, development, and clinical investigation of the chemoprotectants employed most commonly in the clinical treatment of gynecologic malignancies: amifostine, glutathione, and mesna.

AMIFOSTINE

Amifostine or WR-2721 was first used as a radioprotective agent during a classified nuclear warfare project sponsored by the U. S. Army for its unique safety profile (1). WR-2721 is the first pancytoprotective agent to receive approval from the Food and Drug Administration (FDA). FDA approval stemmed from completion of a phase III study of epithelial ovarian cancer patients treated with cisplatin and cyclophosphamide that documented amifostine's chemoprotective effects on bone marrow suppression, renal, and neural function. Subsequently, multiple phase II trials have been published in patients treated for melenoma, head and neck, small cell lung, ovarian, cervical, and breast cancers suggesting the ability of amifostine to protect normal tissue without compromising the antitumor activity of the antineoplastic agents. In addition to the chemoprotective effects, many researchers have explored its role as a radioprotectant during the treatment of cervical cancer. Today, it is the most extensively investigated chemoprotective agent available.

Mechanism of Action

Amifostine is an organic thiophosphate cytoprotective agent (2-[(3-amino-propyl) amino] ethanethiol dihydrogen phosphate) that is administered as an inactive prodrug. The inactive nucleophilic sulfur prodrug is incorporated into the cell after dephos-

phorylation by alkaline phosphatase to WR-1065 (Fig. 1). After administration, the amifostine is taken up rapidly by a disproportionately greater number of normal cells when compared to tumor cells at a concentration of 1:50 to 1:100 (2–3). The neoplastic cells limited membrane alkaline phosphatase activity and the acid–base environment is the main factor that prevents the accumulation of amifostine within these cells and leads to their vulnerability when compared to normal cells. Once inside the normal tissue, amifostine has been demonstrated to work as a chemoprotectant through various mechanisms of action. WR-1065, a sulfhydryl compound, scavenges oxygen free radicals and donates a hydrogen ion to DNA damaged by platinum agents. Treskes et al. reported on the ability of amifostine to prevent the formation of platinum–DNA adducts as a dose-dependent reaction (4). Although the paclitaxel mechanism of action is related to stabilization of cellular microtubules, recent data suggest paclitaxel also directly injures DNA strands. Investigators have discovered amifostine exerts a protective effect by formation of a disulfide metabolite that prevents DNA platination (4–5). Furthermore, the polyamine-like structure acts to enhance the induction of error-prone repair systems and stabilizes the chromatin.

Pharmacodynamics

Numerous phase I trials have been conducted to determine the appropriate dose of administration, clearance, and toxicities of amifostine. The most frequently recommended adult dosing schedule is 910 mg/m^2 administered over a 15-min infusion 30 min prior to initiation of the chemotherapy. Vijgh and Korst reported that amifostine is rapidly cleared by a biphasic decay pattern with a half-life of 8.8 min. Once administered, the prodrug (WR-2721) is metabolized by alkaline phosphatase to WR-1065 and incorporated intracellularly, and further oxidized to WR-33278, a

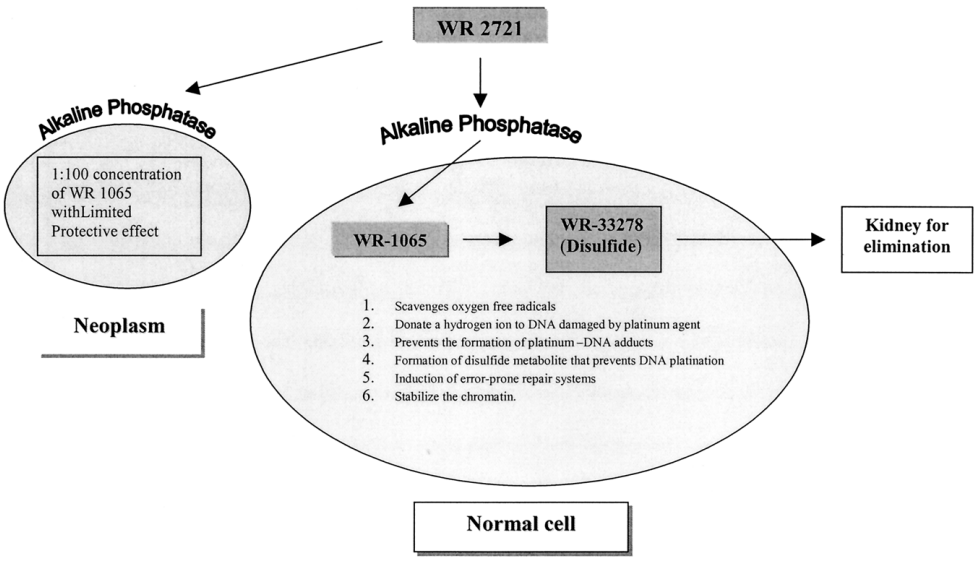

Figure 1 Amifostine conversion into active substrate.

symmetric disulfide and other disulfides (6). The active form and the metabolites are eliminated by renal excretion.

Clinical Application

Amifostine is the most extensively investigated chemoprotective agent in the literature to date. Preclinical experiments on mice have elucidated the mechanism by which amifostine can be utilized in the clinical setting to optimize patient care. The strategy employed is to add amifostine to the traditional cytotoxic regimen with the goal of limiting the toxicity and possibly increasing the delivery of dose intensity to the target neoplastic tissue. Limited phase I and II trials incorporating amifostine into the treatment of melanoma and lung cancers have allowed for only modest increases in the dose of cytotoxic agent administered (7–8). No phase III trials have been completed exploring this strategy.

Numerous clinical trials involving nongynecologic malignancies have demonstrated improved toxicity profiles within the amifostine arm. Glover et al. using high-dose cisplatin in the treatment of metastatic melanoma and Schiller et al. using cisplatin and vinblastine in the treatment of lung cancer reported a decreased incidence of neurotoxicity when therapy was combined with amifostine (7–8). DiPaola el al. reported no significant cumulative neurotoxicity in patients treated with paclitaxel in escalating dosing up to 310 mg/m^2 (9). With respect to hematologic toxicities, Glover et al. also reported a significant decrease in the duration (average of 2.7 days) and nadir of neutropenia ($>700/\mu L$) in patients treated with cyclophosphamide (10). Budd et al. and Betticher et al. evaluated the efficacy of amifostine in preventing carboplatin toxicities in the treatment of advanced solid tumors and nonsmall-cell lung cancer (11–12). Both reported no difference with respect to nadir in neutrophil count or incidence of neutropenia but a significant higher mean platelet count and shorter time to its recovery. The largest randomized study analyzing the chemoprotective efficacy of amifostine was performed by Kemp et al. (13). A total of 242 patients with stage III and IV epithelial ovarian cancer treated with cisplatin 100 mg/m^2 and cyclophosphamide 1000 mg/m^2 every 3 weeks were randomized to receive amifostine 910 mg/m^2 given as a 15-min infusion prior to chemotherapy or chemotherapy alone. A significant decrease with respect to discontinuation of treatment, incidence of neutropenia with fever, days of hospitalization, and dose reductions due to nephrotoxicity, neurotoxicity, and ototoxicity was seen. Interestingly, an increase in overall response was found in the amifostine group vs. control, 75.0% vs. 65.4 %, respectively (Table 2).

Radioprotectant

The scope of amifostine's utility in the treatment of gynecologic cancers is not limited to the cytoprotection during chemotherapy. Promising new avenues with regard to radiotherapy are being explored. The practical benefits of concomitant administration of amifostine with radiation are promotion of DNA repair, maintaining immune system function, reducing mutagenic potential of irradiation to normal tissue. A phase II clinical trial by Tanaka and Sugahara reported more than 50% protection against overall cytoxicity after radiation treatment for uterine, breast, lung, and head and neck cancers (14). The New York Gynecologic Oncology Group performed a study with

Table 2 Chemoprotective Effects of Amifostine in the Treatment of 242 Ovarian Cancer Patients

Toxicity	Cisplatin/cyclophosphamide (n = 120)	Amifostine + cisplatin/cyclophophamide (n = 122)	p value
Neutropenic fever	21%	10%	.019
Grade 4 neutropenia day 22	65%	44%	.004
Days of hospitalization	226	89	.019
Days of antibiotics	284	111	.031
Nephrotoxicity with discontinuation of cisplatin	12.5%	1.6%	.001
40% reduction in creatinine clearance	30%	13%	.001
Neurotoxicity grade 2/3 cycle 6	67%	54%	.029
Dose limiting ototoxicity	16%	9%	.108
Overall dose-limiting toxicity (renal, neurologic, and ototoxity)	26%	10%	.001
Overall response rate	65%	75%	—

cervical cancer patients treated with amifostine followed by cisplatin and whole-abdominal radiation and found a reduction in late radiation toxicities such as fistula formation and proctitis in the study group compared with historical controls (15). However, a retrospective review of 84 patents treated for cervical cancer with external beam and brachytherapy evaluating long-term radioprotective effects of amifostine found no difference when compared with historic control (16). Prospective randomized trials are needed to further delineate the protective effects of amifostine as either a chemoprotectant or radioprotectant in the treatment of gynecologic malignancies.

Administration and Management of Amifostine

Amifostine can be safely administered to patients with relatively few side effects if properly managed. A thorough understanding of the preventive and management schemes for the most common side effects will ensure successful administration and tolerance. This approach will promote a safe therapeutic environment and patient compliance. The most common adverse outcomes encountered in the treatment with amifostine include nausea, vomiting, hypotension, hypocalemia, and allergic reactions. Prehydration with 1 L of normal saline is recommended to prevent the most common side effect, which is hypotension. The patient should be advised to drink 1 L of fluids prior to the scheduled dose and to hold all antihypertensive medications 24 hr prior to the day of treatment. Time of administration has been shown to directly influence the incidence of hypotension with longer infusion times associated with larger falls in blood pressure. The patient should be placed in the supine or recumbent position and amifostine administered over 5–10 min (17). Administering antiemetic medication 60 min prior to amifostine can minimize nausea and vomiting. The most effective antiemetic regimens include dexamthasone, diphenhyramine, and serotonin 5-HT_3 antagonist, lorazepam and cimetidine (18). Hypocalmemia has been reported which can be life-threatening. For this reason monitoring serum calcium levels prior to therapy is important and calcium replacement instituted when appropriate.

GLUTATHIONE

Glutathione (GSH) is a ubiquitous, nonprotein cytoplasmic sulfhydryl compound that has been shown to confer protection to normal cells by reducing peroxides and binding to free oxygen radicals. Renal and neural rat cells with glutamyl transpeptidase intracellularly catalyze the incorporation of GSH thus conferring protection. This is the proposed mechanism against cisplatin-induced nephrotoxicity from administered GSH. Glutathione is administered at a dose of 2.0–4.0 g/m^2 over 15–30 min. The shorter the infusion interval the less episodes of hypotension.

A number of early clinical trials have reported a decrease in cisplatin-induced nephrotoxicity (19). Smyth et al. conducted a double-blind randomized trial of a total of 151 women with ovarian cancer treated with six cycles of 100 mg/m^2 of cisplatin with or without GSH 3 g/m^2 every 3 weeks for six cycles. They reported a significant difference in reduction of creatinine clearance (74% vs. 62%, $p = 0.0006$) and depression, emesis, peripheral neurotoxicity, hair loss, and shortness of breath (20). Two other randomized trials by Smyth et al. and Colombo et al. showed a trend toward less neurotoxicity without an effect on response rates (20 21).

Glutathione appears to show promise in diminishing neurotoxicity and nephrotoxicity caused by platinum-based products, but additional randomized prospective studies will be required to confirm results.

MESNA

Mesna or mercaptoethanesulfonate is a specific chemoprotective agent developed to prevent the urotoxic effects of ifosfomide and cyclophosphamide. Ifosfamide and cyclophosphamide are alkylators activated by the hepatic microsomal enzyme system to form acrolein and phosphoramide mustard. Acrolein is subsequently excreted into the urinary system affecting the bladder mucosa resulting in hemorrhagic cystitis (22). In the absence of a chemoprotective agent, both ifosfamide and cyclophosphamide are associated with dose-limiting urothelial toxicity.

Mechanism of Action

Mesna or sodium-2-mercapto-ethane sulfonate is a specific chemoprotectant that blocks the destructive nature of acrolein-induced bladder toxicity. Mesna upon administration enters the bloodstream and is converted to an inactive disulfide form. Dimesna is subsequently excreted by the kidney where it is reduced back to mesna by thiol transferase and glutathione reductase. In the urinary system, mesna forms thioesthers with acrolein resulting in an inactive substrate.

Pharmacokinetics

The half-life of mesna is about 1 hr. The peak urinary concentration is reached in 1 hr when given intravenously and 3 hr when given orally. The bioavailability of mesna in the urinary system is 50% after intravenous administration and 35% after oral administration. As a result of the short half-life and delay in achieving adequate urinary concentrations, mesna is administered as a continuous intravenous infusion during

and following chemotherapy dosing (23). With a push for outpatient treatment, Goren performed a review of current studies evaluating mesna and concluded that oral administration is a viable alternative to the intravenous route provided it is not used concomitantly with severely emetogenic chemotherapies (24). Mesna has been found to produce mild nausea and vomiting provoked by the sulfur taste.

Clinical Application

The literature is replete with studies confirming the protective effects of mesna against ifosfamide and cyclophosphamide-induced cystitis. In a randomized placebo-controlled trial, mesna was found to be superior to placebo control, 32% vs. 6.7% (25). Other clinical trials comparing acetylcysteine with intravenous mesna against ifosfamide-induced urinary toxicity have proven the overwhelming protective effects of mesna over acetylcysteine, 4.2% vs. 27.9%, respectively (26).

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Chemoprevention in Gynecological Oncology

Ramin Mirhashemi and Talia Donenberg
David Geffen School of Medicine at UCLA, Los Angeles, California, U.S.A.

INTRODUCTION

Despite major advances in early diagnosis and cancer treatment, mortality from cancer remains a significant public health concern in most developed countries. In the past two decades, the focus of medicine in the public health arena has evolved from disease treatment to risk reduction and, ultimately, prevention. Advances in molecular biology, genetics, drug discovery, and imaging technology have given way to a more sophisticated understanding of the etiology and development of disease. Elucidation of the multiple molecular steps of carcinogenesis involving a continuum of DNA damage (Vogelstein et al., 1988; Fearon, 1990) and enhanced detection of precancerous conditions has given rise to the prospect that the carcinogenic process might somehow be averted, incapacitated, or even reversed. This concept has been demonstrated by several recent clinical trials, several of which will be discussed here, but is still in its initial stages of development.

The identification of cigarette smoking as a risk factor for lung and other cancers has led to effective preventive strategies involving lifestyle changes. However, the etiologies of all cancers are not as well known, and lifestyle modification has so far done little to protect against most malignancies, including gynecological cancers. This has led to the search for more dynamic approaches to cancer prevention such as the use of nontoxic pharmacological agents, known as "chemoprevention" (Sporn et al., 1976), which refers to the reduction of cancer incidence by the administration of agents or drugs that inhibit, reverse, or stall the cancer process.

Thus far, scientists have identified hundreds of agents with preventive potential from established medical treatments, animal research, and epidemiological studies (Lippman et al., 1998). Conceptually, chemoprevention is divided into three different models: (a) primary prevention—preventing initial cancer in healthy individuals; (b) secondary prevention—preventing cancer in patients with premalignant conditions; and (c) tertiary prevention—preventing second primary cancer in patients cured of an initial cancer (Hong et al., 2000). This report summarizes current scientific evidence of advances in the chemoprevention of human gynecological malignancies, specifically

breast and ovarian cancers, focusing on primary prevention and drawing from secondary and tertiary prevention studies as applicable. The development of preventive concepts and their application in clinical trials will be included for agents discussed. We will begin with a brief overview of the rationale for clinical trials and appropriate target populations.

RATIONALE FOR CLINICAL TRIALS

If the ultimate goal of chemoprevention is to reduce the burden of cancer in the healthy at-risk population, then a successful chemopreventive agent should not pose more risks than benefits. The ethical considerations of putting healthy individuals at risk for drug toxicity are vast. From the individual perspective, risks and burdens associated with chemoprevention will be incurred, but the benefits may accrue only to others (Vogel and Parker, 1997). Individuals motivated by their perceived risk would be ideal participants; however, studies show that perceived risk does not necessarily correspond to established risk (Smith et al., 1996). As such, the identification of high-risk cohorts, which may benefit most from an agent, is of primary importance in the design of a clinical trial. Also of high importance is the design of obtainable endpoints.

Randomized large-scale double-blinded phase III clinical trials are generally considered the best means available to test whether chemopreventive interventions reduce cancer risk. Usually involving thousands of subjects, these trials can take 10 years or longer to complete and include studies in high-risk populations as well as the general population (Fabian and Kimler, 1997). The primary endpoint of phase III trials is to determine the cancer-preventive effectiveness of the intervention. However, such studies are extremely costly and, in addition, the size and length often lead to problems in recruitment, motivation, and compliance (Hong and Sporn, 1997; Fabian et al., 1998). Phase II trials, in contrast, utilize high-risk subjects who have been demonstrated to have premalignant changes such as atypical hyperplasia or in situ carcinomas, and involve fewer subjects, trial years, and reduced costs. However, they must rely on advancements in molecular technology and validated endpoints, which are difficult to establish (Fabian et al., 1998).

Before phase III primary prevention trials using a selected agent can be launched, a strong mechanistic or experimental basis for inhibition of carcinogenesis is required, such as the ability to reverse tissue morphological, proliferative, and molecular changes associated with premalignancy or intraepithelial neoplasia (Hong and Sporn, 1997; Fabian and Kimler, 1997; Kelloff et al., 1999). Many classes of agents have shown promising chemopreventive activity for gynecological as well as other malignancies including antioxidants, anti-inflammatories, antiestrogens, and antiandrogens (Kelloff et al., 1999). Agents that have gone through extensive clinical evaluation of their efficacy and practical utility for secondary and tertiary prevention are likely to be promising candidates for primary prevention. Currently, more that 50 candidate chemopreventive agents are under clinical development in phase II trials for various types of cancer, and the agents deemed highly effective may be placed in priority for definitive phase III cancer incidence reduction studies (Kelloff et al., 1999).

BREAST CANCER PREVENTION

The lifetime risk of developing breast cancer among Western women is approximately 10%. Established risk factors for breast cancer include age, family history, estrogen (early age at menarche, late age at first childbirth, late age at menopause, and postmenopausal obesity), and a sedentary lifestyle (McTiernan, 2000). Because the breast cancer incidence in Western countries is greater than in Asia and Africa, and migrants from these countries assume higher U.S. risk, it has been proposed that diet is an important environmental risk factor (Offit, 1998). Other environmental risk factors include high alcohol consumption and radiation exposure.

BRCA1/BRCA2 carriers have the highest risk for breast cancer, varying from 56% to 87% (Ford et al., 1994, 1998). Other genetic syndromes involving increased risk for breast cancer include the rarer Li–Fraumeni, Cowden, Peutz–Jeghers, and Muir–Torre syndromes and ataxia–telangiectasia heterozygotes (Offit, 1998). Because of the high lifetime risk involved, those with inherited mutations are ideal candidates for chemoprevention studies. However, only 5–10% of breast cancer is associated with inherited mutations, and ascertainment of potential BRCA1/BRCA2 families is still suboptimal. Furthermore, women at these highly increased risks may not opt to enter into placebo-controlled trials, and may be more likely to follow established risk-reducing methods such as surgical prophylaxis. Therefore, it might be difficult to accrue a substantial number of mutation carriers for trials.

Selective Estrogen Receptor Modulators (SERMs)

The role of estrogen in the promotion of breast cancer has long been implicated (Dao, 1962).

Estrogen, upon binding to its receptor, triggers the expression of multiple genes involved in the regulation of cell proliferation and differentiation (Levenson and Jordan, 1999). The development of antiestrogens for adjuvant therapy of breast cancer and the observation of minimal side effects provided a conduit to testing this class of drugs in primary chemoprevention (Early Breast Cancer Trialists' Collaborative Group, 1992, 1998). Antiestrogens are more appropriately known as SERMs because they have estrogenic properties in some tissues and antiestrogenic effects in others. The best known SERM, tamoxifen, has achieved unique distinction as evidenced by a large U.S. trial, which led to the U.S. Food and Drug Administration (FDA) approval of this drug as the first cancer risk reduction agent for women at increased risk for breast cancer (Fisher et al., 1998).

SERMs exert their action by competitively inhibiting estrogen binding (Levenson and Jordan, 1999). Tamoxifen is antiestrogenic to the breast and partially estrogenic to the endometrium, as well as estrogenic to the bones and cardiovascular system. Tamoxifen also stimulates production of TGF-β, which in turn inhibits the growth of many epithelial cell lines (Whittemore, 1999). The biological effects of estrogen are known to be mediated by two receptors: ER-α and ER-β. The existence of these two subtypes provides a possible explanation for the tissue selectivity of SERMs (Levenson and Jordan, 1999). Moreover, the shape of an antiestrogenic ER complex can dictate how or if any other protein in a transcription unit will bind.

In 1992, the National Surgical Adjuvant Breast and Bowel Project (NSABP) initiated the Breast Cancer Prevention Trial (BCPT), also known as the P-1 study (Fisher et al., 1998). This was a randomized, double-blind, placebo-controlled study in which the primary endpoint was to determine whether tamoxifen, administered for at least 5 years, could reduce the incidence of invasive breast cancer in women at increased risk. Between June 1992 and September 1997, 13,388 women were randomized into the P-1 trial throughout the United States and Canada. Participants were assigned to receive either placebo or 20 mg/day tamoxifen for a 5-year period. Eligibility criteria included: women over 60 years, or between 35and 59 years with a risk of breast cancer equal to a 60-year-old, or above 1.66% over a 5-year period based on a modified Gail model assessment (Gail et al., 1989). Women with a history of LCIS treated by excision alone were also eligible for the trial.

Secondary aims included determination of whether drug administration would lower the incidence of fatal and nonfatal myocardial infarctions and reduce the incidence of bone fractures, as tamoxifen is known to reduce total cholesterol and to stabilize bone loss in postmenopausal women. An independent data and safety monitoring committee reviewed the conduct of the trial from its beginning and at regular intervals (Fisher et al., 1998). In March 1998, the data monitoring committee (ERSMAC) recommended that the study be unblinded because the primary endpoint had been achieved with statistical certainty and that additional follow-up time would not result in improved estimates of treatment . These were stopping rules that had been established before the onset of the trial. Participants were notified of their status and results were publicly announced in April 1998 (Wickerham, 2000; Fisher et al., 2000).

Of the 13,175 participants included in the analysis, the age breakdown is as listed in Table 1. Almost all participants were white (96.4%) despite efforts to include more diverse populations (Fisher et al., 1998, 2000). More than one-third (37.1%) had had a hysterectomy, 6.3% had a history of LCIS, and 9.1% had a history of atypical hyperplasia. Almost one-fourth (23.8%) of participants had no first-degree relatives with breast cancer. More than one-half (56.8%) had one first-degree relative with breast cancer, 16.4% had two, and 3.0% had three or more.

A total of 368 invasive and noninvasive breast cancers occurred: 244 in the placebo group and 124 in the tamoxifen group, thereby demonstrating an overall risk reduction of 49% ($P < 0.00001$) (Fisher et al., 1998). For noninvasive breast cancer, the reduction in risk was 50% ($P < 0.002$). Particularly important was the observation that the drug reduced the incidence of ER^+ invasive tumors by 69%. There was, however, neither an increase nor a decrease in the incidence of ER^- tumors among

Table 1 NSABP Trial

Age of participants (years)	Percentage of total	Risk reduction by age group (%)
35–49	39.3	44
50–59	30.7	51
>60	30	55
(>70)	(6)[a]	

[a] Not included in percentage of total.

women in either the tamoxifen or placebo group. The reduction was noteworthy among those with a history of premalignant lesions. In women with a history of LCIS or ductal or lobular hyperplasia (most often ER^+), the risk of invasive cancer after removal of such lesions was reduced by 56% and 86%, respectively. During each of the first 6 years of follow-up, tamoxifen administration resulted in a significant reduction in the risk of invasive cancer; the rates of decrease in years 1–6 were 35%, 55%, 39%, 49%, 69%, and 55%, respectively. Rates of invasive breast cancer by selected tumor characteristics varied. The rate of invasive breast cancer among women in the tamoxifen group was less than that among women in the placebo group in all tumor size categories (Fisher et al., 1998).

Adverse effects of the P-1 trial included excess risk of endometrial cancer and of vascular-related events observed in the tamoxifen group, as compared with those in the placebo group (Fisher et al., 1998; Lippman and Brown, 1999). Participants who received tamoxifen had a 2.43 times greater risk of developing invasive endometrial cancer (95% CL = 1.35–4.97) than did women who received placebo. The relative risk (RR) varied among age groups and was found to be predominant in women aged 50 years or over. Through 66 months of follow-up, the cumulative incidence was 5.4/1000 in the placebo group and 13.0/1000 in the tamoxifen group. All cancers in the tamoxifen group were in situ or FIGO stage I. Invasive cancers at other sites were equally distributed.

Overall, the average annual rate of ischemic heart disease was 2.37/1000 women vs. 2.73/1000 in placebo vs. tamoxifen groups, respectively (Fisher et al., 1998). Fractures of the hip, radius, and spine were evaluated and revealed a 19% risk reduction in the tamoxifen group. The difference in serious cardiovascular events such as stroke or pulmonary embolism was not statistically significant, with an RR of 1.59 (95% CL 0.93–2.77). A significant excess of cataracts was observed. Twelve percent more women in the tamoxifen group experienced some degree of hot flushes and 20% reported vaginal discharge.

Other tamoxifen trials, however, have not shown the same encouraging results with respect to decreased risk for breast cancer. In 1986, the Royal Marsden Hospital in England started a small feasibility trial of 200 healthy premenopausal and postmenopausal women aged 35–65 years old, who were randomized to receive either tamoxifen 20 mg/day or placebo for 5 years. In 1988, the interim analysis of this feasibility trial indicated that healthy women could be accrued to a chemoprevention trial, acute toxicity was very low, and compliance was correspondingly high (Powles et al., 1989, 1998). This trial subsequently resulted in the main pilot trial, which accrued 2494 women over the following 8 years between ages 30 and 70 years. Women who had no clinical evidence of breast cancer and an elevated risk due to strong family history were eligible. Women with a history of benign breast biopsy with at least one first-degree relative with breast cancer were also eligible. Accrual ended in 1996. It achieved 70% compliance at 5 years and a median follow-up time of 70 months, and documented a total of 70 breast cancers. However, the investigators were unable to demonstrate any effect on breast cancer incidence (Powles et al., 1998). In 1992, the International Breast Intervention Study began accruing subjects in Australia and then the UK, with a goal of 7000 participants (Cuzick, 2000). Entry criteria for IBIS include family history, benign breast disease, and nulliparity. The results of this trial and others will continue to be of important potential for further evaluating tamoxifen's chemopreventive use.

In 1991, the National Cancer Institute in Milan commenced a randomized clinical trial, recruiting healthy women over 35 years of age who were not at high risk of developing breast cancer but who had undergone a hysterectomy for reasons other than malignancy. By 1996, over 5408 women with a median age of 51 years had been randomized to tamoxifen (daily dose, 20 mg) or placebo (Veronesi et al., 1998; Decensi et al., 2000). As of 1998, however, 1422 (26.3%) of the participants dropped out of the study, 17% of which reported adverse events. Bad publicity in the media was a main factor attributed to the high dropout rate (Decensi et al., 2000). Preliminary results after a median of 46 months showed no difference in breast cancer incidence between the arms. Among women on intervention for more than 1 year, there was a trend to a beneficial effect of tamoxifen. A borderline significant reduction of breast cancer was observed among women who were hormone replacement therapy (HRT) users and received tamoxifen. There was an increased risk of venous vascular events [38 (tamoxifen):18 (placebo), $P = 0.0053$] consisting mainly of superficial phlebitis and 15:2 cases of severe hypertriglyceridemia in the tamoxifen:placebo arms ($P = 0.0013$) Among this group of women at low-normal risk of breast cancer, the postulated effects of tamoxifen were not deemed apparent (Veronesi et al., 1998).

Comments on Tamoxifen Trials

The three trials are impractical to compare due to their differences in target population and numbers. The strength of the NSABP lies in the numbers recruited, and the fact that the Gail risk (Table 2) is considered a validated and accepted model for determining breast cancer risk (Rockhill et al., 2001). However, certain issues remain unanswered from the NSABP trial. It is unknown whether these results are applicable to certain risk groups such a BRCA carriers. Although information on a subset tested for BRCA status might be available in the not too distant future, it is unlikely to yield large numbers. Because most BRCA1 tumors are ER^-, the question has been raised about its potential efficacy for this group. A recent study reported on both BRCA1 and BRCA2 carrier women with primary breast cancer who took tamoxifen as adjuvant therapy (Narod et al., 2000). Both groups were found to have a 50% reduction in risk for contralateral breast cancer. Moreover, this effect was felt to be independent of oophorectomy and possibly additive, but information on ER status was not available for all cases.

Both European studies were done on much smaller numbers and lack the same statistical magnitude as NSABP. Both European studies also included women who were on HRT. However, in the Italian trial (Table 3), the group on HRT and tamoxifen appeared to have the most significant effect (Veronesi et al., 1998). The Royal Marsden study relied more heavily on high-risk cases due to family history and,

Table 2 Gail Model Risk Breakdown

5-year risk	Study group (%)
1.66–2	25
2.01–5	57.6
>5	17.4

Table 3 Italian Trial

Age of participants (years)	Percentage of total
35–49	37.0
50–59	50.3
60–69	11.5
70	0.2

therefore, possible genetic factors that have not yet been classified (Powles et al., 1998). The Italian study, due to the inclusion of women who had previously undergone oophorectomy, used many participants who were at average to low risk. Lastly, questions about applicability to different cultural groups remain from all three studies.

Raloxifene

Due to the risks and disparate findings of the above-mentioned trials, widespread use of tamoxifen in healthy women may still be limited. In contrast to the estrogenic effects of tamoxifen on the uterus, the drug, raloxifene, has shown no estrogenic effects on the endometrium in clinical trials and is not associated with an increased risk of endometrial cancer after 40 months of exposure in this clinical trial (Cohen et al., 2000; Cummings et al., 1999). Raloxifene effectively maintains bone density and reduces risk of vertebral fractures (Delmas et al., 1997). The effect of raloxifene on breast cancer was a defined secondary endpoint in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, which had, as its primary endpoint, the testing of whether 3-year raloxifene use reduces the risk of fracture in postmenopausal osteoporotic women. Among 7705 women randomized to either raloxifene or placebo, the risk of invasive breast cancer was decreased by 76% during 3 years of treatment (Cummings et al., 1999). The 3-year treatment phase was extended to 4 years after the trial was initiated. Raloxifene significantly decreased the incidence of invasive ER^+ cancers compared with placebo (RR 0.16, 95% CI 0.09–0.30) but had no effect on estrogen-negative tumors (RR 1.13, 95% CI 0.35– 3.66). The decreased incidence was 62% for all breast cancers and 72% for invasive cancers compared with placebo (Cauley et al., 2001).

It is important to note that women in the MORE trial were not randomized according to risk, and that the study population at high risk for osteoporosis may have had a lower overall risk for breast cancer. On the other hand, because 82% of the cohort was older than 60 years, this is more representative of the postmenopausal population with respect to breast cancer risk (Cummings et al., 1999; Cauley et al., 2001). The longer-term effects of raloxifene on the incidence of breast cancer in postmenopausal women will be evaluated in the Continuing Outcomes Relevant to Evista (CORE), which will follow the incidence of breast cancer in a subset of the MORE cohort in the next 4 years (Fisher et al., 1998; Cummings et al., 1999). Although raloxifene was not associated with an increased risk for uterine cancer, other adverse effects were somewhat similar in scope to tamoxifen. Raloxifene, tamoxifen, and estrogen increase the risk of thromboembolic diseases to a similar degree.

STAR Trial

Finally, results of the SERM trials have culminated in the first nonplacebo-controlled, head-to-head trial of the two SERMs (raloxifene vs. tamoxifen) in postmenopausal women at high risk for breast cancer, called the Study of Tamoxifen and Raloxifene (STAR) or P-2 trial (National Institutes of Health, Office of Cancer Communications, 1999). As of January 2001, enrollment of some 8500 participants is on target, with an overall goal of 22,000 women for the 5-year treatment study. However, some participating study centers have reported falling short of their accruement goals, citing problems with physicians who have already decided that raloxifene is a better choice (Vastag, 2001).

New SERMs

A variety of new SERMs are currently being studied for potential clinical use in chemoprevention. One of this new generation, SERM LY353381, is now designed to be more bioavailable than raloxifene so that a more sustained blood level can be maintained (Hong and Sporn, 1997). It was found to be 30 times more potent in bone than raloxifene in animal studies (Sato et al., 1998) and, like raloxifene, this SERM also offers potential for breast cancer prevention without risk of uterine cancer (Levenson and Jordan, 1999). This agent, also called SERM-III, has undergone phase IA and IB multicenter trials in ductal carcinoma in situ (DCIS) patients and was reported to be well tolerated (Fabian et al., 2000).

Other Estrogen Modulators

Aromatase inihibitors modulate estrogen through inhibition of steroid aromatase (Kelloff et al., 1998). Aromatase catalyzes the final and rate-limiting step in estrogen biosynthesis. This class of agents includes nonsteriodal and steroid aromatase inhibitors and is indicated for breast cancer treatment in postmenopausal women who have failed tamoxifen treatment. The nonsteroidal agent, vorozole, has potent chemopreventive activity in animal models and is one of the few aromatase inhibitors reported to influence estrogen levels in premenopausal women. In addition, the steroidal drug, exemestane, is currently in early clinical BCPTs (Lawrence et al., 2000).

Other Hormonal Approaches

Pike and Spicer (2000) have suggested an approach to blocking ovarian function with a gonadotropin-releasing hormone (GnRHA) and to counteracting the induced hypoestrogenism with a low dose of estrogen and intermittent progestin (Spicer and Pike, 1993; Pike and Spicer, 2000). This approach avoids having to use high doses of estrogen–progestin to block ovulation. The main aim of this approach is chemoprevention of breast and ovarian cancer while providing a hormonal contraceptive that may be acceptable to most women. In a randomized trial, the GnRHA agent, zoladex, was given to premenopausal breast cancer patients and a 40% reduction in contralateral breast cancer was observed (Pike and Spicer, 2000). Spicer et al. (1994) carried out a small randomized trial using Lupron plus addback estrogen plus progestin regimen in women at high risk for breast cancer. Mammographic densities

of women were dramatically decreased after 1 year (Spicer et al., 1994). This could lead to greatly improved efficacy of screening mammography in younger women. Therefore, it may be a useful endpoint for future trials. A similar study is in progress for healthy premenopausal BRCA carriers at several centers in the United States.

Retinoids

Several epidemiological studies have suggested that the retinoids reduce cancer incidence or recurrence at various sites, including the breast (Costa et al., 1994). As with SERMs, retinoids also seem to have a complex mix of benefits and risks. They appear to exert their anticarcinogenic effects by binding to retinoic acid receptors and acting as transcription factors, thus binding to multiple targets including TGF-β. Experimental evidence also suggests a strong role in the induction of apoptosis (Sabichi et al., 1998). The synthetic retinoid, 4-HPR or fenretinide, has shown promise as a chemopreventive agent in breast cancer. Its encouraging clinical activity was observed in a randomized trial conducted at the Istituto Nazionale Tumori in Italy. In this trial, 2849 women who had surgery for localized breast cancer were randomly assigned to receive 200 mg/day 4-HPR or placebo for 5 years to determine whether 4-HPR could reduce the incidence of second primary tumors (Veronesi et al., 1992). Study observations revealed a different effect of fenretinide on the risk of contralateral and ipsilateral breast cancer depending on menopausal status or age, with a beneficial effect in premenopausal women and a reversed trend in postmenopausal women. Further trials in younger women may be indicated before any conclusions can be drawn.

Anti-Inflammatories

Much may be learned about previous studies in colon cancer prevention using anti-inflammatories. Nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with a reduced incidence of, and mortality from, sporadic adenoma and colon cancer epidemiological studies (Thun et al., 1991). In early clinical studies and small, randomized, placebo-controlled trials, sulindac caused regression of colorectal adenomas in patients with familial adenomatous polyposis (FAP) (Giardello et al., 1993). Due to adverse gastrointestinal effects, which are in large part attributed to cyclooxygenase-1 (COX-1) inhibition, selective inhibition of cyclooxygenase-2 (COX-2) was focused on as a pharmacological strategy. COX-2 is a prostaglandin synthase, which has been observed to contribute to carcinogenesis by suppression of apoptosis, direct stimulation of cell growth, and possibly stimulation of proliferation indirectly by increasing estrogen biosynthesis (Howe et al., 2001).

COX-2 is upregulated in colonic neoplasms, including adenomas and carcinomas in humans and rodents, and in early adenomas in mice with germline APC mutations causing FAP; its inhibition was observed to reduce the incidence of adenomas (Kawamori et al., 1998). Finally, in a double-blind, placebo-controlled study, 77 patients with FAP were randomly assigned treatment with a COX-2 inhibitor, celecoxib. In the patients treated with 400 mg of celecoxib, researchers found a significant reduction (30.7%) in the number of colorectal polyps compared to those on placebo (Steinbach et al., 2000). This work led to the U.S. FDA approval of celecoxib as an adjunct in the treatment of FAP in December 1999.

COX-2 inhibition has been studied in relation to epithelial cancers in general. COX-2 expression is shown to be upregulated in well-differentiated and moderately differentiated carcinomas of the breast as well as DCIS (Soslow et al, 2000). In animal studies, administration of celecoxib was found to dramatically suppress mammary carcinogenesis (Harris et al., 2000). Breast cancer and COX-2 overexpression have been studied as a function of HER-2/neu receptor status (Howe et al., 2001). Evidence exists that Her-2/neu$^+$ tumors more often demonstrate COX-2 overexpression than Her-2/neu$^-$tumors, suggesting that overexpression may be a factor in only a subset of human breast cancers (Howe et al., 2001). Future clinical studies using these agents may be of promise for breast cancer prevention, as they have been of promise in colon cancer.

Dietary

Phytoestrogens derived from soybeans have been the subject of many attempts at suggestive dietary interventions for breast cancer risk reduction. At the cellular level, phytoestrogens such as genistein compete with estradiol for binding to ERs and may stimulate estrogen responses, although less effectively. The in vitro effect of genistein, however, is biphasic: low concentrations stimulate cell growth and gene expression, whereas higher concentrations inhibit cell growth (Lawrence et al., 2000). Indole-3-carbinol (I3C) is the component implicated in epidemiological studies of cruciferous vegetables associated with decreased risk for cancer in humans. Metabolites of I3C may exhibit direct antiestrogenic activity by downregulation of ER (Lawrence et al., 2000).

Combination Therapy

Since the 1960s, the concept of multiagent therapeutics for cancer treatment with nonoverlapping toxicity has enhanced treatments for various cancers (Brenner, 2000). A similar rationale is being considered in the hope of maximizing the preventive power of chemoprevention by instituting different mechanisms of action concomitantly. The combination of a promoter of differentiation, an antiproliferative agent, and an inducer of apoptosis would be particularly appropriate for the treatment of premalignant lesions (Hong and Sporn, 1997). The UK and Australia have started a pilot study of raloxifene and zoladex (goserelin), called the RAZOR study, which will initially assess the acceptability, compliance, and quality-of-life issues in offering monthly zoladex and daily raloxifene to women aged 35–45 years who are at very high risk for breast cancer due to strong family history (Eeles and Powles, 2000).

A combination of fenretinide and tamoxifen was proposed as they appear to have an enhancing effect in preventing mammary tumor development in animal models and because of fenretinide's ability to induce apoptosis in ER$^-$ tumors (Veronesi et al., 1999). A pilot study of 32 women at high risk for breast cancer was initiated using the combination of 4-HPR and tamoxifen, and concluded acceptable tolerability for the cohort (Conley et al., 2000).

Combination therapy has also been proposed to minimize side effects. Recently, a randomized, double-blinded, placebo-controlled phase III trial has been designed to address this issue, called the Hormones and Tamoxifen (HoT) Study (Bonanni et al.,

2000). The primary objective of this trial is to assess if tamoxifen at low doses reduces the incidence of breast cancer in healthy postmenopausal women undergoing, or willing to start, HRT. The primary endpoint is the incidence of DCIS and invasive breast cancer after 5 years of intervention. Secondary endpoints are similar to those of the P-1 trial. It is proposed that the combination of HRT and tamoxifen at low doses might reduce risks and side effects while retaining the benefits of either agent. Specifically, tamoxifen's agonistic activity on the endometrium could be neutralized by progesterone. In addition, dose reduction of tamoxifen itself is postulated to reduce endometrial cancer risk (Jordan, 1999).

Utility of Biomarkers

The development and validation of surrogate (intermediate) endpoint biomarkers (SEBs) for use in clinical chemoprevention trials is an important step toward speeding up the pace of research (Kelloff et al., 2000). Intermediate biomarkers are the phenotypical, genotypical, and molecular changes that occur during carcinogenesis and can be useful tools for measuring drug response (Kelloff et al., 1999) and, therefore, reversal or inhibition of the carcinogenic process. In addition, the validation of biomarkers is important for more tangible characterization of short-term risks. Three types of biomarkers have been identified as important to the conduct of early prevention trials: biochemical activity markers, risk biomarkers, and SEBs (Fabian et al. 1998). To be validated, a potential SEB must show evidence of modulation in phase II studies, and this modulation must be linked to decreased cancer incidence in phase III studies.

Because of the shorter latency to intermediate biomarker endpoints and the smaller cohorts required for treatment such as those employed in phase II studies, biomarkers are critical to the progress of chemoprevention and for cost-effectiveness in development of agents.

For instance, progressive genomic instability as measured by loss of heterozygosity or amplification at specific microsatellite loci has been used to characterize some of the genotypical changes during head and neck carcinogenesis (Sidransky et al., 1992). This may also prove useful in other tissues such as colon or uterine cancers associated with hereditary nonpolyposis colon cancer (HNPCC) syndrome, which are characterized by microsatellite instability. New technologies such as computer-assisted pathology, high-volume gene chip-based assays, and improved diagnostic tools such as magnetic resonance imaging (MRI), digital mammography, ductocopy, confocal microscopy, light-induced fluorescence endoscope (LIFE), and magnifying endoscopes will be critical in ensuring the adequate development of SEBs for future studies (Kelloff et al., 1999).

Fabian et al. (1998) have described high-risk breast cancer subjects suitable for chemoprevention studies based on the presence of early biomarkers of carcinogenesis. They demonstrated, through fine needle aspiration (FNA) of healthy high-risk women (first-degree relative with breast cancer, history of node-negative breast cancer, or premalignant condition), the feasibility of ascertaining morphological and molecular markers indicative of short-term high risk for breast cancer. A significant portion of those aspirated had proliferative breast cytology as demonstrated by hyperplasia with or without atypia, p53 overexpression, DNA aneuploidy, HER-2neu, and ER and EGFR overexpression (Zalles et al., 1995; Fabian et al., 1997; Kimler et al., 2000). In

addition to these SEBs, biochemical biomarkers of serum IGF-I and IGFBP-3 will be monitored in future trials along with breast density (Fabian, 2000). Several phase II trials have been initiated using DFMO, SERM-III, and, more recently, a COX-2 inhibitor in healthy high-risk women (including BRCA mutation carriers) who display increased biomarker expression as detected by FNA (Fabian, 2001). These study groups are followed every 6 months by repeat FNA to follow biomarker and cytological subcategory changes as primary trial endpoints.

Acquiring tissues to study SEBs for breast cancer still presents a challenge, as few data are available regarding the feasibility of obtaining adequate sampling (Fabian et al., 1998). Recently, Dooley et al. (2001) have performed ductal lavage on high-risk women to retrieve cells for cytological evaluation. Of 470 breasts lavaged, 20.2% revealed abnormal cytology consisting of atypia or premalignant cells and malignant cells (Dooley et al., 2001). Approximately 20 institutions are investigating the use of this technique to screen for abnormal cytology in the otherwise clinically asymptomatic population at high risk.

OVARIAN CANCER

The lifetime risk for ovarian cancer is about 1.4%. Risks for ovarian cancer have been documented to be age, family history, parity, and breast feeding. Hereditary syndromes may be responsible for up to 10% of ovarian cancers. BRCA1/BRCA2 carriers have a risk ranging from 10% to 80% (Easton et al., 1995) and account for most hereditary ovarian cancers. Other genetic syndromes include HNPCC syndrome, increasing the risk fourfold. The incessant ovulation hypothesis for ovarian cancer that has been proposed is that ovarian cancer risk is determined by the increased proliferative activity of the ovarian surface after ovulation (Fathalla, 1971). The epidemiological data do not support strong etiological roles in ovarian cancer for diet, physical activity, and body size (Whittemore, 1999). There is, however, a discrepant risk between Asians and Caucasians, with the Caucasian population displaying a 4.8-fold increased risk, which is not easily explained by the incessant ovulation hypothesis. One possible explanation for the observed difference in rates can be accounted for by the hypothesis of intraovarian estradiol levels (Pike and Spicer, 2000). Interestingly, women in low-risk Asian countries have serum estradiol levels about 25% lower than those of American women (Bernstein et al., 1990).

Oral Contraceptives (OCs)

Chemoprevention of ovarian cancer was first demonstrated in the 1970s (Spicer and Pike, 1993). The agent, OC, was shown to be clinically protective, depending on the duration of use: 5 years of OC use provides a long-term reduction in risk of about 32% and 10 years of use provides a reduction of about 54% (Stanford, 1991; The Cancer and Steroid Hormone Study Group, 1987). The mechanism of action is the blockage of ovulation and concomitant reduction in intraovarian estrogen levels. This effect has been shown to be independent of the doses of estrogen and progestin, and available data indicate that this effect continues for 30 years or more after discontinuation (Ness et al., 2000). The mechanism of action is the blockage of ovulation and concomitant reduction in intraovarian estrogen levels. OC use has been shown to be equally

protective against BRCA1/BRCA2-related ovarian cancer in families carrying mutations (Narod et al., 1998).

Fenretinides

Persisting concern over increased risk of breast cancer associated with OC use in women with a family history of breast cancer has warranted further research into other agents with preventive potential (Grabrick et al., 2000; Veronesi and Decensi, 2001; Offit, 1998; Eeles and Powles, 2000). Fenretinide has also been shown as a promising candidate for ovarian cancer chemoprevention. In the aforementioned Italian 4-HPR trial, a second finding of the 4-HPR trial was that statistically significantly fewer ovarian cancers developed in women who received 4-HPR. The apparent benefit, however, was lost during the subsequent follow-up period, suggesting that the potential preventive effect of fenretinide was not lasting (Veronesi and Decensi, 2001). In vitro data suggest that clinically achievable concentrations of retinoids can decrease the growth fraction of, and induce glandular differentiation and apoptosis in, ovarian cancer cells and tissues (Supino et al., 1996; Guruswamy et al., 2001). The induction of glandular differentiation and concomitant increase in mucin expression evidenced by observed *MUC1* gene expression patterns demonstrate reversal of the tumorigenic phenotype (Guruswamy et al., 2001). Furthermore, the overall effect of retinoids on the ovarian cancer cell morphology also demonstrated a reversal of the tumorigenic process. These data, together with previous clinical observations, suggest retinoids as potential agents for the development of clinical trials in ovarian cancer chemoprevention (Veronesi and Decensi, 2001).

NSAIDs

The capacity of NSAIDs for preventing ovarian cancer has been suggested (Cramer, 1998; Rosenberg et al., 2000). So far though, studies have shown only weak support for reduction in risk of epithelial ovarian cancer among several different analgesic users. Clearly, more biological and epidemiological data are needed to clarify the relation of use of certain NSAIDs to risk of ovarian cancer.

ENDOMETRIAL CANCER

Obesity in both premenopausal and postmenopausal women, nulliparity, estrogen replacement therapy in postmenopausal women, and certain genetic predisposition conditions such as HNPCC significantly increase endometrial cancer risk. Aside from inherited conditions, the risk factors of endometrial cancer may be explained by the mitogenic action of estrogen in the absence of progestin (Pike and Spicer, 2000).

Hormonal prevention of endometrial cancer was first demonstrated in the 1980s (Centers for Disease Control, 1987). The agent was again OC. The protection was clinically highly significant and dependent on the duration of use: 5 years of use provides a reduction in risk of 46%, and 10 years provides a reduction of 71% (Pike and Spicer, 2000). The GnRHA approach of Spicer and Pike (1993), which has been suggested mainly for protection of ovarian and breast cancers, is not as effective in

endometrial cancer, unless intermittent progestin is administered for at least 13 days along with low-dose estrogen.

CERVICAL CANCER

A strong correlation between exposure to human papillomavirus (HPV) and cervical cancer has been known for some time. In addition, smoking has recently been shown to have a causative effect. Hereditary cervical cancer is rare, but has been reported in literature. OC use has also been observed to cause an increased risk of cervical cancer, although it is difficult to ascertain because of the positive association of OC use with sexual history risk factors. Several trials, though, have adjusted for both history of Pap screening and sexual history, and still found an increase in cervical cancer risk from OC use (Spicer and Pike, 1993). The GnRHA approach, particularly including reduced intermittent progestin dose, is likely to produce less proliferative stimulation of the cervix.

Cervical pathology lends itself as an excellent model for studying the progression of cancer. The accessibility allows the cervix to be easily sampled cytologically by Pap smear and through the colposcope. The cervix is, therefore, amenable to screening and diagnostic intervention. Because HPV is an important pathogenic contributor to the onset of cervical cancer, biomarkers can concentrate on HPV. HPV viral load, DNA content, proliferation (Ki-67), and the nuclear protein PCNA have been studied as potential useful biomarkers in gauging the activity of chemopreventive agents. Agents that pose promise for risk reduction and prevention of cervical cancer include: difluouromethylornithine (DFMO) as an antiproliferative, retinoids, folic acid, and antioxidants (Kelloff et al., 1995).

CONCLUSION

The concept of chemoprevention is relatively new to the public health setting in the context of primary cancer prevention. Chemoprevention of cancer lags far behind that of cardiovascular disease with respect to surrogate endpoint development, effective agent combinations, extrapolation of findings in high-risk populations to the general population, and overall acceptance by the public and even professionals (Lippman and Brown, 1999).

The potential of chemoprevention to benefit individuals with extremely high molecular genetic risk has been illustrated by the U.S. FDA's approval of celecoxib in FAP patients. These findings may ultimately yield approaches similar to other high-risk genetic predisposition syndromes. Identification of common genetic polymorphisms that influence risk of cancer will also help define risk subgroups in the absence of obvious premalignant features. Future directions in chemoprevention undoubtedly will rely on the development of molecular risk models and translational/mechanistic studies to expose novel agents (Hong et al., 2000). Identification of those at risk should inevitably improve as our understanding of carcinogenesis becomes more sophisticated. Integrating genomics with tissue histomorphometry and imaging technology may contribute to best defining the human risk of cancer development (Kelloff et al.,

1999). Because most cancers do not appear to occur unless preceded by an abnormal histological cancer phenotype, a focus on this abnormal phenotype appears to provide the best opportunity for defining target populations and validating surrogate endpoints. In effect, this approach provides measurable parameters that, when modulated by drugs, have the potential of furnishing compelling evidence of risk reduction (Kelloff et al., 2000).

The potential of primary chemoprevention to benefit larger portions of the population has recently been illustrated by the U.S. FDA's approval of tamoxifen. Because the group that may benefit from tamoxifen use seems to be more diversified than merely high genetic risk or premalignant phenotype, this has tremendous implications for the population at large.

In the near future, patients diagnosed with premalignancy or with validated risk factors are likely to become a growing subset of medical and gynecological oncology practice, and chemopreventive approaches may eventually prove to be an effective therapeutic option for these individuals.

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Role of Psychological Support During Chemotherapy

Sabine Hawighorst-Knapstein, Götz Schönefuß, and Paul G. Knapstein
University of Mainz, Mainz, Germany

In recent years, not only surgical but also conservative options for cancer treatment have improved. The treatment modality in chemotherapy has a strong influence on the patients' daily life. Physical and psychological changes occur for months with visible consequences such as alopecia and gain weight. Family members and especially children may become irritated by their mother's physical and psychological changes.

Nausea and vomiting are additional stressors for many women and thus reduce the level of their daily activities. Much progress has been made in understanding the impact of somatic, psychological, and sociological factors on cancer patients to improve standards of patient care in recent years. The introduction of new diagnostic and therapeutic strategies pose new challenges to the doctor–patient communication.

Meyerowitz et al. (1983) studied women with breast cancer, and noted that 44% of them had continuing physical problems 2 years later. Communication with family and friends is quite difficult for about one third of all women treated by chemotherapy, because they felt that they might burden other family members or contacts might be too superficial in order to act "normal" (Frank-Stromborg and Wright, 1984). Our clinical experience with a longitudinal study on women with cancer confirm the long-lasting psychosocial effects of cancer treatments including chemotherapy for breast cancer (Hawighorst-Knapstein et al., 1997a,b, 1998, 2000; Knapstein et al., 2000; Schönefuß et al., 2001).

PSYCHOLOGICAL PROBLEMS BEFORE CHEMOTHERAPY

The patient is unprepared for the situation she will face and may be hampered by unrealistic expectations. Thus, her psychological status may reflect emotional discomfort as a result of the life-threatening diagnosis of cancer and the radical treatment. The patient may struggle through feelings of confusion, anxiety, anger, and depression or resignation. Her coping skills will be as important for her future well-being as well as the treatment modality that will be chosen by her and the medical staff.

Serious psychiatric disturbances may be limited to 5–15% of patients. These prevalence rates vary according to type of diagnosis and stage of disease. Anxiety has been found to be associated with more severe post-treatment symptoms, degrading the quality of life, especially for patients with metastatic cancer and pain (Holland, 1989; Edgar et al., 1992; Wells et al., 1995). Sexual dysfunction is a common problem for many cancer patients depending on the treatment procedure, whereas the marital relationship remains stable. Women with chemotherapy will report more complaints after ablatio than after breast-conserving surgery. Quality of life may be reduced in physical and psychosocial aspects for several months (Schover et al., 1995; Levy et al., 1992; Andersen, 1994).

The individual anxiety level is also a predictor for problems with medical interaction and compliance: the more anxious the patient will feel, the more she may experience stress (Schönefuß et al., 1999).

Behavior therapy may be helpful to mitigate the pretreatment anxiety level by relaxation and biofeedback to learn new ways to manage behavior. The treatment of symptoms right from the beginning of chemotherapy also prevents psychiatric labeling, and may also help to improve compliance during the treatment phase.

Freud described the central role of anxiety in mental conflict and related the development of anxiety to four typical danger situations during childhood. An additional and important aspect of Freud's fundamental theory of anxiety for medicine was the "signal anxiety" related to a danger situation. This signal initiates psychological defense reactions to regulate and protect against further disturbing feelings. These reactions are involuntary and unconscious, and are meant to protect the psyche from anxiety, shame, or guilt. They are not necessarily psychopathologic, but are adaptive aspects of personality development and functioning. Our own research results underline this theory clearly (Hawighorst-Knapstein et al., 1997a,b, 1999, 2001; Schönefuß et al., 1997, 1999a,b).

CHOICE OF THE MOST IMPORTANT DEFENSE MECHANISMS BEFORE TREATMENT

Denial—denial of external reality.
Intellectualization—the analysis of a problem in purely intellectual terms, feelings and emotions are ignored.
Aggression, turning against object—any response to frustration as a hostile attitude against a person or thing.
Aggression, turning against self—turning a hostile attitude toward one's self.
Projection—attributing one's own attitudes to others.
Repression—forceful ejection from consciousness of experiences that are painful and generate a high level.

The theory of defense mechanisms helps us to understand the emotional stress-related reactions of anxious, angry, or depressed patients (Thompson and Collins, 1995). Aggression against the physician, for example, may be an attempt to maintain control and strength. As our studies indicate, in situations of conflict, for example, before treatment, the defense mechanism "turning against object" (aggressive behavior) may also be suppressed in order to reduce state anxiety (Schönefuß et al., 1998a,b).

In daily life without threatening situations, the above-mentioned defense mechanisms are used in a balanced way. Cancer patients may also tend to react passively as a shock reaction, and should be encouraged to become active to find solutions concerning their physical and psychosocial problems (also by support groups, recreational activities, etc.). This procedure will reduce the patient's dependent expectations on the physician's attentiveness, and will satisfy the wish for concrete thinking by providing concrete information, also by literature and videotapes. Instead of a few abilities, an increasing number of perspectives will come up and support the patient's autonomy and self-esteem.

Many patients do not know how to get any kind of care or attention without complaining. When their complaints are not effective, they persevere and complain even more. Thus, there is a need for cognitive interventions instead of arguing with the patient, which might damage the patient's self-esteem.

Supportive techniques are also necessary to handle depressed patients by encouraging them to make some small, but realistic changes in their daily life.

All situations may occur before, or during chemotherapy also with family members. It is important for the medical staff not to get into a power struggle and, in general, avoid confrontation. In showing respect for the patient's or family members' worries, the physician defuses any potential defensiveness by confirming their concerns.

PSYCHOLOGICAL PROBLEMS DURING CHEMOTHERAPY

During treatment, the patients cannot expect to function at optimal levels and might be encouraged to learn stress management techniques, such as focusing on breathing, progressive relaxation, or meditation. Regular exercise and healthy life style might change their thinking patterns to get back to a balanced view.

The physician should make an honest comment focusing on some positive aspects of how the patient is dealing with the situation of chemotherapy. Keeping connection with the patient might be initiated by regular meetings involving psychologists, social workers, and physicians to improve coping mechanisms with the potentially life-threatening diagnosis.

Dealing with conflict between family members is helpful to achieve consensus concerning the welfare of the patient as the main goal, especially when chemotherapy for recurrent cancer must be applied. The latter patient group may be very demanding concerning the supportive environment of the medical office. It is not easy to meet their individual emotional needs, especially for unskilled physicians; such patients tend to resort to alternative medicine to get comfort, to reduce stress, and to improve self-control in this difficult situation. Thus, the process of the doctor–patient relationship is essential for the patient's well-being during chemotherapy.

To understand the patient's needs in a more efficient way, the biopsychosocial model as a multifactorial approach may be helpful (Engel, 1977). According to Engel's opinion, biological bases are fully exposed and touched, while at the same time, the psychosocial context should be incorporated. Neither illness nor health can be understood purely as personal events, but should be seen in the context of family and cultural ties especially for cancer patients. The physician can help patient and family to set realistic expectations and provide social support.

McWhinney (1983) suggested incorporating the following concepts for patients:

1. More attention should be paid to health promotion and disease prevention.
2. We should keep separate disease categories, but recognize the effects of interactions and disease susceptibility.
3. We should pay more attention to nonorganic factors such as environmental and relationship characteristics when determining the etiology of disease.
4. The role of the physician is to mobilize the patient's own healing power.
5. Physicians should develop advanced communication skills to diagnose and treat patients rather then diseases.
6. Physicians should develop skills to determine the meaning of illness for the patient.
7. The body, mind, and spirit are integrated.

To improve daily clinical care in a most sufficient way, we would recommend to focus on the woman's individual biography right from the first medically oriented interview. Before treatment, the patient will feel anxious and stressed in the dependent role as mentioned above.

Four aspects of medical care might be integrated into the physician–patient relationship in the sense of individually tailored medical concepts:

1. Coping strategies
2. Psychosocial environment
3. Pretherapeutic experiences
4. Organic medical interview

These domains should be evaluated during therapy several times, and thus lead to a strong confidential relationship between patient and physician.

After surgery for genital cancer, many women have to face the additional stressful situation of aggressive chemotherapy, in recent times even dosis-intensified with short intervals. A time of decision making and problem solving is coming up and requires a lot of patience, a seemingly difficult proposition under such a hectic environment. Emotional stress becomes a normal daily issue and yet medical treatment procedures do not incorporate information and intervention models into the patient's daily care management. Before any intervention models might be initiated, the patient's individual living situation should be precisely evaluated by the medical interviewer, according to the three-function approach (Cohen-Cole, 1991).

We would recommend to start the interview before treatment with questions concerning the family history as a "psychosocial screening." Moreover, information on family history and present life circumstances is not only a medical issue, but also includes social and emotional aspects because everyone has feelings regarding close relatives, especially children or parents in the life-threatening situation of cancer diagnosis.

Thus, women with gynecologic cancer most often feel very irritated in their familiar situation, and may be extremely affected in their social and emotional well-being. Because of this, the integration of close relatives and—most often—the patient's husband during the pretherapeutical consultation might be helpful, because the partner will have to face a different situation at home with respect to the cancer disease and the treatment.

Marital interaction is usually not associated with significant problems by the disease: patients with long-term relationships often indicate less problems than couples with young partnerships. However, communication problems may increase for couples who have had problems in this area before the diagnosis. Family structure profoundly influences patient care and outcome. For example, family stability is associated with compliance with medical treatment. Social stress and support are significant risk factors for most physical, as well as mental illnesses (Cohen, 1985; Reifman, 1995). However, this is not a regular problem for many cancer patients.

Former experiences with relatives who died of cancer may burden the patient's fantasy on the approaching chemotherapy.

Knowing if the patient is married or widowed is essential for further information on the availability of family members and other relatives during chemotherapy. Side effects such as nausea, vomiting, alopecia, stomatitits, leukopenia, cardiotoxicity, and destruction of healthy cells will diminish the patient's quality of life during daily life. Thus, based on the family's daily life cycle, stressors may increase.

Women with preschoolers may be overwhelmed, not only by the shock of diagnosis and the necessity of chemotherapy, but also by the lack of daily support (Dunkel-Schetter et al., 1992). Child care may become very difficult during chemotherapy, as well as caring for other family members who might also be ill at the same time. The pressure and fatigue of maternal stresses may be influential on the childrens' mental well-being.

Emotional and psychosocial support is necessary, not only for the patient herself, but also for the children and her spouse. Responsibilities for household work are compounded by the unavailability of qualified household help, or by the available help being unskilled in child care. Husbands generally confide more in wives than vice versa, and spouses feel less support from their husbands than husbands do (Barnett et al., 1987). Feelings of guilt may rise and the couple should decide about models of support for child care and domestic help before starting the therapeutical procedure with chemotherapy. Alopecia may be frightening to (pre-)schoolers and should also be anticipated with the whole family and teachers. Sometimes, additional counseling with a family physician or psychologist may be advisable to shift the priorities of family roles and habits.

Unrealistic expectations may arise because the public is bombarded daily by the media with information about miracle cures and new technologies to save their lives. Families expect to be healed when generally cures are not possible. Stress results not only for the family members, but also for the medical staff. Ongoing illness can be seen by the patient's family as a failure of the physician. Therefore, it is not uncommon for a family member to turn on the physician with verbal or legal hostility when the patient outcome is not ideal.

An additional situation of stress may develop if the patient is divorced, or just lost a family member. The "Holmes–Rahe Scale of Social Readjustment" (Holmes and Rahe, 1967) has proven to be an affective prognosticator of stress-related illnesses and may be helpful to indicate that chemotherapy may cause further stress and imbalance in the patient's coping mechanisms. An active–cognitive style of coping was positively associated and avoidance-coping was negatively associated with health status. Active–cognitive coping include trying to see the positive side and to step back from the situation and to be more objective.

Attempting to block stress-producing beliefs through positive self-statements and positive imagery is called stress inoculation (King et al., 1987). Both methods are difficult to carry out during the incidence of cancer and chemotherapy, but the resolution of the crisis is favorable if new coping skills are learned and confidence in the self and others is enhanced so that the individual will function at a higher level of adjustment.

(1) Stress-reducing techniques such as progressive relaxation before or during chemotherapy are valuable, positive coping mechanisms. Progressive relaxation is based on the assumption that stress and anxiety are directly related to muscle tension. If stress caused the tightness of muscles, the relaxation of these muscles should reduce stress (Mc Lean, 1982).

(2) Support groups have been mentioned many times in recommendation for stress reduction and a fair amount has been written about their benefits, particularly to women with breast cancer. Groups have been found to be of great benefit in increasing the capacity to deal with hostility and to help establish sustained friendships. As a result of group experience, there is usually an increased feeling of closeness and solidarity accompanied by decreased feelings of threat. Outside of the group experience, there may be a decrease in the use of negative coping mechanisms and an increase in the use of positive coping mechanisms.

(3) Time management is another important stress factor for women with and even without chemotherapy. A time analysis is necessary for listing personal stress factors. The first step in organizing time management is setting up of priorities. Help should be hired to improve health in daily life and to reduce stress although this costs money.

(4) Professional counseling may be helpful to learn sufficient coping techniques by supportive psychotherapy. Patients often fear obtaining professional psychological help, but they should not hesitate to do so in order to prevent impairment. In most cases, just a few hours of resource-oriented psychological aid may help to cope better with the stress of cancer diagnosis and therapeutic procedures.

(5) Social support can have an ameliorating affect on perceived stress and a positive impact on health. Several studies have found increased rates of psychological impairment, particularly depression, in people with poor supports (Blake and Vandiver, 1988).

(6) Involvement in religion is associated with decreased morbidity and better physical and mental health (Craigie et al., 1988). This effect may also occur because of an increased level of social support and commitment to a major life goal.

Thus, it is essential to integrate the family's living circumstances into the standard basis of medical history before starting chemotherapy. It is not only important to know about the family history, but also the family's present lifestyle. Problems of aggression against small children, for example, may decrease if the health care team is willing to talk about personal life circumstances, and to incorporate their knowledge to the decision-making stage of the therapeutical procedure.

The following specific questions for a detailed family history may be used to start the medical interview:

Are you married?
Do you have children and how old are they?
How would you describe your partnership?
Do you have social support and help in daily life?

Are there any current health problems in your family?
Do you have cancer in your family?
Do you have child care?
Do you have domestic help?

PSYCHOSOCIAL ENVIRONMENT

The standard database should uncover additional facts that might be essential for present or future complaints about physical and psychological problems. Aside from the family life cycle (partnership, age of children), the patients' professional work is also of importance. The tasks of daily living can no longer be maintained during chemotherapy, especially in cases of dosis-intensified protocols. Personal stress should be identified to decrease physical and psychological complaints during chemotherapy. After a personal evaluation, the patient should desire to change her stress level and develop a realistic daily plan to follow. Specific stress-reducing activities might be incorporated in daily life, such as relaxation techniques and social contacts with support groups as mentioned above.

According to an old maxim, the best treatment of disease is its prevention. In this case, carcinogenesis is the disease, and not cancer, thus prevention strategies of illness and side effects of chemotherapy should be incorporated in the patients' life style before starting treatment. The risk factors in 50–70% of all human cancers are preventable such as smoking, infections, chemical including hormonal risk factors, and diet. Smoking and diet, in particular, are negative stress prevention strategies and worsen the risk of cancer. The word chemoprevention indicates the necessity of early detection of life's risk factors. Thus, the period preceding chemotherapy is a good moment to talk about risk factors and stressors in the patient's daily life and to offer options for support including professional changes. The time of rehabilitation starts before any treatment will be performed.

Cognitive differences occur according to preknowledge. For example, a journalist with breast cancer may have a different set of expectations concerning the treatment phase compared to a nurse or a teacher. It is necessary to discuss the different attitudes and expectations about chemotherapy before treatment. Previous experiences concerning family members with cancer may also influence the patient's compliance during chemotherapy, in a positive or a negative way.

Some women are most willing to continue with their daily professional lives, and this may be possible depending on a patient's own attitude and her professional environment. However, sources of stress in daily life increase in times of severe illness; this might be an opportunity to positively change its potential impact.

PSYCHOLOGICAL PROBLEMS AFTER CHEMOTHERAPY

Physical complaints may improve but psychosocial worries, especially concerning the fear of recurrence and the impact upon the whole family system, may persist even for many years thereafter. Changes in the patient's sexual life and body image may affect

also the daily quality of her life depending on the therapeutical procedure being adopted (Hawighorst-Knapstein et al., 2001; Schönefuß et al., 2001).

Women who have undergone mutilating surgery for breast or genital cancer will suffer more frequently from problems regarding quality of life and the consequences of the mode of their medical treatment. Subsequently, they may not only require medical care, but also mental health care. Therefore, during the follow-up phase, physical and psychological symptoms should be addressed by the physician to encourage a healthy lifestyle for tumor prevention and to reduce the patient's distress.

Additional supportive therapy—including individual, group, and family therapy— may be helpful. During follow-up, the physician should be encouraged to integrate medical and psychosocial concerns, treating the patient in the context of the total life situation. Sexual problems and impaired self-image may decrease a female patient's sexual response, especially after mastectomy or any other radical genital surgery (Auchincloss, 1989; Andersen, 1994).

The fear of recurrence remains persistent and some patients will have a metastatic disease. Several treatment options will be offered to the patient. This will require time for discussion and medical interaction may become difficult. Psychological support and advice may be helpful especially for younger women with small children or elder women without partners. Therefore, family support should be encouraged by the physician as an interactive team approach.

Thus medical care and counseling are broad names for a wide variety of procedures for helping individuals achieve adjustment, such as giving advice, therapeutic discussions, administration and interpretation of tests, and vocational assistance. An emerging emphasis on preventive health reveals effective counseling skills due to the patient's satisfaction, to time-related and financial issues in order to improve the patient's quality of life and welfare during invasive cancer therapy.

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Quality of Life During Chemotherapy: Recent Results and Methodological Challenges of Conducting Quality-of-Life Studies with Gynecological Cancer Patients

Elfriede R. Greimel
University of Graz, Graz, Austria

Andrew D. Bottomley
European Organization for Research and Treatment of Cancer (EORTC) Data Center, Brussels, Belgium

INTRODUCTION

For a woman, the diagnosis of gynecological cancer is a truly overwhelming experience. Then, before she has had time to work through her feelings of shock and grief, she must begin treatment. The long-term and short-term side effects of treatment may also impact on a woman's self-worth and sexuality. Much recent work has shown that we must not only focus on survival times and disease-free survival issues, but also focus on women's quality of life. For many years, this has proven to be difficult, as researchers have argued about exactly what is meant by the term "quality of life," also sometimes referred to as Health-Related Quality of Life (HRQOL). A number of definitions have been proposed by various authors as to the exact nature of this concept, and it has taken some years for a consensus to emerge about exactly what HRQOL really means (see Table 1 for some definitions). We suggest that we now have a general consensus in the literature, and that it is a multidimensional construct and is regarded as covering the clinical subjective perceptions of positive and negative aspects of cancer patient domains, including physical, emotional, social, and cognitive functions, and, more importantly, disease symptoms and treatment (Leplege and Hunt, 1997). When we examine the medical literature, we see that only a couple of decades ago, few studies reported examining HRQOL, and very few of these were in the field of gynecological cancer. However, over recent years, a significant increase has been noted in studies reporting the assessment of HRQOL in cancer, in general, as well as in patients with gynecological cancer (Sanders et al., 1998).

Table 1 Common Definitions of Quality Of Life

Quality of life is not easy to define, but the literature yields a number of attempts to define this subjective term. Here are some of them.

Quality of life:

- Is the state of well-being that is a composite of two components: the ability to perform everyday activities that reflect physical, psychological, and social well-being; and patient satisfaction with levels of functioning and control of the disease (Cook Gotay et al., 1992).
- Is the subjective evaluation of the good and satisfactory character of life as a whole (van Knippenberg and de Haes, 1988).
- Is the gap between the patient's expectations and achievements. The smaller the gap is, the higher is the quality of life (Calman, 1984).
- Represents the functional effect of an illness and its consequent therapy upon the patient as perceived by the patient (Schipper and Clinch, 1988).
- Is an individual's overall satisfaction with life and general sense of personal well-being (Schumacher et al., 1991).
- Is patients' reception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns (WHOQOL Group, 1993).

The purpose of this chapter is to aid clinicians in understanding the value of quality of life, and to provide insights into key studies that have been undertaken with gynecological cancer patients. We aim to highlight where positive effects have been seen, and to suggest future ways forward in terms of better incorporating HRQOL into robust clinical studies.

TREATMENT-RELATED PROBLEMS IN GYNECOLOGICAL CANCER

Women with gynecological cancer are affected by the physical effects of the disease itself and by the side effects of various treatment modalities. Patients are faced with pelvic surgery, chemotherapy, and/or radiotherapy, which have serious short-term as well as long-term impacts on their HRQOL. The most common treatment regimens are combined therapeutic approaches, and we briefly note the use of each with more detailed analyses of chemotherapy treatments.

Surgery

Surgery is often used to diagnose and treat gynecological cancer. Abdominal hysterectomy with removal of the ovaries is a common procedure to treat ovarian, uterine, or cervical cancer. In advanced disease, radical pelvic surgery is often required due to lymph node involvement. Although patients with endometrial cancer surgery are mostly limited to abdominal hysterectomy, extensive radical surgery including lymphadenectomy is performed particularly for progressive ovarian cancer, as well as for recurrent or persistent cervical cancer (Corney et al., 1993). Such treatment can

provoke risks of pain, infection, and hemorrhage. In addition to the common psychological reactions associated with cancer surgery, a hysterectomy can affect a woman's psychological and emotional state.

Radiotherapy

Radiation therapy is performed either as primary treatment, or in combination with surgery or chemotherapy, depending on the site and stage of disease. It is commonly used to cure or control cervical cancer in its more advanced stages. Radiation causes irritation to the intestinal lining, which causes diarrhea. Common side effects of radiation therapy to the abdomen are fatigue, loss of appetite, nausea, vomiting, urinary discomfort, and diarrhea. Most patients suffer from acute symptoms at the end of treatment and up to 3 months later (Klee et al., 2000a,b). Emotional distress due to multiple inconveniences such as prolonged isolation, difficulty in eating, and limited personal hygiene is frequently reported (Karlsson and Andersen, 1986). Radiation also causes changes in the vagina such as atrophy of the vaginal mucosa, inadequate lubrication, vaginal irritation, or formation of vaginal adhesions. Vaginal stenosis, or an alteration in the depth of the vagina, may result in long-term sexual dysfunction and painful sexual intercourse (Weijmar Schultz et al., 1992a,b). Depending on the extent of disease and treatment, 20–90% of gynecological cancer patients experience significant sexual difficulties (Andersen and van der Does, 1994). Sexual dysfunction was found in the areas of desire, excitement, orgasm, and dyspareunia, which were still evident at 12 months posttreatment (Schover et al., 1989)

Chemotherapy

Chemotherapy can have a significant impact on a woman's HRQOL. However, the side effects largely depend on specific drugs and the dose. Cytostatic drugs provided for patients with advanced ovarian cancer cause severe toxicity (Neijt et al., 1998; Guidozzi, 1993). Nausea and vomiting, hair loss, peripheral neuropathy, and fatigue are the most prevalent side effects experienced by these patients. Chemotherapy-induced emesis has been reported as one of the most severe symptoms (Coates et al., 1983; Griffin et al., 1996) Acute emesis (within 24 hr postchemotherapy) has been experienced in 20–40%, and delayed emesis (after 24 hr) in 22–89% of patients undergoing chemotherapy. Despite effective antiemetic therapies, total control of nausea and vomiting remains insufficient (Aapro, 1996; Roila et al., 1996). Therefore, HRQOL in relation to health economics in antiemetic therapy has become a new area of research. Uyl-de Groot et al. (2000) provide an overview of studies concerning chemotherapy-induced emesis in cancer patients and offer recommendations of clinical trials for new antiemetic therapies.

HRQOL has also been studied as a prognostic factor in patients undergoing chemotherapy (Osoba et al., 1997; Carter et al., 1997; Patnaik et al., 1998). Pretreatment HRQOL measures can provide significant independent prognostic information (Dancey et al., 1997; Coates, 1997). Osoba et al. (1997) found in a sample of 832 cancer patients including gynecologic sites that prechemotherapy HRQOL scores had an impact on postchemotherapy nausea and vomiting. Patients undergoing first-line

chemotherapy showed that emesis occurred significantly more often when HRQOL was low before treatment. In patients with advanced ovarian cancer receiving second-line or third-line chemotherapy, HRQOL improvements were shown even in patients receiving more than six cycles (Carter et al., 1997). After two to three cycles, there was a sustained improvement in emotional and global health status and pain control. Although median survival was less than 1 year and despite substantial impairments in HRQOL, the majority of respondents felt their treatment had been worthwhile (Patnaik et al., 1998; Lutgendorf et al., 2000). Carter et al. (1997) found that the prescription of prolonged cytotoxic chemotherapy (up to 17 cycles) to patients with gynecologic cancer does not result in an overall deterioration of HRQOL. Patients who were able to attain a compete clinical response achieved higher scores in the subscales of social well-being, emotional well-being, relationship with the doctor, and overall quality of life, whereas their physical well-being scores were not statistically significant from patients with stable or progressive disease. Carlsson et al. (2000) studied the effects of different treatment modalities on long-term HRQOL in 235 women with gynecological cancer. Patients previously treated with chemotherapy had poorer role and cognitive functioning and more problems with fatigue, nausea, vomiting, dyspnea, constipation, and financial problems, compared with those not treated with chemotherapy. Patients who received intensive chemotherapy continuously or intermittently for at least 1 year reported decrements in physical, emotional, and functional well-being, with more fatigue and less vigor compared to early-stage patients (Lutgendorf et al., 2000).

Recently, research has been undertaken on fatigue. This symptom is an extremely common and distressing symptom during and following chemotherapy. Causes of fatigue include the impact of the underlying disease and treatment-related side effects. Although fatigue clearly remains an important issue, more research on the use of Epo in gynecological patients is needed. In a prospective multicenter study of 2289 subjects including 297 gynecologic cancer patients, the effect of Epoetin alfa on HRQOL was studied. The HRQOL of patients, who were sensitive to the erythropoietic effects of Epoetin alfa, improved significantly independent of disease response to treatment (Demetri et al., 1998). In this large study, HRQOL was used as the primary outcome.

However, it is important to note that chemotherapy-related toxicities are perceived differently by patients and oncologists. In a study, 15 patients with advanced-stage ovarian cancer and 15 gynecologic oncologists were asked to assess neurotoxicity and nephrotoxicity in a time tradeoff methodology. Women treated with platinum chemotherapy were willing to tolerate increasing levels of toxicity to stabilize their disease, whereas physicians tended to expect more clinical benefits in relation to toxicity levels (Calhoun et al., 1998).

KEY STUDIES OF HRQOL

There is evidence that the effects of treatment can influence the HRQOL of patients with gynecological cancer. Researchers have a clear role here in helping to understand the effects of treatment on patients' HRQOL and indeed reduce any negative effects. In line with this, a number of new studies have recently been activated to examine in detail

the consequences and impact of treatment and disease in these patients. These ongoing studies are briefly discussed below.

EORTC—CHEMOTHERAPY TRIALS WITH HRQOL OUTCOMES

Randomized Trial of Adriamycin (A) and Cisplatin (P) Chemotherapy Vs. Paclitaxel (T), Adriamycin (P), and Cisplatin (P) in Advanced/Metastatic Endometrial Cancer (EORTC Trial 55984)

In this study, HRQOL is a secondary endpoint. The main objective of HRQOL assessment within this clinical trial is to determine the impact of paclitaxel additionally to an adriamycin and cisplatin regimen vs. adriamycin and cisplatin chemotherapy on overall health/quality of life in advanced or recurrent endometrial cancer patients. A secondary objective is to evaluate the effect of paclitaxel combined with adriamycin and cisplatin on various symptoms and functioning scales as treatment-related side effects may have a (temporary) negative influence on the health-related domains of the quality of life of these patients. The aim of the HRQOL evaluation in this study is to obtain a better understanding of the effects of paclitaxel combined with adriamycin and cisplatin in terms of frequency and degree of treatment-related side effects from the patients' perspective.

Randomized Phase III Study of Neoadjuvant Chemotherapy Followed by Surgery Vs. Concomitant Radiotherapy and Chemotherapy in FIGO Stage IIB Cervical Cancer (EORTC Trial 55994)

This study focuses on patients with advanced ovarian carcinoma comparing two different therapeutic strategies. A major objective of this study is to assess HRQOL benefits in relation to different therapeutic strategies (arm A vs. arm B) and to determine whether the various HRQOL domains (physical, psychological, and social symptoms) are enhanced by one treatment arm.

Randomized Phase III Study Comparing Gemcitabine Plus Carboplatin Vs. Carboplatin Monotherapy in Patients with Advanced Epithelial Ovarian Carcinoma Who Failed First-Line Platinum-Based Therapy Intergroup AGO-EORTC-NCIC-CTG Trial (EORTC Trial 55005)

This study aims to take a broad look at both treatment approaches on both short-term treatment effects and longer-term HRQOL issues. Presently, this study is not active, but HRQOL will serve as a secondary endpoint. If gemcitabine/carboplatin proves to be more effective in second-line therapy than carboplatin alone, this combination may become the standard of care in the studied patient population.

Randomized Phase III Study for the Treatment of Recurrent Epithelial Ovarian Cancer: Chemotherapy Alone Vs. Chemotherapy Followed by Secondary Cytoreductive Surgery in Patients with a Treatment-Free Interval of More Than 12 Months (EORTC Trial 55963, LAROCSON)

In this study, HRQOL is a secondary endpoint and patients are assessed with the EORTC QLQ-C30. The general purpose of the study is to evaluate the benefits and risks of secondary cytoreductive surgery in patients with late-onset recurrent epithelial

ovarian cancer. The concept of secondary cytoreductive surgery followed by chemotherapy will be addressed. Presently, this study is still recruiting patients.

Randomized Trial of Paclitaxel/Epirubicin/Carboplatin Combination (TEC) Vs. Paclitaxel/Carboplatin (TC) in the Treatment of Women with Advanced Ovarian Cancer (EORTC Trial 55981)

This is an interesting intergroup study led by the EORTC in collaboration with the Nordic Society of Gynecological Oncology and the NCI-C. The primary endpoint of this trial is survival, with patients randomized between TEC and TC. Over 800 patients are expected to be recruited, and the possibility is that the expected difference in survival between the two treatment arms will be relatively small. HRQOL is a key secondary endpoint in this trial.

Phase II Clinical Trial on Taxol as Single Agent in Locally Advanced and/or Metastatic or Recurrent Vulva Cancer Not Amenable for Surgery and/or Radiotherapy (EORTC Trial 55985)

The use of Taxol can have an influence on cancer patients' HRQOL. In this study, we aim to examine the short-term and long-term effects of treatment on patients' HRQOL using the EORTC QLQ-C30. HRQOL is a secondary endpoint in this planned trial.

PRACTICAL CHALLENGES IN RESEARCHING ON HRQOL IN GYNECOLOGICAL CANCER

What we have seen from the above studies is that HRQOL is now a key factor in understanding the value of many treatments for gynecological cancer patients. However, it is clear that there are still a number of challenges that face researchers when considering HRQOL as an endpoint in gynecological clinical trials. We discuss some of these issues below.

DESIGNING ROBUST STUDIES WITH HRQOL

Although many of the studies reported over the last decade were well designed, this has not always been the case and it is important that robust quality-of-life studies are developed on a sound methodological basis. Given that HRQOL is a new field, it is critical that the same standards applied to designing such studies are applied to designing clinical trials in general. We select a few key areas that are important to researchers in gynecological cancer and comment below.

WHEN SHOULD HRQOL BE ASSESSED?

The key to assessing HRQOL is measuring this aspect when differences in HRQOL between treatment arms can be expected. Generally, one should have a good degree of confidence that differences between treatments can be detected. There are, of course, some key circumstances when HRQOL is so critical that it is a primary endpoint. For example, we expect a difference in disease-free survival or cure, but could this be at the expense of HRQOL in terms of treatment toxicity?

MEASUREMENT CHALLENGES—WHICH TOOLS TO USE WITH GYNECOLOGICAL PATIENTS?

One key issue frequently raised concerns the appropriateness of the measures used. In many cases, if well-validated instruments have not been used in the correct manner, there is already an issue of concern regarding appropriate interpretation (Green, 1997). If the HRQOL instrument is not well known, it needs to be examined in detail to ensure that its psychometric properties of reliability and validity are suitable before any useful interpretation of the results are made. Kong and Gandhi (1997) note that, of 265 articles reviewed reporting to assess HRQOL in clinical trials, only 23% provided reliability data and only 21% provided validity data. Given the multidimensional nature of HRQOL data, it is important that researchers provide information on all measures used including the domain investigated, even if not significant (Lydick and Epstein, 1993). In the field of gynecological cancer, there are only a limited number of robust tools that can pick up the key issues facing this patient population. For patients with gynecological cancer, the issues are sexuality, pain, and fertility. For example, in a study of 107 gynecological cancer patients with a partner, only 37% of those over 55 years were sexually active (Thranov and Klee, 1994).

One of the most frequently used tools is the EORTC QLQ-C30, which has been shown to be robust and valid in many publications of gynecological cancer patients (e.g., Zhao and Khanda, 2000; Osoba et al., 1997).However, this tool lacks some dimensions specific to gynecological cancer patients. For example, Bye et al. (1995) conducted a randomized clinical trial to evaluate the effect of a diet low in fat and lactose in preventing acute radiation-induced diarrhea in 143 women with gynecological malignancies. Although the EORTC QLQ-C30 proved useful, it was limited when measuring specific phenomena such as diarrhea, as it lacked sensitivity. However, with that said, a recent review by Montazeri et al. (1996) did find that the EORTC QLQ-C30 was one of the most widely used and valuable measures for patients with ovarian cancer. Fortunately, an additional module to supplement the EORTC QLQ-C30 has been produced for patients with ovarian cancer. The ovarian cancer module (EORTC QLQ-OV28) has been developed in a multicultural setting within the EORTC Quality of Life Group. This tool has undergone international field testing and has proven to be a valuable instrument. In conjunction with the EORTC QLQ-C30, all major dimensions of HRQOL as well as specific symptoms related to ovarian cancer are addressed. The module incorporates 28 items specifically relevant to symptoms of local and advanced ovarian cancer, and to effects of surgery and chemotherapy. The following subscales are included: abdominal/gastrointestinal symptoms, body image, peripheral neuropathy, other chemotherapy side effects, hormonal/menopausal symptoms, sexuality, and attitude toward disease and treatment. All items are scored using a four-point Likert scale compatible with the EORTC QLQ-C30. According to pretesting, the module meets the standards for reliability (Cull et al., 2001). The evidence to date shows that the core questionnaire and the 28-item ovarian module can be completed in less than 20 min and are therefore highly practical and acceptable to patients. The application of the generic core questionnaire and the disease-specific module can provide more detailed information relevant to ovarian cancer to evaluate their quality of life. The Quality of Life Group is planning to develop further modules for gynecological cancer sites (e.g., cervical cancer module). Another instrument for assessing HRQOL in gynecological oncology is the FACT scales developed in the United States (Cella

and Bonomi, 1996). There are several available disease-specific and treatment-specific tools that can also be used in chemotherapy trials.

COLLECTING DATA—A CHALLENGE

One of the challenges of collecting HRQOL data is that it is patient-based and not collectable retrospectively. Several studies have repeatedly shown that when information is collected from doctors, they underestimate the treatment effect. For example, Calhoun et al. (1998) found that among ovarian cancer patients undergoing cisplatin treatment, they reported far greater problems (more toxic, greater impact on QOL) when compared with the findings of their treating gynecologic oncologists. Although it is possible to go back after a patient has been treated and review medical data such as blood count, etc., it is impossible with HRQOL, as the patients' experiences are dynamic and changing over time. Failure to collect HRQOL at the appropriate time can significantly hinder what we understand of women's experience of treatments and interventions. In general, compliance is a globally recognized problem in HRQOL research in oncology and can significantly hinder interpretation of results. Thus, all strategies to improve compliance should be investigated by clinicians and researchers. A number of solutions have been proposed, such as increased nurse-based interventions and support, dedicated data managers to collect data, and even novel electronic methods that are now becoming available to overcome some of the problems experienced. Training programs for both nurses and clinicians can also help improve compliance, as when the nurse and doctor recognize the value of HRQOL, there seems to be an increase in compliance by patients. Further information can be seen in Young et al. (1999).

CLINICAL SIGNIFICANCE

Experience in medicine has led to an understanding that certain clinical events are related to health outcomes. A classical example, often cited in the literature, concerns a blood pressure reading of 110/60 mm Hg being normal for a healthy, young adult but dangerously low for a trauma victim. A change of 2 or 3 mm Hg in blood pressure probably has little or no clinical significance, but a 10-mm Hg decrease could indicate shock or hypertension, depending on the situation. However, although this is a well-established fact, this level of clarity in the interpretation of HRQOL scores has not yet been achieved (Green, 1997). This is particularly true for gynecological cancer patients, where there is no accepted gold standard HRQOL measure. Questions must be asked: What do scores of 20 or 40 on a sexuality scale mean clinically? What degree of change is needed on a pain scale for a clinically meaningful change for women with gynecological cancer? If an ovarian cancer patient has a 5% loss on a sexual activity scale, is this clinically relevant?

One of the most common ways to deal with this issue is to anchor the changes seen in disease-specific questions to a global rating question—one that asks about overall HRQOL changes such as, "In general, how would you rate your quality of life?" Then, researchers would look at changes in answers to such a global HRQOL question over time and compare this with changes seen on the disease-specific ques-

tionnaire (Koller et al., 1999) In effect, the changes in the disease-specific measures are thus anchored to report changes in overall health status. Also, it is possible to use time as an anchor, or, for that matter, changes in therapy. Changes in therapy or time can help in interpreting HRQOL scores. However, although these anchor-based interpretations can help clinicians understand a little more about the meaning of HRQOL, it is important to recognize that they only reflect changes in HRQOL—that they do not reflect score distribution. Recent work by Klee et al. (1999) have tried to examine clinical relevance with data from 118 advanced-stage cervical cancer patients. This proved to represent a challenge, as factors such as variability in data and problems of nonrandom dropout make selecting a clinically relevant endpoint difficult. Clearly, more work in this field is urgently needed to help design and interpret results from studies with gynecological cancer patients.

SUMMARY

HRQOL data can be invaluable for understanding the experiences of women who undergo treatments to help them cope with their gynecological cancer. We have seen that there are a number of interesting studies which reflect that HRQOL is important in this patient population, and we expect that in future years, this will become a standard endpoint in many clinical trials for patients with gynecological cancer. However, there are a number of key issues that clinicians and researchers will need to address in the future in terms of employing better and more robust study designs. Hopefully, in the coming decade, results will be based on even stronger methodologies and we will see the importance of HRQOL set firmly in the minds of treating clinicians.

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Ovarian Cancer

Roberto Angioli and Pierluigi Benedetti Panici
University of Rome Campus Bio-Medico, Rome, Italy

Manuel Penalver
University of Miami School of Medicine, Miami, Florida, U.S.A.

Claes Tropé
Norwegian Radium Hospital, Oslo, Norway

Sergio Pecorelli
University of Brescia, Brescia, Italy

INTRODUCTION

Epidemiology

Epithelial ovarian carcinoma represents the third most frequent cancer of the female genital tract with an estimated 191,000 newly diagnosed cases per year worldwide (1). The incidence is highest in the United States, Europe, and Israel, and is lowest in Japan and developing countries (2). In high-incidence areas, the lifetime risk of developing the disease is 1–2%.

Survival by FIGO stage is shown in Fig. 1.

Epithelial ovarian cancer is predominantly a disease of perimenopausal and postmenopausal women, with 80–90% of cases occurring after the age of 40 years. The median age at the time of diagnosis is 58 years (3). Hereditary ovarian cancers generally occur about 10 years earlier (4).

The disease occurs sporadically in over 90% of the cases. An estimated 10% of all epithelial ovarian carcinomas is familial (5). Nearly 75% of the cases of hereditary ovarian cancers is represented by the so-called breast and ovarian cancer syndrome, with germline mutations of the *BRCA1* and *BRCA2* genes. Women who carry a *BRCA1* or *BRCA2* mutation have a 60% (6) and 27% lifetime risk of developing ovarian cancer, respectively (7).

Less frequent familial ovarian cancer is associated with hereditary nonpolyposis colon cancer, or Lynch II cancer syndrome (8).

The most important known risk factor is a family history of ovarian cancer. Genetic counseling and discussion of various preventive strategies such as screening, oral contraceptives, and prophylactic oophorectomy are recommended in high-risk women. A history of infertility, low parity, and a long time from menarche to

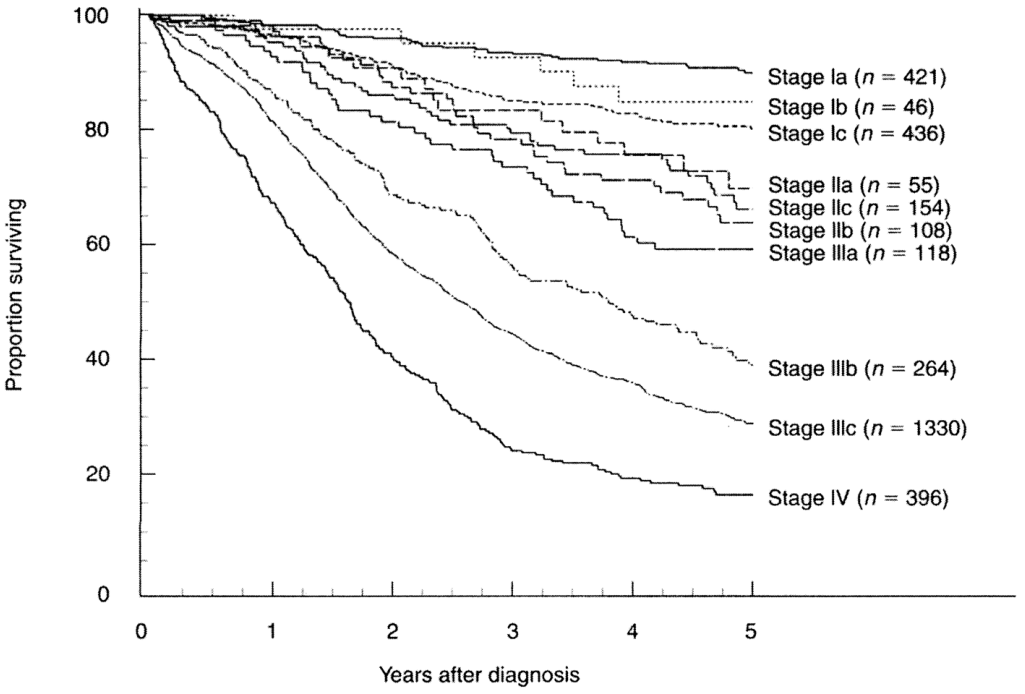

Figure 1 Carcinoma of the ovary: survival by FIGO stage, obviously malignant. (From Heintz APM, et al. Carcinoma of the ovary. J Epidemiol Biostat 2001; 6(1):119.)

menopause are reported to be associated with an increased lifetime risk of ovarian cancer (9–11). These observations have led to the concept of "incessant ovulation" as being a factor in the genesis of epithelial ovarian malignancies.

There is a significant protective association between oral contraceptive use and ovarian cancer. The protective effect appears to increase with the duration of the oral contraceptive use: a review of the literature demonstrated a 10–12% decrease in risk associated with use for 1 year, and an approximate 50% decrease after 5 years of use (12).

Upon diagnosis, 62% of the cases of epithelial ovarian cancers presents as advanced disease (FIGO stages III and IV) (13) because most women with the disease do not experience any symptoms for a long time. The most common presenting symptom is abdominal discomfort or pain with or without abdominal distention due to the presence of ascites or large abdominal masses. Symptoms of nausea, dyspepsia, constipation, anorexia, and food intolerance are common but, unfortunately, non-specific. These patients must undergo complete physical examination; greater attention should be directed toward bimanual pelvic examination to detect adnexal masses. Ultrasonography is frequently used to aid in the evaluation of adnexal pelvic masses. The preoperative evaluation of patients with suspected ovarian carcinoma should include a serum Ca125 level.

Ca125 has proven to be the most useful, currently available marker for epithelial ovarian cancer, primarily because of its utility in monitoring results of therapy (14). The value of screening for ovarian cancer is uncertain. Even if a significant reduction in

mortality could be demonstrated with screening programs that use ultrasound and serum markers, this approach may not be practical because of the high cost associated with screening for a low-incidence disease. On the other hand, screening might be more practical in *BRCA1* and *BRCA2* carriers in whom the incidence of ovarian cancer is much higher. Some authors have confirmed that the combination of CA125 measurement with ultrasound and pelvic examination achieves acceptable specificity and offers the highest hope for a specific and sensitive method for early detection. The positive predictive value of this multimodal screening strategy is 21% (15). Nevertheless, cost–benefit is still an issue. Recently, Petricoin et al. (16) proposed the use of proteomic patterns in serum to identify ovarian cancer patients. This method yielded a sensitivity of 100%, a specificity of 95%, and a positive predictive value of 94%. These findings justify a prospective population-based assessment of proteomic pattern technology as a screening tool for all stages of ovarian cancer in high-risk populations and the general population.

Ovarian malignant germ cells tumors account for only 3% of all ovarian malignancies, and they are the most common ovarian malignancies in young women with an average age at diagnosis of 20 years (17). The two main categories of ovarian germ cell tumors include dysgerminomas and nondysgerminomatous tumors. Dysgerminomas are composed of undifferentiated germ cells and account for 40% of germ cell malignancies. Nondysgerminomatous cancers are composed of abnormally differentiated germ cells. This category includes immature teratoma, endodermal sinus tumor, embryonal tumor, polyembryoma, and choriocarcinoma. Signs and symptoms in these patients are consistent: abdominal pain associated with a palpable pelvic–abdominal mass is often reported. Many germ cell tumors possess the unique property of producing biological markers that can be detected in the serum [human chorionic gonadotropin (HCG), α-fetoproteins (AFP)] (Table 1). Serial measurements of these serum markers may help in the diagnosis and, most importantly, monitoring of the response to treatment of these tumors.

Ovarian sex cord stromal tumors account for 7% of all malignant ovarian neoplasms and develop from gonadal nongerm cell components such as granulosa, Sertoli, or Leydig cells. The clinical presentation of patients with ovarian sex cord stromal tumors most often is associated with excessive production of steroid hormones (menstrual irregularities, virilization); abdominal swelling and pain are also frequent. Most of these tumors are benign and almost all are localized unilaterally.

The majority of ovarian malignant germ cells and sex cord stromal tumors are associated with a favorable prognosis, and the last two decades have seen great

Table 1 Ovarian Tumors and Tumoral Markers

Marker	Epithelial ovarian cancer	Germ cells ovarian tumors	Stromal ovarian tumors
AFP	–	+	–
HCG	–	+	–
Inhibina	–	–	+
Lactate dehydrogenase	–	+	–
CA125	+	–	–

improvements in their management. The results are an excellent example of the value of cooperation of different disciplines (surgery, radiotherapy, and chemotherapy). Moreover, treatment of these pathological entities has to be individualized according to patient age, stage of tumor, and degree of differentiation, as detailed in the following chapter.

Ovarian Cancer Carcinogenesis

Delineation of the molecular pathways involved in the evolution of ovarian serous carcinoma would have an important impact on our understanding of its pathogenesis, thereby providing a rational basis for the development of new diagnostic tests and therapeutic strategies.

Despite the efforts aimed at elucidating the molecular mechanisms of ovarian serous carcinoma, its pathogenesis is still poorly understood mainly because of the lack of an established model for its development. Until now, the most widely held view is that ovarian serous carcinoma consists of a relatively homogeneous group of neoplasms that arise directly from transformation of the ovarian surface epithelium or inclusion cysts through a de novo process because definitive precursor lesions have not been detected.

Recent clinical and histopathological studies of a large series of serous neoplasms (18–20) have led to the recognition of a variant of serous carcinoma designated as "micropapillary serous carcinoma" (MPSC) with distinctive histopathological and clinical features. Most MPSCs are noninvasive and are frequently associated with serous borderline tumors (SBTs), also referred to as atypical proliferative serous tumors, a benign form of serous neoplasms. Histological transitions from SBTs to noninvasive MPSCs can be observed, as well as areas of infiltrative growth (stromal invasion) immediately adjacent to the MPSC component of these neoplasms.

The morphology of the invasive component resembles that of noninvasive MPSCs and can also be seen in frankly invasive low-grade serous carcinomas. Such tumors were designated as invasive MPSCs (18). These neoplasms appear to represent a morphological spectrum ranging from a benign proliferative tumor to a low-grade invasive carcinoma (invasive MPSC). Preliminary clinical data indicate that MPSCs (both noninvasive and invasive) generally behave in an indolent manner. The frequency of MPSCs in the general population is not known, but data from a population-based study of noninvasive MPSCs suggest that the prevalence is around 20–25% of all ovarian serous tumors.

In contrast to invasive MPSCs, conventional serous carcinomas present as high-grade, aggressive neoplasms that evolve rapidly.

By stratifying ovarian serous carcinomas into two histopathologically distinct groups—a low-grade carcinoma designated as invasive micropapillary serous carcinoma with its putative precursors (SBT and noninvasive MPSC) and a high-grade carcinoma (conventional serous carcinoma)—it was possible to demonstrate that these neoplasms displayed very different and characteristic molecular genetic alterations.

First, *K-ras* mutations were found in nearly half of invasive MPSCs and their putative precursors, but not in conventional serous carcinoma, suggesting that aberrations in the *K-ras* signaling pathway may play an important role in the development of invasive MPSCs.

Second, it was found that the allelic imbalance index gradually increased from SBTs to noninvasive, and then to invasive MPSCs. In contrast, all conventional serous carcinomas, including the earliest (tumors less than 0.8 cm confined to one ovary), showed high levels of allelic imbalance.

Clear-cut morphologically recognizable precursor lesions of conventional serous carcinomas are rarely observed. Conventional serous carcinomas show massive, clonal allelic imbalance among differential chromosomal arms. This finding, together with morphological observations that early conventional serous carcinoma are high-grade, underlies the notion that they arise de novo.

It must be acknowledged, however, that the absence of morphologically established intermediate steps may be due to a higher rate of cellular proliferation resulting in rapid evolution to conventional serous carcinoma, obscuring morphological intermediate stages.

This is supported by a substantially higher Ki-67 nuclear labeling (proliferative) index in early conventional serous carcinoma as compared with SBTs, noninvasive MPSCs, and invasive MPSCs (21).

Thus, the rapid progression of conventional serous carcinoma suggests that a profound loss of cell cycle regulation occurs very early in its development. This interpretation is supported by the finding of *p53* mutations in small conventional serous carcinoma confined to the ovary and in adjacent "dysplastic" epithelium; in contrast, *p53* mutations have as yet not been detected in MPSCs (19).

In summary also, the molecular findings support the stratification of ovarian serous carcinomas into two distinct groups with two different pathways of tumorigenesis.

In one pathway, a low-grade carcinoma (invasive MPSC) develops in a stepwise fashion from an SBT (atypical proliferative serous tumor) and then a noninvasive MPSC.

This tumor and its precursors exhibit frequent *K-ras* mutations. As the precursors evolve into invasive MPSCs, the gradually acquire more genetic abnormalities.

In the second pathway, a high-grade carcinoma (conventional serous carcinoma) develops by transformation from the ovarian surface epithelium or inclusion cysts without morphologically recognizable intermediate stages. These tumors, even early in their development, demonstrate wild-type *K-ras* and frequent allelic imbalance (22).

Future studies focusing on gene expression profiles and early molecular genetic alterations of these two types of serous carcinomas will be necessary to better elucidate the molecular pathogenesis of ovarian serous carcinoma.

Patterns of Spread

Patients affected by epithelial ovarian cancer have metastases most commonly in the peritoneal cavity and, occasionally, also in extraperitoneal locations. The risk for early peritoneal seeding depends on the stage as well as biological factors not included in the current FIGO 1988 staging system (23).

It has been postulated that neoplasms originating in the ovary have two major routes of spread: the first is migration of exfoliated cells within the normal circulation of peritoneal fluid, reaching the domes of the diaphragm and omentum through the paracolic gutters, followed by local stromal activation and then invasion; the other route is by lymphatic permeation (24,25). Six to eight lymphatic channels originate

from the ovarian surface and drain by three main routes: along the infundibulopelvic ligament to the supracaval and intercavoaortic nodes, along the broad ligament to the interiliac and upper gluteal nodes, and by the round ligament to the external iliac and inguinal nodes. Lymphatic involvement, common in advanced-stage patients, can be explained, in part, by local invasive activity and local blood and lymph vessel angiogenesis, but may be considered a step earlier in metastatic activity, prior to parenchymal involvement. Furthermore, there are no data indicating that the presence of lymph node disease is a marker for, or a precursor of, synchronous or late-presenting parenchymal disease. There is evidence of a third way (although rare, 1.9%) of hematogenous circulation of epithelial ovarian, as has been shown in blood and bone marrow studies (26). Controversy exists as to the prognostic importance of these findings as at least one large study has not documented a worse outcome in case of the presence of ovarian cancer cells in the bone marrow or blood.

Surgical Staging

Staging ovarian cancer is based on the findings at the initial operation and on histological examination procedures (Table 2).

For all patients, a comprehensive surgical staging should be performed (total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal biopsies, peritoneal washing cytology, and lymph node evaluation in accordance with FIGO guidelines) (27).

Table 2 Carcinoma of the Ovary (FIGO Staging)

Stage	Definition
I	Tumor limited to the ovaries
IA	Tumor limited to one ovary; capsule intact; no tumor on ovarian surface; no malignant cells in ascites or peritoneal washings
IB	Tumor limited to both ovaries; capsule intact; no tumor on ovarian surface; no malignant cells in ascites or peritoneal washings
IC	Tumor limited to one or both ovaries with any of the following: capsule ruptured, tumor on ovarian surface, malignant cells in ascites or peritoneal washings.
II	Tumor involves one or both ovaries with pelvic extension
IIA	Extension and/or implants on uterus and/or tubes; no malignant cells in ascites or peritoneal washings
IIB	Extension to other pelvic tissues; no malignant cells in ascites or peritoneal washings
IIC	Pelvic extension with malignant cells in ascites or peritoneal washings.
III	Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph node metastasis
IIIA	Microscopical peritoneal metastasis beyond pelvis
IIIB	Macroscopical peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension
IIIC	Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis.
IV	Distant metastasis (excluding peritoneal metastasis).

Problems of "understaging," especially in apparent early-stage diseases, are well documented (28–31). In an often-cited report, Young et al. (32) showed that staging was often carelessly performed. They performed prospective systematic restaging of 100 patients referred as stage I to stage IIb patients within 4 weeks. Only 25% of the patients were found to have an initial surgical incision large enough for complete examination of the abdomen. Of the 68 patients restaged by laparotomy, 61 were referred by their physician as free of residual cancer, but at the time of restaging laparotomy, 22 of these patients were upstaged. Out of a total of 100 patients, 31 were upstaged and 23 of these had stage III disease. The most common sites of occult cancer are within peritoneal fluid or washings, the pelvic peritoneum or omentum, or in subdiaphragmatic areas or nodes (33). Rosenoff et al. (30) reported that only 54% of 291 patients with ovarian cancer received proper staging procedures. The completeness of staging varied depending on the type of specialist performing the procedure: gynecological oncologists, 97%; obstetricians–gynecologists, 53%; and general surgeons, 35%. Trimbos et al. (33) showed in a multicenter study from Holland that proper staging was done only in 53% of the patients and, in another study, Munõs et al. (34) found that only 15% of women with presumptive stage I and stage II ovarian cancer received recommended staging and treatment.

The most frequently omitted step in the staging procedures in these studies was the sampling of retroperitoneal lymph nodes. Their conclusion was that general gynecologists should have better oncological surgery education, or patients should be referred to a center for gynecological cancer. Staging should be done through a vertical midline incision to allow palpation and biopsy of all peritoneal surfaces (35,36). It does not seem to be necessary to sample the subdiaphragmatic area routinely (37). In patients with stage II disease and peritoneal extension, total excision of the pelvic peritoneum is recommended (35,37).

The emphasis on surgical staging has increased the interest on retroperitoneal nodal involvement associated with epithelial ovarian cancer (38). Data from the literature show that when cancer is apparently confined to the ovaries, positive nodes can be found in 4–25% of the cases (25,39–49), and if only data from systematic pelvic and para-aortic lymphadenectomy are considered, the node positivity rate ranges between 13% and 25%, with a total percentage of 16% (42–49).

When systematic lymphadenectomy (median number of nodes removed, >20) was performed, the median number of positive nodes was two (range 1–46) and, in more than two-thirds of the cases, metastases occurred in both the pelvic and para-aortic regions. This means that a considerable number of patients with apparent stage I and stage II disease would be upstaged to stage IIIc as a result of lymphadenectomy. However, the 5-year survival (60%) for stage IIIc with only retroperitoneal spread is clearly higher than for stage IIIc with intra-abdominal dissemination, which varies between 20% and 30% (20).

As to advanced-stage ovarian cancer, the incidence of lymph node metastases reported in the literature varies between 3% and 40% for pelvic nodes and between 2% and 49% for aortic nodes in different series (40,41,44,45). Some studies have shown that the incidence of nodal disease is highest in grade III or (33%) serous (27%) and clear cell (14.5%) tumors, whereas the chance of nodal disease in grade I and mucinous tumors is extremely small (25).

However, only few reports have specifically addressed the prognostic significance of lymph node metastases in ovarian cancer. A therapeutic benefit of lympha-

denectomy was suggested by some reports where lymphadenectomy was an integral part of the surgical treatment for ovarian cancer (42). In particular, Burghardt et al. (42) retrospectively analyzed the 5-year actuarial survival rate of patients affected by stage III ovarian cancer, optimally debulked, with or without pelvic lymphadenectomy: the observed survival rate was 53% and 13%, respectively. Similar results were later reported by other studies (50). These data suggest that lymphadenectomy may improve the survival of patients with advanced ovarian cancer optimally cytoreduced, with limitations of nonrandomized studies. To confirm these observations, an international randomized study comparing systematic lymphadenectomy vs. lymphadenectomy of bulky nodes only in patients affected by advanced ovarian cancer is presently ongoing.

Concerning ovarian germ cell and sex cord stromal malignancies, a proper surgical staging is important for both diagnosis and therapy. However, germ cell tumors are generally much more chemosensitive than are epithelial tumors; this may permit a more conservative surgery in well-selected cases of patients.

Treatment

Surgery is the cornerstone of the treatment of ovarian cancer. Women affected by early-stage disease in which there is the desire to preserve fertility may be treated with a conservative approach; in the case of aggressive histotype such as clear cell, mixed, or undifferentiated carcinomas, the question of conservative surgery should not be considered. However, some authors have suggested the possibility of a conservative approach in patients with unfavorable prognostic factors (51–53). In advanced ovarian cancer (FIGO stages IIC, III, and IV), cytoreductive surgery is often a technical challenge. It has been well known, since the report of Griffiths (54), that the survival (progression-free and overall) outcome of these patients is directly related to the amount of residual disease left after primary cytoreductive surgery. Many studies have subsequently confirmed these data (55,56).

Nowadays, it is well accepted that the optimal residual disease left after primary debulking should not be macroscopical or minimal residual disease, whenever possible, before the start of first-line chemotherapy. In the last decade, clinicians have paid special attention to "interval debulking surgery" (IDS), defined as a surgical procedure with debulking intent performed midway of a complete chemotherapy treatment. IDS should be considered a good opportunity in patients with suboptimal primary surgery, even if it cannot replace primary debulking, which still remains the gold standard in the management of advanced epithelial ovarian cancer patients. A European Organization for Research and Treatment of Cancer (EORTC) trial comparing neoadjuvant chemotherapy–IDS–adjuvant chemotherapy vs. primary cytoreductive surgery plus adjuvant chemotherapy is presently ongoing to define the role of IDS in the management of advanced epithelial ovarian cancer (EORTC no. 55971).

Concerning ovarian germ cell and sex cord stromal neoplasms, the combination of surgery and chemotherapy makes the outcome of these patients excellent: in most of the cases, the preservation of ovarian function and fertility, when desired, is feasible through a conservative surgical procedure (cystectomy or unilateral adnexectomy) (57). Anyway, surgery should always include a staging procedure with sampling of pelvic and para-aortic lymph nodes, omentectomy, washings, and exploration of all peritoneal surfaces. The combination of bleomycin, etoposide, and cisplatin is the

standard regimen recommended for most high-risk germ cell and sex cord stromal tumors (58).

Chemotherapy Treatment

Among solid tumors, ovarian cancer is considered a highly chemosensitive malignancy. The following chapters will shed light on the indications, timing, and different drugs used for optimal medical management of this disease.

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Management of Early Epithelial Ovarian Cancer

Claes Tropé, Tobjørn Iversen, and Mark Baekelandt
Norwegian Radium Hospital, Oslo, Norway

INTRODUCTION

Adjuvant chemotherapy most often involves the systemic administration of chemotherapeutic agents after the removal of the primary tumor, without evidence of residual tumor remains. This approach is based on data from 1950 to 1960, which noted an inverse relationship between response to chemotherapy and number of tumor cells. The possibility of improved survival in patients with minimal disease after surgery, coupled with a poorer response in advanced disease, provided a good rationale for the use of adjuvant chemotherapy. Early ovarian cancer signifies localized disease and is equivalent to FIGO stages IA, IB, and IC (sometimes also including stage IIA). A truly localized disease is curable by surgery. Two problems are encountered with regard to adjuvant therapy in early ovarian cancer (1) The first is to find prognostic factors that can predict the presence of micrometastasis (the disease is no longer localized), and the second is to find adjuvant therapies that are both effective in controlling micrometastatic disease and with tolerable short-term and long-term side effects. Patients with a significant statistical risk for having persistent disease will be treated with adjuvant therapy (Table 1). This means that only a fraction of the patient population treated actually has micrometastasic disease and could potentially benefit from the treatment. Therefore, the role of adjuvant treatment in patients with early epithelial ovarian cancer still is controversial. There is, however, little argument about the role of platinum-based chemotherapy after primary surgery in all patients with FIGO stage II disease (2).

Because a considerable number of these cases are understaged FIGO stage III disease, it seems appropriate to recommend chemotherapy rather than pelvic irradiation. This view is supported by data showing that systemic chemotherapy may be less hazardous than radiotherapy following lymphadenectomy (2).

The unsettled questions regarding adjuvant therapy of early ovarian cancer are: (1) Which therapeutic options for adjuvant treatment are reasonably justifiable? (2) Which patients have a prognosis poor enough to justify adjuvant therapy? (3) Do any of the existing adjuvant therapies benefit patients? (4) Is it possible to develop a new therapy that might be more effective?

Table 1 High-Risk Early Ovarian Carcinoma

- FIGO stage I C
- Moderately and poorly differentiated
- Aneuploid tumors
- Clear cell histology

THE NATURAL COURSE OF EARLY OVARIAN CANCER

Three prospective observational studies have been published where patients did not receive adjuvant therapy after surgery (3–5) (Table 2). Högberg (1) has reviewed these studies which demonstrate the natural course for patients with early ovarian cancer.

Ten Canadian institutions recruited 82 patients (68 eligible) with FIGO stage I epithelial ovarian cancer (3). With a median follow-up time of 4 years, three patients with disease progression where identified (two had clear cell tumors). One died of disease, while two were disease-free after salvage chemotherapy. However, in this study, patients with FIGO stage IC disease and with poorly differentiated tumors where under-represented presumably because of reluctance to withhold treatment.

Trimbos et al. (5) demonstrated the excellent prognosis with surgery only, provided surgical staging is performed according to state-of-the-art. Patients with incomplete surgical staging had an 88% 5-year progression-free survival (PFS) compared to a 100% PFS in patients properly staged according to the FIGO recommendations.

The third study by Ahmed et al. (4) from Royal Marsden, London, included 194 consecutive patients with FIGO stage I disease. After a median observation time of 54 months, the 5-year overall survival (OS) was 84–94% according to FIGO substage. The 5-year PFS was 62–87%, depending on substage, and 90%, 85%, and 45% for patients with well, moderately, and poorly differentiated tumors, respectively. In a multivariate analysis, grade of differentiation, ascites, and cancer vegetation on the tumor surface were identified as significant independent factors that predicted pro-

Table 2 Early Ovarian Carcinoma (FIGO Stage I): Outcome in Patients Undergoing Surgery Without Adjuvant Therapy

Author	Patients	Median Time Follow Up (months)	5-year PFS	5-year OS
Monga, 1991	68	48	94%[a]	—
Ahmed, 1996	194	54	Stage IA 87%	93.7%
			Stage IB 65%	92%
			Stage IC 62%	84%
Trimbos, 1991	67	50	Incomplete staged 88%	—
			Properly staged 100%	

[a] 3 years PFS.
PFS = progression free survival.
OS = overall survival.

gression. At the ASCO meeting in San Francisco 2001, Kolomainen et al. (6) presented the salvageability of the 61 patients who subsequently relapsed from the original cohort of 194 patients. The median follow-up was 70 months (range 1–19), and the median time from diagnosis to relapse was 17 months (range 6–188). Treatment at relapse was single agent cisplatin for 78% of the patients, platinum-based combination therapy for 11%, and carboplatin–paclitaxel therapy for 3%. Three patients did not receive chemotherapy at relapse. The overall response rate to first line chemotherapy at relapse for those 44 patients was 47%. PFS at 3 and 5 years was 26% and 24%, respectively. OS at 3 and 5 years was 53% and 46%, respectively. Multivariate analysis on the 61 relapsing patients showed that clear cell histology and cyst rupture were the only independent prognostic factor for PFS. Response to chemotherapy was the only statistically significant prognostic factor for survival. Interestingly, these 61 relapsing patients had the same outcome as patients with stage III ovarian cancer who are given chemotherapy at diagnosis.

WHAT HAVE WE LEARNED FROM CLINICAL PROSPECTIVE RANDOMIZED TRIALS OF EARLY STAGE EPITHELIAL OVARIAN CANCER DURING THE LAST 25 YEARS

Högberg et al. (1) has reviewed the literature of early trials of early-stage epithelial ovarian cancer. They found 16 studies that were randomized including 3130 patients. (7–21). However, seven of these studies (9–13,16,18) were excluded in their review because they had methodological flaws, were too small, randomized patients to three arms, or dealt only with radiotherapy.

EXTERNAL RADIOTHERAPY VS. INTRAPERITONEAL RADIOACTIVE AU198

In a randomized study including 418 patients with stage I and II disease, Kolstad et al. (15) compared the results of postoperative external beam irradiation with intraperitoneal (IP) installation of radioactive AU198. There was no significant influence on 5-year survival for patients with stage I disease, whereas it was 54.1% for those treated with AU198 compared with 40% of those treated with radiotherapy in patients with stage II disease. However, the morbidity in the former group was considerably worse.

PELVIC RADIOTHERAPY (PR) PLUS WHOLE ABDOMINAL RADIOTHERAPY (WAR) VS. PELVIC RADIOTHERAPY PLUS CHEMOTHERAPY

In 1979, Dembo et al. (10) published a randomized study showing 25% improvement in survival for patients treated with PR + WAR postoperatively. A total of 76 patients were randomized to PR + WAR and 71 to PR + Chlorambucil. In an update (11), the 5-year OS was statistically better in the PR + WAR arm (78% vs. 51%, $p = 0.006$).

Two patients receiving Chlorambucil later died of acute leukemia. This finding initiated two other studies testing the effect of whole abdominal radiation. Klaassen et al. (14) randomized 284 patients to PR + WAR vs. PR + ^{32}P vs. PR + Melphalan and the Danish ovarian cancer group (DACOVA) (15) randomized 412 patients with FIGO stage IB–IIC to PR + WAR vs. PR + Chlorambucil. In the Klaassen et al. study (14), 29 patients developed secondary cancers, while 19 would have been expected ($p = 0.018$), and PR + Melphalan appeared to be associated with an increased risk of developing acute myelogenous leukemia and myelodysplastic syndrome compared to the PR + WAR arm. These two trials failed to show an advantage for whole abdominal radiation over the use of alkylating agents, and concluded that whole abdominal radiation should not be recommended as adjuvant therapy in early ovarian cancer.

WHOLE ABDOMINAL RADIOTHERAPY VS. CHEMOTHERAPY

The first randomized trial on adjuvant treatment of ovarian carcinoma comparing alkylating agent chemotherapy with whole abdominal or pelvic irradiation was a randomized study from the M.D. Anderson Cancer Center, which showed no benefit for whole abdominal irradiation when compared with oral Melphalan (19). In FIGO stage I, the 5-year PFS was 85% and 90%, and the OS 100% and 86% for WAR and chemotherapy, respectively. The differences were not statistically significant. However, this study was criticized for not irradiating the diaphragm adequately, for giving quite low doses to the liver and kidneys, and for an imbalance in stage distribution between the two treatment arms. Smith et al. (19) concluded that chemotherapy was the preferred treatment because it was as effective as irradiation, but less toxic and less costly. In a later update, two deaths from treatment complications in the radiotherapy arm were reported, and two patients from the chemotherapy arm had developed acute leukemia. Right or wrong, this study had a great impact in that most institutions in the United States abandoned postoperative radiotherapy of ovarian cancer in favor of chemotherapy (1). Young et al. (20) reported a trial by the Gynecologic Oncology Group (GOG), in which 141 patients with high-risk, early stage (moderately to poorly differentiated stage I or stage II tumors) were randomized between ^{32}P and Melphalan. No difference in survival between the two randomized arms was observed. However, deaths due to alkylating agent-induced leukemia were seen in the Melphalan arm. At this time, Cisplatin was considered the most active agent in the treatment for advanced ovarian cancer. Only three prospective randomized trials testing single drug Cisplatin as an adjuvant treatment in early disease have been published. One from the Norwegian Radium Hospital (NRH) in Oslo, Norway (2), one from the GOG (GOG95) (21), and one from Italy (7).

The NRH study compared adjuvant intraperitoneal ^{32}P therapy with six cycles of Cisplatin in a group of 347 patients without residual tumor following primary laparotomy. The NRH study could not disclose any differences in treatment results between radiation and chemotherapy. However, late bowel obstruction occurred more often in the group treated with ^{32}P compared to the Cisplatin group. Because of the absence of therapeutic differences in the NRH report between the ^{32}P and Cisplatin groups, in addition to a low frequency of serious toxicity following Cisplatin therapy and a higher occurrence of bowel complications after ^{32}P therapy, the NRH suggested

that Cisplatin (or other platinum analogs) should be the standard adjuvant treatment in stage I and II ovarian carcinoma (2).

Because of the well-established risk of leukemia after adjuvant treatment with alkylating agents, Young and Pecorelli (22) recommended ^{32}P as standard treatment in subsequent studies. The GOG95 study randomized 251(204 eligible) patients with FIGO stage I or II high-risk ovarian epithelial cancer, after comprehensive surgical staging, to ^{32}P vs. Cyclophosphamide + Cisplatin (21). With a median follow-up of 5 years, 60 patients have recurred. The relapse-free rate was 78% for the chemotherapy arm and 66% for the ^{32}P arm. After adjusting for stage and histologic grade, the group that received chemotherapy had a 31% reduction (not statistically significant) in estimated relapse rate. Two of the patients in the GOG95 study (21) had bowel perforation in connection with the administration of ^{32}P and two patients died of treatment complications, one in each arm. After GOG95, the GOG changed their strategy and because of the longer (although not statistical significant) PFS observed with cyclophosphamide combined with platinum (CP) together with the late bowel toxicity associated with ^{32}P, CP was recommended as standard adjuvant therapy outside of protocol for this subset of patients.

The Italian study group, Gruppo Italiano Collaborative Oncologica Ginecologica (GICOG), performed two multicenter randomized clinical trials between October 1983 and October 1992 (7). In one of these studies, Bolis et al., compared intraperitoneal installation of ^{32}P with Cisplatin intravenously in high-risk early stage patients (FIGO 1973 stage IA_{ii}–B_{ii} and IC). Cisplatin reduced the rate of progression with a relative risk of 0.39 ($p = 0.0007$). There was no difference in OS (79% and 81%). It was the first randomized study to show an impact of chemotherapy on PFS in high-risk early stage ovarian cancer patients. Interestingly, the two GICOG studies showed that cisplatin-treated patients had a poorer outcome at relapse than noncisplatin treated patients. This could be explained by a different response rate to second line therapy because noncisplatin-treated patients were crossed over to cisplatin while no effective second-line therapy existed for cisplatin treatment patients. Alternatively, the adjuvant cisplatin therapy may have selected a resistant population of cells at recurrence.

RANDOMIZATION BETWEEN DIFFERENT CHEMOTHERAPY REGIMENS

Although CP was the preferred treatment in GOG95, the toxicity and duration of therapy was not optimal and 22% of the patients had recurred at 5 years (21). Based on results of GOG111 (23), GOG157 was activated in March 1995 (24) and randomized patients with high-risk stage I ovarian cancer, after complete surgical staging, received carboplatin (AUC = 7.5) and paclitaxel every 21 days for 3 cycles or the same chemotherapy regimen every 21 days for six cycles. Carboplatin has replaced cisplatin in the combination chemotherapy therapy regimens, because of equal efficacy, but less toxicity (25,26). As in the previous trial GOG95, the end-points for GOG157 were PFS, OS, and comparative toxicities. This trial was closed May 1998. Preliminary results were published by Young (27). A total of 457 patients entered the study and 331 patients were evaluable for the preliminary analysis. At a median follow-up of 3 years, 290 (88%) of the 331 evaluable patients on both arms of the trial were alive and

recurrence-free. It was too early to report any comparisons between the randomized groups.

OBSERVATION VS. CHEMOTHERAPY IN LOW-RISK EARLY OVARIAN CANCER

The comparison of survival results in nonrandomized studies using different types of adjuvant treatment and no adjuvant treatment at all is difficult. Most prior randomized trials compared two or three different treatment modalities. However, without an untreated observation group, the efficacy of any adjuvant treatment cannot be firmly established. Only two randomized studies including such a control arm have been published thus far in low-risk early ovarian cancer (7,20). In the first study by the GOG, 81 patients with low-risk, well- or moderately differentiated tumors (FIGO 1973, stage IA or IB) were randomized between adjuvant Melphalan therapy and no treatment (20). Unfortunately, 30% of the patients were at subsequent central pathology review, found to have tumors of borderline malignancy and were therefore excluded. After a median follow-up period exceeding 6 years, no significant difference in OS (94% vs. 98%) or PFS (91% vs. 94%) could be seen. One patient in the Melphalan arm died of aplastic anemia.

The second study by GICOG (7) showed a significant PFS advantage in the cisplatin group, 83% vs. 64% in the untreated group ($p = 0.028$). When the control group patients were tested with cisplatin at relapse, they had the same overall 5-year survival as the group receiving immediate cisplatin treatment (82% and 88%); however, few events had occurred at the time of analysis. This suggests that 8 out of 10 women in the cisplatin group had been overtreated (28). It was observed that once progression had occurred, the risk of dying was greater for patients treated with cisplatin up front.

These two studies did not show any significant OS differences between the treatment arm and the control arm. One would not expect such a difference because approximately 1000 patients are required to detect a difference in survival of 5% at a significance level of 5% and power of 90% when the expected survival is 90% (29)

Table 3 Observation vs. Chemotherapy in Low-Risk Early Ovarian Cancer

Author	No PTS	Treatment	Median time follow up (months)	PFS (%)	OS (%)
Young, 1990	81	OBSERVATION, No pts: 38	78	91	94
		CT (Melphalan), No pts: 43		98	98
Bolis, 1995	85	OBSERVATION, No pts: 44	69	65	82
		CT (Platinum), No pts: 41		83	88

(Table 3). Because the prognosis is so good in stage I low-risk ovarian cancer patients, it is generally accepted today that no adjuvant treatment should be given provided the patient was properly staged.

OBSERVATION VS. CHEMOTHERAPY IN HIGH-RISK EARLY OVARIAN CANCER

Only a large prospective trial of poor-prognosis early ovarian cancer patients with an untreated control arm will be able to resolve the question of whether any adjuvant therapy contributes to survival. However, it has been very difficult to conduct such studies because patients hesitate to be randomized to a control arm with no active treatment when they are informed about the increased PFS with cisplatin (the banana effect) (7,21). We have found that many patients refuse to participate in such a trial, which includes the important control arm (8). In spite of these difficulties, there have been three very important studies conducted in Europe to determine if adjuvant treatment in high-risk patients significantly improves long-term survival.

The Nordic Cooperative Ovarian Cancer Group (NOCOVA) study (8) was closed prematurely because of slow randomization. Between 1992 and 1997, 230 radically operated patients (162 eligible) with FIGO stage I invasive epithelial ovarian cancer, moderately and poorly differentiated, or well-differentiated aneuploid, or with clear cell histology were randomized to observation vs. postoperative carboplatin (AUC = 7) for six courses. With a median follow-up of 60 months, progression was registered in 46 patients, 25 in the treatment group and 21 in the control group. The estimated 5-year OS and the PFS rate were 86% vs. 85% and 70% vs. 71% for the treatment and control groups, respectively. The hazard ratio (HR) was 0.98 (CI 0.52–1.83) in favor of the treatment group regarding PFS, while the HR was 0.94 (CI 0.37–2.36) also in favor of the treatment group regarding disease-specific survival. The wide confidence intervals emphasize the inconclusive nature of the study.

The other two prospective randomized studies addressing this question have recently been presented at the 2001 ASCO meeting in San Francisco (30). The Adjuvant Clinical Trial in Ovarian Neoplasms (ACTION) is an European Organization for Research and Treatment of Cancer (EORTC) randomized trial comparing observation with chemotherapy (either cisplatin at least 75 mg/m^2 or carboplatin at least 450 mg/m^2 for a minimum of four cycles). A total of 448 patients were randomized, 224 in each arm.

The other large trial, the International Collaborative Ovarian Neoplasm Studies (ICON1) was organized by the British Medical Research Council (MRC). This trial randomized patients to immediate platinum-based chemotherapy (80% carboplatin AUC = 7) vs. observation. Over 445 patients have been randomized. Both studies closed in January 2000, and the median follow-up time was 5.5 years. Both studies were well balanced concerning prognostic factors. Both studies showed a significant difference in both PFS and OS in advantage of immediate adjuvant treatment. In the ACTION study, the PFS and OS differences were 11% and 8%, respectively ($p = < 0.01$ and $p = < 0.02$). In the ICON 1 study, the PFS and OS differences were 10% and 7%, respectively ($p = 0.02$ and $p = 0.05$). When all 923 patients included in the two studies were analyzed together, a significant improvement was noted in PFS by 11%

Table 4 Observation vs. Chemotherapy in High-Risk Early Ovarian Cancer

Author	No. of PTS	Median time follow up (months)	5 years OS differences (%)	PFS differences (%)
Trope, 2000	162	60	1	1
Action study	448	65	8	11
Icon 1 study	475	65	7	10

and in OS by 7% for high-risk patients receiving chemotherapy compared to follow-up without adjuvant treatment. This is the first evidence that immediate treatment is significantly better than treatment at relapse (Table 4). The comprehensiveness of surgical staging was a significant prognostic factor for tumor recurrence in the observational arm, and when subset analysis was performed in correctly staged patients, no difference in PFS or OS between immediate treatment and observation was noted. This probably means that there were a number of patients with occult stage III disease in the suboptimally staged group.

INTRAPERITONEAL CHEMOTHERAPY IN EARLY OVARIAN CANCER

Dedrick et al. (31) have shown that there may be a great pharmacologic advantage in using intraperitoneal (IP) administration of chemotherapeutic agents. Depending on several factors this advantage varies from 1 to 3 log for different drugs (32,33). The exposure of the peritoneal cavity to cisplatin and carboplatin after IP delivery is approximately 10- to 20-fold greater than that of the systemic compartment (34), while this ratio for paclitaxel is at least 1000-fold (35,36). It is now well known that IP treatment should not be used in large volume intraabdominal disease or chemotherapy resistant ovarian cancer (34), but it may be rational in patients with high-risk early disease (stage I, grade 3, clear cell, stage II) where there is a significant risk for undetected microscopic disease in the upper abdomen. The recent report from Alberts et al. (37) showing an advantage for small-volume stage III patients when IP cisplatin was substituted for intravenous cisplatin is interesting. A recently completed GOG study (38) has used IV vs. intraperitoneal cisplatin as part of initial therapy. Patients on the intraperitoneal arm received an initial two cycles of moderate dose systemic carboplatin (AUC = 9). The preliminary results of that study showed a significant ($p = 0.04$) improvement in recurrence-free survival for the intraperitoneal arm but no effect on ultimate survival (38). Paclitaxel has also been shown to be active via the intraperitoneal route and ongoing studies in optimally debulked ovarian cancer are justifiably exploring this lead (39).

The combination of cisplatin and paclitaxel should be of particular interest in IP therapy of high-risk early ovarian cancer Therefore, it would be very reasonable to do a prospective randomized trial in this disease, comparing the combination of the two drugs by the IP route in the experimental arm.

Nevertheless, even if the hazard ratio for survival with intraperitoneal, as compared with IV therapy, is equivalent to that for the incorporation of paclitaxel,

this therapy will likely not be uniformly adopted. This may in part be due, according to McGuire (40), to a perception that intraperitoneal therapy is difficult and toxic.

DOSE INTENSITY OF CHEMOTHERAPY AGENTS WITH AUTOLOGOUS BONE MARROW TRANSPLANTAION

Despite different postoperative adjuvant chemotherapy regimens, a significant improvement in long-term survival in these patients has not been achieved during the past 20 years. Therefore, we should look into other systemic treatment modalities, i.e., dose intensity of chemotherapeutic agents with autologous bone marrow transplantation (ABMT). However, there are as yet no randomized trials showing that it is superior to more standard forms of salvage therapy. A recently activated intergroup study, GOG protocol 164, selects patients with both drug-sensitive and small-volume disease following primary courses of standard salvage therapy or ABMT following very high doses of carboplatin (AUC 28), cyclophosphamide (120 mg/kg), and mitoxantrone (75 mg/m^2). However, the morbidity and mortality of ABMT has steered investigators away from using high-dose chemotherapy as part of the initial treatment for ovarian cancer. High-dose chemotherapy with peripheral hematopoietic cell support (PBPC) should be tested up front in patients with stage I poor prognosis. Results from trials using PBPC in patients with recurrent disease has encouraged the use of such aggressive treatment up front. High-dose chemotherapy with PBPC stem cell support should be tested in patients with high-risk stage IA and II ovarian cancer (41–43).

We encourage investigators worldwide to participate in this or similar trials to answer the important question of whether this approach is worth the toxicity and expense in terms of improving long-term survival.

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Chemotherapy for Advanced Primary Epithelial Ovarian Cancer: Neoadjuvant and Adjuvant

Jan B. Vermorken
University Hospital Antwerp, Edegem, Belgium

INTRODUCTION

Surgery and chemotherapy are the major contributors to the management of patients with advanced epithelial ovarian cancer. The role of surgery has been basically twofold, i.e., for diagnosis and treatment (cytoreduction) (1). Some clinicians feel that surgery, as a diagnostic test for advanced ovarian cancer, has been rendered rather obsolete by the current state of medical imaging and invasive radiology (2). However, most still accept the present standard to perform cytoreductive surgery up front when it may result to zero or minimal residual disease (3). Alternative approaches have been applied for patients with very advanced ovarian cancer with massive peritoneal carcinomatosis and/or stage IV disease in whom optimal debulking seem to be far from realistic (4,5). Unfortunately, to date, no randomized study on initial cytoreductive surgery prior to chemotherapy has been reported and so the value of this standard approach to the management of patients with advanced ovarian cancer is mainly based on retrospective evidence.

The feasibility of complete or optimal debulking surgery is highly dependent on the surgeon's experience in the field of gynecologic oncology, as well as on his philosophy and motivation to approach these patients in a multidisciplinary therapeutic fashion. One unsolved issue with respect to optimal debulking is whether it is the biological behavior of the tumor or the surgical intervention itself that allows optimal cytoreduction and prolonged survival (6). One randomized trial on interval debulking surgery in patients who could only be suboptimally debulked up front indicated that induction chemotherapy prior to interval debulking allowed more patients with suboptimal disease to be optimally debulked at that time, leading to an improvement in survival (7). The fact that there seems to be a strong correlation between chemosensitivity, successful debulking surgery, and survival supports the concept that it is the biological characteristics of the tumor that allow the patient to have successful cytoreduction rather than the aggressiveness of the surgery itself (6). These facts have led several investigators to believe in the concept of neoadjuvant chemotherapy.

Good evidence based on sound randomized clinical trials has indicated which drugs should be used to obtain the best results in this disease in terms of response and survival. This review describes the potential role and present status of neoadjuvant chemotherapy in patients with advanced ovarian cancer, and summarizes the data on what should be considered optimal adjuvant chemotherapy in such patients.

THE POTENTIAL ROLE OF NEOADJUVANT CHEMOTHERAPY

Treating advanced ovarian cancer patients with chemotherapy prior to surgery has three theoretical advantages: (1) improvement of the patient's performance status prior to the operative procedure; (2) reduction in tumor volume which could lead to less extensive surgery, decreasing operative and postoperative morbidity; and (3) increased rate of optimal cytoreduction, which may translate into an improvement of survival (8). An additional advantage of neoadjuvant chemotherapy is knowing, intraoperatively, the patient's sensitivity to chemotherapy, which allows the surgeon to be appropriately aggressive, i.e., to pursue a maximal attempt in those with an excellent response to chemotherapy and to remain rather restricted in those with poor response who would be left with suboptimal disease. Indeed, initial investigations of neoadjuvant chemotherapy have suggested that (a) survival might not be different when patients are treated first with chemotherapy followed by surgery compared to those receiving the standard approach in case such patients cannot be optimally debulked initially, and (b) optimal surgical cytoreduction is more likely to be achieved after administration of chemotherapy (8–14).

Lawton et al. (9) treated 36 patients who had undergone suboptimal primary surgery with cisplatin-based combination chemotherapy in the neoadjuvant setting. There was the intention to perform a surgical debulking after three cycles in case of response. In fact, interval debulking surgery could be performed in 28 of the 36 patients (78%) at a median interval of 12.7 weeks from primary diagnosis, and 89% could be optimally debulked at that time. Postoperative complications were few and chemotherapy could be restarted with a median interval of 21 days.

Jacob et al. (10) described the outcome of 22 patients with bulky FIGO stage III and IV ovarian cancer (group A) who were referred to the M.D. Anderson Cancer Center after an initial laparotomy and biopsy alone performed elsewhere. These patients were treated with 2–4 cycles of cisplatin-based chemotherapy followed by interval debulking surgery and then another 6 cycles of cisplatin-based chemotherapy. These patients were compared with 22 matched patients, suboptimally debulked at first surgery, and planned to be treated with 6 cycles of cisplatin-based chemotherapy plus second-look laparotomy (group B), and 18 other matched controls who, after initial laparotomy and biopsy, only received immediately reexploration and debulking followed by 6 cycles of cisplatin-based chemotherapy plus second-look surgery (group C). Optimal cytoreduction to ≤ 2 cm was achieved for 77% of patients in group A vs. 39% in group C. Median survival in times for groups A, B, and C were 16, 19.3, and 18 months, respectively ($p = 0.58$).

Onnis et al. (11) observed a similar survival rate in 88 patients who were treated with primary (variable) chemotherapy, as compared to contemporary patients treated with primary debulking surgery. Forty-two percent of the 88 patients receiving neoadjuvant chemotherapy could be optimally (<2 cm) debulked vs. 29% of patients

receiving primary surgery. Optimal cytoreduction to <2 cm was possible in 80% of patients after platinum-based combination chemotherapy (PAC regimen).

Surwit et al. (8) described the outcome of 29 patients bulky advanced ovarian carcinoma who were treated with platinum-based chemotherapy prior to definitive cytoreductive surgery at the University of Arizona. The decision to treat with neoadjuvant chemotherapy was made on the basis of the extent of the patient's disease, utilizing chest X-ray, computerized tomography (CT), and clinical examination. Thirteen patients met the criteria established by Nelson et al. (15) to be unlikely to achieve optimal cytoreductive surgery. Only 8 patients had stage IV disease with pleural effusion, and 28/29 patients had ascites. Eight of these patients with ascites who did not meet the Nelson's criteria for unresectable disease had extensive omental disease and cul-de-sac modularity. Preoperative chemotherapy consisted of either: (a) two courses of dose-intensive cisplatin or (b) three courses of high-dose carboplatin. Postoperative chemotherapy consisted of either three courses of dose-intensive cisplatin (or in case of neuro- or ototoxicity carboplatin) or 4–6 cycles of paclitaxel/cisplatin. Overall, 55% of patients were optimally cytoreduced (< 1 cm) after neoadjuvant chemotherapy. Median survival of all patients was 22.5 months and was noted by the authors to be comparable with the survival in the series reported by Heintz et al. (16) of patients with ascites who had primary cytoreductive surgery. An interesting aspect in the Arizona study was the fact that the CA125 response to neoadjuvant chemotherapy was highly predictive of survival ($p < 0.0005$). A 2-log decrease in CA125 prior to surgery resulted in a median survival of 37 months, while patients with less than 1-log response in CA125 all had an unsuccessful cytoreductive surgery and a mean survival of 18 months. Another interesting observation was the reduced morbidity of surgical debulking in comparison with other series using up front surgery referred to in this report. The operative time, blood less, morbidity, and hospital stay all seemed to be less.

Similar conclusions were made by Schwartz et al. (12). They described the long-term follow-up of 59 patients with advanced ovarian cancer (FIGO stages IIIC and IV) treated with neoadjuvant platinum-based combination chemotherapy at the Yale–New Haven Hospital from 1979 to 1996 and considered the outcome of these patients similar to that of 206 consecutive women with stage IIIC and IV ovarian cancer treated with conventional cytoreductive surgery followed by platinum-based combination chemotherapy during the same era. However, looking in detail at the presented data, it became clear that the median survival of all patients was 13 months, that of the 41/59 who had had interval debulking surgery following neoadjuvant chemotherapy was 18 months, while the median survival of the conventionally treated group was 26 months. Moreover, for those in the neoadjuvant chemotherapy group who were rendered visibly disease-free at interval cytoreduction, the estimation of the median survival was 36 months, and that of the 5-year survival 30%. Strong disagreement with the conclusion of the paper was expressed by Dr. Eisenkop (17). He considered the outcome of this latter highly selected subset of patients clearly worse when compared with the outcome of a similar group of patients who received primary cytoreductive surgery (median survival 62 months, 5-year survival 52%) described by him in 1998 (18). However, it should be noted that patients in the Yale study who received neoadjuvant chemotherapy in the first part of the study were selected based on medical conditions that, in the view of the gynecologic oncologist, precluded them from undergoing aggressive cytoreductive surgery. Only in the latter part of the study were Nelson criteria

used. Surgery after neoadjuvant chemotherapy again was tolerated better than surgery used up front when evaluated by three surgical parameters, i.e., median estimated blood loss (600 vs. 1000 cm^3; $p = 0.001$), mean surgical intensive care unit stay (1.03 vs. 1.26 days; $p = 0.01$), median number of postoperative hospitalization days (7.0 vs. 11; $p < 0.001$)

A report from Belgium (13) examined 75 patients treated from 1989 to 1997 with a neoadjuvant approach (nearly all with platinum-based chemotherapy), and compared them to 98 patients treated during the same interval with primary debulking surgery followed by chemotherapy. Although the authors felt the neoadjuvant approach was a valid one, the 3-year survival of patients treated in this manner was 25%, compared with a 3-year survival of 53% in their primary debulking patients. However, this difference was a logical result from the fact that, in the neoadjuvant group, only stages IIIC (59%) and IV (41%) were included, while in the primary debulking group 8% had stage IIIa, 12% stage IIIB, 68% stage IIIC, and only 11% stage IV.

A French multicenter study, comprising 54 stage IIIC or IV ovarian cancer patients treated with neoadjuvant platinum-based chemotherapy, concluded that with such an approach, a subset of patients could be selected in whom optimal cyto-reduction could be achieved (14). In that study, 39 of the 43 responding patients could be optimally debulked (91%, i.e., 72% of the initial series). Conversely, aggressive surgery could be avoided in patients with initial chemoresistance, in whom prognosis anyhow is poor, regardless of treatment.

Table 1 summarizes the relevant response and survival data for those studies in which platinum-based chemotherapy was used for induction.

From these retrospective data on the role of neoadjuvant chemotherapy followed by interval debulking surgery in case of response in patients with FIGO IIIC and IV ovarian cancer, it seems reasonable to conclude that with this approach, operative morbidity is most likely decreased and in that sense may improve the quality of life. Although most investigators state that survival is not negatively influenced,

Table 1 Neoadjuvant Platinum-Based Chemotherapy in Advanced Ovarian Cancer: Response/Survival Data

Reference	No. of patients	Cy. of NACT	Response to NACT	No. with IDS	No. with ODS[b]	Median survival (mo)	
						ALL	With ODS
Jacob et al. (10)	22	2–4	10/20 (50%)	22	17 (77%)	16	18.1
Surwit et al. (8)	29	2–3	18/29 (62%)[a]	29	16 (55%)[b]	22.5	32
Schwartz et al. (12)	59	6	NR	41	NR	13	NR
Ansquer et al. (14)	54	3–6	43/54 (80%)	46	39 (72%)	22	NR

NACT = neoadjuvant chemotherapy; IDS = interval debulking surgery; ODS = optimal debulking surgery; NR = not reported.

[a] CA 125 response.

[b] ≤2 cm (except in Ref. 8: <1 cm).

there exist reasonable doubt among clinicians. However, nonbelievers of the neoadjuvant approach also agree that some patients simply are not candidates for up front debulking, for instance, those in such a precarious condition because of severe preexisting medical problems or the cancer itself, that debulking surgery could be life-threatening. In addition, gynecologic oncologists may, on occasion, see patients with presumed advanced ovarian cancer in whom imaging studies clearly show unresectable bulky tumor, usually manifested as massive disease in the porta hepatis or on the diaphragm. Such patients are considered by many as a candidate for a neoadjuvant approach, because, predictably, suboptimal debulking is of no benefit to the patient. It should therefore be stressed that the neoadjuvant approach in general does not serve as a replacement of the standard approach at the present time, and it certainly does not obstruct the concept of cytoreductive surgery for those who can be optimally debulked up front. To verify the conceptual advantages of chemical vs. surgical up front debulking, a prospective randomized phase III trial has been initiated within the European Organization for Research and Treatment of Cancer (EORTC) Gynecologic Cancer Group and is at present ongoing in cooperation with several European and non-European cooperative groups (Intergroup trial).

ADJUVANT CHEMOTHERAPY

The recommended treatment strategy for most patients with advanced ovarian cancer is up front radical cytoreductive surgery, followed by combination chemotherapy with a taxoid and a platinum compound (19). This recommendation is based on level-one evidence of two large prospective randomized trials which established that a combination of paclitaxel plus cisplatin (TP) was superior to cyclophosphamide plus cisplatin (CP) in patients with advanced ovarian cancer and applied to both optimally and suboptimally debulked patients (20,21).

The first study, performed by the Gynecologic Oncology Group (GOG) (protocol # 111) in the United States, included 410 suboptimally debulked stage III or IV epithelial ovarian cancer patients. Patients were randomized to receive either 24-hr paclitaxel given at a dose of 135 mg/m^2, followed by cisplatin at a dose of 75 or 750 mg/m^2 of cyclophosphamide plus 75 mg/m^2 of cisplatin. Both regimens were given at 3-week intervals for 6 cycles. Because of the restricted availability of paclitaxel at the time, only 8% crossed over to paclitaxel on first progression of the disease in that study (20). Early (positive) results were presented at the 29th annual meeting of the American Society of Clinical Oncology in 1993. Although the data on response and progression-free survival were impressive, they were not considered conclusive enough to adapt TP as a new standard (1). For that reason, investigators from Europe and Canada planned a confirmatory phase III trial. This large intergroup trial, which included 680 patients, differed from the GOG trial with respect to: (1) patient selection (i.e., patients with optimally debulked stage III or IV disease could also enter the study, as well as those with FIGO stages IIB and IIC); (2) a flexible center policy concerning secondary surgery; (3) the introduction of interval debulking surgery as an option for patients who could not be optimally debulked up front (7); (4) the paclitaxel infusion schedule (i.e., 3-hr paclitaxel instead of 24 hr); (5) paclitaxel dose (i.e., 175 mg/m^2 instead of 135 mg/m^2 and with a possible escalation to 200 mg/m^2); and (6) the number of treatment cycles (i.e., up to 9 cycles were allowed). Moreover, in case of substantial

neurotoxicity, cisplatin could be replaced by carboplatin. This proved to be of importance as, indeed, a 14% rate of grade 3 neurotoxicity was observed during the time of the first six treatment cycles with TP (vs. 4% observed in the GOG study). A relatively low proportion of patients (12% in the TP arm and 9% in the CP arm) had cisplatin replaced by carboplatin during the course of their chemotherapy. The results after a median follow-up of 38.5 months were recently reported (21). Indeed, because of the wider availability of paclitaxel when this second study was performed, 48% crossed over to paclitaxel on first progression in the CP arm. Nevertheless, again, a significantly longer progression-free survival (primary trial endpoint) and overall survival (OS) were obtained in the TP arm (see Table 2). The trial did not have the power to compare the chemotherapy regimens in the subsets of patients having optimal or suboptimal residual disease. However, treatment effects observed in both categories looked alike in the same direction.

GOG protocol 132 compared single agent cisplatin (100 mg/m^2) with single agent 24-hour paclitaxel (200 mg/m^2), and with the combination of both (as used in GOG-111). This trial again confirmed the importance of cisplatin, and showed a significantly higher response rate than that obtained with paclitaxel (67% vs. 46%). The median survival with all three regimens was the same (see Table 2, Ref. 22). This study was complicated in its evaluation because many patients treated in the single drug arms changed to the other arm before clinical progression based on persistent disease radiographically or findings of residual disease at second-look laparotomy or otherwise (i.e., clearly differing from the policy followed in the European–Canadian intergroup trial). Therefore, protocol GOG-132 has been interpreted (rightly or wrongly) as a comparison of using the two drugs sequentially vs. concomitantly. The balance was in favor of the combination because of better tolerance, and this trial, in that sense, was not felt as contradictory to GOG-111 and the Intergroup trial.

More puzzling is the outcome of the only randomized trial which compared a paclitaxel–carboplatin combination with two nontaxoid-containing regimens. This

Table 2 Progression-Free Survival and Overall Survival Data of Various Randomized Trials Studying the Role of Paclitaxel in First Line for Patients with Ovarian Cancer

Trial Group	Treatment Arm (mg/m^2)	Overall Response (%)	Median PFS (mo)	Median Survival (mo)
GOG-111	CP (750/75)	60	13.0	24.0
	TP (135–24 h/75)	73	18.0	38.0
INT	CP (750/75)	67[a]	11.5	25.8
	TP (175–200–3 h/75)	78[a]	15.5	35.6
GOG-132	P (100)	67	16.4	30.2
	T (200–24 h)	46	11.4	26.0
	TP (135–24 h/75)	67	14.1	26.6
ICON-3	CTR (CAP or Cb)	NA	16.2	36.0
	TCb (175–3 h/AUC6)	NA	16.7	38.7

GOG = Gynecologic Oncology Group study, INT = European–Canadian intergroup study, ICON = International Collaborative Ovarian Neoplasm study, NA = not available, PFS = progression-free survival, C = cyclophosphamide, A = doxorubicin, P = cisplatin, T = paclitaxel, CTR = control, Cb = carboplatin, AUC = Area under the concentration-time curve.

[a] Including unconfirmed responses.

trial, performed under the sponsorship of the British Medical Research Council, was recently updated and presented at the 36th annual meeting of the American Society of Clinical Oncology in New Orleans by Colombo on behalf of the ICON collaborators (23). In this very large trial, 2074 patients with ovarian cancer stages I–IV were randomized to an experimental arm consisting of paclitaxel plus carboplatin (TCb) vs. either of two control arms, which could be carboplatin alone ($n = 1421$) or the traditional CAP regimen ($n = 653$). All treatments were given every 3 weeks for 6 cycles. Paclitaxel dose was 175 mg/m^2 (3-hour infusion), carboplatin was given at a minimum dose of 6 mg (calculated GFR + 25), and the dosage of cyclophosphamide was 500 mg/m^2, doxorubicin 50 mg/m^2, and cisplatin 50 mg/m^2. After a median follow-up of 29 months, 925 of the 2074 patients died and 1293 had progressed; so the data were considered secure up to 3 years. The study showed no difference in progression-free survival (1% at 1 year) and no difference in overall survival (2% at 2 years). Thirty percent of the patients in the control arm had received a taxoid-containing regimen on progression. There was no evidence of different effects in different subgroups. The exploratory subgroup analysis included the randomizing group, the number of patients randomized by a center, age, FIGO stage, residual bulk, histologic type, and differentiation. The reason for the confusion is evident from Table 2, in particular, taking into account that only 6% seemed to have received a taxoid-containing regimen prior to documented progression in the control arm. Although criticism has been expressed related to the nonrandom selection of the control arm—the unusually high number of institutions involved and the seemingly paradoxical effect in patients with small-volume disease—these are not strong enough to refute the outcome of the study. The simple fact remains that this very large trial, the only one comparing a carboplatin/paclitaxel combination vs. a nontaxoid-containing regimen, did not show superiority over either optimally dosed carboplatin alone or the CAP regimen. In that respect, it is of importance to recall that a meta-analysis, using individual patient data, has indicated that CAP is superior to the CP combination at a cisplatin dose of 50–60 mg/m^2 (24), while the control arm in GOG-111 and in the European–Canadian intergroup study used CP at a cisplatin dose of 75 mg/m^2. Moreover, if indeed better results could be achieved with carboplatin alone at an optimally tolerated dose than with the CP combination and survival curves with carboplatin (or for that matter cisplatin) at an optimally tolerated dose would be no different from those obtainable with CAP, then a lot of rethinking would be necessary.

Carboplatin was developed as a less toxic alternative to cisplatin, and following its introduction into clinical practice, its advantages over cisplatin in terms of toxicity became evident. Considering the fact that carboplatin in some curable diseases (i.e., testicular cancer) has shown to be inferior to cisplatin, concern has been expressed as to whether this drug could replace cisplatin in the treatment of patients with ovarian cancer, in particular those with optimal stage III disease (25). However, a series of studies demonstrated equivalent activity, and a recently updated meta-analysis confirmed this lack of difference, for patients overall and in any specific subgroup (26). Nevertheless, the fact that the equivalence of carboplatin and cisplatin has been suggested from trials without a taxoid does not automatically mean that this is also true for carboplatin/paclitaxel combinations vs. cisplatin/paclitaxel combinations. For, if the interaction between carboplatin and paclitaxel on the megakaryocyte leads to less carboplatin-induced thrombocytopenia when given in combination than when given alone, then why would this effect not be likewise present at the level of the tumor

Table 3 Randomized Trials of Paclitaxel–Cisplatin Vs. Paclitaxel–Carboplatin

Study group	Stages of disease	Study arms (mg/m^2)	No. of patients	RR (%)	Median PFS(wk)
Dutch–Danish	IIB–IV	TP (175–3 h/75)	208	73	73
		TCb (175–3 h/AUC5)		71	75
AGO	IIB–IV	TP (185–3 h/75)	798	80	71
		TCb (185–3 h/AUC6)		68	69
GOG 158	optimal	TP (135–24 h/75)	840	NA	94
	stage III	TCb (175–3 h/AUC7.5)		NA	95

AGO = Arbeitsgemeinschaft Gynaekologische Onkologie, GOG = Gynecologic Oncology Group, TP = paclitaxel plus cisplatin, TCb = paclitaxel plus carboplatin, NA = not available, RR = response rate, PFS = progression-free survival.

cell? It is therefore reassuring to know that, so far, in three prospective randomized trials, including one in patients with only optimal stage III disease (GOG protocol 158), comparison of cisplatin plus paclitaxel vs. carboplatin plus paclitaxel have shown no difference in response rates or progression-free survival (27–29, see Table 3). In fact, an update of GOG protocol 158 has even indicated a slight superiority in the survival of the carboplatin/paclitaxel arm over cisplatin/paclitaxel (R.F. Ozols, personal communication). Of importance in that respect is to note that, in GOG 158, a carboplatin AUC dose of 7.5 is used instead of the usual AUC of 5 or 6. All three studies concluded that carboplatin plus paclitaxel is the preferred regimen in terms of (less) toxicity and, where studied, in terms of quality of life. Final reports of the AGO trial and GOG 158 are eagerly awaited with respect to overall survival data. Although mature data still have to be awaited, the paclitaxel/carboplatin regimen has been adopted in many institutions as the new standard. It is also used as "the control arm" in all recent randomized trials.

INTRAVENOUS PACLITAXEL/PLATINUM AND WHAT NEXT?

Intraperitoneal Chemotherapy

The preferred regimen for the treatment of ovarian cancer should not only provide the best long-term survival rates, but also meaningful palliation and acceptable quality of life for the majority of patients with less favorable prognosis (30). For patients with suboptimally debulked disease, paclitaxel/carboplatin might well be the treatment of choice if long-term survival data from the randomized trials show equivalent results. But what about the patients with optimally debulked disease? As mentioned earlier, GOG protocol #158 will possibly indicate a slight superiority in survival for patients treated with paclitaxel/carboplatin when using a carboplatin AUC dose of 7.5. This may suggest an impact of dose. In that same category of patients, another form of therapy deserves further attention, i.e., intraperitoneal chemotherapy. There is ample data to suggest that intraperitoneal chemotherapy may be of benefit to advanced ovarian cancer patients with no gross residual disease or small-volume residual disease after initial surgical tumor debulking. At least three large randomized trials have indicated a striking risk reduction of dying when treated with intraperitoneal chemotherapy compared to intravenous chemotherapy (31–33, see Table 4). The last study

Table 4 Results of Randomized Trials of First-Line i.p. Vs. i.v. Chemotherapy in Advanced Epithelial Ovarian Cancer

Study group	No. of patients	Disease stages	Survival evaluation	MDS (mo)		*P* Value	% Increase
				i.p.	i.v.		
INT-1	546	III	PFS	ND	ND	ND	ND
			OS	49	41	0.02	20%
INT-2	523	III	PFS	28	22	0.02	27%
			OS	63	52	0.056	21%
GOG #172	417	III	PFS	24.3	19.3	0.029	26%

INT-1 = intergroup trial (Ref. 31), INT-2 = intergroup trial (Ref. 32), GOG # 172 = Gynecologic Oncology Group trial # 172 (Ref. 33), MDS = Median duration of survival, ND = no data.

was recently presented at ASCO 2002. This study, GOG #172, only included patients with optimal stage III ovarian cancer and randomized patients to receive TP as in GOG #111 or to receive paclitaxel (i.v. and i.p.) and cisplatin (i.p.) (i.e., paclitaxel at a dose of 135 mg/m^2 i.v. day 1, cisplatin 100 mg/m^2 i.p. day 2 and paclitaxel 60 mg/m^2 i.p. day 8). Progression-free survival (the primary endpoint of the study) was significantly longer in the i.p. arm (24.3 vs. 19.3 months: $p = 0.029$, one-tail test). However, it was still too early to obtain data on overall survival. The i.p. arm induced more toxicity, in particular, grade 3–4 metabolic, neurological, and gastrointestinal toxicity, and infection.

All these studies made use of cisplatin, being the platinum drug of choice for intraperitoneal use (35). Because the beneficial effect of intraperitoneal chemotherapy has not been confirmed in a second trial with the newly accepted intravenous standard in the control arm, it seems realistic to await the survival outcome of protocol GOG #172. A disadvantage of protocol #172 is that two items were changed at the same time, i.e., not only the way of administration but also the dosis of the two drugs were different in the two arms. Therefore, because of issues raised by nonbelievers, again the discussion on the value of i.p. chemotherapy is not closed. A simple trial using the present standard in the i.v. control arm and changing only the way of administration in the comparator arm still needs to be carried out. Until such time, we still should consider i.p. therapy as in its investigational stage (34).

Optimizing Dose, Schedule, and Duration of Treatment

Many questions remain regarding these three issues, and studies both in the United States and in Europe have been carried out or are ongoing. With respect to dose, there is no consensus regarding the optimal dose of carboplatin when used in combination with 3-hr paclitaxel. The optimal dose of paclitaxel, in combination with a platinum compound, in first line also is unclear (35). GOG # 185 might suggest that higher doses of carboplatin in combination with paclitaxel are needed. Ultrahigh doses of chemotherapy as used with autologous stem cell support does not have an established role in patients with ovarian cancer (36). With respect to schedule, there is an indication that the weekly regimen of 3-hr paclitaxel (67 mg/m^2/week) might be as active as the 3-weekly, 3-hr paclitaxel (200 mg/m^2) regimen. This was suggested from a randomized trial comparing these two schedules in 208 patients who had been previously treated

with platinum-based therapy (37). Response rates, progression-free survival, and overall survival were all comparable between the two arms. However, in terms of safety profile, there was a preference for the weekly regimen; grade 3–4 neutropenia, neuropathy, alopecia, and arthralgia/myalgia occurred more frequently with the 3-weekly regimen. Only severe nail changes were observed with the weekly regimen (9%). The issue of treatment duration remains open and, in particular, with respect to the antiangiogenic properties of paclitaxel, this might be an interesting field of research. The value of consolidation therapies in patients with clinical complete response, or maintenance therapy in patients with at least stabilization after induction chemotherapy has been rather disappointing in the past (34,38–40). However, at present, there is a renewed interest in this topic because interim data of a trial comparing 12 vs. 3 consolidation cycles with paclitaxel (175 mg/m^2 (3 h) q 28 days) in patients who have reached a clinically defined complete response to 5 or 6 cycles of platinum/paclitaxel-based chemotherapy showed an outcome in favor of the long treatment arm (41).

The Use of Alternative Platinum Compounds or Taxoids

Oxaliplatin is an interesting platinum analogue because of its lack of any significant bone marrow suppression and lack of nephrotoxicity. The antitumor activity so far observed in phase II studies, in which oxaliplatin was mainly given at the dose of 130 mg/m^2 as a 2-hr infusion, ranged between 15% and 30%, and confirmed preclinical data. A peculiar sensory neuropathy is the most important side effect. The importance of oxaliplatin was shown in a first-line randomized study, which was recently updated and presented at ASCO 2000 (42). It concerned a French study, in which oxaliplatin plus cyclophosphamide (OXC) was compared with cisplatin plus cyclophosphamide (PC) in 177 advanced chemonaive ovarian cancer patients. A similar efficacy was obtained with OXC or PC in terms of response rate (both clinically and pathologically), progression-free survival, and overall survival. However, OXC was favored in terms of toxicity, i.e., less grade 3–4 anemia, less red blood cell transfusions, less grade 3–4 vomiting, and less grade 3–4 leukopenia. Moreover, less nephrotoxicity was observed with OXC. Of course, this regimen seemed somewhat outdated, but the role of oxaliplatin should be further explored in combination with other platinum compounds, taxoids, and other promising new agents.

Docetaxel, although less extensively studied in ovarian carcinoma than paclitaxel, is of particular interest because of its comparable activity in patients with refractory disease and because of its somewhat lower neurotoxicity. Combinations with cisplatin in first line (both drugs given at a dose of 75 mg/m^2) showed activity (overall response rate 70%), but one third of 100 patients in a Scottish trial were not able to complete the planned six cycles of therapy (43). In contrast, 90% of 141 patients could tolerate six cycles of docetaxel (75 mg/m^2) plus carboplatin (AUC 5) in a successive study, at the cost of very little neurotoxicity. For that reason, a large international trial has been performed, comparing docetaxel–carboplatin (75 mg/m^2 and AUC5) with paclitaxel–carboplatin (175 mg/m^2 and AUC5). Early results were presented at ASCO in 2001 and 2002 (44,45). The paclitaxel arm showed greater neuropathy, arthralgia/myalgia, and hair loss, while the docetaxel arm showed greater neutropenia, febrile neutropenia, edema, allergy, and stomatitis. Progression-free survival curves are overlapping, and data on overall survival are still too premature at this stage. It was generally felt at the meeting that paclitaxel plus carboplatin should

remain the standard, but that docetaxel substitution can be considered in circumstances where neuropathy has to be avoided.

The Addition of Other New Drugs

An additional way to build on the results obtained with standard paclitaxel/platinum treatment is to incorporate another active agent into the initial chemotherapy approach. Several new cytotoxic agents with activity in relapsed ovarian cancer are being combined with paclitaxel plus platinum as the first step to assess their impact in randomized trials against the standard treatment. Criteria used to select drugs for further development include: (1) significant activity in paclitaxel- and platinum-resistant patients; (2) demonstration in randomized trials that the drug added a clinical benefit; and (3) a phase II trial showing a high degree of activity in combination, or in sequence, with paclitaxel and platinum (46). Promising examples include topotecan, gemcitabine, epirubicin, and liposomal doxorubicin. Because of overlapping toxicities, it has been sometimes difficult to combine some of these agents in full dose with the combination of paclitaxel and platinum. This has been overcome by using the drugs in sequence (47). As an example, the introduction of topotecan (a topoisomerase I inhibitor) in first line, in combination with the other two drugs, is taken: its use as a third drug in combination proved to be difficult (48) because of apparently synergistic toxic effects when combined with either paclitaxel and cisplatin (49,50). A solution was found in giving the topotecan as part of a couplet with cisplatin, followed by therapy with paclitaxel/cisplatin (or carboplatin). In a feasibility study, these sequential couplets proved to be feasible and the efficacy appeared encouraging (51). Another solution is to use single agent topotecan to "consolidate" first-line therapy following standard paclitaxel/platinum. Also, this second possibility has been piloted (52) and the study of both approaches in randomized trials is being awaited. Two Gynecologic Cancer Intergroup (GCIG) trials on the integration of topotecan in first-line regimens are presently ongoing; one performed by National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG)/EORTC-GCG and the Spanish Cooperative Group GEICO, and one by GOG/ICON.

Gemcitabine is a novel nucleoside analogue with a mild toxicity profile and a broad spectrum of activity against solid tumors, including ovarian cancer. Preliminary data from phase II studies in chemonaive patients with advanced ovarian cancer showed that the combination of cisplatin and gemcitabine produced an overall response rate of 53–72% with an acceptable toxicity profile (53–55). Hansen recently presented data of a triple regimen (gemcitabine/carboplatin/paclitaxel) in Indianapolis in May 2000 (56). Doses given were 800 mg/m^2 for gemcitabine on days 1 and 8, an AUC 5 (51Cr-EDTA) for carboplatin on day 1, and 175 mg/m^2 (3-hour) for paclitaxel, also on day 1. This regimen could be repeated every 3 weeks for a total of 6–8 cycles. In 28 patients (25 evaluable) treated in first line 100% responded (60% CR and 40% PR), with significant, but acceptable toxicity. In order to confirm these single institution data, a multicenter phase II trial in previously untreated patients with stages IIB–IV ovarian cancer was started in November 1998. After the initial 60 patients, who received carboplatin at a dose AUC 5, the next group of patients received an AUC of 4.5 in order to reduce thrombocytopenia. A first analysis in 27 patients again revealed a high response rate (93% with a 95% confidence interval: 76–99%) and a high clinical complete response rate (70%). Two GCIG trials are ongoing to test the inclusion of gemcitabine in first-line regimens; one by GOG/ICON and one by

AGO/Nordic Society of Gynecologic Oncology (NSGO) and the French GINECO group.

There has been a renewed interest in the use of anthracyclines. Knowing that the addition of anthracyclines to the CP combination has a real impact on survival, and considering the promising interaction between anthracyclines and taxoids in breast cancer, several groups have investigated the addition of an anthracycline (mostly epirubicin or doxorubicin, but recently also liposomal doxorubicin) to paclitaxel plus platinum. So far, the combination of epirubicin with paclitaxel and carboplatin has been the most promising because full doses of all three drugs can be given without growth factor support (57). Two large randomized trials have been launched, in which the three-drug combination (TECb) is compared with the standard-dose two-drug combination (TCb). The preliminary data of the AGO/GINECO trial of TECb vs. TCb were reported at ASCO 2001 (58). In this trial, an epirubicin dose of 60 mg/m^2 was used. Complete response rates were higher with TECb, but toxicity was likewise greater. Progression-free survival, so far, has not shown any advantage, but overall survival data were still premature. The second trial (performed by NSGO/NCIC-CTG and EORTC-GCG) used a higher dose of epirubicin (75 mg/m^2). An interim report on 784 patients again showed a somewhat higher complete response rate and greater toxicity (febrile neutropenia, nausea, vomiting, mucositis) with TECb. Data on progression-free survival and overall survival were still premature (59). Finally, GOG # 182/ICON5 studies the inclusion of liposomal doxorubicin in first line.

CONCLUSION

There has been a steady improvement in the median survival of patients with advanced ovarian cancer as result of a more skilled surgical approach to these patients and the development of more effective chemotherapy with a better integration of both modalities in first-line treatment. The current optimal chemotherapeutic approach consists of a platinum compound together with paclitaxel. Many have adopted carboplatin/paclitaxel as the new standard. There is still room for further study on how to use and to combine these two classes of compounds in the most optimal manner. Clinical trials have recently been initiated, whereby the introduction of a third drug, either combined or in sequence with the other two, is being studied. Promising examples are topotecan, gemcitabine, epirubicin, and liposomal doxorubicin. Further progress may ultimately depend on the use of novel approaches targeting cell signaling pathways and those aspects of the tumor microenvironment that support cancer invasion, growth, and metastasis. In addition, the usefulness of vaccines, gene therapy, and prevention strategies for selected high-risk patient categories are beginning clinical evaluation.

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Persistent and Recurrent Ovarian Cancer

Don S. Dizon and David R. Spriggs
Memorial Sloan-Kettering Cancer Center, New York, New York, U.S.A.

The primary treatment of ovarian cancer has become both more effective and less toxic over the past two decades (1,2). The sequential introduction of aggressive debulking surgery, cisplatin (CDDP), carboplatin, and taxanes has increased the expected survival from 6–12 months to 3–5 years, while the toxicity burden of treatment has been decreased (Fig. 1). Unfortunately, 20–30% of advanced disease patients will still not achieve a complete response to primary therapy. Even for the patients who achieve a complete response, the prospects for cure are limited. A majority will still relapse with ovarian cancer and eventually succumb to their disease. Consequently, the management of recurrent or persistent disease will involve most of the patients with ovarian cancer. Despite all of the advances in therapy of the past two decades, patients with disease after the end of primary therapy are incurable by present methods. However, the vast majority can be managed in a chronic disease condition for years. Skillful management of patients with relapsed ovarian cancer can lead to years of symptom-free and productive life. It is essential that risk of toxicity and loss of function considerations assume a prominent place in the decision making by these patients and their healthcare providers.

In order to speak clearly about these patients, specific definitions are helpful (3). *primary therapy* refers to the initial surgery and chemotherapy for the diagnosis of ovarian cancer. *Primary refractory disease* is defined by progression of disease during the primary treatment. These patients have a particularly poor prognosis. *Persistent disease* is characterized by either stable disease or a partial response after primary therapy. The persistent disease group may have elevated CA125, radiographic findings, or positive pathologic evidence of disease at the time of second-look assessment. The *recurrent disease* group is defined by a period of complete response without clinical evidence of cancer followed by unequivocal confirmation of ovarian cancer recurrence. The term *salvage therapy* has been applied to all treatment that follows the primary therapy, but should be avoided for several reasons. First, the initial usage of salvage therapy was coined in the lymphoproliferative diseases where a second curative attempt was described. Second, the term is insufficiently precise and encompasses the treatment of women with very different prognoses. Finally, the term "salvage" is considered offensive by some patients. Given the long clinical course of ovarian

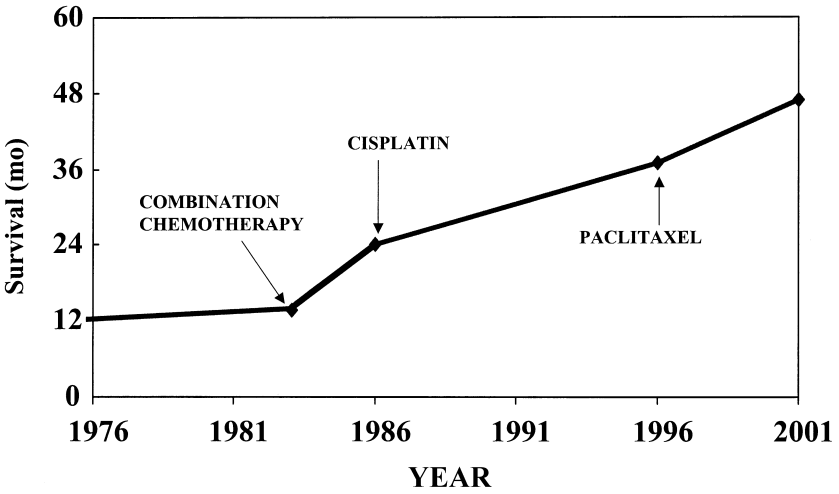

Figure 1 Progress in ovarian cancer. Median survival of advanced ovarian cancer patients participating in phase III clinical trials over the past two decades.

cancer, *chronic therapy* may be a better and more inclusive description of this phase of illness which eventually leads to a *palliative care* treatment phase at the end of life.

The biology of ovarian cancer is unique when considered with other solid tumors of epithelial origins, and knowledge of this behavior is essential to successful management. A schematic of the biology of ovarian cancer is shown in Fig. 2. The illustration is based on the classic Norton–Simon model of Gompertzian growth. The assumptions include a clinical detection limit at roughly 100 cm^3 of tumor volume as well as an expected lethal tumor burden of 1–2 kg of tumor cells (4). Growth rates are defined to predict a 6–12 month survival without effective therapy (5). Several aspects of ovarian cancer biology should be noted. First, because the organs lie deep in the peritoneal cavity, clinical screening and early detection are still terribly inadequate (6). As a consequence, over 70% of patients will have advanced stage disease with a large tumor burden at the time of diagnosis. Detection of small-volume recurrent/persistent disease is equally difficult. Next, ovarian cancer has a consistent pattern throughout its natural history. Nearly all ovarian cancer patients will have their disease confined to the peritoneal cavity and retroperitoneal nodes. Metastases to bone, lung, and brain are rare, although pleural involvement is often seen in advanced disease. Parenchymal liver disease is more common than other organ metastases, although hepatic failure and biliary obstruction are rarely important clinical problems for ovarian cancer patients. The local nature of ovarian cancer has logically led to regional treatment strategies using intraperitoneal administration (7). Finally, re-treatment with the same drugs used during the initial treatment is often highly successful in the treatment of recurrent disease. In ovarian cancer, recurrent disease is not synonymous with resistant disease. Many patients will benefit from repeated treatment with platinum complexes and achieve more than one complete response to such therapy. As shown, however, the emergence of drug resistance eventually will herald the final phase of the disease.

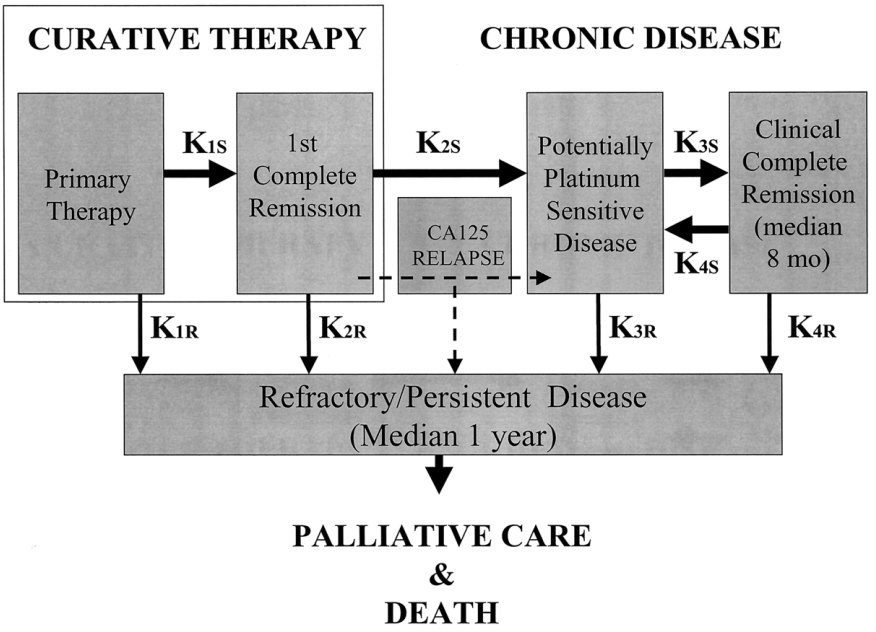

Figure 2 Gompertzian growth model of ovarian cancer.

In order to conceptualize the ovarian cancer disease process, novel frameworks may be useful. Traditional staging has been extremely useful in grouping patients into cohorts with similar prognoses at the time of first diagnosis. However, subsequent treatment and biologic behavior results in an increasing variability in the expected outcome for individual patients within the initial stage. Gynecologic cancers are not unique in this regard. It has been proposed that specific "disease states" can be defined to rationalize our clinical approach (8). A disease state model for ovarian cancer is shown in Fig. 3.

The features of the disease state model are based on the current outcomes of ovarian cancer therapy. The curative disease portion of the management is readily distinguished from the chronic management phase of ovarian cancer. The chronic disease portion of ovarian cancer is separated into homogenous cohorts including patients with serologic relapse only, "chemotherapy-sensitive" (or platinum-sensitive) disease, and platinum refractory disease. Separate groups are defined for those achieving a complete remission and the group receiving palliative care. Each of these groups is clinically defined and represents a potential population for clinical studies. Clinical remission is defined as the absence of detectable disease, using physical exam, computerized tomography, and serologic studies. Patients with abnormal CA125 and normal radiographic evaluation are included in the serologic relapse group. A platinum-free interval of at least 6 months has been used to define the chemotherapy-sensitive group, while a platinum-free interval of less than 6 months defines the platinum refractory disease state. During the natural history of ovarian cancer, the estimated probabilities of entering another disease state (but not the rate of entry) are described by the arrows and the attached numbers. The estimate of average "residence time" is also included. The individual residence times and probability estimates are

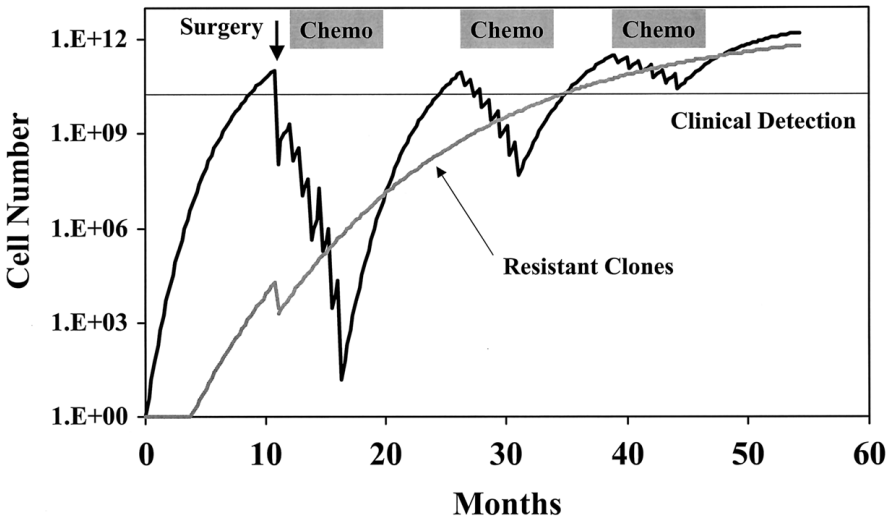

Figure 3 Disease state model of ovarian cancer. The risks of movement between the states are estimated as K1s = 51%, K1R = 49%; K3s = 42%, K3R = 58%; K4s = 54% and K4R = 46% (26,46).

taken from single institution retrospective data when randomized clinical trial data are unavailable. This paradigm of ovarian cancer will be used to structure the remainder of this chapter.

CLINICALLY APPARENT PERSISTENT DISEASE

At the end of primary therapy, those patients with clinically evident disease can be divided into three groups. Those patients with progression or stable disease during primary therapy are a particularly difficult group. While nonplatinum taxane therapy can be considered for these patients, their outlook is poor. Their management is addressed in the platinum refractory disease section. Those patients with a partial response to platinum/taxane therapy should continue on this treatment until the best clinical response is achieved. As described below, the benefits of extended therapy are uncertain, but no superior strategy has yet been established. When patients reach best clinical response, asymptomatic patients with residual disease can be observed for progression and then offered the therapies described in the platinum refractory disease section. Finally, patients with symptomatic disease may require early treatment with other drugs or consideration of a supportive care option. A schematic of this management plan is shown in Fig. 4.

COMPLETE CLINICAL RESPONSE

The biology of ovarian cancer and the heterogeneous nature of the peritoneal contents combine to make noninvasive assessment of persistent, small-volume disease inaccu-

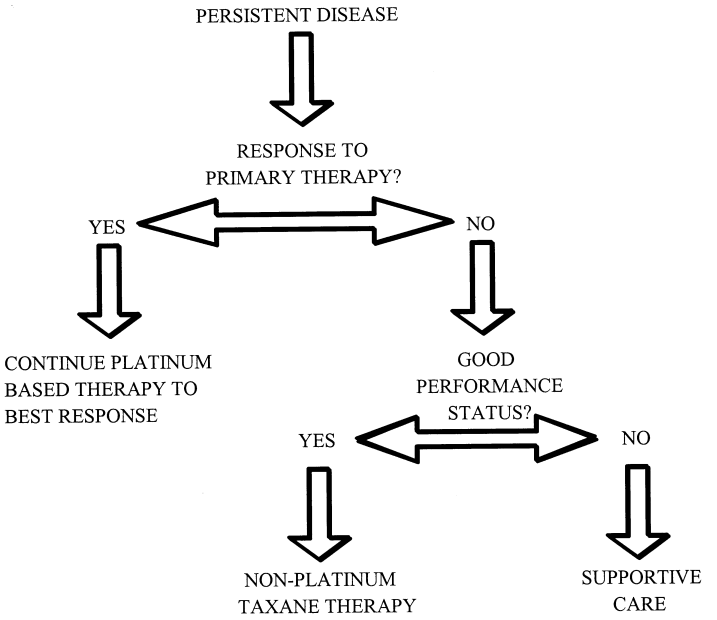

Figure 4 Management of persistent disease. Those patients with persistent disease who have had substantial tumor shrinkage on platinum and taxane therapy should continue on platinum-based therapy to best response (up to 12 cycles of therapy). At the time of best response, the patient can be closely followed for progression. Poor-performance-status patients should be offered palliative care.

rate. Tumor deposits of less than 0.5 cm will be practically invisible by current imaging technology. Yet, since most complete responders eventually relapse, it is clear that many patients in clinical remission harbor undetectable cancer. Historically, this heterogeneity has been addressed through formal surgical reassessment (or second-look surgery) at the end of primary surgery. The reassessment can be performed by either open laparotomy or, more recently, by laparoscopy. It is clear that the procedure itself is not therapeutic but certainly provides prognostic information. Less than one-half of complete clinical remission patients are pathologically negative for persistent ovarian cancer (9). Moreover, roughly one-half of the pathologically negative patients will still recur, making the fraction of cured patients less than a quarter of all clinical complete responders. The high rate of failure in the complete response patients has increased the interest in strategies to "consolidate" the complete remission with additional chemotherapy or radiation therapy.

CONSOLIDATION THERAPY FOR PATIENTS IN 1ST COMPLETE REMISSION

Several different strategies have been proposed to extend the remission or prevent recurrence in this group. All of these treatment plans are investigational. However, this

is an active area for clinical research, and additional studies are certain to continue to appear in this area.

Extended Therapy

It is surprising to realize that the appropriate duration of ovarian cancer therapy remains uncertain. In retrospective analyses, there is some suggestion that longer treatment may be beneficial. For example, a pretaxane era review of 116 optimally debulked ovarian cancer patients treated at the MD Anderson Cancer Center found that 12 cycles of therapy were substantially better than 6 cycles of platinum-based chemotherapy (the progression-free survival was 30 months for the 12-month group and 15 months for patients receiving 6 cycles of treatment; $p < 0.0004$) (10). Two randomized trials have suggested that 5 or 6 cycles of platinum-based therapy is sufficient. In a study of 70 patients, Hakes et al. were able to show no benefit to 10 cycles of cyclophosphamide, doxorubicin, and cisplatin over a 5-cycle control group. In a slightly larger study, 202 patients received either 6 or 12 cycles of therapy with the same regimen. Neither the median nor the 3-year survival rate was different between the two arms. It is notable that neither study included a taxane as the primary therapy. The Southwestern Oncology Group compared 3 cycles to 12 cycles of paclitaxel, administered every 4 weeks, with a disease-free survival for the prolonged treatment aim. In Europe, the "After 6" clinical trials group is comparing weekly paclitaxel to observation. Another strategy is the use of another non-cross-resistant agent, such as topotecan. In a pilot study of small-volume disease patients, 38 women with ovarian cancer received 4 cycles of topotecan, administered in the usual five-consecutive-day schedule. A "third-look" assessment was done for patients without clinical evidence of disease. Ten patients (28%) were free of disease at surgical reassessment (11).

Intraperitoneal Chemotherapy

The unique localization of ovarian cancer to the peritoneal cavity has made this disease a natural target for regional therapy. The literature regarding intraperitoneal therapy is summarized in recent reviews detailing more than two decades of preclinical and clinical work (7,12). To briefly summarize, the theoretical advantages of intraperitoneal administration include very high concentrations of drug, long exposure times, and efficient delivery of drug to small, prevascular tumor cell deposits. All authorities would agree that intraperitoneal therapy should only be considered for patients with platinum-responsive disease, residual tumor less than 0.5–1.0 cm, and an expectation that full abdominal distribution can be achieved. Even for this select group of patients with persistent disease, no randomized clinical trial data currently exist. Table 1 summarizes some of the literature on intraperitoneal therapy. In general, the surgical response rates are high and include complete pathological responses in about 25% of small-volume disease patients. The use of intraperitoneal cisplatin for patients with pathological complete response deserves particular comment. Investigators at Memorial Sloan Kettering Cancer Center enrolled 38 patients in a clinical trial of 3 cycles of intraperitoneal cisplatin and etoposide (13). Only 39% relapsed, including only 28% of those receiving all three courses of treatment. These promising results have not been subjected to randomized clinical trial confirmation. A random-

Table 1 IP Consolidation Therapy for Small-Volume Disease

Author	Ref.	# of points	Regimen	Median Response rate	Median survival
Markman	(79)	58	Cisplatin +	48% (surg) 28% CR	NR
Markman	(80)	11	Mitoxantrone	31% PR	NR
Howell	(81)	25	Cisplatin +	NR	>49 months
Muggia	(82)	39	Mitoxantrone		
		28	FUDR	NR	38 months
Barakat[a]	(13)	38	Cisplatin	NR	>3 years

NR = Not reported.
[a] The Barakat study required negative second-look surgery for entry.

ized trial of IP cisplatin against no therapy for such patients was attempted in Europe but closed for poor accrual.

In a retrospective analysis of intraperitoneal therapy at Memorial Sloan Kettering Cancer Center, the records of more than 400 patients in clinical complete remission who underwent surgical reassessment were reviewed. In this large group, less than a quarter were pathologically disease-free (89 patients), while 131 had only microscopic residual disease, 143 had residual disease less than 1 cm, and 45 had disease greater than 1 cm in size. While these patients received a variety of intraperitoneal treatments, the divergence of outcome was profound. Median survival for those receiving IP therapy as consolidation for a pathologic complete remission to intravenous, frontline chemotherapy (negative surgical assessment at the start of IP treatment) was 8.7 years, while those with microscopic residual survived a median of 4.8 years. Patients with disease less than 1 cm had a better prognosis than those patients whose gross residual disease was greater than 1 cm (3.3 years vs. 1.2 years, $p < 0.01$). While it is uncertain how the intraperitoneal therapy altered the group outcome, it is clear that the clinical complete response group is extremely diverse and many of these patients with small-volume residual disease will enjoy extended survival.

Radiation Therapy as Consolidation

The use of radiation therapy in consolidation has a long and checkered history. In a review of 28 different reports, Thomas found that efficacy was clearly related to the volume of disease (14). A more recent clinical trial also examined radiotherapy consolidation. In a trial of consolidation radiotherapy, 51 patients with persistent disease at second-look assessment received whole abdominal radiation therapy to 22.5 Gy followed by a pelvic boost of 22.5 Gy. Twenty-seven percent of the patients could not complete therapy and one patient experienced a colon perforation. The 5- and 10-year survivals were 27% and 10%, respectively (15).

Immunological Consolidation Strategies

It is thought that molecules like cytokines and antibodies are very slowly removed from the peritoneal cavity because of very slow diffusion. The biology of ovarian

cancer with its predominant peritoneal distribution makes ovarian cancer an attractive target. Immune-based strategies have yet to become established as useful approaches to consolidation of advanced disease. However, the use of cytokines and antibodies has been tested in a limited number of patients with advanced stage ovarian cancer in complete clinical remission.

Interferon-γ has important activity as an activator of a variety of immune cells including T cells and monocytes. It is a potent activator of macrophage-mediated cytotoxicity against ovarian cancer cells in vitro and in vivo (16,17). In patients with persistent disease at second-look surgery, Pujade-Lauraine et al. (18) conducted a phase II study of intraperitoneal interferon-γ at a dose of 50×10^6 IU/m^2 twice weekly. Nearly two-thirds (66%) had residual tumor ≤2 cm. The objective response rate was 31% and complete response rate was 23%. In the multivariate analysis, younger age (60 years vs. <60 years, $p = 0.004$) and small tumor size (≥2 cm vs. <2 cm, 11% vs. 43%, $p = 0.006$) were independent predictors of response. Fever was reported in 94% of the patients and neutropenia was rare.

Interleukin-2 is another cytokine which has enjoyed some success in cancer treatment. Like interferon-gamma, interleukin-2 is a large molecule that has a long intraperitoneal half-life. Interleukin-2 is a potent activator of T-cell-mediated responses including both cytotoxic T cells and natural killer cells. IL-2 therapy has been tested in a small phase II trial of ovarian cancer. Edwards et al. (19) found a response rate of 25.7% including 17% of complete responses among 35 patients with ovarian cancer. Most of the patients had small-volume residual disease (≤2 cm) and only one prior chemotherapy regimen. Surprisingly, the response rates were different for platinum-resistant and -sensitive patients (14.8% and 35.7%, respectively). The median survival for the entire group was 13.7 months. The residual tumor size was an independent prognostic factor for survival (microscopic disease vs. macroscopic disease, $p = 0.005$). The toxicity of IL-2 administration was significantly greater in the 7-day continuous infusion schedule compared to the 24-hr infusion regimen administered weekly. Local toxicity (abdominal pain, fibrosis, enteric fistula, and bowel perforation) was the most common side effect in both schedules. Hypotension complicated more than 3/4 of the treatments. Nausea, anemia, and fever were also common.

A placebo-controlled, double-blind, randomized control trial of the murine monoclonal antibody mAB B43.13 (Ovarex) has been performed in the consolidation setting (20). In this trial, 345 women were randomized to receive either placebo or repetitive intravenous injections of a murine antibody against CA125. In a preliminary analysis of 252 women, Berek et al. found that there was no significant difference between the placebo group and the group receiving murine antibody. The toxicity was modest and additional follow-up is required.

High-Dose Consolidation Chemotherapy

The use of high-dose chemotherapy for patients with ovarian cancer has enjoyed substantial popularity despite the lack of convincing evidence of benefit. A recent review of the American experience was conducted by the Autologous Blood and Marrow Transplant Registry. This report summarizes 421 patients from 57 participating centers transplanted between 1989 and 1996. Although most of these patients

had relapsed prior to transplantation, 32 were in first clinical remission. In this consolidation treatment group, there was a 9% risk of death in the first 100 days and a 62% probability of survival at 2 years. These results are disappointing, given the young age of the patients treated and the exclusion of clear cell cancer patients from the analysis (21). However, a randomized phase III trial of high-dose therapy has been presented in abstract form (22). All patients had platinum-based induction therapy and had either small-volume disease (41%), microscopic residual disease (20%), or a pathological complete response (39%). In this study, patients were randomized between a single high-dose treatment with carboplatin (400 mg/m^2/day $\times$ 4 days) and cyclophosphamide (1500 mg/m^2/day $\times$ 4 days) and three cycles of standard maintenance therapy consisting of carboplatin 300 mg/m^2 and cyclophosphamide 500 mg/m^2. After a median of 36 months of follow-up, the median disease-free interval was 11 months for the conventional dose group and 22 months for the high-dose treatment arm. The disease-free interval is not astonishing for a group of patients in clinical complete response and is similar to the results from GOG 114 (23). Survival data are not yet available for this study. While these early results are somewhat encouraging, there is no place for high-dose therapy outside a clinical trial at the present time.

As yet, none of the consolidation strategies outlined above have been proven to be effective. In small studies, each is associated with apparent benefit in less than 1/3 of patients with persistent disease. The standard of care for patients in complete clinical remission after primary therapy should be routine follow-up.

ROUTINE FOLLOW-UP AND SEROLOGIC RELAPSE

Like other aspects of ovarian cancer management, the best follow-up plan for ovarian cancer patients is uncertain. Most authorities would favor routine follow-up visits every 2–3 months for at least 2 years with every 4–6 month follow-up thereafter. Each visit should include a physical examination and a CA125. Radiographic studies including abdominopelvic CT scans and chest x-rays are recommended as clinically indicated but not as routine follow-up care. When CA125 is employed as a part of standard follow-up care, isolated elevations of the CA125 are common. It is generally thought that an elevated CA125 is a reliable harbinger of recurrence, and this has been confirmed in prospective trial. In a study of 255 patients, a single CA125 of >60 U/ml had an 85.9% sensitivity and a specificity of 91.3% (24). A second confirmatory CA125 reduced the false positive rate to $<2\%$. This early diagnosis appears to lead the development of radiographically detectable disease be several months. Unfortunately, there are no data to support the initiation of treatment at the time CA125 is noted to be elevated. At the time of an elevated CA125 value, a careful reevaluation is required, including full physical examination, abdominal/pelvic computerized tomography, and at least a chest x-ray. For asymptomatic patients with little or no disease after full evaluation, hormonal therapy with tamoxifen has been advocated. The Gynecologic Oncology Group reported an objective response rate of 18% for tamoxifen administered at 20 mg twice daily and this has been supported in other studies (25). The initiation of chemotherapy for an isolated CA125 should be discouraged, and every effort should be made to delay treatment until detectable disease is present by radiographic evaluation or physical exam.

RECURRENT DISEASE: CHEMOTHERAPY-SENSITIVE DISEASE

Recurrent disease can be defined as disease that is evident by clinical measures including radiographic changes, physical examination, and serologic testing. It is important to emphasize that other diseases, both benign and malignant, can have a clinical presentation similar to recurrent ovarian cancer. While histologic confirmation of recurrent disease is not always required, strong consideration should be given to fine-needle aspiration or biopsy of suspicious lesions at the time of first recurrence. It is particularly important to obtain tissue from patients with atypical clinical histories. The management of recurrent disease should be divided into the "Chemotherapy-Sensitive Disease Group" and the "Platinum Refractory Group."

As noted above, a majority of patients with epithelial ovarian cancer will respond to treatment with a platinum-taxane containing regimen during primary treatment, but most will go on to develop recurrent disease (26,27). Despite this common clinical scenario, there is no consensus on how best to manage these patients. A reasonable treatment plan is shown in Fig. 5. The platinum-free interval, defined as the time between the end of up-front therapy and the initiation of second-line

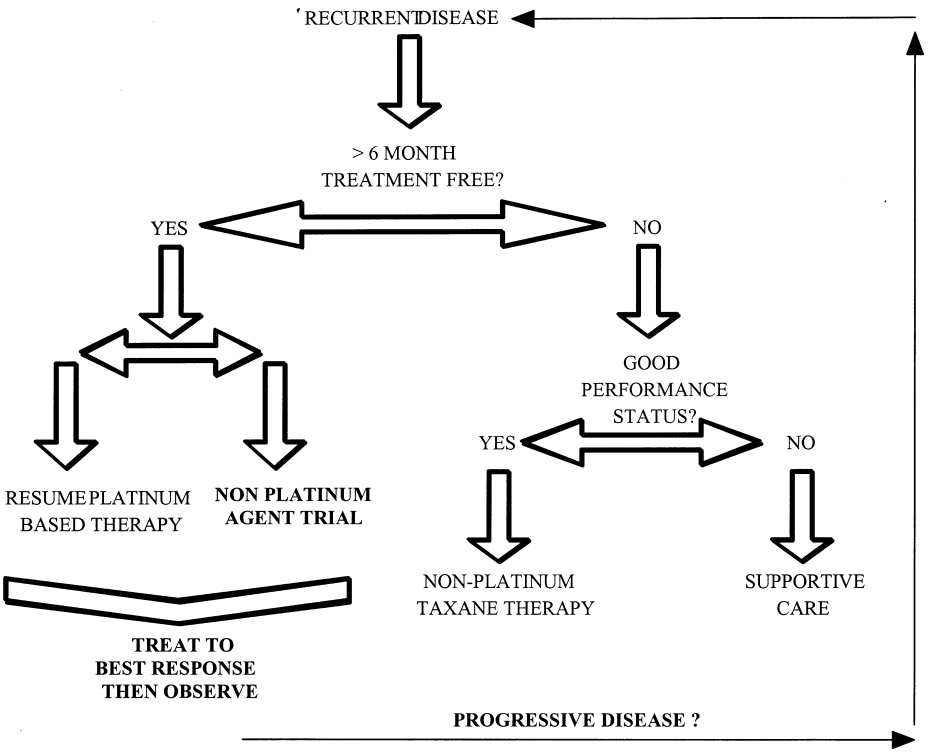

Figure 5 Management of chemotherapy-sensitive disease. For patients with a greater than 6-month treatment-free interval, a second treatment with platinum-based therapy, usually with a taxane, is recommended. Asymptomatic patients with small volume disease may be carefully treated with a nonplatinum taxane agent or an investigational drug. Early crossover onto platinum/taxane therapy is required for those patients with progressive disease.

treatment, plays an important role in this choice with response rates that range from 27% with a disease-free interval of 1 year to 77% after 2 years (28). Two key questions currently exist for these patients, neither of which has been addressed by published literature. First, is platinum analog therapy, particularly carboplatin, preferred over nonplatinum-based treatment? Second, is there any merit to combination therapy over single agent platinum complex treatment?

Re-treatment with Platinum

There are several small reports published over the past decade that suggest that platinum treatment is probably the preferred choice. Those studies are summarized in Table 2. These studies agree that the response rate to platinum-based therapy is high. It should be noted that carboplatin is markedly less toxic than cisplatin and carboplatin is the preferred agent for nearly all patients receiving platinum-based therapy. However, severe thrombocytopenia problems or allergy to carboplatin may prevent repetitive use of carboplatin. Carboplatin allergy is characterized by appearance after multiple treatments (usually more than 6) and may occur in 25% or more of patients receiving more than 6 cycles of carboplatin (29). The reactions can be severe with bronchospasm and hypotension. A skin testing protocol has been suggested which may help identify those patients at risk (30). While re-treatment with cisplatin has been successfully accomplished, a rechallenge with either carboplatin or cisplatin should be undertaken with great caution since fatal reactions may occur (31). Since recurrent ovarian cancer is not curable, the risk of severe reaction probably outweighs any possible benefit of additional platinum re-treatment in the allergic patient. The most remarkable thing about re-treatment with carboplatin is the high rate of second complete remission. The low toxicity of carboplatin and the high response rate make it an ideal regimen for the treatment of recurrent disease. Patients with an extended second remission (platinum-free interval >6 months) may benefit from multiple courses of carboplatin at the time of second or subsequent relapse.

Re-treatment with Other Agents

Although the platinum re-treatment option has been generally preferred, therapeutic options go beyond cisplatin or other platinum analogs. A variety of agents are currently available for treatment of recurrent ovarian cancer. In addition to carboplatin, cisplatin, and paclitaxel, other agents with known activity include topotecan (32), liposomal doxorubicin (33), gemcitabine (34,35), docetaxel (36–38), and oral etopo-

Table 2 Platinum-Based Therapy for Chemotherapy-Sensitive Disease

Author	Ref.	# of points	Regimen	Response rate (CR)	Survival (months)
Gershenson	(83)	19	Cisplatin	100% (50%)	19
Rose	(84)	25	Carbo/taxol	90% (70%)	9+
Goldberg	(85)	49	CDDP/taxol	53% (37%)	12
Dizon	(46)	84	Carb/Taxol	68% (42%)	>30

side (39). It has been proposed that intervening, nonplatinum complex therapy may be used to "extend the platinum-free interval" and increase the likelihood of a second platinum response (40). There is limited information to support this approach. It is primarily based on a retrospective series of patients from the MD Anderson Hospital who received carboplatin after a taxane (41). In this experience, there was a 21% partial response rate for patients with either persistent disease after platinum-based primary therapy or primary refractory disease. All patients had a taxane as the intervening therapy, and all responding patients had a platinum-free interval of at least 12 months. While this is interesting, several problems exist. First, the response rate is still only 21% and no complete responses were identified. Furthermore, 17 of the 33 patients included had either persistent disease, which had responded to platinum-based therapy, or potentially platinum-sensitive disease. Since the response rate to carboplatin in this population is relatively high, the results are less compelling. Finally, the experience is exclusively relevant for those patients receiving a taxane as the intervening treatment.

Nonetheless, there is no doubt that patients with platinum-sensitive disease are much more likely to respond to nonplatinum therapy. Topotecan has been studied specifically in this population (32). The Gynecological Oncology Group (GOG) enrolled 48 patients with platinum-sensitive recurrent disease and treated them with topotecan 1.5 mg/m^2/day for five consecutive days every 3 weeks. The overall response rate was 32.6% with an additional 48% stable disease rate. Median progression-free interval and overall survival in the cohort were 9.6 and 20 months, respectively. Toxicity associated with this schedule was primarily hematologic including 47 cases of Grade 3–4 neutropenia, 7 episodes of febrile neutropenia, and 19 patients requiring blood transfusions during treatment. In addition, a debilitating fatigue syndrome was reported in 15 patients and represented a common reason for discontinuation. Compared to the 12.4% response rate seen in a large phase II study of platinum refractory disease, this is remarkably better (42). Similar data are available for other alternative agents including etoposide, doxil, and taxanes (see Table 3). Of particular note, a randomized trial was recently conducted evaluating liposomal doxorubicin vs. topotecan in the treatment of patients with relapsed ovarian cancer (33). Of the 474 patients enrolled, 220 patients were considered platinum-sensitive. One hundred nine were randomized to liposomal doxorubicin and 111 were randomized to topotecan. The CR and overall response rates were similar for both agents: 7.3% and 28.4% with liposomal doxorubicin, respectively, and 9.0% and 28.8% with topotecan, respectively. Time to progression for both regimens was identical at 4.5 months. However, overall survival with liposomal doxorubicin was approximately 22 months vs. 16 months with topotecan which was statistically significant ($p = 0.012$). The platinum-sensitive response rates are similar to the 25–35% response rates associated with platinum re-treatment before 24 months has elapsed. Of note, in breast cancer, a randomized phase III study was conducted to evaluate the effect of single agent therapy prior to cyclophosphamide, doxorubicin, and 5-fluorouracil for metastatic disease (43). The use of single agent therapy (even for inactive drugs) did not statistically affect either response rate or survival. Moreover, it has been shown with topotecan that achieving stable disease has the same impact as partial response in both ovarian cancer and small cell lung cancer (44).

Based on the current literature, most authorities would agree that carboplatin or carboplatin + taxane treatment is preferred for patients with symptoms or patients

Table 3 Chemotherapy for Patients with Platinum-Sensitive Ovarian Cancer

Drug	Regimen	N[a]	Overall response rate (%)	Median progression free interval (months)	Median survival (months)
Platinum + Paclitaxel (46)	NA	57	64.9	12	27+
Topotecan (29)	1.5 mg/m^2/day × 5 days q 28 days	46	33	9.6	20.2+
Topotecan vs. liposomal doxorubicin (33)	1.5 mg/m^2/day × 5 days q 28 days	111	28.8	4.5	14.8
	50 mg/m^2 q 4 weeks	109	28.4	4.5	20
Gemcitabine (61)	800 mg/m^2 q week × 3 q 4 weeks	7	14	2.8	6.2
Docetaxel (86)	70 mg/m^2 q 3 weeks	24	33	5[b]	13[b]
Etoposide (39)	50–60 mg/m^2/day × 21 days q 28 days	41	34.1%	6.3+	16.5+

[a] Only patients with platinum-sensitive disease are included in this table.
[b] Reported for entire cohort, not stratified by platinum-free interval.

with a treatment-free interval exceeding 24 months. Treatment of patients with a shorter treatment-free interval is controversial. Asymptomatic patients with a treatment-free interval of 6–24 months and whose disease measures less than 5 cm in greatest dimension may be reasonably offered either platinum or nonplatinum therapy. Early crossover to platinum-based therapy should be provided for patients with progressive disease or significant toxicity.

Combination Therapy for Relapsed Disease

Given the response rates seen with primary therapy, it is logical to ask if combination therapy might improve the outcome for patients with platinum-sensitive recurrent disease. Again, there is little in the way of randomized data to help answer the question of whether combination chemotherapy is superior to single agent therapy. A recent randomized trial of carboplatin vs. combination therapy was recently published by the ARGO Study Group in Italy. In this trial, 190 patients were randomized to the combination of epidoxorubicin and carboplatin vs. carboplatin. The overall response rate for both groups was 52%. The median duration of response was 20 months in the combination group and 16 months in the carboplatin group ($p = 0.16$). A trend toward improved 3-year progression-free and overall survival was seen favoring combination therapy over carboplatin alone, 25% and 42% vs. 12% and 29%, respectively, although this also was not statistically significant. As would be expected, the combination group was also associated with more adverse effects, including leukopenia, anemia, thrombocytopenia, and grade 3 alopecia. The authors concluded that no additional benefit was seen with combination over single agent platinum therapy. However, as proposed in an accompanying editorial, despite not reaching

statistical significance in terms of survival endpoints, it may be more attributable to study size, as opposed to lack of difference, and that a larger study may be needed to show "significance" (45).

The use of carboplatin and paclitaxel at the time of recurrence is favored by the large, randomized ICON4 trial with a significant advantage in overall survival, although the trial includes many taxane-naive patients. Retrospective data also suggest that this combination may be beneficial. In a recent review conducted at Memorial Sloan Kettering, 84 women were identified that received this combination at relapsed from initial therapy for ovarian cancer. The median treatment-free interval was 22 months (7–86 months) (46). The overall response rate was 68% (42% CR + 26% PR). The median progression-free interval (PFI) was 13 months (95% CI: 10.7–13.8 months). Median follow-up was 27 months (range, 3.8–75.2 months) with an estimated 3-year survival rate of 72% (95% CI: 59.4–86.1%). There were no treatment-related deaths associated with this regimen. However, 8% of patients had worsening of their baseline neuropathy prompting discontinuation of therapy. There were also five cases of carboplatin-related allergic reaction.

Re-treatment with Taxanes

Another commonly advocated approach is re-treatment with taxane therapy. In patients who have not received a taxane as part of primary therapy, re-treatment with a regimen including paclitaxel is probably now the treatment of choice. In the initial studies of paclitaxel, a very high response rate (15–30%) was observed in taxane naive patients (47–50). Similar results have been presented for docetaxel (37,51). However, few patients now fail to receive a taxane during primary therapy. The practice of re-treatment with a taxane is quite common in recurrent disease. In this setting, the importance of a treatment-free interval is less well established. In one report of patients with platinum/paclitaxel-treated patients, treatment of relapsed cancer with paclitaxel resulted in a response rate of 44% (52). It has also been proposed that changing either the agent or the schedule of taxane treatment may be beneficial. In small phase II experiences, docetaxel has been advocated as non-cross-resistant with paclitaxel (36,51). Similarly, a weekly paclitaxel schedule (80–100 mg/m^2/week over 1 hr) has also been reported to give responses in patients refractory to paclitaxel treatment (53,54). While neither approach can be considered standard, these approaches are at least equivalent to treatment with a nonplatinum, nontaxane therapy.

A management plan for platinum-sensitive disease patients is shown in Fig. 5. A platinum taxane combination is favored over single agent platinum. The comparative value of other agents with carboplatin is under study in these patients. Until then, the issues regarding management of this population remain somewhat controversial.

RECURRENT DISEASE: PLATINUM-RESISTANT DISEASE

Acquired Drug Resistance

The acquisition of chemotherapy resistance remains one of the most difficult problems in ovarian cancer management. In general, the resistance to cisplatin is associated with resistance to a variety of other agents as shown in Table 4. The mechanisms of resistance and their evolution remain uncertain. In a general sense, resistance can be

attributed to host factors and cellular factors. Host factors are nonspecific and may include altered pharmacokinetics, poor tumor blood supply, hypoxia, and acidosis, increased interstitial pressure, and improved drug inactivation or excretion. Cellular resistance factors include decreased accumulation in tumor cells, intracellular inactivation by cellular sulfhydryls or other defenses, enhanced DNA damage repair, and impaired tumor cell apoptosis. The topic of anticancer drug resistance is broad and a detailed discussion is beyond the scope of this chapter. However, certain specific mechanisms deserve particular mention.

A large number of anticancer agents are excreted by the P-glycoprotein, a 170-kDa transmembrane protein encoded by the MDR1 gene (55). Substrates of the P-glycoprotein include the taxanes, the anthracyclines, the etoposide, and the vinca alkaloids. Increased expression of P-glycoprotein results in a marked diminution of intracellular drug concentrations due to ATP-dependent extrusion. Cisplatin, 5FU, and a variety of alkylating agents do not appear to be substrates for the P-glycoprotein action. However, cell lines treated with these agents appear to have increased MDR1 gene expression (56). The clinical importance of P-glycoprotein expression has been controversial. However, a recent study using the orally bioavailable agent, Valspodar, has suggested that blocking the action of the P-glycoprotein alone reverses paclitaxel resistance in only about 8% of patients (57). From this experience and others like it, one can conclude that resistance is likely to be multifactorial in nature and any single reversal strategy is likely to fail.

Cisplatin resistance appears to be different than the P-glycoprotein substrates. Like the taxanes, however, investigations to date have identified a similar multifactorial basis for cisplatin resistance that involves one or more of four major mechanisms: (1) decreased drug accumulation, (2) increased intracellular detoxification (through elevated levels of glutathione and/or metallothioneins), (3) alterations in DNA repair, and (4) apoptosis failure. Accumulation of cisplatin is decreased in cells with acquired resistance, probably through the loss of a membrane transporter, perhaps from the multidrug-resistance protein family (58,59). Increased DNA repair proficiency has been reported in platinum-resistant cell lines as well, although the loss of mismatch repair is also associated with the acquisition of platinum resistance (60). Both loss of mismatch repair and increased expression of ERCC-1 are potential mechanisms.

Table 4 Response Rates for Common Chemotherapy Agents

	Response %	
Currently available drugs	Cisplatin-sensitive	Cisplatin-resistant
Etoposide	35	25
Liposomal doxorubicin		14–20
Docetaxel	27	38
Topotecan	33	12
Vinorelbine		15
Gemcitibine		15
Hexalen	27	10

In general, it appears that resistance to CDDP appears to be polygenetic. That is, expression of any single gene (ERCC-1, glutathione S transferase, as well as others) in a sensitive cell type provides only a modest increase in CDDP resistance. This has made it difficult to identify appropriate targets for resistance reversal, although both repair and detoxification strategies have been employed clinically, albeit with limited success. Although apoptosis failure has been proposed as a mechanism of action, limited information is available about failure of apoptosis as a mechanism.

Clinical Approach to Platinum-Resistant Disease

The most difficult aspect of ovarian cancer management is the treatment of platinum-resistant disease. Patients with platinum-resistant disease are less likely to respond to other chemotherapy agents, and complete response to chemotherapy is rare in this group of patients. Although some patients are asymptomatic in the platinum-resistant disease state, many will experience pain, abdominal bloating, ureteral obstruction, and even intestinal obstruction in this phase of their illness. Worse, the toxicity of the second-line agents is more onerous than the side effects associated with carboplatin and the taxanes. Even with the best of medical management, the life expectancy of patients with platinum-resistant disease is generally about 1 year or less.

The goal of treatment must be palliation of symptoms. However, it appears that the limited goals of therapy are often not communicated to the patient. In a study from the Princess Margaret Hospital, 27 patients were queried about the goals and success of their second- and third-line chemotherapy (61). Seven of the twenty-seven experienced an objective response. Yet, 65% of women expected that chemotherapy would extend their life, while 42% expected the therapy to cure them. Nonetheless, after 2 cycles of therapy, both global functioning and emotional functioning were clearly improved. Certain factors can be used to select patients for chemotherapy intervention to decrease the risk of futile therapy. In a study from the late 1980s, Blackledge et al. (62) showed that response to treatment with Phase II investigational drugs was most dependent on original stage of disease and interval since last therapy. The best prior response was also found to be a useful predictor of response. More recently, Eisenhauer et al. (63) looked at 704 patients previously treated with platinum and their response to subsequent therapy. Serous histology, performance status, tumor size less than 5 cm, normal baseline hemoglobin, and $\geq$6 months since last therapy were all individually associated with response. Number of prior regimens was not found to be predictive. In the multivariate analysis, only serous histology, tumor size, and number of lesions were significant variables (63). In a study from Memorial Sloan Kettering Cancer Center, the success rate for patients with complete intestinal obstruction was also examined (64). In the relapse setting, no patient with intestinal obstruction had resumption of normal bowel function. While these analyses are incomplete, they do provide insight into the likelihood of benefit for individual patients.

The number of alternative treatments for patients with platinum-resistant disease has increased dramatically in the past decade. A number of the most common alternatives are shown in the Table 5 along with the usual schedule and most common side effects. For any of these agents, the response rates for patients with platinum-resistant disease are generally in the 10–20% range. Combination therapy in the setting of platinum-resistant disease is a toxic undertaking of uncertain value. There

Table 5 Agents for Treatment of Platinum-Resistant Disease

Agent	Schedule	Toxicities
Paclitaxel	Weekly	Neuropathy
Docetaxel	Once every 3 weeks	Myelosuppression
Topotecan	Daily × 5 q 3 weeks	Myelosuppression
Irinotecan	Weekly × 4 q 6 weeks	Diarrhea, myelosuppression
Liposomal Doxorubicin	Once q 4 weeks	Erythrodysesthesia
Epirubicin	Once every 3 weeks	Myelosuppression
Etoposide	Oral for 2–3 weeks	Mucositits, myelosuppression
Vinorelbine	Weekly	Myelosuppression, neuropathy
Gemcitabine	Weekly × 2 q 3 weeks	Myelosuppression
Ifosfamide	Daily × 3–5 q 3 weeks	Myelosuppression, hematuria
Capecitabline	Twice daily for 14 days	Erthrodysesthesia, mucositis
5FU/Leucovorin	Multiple	Mucositis, myelosuppression

are no randomized trials comparing nonplatinum/taxane combinations against single agent therapy. For advanced, incurable cancers, combination therapy generally has slightly higher response rates that are usually offset by higher toxicity as well. As a consequence, single agent therapy will be the preferred choice for most practitioners. The choice among these treatments is based on most acceptable toxicity, schedule, and sometimes cost. The duration of treatment is also controversial. Both McGuire et al. (32) and Gordon et al. (33) reported a high frequency of stable disease during therapy with topotecan and liposomal doxorubicin. Since cumulative toxicity is not often seen, patients may be maintained on therapy until either toxicity or progression forces an end to their therapy (32,33). Extended periods of stable disease are sometimes beneficial to patients in this setting (44).

Randomized Trials

There are a small number of randomized trials for patients in the chronic disease state and only two substantial trials for nonplatinum-based treatment. The first is the pivotal trial for topotecan, comparing topotecan to paclitaxel in taxane naive disease. In this study of 226 patients with prior platinum treatment, topotecan (1.5 mg/m^2 daily × 5) was compared to paclitaxel (175 mg/m^2), administered once every 3 weeks (65). The response rate was 20.5% for topotecan treatment and 13.2% for paclitaxel treatment. Roughly 30% of each group achieved stable disease for ≥8 weeks. Only about 5% of the patients reached a complete response with either agent. In the platinum refractory subgroup, the response rates were 13.3% for topotecan and only 6.7% in the paclitaxel arm. As in the previously studied groups, patients with bulky (>5 cm) tumors had response rates much lower than the small-volume disease group. The median survival was 61 weeks for the topotecan group and 43 weeks for the paclitaxel group. Because of the small sample size, none of these differences were statistically significant. Both agents caused significant (Gr 3/4), noncumulative myelosuppression, although the topotecan was clearly worse. Although interesting, it must be noted that the observed paclitaxel response rate in this study is among the lowest

ever reported. In a recent follow-up report, the crossover response rates were also assessed. In the 61 patients who received topotecan as third-line therapy, 13.1% responded, while among the 49 patients receiving paclitaxel at the time of crossover, the response rate was 10.2% for paclitaxel (66). The authors conclude that topotecan and paclitaxel appear to be clinically non-cross-resistant agents.

The other major randomized clinical trial compared pegylated liposomal doxorubicin (Doxil) to topotecan. In this study, 474 patients were randomized to receive either pegylated liposomal doxorubicin (50 mg/m^2 every 4 weeks) or topotecan (1.5 mg/m^2 daily $\times$ 5, every 3 weeks) (33). Patients were stratified for platinum-free interval and bulk of disease. In an interim analysis report of all patients, the response rate for pegylated liposomal doxorubicin was 20% while the topotecan response rate was 17% ($p = 0.393$). The complete response rate was $<5\%$ for either arm. The median survival was 49 weeks for topotecan and 53 weeks for the pegylated liposomal doxorubicin. However, for the platinum-resistant disease group, the response rates were 12.3% for liposomal doxorubicin and 6.5% for the topotecan arm. The median survival for the two arms was 33 and 37 weeks, respectively.

Single Agents: Topotecan

Topotecan is the best studied of the new agents for refractory disease. Topotecan is a topoisomerase I inhibitor, leading to single-strand breaks, DNA fragmentation, and death (67,68). It is usually administered in a 1.2–1.5 mg/m^2 dose consecutively once every 3 weeks. However, in patients with prior carboplatin exposure, a dose of 1.0–1.2 mg/m^2 is probably more appropriate. In the face of renal insufficiency, even lower doses are needed (69). As noted above, the improvement rate is expected to be in the 10–15% range for platinum refractory patients with another 30% achieving stable disease. This stable disease may persist for an extended period, providing selected patients with substantial clinical benefit from prolonged treatment. Since the toxicity of topotecan is not cumulative, this represents a potentially useful approach. The principal toxicity of topotecan is myelosuppression, including white cells, platelets, and red cells. Granulocyte colony stimulating factor support and erythropoeitin treatment are often required, adding substantially to the cost of therapy.

Single Agents: Liposomal Doxorubicin

Pegylated liposomal doxorubicin (Doxil) is also active in the treatment of ovarian cancer (70). Because of its liposomal vehicle, the toxicity and efficacy profile of the anthracycline base is altered. Like topotecan, it is more active in platinum-sensitive disease, although it has modest activity in platinum refractory disease as well (33). The usual dose is 50 mg/m^2 every 4 weeks, although patients with significant prior therapy may tolerate a 40 mg/m^2 dose much better. Unlike topotecan, liposomal doxorubicin has little myelotoxicity. Instead, its principal side effect is a characteristic erythrodysesthesia or hand–foot syndrome. This skin toxicity is characterized by erythema, peeling and pain involving the palms and soles. The hand–foot syndrome is best managed by emollients and treatment delay since it appears that treatment interval and not dose is the principal determinant of toxicity. While cardiotoxicity from

pegylated liposomal doxorubicin is very uncommon, care to monitor ejection fraction beyond the 400 mg/m^2 cumulative dose is reasonable.

Single Agents: Gemcitabine

Another agent of potential use in advanced ovarian cancer is Gemcitabine. This deoxycytidine analog is incorporated into DNA as a fraudulent nucleotide and results in reduplication and early chain termination events. It has not yet been studied in a direct comparison with either liposomal doxorubicin or topotecan. In small phase II trials, it appears to provide partial responses of 10–15% of patients treated (71–73). Gemcitabine is dosed at 800–1000 mg/m^2/week for two or three consecutive weeks followed by a rest week. Its principal toxicity is myelosuppression, affecting both white cells and platelets. Of particular note is its preclinical synergy with cisplatin, making it a potentially interesting combination for further testing in both the primary treatment and recurrent disease settings (74,75).

Single Agents: Etoposide

Although IV etoposide has little activity, protracted oral etoposide appears to be highly active in the treatment of relapsed ovarian cancer, with response rates that exceed 25% (39,76,77). The drug is generally given at a dose of 50 mg/m^2 daily for 14–21 days, followed by a 1-week rest. In this schedule, the toxicity is primarily mucositis, diarrhea, and myelosuppression. All are reversible and usually controlled with conservative management. However, there appears to be a 2–4% risk of secondary leukemia in etoposide-treated ovarian cancer after 1–2 years. Until the risks of leukemia are better defined, etoposide will remain useful only in the late, chronic phase of ovarian cancer treatment.

Single Agents: Other drugs

A variety of other drugs have been employed in ovarian cancer and the response rates are similar to the drugs listed above (see Table 5). In each case, the schedule and toxicity are different, but the overall response rates are similar. In an editorial, Ozols (78) summarized the current state of affairs as "Increasing Options—Recurrent Results." Newer agents, targeted at growth factor receptors, signal transduction pathways, and tumor angiogenesis, may alter the balance during the next decade.

An Approach to Platinum Refractory Disease

At the present time, the management of ovarian cancer in the platinum refractory disease state is limited to palliative intent. Patients with advanced, bulky tumors, poor performance status, and nutritional compromise are unlikely to respond to therapy and may be best served by supportive care. The clinical management of refractory disease requires both patience and persistence. The diagram in Fig. 6 describes a common management plan. A patient with platinum refractory disease is begun on one of the agents with activity, and an evaluation of response is made every 6–8 weeks of therapy. As long as the patient shows no signs of disease progression, the therapy

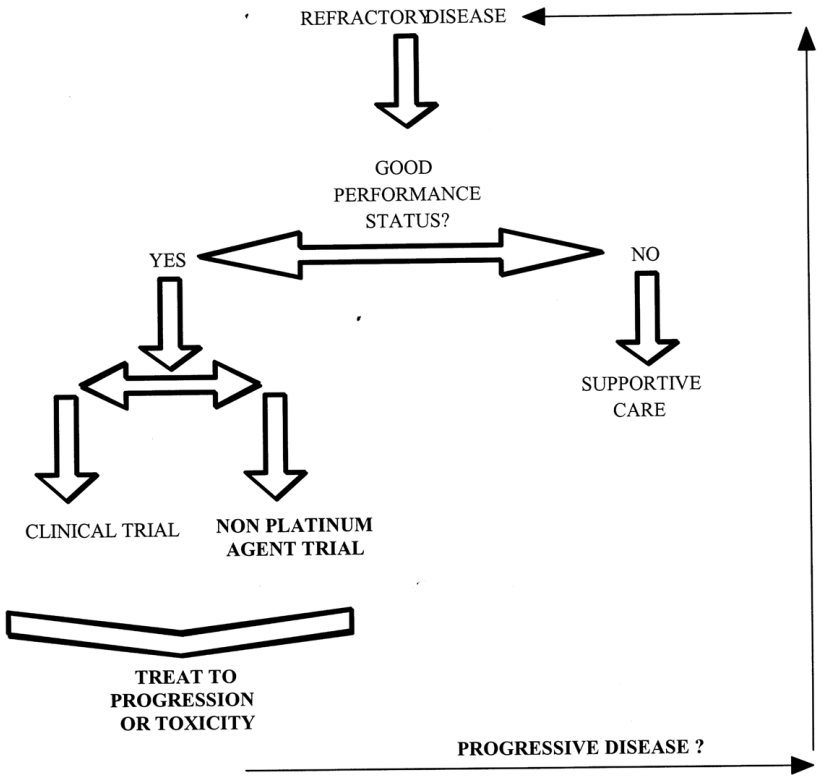

Figure 6 Management of platinum refractory disease. Those patients with platinum refractory disease should be offered a clinical trial as the first choice of management. The alternative is a choice from the agents listed in Table 4, usually either doxil or topotecan, followed by the other at the time of progression. Gemcitabine, etoposide, and vinorelbine are used subsequently for good-performance-status patients.

can be continued unless there is unacceptable toxicity. When progressive disease is observed, another of the list of available agents can be used. It is likely that patients will receive multiple single agents during the chronic phase of their illness. Every effort should be made to balance disease response with toxicity and quality of life.

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Intraperitoneal Chemotherapy: Basic Concepts and Clinical Trials

Maurie Markman
The Cleveland Clinic Foundation, Cleveland, Ohio, U.S.A.

INTRODUCTION AND BASIC CONCEPTS

The basic concept supporting the intraperitoneal administration of cytotoxic (or biological) agents in ovarian cancer is rather simple: administer the drug(s) at higher concentrations and for more prolonged periods of time than possible with systemic drug delivery. In essence, intraperitoneal treatment can be viewed as a regional attempt to increase dose intensity and/or the duration of exposure of cancer cells to cycle-specific antineoplastic drugs (1,2).

Over the past two decades pre-clinical data and clinical trial experience have helped to more clearly define both the realistic promise and limitations of intraperitoneal drug delivery in the management of ovarian cancer (3–5). Table 1 outlines characteristics of the "ideal drug" for intraperitoneal treatment of ovarian cancer. Table 2 briefly describes both practical and theoretical concerns that must be recognized when considering the use of the regional management strategy.

Of note, pre-clinical evaluation has shown that antineoplastic agents will directly penetrate only several cell layers to a few millimeters into tumor tissue by direct diffusion following regional delivery (6–10). These data would strongly suggest that at the clinical level the only patients likely to benefit from this therapeutic approach (over that achieved with systemic drug administration) would be those with microscopic residual disease or very small tumor nodules (e.g., <0.5 cm in maximal diameter) when the intraperitoneal program is initiated.

CLINICAL EXPERIENCE WITH INTRAPERITONEAL DRUG DELIVERY IN THE MANAGEMENT OF OVARIAN CANCER

A number of antineoplastic drugs have been examined for their pharmacokinetic advantage and safety following intraperitoneal administration (Table 3) (3–5,11–13). For agents that are not limited by their local toxic effects (e.g., cisplatin, carboplatin), the dose delivered can be escalated to attain the same systemic levels as achieved with

Table 1 Characteristics of the "Ideal Antineoplastic Drug" to Be Employed for Regional Therapy of Ovarian Cancer

Known activity in ovarian cancer
Pre-clinical data suggesting the relevance of higher drug concentrations or more prolonged exposure in enhancing the agent's cytotoxicity against ovarian cancer
Not toxic to the peritoneal lining following regional delivery
Slowly exits the peritoneal cavity following regional delivery or quickly cleared from the systemic compartment (increasing the pharmacokinetic advantage between the cavity and systemic compartment associated with intraperitoneal administration)
Metabolized in the liver (drug uptake from the peritoneal cavity is principally via the portal circulation)

intravenous drug administration. In this situation, systemic toxicity ultimately will be dose limiting.

In contrast, when local side effects (e.g., abdominal pain) have been shown to prevent further dose escalation of an agent, there will be less drug delivered to the systemic compartment compared to intravenous infusion (e.g., doxorubicin, mitoxantrone, paclitaxel). With such drugs it may be necessary to administer treatment by the intravenous and intraperitoneal routes to achieve optimal delivery by both direct diffusion and capillary flow.

It should come as little surprise that cisplatin has been the antineoplastic agent that has undergone the most extensive evaluation for intraperitoneal use in the management of ovarian cancer (14–17). Phase 1 studies have demonstrated a modest pharmacokinetic advantage associated with this method of drug delivery (20-fold increased exposure of the cavity compared to the systemic compartment) and the safety of the approach has been documented in numerous trials (including three phase 3 randomized studies). The major toxicities of intraperitoneal cisplatin are the systemic effects of the agent (e.g., emesis, nephrotoxicity, neurotoxicity).

A summary of data from phase 2 efficacy trials employing intraperitoneal cisplatin as second-line therapy of ovarian cancer is provided in Table 4. In these studies responses were documented at the time of a performance of a third-look laparotomy or laparoscopy. As previously suggested by pre-clinical data, responses to intraperitoneal cisplatin are almost exclusively observed in women with microscopic or very small volume residual macroscopic disease (15–20).

Table 2 Practical and Theoretical Issues Associated with Regional Antineoplastic Drug Delivery

Local toxicity (e.g., infection, inflammation leading to adhesion formation and subsequent bowel obstruction)
Requirement to establish a safe, cost-effective and convenient method of drug delivery
Adequacy of drug distribution throughout the peritoneal cavity
Limited depth of penetration of antineoplastic agents directly into tumor tissue
Limited delivery of antineoplastic drugs to tumor via capillary flow following regional administration

Table 3 Pharmacokinetic Advantage Associated with Selected Antineoplastic Agents for Intraperitoneal Delivery

Agent	Peak peritoneal cavity/ plasma concentration ratio
Cisplatin	20
Carboplatin	18
Paclitaxel	1000
5-fluorouracil	300
Doxorubicin	470
Melphalan	80
Interferon-alpha	100

Carboplatin has also been examined for intraperitoneal delivery in ovarian cancer, although the overall experience is considerably less than with cisplatin. The drug has a pharmacokinetic advantage, similar to that of cisplatin, when delivered regionally (21,22). Dose limiting toxicity is the systemic effects of the agent (principally bone marrow suppression). Objectives responses, including surgically-defined complete remissions, have been documented following intraperitoneal carboplatin administration (23,24).

More recently, paclitaxel has been explored following administration by the intraperitoneal route (12,13). Due to its large size, hepatic metabolism, and limited solubility, a rather profound pharmacokinetic advantage associated with regional delivery has been documented (>1000-fold). In contrast to both cisplatin and carboplatin, the dose limiting toxicity of paclitaxel is local (eg., abdominal pain).

A large phase 2 trial has documented intraperitoneal paclitaxel administration can result in surgically-defined complete responses (25). However, also in contrast to cisplatin or carboplatin, activity is almost exclusively limited to those individuals with microscopic disease only at the initiation of treatment. This is likely due to the large size and limited solubility of paclitaxel within the peritoneal cavity, preventing direct penetration into even the smallest macroscopic tumor nodules.

Other agents examined in small clinical trials for potential clinical utility following regional delivery in ovarian cancer include mitoxantrone, etoposide, thiotepa, doxorubicin, interferon-alpha, interferon-gamma, and interleukin-2 (3–5,11).

Table 4 Summary of Results of Intraperitoneal Cisplatin Employed as Second-Line Therapy of Ovarian Cancer

Size of largest residual tumor mass	Surgically-documented complete response rate
Microscopic disease only	35–45%
Macroscopic disease <0.5 cm	20–30%
Macroscopic disease >1 cm	<5%

RANDOMIZED PHASE 3 TRIALS OF INTRAPERITONEAL CHEMOTHERAPY IN OVARIAN CANCER

The results of two large well-designed and conducted randomized trials comparing intravenous to intraperitoneal cisplatin when employed as initial treatment of small volume residual ovarian cancer have been reported (Table 5) (26,27).

In the initial trial, the Southwest Oncology Group and Gynecologic Oncology Group randomized patients to receive cisplatin either by the systemic or regional route of drug delivery, with all individuals also receiving intravenous cyclophosphamide (26). Patients randomized to the intraperitoneal program experienced a statistically significant improvement in survival (49 months versus 41 months) compared to women treated with intravenous cisplatin ($p = 0.02$).

Of interest, there was less neutropenia and tinnitus associated with the regional drug delivery, and (not surprisingly) a higher incidence of abdominal discomfort in patients treated by the intraperitoneal route. However, in most individuals the abdominal discomfort was only mild to moderate in severity and did not prevent patients from continuing with the regional treatment program.

As this landmark study was initiated in the early 1980's paclitaxel was not a component of standard treatment of ovarian cancer. Thus, it was questioned whether any benefit associated with intraperitoneal drug delivery might be eliminated if women received paclitaxel, rather than the alkylating agent, cyclophosphamide.

Therefore, a second randomized trial was undertaken to compare intraperitoneal to intravenous cisplatin, with all patients also receiving paclitaxel (27). In this trial patients randomized to the intraperitoneal cisplatin treatment arm also received two courses of "moderately high dose" carboplatin (AUC 9) prior to intraperitoneal

Table 5 Randomized Phase 3 Trials of Intraperitoneal Therapy as Initial Treatment of Small-Volume Residual Advanced Ovarian Cancer

Alberts, et al. (26)
IP cisplatin (100 mg/m^2) + IV cyclophosphamide (600 mg/m^2) every 21 days × 6
Vs.
IV cisplatin (100 mg/m^2) + IV cyclophosphamide (600 mg/m^2) every 21 days × 6
Markman et al. (27)
IV carboplatin (AUC 9) every 28 days × 2, followed by
IV paclitaxel (135 mg/m^2 over 24 hours) + IP cisplatin (100 mg/m^2) (day 2) every 21 days × 6
Vs.
IV paclitaxel (135 mg/m^2 over 24 hours) + IV cisplatin (75 mg/m^2) every 21 days × 6
Gynecologic Oncology Group trial (recently completed)
IV paclitaxel (135 mg/m^2 over 24 hours) +
IP cisplatin (100 mg/m^2) (day 2) + IP paclitaxel (60 mg/m2) (day 8) every 21 days × 6
Vs.
IV paclitaxel (135 mg/m^2 over 24 hours) + IV cisplatin (75 mg/m^2) every 21 days × 6

AUC = area under the concentration vs. time curve; IP = intraperitoneal; IV = intravenous

therapy. This approach was designed to "chemically debulk" any residual tumor to as small a volume as possible prior to initiation of the regional drug delivery strategy.

Unfortunately, the initial two carboplatin courses were associated with unanticipated significant bone marrow suppression, principally thrombocytopenia. As a result, almost 20% of the patients randomized to the intraperitoneal treatment arm received two or fewer courses of the planned regional treatments. Despite this fact, the median progression-free survival associated with the intraperitoneal therapy program was superior (28 months versus 22 months, $p = 0.01$) to the intravenous treatment regimen. Overall survival was marginally improved for patients receiving regional therapy (63 months versus 52 months, $p = .05$).

A third phase 3 study was initiated by the Gynecologic Oncology Group based on the favorable, but inconclusive, results of these two randomized trials (Table 5). In addition, this study added intraperitoneal paclitaxel to the experimental arm, based on the impressive pharmacokinetic advantage associated with regional delivery of this antineoplastic agent. Thus, patients received either a "control regimen" of intravenous cisplatin/paclitaxel or an "experimental program" of intraperitoneal cisplatin plus both intravenous and intraperitoneal paclitaxel. This study has recently completed accrual with preliminary results hopefully being available within the next year.

WHO SHOULD BE TREATED WITH INTRAPERITONEAL THERAPY?

On the basis of available data, what is the current status of intraperitoneal therapy of ovarian cancer?

While it is appropriate to state that data regarding the use of intraperitoneal therapy as initial therapy of small volume residual advanced disease suggests this is an attractive management option, the overall impact on survival is limited. The results of the most recently completed randomized trial described above will hopefully more clearly define a possible role for intraperitoneal cisplatin and paclitaxel in initial treatment of ovarian cancer.

Unfortunately, randomized trials evaluating intraperitoneal antineoplastic therapy as a second-line management strategy have not been conducted to help in establishing the benefits associated with this strategy. However, based on available information (both surgically-defined response rates and long-term survival data (28–30)), it is reasonable to suggest patient populations where this would be a rational management approach outside the clinical trials setting (Table 6).

Of particular interest would be the use of intraperitoneal therapy as a "consolidation strategy" in women with high grade advanced ovarian cancer achieving a surgically-defined complete response to standard intravenous drug delivery where it is known the ultimate relapse rate is approximately 50% (31). In this setting where only microscopic disease persists in a patient with a documented response to initial systemic treatment it is theoretically possible the high local concentrations of drug achievable within the peritoneal cavity can be translated into an improvement in both progression-free and overall survival.

While limited phase 2 trial experience supports this hypothesis (32), definitive data from randomized trials directly addressing this issue do not exist. Thus, while a decision to employ regional drug delivery to "consolidate" an excellent clinical

Table 6 Clinical Characteristics Suggesting Intraperitoneal Therapy is a Rational Second-Line Management Option in Ovarian Cancer

1. Major response to initial platinum-based systemic therapy
2. Minimal residual disease ("negative findings", microscopic disease only or largest mass <0.5 cm in maximum diameter) documented at a second-look surgical assessment (laparotomy/laparoscopy)
3. Minimal or no intraperitoneal adhesions which would interfere with adequacy of drug distribution

response is reasonable, patients must be informed regarding the lack of randomized trial experience to define the ultimate clinical utility of this approach.

Finally, while cisplatin is the agent most studied for regional delivery in ovarian cancer, a strong argument can be presented to suggest many patients would be candidates for treatment with carboplatin. As previously noted, carboplatin results in a similar pharmacokinetic advantage and safety profile following intraperitoneal treatment (21,22), objective responses are observed following this method of drug delivery (23,24), and it is now well-established that the two platin drugs are equivalent in efficacy when administered intravenously.

However, the major justification for employing carboplatin, rather than cisplatin, is the more favorable systemic toxicity profile of the newer agent. Thus, for example, patients may find continuation of treatment with intraperitoneal carboplatin (following 6 courses of intravenous therapy) easier to tolerate than delivery of cisplatin (e.g., emesis, neurotoxicity). This point should be taken into consideration when selecting therapy for individual patients where regional antineoplastic drug delivery is an appropriate management option.

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Chemotherapy for Germ Cell Tumors

Christina A. Bandera
Harvard Medical School, Boston, Massachussetts, U.S.A.

Stephen C. Rubin
University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.

INTRODUCTION

Malignant germ cell tumors account for only 3% of ovarian cancers. Nonetheless, they are the most common ovarian malignancies in young females, with an average age of presentation of 20 years old. Fortunately, the majority of patients are curable. Current treatment recommendations stress conservative surgery to retain fertility, and selective adjuvant chemotherapy.

The classification of ovarian germ cell tumors parallels male germ cell tumors. The two main categories include dysgerminomas and nondysgerminomatous tumors (analogous to seminomas and nonseminomatous tumors in males). Dysgerminomas are composed of undifferentiated germ cells and account for 40% of germ cell malignancies. Nondysgerminomatous cancers are composed of abnormally differentiated germ cells. This category includes immature teratoma, endodermal sinus tumor, embryonal tumor, polyembryoma, and choriocarcinoma. Many of these germ cell tumors produce unique fetal proteins that are useful tumor markers for diagnosis and follow-up care. Approximately 10% of germ cell tumors are a combination of two subtypes, most commonly a dysgerminoma and a nondysgerminomatous element. An uncommon third category of germ cell malignancy is cancer derived from malignant teratoma including squamous cell carcinomas, malignant struma ovarii, and carcinoids.

The first step in the treatment of germ cell tumors is surgical removal of the abnormal ovary. In cases of limited diseases affecting young nulliparous females, it is often appropriate to preserve a normal contralateral ovary and uterus. Metastatic spread beyond the ovaries may occur through lymphatic channels, hematogenous spread, or peritoneal shedding. For this reason, surgery should include a staging procedure with sampling of pelvic and para-aortic lymph nodes, omentectomy, washings, and exploration of all peritoneal surfaces. Stage is assigned according to the standard FIGO classification of ovarian tumors. In cases of advanced disease, clinicians agree that an effort should be made to debulk tumor. Based on data from the Gynecologic Oncology Group (GOG), patients with no residual germ cell tumor are more likely to

Table 1 Fast Facts About Germ Cell Malignancies

	Frequency	Markers	Bilaterality	Surgery	Adjuvant treatment	Prognosis
Dysgerminoma	40%	Occasional inhibin, LDH, HCG	20% total 10% macroscopic 10% microscopic	Staging,[a] debulking, preservation of uninvolved ovary and uterus	Stage IA—no adjuvant treatment Stage IB or greater—BEP	95% 5-year survival
Immature teratoma	20%	Occasional AFP	Rare	Staging, debulking, preservation of uninvolved ovary and uterus	Stage IA, grade 1—no adjuvant treatment Stage, IA, grade 2 or greater, adult—BEP[b] Stage IA, grade 2 or greater, child—careful follow-up or BEP[b]	100% survival for stage IA, grade 1; >90% survival for stage IA3 or greater with chemotherapy[b]
Yolk sac tumor	20%	AFP	Rare	Staging, debulking, preservation of uninvolved ovary and uterus	Completely resected disease—BEP × 3 Residual disease—BEP for two cycles beyond normal AFP Begin chemotherapy immediately	96% survival for completely resected disease; 55% survival for advanced unresectable disease

Embryonal	Rare	HCG, occasional AFP	Rare	Staging, debulking, preservation of uninvolved ovary and uterus	BEP for at least four cycles, continue for two cycles beyond normal AFP	30% survival
Nongestational Choriocarcinoma	Rare	HCG	Rare	Staging, debulking, preservation of uninvolved ovary and uterus	BEP or EMACO	80% survival
Polyembryonal	Rare	HCG, occasional AFP and HPL	Rare	Staging, debulking, preservation of uninvolved ovary and uterus	BEP	Cures have been reported for stage IA tumors treated with surgery and chemotherapy
Mixed germ cell tumor	10%	Variable	Variable	Staging, debulking, preservation of uninvolved ovary and uterus	Treatment based on most severe elements	Based on most severe elements
Malignancy associated with dermoids (squamous cell carcinoma, malignant struma ovarii, malignant carcinonoid)	Rare	Variable	Rare	Staging, debulking, preservation of uninvolved ovary and uterus	No consensus	Variable

[a] Surgical staging includes removal of involved ovary and tube, sampling of pelvic and para-aortic lymph nodes, omenectomy, washings, and exploration of all peritoneal surfaces.

[b] See text for controversies regarding treatment of immature teratomas.

respond to chemotherapy than patients with gross residual tumor (1). Furthermore, patients with small residual disease have better response rates than patients with suboptimal tumor debulking (2).

This chapter summarizes current recommendations for chemotherapy for each type of ovarian germ cell malignancy (Table 1). Short-term and long-term concerns of chemotherapy use in this population are discussed. Strategies for surveillance after primary treatment are also reviewed. Fortunately, appropriate treatment yields an excellent cure rate and preservation of fertility for the majority of young women affected by these malignancies.

DYSGERMINOMA

Dysgerminomas arise from undifferentiated germ cells of the ovary and account for 40% of malignant germ cell tumors. The majority of cases occur in patients aged 10–30 years old. Sixty to 70% of patients have stage I disease at the time of surgical diagnosis. In contrast to other categories of germ cell tumors, dysgerminomas are often bilateral. Ten percent of patients will have grossly visible bilateral disease, and an additional 10% will have microscopic disease in the contralateral ovary (3). When preservation of fertility is desired, it is appropriate to treat these patients with unilateral salpingo-oophorectomy and cystectomy to remove gross tumor from the contralateral ovary. This cancer is exquisitely sensitive to chemotherapy, thus the presence of tumor in an ovary left in situ does not appear to change the long-term prognosis of the patient (4).

After surgical resection, this cancer was historically treated with radiation, and cure rates were excellent. A 5-year survival of 100% was noted for stage I patients receiving radiation therapy. A review of 12 patients with stage III disease reports a 5-year relapse-free survival of 61% and an overall survival of 89% with adjuvant radiotherapy (1,5). Radiation therapy has fallen out of favor due to the resultant sterility and long-term side effects, although it is a reasonable alternative for rare patients with a contraindication to adjuvant chemotherapy. In general, cisplatin-based chemotherapy is now considered standard for postoperative treatment of dysgerminoma.

Stage I Dysgerminoma

Adjuvant chemotherapy is not recommended for well-staged dysgerminomas encapsulated in one ovary. The reported risk of recurrence for stage IA disease ranges from 17% to 53% (6–9). However, many of these reported cases probably had more advanced diseases, which were not identified due to leaving the contralateral ovary in situ, or inadequate staging. A recent review of surveillance for nine patients with stage IA dysgerminoma revealed three recurrences (9). As with earlier reports, not all patients were surgically staged, although patients underwent radiographical staging and measurement of tumor markers prior to assignation of stage. All three recurrences responded to chemotherapy and appeared to be cured. The importance of adequate staging, including pelvic and para-aortic node sampling, omentectomy, and washings, needs to be stressed. Most clinicians choose to observe patients who appear to have stage IA dysgerminoma because patients with progressive disease are curable with chemotherapy. However, a recent report shows that 3 of 13 patients with apparent

Table 2 The BEP Regimen

Bleomycin, 20 U/m^2, IV (maximum 30 units), weekly
Etoposide, 100 mg/m^2, IV, daily for 5 days every 3 weeks
Cisplatin, 20 mg/m^2, IV, daily for 5 days every 3 weeks

stage IA diseases were found to have stage IIIC cancer when they were re-explored within 2 months of initial oophorectomy (10). Offering these patients adjuvant chemotherapy in a timely fashion will save them the anxiety of disease recurrence in the future.

Approximately 20% of stage I dysgerminoma patients will have disease involving both ovaries. For these patients, the risk of recurrence is probably higher than stage IA disease, and chemotherapy should be recommended. Patients with capsular disease, tumor rupture, or malignant ascites also probably have a $>20\%$ chance of recurrence. These stage IC patients should be offered adjuvant chemotherapy. Standard treatment would be three cycles of bleomycin, etoposide, and cisplatin (BEP) (7) (Table 2). A study from the GOG explored the use of three treatments of carboplatin and etoposide without bleomycin for postoperative treatment of dysgerminoma. The goal of this study was to explore a low-toxicity regimen for this very chemotherapy-sensitive disease. Eighteen patients with stage I tumors were enrolled and no relapses were noted. Despite these encouraging results, the study was closed prior to reaching accrual goals because of data suggesting that metastatic seminoma response rates to cisplatin and bleomycin were superior to carboplatin (11).

Advanced Dysgerminoma

Prior to the era of cisplatin-based chemotherapy, patients with advanced dysgerminoma experienced failure rates of approximately 40% following radiation. With adjuvant chemotherapy, response rates are close to 100%. Following early reports of excellent cure rates with platinum-based regimens for seminomas and dysgerminomas, the GOG organized two studies enrolling patients with stage III or IV dysgerminoma to confirm these findings. GOG 45 involved the administration of three to four courses of cisplatin, vinblastine, and bleomycin (BVP). In GOG 90, patients received three courses of cisplatin, etoposide, and bleomycin (BEP), followed by consolidation with three courses of vincristine, dactinomycin, and cyclophosphamide (VAC). A total of 20 patients with dysgerminoma were enrolled in these two studies, including 11 patients with residual disease. Within a mean follow-up period of 26 months, 19 patients (95%) were disease-free at the end of treatment, with one death reported (12). Interim review found that response to BEP was dramatic and, therefore, consolidation therapy with VAC was dropped from the protocol. In the final interpretation of these studies, BEP was recommended over BVP because of its superior toxicity profile. In particular, BEP is associated with less neuropathy and gastrointestinal distress.

POMB/ACE (cisplatin, vincristine, methotrexate, bleomycin, dactinomycin, cyclophosphamide, and etoposide) is another cisplatin-containing regimen, which has comparable activity in advanced dysgerminoma without apparent excessive toxicity (Table 3) (13).

Table 3 The POMB/ACE Regimen (Administered Every 14 Days)

POMB	
Day 1	Vincristine, 1 mg/m^2, IV bolus (maximum: 2 mg)
	Methotrexate, 300 mg/m^2
Day 2	Bleomycin, 15 mg, IV infusion over 24 hr
	Folinic acid, 15 mg, at 24, 36, 48, and 60 hr after methotrexate
Day 3	Cisplatin, 120 mg/m^2, IV infusion over 12 hr
ACE	
Day 1	Etoposide, 100 mg/m^2, IV infusion
	Actinomycin D, 0.5 mg, IV bolus
Day 2	Etoposide, 100 mg/m^2, IV infusion
	Actinomycin D, 0.5 mg, IV bolus
Day 3	Etoposide, 100 mg/m^2, IV infusion
	Actinomycin D, 0.5 mg, IV bolus
	Cyclophosphamide, 500 mg/m^2, IV infusion in 250 mL of normal saline over 30 min

The first two cycles are POMB, then POMB and ACE are alternated.

NONDYSGERMINOMATOUS TUMORS

The nondysgerminomatous tumors account for 50% of germ cell tumors and include yolk sac tumors (endodermal sinus tumors), immature teratomas, embryonal carcinomas, polyembryomas, choriocarcinomas, and mixed germ cell tumors. Similar to dysgerminomas, they tend to present in women of reproductive age, and fertility conservation should be considered when planning treatment. In contrast to dysgerminomas, these cancers are rarely bilateral. The clinical behavior of nondysgerminomatous tumors is variable, and each cell type is considered separately in this section.

Immature Teratoma

Immature teratomas account for 20% of germ cell tumors, and usually present in the first two decades of life. This cancer is composed of differentiated fetal tissues from all three embryonic germ cell layers (ectoderm, mesoderm, and endoderm), and may occasionally be associated with mildly elevated α-fetoprotein (AFP) levels. The immature elements are usually neuroectodermal, but other cell types may be present such as hepatocytes, cartilages, or skeletal muscles. Tumor is classified as grade 1, 2, or 3 according to the amount of immature tissues present in a low-power microscope field. The grade of immature teratomas is the basis of prognosis and treatment planning, even though reproducibility by different pathologists is only moderate (14). Peritoneal implants of mature glial tissues are common, and a benign teratoma is present in the contralateral ovary of 10% of cases. However, only immature metastases influence the stage of the cancer. Although immature teratomas are rarely bilateral, a benign dermoid cyst may be present in the contralateral ovary in 10% of cases. When preservation of fertility is desired, the surgeon should consider removal of abnormal lesions in the centralateral ovary via cystectomy, rather than oophorectomy.

Adjuvant chemotherapy recommendations for immature teratomas are controversial. There is general agreement that patients with grade 1 tumors isolated to one

ovary (stage IA) are virtually all cured with surgery alone (15,16). For cases of stage IA, grade 2 and 3 immature teratomas, the oncology literature refers to a single pathology review published in 1976 (17). In this study, 20 stage IA, grade 2 and 6 and stage IA, grade 3 patients were found to have 60% and 30% survival, respectively. Note that these patients were not surgically staged, and the poor survival rates are probably due to an underestimation of stage in some cases. On the basis of this review, adjuvant treatment was sought for these patients. GOG 78 enrolled patients with grade 2 or 3 immature teratomas of any stage following complete surgical debulking for treatment with three courses of BEP. Thirty-nine of 42 patients were free of disease recurrence. Therefore, BEP became the standard recommendation for patients with grade 2 or 3 immature teratoma of any stage.

These chemotherapy recommendations for immature teratomas were challenged by three articles in recent years (9,18,19). The first report from the University of Milan was published in 1994. Nine patients with stage IA, grade 2 or 3 tumors did not receive adjuvant therapy and remained cancer-free. The second report, from Mount Vernon Hospital and Charing Cross Hospital in the UK, was published in 1997 and presents nine stage IA, grade 2 or 3 immature teratomas, and six women with yolk sac tumors with or without elements of immature teratoma. Three of these patients relapsed, including two who remained free of disease following combination chemotherapy, and one who died from a pulmonary embolism. The authors point out that their surveillance program included a 20% relapse rate, but saved 80% of these patients from unnecessary chemotherapy treatment.

The last and most important publication arguing against adjuvant therapy for grade 2 and 3 immature teratomas presents a study performed by the Pediatric Oncology Group and the Children's Cancer Group. This study enrolled 44 patients from age 1.5 to 15 years old with ovarian immature teratoma, including 17 patients with grade 1 disease, 12 with grade 2 disease, and 2 with grade 3 disease. Thirteen of these patients had microscopic foci of yolk sac tumor. Although patients were not consistently staged in this study, three patients had nodal metastases and eight had omental metastases. Patients were treated with surgery alone. Median follow-up time was 4.2 years with a range of 0.1–7 years. Only one child with a mixed tumor recurred and remains free of disease 57 months after combination chemotherapy.

These three studies are small in scale, but they raise controversy about the need for chemotherapy for completely resected grade 2 and 3 immature teratomas. Chemotherapy toxicity may outweigh the theoretical benefit of prophylaxis against recurrence, especially because cases of recurrent disease are probably curable. Critics of these studies suggest that the number of patients evaluated is too small to change practice recommendations. On the other hand, it must be remembered that the recommendations advocating chemotherapy in this patient population were also based on outcome data from a small number of inadequately staged patients (17). Another caveat in the applicability of these studies is the possibility that the clinical behavior of immature teratomas in children may be very different from the behavior in adults. Indeed, a recent review of three women over the age of 40 years old with immature teratomas reported two deaths within 1 year of diagnosis (20). All three women had stage III, grade 2 or 3 tumors at the time of diagnosis, as did some of the girls in the pediatric series, although the outcomes reported are very different. Given the incomplete data available, we recommend that all adults with grade 2 and 3 immature teratomas receive adjuvant chemotherapy. In the pediatric population,

follow-up with physical exams, radiological studies, and tumor markers is reasonable, although there is a real risk of disease recurrence. The authors' personal experience includes a 15-year-old girl who chose to forego treatment for a stage IA, grade 2–3 immature teratoma, resulting in cancer recurrence requiring surgery and chemotherapy. She has been free of the disease for 2 years. The age at which a female should be considered "an adult" for purposes of counseling regarding treatment of immature teratoma is not known. Clearly, clinicians must educate patients about the risks and benefits of adjuvant chemotherapy, and help them make decisions about their cancer management.

Yolk Sac Tumors

Yolk sac tumors account for 20% of germ cell tumors and usually occur in the second and third decades of life. This tumor releases the fetal antigen AFP into the blood, facilitating diagnosis, assessment of disease response to treatment, and monitoring for disease recurrence. Although more than two-thirds of patients present with stage I disease, prognosis before the use of platinum-based chemotherapy was dismal. A series published in 1976 reported a 13% 3-year survival for 65 patients with pure yolk sac tumors (21). It is clear that all patients, regardless of stage or grade of tumor, benefit from adjuvant chemotherapy.

In 1985, the GOG reported a 73% disease survival in 11 patients with yolk sac tumors treated with VAC (22). Subsequently, the GOG reported a 96% disease-free survival in 25 patients with completely resected yolk sac tumors treated with BEP (23). Another GOG trial involved PVB to treat women with advanced, unresectable, or recurrent yolk sac tumors (2). In this study, 55% of 29 patients remained disease-free for 2 years of follow-up. Toxicity, especially neuromuscular symptoms, was significant. For this reason, BEP, rather than PVB, is recommended for treatment of all yolk sac tumors.

The POMB/ACE regimen from the Charing Cross Group is an alternative regimen that may have utility in the treatment of advanced yolk sac tumors without excessive toxicity (13).

Regardless of the stage of disease, it is recommended that chemotherapy for yolk sac tumors be started as quickly as possible because of the potential for rapid tumor growth (24). Ideally, chemotherapy should begin within 2 weeks of initial surgery. Chemotherapy is well tolerated in the postoperative period and is not associated with increased infectious risk or wound problems. The recommendation for rapid adjuvant treatment is most difficult to execute in the special case of a yolk sac tumor diagnosed during pregnancy. There are three management options. The first option is pregnancy termination. The second option is chemotherapy during pregnancy. There are several reports of uncomplicated administration of cisplatin, etoposide, and bleomycin in various combinations given during pregnancy (25–29). Premature delivery and some neurological sequelae have been reported with BEP therapy, as well as healthy term infants (24–27,30,31). Fetal outcome is best when chemotherapy is administered after completion of the first trimester. Finally, the patient may consider delaying chemotherapy until after delivery. For pregnant patients with completely resected stage I disease, follow-up with serial study of the nonbinding fraction of maternal serum AFP as a reflection of ovarian AFP has been reported (32). A rising tumor marker suggests progressive disease, at which point chemotherapy may be initiated. This approach may buy time to allow the baby to mature to a gestation when delivery is acceptable. For

cases of recurrent or incompletely resected disease, chemotherapy should be started in a timely fashion to ensure the best outcome for the mother.

Embryonal Tumors

Embryonal tumors were described as a distinct cancer type in 1976 (33). The embryonal ovarian tumors are rare, highly malignant cancers composed of undifferentiated embryonal cells. The tumors are associated with human chorionic gonadotropin (hCG) production and occasional AFP production. They are usually isolated to one ovary. Regardless of the stage at diagnosis and use of adjuvant therapy, the prognosis is poor. Overall survival is approximately 30%, with the majority of patients dying within months of diagnosis. The GOG reported two patients who recurred following VAC, and three of four patients with stage III embryonal ovarian tumors progressed following PVB. Series of pediatric patients are inconsistent with survivals of 25–61% described (32,34). Improved survival statistics may be forthcoming as more patients are treated with platinum-based combination chemotherapy.

Polyembryoma

Polyembryoma is a rare primitive germ cell tumor that can occur at any age. Elevated AFP and hCG levels are typical. Precocious pseudopuberty may be noted in premenarchal girls. Cure has been reported with the surgical resection of a stage IA tumor and with surgery followed by chemotherapy (35,36).

Choriocarcinoma

Choriocarcinoma of the ovary that is not associated with gestation is a rare tumor composed of malignant placental elements. To be certain of the diagnosis of nongestational choriocarcinoma, the clinician must be satisfied that the patient could not have a history of pregnancy. DNA analysis for a paternal genetic component in the tumor is the ultimate diagnostic tool for ruling out gestational choriocarcinoma; however, this technology is not widely available for clinical use (37). Choriocarcinomatous differentiation of an ovarian carcinoma must also be considered as a possible diagnosis (38). The majority of reported cases describe patients in the first two decades of life. This cancer produces hCG and can be very aggressive. A recent review of 30 cases from the literature notes a survival rate of 81% for patients who received chemotherapy vs. 28% in those who did not receive chemotherapy following initial surgery (39). Optimal treatment is unknown. As with other germ cell tumors, BEP may be administered. Methotrexate-containing regimens used in the treatment of metastatic gestational trophoblastic tumors also appear to have activity (for example, the EMA-CO regimen containing etoposide, methotrexate, actinomycin-D, vincristine, and cyclophosphamide). Serum hCG levels should be followed to document response to chemotherapy and to monitor for disease recurrence.

Mixed Germ Cell Tumors

Mixed germ cell tumors account for 10–20% of germ cell malignancies of the ovary. The largest series of 42 patients reports that 81% of mixed germ cell malignancies contain two tumor types, whereas 16% contain three or more tumor types (40). The

most common combination is dysgerminoma and yolk sac tumor. Measurements of serum tumor markers will reflect the presence of elements that produce specific antigens. For example, a patient with a dysgerminoma and an elevated AFP or hCG is likely to have a mixed germ cell tumor upon further pathological investigation. When there is a dysgerminomatous component, the contralateral ovary is involved in 10–19% of cases; otherwise, bilaterality is rare. Generally, prognosis and therapy are based on the most worrisome element within the tumor. However, microscopic yolk sac elements do not appear to affect prognosis in tumors predominantly composed of immature teratomas (18).

Dysgerminoma and Nondysgerminomatous Tumors Associated with Gonadoblastoma

Germ cell tumors may be associated with gonadoblastomas within dysgenetic ovaries. A gonadoblastoma is a tumor composed of germ cells and sex cord stromal cells resembling immature granulosa and Sertoli cells (41). Genotyping of patients with gonadoblastoma usually reveals the presence of a Y chromosome. Common karyotypes include 46XY pseudohermaphrodites with androgen insensitivity (approximately 50%) and 45X/46XY mosaics with mixed gonadal dysgenesis (approximately 25%). Rare cases with the 45XO Turner syndrome karyotype have been reported, as have various mosaic patterns (42). Patients with gonadal dysgenesis are usually phenotypic females with primary amenorrhea who may report virilization or abnormal external genitalia. A pelvic mass may also be a presenting complaint. The risk of gonadoblastoma in these patients is not known. Bilaterality occurs in 40% of reported cases (43). Approximately 50% of gonadoblastomas are associated with dysgerminomas (44). These dysgerminomas tend to be isolated to the ovaries and cured with oophorectomy. Case reports of aggressive germ cell tumors including yolk sac tumors, embryonal carcinomas, and choriocarcinomas describe poor outcomes (45). However, many of these reports predate the use of multiagent cisplatin-based chemotherapy (46).

Prophylactic bilateral salpingo-oophorectomy has traditionally been recommended for all patients with dysgenetic ovaries. However, pregnancy has been reported in two true hermaphrodites with mixed 46XX/46XY karyotype after unilateral salpingo-oophorectomy. With careful follow-up and counseling, fertility-sparing surgery may be appropriate for some of these patients (47,48).

TERATOMA-DERIVED MALIGNANCIES

Benign teratomas or dermoid cysts are common ovarian neoplasms accounting for 25–30% of ovarian tumors. They are made of cells derived from the ectoderm, mesoderm, and endoderm. Typically, the cysts contain sebaceous materials and hair, although many other differentiated tissues may be present. Monodermal teratomas include struma ovarii (thyroid tissue) and carcinoids. Malignant transformation of teratomas is rare, occurring in about 1.8% of cases, usually in women over the age of 40 years (49,50).

Squamous carcinoma is the most common cancer arising from a teratoma. This cancer may also be associated with endometriosis, or present in a pure form in the

ovary. Squamous cell carcinomas arising from a teratoma appear to be the result of dysplastic changes similar to cervical squamous cancer. Patients with stage I disease are occasionally cured with surgery alone. Advanced disease appears to be resistant to adjuvant therapies including radiation and chemotherapy (50,51).

Endocrine-type tumors arising in dermoid cysts include struma ovarii and carcinoids. Struma ovarii is the term for thyroid tissue within the ovary. Less than 5% of cases will result in clinical hyperthyroidism. Cases of malignant thyroid carcinoma within struma ovarii are usually cured with surgical resection. Rare cases of thyroid carcinoma metastatic from an ovarian primary have been reported (52). Ovarian carcinoid is hormonally active in one-third of cases, producing classical symptoms associated with release of bioactive amines and peptides including flushing, diarrhea, facial cyanosis, bronchospasm, and hypotension. The majority of cases are stage IA and are surgically cured. However, stage III and IV ovarian carcinoids have been described. These tumors are chemotherapy-resistant and prognosis is guarded. Treatment with a somatostatin analogue such as octreotide or lamreotide may produce long-term palliation for some patients (53). Other tumors associated with teratomas include basal cell carcinomas, sebaceous tumors, malignant melanomas, adenocarcinomas, sarcomas, and neuroectodermal tumors.

TREATMENT WITH BEP OR POMB/ACE

The combination of bleomycin, etoposide, and cisplatin is the standard regimen recommended for most high-risk germ cell tumors (Table 2). In conjunction with an aggressive antiemetic regimen, this treatment is a well-tolerated outpatient protocol (Table 4). A typical regimen involves 5 days of cisplatin and etoposide, and weekly bleomycin. In a 21-day cycle, a patient will receive chemotherapy on 7 days. For patients who have logistical difficulty reaching the treatment unit, chemotherapy may be administered at home by a visiting nurse. The minimal duration of treatment has not been established. GOG trials are administered for three to four cycles based on data from the treatment of testicular cancer. In cases where response can be measured by a tumor marker, treatment may be continued one to two cycles beyond a normal value if toxicity is not dose-limiting.

All patients must be monitored for acute side effects. Although neutropenia is common, treatment is usually given on schedule regardless of hematological parameters. Granulocyte colony-stimulating factor (GCSF) should be considered for patients who experience febrile neutropenia.

Bleomycin has the classical side effect of pulmonary fibrosis. The finding of basilar crackles on examination is an indication to discontinue bleomycin immediately. Other side effects of bleomycin include fever within a few hours of administration and hyperpigmentation. Hyperpigmentation, in the form of dark streaks on the abdomen and extremities, will fade but will usually not disappear. If this symptom is disfiguring, then it may be an indication to reduce the dose, or to discontinue bleomycin in a patient with a good prognosis. Etoposide is a vesicant that must be administered by a nurse or physician who is appropriately trained. Acute side effects associated specifically with etoposide include neuropathy, alopecia, neutropenia, and gastrointestinal upset. Cisplatin is known to be nephrotoxic and must be administered

Table 4 Typical Antiemetic Regimen for BEP

Granisetron, 1 mg, IV or PO, 30 min prior to cisplatin daily for 5 days of treatment, or ondansetron 8–24 mg, IV or PO, 30 min prior to cisplatin daily for 5 days of treatment
Dexamethasone, 20 mg, IV or PO, 30 min prior to cisplatin daily for days 1 and 2
Lorazepam, 1 mg, PO, 30 min prior to cisplatin daily as needed

with copious intravenous hydration. Use of other nephrotoxic agents, such as the antibiotic gentamicin, should be avoided during chemotherapy treatment.

Fertility is a major concern for young women undergoing surgery and chemotherapy for a germ cell tumor. More than 95% of postpubertal females will develop hypergonadotropic amenorrhea during chemotherapy treatment with BEP (54), but permanent ovarian failure is rare. The majority of females who retained one normal ovary and uterus then received combination chemotherapy were able to become pregnant (4,54–59). No increased risk of miscarriages or birth defects has been noted. Another concerning risk of treatment is the association of etoposide and acute myeloid leukemia. This phenomenon has been studied in males treated for germ cell tumors. An excellent review of five large studies describes a dose-dependent risk (60). A total of 1868 patients received an etoposide dose of < 2 g/m^2, resulting in eight cases of leukemia (0.4%) In the standard BEP regimen, this coincides to four or fewer treatments. The 537 patients who received higher cumulative doses developed 11 etoposide-related cases of leukemia (2.0%). These data must be taken into account when planning the duration of treatment. Fortunately, most ovarian germ cell tumors are cured with three to four treatments of BEP. Only rare cases of leukemia after treatment for ovarian germ cell tumors have been reported (23,61).

POMB/ACE is an alternative multiagent regimen developed to treat male germ cell tumors at the Charing Cross Hospital in England (Table 3). This seven-agent protocol was designed to minimize the development of drug resistance. In 1996, data were published on 59 patients with dysgerminomas or nondysgerminomatous tumors who received the treatment (13). All patients had stage I progressive disease, or stage II–IV disease. Fifty-five patients achieved complete responses, with four patients eventually relapsing. Three-year survival was 87.8%. The authors did not give details about which types of germ cell tumors were not cured. Alopecia and nausea were the most common toxicities. Myelosuppression was moderate, and most patients remained on a 2-week schedule. Mucositis, neuropathy, pulmonary toxicity, and one case of acute myeloid leukemia were also noted. Menstruation returned within 2–6 months following completion of treatment, and 14 normal children were born to their patients. The authors conclude that the POMB/ACE regimen is well tolerated with efficacy comparable to BEP. The effectiveness of this regimen was confirmed in another series of ovarian germ cell tumors from Spain (62). It has been suggested that POMB/ACE be used for patients with tumor metastatic to the liver or brain, or with massive metastatic disease (63).

FOLLOW-UP RECOMMENDATIONS

The majority of patients treated for ovarian germ cell malignancies are cured. Nonetheless, the clinician must have a plan for identifying those patients who might

be at risk for persistent or recurrent disease. One follow-up option is performing a second-look surgery following completion of chemotherapy. The GOG reviewed its experience of 117 reassessment laparotomies performed in conjunction with three protocols of cisplatin-based chemotherapy for germ cell tumors (GOG 45, 78, and 90). Four of 24 patients with incompletely resected immature teratoma had persistent disease identified. Two of these patients remained free of disease following surgery and second-line chemotherapy with VAC. The GOG concluded that a patient with immature teratoma that is incompletely resected at the primary operation might benefit from a second-look operation (64). A French review of 22 posttreatment operations concluded that patients with immature teratoma and persistent radiological abnormalities might benefit from reassessment surgery (65). Both the GOG and the French group did not feel that patients with germ cell tumors other than immature teratomas benefited from this type of surgery.

Recurrent ovarian germ cell cancers usually present within 2 years of initial diagnosis. For at least 1 year following completion of treatment, it is recommended that frequent physical examinations be performed, and that tumor markers be evaluated monthly (9,40). Tumor markers known to be useful in the follow-up of germ cell tumors include AFP, hCG, CA125, and LDH (66–68). The use of markers, according to subtype of tumor, is summarized in Table 1. Radiological studies such as computerized tomography (CT), magnetic resonance imaging (MRI), or ultrasound should be performed every 6–12 months during the first 2 years after treatment. In the case of immature teratoma, benign gliomatosis may produce a palpable mass or radiological abnormalities. Usually, exploratory surgery is the only way to rule out cancer recurrence. Occasionally, recurrent germ cell malignancies are identified 10–20 years after primary therapy (69–71). Therefore, we recommend lifetime follow-up with a specialist every 6–12 months. Each visit should include a pelvic examination and assessment of tumor markers. Radiological studies should be performed as indicated.

SALVAGE CHEMOTHERAPY

The prognosis of patients with germ cell tumors who fail frontline platinum-based chemotherapy is poor. Secondary surgical debulking as a component of treatment for recurrent disease may improve survival for some patients, especially those with recurrent immature teratoma (72). Second-line chemotherapy will also be beneficial for some patients. In the GOG study of recurrent or advanced germ cell tumors, patients who failed treatment with PVB were salvaged with VAC, or etoposide and cisplatin in approximately 40% of cases (2).

Additional strategies for recurrent germ cell tumors must come from the literature oriented toward treatment of males. Patients who relapse more than 6–8 weeks after platinum therapy can be considered platinum-sensitive; treatment with a platinum-based regimen such as cisplatin, ifosfamide, and vinblastine, or cisplatin, ifosfamide, and etoposide will produce a response in approximately one-third of patients (73,74). Optimal treatment for patients with platinum-resistant germ cell tumors is not known. Some responses to paclitaxel-containing regimens have been described (75). High-dose chemotherapy with autologous bone marrow support has also been found to be effective against some germ cell tumors of the testes and ovaries (76). Patients with recurrent germ cell tumors should be encouraged to participate in clinical trials, which are often open to both males and females.

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Chemotherapy for Sex Cord–Stromal Tumors

Nicoletta Colombo and Gabriella Parma
European Institute of Oncology, Milan, Italy

INTRODUCTION

Sex cord–stromal tumors account for approximately 7% of all malignant ovarian neoplasms and their extreme rarity represents a limitation in our understanding of the natural history, management, and prognosis. Sex cord–stromal tumors of the ovary are derived from the sex cords and the ovarian stroma or mesenchyme. This category of ovarian neoplasms usually is composed of various combinations of elements, including the "female" cells (granulosa cells, theca cells, and their luteinized derivatives), "male" cells (Sertoli cells and Leydig cells), fibroblasts of gonadal–stromal origin as well as morphologically indifferent cells. A classification of this group of tumors is presented in Table 1.

While it is generally accepted that both granulosa and Sertoli cells derive from the sex cords of the developing gonad which originate from celomic epithelium, disagreement exists as to the ultimate fate of the sex cord cells. Some authors believe that granulosa cells derive from the cortical sex cord while the Sertoli cells originate from medullary cords of mesonephric origin; others believe that sex cord cells differentiate into granulosa cells or Sertoli cells depending on the gonad development toward an ovarian or testicular pathway. The stromal elements of sex cord tumors can exist in a pure form or may be admixed with epithelial elements of putative sex cord origin. Very little is known about the etiology of these tumors in the human. However, sex cord tumors can be easily induced in animals provided that oocyte depletion has occurred and the pituitary gland is functioning normally. The most accepted hypothesis is that the degeneration of follicular granulosa cells after oocyte loss and the consequent compensatory rise in pituitary gonadotrophins may induce irregular proliferation and eventual neoplasia of the granulosa cells. This hypothesis is consistent with the observation that most granulosa-cell tumors occur soon after menopause when a similar situation of oocyte depletion and high levels of gonadotrophin are observed. However, this etiology cannot be applied to those tumors developing during the reproductive years or even before menarche.

The vast majority of these tumors are of low malignant potential and associated with a very favorable long-term prognosis. The following discussion will address the

Table 1 Classification of Sex Cord–Stromal Ovarian Tumors

Granulosa–stromal-cell tumors
Granulosa-cell tumors
– Adult type
– Juvenile type
Tumors in the thecoma–fibroma group
– Thecoma
– Fibroma–fibrosarcoma
– Sclerosing stromal tumor
Sertoli–Leydig-cell tumors (androblastomas)
Sertoli-cell tumors
Leydig-cell tumor
Sertoli–Leydig-cell tumors
– Well differentiated
– Of intermediate differentiation
– Poorly differentiated
– With heterologous elements
– Retiform
– Mixed
Gynandroblastoma
Sex cord tumor with anular tubules
Unclassified

clinical features and management of the major classes of ovarian sex cord–stromal tumors.

GRANULOSA–STROMAL-CELL TUMORS

This group of tumors includes granulosa-cell tumors, thecoma, fibroma–fibrosarcoma, and sclerosing stromal-cell tumors. Stromal-cell tumors are considered benign ovarian neoplasms. Exceptionally, a thecoma that exhibits mitotic activity and nuclear atypia presents a malignant course and merits the diagnosis of "malignant thecoma," but at least some of these are better interpreted as fibrosarcoma or diffuse forms of granulosa-cell tumors. Rarely, fibromatous tumors have malignant cytological features and merit designation as cellular fibroma and fibrosarcoma. The prognosis for patients with cellular fibroma is generally quite favorable: recurrences are correlated only with rupture or incomplete removal at the time of primary surgery. Fibrosarcomas are biologically aggressive and are associated with an extremely poor prognosis. Sclerosing stromal-cell tumors, initially described by Chalvardjian and Scully in 1973 (1), commonly become manifested during the second and third decades of life and present a good prognosis. Granulosa-cell tumors account for approximately 70% of ovarian sex cord–stromal tumors and represent 3–5% of all ovarian neoplasms (2–8). The incidence in developed countries varies from 0.4 to 1.7 cases per 100,000 women (6,9). The average age at time of diagnosis is 52 years, but granulosa-cell tumors have been diagnosed from infancy to the 10th decade of life. Because the clinical and pathological characteristics of the tumors occurring after menopause are different

from those occurring in children and younger patients, the adult and juvenile granulosa cell type will be considered separately.

Granulosa-Cell Tumors: Adult Type

The adult type accounts for 95% of all granulosa-cell tumors. Hormone production is frequent, with predominance of estrogen production, and results in abnormal vaginal bleeding in about two-thirds of the patients. The typical endometrial alteration associated with functioning tumors is simple hyperplasia, usually exhibiting some degree of precancerous atypicality (range: from 24% to above 80%). Gusberg and Kardon (10) reported in a retrospective study of 69 patients 13% of cystic glandular hyperplasia, 42% of atypical hyperplasia, 5% of adenocarcinoma in situ, and 22% of invasive adenocarcinoma. Similarly, a study by Evans et al. (2) of 76 patients with granulosa-cell tumors and in whom endometrial tissue was available shows a high incidence of endometrial hyperplasia (55%) and adenocarcinoma (13%). If strict criteria for the diagnosis of carcinoma are used and if all patients are considered, the estimated frequency of associated endometrial adenocarcinoma is about 5% (11). In addition, granulosa-cell tumors are associated with an increased incidence of breast cancer (12). Rarely, androgenic changes such as oligomenorrhea, hirsutism, and other virilizing signs may be present. The most common clinical symptoms at presentation include abdominal distension and abdominal pain, due to the gross size of the tumor and the presence of ascites. The etiology of acute severe pain is generally adnexal torsion, hemorrhage into the tumor, or rupture of a cystic component. About 15% of patients who have cystic granulosa-cell tumors are first examined for acute abdomen associated with hemoperitoneum. Adult granulosa-cell tumors vary in size from microscopic lesions, not detected by pelvic examination (10–15% of cases), to very large masses measuring 40 cm in diameter; the average diameter is approximately 12 cm. At operation the tumor may present predominantly solid, with large areas of hemorrhage and necrosis, or cystic, with numerous locules filled with serosanguinous or gelatinous fluid, and is unilateral in more than 95% of the cases. Microscopic examination reveals an almost exclusive population of granulosa cells or, more often, an additional component of the thecal cells, fibroblast, or both. Granulosa cells grow in a wide variety of patterns. The better-differentiated tumors typically present microfollicular, macrofollicular, insular, or trabecular patterns. The microfollicular type is characterized by the presence of the rosette-like structure (Call–Exner bodies) which contains eosinophilic material and nuclear debris. The microfollicles are separated by well-differentiated granulosa cells that contain scanty cytoplasm and pale, angular or oval, often grooved nuclei. The macrofollicular finding is characterized by cysts lined by well-differentiated granulosa cells. The trabecular and insular forms usually present bands and islands of granulosa cells separated by a fibromatous or thecomatous stroma. The less well-differentiated tumors (moderately differentiated category) typically have a diffuse (sarcomatoid), watered silk (moire silk) or gyriform pattern alone or in combination. Although attempts have been made by many authors, no distinct correlation between histological structure and prognosis has yet been substantiated. The adult granulosa-cell tumors may be confused with undifferentiated carcinomas (the most frequent error in ovarian tumor pathology), adenocarcinomas, and carcinoids of the ovary. The typical histological features of granulosa-cell tumors are helpful in the differential diagnosis.

Granulosa-cell tumors are frequently considered as low-grade malignancies and are prognostically similar to epithelial borderline neoplasm of the ovary. This issue is a reflection of the propensity of the tumor to remain localized and demonstrate an indolent growth pattern. A large majority of these tumors are diagnosed in stage I, although it must be remembered that accurate and complete surgical staging is not available in most of the published series. In three of the largest series (2,5,11) the frequency of stage I disease ranges from 78% to 91%. Bilateral ovarian involvement is unusual, ranging from 0% to 8%. The prognosis of this tumor is excellent: the relapse rates range from 10% to 33%. The average time to recurrence is between 5 and 10 years (11), with some recurrences occurring as late as 25 years after the initial diagnosis. The long-term survival rates range from 75% to 90% for all stages. The collective assessment of 190 surgically staged patients demonstrated a 5-year survival of 92–100% in stage I disease (2,9,13). The earlier presentation, the infrequency of bilaterality, the long median-time to recurrence (6.0 years), the long-term survival and the long-median survival after recurrence (5.6 years) demonstrate a behavior very different from epithelial ovarian cancer (5,14). However, stage III disease, although rare, carries a poor prognosis with a 5-year survival of 0–22%, similar to that observed with epithelial ovarian cancer. Furthermore, over 70% of patients with recurrent disease will die of granulosa-cell tumors suggesting the limitation of nonsurgical therapeutic options and possibly a different tumor biology. The patterns of spread and recurrence indicate that the tumor disseminates by the same routes as do epithelial ovarian cancers: exfoliation of clonogenic cells into the peritoneal cavity, direct extension to adjacent organs, and lymphatic and hematogenous metastases. While stage has been recognized as the most important prognostic factor for granulosa-cell tumor, tumor size, rupture, histological subtype, nuclear atypia, mitotic activity, and ploidy have shown various correlation with survival. While rupture adversely impacts survival, tumor size loses independent predictability when assessed according to stage (3,9,11,15). Tumors at more advanced stages present a higher grade of atypia and/or more mitotic figures (3,5,9). The importance of histological subtype and ploidy status appears to be of minimal value, as several reports have failed to confirm a previous observation of the prognostic value of histological pattern (3–5,9,11,14), and the reported studies utilizing flow cytometric analysis of DNA content have been inconsistent (14,16,17). The identification of a specific tumor marker would facilitate early detection of recurrent disease. Among proteins derived from granulosa cells, inhibin, a follicle-regulating protein and mullerian-inhibiting substance, is assayable in serum. The granulosa cells of the ovary secrete inhibin, a peptide hormone composed of an alpha and one of two beta subunits (18). Its major physiological function is to inhibit the secretion of FSH by the anterior pituitary gland (19). It functions locally by stimulating progesterone production while inhibiting the production of estradiol and serves as a negative regulator of gonadal-cell proliferation (20). Inhibin is expressed in excessive quantities by granulosa-cell tumors. The first report of elevated serum inhibin levels associated with these tumors came in 1989 by Lappohn et al. (21). In this study 4 out of 6 patients with granulosa-cell tumors presented elevated levels of inhibin before surgery, all 6 patients had a normal level after surgery, and in 2 patients with recurrence elevated serum level was observed 5 and 20 months prior to clinical evidence of the disease. Similarly, in a prospective evaluation of 27 patients with granulosa-cell tumors, Jobling et al. (22) demonstrated a sevenfold elevation of inhibin levels before surgery and rising inhibin levels several months before clinical recurrence.

Inhibin has been demonstrated to be a useful tumor marker in granulosa-cell tumors and further studies are needed to delineate the effects of its use on prognosis, morbidity, and mortality.

Granulosa-Cell Tumors: Juvenile Type

Ovarian neoplasms are relatively rare in childhood and adolescence and, when encountered, the majority are of germ-cell origin with only 5–7% consistent with a sex cord–stromal derivation. Young et al. have described a variant of granulosa-cell tumors that tend to occur in younger women with natural history and histological characteristics very different from the typical granulosa-cell tumors (23). About 90% of granulosa tumors occurring in prepubertal girls and many of those seen before the age of 30 years are of this juvenile type. In Young et al.'s series of 125 cases, 44% of the tumors occurred prior to age 10 and only 3% after the third decade of life. The tumor usually arises in otherwise normal children, although there is a suggestion for a specific association with Ollier's disease (enchondromatosis) and Maffucci's syndrome (enchondromatosis and hemangiomatosis) (24–28). Similarly with the adult type, the frequency of bilaterality is 5% (23) and most tumors present at an early stage. An extraovarian spread is infrequently observed at exploration while rupture of the tumor is noted in approximately 10% of cases. The majority of prepubertal patients present with clinical evidence of isosexual precocious pseudopuberty, which may include breast enlargement, development of pubic and axillary hair, vaginal secretions, irregular uterine bleeding, advanced somatic and skeletal development, and other secondary sex characteristics (23,29–32). Infrequently, patients present an androgen-secreting tumor accompanied by a virilization syndrome. When it occurs after puberty, the juvenile germ-cell tumors present with abdominal pain or swelling, sometimes associated with menstrual irregularities or amenorrhea. A surgical emergency following spontaneous rupture or torsion of the adnexal mass is encountered approximately in 6% of cases.

The gross appearance of juvenile germ-cell tumors is similar to that of an adult type. The tumors are largely solid, although cystic forms are occasionally encountered. Microscopic examination reveals a predominantly solid cellular tumor with follicle formation and an edematous, loose stroma. The tumor has distinct histopathological features, including hypercromatic granulosa cells with round nuclei, abundant content of eosinophilic (luteinized) cytoplasm, and generally high mitotic rate.

Although the juvenile germ-cell tumors usually appear less well differentiated than the adult form, follow-up data indicate a high cure rate. Young et al. (23) observed that in 95 patients with an average of 5 years of follow-up 92% of the patients were alive and free of disease. In contrast to the adult-type tumors that present recurrences remote from initial diagnosis, the juvenile form is characteristically aggressive in advanced stages and the time to relapse and death of limited duration. Only 3 out of 13 cases (23%) with advanced disease (stage II, III, or IV) extracted from three series (23,31,32) were alive, and recurrences and deaths occurred within 3 years. Young et al. (23) noted that stage at surgical exploration represents the most important prognostic indicator. Tumor size, mitotic atypia, and nuclear atypia lose their significance when applied only to stage I. Furthermore, no impact on recurrence or survival was associated with tumor rupture. In a limited number of patients with advanced disease, aneuploidy was correlated with a worse prognosis (33).

SERTOLI–LEYDIG-CELL TUMORS (ANDROBLASTOMAS)

This group of tumors occurs most frequently in the second and third decades, with 75% of the lesions seen in women younger than 40 years. These neoplasms are extremely rare, accounting for less than 0.2% of ovarian cancer (34). The tumors typically produce androgens and clinical virilization is noted in 70–85% of patients (35). The most frequent androgenic symptom includes oligomenorrhea followed by amenorrhea, breast atrophy, acne, hirsutism, clitoromegaly, a deepening voice, and a receding hairline. The prevalence of androgenic manifestations appears independent of degree of histological differentiation but is observed less frequently in heterologous and retiform lesions. Measurement of plasma androgens may reveal elevated testosterone and androstenedione, with normal or slightly elevated dehydroepiandrosterone sulphate (34). Surgical excision of the tumor results in a precipitous drop in androgen levels and partial to complete resolution of the clinical signs associated with androgen excess is noted. Approximately 50% of patients with these tumors have no endocrine manifestations and usually complain of abdominal swelling or pain. Occasional tumors are correlated with various estrogenic syndromes. Sertoli–Leydig tumors are unilateral in 98% of cases and are variable size, averaging about 10 cm in diameter. In a series of about 200 patients, tumors are stage Ia in 80% of the cases; in 12% the tumor has either ruptured or involved the external surface of the ovary and in 4% ascites is present (36). The majority are solid and firm, often yellow and lobulated. Poorly differentiated tumors contain areas of hemorrhage and necrosis, while heterologous and retiform tumors are more often cystic. Sertoli–Leydig tumors are traditionally categorized according to their degree of differentiation. Well-differentiated neoplasms are characterized by clearly defined tubular pattern, lined by Sertoli cells. These tubules are separated by a fibrous stroma that contains a variable number of cells resembling Leydig cells. Sertoli–Leydig tumors of intermediate and poor differentiation are characterized by a variety of patterns and combinations of cell types. When a significant amount of stroma component is made of immature, cellular mesenchymal tissue with high mitotic activity resembling a nonspecific sarcoma, the tumor is poorly differentiated. Approximately 10% of Sertoli–Leydig tumors have a retiform component, resembling the rete testis, and 20% show heterologous elements, such as intestinal-type epithelium, islands of cartilage, and areas of embryonal rhabdomyosarcoma.

Sertoli–Leydig-cell tumors are most frequently low-grade malignancies, although occasionally a poorly differentiated variety may behave more aggressively. The prognosis is closely related to their degree of differentiation and stage of disease. In the report by Young and Scully (36), none of the well-differentiated tumors, 11% of those with intermediate differentiation, 59% of the poorly differentiated tumors, and 19% of those with heterologous elements were clinically malignant. The only clinically malignant tumor in Roth's study (37) was poorly differentiated and 4 out of 20 poorly differentiated tumors described by Zaloudek and Norris (38) were malignant in contrast with 1 out of 44 tumors of intermediate differentiation and none of the 7 well-differentiated tumors. The natural history of the malignant variant includes early recurrences, with approximately 66% becoming evident within 1 year of treatment and only 6–7% recurring after 5 years. The abdominal cavity and the retroperitoneal nodes are the most frequent sites of recurrences. In addition, controlateral ovary, lung, liver, bone, and brain may be involved. The collective salvage rates in patients with clinically

malignant disease are less than 20%. Stage is the second important predictor of outcome in Sertoli–Leydig-cell tumors. Fortunately, more than 90% of these tumors are classified as stage I at the time of diagnosis and less than 20% become clinically malignant. The rare tumors that present in an advanced stage have a poor prognosis, with a mortality rate of 100%. The overall 5-year survival is 70–90% and recurrences thereafter are uncommon. Poorly differentiated lesions comprise the majority of fatalities.

MANAGEMENT

Our understanding on the optimal management of sex-cord ovarian tumors is limited by their extreme rarity, their multiplicity of histological patterns, and their variable biological behavior. Contemporary treatment principles have generally developed based on observations of small groups of patients and on information extrapolated from clinical management of epithelial tumors. Adequate knowledge of these tumors is imperative to appropriately diagnose and individualize definitive surgical and adjuvant therapy.

Surgery remains the cornerstone of treatment for patients with sex-cord ovarian tumors. The diagnosis of these tumors is often not made until surgery and a correct frozen section diagnosis can be a challenge even for experienced gynecological pathologist. Many reports indicate that more than 90% of these neoplasms are unilateral and more than 90% are confined to the ovary (2,3,11,23,36–38). Thus conservative surgical approach with unilateral salpingo-oophorectomy seems to be reasonable in patients wishing to preserve their fertility, following careful staging and in the absence of extraovarian spread. In such case, in patients with granulosa-cell tumors, an endometrial curettage must be performed to rule out concomitant endometrial pathology. If reproductive potential is not an issue and in patients with advanced stage disease or with bilateral ovarian involvement, abdominal hysterectomy and bilateral salpingo-oophorectomy should be performed. In addition, a careful surgical staging should be undertaken. This includes a thorough exploration of abdominal cavity, washing for cytological analysis, multiple biopsies, omentectomy, and pelvic and para-aortic lymph node sampling/dissection. Although no scientific evidence exists on the efficacy of cytoreduction, efforts should be made to remove metastatic disease.

In order to select those patients who should receive postoperative therapy, an understanding of prognostic factors is essential. Unfortunately, available information is controversial and incomplete. For granulosa-cell tumors the only prognostic factor that is consistently significant is the stage of disease; patients with advanced disease have been reported to have a poorer survival rate (2,5–7,11). Others factors such as patient age, tumor size, number of mitoses and, more recently, DNA ploidy and S-phase fraction determined by cytometry have been reported to be of prognostic importance (2,3,5,9,14,39,40). There are no data to support any kind of postoperative adjuvant treatment for patients with stage I granulosa-cell tumors, given the indolent nature of this neoplasm and the overall good prognosis for these cases. Evans et al. (14) reported a 9% risk of recurrence in stage Ia. It would appear that patients with stage I disease based on optimal surgery have a very low risk of recurrence. In Bjorkholm's retrospective series (4,5), there was no observed benefit to adjuvant irradiation in early-stage disease.

For Sertoli–Leydig-cell tumors stage, histological differentiation, and, less frequently, mitotic index, the presence of heterologous elements and tumor rupture appears to have a prognostic significance (36–38). Based on these evidences, the candidates for postoperative adjunctive therapy generally should be patients with stage I Sertoli–Leydig-cell tumors that are poorly differentiated or that contain heterologous elements or those with advanced disease of any histological subtype. For patients with adverse prognostic factors, however, the adjuvant treatment of choice remains unknown, but responses to radiation, chemotherapy, and hormonal therapy have been reported (7,41–43). Information concerning chemotherapy for patients with sex-cord ovarian tumors has been limited to a small number of patients in each report with different regimens, and the tendency to have late recurrences makes it difficult to draw definitive conclusions. Single alkylating agents have been used in the past with 25% partial response reported (43–46). In recent years the few available series suggest a possible advantage for multidrug regimens over single alkylating agents monotherapy. The combination of actinomycin-D, 5-fluorouracyl, and cyclophosphamide has shown activity in 2/2 stage III granulosa-cell tumors (44). The same investigators also treated two patients with recurrent Sertoli–Leydig-cell tumors with vincristine, actinomycin-D, and cyclophosphamide (VAC) regimen , achieving two complete responses to treatment. Tavassoli and Norris (47), instead, reported no response in one patient with recurrent Sertoli–Leydig-cell tumor after receiving VAC therapy. With the introduction in the 1970s of cisplatin for the treatment of testicular cancer, platinum-based chemotherapy has been the favored choice over the past decade. Complete responses have been observed in patients treated with doxorubicin–cisplatin regimens (48) and with doxorubicin–cisplatin–cyclophosphamide combinations (49–51). Gershenson et al. (49) reported an overall response rate of 63% in 8 patients with metastatic sex-cord ovarian tumors treated with PAC. Overall, durable remissions seem to occur in no better than 50% of patients receiving PAC combination. The highest activity has been demonstrated with the cisplatin–vinblastine–bleomycin (PVB) regimen: in two separate Italian studies (52,53) and in an EORTC series (54) response rates ranged from 57% to 92%. In our series we observed six complete and three partial responses in 11 untreated recurrent or metastatic granulosa-cell tumors. All six clinically complete responders were verified by second-look laparotomy. Zambetti et al. administered the same regimen to 7 patients with granulosa-cell tumor and observed one complete response and three partial responses. In both series, hematological and nonhematological toxicities were considerable with one and two toxic deaths, respectively. As for the treatment of germ-cell tumors, the substitution of vinblastine with etoposide could produce lower myelosuppression while retaining similar efficacy. Gershenson et al. (55) observed an overall response rate of 83% in a series of 9 patients with poor-prognosis sex cord–stromal tumors of the ovary treated with bleomycin, etoposide, and cisplatin combination therapy (PEB). Toxicity was acceptable; two patients developed mild bleomycin pulmonary toxicity. Of the 7 patients with metastatic disease, only 1 (14%) had a durable remission. Median progression-free survival was 14 months and median survival time was 28 months. Very recently, Homesley et al. (56) reported the results of a Gynecological Oncology Group (GOG) study on the use of PEB regimen of ovarian granulosa-cell tumors and other stromal malignancies. This report represents the largest series of women with sex-cord ovarian tumors treated with chemotherapy. The patient selection included both primary metastatic (stages II–IV) and recurrent

disease. Of the 57 patients evaluated, there were 48 cases with granulosa-cell tumors, 7 with Sertoli–Leydig-cell tumors, 1 with a malignant thecoma, and 1 with an unclassified sex-cord-cell tumor. The frequency of negative second-look was the primary end point for this trial. Thirty-seven percent (14/38) of the patients undergoing second-look laparotomy had negative findings. With a median follow-up of 3 years, 11/16 patients (69%) in the primary advanced disease category and 21/41 of recurrent patients (51%) were progression-free. Although active, this regimen was associated with a severe toxicity with two bleomycin-related toxic deaths. Moreover, grade 4 granulocytopenia was observed in 60% of patients, despite the reduction of bleomycin total dose in the subsequent patients. Thus while sex cord–stromal ovarian tumors have been shown to respond to platinum-based therapy, toxicity is considerable. Future strategies should include the search for equally active but less toxic combination regimens, particularly with reduction or deletion of the bleomicyn dose. Furthermore, there is a need for alternative treatment after PVB/PEB failure. Some promising antitumor activity has been reported with paclitaxel therapy. The use of single-agent paclitaxel has shown a dramatic response in a patient with recurrent granulosa-cell tumor by Tresukosol el al. (57). Currently, a phase II GOG trial is being conducted by the National Cancer Institute using paclitaxel to treat recurrent ovarian stromal tumors (GOG 0187). The combination of paclitaxel and a platinum drug seems to be a reasonable candidate for future trials. To generate high-quality evidence for the efficacy of chemotherapy in ovarian sex cord-stromal tumors, an international cooperative randomized controlled trial will be necessary.

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Ovarian Cancer: Rationale and Strategies Beyond First-Line Treatment

Franco M. Muggia and Maitreyee Hazarika
New York University School of Medicine, New York, New York, U.S.A.

INTRODUCTION

In spite of a large number of active drugs against this disease (Table 1) (1–29), current drug treatments for ovarian cancer are based mostly on two premises: (a) that the platinum up to an optimal dose intensity represents the "core" of any treatment regimen; and (b) that cisplatin and carboplatin yield similar results. Recent therapeutic concepts applicable to all patients presenting in stages III and IV have stressed that the initial treatment should consist of six cycles of taxane plus platinum-based combination (1,2,9). Paclitaxel plus carboplatin have been widely adopted worldwide as the standard chemotherapy treatment following surgical debulking (11,12). These recommendations are based on two clinical trials that have established the superiority of paclitaxel + cisplatin (13) over the prior standard of the Gynecologic Oncology Group (GOG) and the European Organization for Research and Treatment of Cancer (EORTC), which consisted of cisplatin plus cyclophosphamide (5,6), and several clinical trials establishing equivalence of carboplatin with cisplatin in this combination. Efforts have been ongoing to improve on these results primarily by devising triplets or by sequential doublets, and a large trial comparing new regimens has been launched by the GOG with international collaborators. To date, large trials of newer regimens by the German Arbeitgemenschaft Gynaekologische Onkologie (AGO) and others have not shown clear superiority over the current standard, but await full publication.

FIRST-LINE CONSIDERATIONS IMPACTING ON SECOND LINE

It is important to dissect the rationale for components of first-line treatment as one considers how to approach treatment failures. Such failures, incidentally, may occur *during* treatment in approximately 20% of patients with stage III and stage IV disease, and after an average of 18 months *after stopping* therapy in another 60% of these patients. Only up to 20% will have prolonged disease-free survival after paclitaxel plus carboplatin. These percentages may vary across patients in accordance with recog-

Table 1 Cytotoxic Drugs Active in Epithelial Ovarian Cancer

Platinums	*Topoisomerase II inhibitors*
Cisplatin[a]	Liposomal doxorubicin[a] (14,15)
Carboplatin[a]	Epirubicin (17)
Oxaliplatin and (16) other platinum analogues (see Tables 3 and 4)	Mitoxantrone (17)
	Oral etoposide (18)
Mitotic inhibitors	*Antimetabolites*
Paclitaxel (Taxol) (20)[a]	Gemcitabine[a] (22)
Docetaxel (Taxotere) (21)[a]	5-Fluorouracil (23)
Vinorelbine (Navelbine) (19)	Methotrexate (23)
Topoisomerase I inhibitors	*Alkylating agents and nonspecific cytotoxics*
Topotecan[a] (24)	Cyclophosphamide (Cytoxan) (23)
Irinotecan (CPT-11) (25)	Ifosfamide (28)
Liposomal lurtotecan (OSI-211) (26)	Melphalan (23)
Rubitecan (27) (9-nitrocamptothecin)	Thiotepa (23)
	Mitomycin C (23)
	Hexamethylmelamine (Altretamine) (29)

[a] Used in first line and second line.

nized prognostic factors, but are a useful operational subclassification of patients into platinum-refractory, eventually platinum-resistant, and platinum-sensitive populations (4), which will be referred to in subsequent sections.

Rationales and issues for the following first-line ingredients include:

(a) *Duration of treatment*: The habitual six cycles continue to dominate principally because most data are based on six cycles and because patient tolerance of a platinum-based regimen is often problematical after six cycles. However, one should consider increasing the number of cycles for individual patients if the clinical complete response (CCR) is only gradually achieved (e.g., as may occur with liver metastasis). Conversely, it may be appropriate to decrease the cycles in high-risk situations (where CCR has been achieved rapidly) as part of an early reassessment strategy, or with consolidation.

(b) *Selection of platinum*: Carboplatin is the usual choice because equivalence with cisplatin has been noted in phase III studies. However, it is more myelosuppressive than cisplatin and the latter is occasionally an appropriate substitute if given intraperitoneally (IP) or in situations of a compromised marrow. One already dated and underpowered trial indicates equivalence for oxaliplatin in first-line treatment (16), and additional data are needed to consider such substitution.

(c) *Selection of taxanes and other active drugs*: A recent study has shown equivalent results and substantially less neuropathy with docetaxel substituting for paclitaxel (2). However, febrile neutropenia occurs more often with docetaxel. The key question currently is whether these or other drugs should routinely partner with cisplatin or carboplatin. Protocol GOG 132 and International Collaborative Ovarian Neoplasm (ICON) 3 support the

notion for beginning with a single-agent platinum in some circumstances (e.g., in the immediate postoperative period when the patient faces life-threatening tumor-related problems such as effusion). Other drugs may have toxicity profiles more acceptable to some patients (e.g., gemcitabine in women strongly objecting to alopecia, or topotecan in women with pre-existing neuropathy).

(d) *Interval cytoreduction*: One trial and several reviews support the notion of debulking strategy (5). This step could give the opportunity to combine the initial induction with insertion of an intraperitoneal device for IP consolidation.

(e) *Laparoscopic reassessment*: The recent GOG trial 158 (12) permitted institutions to select reassessment or not. Such selection per se was not associated with differences in progression-free survival (PFS) from early institution of a second-line treatment. However, this cannot be used in support, or against, a particular therapeutic strategy plan, such as IP therapy. Nevertheless, a reassessment strategy should likely exclude women at low risk for persistent or predominant peritoneal metastasis and be directed primarily to those at higher risk, and is logistically best applied to include all such patients, whether or not positive findings are documented.

CONSOLIDATION: CONCEPT AND TREATMENTS

Consolidation is defined as a treatment given without intervening relapse (assessment variably defined clinically, by imaging, and/or by tumor markers). Table 2 describes such treatments currently under study. It is unfortunate that a trial of IP cisplatin as consolidated by the EORTC did not meet its accrual goals, although a trend in favor of such consolidation became apparent prior to termination (S. Pecorelli, personal communication). A study of IP α-interferon for pathological complete response (pCR) was also closed early as was a study of high-dose chemotherapy (GOG 164). Therefore, consolidation treatment has no established role principally because this has been an evolving concept and an understudied area; again, a recent study by SWOG/GOG was closed early after showing a 7-month superiority in PFS (28 vs. 21) with 12 doses of every-4-week paclitaxel vs. only three doses (Markman et al., in press). This premature closure clouds the clinical applicability of this finding and any possible impact on survival. Ongoing is a phase III study of intravenous paclitaxel consolidation in stage I; in this study, also by the GOG, the drug is given weekly for 20 weeks and compared with no further treatment after an identical induction regimen of paclitaxel + carboplatin.

SECOND-LINE CYTOTOXIC THERAPIES

In general, other cytotoxic drugs represent the major choice for these patients, although retreatment with platinums or platinum drugs as single agents (Tables 3 and 4) could be considered. The longer the initial remission proves to be and the better prior tolerance to these drugs, the more likely one favors reinduction with the same agents,

Table 2 Drugs and Regimens Used in Consolidation, Following Initial Platinum-Based Induction Regimen

Treatment	Route	Study/rationale/comments
Cisplatin[a]	IP	EORTC[b]/ locoregional dose intensity/ dose poor accrual
Paclitaxel (8–10)	IV	SWOG and GOG[b]/antitumor activity/PFS ↑ by 9m (stage III)
Paclitaxel	IV	GOG[b]/antiangiogenesis/ongoing (stage I)
α-Interferon (30)	IP	SWOG and GOG/antitumor activity/closed poor accrual
Floxuridine (31)	IP	SWOG[b]/antitumor activity/did not go on to phase III
Floxuridine + platinums (32)	IP	Pilot study NYU/antitumor activity in phase I
Topotecan + cisplatin (33)	IP	Pilot study NYU/antitumor activity
Etoposide + cisplatin (34)	IP	Pilot study Memorial Sloan-Kettering/ antitumor activity/PFS ↑ (historical controls)
Yttrium 90 Ab (35)	IP	Amersham study[b]/radioimmunoconjugate/ for NDA
Altretamine (36)	PO	SWOG[b]/antitumor activity/achieved targeted PFS at 2 years
Tamoxifen (37–39)	PO	GOG (proposed)/antitumor activity
Thalidomide (40)	PO	GOG (proposed)/antitumor activity
Bayer MMPI[a]	PO	Multicenter trial[b]/antimetastatic/closed at interim analysis; no advantage over control
Ovarex (41)	SC	Second multicenter trial ongoing[b]; first negative overall results[b]

NYU = New York University; PFS = progression-free survival; SWOG = Southwest Oncology Group.
[a] Unpublished.
[b] Randomized trial.

Table 3 Platinum Compounds for Ovarian Cancer

Drug	Special features	Comments
Cisplatin (42)	First of its class since 1971; synergy in combination with a wide variety of drugs	Advantages: combination with myelosuppressive drugs; IP route
Carboplatin (43)	Improved therapeutic index; same platinum–DNA adducts as cisplatin	Results similar to cisplatin with less toxicity; combines well with paclitaxel
Oxaliplatin (44)	Diaminocyclohexane, activity against cisplatin-resistant tumors; unique adducts	Needs more definition, but clearly active and combines well with other drugs
Aroplatin (45)	Diaminocyclohexane; unique adducts	Active by the IP route; attenuated neurotoxicity
Lobaplatin (46,47)	Diaminocyclohexane	Not established in United States
Nedaplatin (48)	Improved therapeutic index	Not established in United States
JM-216 (49)	Orally bioavailable (Pt-IV)	Not established in United States

Table 4 Platinum Drug Combinations Studied in Second Line

Drug regimen	Study design	Comments
Cisplatin + doxorubicin + cyclophosphamide (50)	Randomized vs. paclitaxel	Combination superior survival
Carboplatin + epirubicin (51)	Randomized vs. carboplatin	No difference
Carboplatin + Doxil/Caelyx	Randomized vs. carboplatin	SWOG ongoing
Carboplatin + gemcitabine	Randomized vs. carboplatin	AGO ongoing
Carboplatin + paclitaxel	Randomized vs. carboplatin	ICON 4 (66)
Oxaliplatin + paclitaxel (52)	Pilot	82% response rate

ICON = International Collaborative Ovarian Neoplasm studies; AGO = Arbeitgemenschaft Gynaekologische Onkologie; SWOG = Southwest Oncology Group.

or with other platinums, alone or in combination. Drugs other than platinums are, in general, less efficacious than either cisplatin or carboplatin, and do not lead to sustained CCR. However, they have fewer side effects and may have potential advantages that vary with the setting (Table 5). One new agent, TLK286, is activated by GST-P1 and may have greater activity when this enzyme is overexpressed, such as when platinum resistance has been acquired (54). A small number of randomized trials indicate only small differences when used in platinum-resistant circumstances, but differences requiring confirmation have been found in platinum-sensitive patients (14). In addition to comparative trials, they need to be studied more extensively in various settings including front line.

SECOND LINE: NONCYTOTOXIC THERAPIES

All these noncytotoxic approaches are considered experimental (Table 6). It is likely that the role of these therapies initially will be in combination with cytotoxic drugs, or by themselves in consolidation. Moreover, concepts will be refined as the molecular pathogenesis of ovarian cancer becomes better delineated (Table 6).

TOXICITY CONSIDERATIONS AND CYTOPROTECTORS

Myelosuppression, emesis, and neuropathy are strongly influenced by prior treatment. In general, platinums, alkylating drugs, and radiation diminish bone marrow reserves. Moreover, after several prior treatment with carboplatin, the baseline neutrophil count is often low (below 1000). In the experience of the senior author, a low baseline does not preclude treatment at the usually accepted interval and doses, if platelets are normal. Nevertheless, protective measures may be considered in addition to the selection of drugs based on their lesser likelihood to compound prior toxicities. These measures include:

(a) *Neuroprotectors*: Amifostine has been used to reverse toxicity and to protect against the toxicity of platinum. Recently, other drugs also have

Table 5 Nonplatinum Cytotoxic Drugs: Advantages and Disadvantages for Second-Line Therapy

Drug	Route	Activity	Potential advantages	Disadvantages
Paclitaxel[a]	IV	Active in platinum-pretreated patients (20); in phase III objective responses: 6.7% platinum-refractory, 20% platinum-sensitive (10)	Subjective tolerance	Neuropathy, total alopecia, common allergic reactions on first exposure
Docetaxel	IV	Platinum-refractory patients had a response rate of 25% compared with 33% in platinum-sensitive patients; active after paclitaxel (21)	Less neuropathy than paclitaxel (2)	Some cross-resistance to paclitaxel; ↑ capillary leak, total alopecia
Topotecan	IV	In phase III studies, objective responses: 12.4% in platinum-resistant, 19.2% in platinum-sensitive (10,14)	No neuropathy	Leukopenia, neutropenia, alopecia, nausea/vomiting
Irinotecan	IV	13 (48.1%) of 27 cases were irinotecan-sensitive (25)	Less schedule-dependent than topotecan	Diarrhea
Doxil	IV	In phase III studies, objective responses: 20.3% in platinum-resistant, 12.1% in platinum-sensitive (14)	No cardiotoxicity, and minimal or no alopecia	Skin and mucosal toxicities; acute hypersensitivity reactions on first exposure
Etoposide	PO	Activity comparable to above drugs: 26% objective response (18)	No sensory neuropathy; orally active	Total alopecia, gastrointestinal and hematologic toxicity, leukemia
Ifosfamide	IV	Active in platinum-pretreated patients: 12% objective response (28)	No sensory neuropathy	Alopecia, gastrointestinal and hematologic toxicity, central nervous system (CNS) toxicity, cystitis, leukemia
Cyclophosphamide	IV/PO	Established activity in first line, prior to platinum use (23)	No neurotoxicity	Same as ifosfamide but less CNS toxicity
Gemcitabine	IV	Activity alone (22) and in combination with platinum compounds	Subjective tolerance, no sensory neuropathy	Myelosuppression
Vinorelbine	IV	No comparative data: some activity reported (19,47)	Minimal alopecia	Usually requires central line; sensory neuropathy
Epirubicin	IV	41% in platinum-sensitive (17,25)	No cardiotoxicity	Myelosuppression (neutropenia), nausea/vomiting, some alopecia
Capecitabine	PO	Not established but 5-FU has some study activity (23)	Less myelosuppression than with 5-FU; orally active	Skin and mucosal toxicities
Altretamine	PO	Activity in platinum-resistant, not clear in platinum-sensitive (53)	No sustained hematological toxicities	Unpredictable gastrointestinal, CNS, and peripheral sensory neurological toxicity
TLK-286	IV	Active in second line with long survival noted (54)	No major myelosuppression	Gastrointestinal and bladder toxicities

[a] Analogs, liposomes, and polymers also show activity, with modified toxicities.

Table 6 Noncytotoxic Drugs and Their Targets

Drug(s)	Route	Type of drugs	Reference
ZD-1839 (gefitinib, Iressa®)	PO	Epidermal growth factor receptor tyrosine kinase inhibitor	(55)
OSI-774 (erlotinib, Tarceva®)	PO	EGFR tyrosine kinase inhibitor	(56)
CI 1033	PO	Pan-erbB tyrosine kinase inactivator	(57)
Trastuzumab (Herceptin™)	IV	Anti-her-2 receptor monoclonal antibody	(55)
IMC-225 (Erbitux™)	IV	Anti-EGF receptor monoclonal antibody	(58)
MMPIs	PO	Matrix metalloproteinase inhibitor	(59,60)
FTIs	PO/IV	Ras farnesyltransferase inhibition	(61)
P53 vector	IP	Gene therapy	(62)
Raf-1 kinase inhibitor	PO	Antioncogenic	Ongoing trials by Bayer and the NCI

been undergoing testing. At present, the role of these protective drugs has not been established.

(b) *Bone marrow stimulators*: Erythropoietin has a well-defined role in decreasing the need for transfusions and in increasing well-being. Anemia is more likely to occur with some therapies (e.g., topotecan or platinums). Moreover, any platinum-pretreated patient may benefit, and some with renal damage may be particularly predisposed to anemia from second-line treatment. Granulocyte colony-stimulating factor (G-CSF) is not usually necessary in delivering these regimens, but may be needed if maintenance of dose intensity is desirable. However, platelets are often the dose-limiting toxicity in second line because both carboplatin and cisplatin have cumulative effects on platelets.

(c) *Bone marrow protectors*: Amifostine was considered an ideal drug to protect against platinum myelosuppression based on preclinical and clinical studies. However, a randomized study recently completed by our group casts doubt on this protection (63).

(d) *Cardioprotectors*: Clinical trials have established that dexrazoxane protects against anthracycline cardiotoxicity. There is no evidence that Doxil, however, requires cardioprotection even at high cumulative doses (64).

(e) *Other toxicity protection*: Anecdotally, B6 has protected against hand–foot syndrome or other toxicities that contribute to long-term morbidity including ototoxicity, nephrotoxicity, and alopecia. The choice of drugs often allows minimizing certain risks. At present, no reliable way of prevailing against alopecia is available. However, weekly paclitaxel does spare alopecia to some extent, and ice caps, used in the past to protect against

low doses of weekly doxorubicin or epirubicin, may be considered but have not had clinical trial. Polymers may have improved therapeutic index. Glutamine has been used to protect against mucositis, but effects are not verified by randomized studies. Similarly, the usefulness of budesonide against diarrhea of irinotecan has not been confirmed (65).

CONCLUSION

Major strides in the treatment of ovarian cancer have been made since 1950. These are reflected in both national mortality statistics and in results of clinical trials. The introduction of platinum compounds and surgical principles is the major factor responsible for such advances. Nevertheless, late stage at presentation, treatment morbidity, and the need for prolonged treatment contribute to unwarranted nihilism and frequent pessimistic statements. In this chapter, we have described the rationale and treatment strategies for recurrent or persistent disease, with most of these under investigation. In spite of shortcomings of clinical data beyond first line, it is likely that several of these are contributing to improved survival of these patients. However, we have refrained from a prescribed sequence of treatments because clinical trials represent the best method for documenting potential advantages and any treatment-associated morbidity. In fact, recent results of a large ICON clinical trial support treatment with a combination of carboplatin + paclitaxel over carboplatin alone when faced with the first recurrence of disease (66).

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Fallopian Tube Cancer

Pierluigi Benedetti Panici, Roberto Angioli, and Marco Calcagno
University of Rome Campus Bio-Medico, Rome, Italy

Jacobus Pfisterer
Universitätsklinikum, Schleswig Holstein, Kiel, Germany

INTRODUCTION

The fallopian tube is a frequent site of metastasis. Ovarian, endometrial, and cervical cancer metastasis are reported in up to 50%, 12%, and 4% of the patients, respectively (1–4). The importance of these implants has been recognized by the FIGO that has therefore introduced adnexal pathologic examination as part of the ovarian staging system. Therefore the clinical relevance of fallopian tube metastasis has already been discussed in the chapter on the primary ovarian tumors. For these reasons, in the following chapter, we are going to discuss only primary disease.

Epidemiology

Fallopian tube carcinoma is the least common gynecologic malignancy with an expected incidence of 0.1–1.8% among this group of patients. It is much rarer than ovarian cancer, with the relative frequency ranging between 1:20 and 1:150. Although it may occur at any age, it is mostly found after menopause (peak incidence is between 55 and 64 years), and cases below 30 years are extremely rare (5,6). According to the 24th FIGO annual report, 5-year survival of stage I is 70.1%, 59.3% for stage II, 25.3% for stage III, and 22.2% for stage IV (Fig. 1). The prognosis by stage is much worse compared to ovarian cancer (7) .The distinction of fallopian tube carcinoma and ovarian carcinoma is based on histopathological and topological factors as initially suggested by Hu et al. (8) and successively redefined by Sedlis (9). Despite these differences (Table 1), both malignancies share a common Müllerian origin, and this explains the gross, microscopic, and clinical similarities (10). Furthermore, a common molecular pathogenesis is suggested by the similar patterns of genomic alterations in these tumors (11).

Possible risk factors are pelvic inflammatory disease (especially tuberculous salpingitis) and nulliparity (5,12). Histopathological fallopian tube changes such as prior chronic salpingitis are probably etiologically related to fallopian tube carcinoma

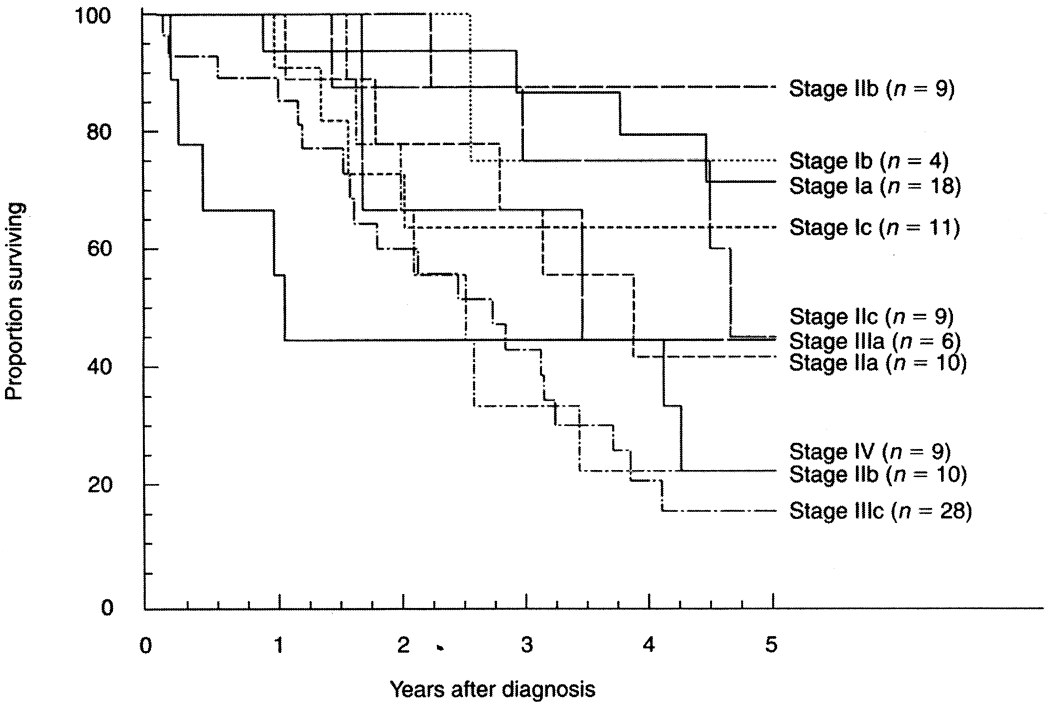

Figure 1 Carcinoma of the fallopian tube: survival by FIGO stage, $n = 114$. (From Ref. 7.)

(13). In addition, as for ovarian cancer, BRCA gene mutations have recently been correlated to this disease (14).

Patterns of Spread

The pattern of spread of fallopian tube cancer is similar to ovarian cancer. Most frequent sites of metastasis at surgery are ovaries, peritoneum, omentum, and bowel. Exfoliation from the distal end has been suggested as means of spread (15). Trans-

Table 1 Differences in Clinical Appearance of Fallopian Tube and Ovarian Cancer

	Fallopian tube cancer	Ovarian cancer
Median age (years)	55	63
FIGO I/II	68%	35%
LK involvement	38%	15%
Distant spread (lung, liver a.o.)	21%	13%
5-year survival FIGO I/II	68%	93%
FIGO III/IV	32%	7%

Source: Baltzer et al., 1999, Praxis der gynäkologischen Onkologie. Stuttgart, New York: Georg Thieme Verlag, 1999:253–256.

coelomic is another important mode of spread (16). Lymphatic metastasis most frequently begins through para-aortic lymph nodes (17). Pelvic and para-aortic lymph node involvement has been identified in 10–30% of patients undergoing primary surgery (17,18). Hematogenous diffusion may be suggested by the extraperitoneal sites of recurrence. Frequent sites of extraperitoneal recurrences are pelvic and para-aortic lymph node, liver, lung, pleura, vagina, kidney, brain, cervix, and skin (19–21).

Clinical Presentation

Most common signs and symptoms are abnormal vaginal bleeding, abdominal pain, abnormal watery discharge, palpable pelvic and/or abdominal mass, and clinical suspicion of ascites (6,22,23). The pathognomonic symptom complex "hydrops tubae profluens" with intermittent, colicky pain and sudden watery discharge from the vagina is rare (<5% of cases). Serum Ca125 level is frequently elevated even in low-

Table 2 FIGO Fallopian Tube Cancer Staging

Stage 0	Carcinoma in situ (limited to tubal mucosa)
Stage 1	Growth limited to fallopian tubes
Stage IA	Growth limited to one tube with extension into submucosa and/or muscularis but not penetrating serosal surface; no ascites
Stage IB	Growth limited to both tubes with extension into submucosa and/or muscularis but not penetrating serosal surface; no ascites
Stage IC	Tumor either Stage IA or Stage IB but with extension through or onto tubal serosa or with ascites containing malignant cells or with positive peritoneal washings
Stage II	Growth involving one or both fallopian tubes with pelvic extension
Stage IIA	Extension and/or metastasis to uterus and/or ovaries
Stage IIB	Extension to other pelvic tissues
Stage IIC	Tumor either Stage IIA or Stage IIB and with ascites containing malignant cells or with positive peritoneal washings
Stage III	Tumor involving one or both fallopian tubes with peritoneal implants outside pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastasis equals Stage III. Tumor appears limited to true pelvis but with histologically proved malignant extension to small bowel omentum
Stage IIIA	Tumor grossly limited to true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces
Stage IIIB	Tumor involving one or both tubes with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter. Lymph nodes are negative
Stage IIIC	Abdominal implants >2 cm in diameter and/or positive retroperitoneal or inguinal nodes
Stage IV	Growth involving one or both fallopian tubes with distant metastases. If pleural effusion is present, cytologic fluid must be positive for malignant cells to be Stage IV. Parenchymal liver metastasis equals Stage IV

Staging for fallopian tube carcinoma is by the surgical pathologic system. Operative findings designating stage are determined before tumor debulking.
Source: Ref. 7.

stage disease and may be useful in preoperative diagnosis as well as for monitoring during therapeutic interventions. Fallopian tube carcinoma may be detected cytologically in cervical smears; however, positive results are inconsistent (6,22). Irrespective to symptomatology and diagnostic procedures, a correct preoperative diagnosis of fallopian tube cancer only seems to be possible in approximately 5% of all cases (24). Frequently, fallopian tube cancer may be misdiagnosed as hematosalpinx, hydrosalpinx, or pyosalpinx intraoperatively (10).

Prognostic Factors

Several prognostic factors have been identified. However, the most relevant were FIGO stage, presence of residual tumor, and hydrosalpinx-like appearance. In early-stage disease, even depth of infiltration in the tubal wall and intraoperative are prognostic factors (6). Finally, patient age, histology, and fimbrial ostium closure appear to be significant prognostic factors (7,10,22).

Surgical Staging

Surgical staging of fallopian tube carcinoma was first proposed by the International Federation of Gynecology and Obstetrics (FIGO) in 1991 (Table 2). This includes total abdominal hysterectomy with bilateral salpingo-oophorectomy, infracolic omentectomy, retroperitoneal lymph nodes evaluation, peritoneal cytology, and peritoneal biopsies. Sites that should always be bioptized should be cul-de-sac, rectal and bladder serosa, both sides of pelvic sidewalls, paracolic gutters, and diaphragms. In addition, since microscopic implants tend to lead to formation of adhesions, biopsy of all adhesions is recommended. Several investigators reported the importance of pelvic and/or para-aortic lymph node involvement in fallopian tube cancer even in early-stage disease (17,22,25). These observations suggest the need for routine pelvic and para-aortic lymph node sampling especially in low-stage fallopian tube cancer. This demand is further supported through observations that lymph nodes represent a common site of persistent or recurrent disease (22,26,27).

In comparison to ovarian cancer, fallopian tube carcinoma tends to be more often diagnosed as being of low FIGO stage at time of primary diagnosis (Table 1). This difference may be explained by earlier symptoms, different tumor biology, and inadequate operative staging.

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Chemotherapy of Fallopian Tube Cancer

Jacobus Pfisterer and Felix Hilpert
Universitätsklinikum, Schleswig Holstein, Kiel, Germany

Primary fallopian tube cancer is a rare gynecologic tumor. Therefore it is difficult to carry large clinical trials on this disease. It shares, with ovarian cancer, many etiological, histological, and clinical characteristics. This justifies the similarities in the treatment of these two tumors.

PRIMARY THERAPY

There is a scarcity of randomized prospective trials looking into the treatment of fallopian tube cancer. Moreover, distinction from ovarian cancer with regard to clinical management is unclear. As a result, one is left with a dilemma in our times of evidence-based medicine. Most therapeutic concepts are derived from smaller retrospective studies with data collected over long time periods. Several modifications of treatment and staging modalities have resulted in a poorly defined management of this disease. Demanding larger prospective trials makes sense from a theoretical standpoint; however, the rarity of fallopian tube cancer prevents the initiation of such studies, and there is only little hope that this problem will be solved in the near future.

CHEMOTHERAPY

General Aspects

Fallopian tube cancer tends to recur even in a large percentage of low-stage patients. Common sites of recurrence are the pelvis, the upper abdomen, and the retroperitoneal lymph nodes. Distant sites such as liver, pleura, lung, vagina, distant lymph nodes, bones, and brain are also observed (1–3). Taken together, occult spread to lymph nodes and high recurrence rates with distant spread even in low-stage fallopian tube cancer require effective adjuvant treatment.

Chemotherapeutical approach has shown promising results; combination chemotherapy is nowadays considered the gold standard in the postoperative treatment of fallopian tube cancer (1,4,5).

During the past decades, different chemotherapeutical regimens have been used in the postoperative treatment of fallopian tube cancer. As mentioned before, all results have been originated from retrospective studies and there is a total lack of prospective data. As a result, every clinician is forced to decide on the basis of a low level of evidence. Alternatively, treatment of fallopian tube cancer may follow concepts derived from large prospective randomized trials in ovarian cancer. Tempting as this approach may be, there have been suggestions that, notwithstanding the clinical and histopathological similarities, there might be important biological differences between these entities evidenced by the higher rate of hematogenous and lymphatic spread even in low-stage fallopian tube cancer. On the other hand, these suggestions have never been transferred into different treatment modalities for fallopian tube cancer, and we doubt that this will ever happen due to the current lack of alternatives and to recent results suggesting a common molecular pathogenesis of fallopian tube and ovarian cancer.

While interpreting results on chemotherapeutical treatment of fallopian tube cancer, one has to be cautious. Besides the retrospective character of all studies, one has to take into account that results especially from larger series are obtained over several decades of a study period and that surgical and staging procedures as well as treatment patterns may have changed dramatically during the study period. Consequently, results comparing response rates and survival data from various regimens should be interpreted with great caution.

NONPLATINUM CHEMOTHERAPY

Fallopian tube cancer has consistently been shown to be a chemosensitive malignancy comparable with ovarian cancer. Several investigators demonstrated clinical efficacy of single-agent chemotherapy including the alkylating agents melphalan, cyclophosphamide, thiothepa, and others like anthracyclines, platinum, paclitaxel, and topotecan (4,6–10). Boronow first reported a complete remission in a patient receiving a single alkylating agent. Although others confirmed these early observations, further evaluation of this treatment option has been discouraging with response rates as low as 9% in advanced disease and a median survival of only 22 months as reported by Peters et al. and Eddy et al. (2,8,11–13).

In past decades, nonplatinum combination therapies have also generally been employed for adjuvant treatment of fallopian tube cancer. Representative for nonplatinum combination therapies, cyclophosphamide and doxorubicin have been reported to be active in advanced disease with occasional long-term remissions (14,15). However, comparison with platinum-based chemotherapy is disappointing: Peters et al. reported a response rate of only 29% for nonplatinum regimens in comparison to 81% with platinum-containing chemotherapies.

On the basis of these results, and taking experiences from ovarian cancer into consideration, there is no rationale for the use of nonplatinum-based chemotherapy in the postoperative treatment of fallopian tube cancer.

PLATINUM AND PACLITAXEL

Following the introduction of platinum as the most active drug for ovarian cancer, its frequent use in the treatment of fallopian tube cancer started and gave promising results compared to other treatments. A summary of publications focusing platinum-based chemotherapy in predominantly advanced or recurrent but platinum-naive fallopian tube cancer is given in Table 1 (1,2,4,7,8,16–19). Overall response rates range between 29% and 92% with an average of 79% comparable to results from large prospective randomized trials in advanced ovarian cancer (20,21). In addition to higher response rates, there is also a distinct increase in survival as reported by Barakat et al., Pectasides et al., and Gadducci et al. However, for reasons discussed previously, the level of evidence is low.

Analogous to the development in ovarian cancer, cisplatin was used when platinum-based chemotherapy in fallopian tube cancer was first established. During the past decade, the use of carboplatin increased. Large prospective trials with cisplatin and carboplatin in combination with paclitaxel in ovarian cancer resulted in similar efficacy, but a better toxicity profile and quality of life for the carboplatin combinations. Due to the rarity of this malignancy, no valid conclusions could thus far be drawn with respect to efficacy of different platinum agents or escalated dosages (21).

As of now, there are only a few nonanecdotal data concerning the use of paclitaxel in fallopian tube cancer. Tresukosol et al. (6) reported a successful salvage treatment with "high-dose" paclitaxel in platinum-refractory fallopian tube cancer. Due to response rates higher than average with carboplatin/paclitaxel in their series, Baekelandt et al. (1) are prompted "...to suggest that, parallel to the situation in patients with ovarian cancer, a combination of a platinum compound and paclitaxel should be regarded as the chemotherapy standard in the treatment of patients with fallopian tube cancer...." A recent study from Gemignani et al. (22) showed paclitaxel/platinum to be effective in the postoperative treatment of fallopian tube

Table 1 Platinum-Based Chemotherapy in Fallopian Tube Cancer

Authors	Year	CR	PR	NC/PD	RR (%)	Median survival (month)	5-YS
Maxson et al. (16)	1987	9	2	1	92	–	–
Peters et al. (8)	1989	12	1	3	81	–	–
Gurney et al. (2)	1990	2	5	1	88	21	–
Morris et al. (17)	1990	2	0	5	29	44[a]	–
Muntz et al. (18)	1990	3	2	2	71	–	–
Pectasides et al. (19)	1994	8	2	1	91	33	48
Cormio et al. (7)	1997	15	4	5	80	38	29
Baekelandt et al. (1)	2000	14	12	11	70	–	–
Gadducci et al. (4)	2001	29	8	8	82	–	56[b]
Total	–	94	36	37	79	–	–

[a] Stage II–IV.
[b] For complete remissions.

cancer (71% FIGO III/IV) with an overall survival of 96% at 12 months and 90% at 3 years. Large prospective randomized trials in advanced ovarian cancer showed that the combination of platinum and paclitaxel significantly improves survival, and similarity of ovarian and fallopian tube cancer allows suggestions that this may also be valid for the latter (20).

Based on these data, the combination of platinum and paclitaxel should be recommended as the standard first-line treatment for fallopian tube cancer.

CHEMOTHERAPY IN EARLY-STAGE DISEASE

Postoperative chemotherapy in early-stage fallopian tube cancer may be effective taking into consideration its supposed aggressiveness. This concept is supported by recent data for "high-risk" early ovarian cancer comparing adjuvant chemotherapy with no further treatment following surgery reported by Vergote et al. (23). As a conclusion, single-platinum chemotherapy or a platinum-based combination (e.g., platinum/paclitaxel) for at least four cycles should be recommended for postoperative treatment of early-stage fallopian tube cancer. An extension for up to six cycles should be considered in those early-stage cases with potentially unfavorable prognostic factors such as deep muscle invasion within the tubal wall, a fimbrial location, or the absence of fimbriated-end closure (24).

CHEMOTHERAPY IN ADVANCED-STAGE DISEASE

According to results from larger retrospective series, prognostic significance of stage seems to be most apparent when stages IIA and lower are compared with stages IIB and higher (24). Thus only stage IIB–IV should be defined as "advanced-stage" tumors.

For advanced-stage fallopian tube cancer, combination chemotherapy with carboplatin and paclitaxel should be recommended as the standard postoperative therapy with a dose of AUC 5 and 175 mg/m^2 (3-hr infusion), respectively, in a 3-week schedule (Table 2). Alternatively, carboplatin could be substituted with cisplatin in a dose of 75 mg/m^2, but results from large prospective randomized trials in ovarian cancer showed similar efficacy of both platinum compounds in combination with paclitaxel but better toxicity and quality of life for the carboplatin combination. Both regimens could be administered on an outpatient basis with frequent assessment of hematological (weekly) and nonhematological toxicity.

There is no evidence that incorporation of a third drug into first-line combination chemotherapy may improve response or survival of fallopian tube cancer patients. Results from ongoing studies in ovarian cancer may help to clarify this issue also for fallopian tube cancer. Until then, three drug combinations should only be administered in the context of clinical studies.

In the literature, there are case reports of successful single platinum use in fallopian tube carcinomas. No general conclusions could be drawn from these observations especially in the light of an ongoing dispute concerning single platinum chemotherapy in comparison to platinum-based combination chemotherapy in advanced ovarian cancer. As for three drug combinations, results from ongoing large

Table 2 Chemotherapy Schedules for Fallopian Tube Cancer

Carboplatin/Paclitaxel			
Carboplatin	AUC 5–6	30-min i.v. infusion	day 1
Paclitaxel	175 mg/m^2	3-hr i.v. infusion	day 1
			q21 × 6
Cisplatin/Paclitaxel			
Cisplatin	75 mg/m^2	30-min i.v. infusion	day 1
Paclitaxel	175 mg/m^2 or	3-hr i.v. infusion	day 1
			q21 × 6
	135 mg/m^2	24-hr i.v. infusion	
Carboplatin-mono			
Carboplatin	AUC 5–6	30-min i.v. infusion	day 1
			q21 × 6
Paclitaxel-mono			
Paclitaxel	175 mg/m^2	3-hr i.v. infusion	day 1
			q21 × 26
	135 mg/m^2	24-hr i.v. infusion	
Carboplatin/Gemcitabine			
Carboplatin	AUC 4	30-min i.v. infusion	day 1
Gemcitabine	1000 mg/m^2	1-hr i.v. infusion	day 1 + 8
			q21 × 6
Topotecan-mono			
Topotecan	1.25–1.5 mg/m^2	30-min i.v. infusion	days 1–5
			q21 × 6
Etoposid-mono			
Etoposid	100 mg or	p.o.	days 1–14
	200 mg	p.o.	days 1–5
			q21–28 × 6
Gemcitabine-mono			
Gemcitabine	1000 mg/m^2	i.v.	day 1 + 8
			q21 × 6
Liposomal doxorubicin			
Lipos. doxorubicin (Doxil, Caelyx)	40–50 mg/m^2	i.v.	day 1
			q28 × 6
Tamoxifen			
Tamoxifen	40 mg	p.o.	daily

prospective randomized trials in ovarian cancer should be waited until final conclusions are drawn for the treatment of fallopian tube cancer.

RECURRENT DISEASE

Data on the salvage treatment of fallopian tube cancer are exceedingly rare prohibiting any evidence-based conclusions. Consequently, one is left with applying the current concepts of salvage therapy of ovarian cancer to fallopian tube cancers.

Therapy of recurrent fallopian tube cancer is strictly palliative as in ovarian cancer.

Data on the importance of surgery in the case of recurrence are lacking, but one can estimate that cytoreduction may only be reasonable for tumors with a recurrence-free interval of at least 12 months after completion of first-line chemotherapy and also only if complete debulking seems to be possible in the preoperative assessment. Further surgical procedures which may be indicated in recurring fallopian tube cancer are preternatural anus, pleurodesis, nephrostomy, and others.

Several investigators reported successful platinum-reinduction therapy in fallopian tube cancer and also noneffective salvage treatment after progression under platinum therapy or early relapse. These findings led to the suggestion that ovarian and fallopian tube cancer have a similar tumor biology with regard to their platinum sensitivity and resistance.

Consequently, a modified classification for relapsed ovarian cancer from Markman and Hoskins (25,26) may be applicable for fallopian tube cancer. According to the latter classification, one can differentiate three different groups:

Recurrent platinum-naive patients. For these patients, application of platinum-based chemotherapy should be recommended as salvage treatment.

So-called platinum-sensitive patients with a progression-free interval >6 months after finishing first-line platinum-based chemotherapy. These patients should be recommended for platinum-reinduction therapy with single platinum agent. In view of platinum-based combination chemotherapy, no conclusions could be drawn because data from ongoing trials for relapsed ovarian cancer are preliminary. Concerning the combination of platinum and paclitaxel as second-line treatment following the same combination as first-line therapy, long-lasting neuropathy may prevent its usage and single platinum use should be considered.

Patients with platinum-refractory tumors who progress during platinum-based first-line chemotherapy or relapse early within the first 6 months after finishing first-line platinum-based chemotherapy. In these cases, further application of a platinum-containing chemotherapy does not seem to be effective, and prognosis is generally poor. Therapy should follow rules of best supportive care with low toxicity and high quality of life as much as possible.

As before, no recommendations according to third-line chemotherapy could be made due to missing data. Single-agent chemotherapy with topotecan, gemcitabine, anthracyclines, treosulfan, or etoposide may be effective taking into consideration published experiences with these compounds as effective third-line chemotherapy in ovarian cancer. It is well conceivable that they also have efficacy in third-line chemotherapy of fallopian tube cancer as was suggested in several case reports (9). A collection of different schedules of these compounds is listed in Table 2.

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Endometrial Cancer

Roberto Angioli, Innocenza Palaia, and Pierluigi Benedetti Panici
University of Rome Campus Bio-Medico, Rome, Italy

Alessandro Bovicelli
University of Bologna, Bologna, Italy

INTRODUCTION

Epidemiology and Predisposing Factors

Malignant uterine tumors are comprised of epithelial or mesenchymal elements, or combinations of these two components.

The first two categories are designated as carcinomas and sarcomas, respectively, and the latter are defined as biphasic or mixed carcinosarcomas; rare variants include those with sex cord-like and germ cell elements.

Although malignant uterine tumors represent 10–15% of all cancers in females, approximately 90% of them are represented by endometrial adenocarcinomas.

Endometrial carcinoma has become the most common female genital tract malignancy in North America and Northern Europe. The National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program, which regularly tracks site-specific cancer frequencies and incidence rates in the United States, reported that 48.2% of histologically confirmed invasive female genital tract cancers arose in the uterine corpus; of that group, 94% were composed of purely epithelial elements.

This large proportion of uterine corpus cancer is due, at least in part, to the continuing decline in the incidence of squamous cell carcinoma of the uterine cervix consequent to the early detection of its precursors.

Actually, however, the incidence of endometrial carcinoma has varied during the last few decades—a manifestation not only of an overall increase in longevity, but also of changes in the attitude of exogenous hormone use.

In the decade from 1970 to 1980, an increased incidence of endometrial carcinoma occurred in developed countries; subsequently, the trend appears to have been reversed (1).

In low-risk populations, such as in Africa and Asia, unusual histological variants predominate over the typical endometrioid type of adenocarcinoma.

According to the 24th FIGO annual report, the 5-year survival of stage I is 86.5%, for stage II is 76.1%, for stage III is 51.1%, and for stage IV is 18.5% (Fig. 1).

The role of hyperestrinism (2,3) in the pathogenesis of ordinary endometrial carcinoma is now well documented and supported by a twofold to threefold increased risk of the latter in women receiving unopposed estrogen for 2 years or more (4).

The same pathophysiological mechanism explains the higher risk of endometrial cancer associated with nulliparity, late menopause, estrogen-producing tumors, polycystic ovarian syndrome (PCO), and obesity (5).

In several relatively recent studies, a significant percentage of endometrial carcinomas has also been reported in women treated with tamoxifen for breast cancer (6,7).

On the other hand, oral contraceptives appear to have a protective effect; 1 year of their use has been affirmed to decrease the risk of endometrial cancer by virtually one-half for a period of 15 years (8).

Other less understood predisposing factors include diabetes mellitus, hypertension, high-fat diet, and previous radiation therapy for other malignant conditions.

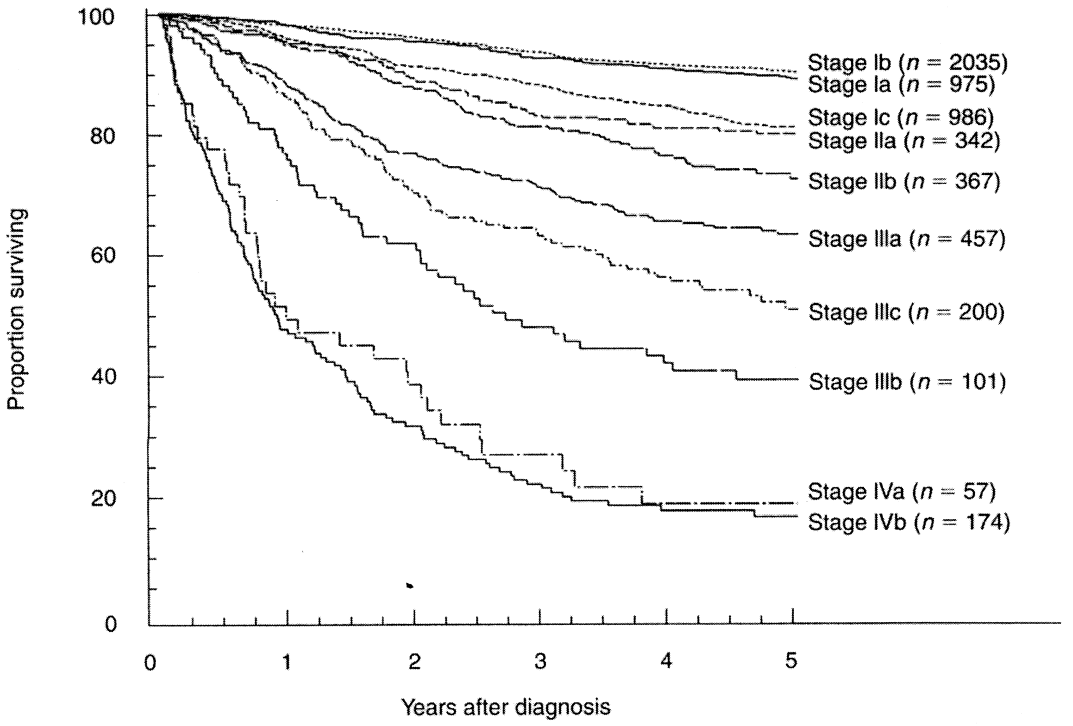

Figure 1 Carcinoma of the corpus uteri: survival by FIGO stage, $n = 5694$. (From Creasman WT, et al. Carcinoma of the corpus uteri. J Epidemiol Biostat 2001; 6(1):62.)

Several studies also suggest a predisposing genetic factor by demonstrating a higher incidence of both endometrial and breast cancers in direct relatives of individuals diagnosed with endometrial carcinoma.

Endometrial cancer is related also to Lynch syndrome. Lynch syndrome is a peculiar disease, accounting for 5% of the total burden of colon cancer. Characteristics of this disease are autosomal dominant transmission, early onset, and frequent right colon localization. Lynch syndrome has specific biomolecular features (microsatellite instability); mismatch repair genes have been identified as the ones responsible of this syndrome. Lynch syndrome poses a high risk for extracolonic malignancies, particularly for endometrial cancer, which is supposed to be related to the mutation of the *MSH2* gene. Genetic tests allow the identification of the state of mutation carriers and the selection of patients for screening.

Classical Pathway of Endometrial Carcinogenesis (Genesis of Type 1 Tumors)

Most endometrioid carcinomas (type 1 tumors) develop in the setting of excess estrogen relative to progesterone. These imbalances may result from absolute excesses of endogenous or exogenous estrogen, or relative deficiencies of progesterone. Androgens and other growth factors may also play a role in this pathway, but this has not been well studied. Hormone levels reflect multiple interrelated processes including exposure (exogenous intake and endogenous production), catabolism, and excretion, which in turn reflect the levels and functional activity of specific metabolic enzymes in the uterus, liver, and other organs. Because hormone balance reflects complex gene–environment interactions, every woman has her own unique hormonal physiology, which may vary over lifetime.

The development of endometrial hyperplasia and endometrioid carcinoma in women with irregular or anovulatory cycles suggests that prolonged periods without endometrial sloughing may be important in the development of fixed endometrial lesions. Although risk factors may be operative in premenopausal women, initiating events occurring in young women may be masked as a result of endometrial shedding. However, these occult alterations may develop into hyperplasia or neoplasia in the postmenopausal period.

Because anovulatory states are often associated with concurrent hormone imbalances, entangling the relative importance of these two potential mechanism would be difficult. Nevertheless, progression of endometrial hyperplasia, including Atypical Hyperplasia, to invasion is neither inevitable nor rapid.

The identification of Myometral Invasion in Atypical Hyperplasia without associated carcinoma suggests that mismatch repair defects may occur in the transition between the two lesions.

The factors that are related to the acquisition of atypia in endometrial hyperplasia have not been well investigated, but data suggest that AH shares features with carcinoma that are not found in hyperplasia without atypia.

Specifically, Atypical Hyperplasia seems to represent a clonal lesion associated with Myometral Invasion and mutations in *ras* and PTEN.

In addition, cells of debated histogenesis, referred to as "foam cells," are a frequent finding in carcinoma and its well-developed precursors, and they may be in-

volved in tumor development through production of inflammatory mediators that stimulate aromatase production and proliferation.

The molecular changes associated with the development of myometrial invasion require further study because endometrioid tumors without myometrial invasion almost never metastasize.

In addition, histopathological examination suggests that grade 3 endometrioid carcinomas develop from grade 1 tumors that have undergone clonal evolution and dedifferentiation.

This process of tumor progression may be associated with loss of hormone receptor expression and development of *p53* mutations.

Alternative Pathway of Endometrial Carcinogenesis

Serous carcinomas typically develop in elderly women with atrophic endometrium. Risk factors for serous carcinoma have not been identified, but the actual evidence suggests that excess estrogen exposure is not a risk factor for the development of serous tumors. Therefore, the only definite risk factor for serous carcinoma is age. Serous carcinomas are usually diagnosed in women over 60 years and these neoplasms are uncommon in younger women.

One possible approach to understanding the etiology of these tumors is to evaluate factors that seem related to the development of *p53* mutations in experimental systems. The nearly universal detection of *p53* mutations in serous carcinomas and its precursor, endometrial intraepithelial carcinoma (EIC), including examples of EIC without associated invasion, suggests that *p53* mutation may represent the molecular characteristic of serous carcinoma and possibly define the entity in combination with morphology. From a histopathological perspective, serous carcinomas seem to develop rapidly from EIC in the setting of endometrial atrophy in an estrogen-deficient hormonal milieu (9). Koul et al. (10), in a recent study, described these two pathways in complete agreement with the conclusions of Sherman.

DIAGNOSIS AND SAMPLING METHODS

Endometrial carcinoma can occasionally be detected by cervical cytology, but the yield of this method is low. Direct endometrial cytological sampling has been tested as a detection tool, and reported results have been variable, with the diagnostic accuracy ranging from 57% to 92% (11,12).

Although this technique may be useful in experienced hands (13), it is probably best regarded as inappropriate for routine screening or diagnostic purposes.

About the accuracy of hysteroscopy without biopsy in diagnosing endometrial cancer and hyperplasia in women with abnormal uterine bleeding, Clark et al. demonstrated that a positive hysteroscopy result increased the probability of cancer to 71.8% (from a pretest probability of 3.9%), whereas a negative hysteroscopy result reduced the probability of cancer to 0.6% (95% CI). Therefore, the diagnostic accuracy of hysteroscopy is high for endometrial cancer, but only moderate for endometrial disease (cancer or hyperplasia) (14).

Gupta et al. performed a meta-analysis evaluating the accuracy of transvaginal ultrasonographic endometrial thickness measurement for diagnosing endometrial pathology in women with postmenopausal bleeding. A positive test result (>5 mm considering both strands) raised the probability of carcinoma from 14% to 31.3%, whereas a negative test reduced it to 2.5%. Thus ultrasound measurement of endometrial thickness alone, using the best-quality studies, cannot be used to accurately rule out endometrial cancer. However, a negative result at ≤5 mm cutoff level measuring both endometrial layers in the presence of endometrial pathology rules out endometrial pathology with good certainty (15).

Regarding the accuracy of outpatient endometrial biopsy in diagnosing endometrial cancer in women with abnormal uterine bleeding, Clark et al. demonstrated that outpatient endometrial biopsy has a high overall accuracy when an adequate specimen is obtained (14).

A positive test result is more accurate for ruling in disease, rather than a negative test result is for ruling it out. Therefore, in cases of abnormal uterine bleeding where symptoms persist despite negative biopsy, further evaluation will be warranted (isteroscopical guided biopsy).

In conclusion, a definitive diagnosis of either endometrial hyperplasia or adenocarcinoma requires histological confirmation.

STAGING

Endometrial cancer has been staged by several systems. The first classification, developed in 1925, classified the disease as clinically operable, technically operable, or inoperable.

In 1950, FIGO proposed its first classification based on the extent of the disease and operability.

Classifications that were subsequently put forward were sometimes surgical–pathological and sometimes clinical, until 1972, when the revised FIGO classification found greater acceptance.

Following its meeting in 1988, the FIGO Committee on Gynecological Oncology recommended that endometrial cancer be surgically staged.

This new classification had to include not only the extent of the tumor but also the histological differentiation for all stages. Depth of myometrial invasion, lymph nodal involvement, important prognostic factors were taken into account, together with the pathological evaluation of cervical involvement.

Stage 0 includes all preinvasive lesions of the malignant endometrium, together with the controversial pathological entity, the carcinoma in situ.

In stage I, the presence and depth of myometrial invasion (expressed as greater or less than half) are the main prognostic factors, the importance of which must be combined with the degree of differentiation. Cases of corpus uteri should be grouped with regard to the degree of differentiation of the adenocarcinoma as follows: G1, 5% of a nonsquamous or nonmorular solid growth pattern; G2, 6–50% of a nonsquamous or nonmorular growth pattern; and G3, >50% of a nonsquamous or nonmorular solid growth pattern.

Intraoperative assessment of peritoneal cytology, lymph nodal status, and pelvic and abdominal surfaces is conclusive for diagnostic and staging purposes (16).

Stage	Clinical/Pathological Findings
Stage I	
IA	Tumor limited to the endometrium
IB	Invasion to less than half of the myometrium
IC	Invasion equal to or more than half of the myometrium
Stage II	
IIA	Endocervical glandular involvement only
IIB	Cervical stromal invasion
Stage III	
IIIA	Tumor invades the serosa of the corpus uteri and/or adnexa, and/or positive cytological findings
IIIB	Vaginal metastasis
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
Stage IV	
IVA	Tumor invasion of the bladder and/or bowel mucosa
IVB	Distant metastasis, including intra-abdominal metastasis and/or inguinal lymph nodes

TREATMENT

Of all the female pelvic malignancies, endometrial cancer seems to have more advocates for different treatment plans than any other. This is particularly true for tumors clinically confined to the uterine corpus, which represent 75% of all adenocarcinomas of this organ. The standard treatment for this disease has been and remains a total abdominal hysterectomy. However, through the years, hormonal therapy, preoperative and postoperative irradiation, and chemotherapy have also been used.

Hormonal Therapy

A selected group of patients, such as premenopausal women with early endometrial cancer desiring to preserve fertility and patients with endometrial cancer having concomitant serious clinical problems, could be candidates to a conservative hormonal approach.

Conservative management of atypical hyperplasia and early-stage endometrial carcinoma has mainly involved the use of progestins, with other agents occasionally used (17–31).

The most commonly used treatments have been megestrol acetate (Megace) and medroxyprogesterone acetate (Provera).

Concerning endometrial hyperplasia, Ferenczy and Gelfand (24) reported a 25% risk (5 of 20 patients) of eventually developing carcinoma within 2–7 years (mean 5.5 years) after the initial diagnosis while on progestin therapy. Perez-Medina et al. (20)

reported a 5% risk (1of 19 patients) after a 5-year follow-up. The majority of studies with long-term follow-up have reported no cases of progression to carcinoma (19,21–23).

Recurrences of hyperplasia have been successfully retreated with the same progestins. Median time to treatment responses are long, with a median of 9 months (19).

Concerning endometrial cancer, a conservative treatment has been reported in a small number of patients, with complete remission rate varying between 62% and 80% (17,19,32).

Megestrol acetate (40 mg/day for 14 days, every month or continuously) is the recommended treatment, with endometrial sampling every 3–6 months until regression or progression.

In a recent study, Montz et al. (33) have evaluated the feasibility of using a progesterone-containing intrauterine device (IUD) to treat presumed FIGO stage IA, grade 1 endometrioid cancer in women at high risk for perioperative complications. Twelve subjects have been followed up to 36 months; results of biopsies were negative in 7 of 11 at 6 months and in 6 of 8 at 12 months.

The authors conclude that intrauterine progesterone appears to eradicate some cases of presumed stage I A, grade 1 endometrioid cancer in women at high risk for perioperative morbidity.

Surgical Therapy

In patients with grade 1, stage I disease, it is suggested that chances of having lymph node metastases and deep invasion is minimal (less than 5%) and the recurrence rate is also very small (Table 1).

As a result, it would appear that simple abdominal hysterectomy, bilateral salpingo-oophorectomy, and peritoneal cytology are the surgical treatment of choice.

Because the incidence of lymph node metastases is so small in this group of patients, a routine lymphadenectomy probably cannot be justified. The exception to such statement is the patient with a grade 1 lesion who has a deeply invasive cancer. This occurs less than 10% of the time; however, when it is present, approximately 10% will have lymph node metastases.

The determinant of myometrial invasion can be made intraoperatively either grossly or on frozen sections. In this small subset of patients, the addition of a pelvic and para-aortic lymphadenectomy appears appropriate.

Table 1 Prognostic Factors for Surgical Modulation

Surgical pathological findings	Surgery
Stage I <50% G1	TAH BSO
Stage I >50% or G2, G3	TAH BSO LND
Stage II	RAH BSO LND

TAH = total abdominal hysterectomy; BSO = bilateral salpingo-oophorectomy; RAH = radical abdominal hysterectomy; LND = lymphadenectomy.

In grades 2 and 3 diseases, patients are considered to be at higher risk for lymph node metastases and it is suggested that pelvic and para-aortic selective lymphadenectomy be added to abdominal hysterectomy, bilateral salpingo-oophorectomy, and peritoneal cytology (34).

The role of systematic lymphadenectomy is being evaluated in a multicenter Italian study.

Patients with cervical involvement have higher risk of lymph node metastasis and at least 10% risk of microscopical parametrial involvement, and therefore benefit from radical hysterectomy instead of extrafascial hysterectomy, in addition to pelvic and aortic lymphadenectomy.

Adjuvant Treatment

A postoperative treatment plan should take into account the prognostic factors determined by the surgical–pathological staging. Patients can be classified in three categories: those who show a high rate of cure without postoperative therapy (low-risk), those who yield a low rate of cure without postoperative therapy (high-risk), and those who demonstrate a reduced rate of surgical cure but may or may not benefit from additional therapy (intermediate-risk) (Table 2).

The postoperative treatment plan should also consider the available postoperative treatment methods and their associated morbidities. Irradiation of the vaginal cuff, the whole pelvis (with or without para-aortic portals), and the whole pelvis and abdomen are proven techniques. Irradiation target doses are 50–70 Gy surface dose

Table 2 Risk Categories for Endometrial Adenocarcinoma

Low risk
- No myometrial invasion, grade 1 or 2
- Superficial (<1/3) myometrial invasion, grade 1 or 2
- No metastatic disease
- Negative peritoneal cytology
- No lymphovascular space invasion

Intermediate risk
- ≥1/3 but <1/2 myometrial invasion, grade 1 or 2
- No myometrial invasion, grade 3
- <1/2 myometrial invasion, grade 3
- >1/2 myometrial invasion, all grades
- Endocervical glandular extension, all grades
- Cervical stromal involvement, grade 1, 2, or 3

High risk
- Vaginal metastasis
- Lymph node metastasis
- Adnexal/serosal/parametrial spread; positive peritoneal cytology
- Bladder/rectal invasion
- Intraperitoneal spread

for vaginal cuff coverage, 45–50 Gy for pelvic irradiation, 45 Gy for para-aortic fields, and 25–30 Gy for treatment of the whole abdomen.

Chemotherapy as adjuvant treatment for patients with endometrial carcinoma is mainly reserved for radiotherapy-refusing patients, or for those enrolled in clinical trials. Chemotherapy is reserved for advanced and recurrent endometrial cancer, and for mesenchymal tumors.

Chemotherapeutic treatments will be detailed in the following chapters.

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Medical Therapy for Endometrial Hyperplasia and Early Endometrial Cancer in Patients Desiring Future Childbearing

Mario M. Leitao Jr. and Richard R. Barakat
Memorial Sloan-Kettering Cancer Center, New York, New York, U.S.A.

The American Cancer Society estimated that there will be 38,300 new cases of endometrial carcinoma diagnosed in the United States in 2001 (1). It is the fourth most common malignancy in women behind breast, lung, and bowel malignancies and is the most common gynecological malignancy. It will account for about 6600 deaths, making it the eighth most common cause of death from malignancy in women and the second most lethal of gynecological malignancies after ovarian cancer (1). Endometrial cancer is primarily a disease of postmenopausal females, occurring most often in the sixth and seventh decades of life, with the average age of onset being 60 years old (2). Approximately 75% of cases will be diagnosed at an early stage where surgery remains part of the standard of initial treatment (2).

Despite being a disease of postmenopausal women, it is seen in younger premenopausal women where issues of fertility are important. In retrospective reviews, up to 35% of cases were diagnosed in premenopausal women (3–9). Women younger than 40 years of age may account for 3–14% of all cases of endometrial cancer (3–6). It has also been diagnosed, albeit rarely, in women younger than 25 years old and even as young as 15 years (10–13). Young patients who develop endometrial cancer often have some degree of hyperestrogenism, anovulation, obesity, and lipid and carbohydrate imbalance. Nearly half are nulliparous, and the vast majority present with abnormal menstrual bleeding (4,5,7–9,14). These young women often have either coincident or prior endometrial hyperplasia, an estrogen-dependent malignant precursor. However, multiparous, thin, healthy women without apparent evidence of underlying hyperestrogenism may also develop carcinoma (8,9,15).

Two types of endometrial carcinogenesis are recognized (16–18). The first is the development of carcinoma in women who are often anovulatory, frequently infertile, and experience late-onset menopause. Obesity, hyperlipidemia, diabetes, and hypertension are often seen in this group of women. The cancers are mostly endometrioid adenocarcinomas, which are felt to have progressed from hyperplasia. They are often well-differentiated, superficially invasive, and early-stage, with infrequent nodal or

extrauterine metastases. They display a high sensitivity to progestins and carry a favorable prognosis. The second type develops in women with normal menstrual and reproductive histories. Obesity, hyperlipidemia, diabetes, and hypertension are often not present. The tumors arise in atrophic endometria and are often estrogen-independent, poorly differentiated, deeply invasive, and advanced-stage, with frequent nodal and extrauterine metastases. The histology of these tumors is usually serous adenocarcinoma. They are poorly responsive to progestins and carry an unfavorable prognosis. Age of patients is not a criteria for attribution to one or another type, and these two types may be equally distributed among premenopausal and postmenopausal women, although earlier studies demonstrated less aggressive carcinomas in younger women. Fortunately, 60–70% of all endometrial carcinomas are of the first type, and it is important to remember that highly aggressive, unfavorable cancers do arise in younger women.

The classification of hyperplasias recognized by the International Society of Gynecological Pathologists is based on the fact that certain endometrial hyperplasias will more readily progress to carcinoma (2). The four classifications—simple hyperplasia, complex hyperplasia, simple hyperplasia with atypia, and complex hyperplasia with atypia—are differentiated based on architectural complexity and the presence of cytological atypia (19). It is often difficult to distinguish complex atypical hyperplasia from well-differentiated carcinoma (20). The presence of stromal invasion is the most important histological criterion for carcinoma. Invasion is diagnosed if the following criteria are met: (a) an irregular infiltration of glands associated with an altered fibroblastic stroma or desmoplastic response; (b) a confluent glandular pattern in which individual glands, uninterrupted by stroma, merge and create a cribriform pattern; (c) an extensive papillary pattern; and (d) replacement of the stroma by masses of squamous epithelium (20). It is important to distinguish complex atypical hyperplasia from well-differentiated carcinoma because they exhibit different outcomes.

Kurman et al. (19) retrospectively reviewed 170 patients with any degree of endometrial hyperplasia but who did not receive any treatment, either medical or surgical, for at least 1 year (Table 1). The risk of progression to carcinoma was 1% for simple hyperplasia, 3% for complex hyperplasia, 8% for simple atypical hyperplasia, and 29% for complex atypical hyperplasia. The risk for simple atypical vs. complex atypical hyperplasia was not statistically different. The most important determinant of risk for progression to carcinoma was the presence of cytological atypia with only 2%

Table 1 Rates of Progression of "Untreated" Hyperplasias to Invasive Carcinoma

Hyperplasia	Rate of progression (%)	
Simple	1	
Complex	3	
Simple with atypia	8	
Complex with atypia	29	8% vs. 29% (NS)
Hyperplasia—no atypia	2	
Atypical hyperplasia	23	$P = 0.001$

The most important determinant of risk is the presence of cytological atypia.
Source: Ref. 19.

of hyperplasias without atypia, vs. 23% of atypical hyperplasias progressing to carcinoma. Degrees of atypia, epithelial stratification, and mitotic activity did not predict progression. The time to progression from hyperplasia to carcinoma is long for both nonatypical and atypical hyperplasias, with median times of 9.5 and 4.1 years, respectively. In addition, all but one of the 13 patients who eventually developed carcinoma were diagnosed with stage I disease. All 13 patients, including one with stage IV disease, were alive without evidence of disease 4–25 years after definitive therapy.

There also exists a risk of having an underlying "occult" carcinoma once a diagnosis of hyperplasia is made. Retrospective reviews have reported rates as high as 43% of underlying carcinoma in patients with atypical hyperplasia (21–23). The presence of architectural complexity in atypical hyperplasia does not confer a greater risk (22). Simple and complex hyperplasias without cytological atypia do not appear to carry a risk of having an underlying malignancy. Reported rates in the literature of underlying carcinoma, as reviewed by other authors, range from 15% to 57%, with long intervals from the diagnosis of hyperplasia to eventual discovery of carcinoma (22,33). The majority of these "occult" malignancies are early-stage endometrioid adenocarcinomas with excellent prognoses after treatment.

In postmenopausal women and those in whom childbearing is no longer an issue, hysterectomy is the preferred choice of treatment for all atypical hyperplasias because of the relatively high likelihood of having an underlying malignancy or progression to carcinoma. It also effectively eliminates vaginal bleeding that is almost always associated with endometrial hyperplasia. However, in young premenopausal women who desire future fertility, a conservative approach may be considered. Despite the risk of underlying cancer, most occult malignancies are usually early-stage and highly curable, and may also respond to conservative therapies (21–23). In addition, the majority of atypical hyperplasias either regress or persist and, when they progress, are also usually highly curable (19). Therefore, in women who desire fertility and who understand all the risks, a conservative approach is acceptable with many going on to deliver healthy, full-term infants.

The standard of treatment for early-stage endometrial carcinoma is hysterectomy followed by adjuvant therapy in some (2). However, in premenopausal women desirous of childbearing, hysterectomy may not be an acceptable option. Conservative approaches, which will provide a chance at successful pregnancies and deliveries, may be acceptable in a small select group of young patients with endometrial carcinoma.

It is well recognized that tumor grade, depth of myometrial invasion, lymph–vascular space invasion, and histology are strongly associated with outcomes in endometrial carcinoma (2,24). These factors are predictive of advanced disease and risk of recurrence. Survival is highly related to stage, with nearly 100% of patients with cancer limited to the endometrium (stage IA) surviving after surgery alone (2). It is therefore essential that these factors are closely reviewed prior to any consideration of conservative management, and only stage IA patients should be considered for this approach. Because these patients do not undergo the standard surgical staging, it is necessary to carefully and accurately assess them without the use of extensive surgery.

Creasman et al. (24) reported the data of the Gynecologic Oncology Group (GOG) on the surgical pathological features of 621 patients, with clinical stage I disease prior to surgical staging being the standard. A fair number of patients (22%) were noted to have disease outside the uterus after being surgically explored. Grade,

depth of myometrial invasion, and lymph–vascular space invasion were strongly associated with nodal metastases (stage IIIC and above), which confers a much worse prognosis. Only 3% of all grade 1 tumors had positive pelvic nodes as compared to 18% of all grade 3 tumors. Grade was also associated with the depth of invasion, with 77% of grade 1 tumors either limited to the endometrium or superficially ($\leq 1/3$ of the uterine wall) invasive as compared to only 42% of those with grade 3. In contrast, only 10% of grade 1 tumors were deeply invasive as opposed to 42% of grade 3. Depth of invasion itself is highly associated with nodal metastases. Of all tumors limited to the endometrium, only 1% had positive pelvic nodes compared to 25% of all deeply (outer one third) invasive tumors. Assessment of both grade and tumor invasion provided the greatest predictive value for nodal metastases (Table 2). None of the patients with grade 1 tumors limited to the endometrium without intraperitoneal disease had nodal metastases and, therefore, are considered low-risk. Lymph–vascular space invasion was also associated with nodal metastases but histological subtype was not.

Histological subtype, however, is predictive of outcome (17,18,25–31). The aggressiveness of endometrioid carcinomas is related to their tumor grade, whereas serous, clear cell, undifferentiated, and squamous cell carcinomas of the uterus have unfavorable prognoses regardless of grade (2). These unfavorable histologies account for less than 10% of endometrial carcinomas (2). Endometrioid adenocarcinomas are more likely to present as well-differentiated, early-stage tumors, which are associated with hyperplasia and respond to progestins (16–18). Well-differentiated endometrioid tumors carry a good prognosis. Less than 25% of serous tumors are stage I and disseminated disease can be seen in patients with tumor apparently confined to the endometrium or with minimal myometrial invasion (17,18,25,26). In serous tumors, architectural and cytological grade do not always correspond as in endometrioid tumors (17). Stage I serous carcinomas have a high recurrence rate, as high as 44%, and significantly worse survival rates (25–31). Patients with grade 1 endometrioid adenocarcinomas limited to the endometrium without evidence of lymph–vascular invasion nor extrauterine disease appear to be the optimal candidates for conservative therapy.

Pretreatment evaluation of patients considering conservative therapy includes a detailed history and physical examination to look for signs and symptoms of advanced metastatic disease, dilatation and curettage (D&C) under anesthesia, and radiological imaging, preferably contrast-enhanced magnetic resonance imaging (MRI). All of

Table 2 Risk of Pelvic Node Metastases in Apparent Stage I Endometrial Carcinoma

	FIGO grade		
Depth of invasion	1 (%)	2 (%)	3 (%)
Endometrium only	0	3	0
Inner one third	3	5	9
Middle one third	0	9	4
Outer one third	11	19	34

Grade and depth of invasion are strongly associated with nodal metastases.
Source: Ref. 24.

these evaluations may underestimate the extent of the disease but, in combination, should provide an adequate evaluation in patients who will be followed closely.

Office endometrial sampling is probably sufficient for patients who will undergo surgery (32). However, a D&C should be performed on all patients with atypical hyperplasia and endometrial carcinoma prior to the institution of conservative therapy. Office sampling has been shown to confirm over 95% of endometrial carcinomas in patients known to have carcinoma (32). Better agreement with final grade and detection of occult malignancy can be achieved on tissues obtained at a D&C with significantly less cases upgraded at the time of hysterectomy, 26% for office biopsy vs. 10% for D&C (33,34). In addition, 11% of patients will have no residual disease after D&C as opposed to only 2% of those who underwent office biopsy (33). Hysteroscopy is extremely operator-dependent and results have been difficult to interpret (35). In follow-up of patients being managed conservatively, office endometrial sampling is sufficient, with D&C reserved for cases with unclear results. Grade, histology, and lymph–vascular status may be ascertained with a D&C, but determination of depth of invasion must rely on radiological imaging.

Transvaginal ultrasound (TVUS), computed tomography (CT) imaging, and MRI have all been employed in the assessment of endometrial carcinoma (36–41). A meta-analysis of 47 studies demonstrated no statistical differences between the three modalities in overall performance, but assessment of myometrial invasion was best achieved with the use of contrast-enhanced MRI (41). Conventional, noncontrast MRI is about 88–92% accurate in staging endometrial carcinoma, and myometrial invasion is hardly ever found histologically when MRI shows the tumor to be limited to the endometrium (36,38). Actually, the majority of erroneous MRI diagnoses are overestimations of the extent of invasion because of polypoid tumors, endometrial cavity distention, atrophic myometrium, and poor tumor/myometrial contrast (36–39). The addition of contrast to MRI has proven to be essential to increase the contrast among tumor, endometrium, and myometrium (39,41). In patients who all underwent TVUS, CT, and noncontrast MRI prior to surgery, MRI was superior to TVUS and CT in assessing the depth of myometrial invasion (40). Studies on helical (spiral) CT scanning have not been performed. There are no imaging guidelines or algorithms available for use of imaging in the pretreatment assessment of endometrial carcinoma. Available data suggest that contrast-enhanced MRI provides the most reliable, accurate, and comprehensive assessment of patients with endometrial carcinoma. Patients with atypical hyperplasia should probably also undergo MRI in the case that an underlying malignancy was missed at the time of D&C.

Conservative management of atypical hyperplasia and early-stage endometrial carcinoma has mainly involved the use of progestins, with other agents occasionally used (12,13,21,35,42–55). Various regimens have been used to conservatively treat atypical hyperplasia and well-differentiated early-stage carcinoma, with megesterol acetate (Megace®) and medroxyprogesterone acetate (Provera®) being the most extensively studied (Table 3). There are only three small retrospective studies on the use of progestins in endometrial carcinoma and equally small retrospective and prospective trials in the treatment of atypical hyperplasia.

Progestins have been shown to counteract the stimulatory effect of estrogens, decrease glandular cellularity, induce apoptosis, and exert antiangiogenic effects (49,50,56). Unopposed estrogen use is associated with the development of hyperplasia in a dose-dependent manner, with the addition of progestins being able to reverse the

Table 3 Regimens Used for Conservative Therapy of Atypical Endometrial Hyperplasia and Well-Differentiated Early-Stage Endometrioid Carcinoma

Agent	Dosage/schedule (range)	Duration (months)
Megesterol acetate (Megace®)	40–400 mg/day, po, continuous followed by nothing, ovulation induction, OCP, or medroxyprogesterone	2–18
Medroxyprogesterone acetate[a] (Provera®)	10–80 mg/day, po, continuous, or 10–14 days/month, followed by nothing, ovulation induction, tamoxifen	1.5–24
	500 mg, im, every week and triptorelin	3 (MPA)
Hydroxyprogesterone caproate	50–200 mg, im, everyday, then nothing, or 500 mg, im, 2×/week	6–12
Cyproterone acetate	50 mg, po, 6×/day	1
Norethindrone acetate	1 mg, po, everyday	2–3
Oral contraceptive pills		12
Triptorelin	IM, every month, in conjunction with MPA	6 (triptorelin)
Danazol	400 mg/day, continuous	3–6
Ovulation induction (Clomid®)	11–18 cycles followed by IVF in some	
Bromocriptine	10 mg, po, everyday	6

[a] MPA.
Source: Refs. 12, 13, 20, 35, 42–46, and 49–51.

endometrial hyperplasia to normal (56). Discontinuation of exogenous, unopposed estrogens often results in regression of hyperplasia. Glandular cellularity is also significantly decreased in patients treated with progestins (50). This did not coincide with an increase in apoptotic activity in patient samples. However, in a cell line derived from a well-differentiated endometrioid adenocarcinoma expressing functional progesterone receptors, greatly increased apoptotic activity was seen within the first 3 days of treatment, with none seen after 96 hr, suggesting that apoptosis is increased early during progestin therapy and that samples from patients were obtained well after this early period (50). Plasma steroid concentrations and steroid receptor levels have not been associated with therapy nor the ability to predict response to therapy in hyperplasias and well-differentiated tumors (54,55,57,58). A recent study demonstrated that bcl-2 immunoreactivity was significantly decreased in those with complete regression of hyperplasia and not in those with persistence, suggesting that control of bcl-2 expression may be of greater significance than control of steroid receptors in the therapeutic efficacy of progestational therapy (55).

Progestin therapy of atypical hyperplasia results in 50–94% rates of complete regression, with the remaining cases exhibiting persistence of hyperplasia and rarely progression to carcinoma (21,35,43–46). Ferenczy and Gelfand (46) reported a 25%

risk (5 of 20 patients) of eventually developing carcinoma within 2–7 years (mean 5.5 years) after the initial diagnosis while on progestin therapy. Perez-Medina et al. (35) reported a 5% risk (1 of 19 patients) after a 5-year follow-up. All of these cancers were well-differentiated with excellent outcomes. The majority of studies with long follow-up have reported no instances of progression to carcinoma (21,43–45). Recurrences of hyperplasia have been successfully retreated with the same progestins. Median time to treatment responses are long, with a median of 9 months in one study (21).

The only available data on conservative treatment of endometrial carcinoma are three small retrospective studies (13,21,42). Randall et al. (21) reported on 12 patients treated with progestins. Nine patients (75%) demonstrated complete regression and the remaining three patients exhibited persistent disease, and none developed progressive disease. Bokhman et al. (42) reported on 19 patients, with 15 (80%) showing complete regression by 6 months of therapy. Of the four patients with persistent cancer, two had only microfoci of adenocarcinoma in hysterectomy specimens and two had no residual disease. Kim et al. (13) reported on seven patients and on another 14 reported in the literature. Their combined data showed that 62% initially responded, and those that did not respond underwent hysterectomy, with all having stage I disease. They also reported recurrences among initial responders, with one recurring as stage IIIB. There were no deaths reported among the three studies, and all but one patient were alive without evidence of disease. Good reproductive outcomes have been seen among patients treated conservatively for atypical hyperplasia and carcinoma. Other agents, such as danazol, bromocriptine, gonadotropin analogues, oral contraceptive pills, and ovulation inducers, have been less extensively studied with mixed results (12,21,35,47,48,50).

Side effects associated with long-term progestin use have been mild, with nausea, bloating, migraines, vaginal dryness, and weight gain being the most common (35,46,52,53). They are usually well-tolerated, easily managed, and rarely require cessation of therapy. Severe hyperglycemia has also been reported in patients with severe medical comorbidities (52).

The recommended standard treatment of atypical hyperplasia and endometrial carcinoma is surgery, especially in postmenopausal women and in those who have completed childbearing. Based on limited and largely retrospective data, a conservative approach appears to be acceptable in women who desire future fertility and have a full understanding of all the risks (Fig. 1). These women should be initially evaluated with D&C and contrast-enhanced MRI. Conservative therapy should be reserved for those with atypical hyperplasia or those with grade 1 endometrioid adenocarcinomas limited to the endometrium and without evidence of lymph–vascular invasion or extrauterine disease. The optimal progestin regimen has not been established, but it appears reasonable to start with the most extensively used agent, megesterol acetate 40 mg/day, for at least 14 days every month and titrate the dosage according to response, keeping in mind that responses may not be seen for many months. Endometrial office sampling should be performed every 3–6 months, or sooner if necessary, with a D&C reserved for unclear office results. Continuous progestin therapy may be necessary with close monitoring. Because these conditions are often associated with obesity, exercise and weight loss should also be encouraged.

Therapy may be discontinued for those who demonstrate complete regression with maintained close follow-up, and it may be reinitiated if a recurrence develops. Attempts at childbearing should be encouraged as soon as possible. Ovulation

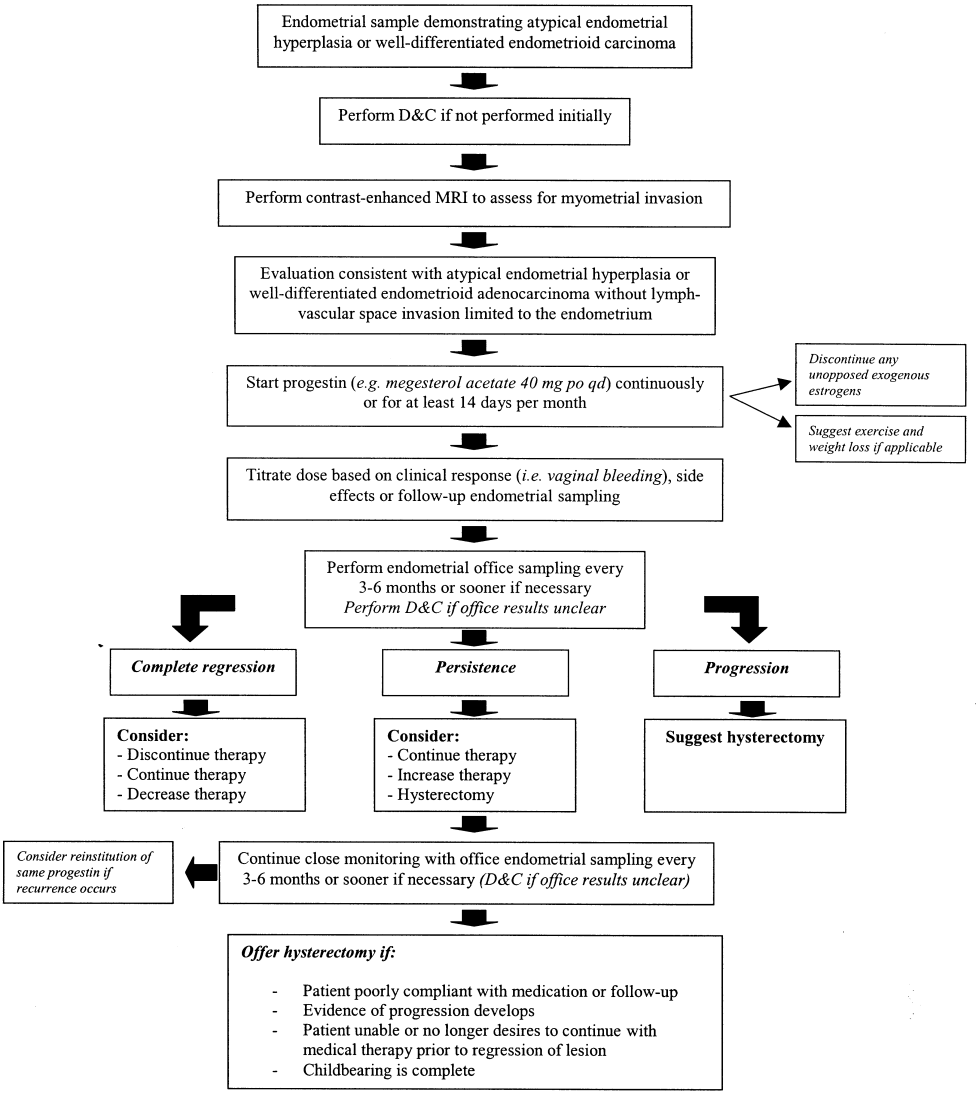

Figure 1 Suggested algorithm for conservative treatment of atypical endometrial hyperplasia and well-differentiated early-stage endometrioid carcinoma.

induction appears to be safe to use (12,21,42). Hysterectomy should be offered to any patient who has evidence of progression, declines further medical therapy without regression of the disease, has poor compliance, or has completed childbearing or no longer desires it.

Currently, the GOG is carrying out a large prospective multi-institutional study to help better define conservative therapy of endometrial atypical hyperplasia. It is a two-part study. The first part addresses the question of the true incidence of underlying carcinoma in patients diagnosed with atypical hyperplasia on sampling or curettage. Patients in this part of the study will undergo immediate hysterectomy within 12

weeks. The second part is a phase II study and will begin after completion of the first. After a confirmed diagnosis of atypical endometrial hyperplasia, patients will be randomized to receive either a continuous daily oral dose of 10 mg of Provera, or three monthly shots of 150 mg of Depo-Provera intramuscularly. Treatment will be administered for 3 months and then patients will undergo a repeat of the procedure used at diagnosis followed by hysterectomy. This feasibility study will help guide future phase III studies and treatment recommendations.

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Uterine Carcinomas: Chemotherapy for Primary and Recurrent Tumors

Levi S. Downs Jr. and Matthew P. Boente
University of Minnesota, Minneapolis, Minnesota, U.S.A.

INTRODUCTION

Endometrial cancer is the most common gynecological malignancy. There were approximately 39,300 new cases in 2002, and it is estimated that 6600 women died from this disease in the same year (1). This large difference is due to the fact that the majority of women will present to their physicians with symptoms that lead to early diagnosis. The primary treatment for patients with early-stage disease is surgery. Hysterectomy and oophorectomy with surgical staging are recommended for patients whose tumor grade, depth of invasion, cervical involvement, or histological subtype suggests that they are at high risk for extrauterine disease or recurrence. Modified radical or radical hysterectomy and oophorectomy are recommended for patients whose initial evaluation suggests clinical involvement of the cervix (2). These therapeutic modalities are limited by the elderly patient population and the morbidity of radical surgery (3). Patients with early-stage disease and low risk of recurrence experience a greater than 90% survival with surgical resection alone. For surgically treated patients at intermediate risk for recurrence, the current standard is to offer adjuvant therapy in the form of radiation (3). The estimated 12% of patients who present with advanced diseases are not curable with surgical intervention alone and will ultimately need chemotherapy to improve survivorship. In addition, those who have a recurrence of their tumor after surgery and radiation therapy are candidates for chemotherapy. The majority of studies performed to evaluate the role of chemotherapy in women with endometrial cancer has been performed on this patient population. This group of patients will be the primary focus of this manuscript. The role of hormonal therapy in the treatment of endometrial cancer has also been studied extensively and will be reviewed as well. A review of the management of endometrial cancers and the histological subtypes at high risk for recurrence will also be performed.

SINGLE-AGENT CHEMOTHERAPY

Many trials have evaluated the effectiveness of single-agent chemotherapy for advanced or recurrent endometrial cancer. Several agents have been shown to have moderate activity in this setting. Doxorubicin is the most extensively studied agent in the treatment of endometrial cancer. The Gynecologic Oncology Group (GOG) first reported the activity of doxorubicin in 1979. Forty-three patients with advanced or recurrent endometrial cancer who were not eligible for surgical or radiotherapy and had failed hormonal therapy were treated with 60 mg/m^2 doxorubicin every 3 weeks. Eleven patients experienced an objective complete response to treatment and five patients had a partial response, for an overall response rate of 37.2%. Unfortunately, as with most chemotherapeutic agents that have activity in this setting, progression-free interval and overall survival are short. In this study, a median progression-free interval of 7.4 and 4.4 months was seen in complete and partial responders, respectively. Median overall survivals were 14 and 6.8 months, respectively (4). Prior to this study, there were no large prospective trials investigating the activity of cytotoxic chemotherapeutic agents in this patient population. Doxorubicin's activity as a single agent has been confirmed in randomized trials by the GOG and other single-institution trials where its response rate has been 24–28% (5–7).

Results from a single-phase II trial suggest that another anthracyclin, epirubicin, has activities in endometrial cancer. In this Spanish cooperative group study of patients with advanced or recurrent endometrial cancer, a response was seen in 26% of patients (8). This is an attractive treatment posture because of epirubicin's more favorable toxicity profile.

Platinum compounds are also active. Reviews of four phase II trials of cisplatin at doses of 50–100 mg/m^2 document response rates of 21% in patients with no prior chemotherapy (9,10) and 25% in patients previously treated primarily with doxorubicin (11,12). Carboplatin has also been studied and at a dose of 300–400 mg/m^2 and has shown an overall response rate of 29% (13). Burke et al. (14) reported a response rate of 33% in 27 patients treated with 360 mg/m^2, although progression-free intervals remain below 8 months in this study.

In 1996, the GOG reported on 28 patients with advanced endometrial carcinoma pretreated with paclitaxel, given at 250 mg/m^2 over 24 hr with granulocyte colony-stimulating factor (G-CSF) support. The overall response rate was 36%, with a complete response seen in 14% of patients. Median progression-free interval for responders was 3.5 months and median survival was 9.5 months. Sixty-two percent of the patients in this trial experienced grade 3 or 4 leukopenia (15). Smaller trials have confirmed the activity of paclitaxel. With lower doses, these trials found response rates of 37–43% and decreased myelosuppression (16,17). Although response to treatment may have an impact on patient symptoms, it is unlikely that these systemic agents have any impact on long-term survival in this patient population.

Another agent that has moderate activity is 5-fluorouracil (5-FU). 5-FU administered in dosages of 15 mg/kg for five consecutive days and then every other day until dose-limiting toxicity has been reached has shown activity (18). Vincristine administered on a weekly schedule was associated with an 18% response rate in 33 patients (19). Hexamethylmelamine administered at a dose of 8 mg/kg daily was associated with a response rate of 30% (20); however, when dosed at 280 mg/m^2, there

were only three objective responses (21). This suggests the importance of dose intensity in this agent.

COMBINATION CHEMOTHERAPY

Multiple studies in the past two decades investigated the addition of a second cytotoxic agent with doxorubicin. Single-institution reports on the combination of doxorubicin and cyclophosphamide showed response rates in the 30–35% range, suggesting that the addition of cyclophosphamide did not significantly add to the activity of doxorubicin (18). This finding was confirmed in a large randomized trial by the GOG. GOG 48 randomized 356 patients with recurrent or advanced endometrial cancer to treatment with 60 mg/m^2 doxorubicin, with or without 500 mg/m^2 cyclophosphamide. Therapy was given every 3 weeks for a total of eight treatments. All patients had received prior therapy with progestins and had subsequently had progression of disease. The authors reported a 24% response rate in the doxorubicin arm and a 30% response rate in patients receiving combination therapy. Median progression-free intervals were 3.2 months in the doxorubicin arm and 3.9 months in the combination arm. Survival was 6.7 months in the doxorubicin arm and 7.3 months in the combination arm. The response rates and durability were not statistically different. The authors concluded that the addition of cyclophosphamide to this regimen added very little to the activity of doxorubicin.

Regimens containing cyclophosphamide, doxorubicin, and cisplatin (22–26), and doxorubicin and cisplatin (27–29) show response rates ranging from 36% to 76%. A review of these reports suggests no difference between the two regimens. These data further support that doxorubicin and cisplatin remain the most active agents in the treatment of advanced endometrial cancer. The GOG also evaluated the activity of a circadian-timed combination doxorubicin–cisplatin regimen in a phase II study of patients with stage III and stage IV diseases. In an attempt to maximize the therapeutic indices of the agents, the time of drug delivery was varied. Patients were treated with 60 mg/m^2 doxorubicin over 30 min at 6:00 a.m., followed by 60 mg/m^2 cisplatin at 6:00 p.m. over 30 min every 28 days. Thirty patients were evaluated for response and toxicity. The overall response rate was 60%, with a median progression-free interval of 7.5 months and a median survival of 14 months. Forty-three percent of patients experienced grade 3 or 4 neutropenia (29). The response rates in both arms were equivalent. The median survival seen in this study is superior to other cisplatin–doxorubicin combination trials; in fact, five patients were alive and free of disease when the report was published.

Another large trial by the GOG evaluated the combination of doxorubicin and cisplatin. This study randomized patients with advanced or recurrent endometrial cancer to receive doxorubicin (60 mg/m^2 every 3 weeks) with or without cisplatin (50 mg/m^2 every 3 weeks). The combination regimen had a significantly higher response rate (45% vs. 27%). However, severe nausea and vomiting, thrombocytopenia ($\leq$50,000 mm^3), and leukopenia (white blood cells $\leq$2000 mm^3) were more common in the combination arm. Progression-free survival was 3.9 months in the doxorubicin arm and 6.2 months in the combination arm ($P < 0.05$), but overall survival was similar for both arms, with a median of 9 months (6,18). In a similar European Coop-

erative Group study (EORTC), not only was the improved response of the doxorubicin–cisplatin regimen confirmed, but there was also a survival advantage in those patients treated with both agents.

More recently, two small single-institution reports and one multicenter trial have evaluated the combination of paclitaxel and cisplatin (32) or carboplatin (33,34). The response rates in these reports range from 50% to 67%. The GOG has reported results from a phase I trial of escalating doses of paclitaxel combined with fixed doses of cisplatin (45 mg/m^2) and doxorubicin (60 mg/m^2). Paclitaxel was escalated from 90 to 250 mg/m^2. Responses were seen in 46% of patients and the authors recommend a paclitaxel dose of 160 mg/m^2 with G-CSF support as the dose to be further studied (35). In a Swiss study that evaluated the combination of cisplatin, epirubicin, and paclitaxel, the authors report an impressive 73% response rate (36), further supporting the addition of paclitaxel to combination regimens.

The GOG recently completed another large randomized trial in metastatic endometrial cancer. The combination of six cycles of cisplatin and doxorubicin was compared to doxorubicin and paclitaxel and 60 mg/m^2 G-CSF in advanced or recurrent endometrial cancer (150 mg/m^2 over 24 hr). This study showed that both of these regimens were active, but that there was no significant difference in response rate or survival between the two arms.

Patients with metastatic uterine papillary serous carcinomas pose a special problem. The biology and natural history of this tumor behave more like ovarian cancer, rather than the garden-variety endometrioid carcinoma. This tumor has a tendency to spread along peritoneal surfaces, as well as to the retroperitoneal lymph nodes and the omentum. Investigators at the Fox Chase Cancer Center recently reported a 68% objective response rate in 24 patients with metastatic or recurrent papillary serous carcinoma of the uterus treated with carboplatin and paclitaxel. The carboplatin was delivered at an area under the curve (AUC) of 6 and Taxol was given at 175 mg/m^2 over 3 hr. This regimen was well tolerated, with only 6% of patients experiencing febrile neutropenia and only 8% of cycles delayed secondary to myelosuppression. Confirmation of these results in a larger multicenter study is necessary, but clearly, carboplatin–paclitaxel is an active regimen in this aggressive subtype of endometrial cancer (37).

HORMONAL THERAPY

Medroxyprogesterone acetate (MPA) has been well studied in patients with advanced or recurrent endometrial cancer. Initial studies evaluated parenteral administration of the progestin (38). After it was shown that oral agents could achieve similar serum concentrations as parenteral agents, studies were designed to evaluate the efficacy of the oral product (39). The first large GOG trial evaluating oral progestins in patients with advanced or recurrent disease showed an overall response rate of 18%, with short median progression-free and overall survival times of 4 and 10.5 months, respectively (40). This finding was confirmed in a second trial where patients were randomized to receive oral 200 or 1000 mg/day MPA. The objective of this study was to assess the importance of prognostic factors such as estrogen and progesterone receptor status as well as histological grade. A second objective was to determine if higher doses of the

progestin would be associated with an increased response rate. One hundred forty-five women received low-dose MPA. The overall response rate in this group was 25%. The 154 women who received high-dose MPA experienced an overall response rate of 15%. Median progression-free survivals were 3.2 and 2.5 months, respectively. Median survival times were 11.1 and 7 months, respectively. The authors concluded that 200 mg/day MPA is active as an initial agent in the treatment of advanced or recurrent endometrial cancer (41).

In an analysis of the importance of histological grade, it was discovered that patients with well-differentiated primary tumors tended to respond more frequently than those with poorer differentiation (41). The response rates were 37%, 23%, and 9% for patients with grades 1, 2, and 3 tumors, respectively. Analysis of receptor status shows that patients with tumors that are estrogen receptor-positive or progesterone receptor-positive are more likely to respond to MPA therapy than those with tumors that have a negative receptor status.

Tamoxifen has been studied in patients with advanced or recurrent endometrial cancer. Several small trials have suggested some activity in this setting. In a report that pooled data from eight studies, tamoxifen use yielded an overall response rate of 22% (11). In an attempt to determine whether or not a phase III trial was warranted to evaluate tamoxifen, the GOG reported on 68 patients with advanced or recurrent disease treated with 20 mg of tamoxifen twice daily. The overall response rate was only 10%, well below that of prior reports (42). An Eastern Cooperative Oncology Group study completed a randomized trial that treated patients with metastatic endometrial cancer with 80 mg of MPA twice daily, or 20 mg of MPA with tamoxifen twice daily. The study had difficulty accruing patients and thus closed the MPA arm at 20 patients and continued to recruit patients to the combination arm. Forty-two patients were analyzed in the combination arm. They reported an overall response rate of 20% in the MPA arm, and a response rate of 19% in the combination arm (43). In combination, these two relatively large trials suggest a limited role of tamoxifen in the treatment of advanced or recurrent endometrial cancer.

Other multicenter trials investigating the role of hormonal therapies include a study by the GOG that evaluates anastrozole (Arimidex), an oral nonsteroidal aromatase inhibitor that is active in recurrent breast cancer. In this small study of only 23 patients, they found a response rate of only 9% (44). Gonadotropin-releasing hormone agonists (45) and luteinizing hormone-releasing hormone agonists (46) have also been studied and found to have essentially no activity.

ADJUVANT THERAPY

The concept of adjuvant therapy for women at high risk for recurrence is obviously attractive. The fact that both cytotoxic agents and hormonal agents have impressive activity in recurrent and advanced disease makes it reasonable to consider using these agents in the adjuvant setting.

First, we must determine those patients who are at increased risk for recurrent disease. Risk factors can be uterine—depth of invasion, histological grade, presence of lymph–vascular space invasion, involvement of the lower uterine segment or the cervix, and/or the presence of aggressive histological subtypes, papillary serous, or clear cell

carcinoma. Patients with documented extrauterine spread to the adnexa, peritoneal surfaces, omentum, or pelvic and para-aortic lymph nodes are at the highest risk for recurrence. Although these risks have been well studied, we have not been able to show the benefit of any adjuvant therapies, and large prospective trials have reported no benefit to adjuvant therapy. Early reports using progestational agents have failed to show any survival advantage (47–49). The nonrandomized studies addressing this question have mostly focused on the use of doxorubicin, cisplatin, and cyclophosphamide in patients at high risk for recurrence.

The GOG initiated a trial that randomized patients at high risk for recurrence to receive adjuvant external beam whole abdominal radiation or doxorubicin and cisplatin. Although the data are still maturing and definitive conclusions cannot be drawn, there does appear to be a slight survival advantage in patients who received chemotherapy. The final results of this study should be interesting because they will also be reporting a quality-of-life difference between the two treatment arms (50). Further studies need to be initiated by cooperative groups before the role of adjuvant chemotherapy can be determined.

FUTURE

At the present time, the GOG has initiated a large randomized study accruing patients for surgically resected stage III and stage IV endometrial carcinomas who have microscopical or small-volume (<2 cm) residual disease. These patients received tailored radiotherapy to the pelvis and para-aortic lymph nodes (if necessary) followed by a randomization to either doxorubicin and cisplatin vs. doxorubicin, cisplatin, and paclitaxel with G-CSF. This is an important study that answers numerous questions about combining radiotherapy and chemotherapy in a traditionally elderly group of patients with many comorbidities.

Finally, questions remain with regard to the appropriate treatment for patients with positive peritoneal cytology (stage III). This has, for years, been a therapeutic dilemma and, unfortunately, remains an accepted poor prognostic feature without any definitive, universally accepted treatment. In addition, there is no well-accepted chemotherapy in endometrial cancer that is being tested for its radiosensitizing properties, and this is also an area for future trials.

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Chemotherapy in Uterine Mesenchymal Tumors

Nicoletta Donadello
University of Insubria, Varese, Italy

Valentino Bergamini and Massimo Franchi
University of Verona, Verona, Italy

INTRODUCTION

Malignant mesenchymal tumors of the uterus are relatively uncommon. Their annual worldwide incidence is between 0.5 and 3 cases per 100 women, accounting for 3% to 5% of all uterine malignancies (1).

These tumors can be classified as pure (only malignant mesenchymal component) and mixed mesodermal tumors (MMT) (malignant mesenchymal component associated with a benign or malignant epithelial component) (Table 1). The most frequent categories of mesenchymal tumors are leiomyosarcoma (LMS) and endometrial stromal sarcoma (ESS) in the pure type, and carcinosarcoma in the mixed type.

Leiomyosarcoma usually occurs in 45–55 years old women, while MMT occurs in women 10 years older. Endometrial stromal sarcoma can be found in premenopausal women and occasionally in young women.

Previous irradiation of the pelvis is the only known risk factor for these neoplasms (2). Recently, it has been suggested that hormone therapy with tamoxifen and unopposed estrogen therapy can enhance the risk of mesenchymal tumors (3–5).

An abdominal or pelvic mass, a rapidly enlarging uterus, pelvic pain, or bleeding are the most common symptoms (Fig. 1).

Preoperative diagnosis of MMT can be obtained by office biopsy or endometrial curettage. Leiomyosarcoma is not usually diagnosed on preoperative biopsy. It can be suspected by a rapidly growing myoma, and magnetic imaging of the pelvis can be helpful in the differential diagnosis. Computed tomography of both the abdomen and pelvis and two-view chest x-rays are recommended for the diagnosis of extrauterine disease.

No specific staging system has been established for uterine sarcomas. Thus the FIGO stage for endometrial carcinoma is usually applied (Table 2) (6).

Leiomyosarcoma can arise de novo from the myometrium or, less frequently, inside a benign leiomyoma (Fig. 2). Lymphatic spread is rare, while hematogenous metastases are frequent, especially in high-grade LMS. In mixed mesodermal tumors,

Table 1 Mesenchimal Tumors Classification

Leiomyosarcoma
Endometrial stromal sarcoma
Mixed homologous mullerian sarcomas (carcinosarcoma)
Mixed heterologous mullerian sarcomas (mixed mesodermal sarcoma)
Other uterine sarcomas

lymphatic involvement is more common (18% positive reported in early stages), but hematogenous and abdominal spreads are also frequent (7).

Grade, mitotic count ($<$ or $\geq$10 mitoses/10 HPF), and stage are the main reported prognostic factors for LMS. Compared to the aggressive behavior of high-grade LMS, low-grade LMS, with a low mitotic count, have good prognoses and recurrences are infrequent and local (7,9,10). Stage is the most important prognostic factor for ESS and MMT, while the role of grade and mitotic count is discussed (11–13).

Primary treatment of these neoplasms consists of surgical excision. Total abdominal hysterectomy and bilateral salpingo-oophorectomy represent the standard surgical procedure. In premenopausal patients with low-grade LMS, the ovary can be preserved, while oophorectomy is recommended in ESS because of their high level of estrogen and progesterone receptors. In selected young patients in whom a low-grade LMS is discovered after myomectomy for presumed benign myoma, fertility preservation and subsequent follow up can be considered (14,15).

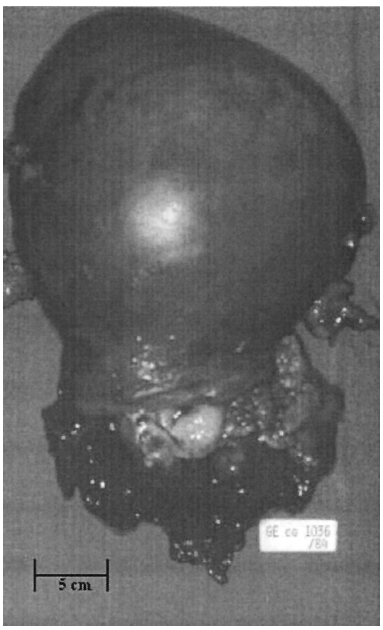

Figure 1 Large uterus filled by a MMT protruding through the cervical os.

Table 2 Staging of Uterine Sarcoma

Stage	Characteristic
I	Sarcoma confined to the uterine corpus
II	Sarcoma confined to corpus and cervix
III	Sarcoma confined to the pelvis
IV	Extrapelvic sarcoma

In clinical early-stage mixed mesodermal tumors, a more aggressive surgical procedure is recommended, including pelvic lymphadenectomy, abdominal biopsies, and washing; in fact, 12% to 40% of clinical early-stage MMT is upstaged after surgical evaluation (8,11,12).

The role of adjuvant radiotherapy after surgical excision in early-stage uterine sarcomas is controversial. Several nonrandomized studies have shown an improvement of local disease control. In ESS, adjuvant irradiation can reduce the recurrence rate by 90% and it is usually recommended (7,13,16–20). However, the impact of radiotherapy on overall survival is unclear. The results of the randomized phase III trial on adjuvant radiotherapy in uterine sarcoma, performed by the EORTC (EORTC Trial 55874) and recently completed, can possibly answer this question (21).

Five-year survival per stage and pathology is summarized in Table 3 (22). Five-year survival for advanced stages is extremely poor; even in stage I disease, it hardly exceeds 50% (20).

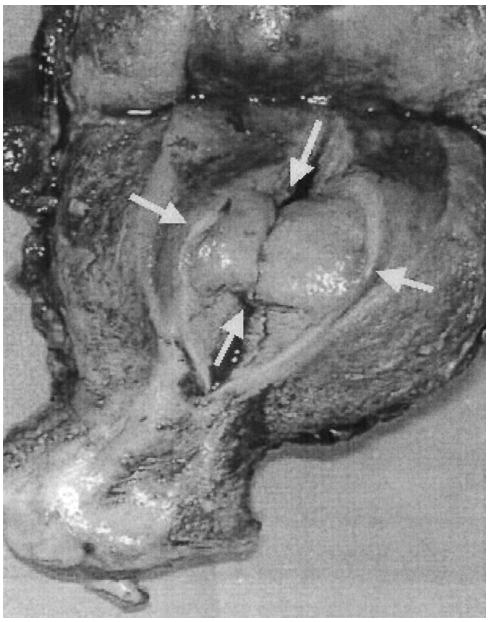

Figure 2 Leiomyosarcoma arising in a benign myoma (arrows).

Table 3 Five-Year Survival per Stage and Pathology

Stage	Histotype (no.)	Five-year survival rate (%)
I	MMT (82)	50
	LMS (113)	53
	ESS (23)	55
II–IV	MMT (100)	12
	LMS (50)	8
	ESS (42)	12

MMT: mesodermal mesenchymal tumor; LMS: leiomyosarcoma; ESS: endometrial stromal sarcoma.
Source: Ref. 7.

The pattern of recurrence site for LMS and MMT is shown in Table 4 (7).

Surgical excision can be considered in pelvic or abdominal recurrence of low-grade LMS and ESS. Pelvic-isolated recurrence can be controlled by radiotherapy.

In advanced disease and in presence of distant recurrence, chemotherapy is the treatment of choice.

The high recurrence rate, even in stage I disease, and the frequency of distant metastases have also advocated the use of adjuvant chemotherapy.

Many studies in the past have analyzed the use of chemotherapy in mesenchymal tumors as a whole. However, the main histological subtypes (LMS, ESS, and MMS) seem to have different biological features and sensibility to chemotherapeutic agents and therefore they should be separately analyzed.

SINGLE-AGENT CHEMOTHERAPY

Leiomyosarcomas

Doxorubicin and ifosfamide are the most active agents tested in monochemotherapy in recurrent and advanced uterine leiomyosarcomas, as shown for other types of soft tissue sarcomas (STS). Hannigan (23) and Omura et al. (24) reported 10% to 25% response rate for adryamicin 60 mg/m^2 every 3 weeks. Sutton et al. (25) have described a 17% response rate in 35 patients treated with ifosfamide 1.5 g/m^2/day (+mesna) for 5 days with acceptable toxicity.

Table 4 Recurrence Site in Early-Stage Disease

	Histotype (no.)	
Recurrence site	MMT (299)	LMS (57)
Pelvic only	10.4%	7%
Distant	38.8%	56%
None	50.8%	37%

MMT: mesodermal mesenchymal tumor; LMS: leiomyosarcoma.
Source: Ref. 22.

Moderate or negligible activity has been shown by other agents such as cisplatin, etoposide, carboplatin, and topotecan. In a study published in 1996 by the Gynecologic Oncology Group (GOG), only modest activity was seen with bolus etoposide (an 11% response rate) (26). Subsequently, a phase II trial of prolonged oral etoposide (27) was conducted in patients with measurable disease and one prior chemotherapy regimen which does not include etoposide. The starting etoposide dose was 50 mg/m^2/day (30–40 mg/m^2/day for prior radiotherapy) as a single dose for 21 days, every 28 days. Based on toxicity, a dose escalation to a maximum dose of 60 mg/m^2/day was prescribed. Thirty-four patients were evaluated for toxicity and 29 for response (27 had received prior chemotherapy and 6 prior radiotherapy). Grade 4 neutropenia occurred in 20.6% and grade 4 thrombocytopenia in 5.8%. This study demonstrated a minimal drug activity as second-line chemotherapy. Only two partial responses (6.9%), in fact, were observed. In August 2000, Miller et al. (28) from University of Texas Southwestern Medical Center published the results of topotecan use (1.5 mg/m^2 iv daily for 5 days, every 3 weeks) in chemotherapy-naive women with persistent, metastatic, or recurrent uterine leiomyosarcoma. Topotecan was administered according to the preestablished scheme until progression of disease or adverse effects prohibited further therapy. Patients received a median of 3 courses. Only 1 patient had complete response (3%), 3 had partial response (8%), 12 had stable disease (33%), and increasing tumor in 20 (56%). The most frequent grade 4 adverse effect was neutropenia (78%).

More recently, the GOG has analyzed the activity of paclitaxel (175 mg/m^2 iv over 3 hr every 3 weeks until disease progression or adverse side effects supervened) in 33 chemotherapy-naive patients with advanced, metastatic, or recurrent disease. Median age was 55 years (range 35–84 years). GOG performance status was 2 in 2 instances, 1 in 9 cases, and 0 in 22 others. Three patients had complete response (9.1%) and 8 patients (24.2%) had stable disease, with a median response duration of 10.7 months, suggesting a limited efficacy of the drug with the dose and schedule tested. Eleven patients (33.3%) experienced grade 3–4 neutropenia, 1 (2.9%) had grade 3 anemia, and 1 (2.9%) had grade 4 thrombocytopenia. When considering this modest drug toxicity, a higher dose of paclitaxel might be evaluated in the future (29). Paclitaxel has been further (30) investigated in 48 evaluable pretreated patients (39 with previous chemotherapy, 15 with prior irradiation). The dose was 175 mg/m^2 iv over 3 hr every 3 weeks (135 mg/m^2 for patient with prior radiotherapy). A median of 2 courses was given. Toxicity was tolerable. Grade 4 neutropenia occurred only in 3 patients (6.3%). The response rate was modest. Four women (8.4%) had a complete or partial response and 22.9% had stable disease.

Because of the low number of active cytotoxic drugs and their limited activity, the evaluation of new anticancer agents for their activity in soft tissue sarcomas is a continuing need.

Gemcitabine has been employed in the treatment of recurrent soft tissue sarcomas, including second-line treatment, in several recent phase II studies. The EORTC Soft Tissue and Bone Sarcoma Group found only 1 partial response among 31 pretreated patients (5 uterine sarcomas); hence they do not recommend this treatment for second-line therapy (31). Similar results have been reported by Okuno et al. (32). However, there are hints that, in the heterogeneous group of soft tissue sarcomas, uterine LMS could be a more sensitive subpopulation: Spath-Schwalbe et al. (33) described partial responses in 3 (2 uterine) over 6 pretreated LMS, while Patel et al. (34) reported responses in 4 (3 uterine) over 10 pretreated LMS. These

preliminary data and the favorable profile of toxicity suggest a possible role of gemcitabine in second-line treatment or in combination chemotherapy.

Liposomal doxorubicin has been studied in phase II trials for the treatment of STS (35,36) with contrasting results. Activity in uterine sarcomas has been occasionally reported (37). It could be further evaluated especially in patients at high risk of cardiotoxicity.

Ecteinascidin (ET-743) is a marine-derived alkaloid with cytotoxic activity against soft tissue sarcomas and a variety of neoplasms (including breast and ovarian carcinoma). It has a complex action mechanism, including inhibition of transcription-dependent nucleotide excision repair, of cell-cycle progression with p53-independent apoptosis, of transcriptional activation, and of multidrug-resistance (MDR1) gene in human sarcoma cells in vivo.

Phase II trials in STS showed a 14% response rate in naive patients and an 8% one in second–third line treatment. In chemonaive patients, 12-month progression-free and overall survival rates were 11% and 55%, respectively, with long-lasting responses in a subset of patients. A pooled analysis of three phase II trials demonstrates a response rate of 9% in pretreated STS, with a progression-free rate at 6 months of 27%, and suggests that responses in LMS (particularly uterine) could be higher (38,39).

These promising data deserve further drug evaluation in phase III studies.

The activity of the main antineoplastic agents in monotherapy is summarized in Table 5.

Carcinosarcoma

Ifosfamide and cisplatin are the most active antineoplastic agents in uterine carcinosarcoma.

The GOG (40) reported a 32% response rate (5 CR and 4 PR) in 28 naive patients with advanced carcinosarcoma treated with ifosfamide 1.5 g/m^2/day + mesna 0.3 g/m^2/day for 5 days every 4 weeks. Response was also observed in 17.9% of patients with ovarian carcinosarcoma failing cisplatin therapy.

The activity of cisplatin (50 mg/m^2 every 3 weeks) was evaluated by the GOG, with an 8% response rate in pretreated patients and 19% in untreated ones (41,42).

Doxorubicin seems to be less effective in leiomyosarcomas, with a reported activity in 4 of 41 patients (10%) (24).

The GOG (43) recently tested the efficacy of paclitaxel in patients with persistent or recurrent uterine carcinosarcoma; other treatments have failed. Thus the women selected were those with histological confirmation of carcinoma or measurable disease not responsive to an appropriate local therapy. The results were published in November 2001. Paclitaxel was administered at a dose of 170 mg/m^2 iv every 3 weeks A lower dose, only 135 mg/m^2, was supplied to those women with previous irradiation. A median of 3 courses was administered (range 1–18). Forty-four patients (33 with previous failed chemotherapy, 15 with previous radiation therapy) were evaluated for response to the drug. Median age was 65 years. Four complete and four partial responses were observed (overall response rate, 18.2%). The response was similar in pretreated patients (21.2%). These results recommend further drug evaluation, also in combination chemotherapy (Table 6).

Table 5 Single-Agent Chemotherapy in Leiomyosarcoma

Author	Drug	Schedule	No. of patients	Response
Omura et al. (24)	Adryamicin	60 mg/m^2 every 3 weeks	28	7/28 (25%)
Thigpen et al. (26)	Etoposide	100 mg/m^2/day for 3 days every 4 weeks	28	3/28 (11%)
Rose et al. (27)		50 mg/m^2/day for 21 days/28 days	29	2/29 (6.9%)
Miller et al. (28)	Topotecan	1.5 g/m^2/day for 5 days every 3 weeks	36	4/36 (11%)
Sutton et al. (29)	Paclitaxel	175 mg/m^2 every 3 weeks	33	3/33 (9%)
Gallup et al. (30)		175 mg/m^2 every 3 weeks	48	4/48 (8.4%)
Spath-Schwalbe et al. (33)	Gemcitabine	200 mg/m^2 weekly for 3 over 4 weeks in 360 min	6[a]	3/6 (50%)
Patel et al. (34)		1g/m^2 weekly for 3 over 4 weeks	10[a]	4/10 (40%)
Demetri (38)	ET-743	1.5 mg/m^2 in 24 hr every 3 weeks	72[b]	10/72 (14%)
Sutton et al. (40)	Ifosfamide	1.5 g/m^2/day for 5 days every 4 weeks	35	6/35 (17%)
Thigpen et al. (42)	Cisplatin	50 mg/m^2 every 3 weeks	33	1/33 (3%)

[a] Pretreated soft tissue LMS.
[b] Soft tissue sarcoma.

Table 6 Single-Agent Chemotherapy in Carcinosarcoma

Author	Drug	Schedule	No. of patients	Response
Omura et al. (24)	Adryamicin	60 mg/m^2 every 3 weeks	41	4/41 (10%)
Thigpen et al. (26)	Etoposide	100 mg/m^2/day for 3 days every 4 weeks	31	2/31 (6%)
Rose et al. (27)		50 mg/m^2/day for 21 days/28 days	34	2/34 (6.9%)
Thigpen et al. (42)	Cisplatin	50 mg/m^2 every 3 weeks	63	12/63 (19%)
Curtin et al. (43)	Paclitaxel	170 mg/m^2 every 3 weeks	44	8/44 (18.2%)
Sutton et al. (44)	Ifosfamide	1.5 g/m^2/day for 5 days every 4 weeks	28	9/28 (32%)

Endometrial Stromal Sarcoma

Endometrial stromal sarcomas are extremely rare and usually not separately considered in phase II studies of uterine sarcomas. As few as 150 cases occur annually in the United States. They represented 11.5% of all early-stage uterine sarcomas in a comprehensive clinicopathologic evaluation conducted by the GOG (7). Early-stage endometrial stromal sarcomas are surgically treated. Patients with metastatic or recurrent disease are uncommon enough that little is known about palliative therapy for these tumors. Therefore, there is a paucity of literature regarding chemotherapy for metastatic endometrial stromal sarcomas.

In May 1996, the GOG published a prospective multi-institutional phase II study about the effectiveness and toxicity of ifosfamide chemotherapy in women with metastatic or recurrent endometrial stromal sarcoma, unexposed to other chemotherapy. Twenty-one patients were included in the study, being valuable for toxicity and response. The administered dose of ifosfamide was 1.5 g/m^2 daily iv for 5 days every 3 weeks, reduced to 1.2 g/m^2 daily in those 8 patients who had been previously treated with radiotherapy. Mesna, a urothelial protector, was supplied (20% of the ifosfamide dose) iv immediately and 4 and 8 hr after ifosfamide. Therapy was stopped if there was cancer progression or unacceptable toxicity. Twelve patients (57%) experienced grade 3–4 leukocytopenia. One patient developed grade 4 renal toxicity, and another one developed grade 3 neurotoxicity. The overall response rate was 33.3%. Three patients had complete response and four women had partial responses. The median response duration was 3.7 months. The median progression-free interval was 3.0 months (44).

COMBINATION CHEMOTHERAPY

Several antineoplastic drugs, active in soft tissue and uterine sarcomas, have been evaluated in combination during phase II trials in order to improve response rate and survival. The regimens most commonly employed in soft tissue sarcomas have been tested in the uterine subtype.

Hannigan (45) treated 74 patients with advanced or recurrent uterine sarcomas with the vincristine, dactinomycin, cyclophosphamide (VAC) regimen: the response rate was 28.9%, with 23% 2-year survival.

Other tested combinations include vincristine, doxorubicin, and dacarbazine (6 patients with leiomyosarcoma); cisplatin and dacarbazine (20 patients with uterine sarcomas); and dacarbazine, etoposide, and hydroxyurea (38 patients with LMS), with 18% to 66% response rates (46–48). Peters et al. (49) evaluated the doxorubicin–cisplatin combination in 11 patients with advanced MMT and ESS, with a 73% response rate.

In 1990, in a study on endometrial stromal sarcoma chemotherapy, Berchuck et al. (50) reported a 50% response rate to doxorubicin or in combination in 10 patients with recurrent disease. Two partial responses were also recorded in women treated with vincristine, dactinomycin, and cyclophosphamide or mitomycin and velban. In the same period, Mansi et al. (51) published a case report in which he described a partial response to chlorambucil therapy and one of three responses to cyclophosphamide, vincristine, doxorubicin, and dacarbazine.

The GOG reported a 30% response rate (9 PR and 1 CR) in 35 patients with LMS, treated with ifosfamide (5 g/m^2/24 hr by continuous iv infusion) and doxorubicin (50 mg/m^2 iv over 15 min), with a median duration of 4.1-month response. Median survival was 11.1 months for responders and 9.6 for the whole population. Two toxic deaths (1 sepsis and 1 cardiac toxicity) were reported. The authors stated that, in presence of nonnegligible toxicity, the benefit over single-agent doxorubicin is unclear (52).

The mitomycin, doxorubicin, cisplatin (MAP) combination, tested with favorable results in non-osseous sarcomas, has been studied in 41 patients with advanced LMS, with 23% responses and 6.3-month median survival. A modified regimen with the association of dacarbazine (DMAP) is under evaluation by the GOG at present (53).

Both gemcitabine and taxanes recently showed activity in LMS, even in pretreated subjects. The gemcitabine and docetaxel association (with recombinant human granulocyte colony-stimulating factor) has been evaluated in 34 patients with unresectable LMS (29 uterine; 16 pretreated with doxorubicin±ifosfamide); 3 CR and 15 PR were observed (53% overall RR and 5.6-month median PFS). It is to be noted that responses were also observed in 8 (50%) pretreated patients. These results, sometimes more favorable than expected, specifically in second-line therapy, have been attributed to a possible synergy between the two drugs or a greater gemcitabine effectiveness in 90-min infusion (instead of the more common 30-min bolus infusion) (54).

The EORTC Gynecologic Cancer Group performed a phase II trial in advanced carcinosarcoma of the female genital tract. After up-front surgical debulking, 48 patients (22 with uterine carcinosarcoma) were treated with the following schedule: doxorubicin 45 mg/m^2, cisplatin 50 mg/m^2, and ifosfamide 5 g/m^2 in 24 hr (plus mesna). Responses (11 CR and 7 PR) were observed in 18 over 32 valuable patients, with a 56% response rate. The median duration of response was 34 months. Median progression-free survival was 11.9 and 25.2 months in patients with and without residual disease after surgery, respectively. Severe myelotoxicity and renal toxicity (one toxic death) were reported. The regimen was considered effective, but with an unfavorable toxicity profile (55).

The results of phase II trials are summarized in Table 7.

Generally, combination regimens show a possible response rate increase in phase II studies, but their impact on overall survival is unclear, and the toxicity is usually remarkable (Table 8).

Phase III trials, comparing single vs. multiagent therapy in terms of response rate, duration of response, and toxicity, are few due to the rarity of the neoplasia.

The GOG randomized 240 patients (146 with measurable disease) between doxorubicin and doxorubicin + dacarbazine (effective in soft tissue sarcoma). The study population included both LMS and MMT; response rate and overall survival rate were similar in the two arms, with increased toxicity in the combination (24).

Similar results were reported in the GOG trial randomizing 104 patients (advanced/recurrent sarcoma) between doxorubicin and doxorubicin + cyclophosphamide (Table 9) (56).

After the understanding of the different biology of LMS and MMT, the two populations have been studied separately, but the completion of phase III trials was extremely difficult.

Table 7 Combination Chemotherapy in Metastatic Uterine Sarcoma (Phase II Trials)

Author	Histology	Schedule	No. of patients	Response	Median overall survival (months)	Median progression-free survival (months)
Currie et al. (46)	LMS	Hydroxiurea, DTIC, Etop	39	18%	15	12.1[a]
Sutton et al. (52)	LMS	Ifos/Dox	33	30%	9.6	4.1[a]
Edmonson et al. (53)	LMS	MAP	41	23%	6.3	NA
Hensley et al. (54)	LMS	Gem/Doce	34	53%	17.9	5.6
Van Rijswijk et al. (55)	MMT	Dox/Cis/Ifos	32	56%	21	11.9

LMS: leiomyosarcoma; MMT: mesodermal mesenchymal tumor; DTIC: dacarbazine; Etop: etoposide; MAP: mitomycin + doxorubicin + cisplatin; Gem: gemcitabine; Doce: docetaxel; Dox: doxorubicin; Cis: Cisplatin; Ifos: ifosfamide.

[a] Median duration of response.

Table 8 Toxicity in Combination Chemotherapy

Author	Schedule	No. of patients	G3–G4 neutropenia (%)	G3–G4 thrombocytopenia (%)	Other G3–G4 toxicity (%)	Toxic death no. (%)
Omura et al. (24)	ADM/DTIC	66	46.9	16.7	Gastrointestinal 12.1; cardiac 4.5	–
Sutton et al. (52)	Ifos/Dox	33	48	–	–	2 (6)
Hensley et al. (54)	Gem/doce	34	20.6	29.4	Dyspnea 21; diarrhea 12; fatigue 21	–
Van Rijswijk et al. (55)	Dox/Cis/Ifos	37	84.8	64.8	Vomiting 48.7; renal 7.9; neurologic 15.4	1 (2.7)
Muss et al. (56)	Dox/Cyc	104	4	–	Vomiting 6; cardiac 1.8	–
Sutton et al. (57)	Ifos/Cis	90	87	58	Vomiting 13; renal 3.3; neurologic 14	6 (6.5)

Ifos: ifosfamide; Dox: doxorubicin; Cis: cisplatin; Gem: gemcitabine; Doce: docetaxel; Cyc: cyclophosphamide; ADM: adryamicin; DTIC: dacarbazine.

Table 9 Combination Chemotherapy (Phase 3 Trials)

Author	Histology	Treatment	Response	Overall survival (months)
Omura et al. (24)	Any	ADM	13/80 (16.2%)	7.7
		ADM + DTIC	16/66 (24.2%)	7.3
Muss et al. (56)	Any	Dox	5/26 (19%)	11.6
		Dox + Cyc	5/26 (19%)	10.9
Sutton et al. (57)	MMT	Ifos	37/102 (36%)	7.6
		Ifos + Cis	50/92 (54%)	9.4

ADM: adryamicin; DTIC: dacarbazine; Dox: doxorubicin; Cyc: cyclophosphamide; Ifos: ifosfamide; Cis: cisplatin.

A Sutton et al. (57) report analyzes 188 patients treated with ifosfamide with and without cisplatin in MMT. The response rate is higher in the combination arm (54% vs. 36%). A slight advantage was detected in PFS for the combination arm (4 vs. 6 months, $p < 0.02$), but overall survival was not significantly different (Table 9).

At the present analysis stage, phase III trials, comparing doxorubicin alone or in association with ifosfamide in uterine LMS, have not been published. However, in a randomized trial conducted by the EORTC Soft Tissue and Bone Sarcoma Group (58), response and survival were similar in three arms of patients with soft tissue sarcomas, treated with doxorubicin, CYVADIC, and doxorubicin plus ifosfamide, respectively.

Pearl et al. (59) used combination of mesna, doxorubicin, ifosfamide, and dacarbazide (MAID) for patients with gynecologic sarcomas. The MAID regimen was administered iv every 4 weeks as follows: mesna 1500 mg/m^2/day for 4 weeks, doxorubicin 15 mg/m^2/day for 3 days, ifosfamide 1500 mg/m^2/day for 3 days, and dacarbazide 250 mg/m^2/day for 3 days. The response rate was 9% with one complete response and one partial response, both in women with uterine leiomyosarcoma. Any responses were observed among the patients with carcinosarcomas of either ovarian or uterine origin. The median progression-free interval and survival were 11 and 29 months, respectively. This regimen was associated with substantial toxicity, including a death for neutropenic sepsis.

ADJUVANT CHEMOTHERAPY

The high distant recurrence rate, even in stage I disease, and the poor prognosis of recurrent disease have suggested the use of adjuvant chemotherapy in early-stage uterine sarcomas.

In phase II trials, adjuvant adryamicin (60–75 mg/m^2) and the vincristine, adryamicin, cyclophosphamide (VAC) regimen seemed to offer some survival benefit in stage I–II disease, compared to historical controls treated with surgery alone (60–63). In a prospective trial on 20 patients, without a control arm, the cyclophosphamide, vincristine, doxorubicin, dacarbazine (CYVADIC) regimen apparently did not impact on survival and caused increased toxicity (64).

The GOG performed a randomized trial, treating 131 patients at stage I–II disease with adjuvant adryamicin (60 mg/m^2) or no further therapy. The recurrence rate was 39% in the chemotherapy arm and 52% in the control arm, with a 73.9- and a 55-month median survival, respectively. No significant difference on overall survival was detected (65). It has been questioned that the adryamicin dose in this trial could be inadequate since it has been shown that a dose intensity of at least 70 mg/m^2 is more effective in the treatment of soft tissue sarcomas (66,67). The studied population was heterogeneous, including both LMS and MMT, but the numbers in each subset were insufficient to perform a separate analysis.

The Cochrane Review evaluated the role of adjuvant adryamicin-based chemotherapy in soft tissue sarcomas. Fourteen trials and 1568 patients were analyzed. In the chemotherapy arm, local recurrence-free interval (0.73, CI: 0.56–0.94), distant recurrence-free interval (0.7, CI: 0.57–0.85), and recurrence-free survival (0.75, CI 0.64–0.87) were improved. Overall survival, however, was not significantly different (0.89, CI 0.76–1.03) (68). The role of ifosfamide (1.5 g/m^2/day for 3 days, repeated every 28 days) in adjuvant setting has been evaluated in 13 consecutive patients with completely resected moderate- to high-grade uterine sarcoma. The overall recurrence rate with ifosfamide in early stage was 50%, with a 60% 2-year progression-free survival; these results were similar to those ones obtained in the GOG trial by utilizing adjuvant adryamicin. It is to be noted that this trial showed a remarkable difference in 2-year PFS between early-stage MMT and LMS (100% vs. 33%), with a significantly longer time to progression, although the small numbers considered do not allow to report a definite conclusion (69).

In order to further investigate the role of adjuvant treatment, a GOG study comparing adjuvant whole abdominal radiotherapy with a pelvic boost to chemotherapy with ifosfamide and cisplatin in optimally debulked carcinosarcoma of the uterus is presently under process.

In conclusion, the available data do not support an impact of adjuvant chemotherapy on overall survival in early-stage disease. However, there are hints that chemotherapy may improve the time to progression. Further evaluation of adjuvant chemotherapy in clinical trials, taking into account the biological difference between MMT and LMS, is recommended.

HORMONAL THERAPY

Few data are available about hormonal treatment in uterine sarcoma.

Endometrial stromal sarcomas (ESS) usually exhibit high levels of estrogen receptors: responses to hormonal therapy with medroxiprogesterone acetate have been reported. Hormonal therapy can be considered for palliative use in this histological subtype. Spano et al. (70) reported two cases of metastatic ESS treated with aromatase-inhibitor therapy. Both patients achieved a complete response; patient 1 remained disease-free with 14+ years of follow-up and patient 2 with 7+ years. Moreover, recent data support the importance of the hormones and suggest that the hormonal treatment options can be expanded by the inclusion of aromatase inhibitors (71). In 2001, Maluf et al. (72) described a case of woman who presented low-grade endometrial stromal sarcoma. After surgery, the patient had recurrent pelvic disease, underwent radiation therapy followed by an attempt at resection. She was treated with

megestrol acetate during the period she received radiation therapy with poor tolerance. Tamoxifen was then given with no tumor response. Megestrol acetate was restarted with disease progression. Letrozole was then given at a daily dose of 2.5 mg with partial response for a duration of 9 months. Piver et al. (73) published the results about treatment in recurrent endolymphatic stromal myosis. One complete response of 19-month duration was reported in a patient who received doxorubicin, methotrexate, and megestrol acetate. Scribner and Walker (74) presented a case report of neoadjuvant hormonal therapy in patient with ESS. Two doses of Depo-Lupron, 7.5 mg, and megestrol acetate, 160 mg/day, were supplied to control uterine bleeding and to shrink the tumor mass. In 9 weeks, significant reduction in the tumor occurred allowing for surgical resection.

Estrogen and progesterone receptors (75) are frequently expressed in uterine leiomyosarcoma as well, but their presence, as demonstrated in a study conducted by Bodner et al. (76), does not correlate with clinical stage, age, vascular space involvement, and recurrence of disease and has no influence on overall and disease-free survival. Despite the lack of prognostic impact, further studies with larger numbers of cases need to be performed in order to verify if estrogen and progesterone receptor positive tumors can be treated by hormonal manipulation.

CONCLUSIONS

Doxorubicin for LMS and ifosfamide and cisplatin for MMT are the most effective antineoplastic drugs in single-agent chemotherapy.

Combination chemotherapy increases response rate as well as toxicity, but the impact on survival is unclear. It should be reserved to selected patients with good performance status, possibly included in clinical trials.

As a matter of fact, adjuvant chemotherapy could improve survival in early-stage disease, but up to now, this notion has not been confirmed by randomized studies. By considering their biological difference, LMS and MMT should be separately considered in clinical trials, but this approach compromises the feasibility of large phase III studies. Data availability from ongoing trials on adjuvant therapy in soft tissue sarcomas could help, at least for LMS.

When taking into account the dismaying prognoses of recurrent and advanced disease, whatever the treatment may be, forthcoming investigation should identify really effective drugs in second-line therapy, with a favorable toxicity profile.

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Cervical Cancer

Pierluigi Benedetti Panici and Roberto Angioli
University of Rome Campus Bio-Medico, Rome, Italy

Manuel Penalver
University of Miami School of Medicine, Miami, Florida, U.S.A.

Sergio Pecorelli
University of Brescia, Brescia, Italy

INTRODUCTION

Epidemiology and Screening

Cervical cancer is the second most common cancer in women worldwide (471,000 annual cases, 233,000 deaths) after breast cancer (1). Almost 80% cases occur in less-developed countries, where cervical cancer accounts for 15% of cancer in women. In more developed countries, it accounts for only 4.2% of new cancers. Age-adjusted incidence rates vary from 10/100,000 in many industrialized nations to more than 40/100,000 per year in developing countries (2).

The highest incidence rates are observed in Latin America and the Caribbean, Sud-Saharian Africa, and Southeast Asia. In more developed countries, incidence rates are generally low, probably because of screening.

Survival by FIGO stage is shown in Fig. 1.

Cervical cancer fulfills established criteria for disease screening: it is a fairly common disease with serious consequences, its etiology and natural history are known, and it is possible to intervene effectively during its precancerous stages; in addition, screening can be performed with the use of a simple and reliable test (Pap test). Recently, new techniques such as computerized methods (PAPNET) (3) and use of liquid solutions (THINPREP) (4,5) have been utilized to improve accuracy. When abnormal cells are detected on Pap smear, a thorough evaluation should consist of colposcopy and directed biopsy. The proper management of premalignant lesions of the cervix, in fact, is an important and integral part of any screening program. The classification of abnormal smears is variable, with different systems for reporting abnormalities (Class System, World Health Organization System, Cervical Intraepithelial Neoplasia System, The Bethesda System). The Bethesda System was introduced to replace the previous Papanicolaou classification and to facilitate precise communication between cytopathologists and clinicians. The first workshop was held in 1988: the most important contribution of the Bethesda System was the creation of a

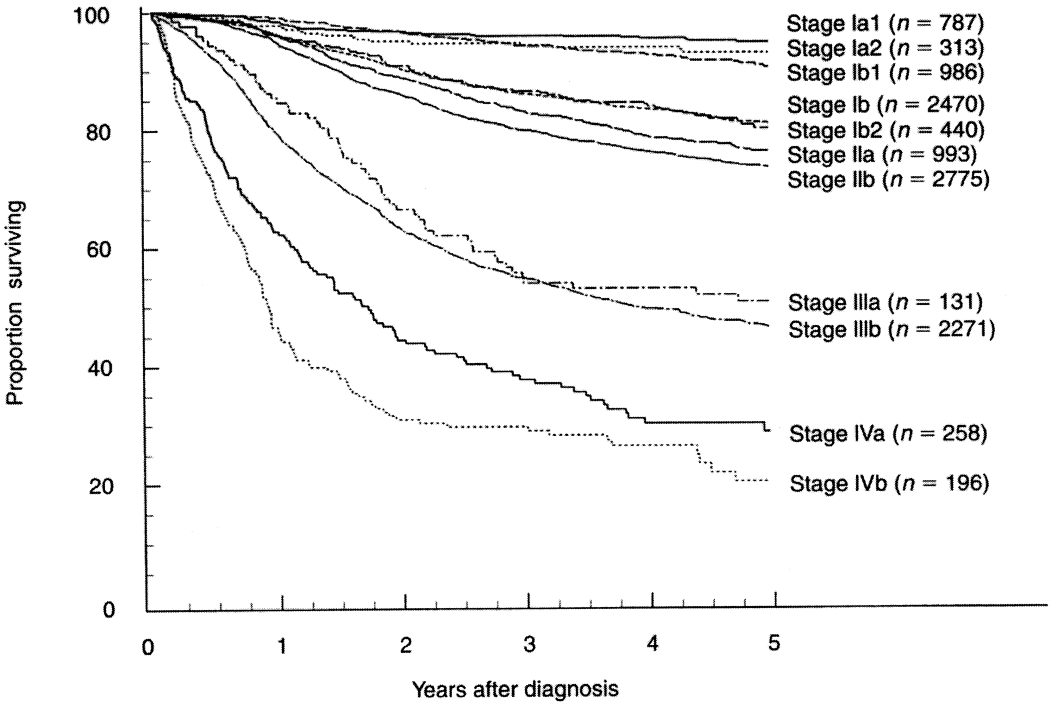

Figure 1 Carcinoma of the cervix uteri: survival by FIGO stage, $n = 11620$. (From Benedet JL et al., Carcinoma of the cervix uteri. J Epidemiol Biostat 2001; 6(1):24.)

standardized framework for laboratory reports that included a descriptive diagnosis and an evaluation of specimen adequacy. A second workshop was held in 1991 to modify the Bethesda System based on actual laboratory and clinical experience after its implementation. With the increased utilization of new technologies and recent findings from research studies, 2001 was considered an opportune time to reevaluate the Bethesda System (6). Moreover, management guidelines for women with abnormal cytology results, based on the 2001 Bethesda System, have been developed at a consensus conference sponsored by the American Society for Colposcopy and Cervical Pathology (7).

Data from the National Cancer Institute's Surveillance, Epidemiology and Results (SEER) have documented a rise in incidence of preinvasive lesion of the uterine cervix (8). The risk factors for preinvasive lesions have been extensively studied and are similar to those for invasive disease (see later). The relationship between preinvasive cervical lesions of the cervix and invasive cancer has been fairly well established by epidemiological studies. Studies examining progression rates of dysplasia have found that the risk is related to the grade of the lesion: approximately 47% of grade 1 CIN will regress spontaneously, while 37% will persist as low grade and 16% progress to higher grade (9); concerning CIN 2 lesions, regress in 43% of the cases, 35% persist, and 22% progress in the absence of treatment. Finally, spontaneous regression, persistence, and progression of CIN 3 to invasive cancer occur in approximately 32%, 56%, and 12%, respectively (10).

Traditional risk factors for cervical carcinoma are linked to sexual behavior (age at first intercourse, multiple partners), reproductive life, socioeconomic factors (low social class, ethnicity), and tobacco. Current etiology focuses on human papillomaviruses (HPV 16, 18, 31, and 45) of which several strains have been recognized as carcinogenic. The results of case-control studies have suggested that oral contraceptives, smoking, and certain nutritional deficiencies maybe cofactors of cervical cancer. In particular, cigarette smoking (11) may have a direct carcinogenic action on the cervical epithelium; moreover, the use of oral contraceptives for more than 5 years is demonstrated to be associated with a modest (up to twofold) increased risk of cervical cancer only in women with persistent HPV infection (12).

Concerning the pathological histotype, up to 90% of cervical cancers are of the squamous cell type, whereas the majority of the remainder are adenocarcinoma and less-common adenosquamous carcinoma. Recent studies from Sweden (13), the United States (14), Australia (15), and Canada (16) have reported that the incidence of invasive cervical adenocarcinoma, which used to account for 10–15% of all cervical cancer, has been steadily increasing in young women. The cause of the increase is unclear: cervical adenocarcinomas are difficult to detect by Pap smear, and changes in the accuracy of diagnosis of cancer and improvements in cancer registration and coding may have led to artifactual changes. Well-established risk factors for cervical squamous cell cancer, including lower social class and cigarette smoking, do not appear to play a major role in the etiology of adenocarcinoma. Earlier studies have postulated several risk factors responsible for invasive cervical adenocarcinoma, such as oral contraceptive use (17), human papillomavirus (HPV) type 18 infection, and obesity (18).

CARCINOGENESIS OF CERVICAL CANCER

Immortalization of human cells can be achieved with either E6 or E7 oncogenes of high-risk HPVs, but more efficiently by the joint function of both of them. Several sets of data exist pointing to the requirement for viral oncogene expression to maintain either the immortalized or the malignant phenotype of the respective cells (19). However, a substantial body of evidence supports the concept that neither the individual genes nor their cooperation is sufficient to convert normal cells into an immortalized or malignant condition. This has been elucidated in a large number of experimental studies. Several studies underline the importance of HPV oncoprotein expression in malignant cervical carcinoma cells: reversible repression of E6/E7 expression in the HPV 18-positive cervical carcinoma cell line SW 756 by dexamethasone blocks their malignant phenotype (20). Reintroduction of the two oncogenes under the control of a dexamethasone-inducible promoter restores malignant growth.

Similarly, viral oncogene antisense constructs selectively inhibited growth of cervical carcinoma cells harboring the respective virus (21–23).

However, somatic cell hybridization studies (24) also reveal that the expression of HPV oncoproteins is not sufficient for the maintenance of the malignant phenotype in cervical cancer cells. Hybrid clones derived of different cervical carcinoma cell lines or immortalized by HPV 16 and converted to malignant growth by additional x-irradiation either complemented each other to senescence or nontumorigenic immortalized growth or retained their malignant characteristics.

This set of data points to the existence of a separate signaling cascade blocking the progression of immortalized cells toward malignant conversion. This signaling pathway is regulated by several cellular genes and may become interrupted during the progression to malignant growth in different individual genes. Thus after somatic cell hybridization of different clones from malignant lines, complementation may occur within this signaling cascade, resulting in an immortalized but not a malignant phenotype of the respective clones.

Complementation of two different malignant cells after somatic fusion should involve complementation within two different signaling cascades.

In line with the requirement for specific host-cell modifications in addition to the expression of viral oncoproteins are observations of specific chromosomal aberrations in HPV-immortalized or in cervical carcinoma cell lines (25,26). A gene locus relatively frequently modified in cervical cancer is located in the chromosomal region 3p 14.2 that harbors the fragile histidine triad (FHIT) gene (27,28). Also, in line with this interpretation, a large-scale, population-based study (29) from Sweden pointed to genetic links in the development of cervical cancer.

An intriguing observation on a role of p53 polymorphism for the risk of cervical cancer (29) has not been confirmed in several other studies (30).

Expression of high-risk HPV oncoproteins may, in part, induce these genetic modifications in host-cell DNA. Chemical and physical mutagens should also interact cooperatively in the development of these changes. In addition, integration of viral DNA could further contribute to specific alterations within the host-cell DNA.

Diagnosis and Staging

Cervical cancers may present with symptoms which warrant further investigation such as postcoital bleeding, postmenopausal bleeding, or vaginal discharge. In others, the presentation is due to abnormal cervical pathology or suspicious lesions at the time of colposcopy. Whatever the presentation, diagnosis is dependent upon taking an appropriate biopsy that will confirm the condition. The staging of cervical cancer is clinical, but, in early stages, the interpretation of the pathological specimen is paramount. Cervical cancers are staged worldwide almost exclusively according to the FIGO classification (Table 1). Initial investigation should include chest x-ray, IVP and cistoscopy, sigmoidoscopy, and pelvic examination. Other investigations, including CT scan or MRI, may be performed as indicated. After surgery, the pathological findings in the removed specimens can form the basis for a precise evaluation of the extent of disease; these findings should not alter the clinical staging but should be recorded to help the management of the patient and as valuable prognostic parameters.

Treatment

In the last few years, a multimodal strategy has modified the therapeutic approach to cervical cancer patients. The treatment of microinvasive cervical carcinoma ranges from local excision to radical hysterectomy and pelvic lymphadenectomy depending case by case: during the last few years, however, there has been a trend toward a more conservative management. In the United States, the microinvasive cervical carcinoma defined by SGO as tumor less than 3 mm in depth, with negative lymphovascular

Table 1 FIGO Staging

Stage	Description
I	Cervical carcinoma confined to the uterus
IA	Invasive carcinoma diagnosed only by microscopy.
IA1	Stromal invasion no greater than 3.0 mm in depth and 7.0 mm or less in horizontal spread.
IA2	Stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less
IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than IA2
IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
II	Tumor invades beyond the uterus but not to pelvic wall or to lower third of the vagina
IIA	Without parametrial invasion
IIB	With parametrial invasion
III	Tumor extends to pelvic wall and/or involves lower third of vagina
IIIA	Tumor involves lower third of vagina no extension to pelvic wall
IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney.
IVA	Tumor invades mucosa of bladder or rectum and/or extends beyond true pelvis
IVB	Distant metastasis.

spaces, can be treated with conservative therapy which means cone biopsy or simple hysterectomy. More invasive tumors need to be treated with a radical surgical approach. Several prospective studies, investigating the possibility of reducing radicality and personalize the treatment, are being conducted.

Concerning early cervical carcinoma (stage IB), it has been accepted for many decades that radical hysterectomy with pelvic lymphadenectomy and radiotherapy are equally effective for the management of these patients. Some randomized studies have been conducted to compare these two different approaches: Hopkins and Morley (30) reported 5-year survival rates of 92% with surgery and 86% with radiotherapy. These findings have been later confirmed by other authors in a randomized trial of surgery vs. radiation in stage IB–IIA patients (5-year overall survival rates 83% and 74%, respectively) (31).

However, surgery—consisting in radical abdominal hysterectomy, pelvic bilateral lymphadenectomy, and, in some institutions, aortic lymphadenectomy—is the gold standard for the treatment of cervical carcinoma stage IB–IIA because side effects of surgery are more acceptable than radiotherapy complications. Surgery is the treatment of choice in young women as well because of the desire to preserve ovarian function. The extent of surgical radicality depends on the size of the tumor and whether there are signs of spread to parametrial tissue or vagina. Adjuvant radio-

therapy is considered the gold standard in patient with negative pathologic prognostic factors.

Early tumors with large volume (IB2) and locally advanced cancer are commonly treated with radiotherapy. Recently, several trials have indicated that concurrent chemoradiation is more effective than radiotherapy alone in patients with locally advanced cervical carcinoma (32–36). The data of these interesting trials will be presented in the following chapters. The promising results of these studies prompted the National Cancer Institute to issue a clinical announcement suggesting that "strong consideration should be given to the incorporation of concurrent cisplatin chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer" (37).

On the other hand, another promising approach for the management of locally advanced cervical carcinoma is the neoadjuvant chemotherapy. Chemotherapy, by inducing regression of cervical tumor and its local spread, could make radical surgery feasible in most locally advanced patients. In the last decades, various pilot studies investigating the feasibility and efficacy of neoadjuvant chemotherapy followed by radical surgery in locally advanced cervical cancer were carried out. These studies have been recently followed by randomized trials comparing radiotherapy and neoadjuvant chemotherapy plus radical surgery which have shown the superiority of the neoadjuvant treatment followed by radical surgery when compared to radiotherapy alone (38).

Recently, a prospective randomized study (EORTC # 55994) has been conducted to compare chemoradiation vs. neoadjuvant chemotherapy followed by surgery to treat locally advanced cervical carcinoma patients. Details of this approach are also being reported in a dedicated chapter of this book.

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Neoadjuvant Chemotherapy in Cervical Cancer

Pierluigi Benedetti Panici and Roberto Angioli
University of Rome Campus Bio-Medico, Rome, Italy

INTRODUCTION

Until 1983, cervical carcinoma was considered a chemo-resistant cancer, and as such, was treated with chemotherapy only after all other treatments have failed. This group of patients are most likely to be nonresponders, therefore, it is not surprising that results were disappointing. Studies carried out in these conditions have several inherited problems. First of all, most patients will have local recurrence, and this condition is frequently associated with ureteral obstruction and consequent impaired renal function, which alters drug excretion. Second, most patients with recurrent cervical cancer will have undergone radiotherapy and will have reduced tolerance to chemotherapy because of impaired marrow reserve. In addition, tissue vascularization in the pelvis may be altered by radiation and may result in drugs not reaching the recurrent tumor. Finally, radiation-induced fibrosis is difficult to distinguish from tumor and this creates problems in both diagnosis of recurrence and evaluation of response to therapy (1).

In 1983, Friedlander et al. (2) reported the first published study on the use of primary chemotherapy. Since then, many studies have been published on the use of chemotherapy as neoadjuvant treatment (NACT) before surgery (RS) or radiation (RT). It is interesting to note that most of the studies have been conducted and promoted in European and Latin American countries where optimal radiation therapy is less frequently available to all population as compared to the United States and Canada. From a historical point of view, it is therefore rational that more aggressive type of surgical radicality and use of chemotherapy has been initially employed in those countries where treatment modalities, such as chemoradiation combination, were least likely to be optimally delivered.

This chapter reviews the use of chemotherapy as neoadjuvant treatment in cervical cancer. The rationale of this treatment, the pilot studies, the latest randomized studies, and the application of chemotherapy before radiation therapy, as well as the intraarterial administration, will be described and discussed.

RATIONALE

Soon after the discovery that uterine cervix carcinoma is a chemo-sensitive tumor (2), the strategy of using chemotherapy as neoadjuvant to either surgery or radiotherapy began to attract increasing interest (3). This therapeutic strategy had been used with success in the squamous carcinoma of the head (4). Grounds for the use of neoadjuvant chemotherapy are listed in Table 1A (5–13). Although tumor size reduction is the most obvious, other important factors also exist. Large-size tumors may distort pelvic anatomy and this may cause some problems for radiotherapists, especially when the vagina is involved (12,13). Tumor size reduction may diminish this radiotherapy problem. Size reduction is also associated with a simplification of surgical procedures, and the possible transformation of inoperable tumor in radically resectable ones (7). At the same time, tumor reduction may be helpful in improving radio sensitivity by reducing the number of cells and by reducing hypoxic cell traction (5,7,11). Side effects preoperatively and intraoperatively are usually well tolerated. Some regimes, especially platinum-based ones, also act directly as radiation potentiators (10). Bonadonna and Robustelli della Cuna (8) exposed different reasons to suggest why micrometastasis may progress after primary surgery, and supposed that NACT may reduce such progression. It is generally accepted that the more precocious the systemic therapy, the higher the benefit that can be obtained (5,7). It should also be emphasized that untreated patients may tolerate higher intensity chemotherapeutic regimes and higher total chemotherapeutic dose. This can be justified by the intact bone marrow reserve (5,7), and by the undamaged nephro-ureteral system (1). A further advantage is that vascularization and consequent drug distribution is better in a nondamaged tissue compared to an iatrogenically damaged one (5,6). To conclude, it must be noted that response to NACT is an important prognostic factor (9), and this helps in the decision of the successive therapeutic approach (7,10). Different authors have highlighted the disadvantages correlated with NACT (Table 1B) (14–17). Potentially effective treatment has to be necessarily delayed and this is particularly severe for computerized tomography (CT) nonresponders. Overall treatment duration, toxicity, and costs are inevitably increased (7). Tumor pharmacological debulking may determine a replication rebound (14,15) and induce selection of chemo- and/or radio-resistant clones (7).

Table 1A Rationale of Neoadjuvant Chemotherapy

Reduces tumor size
Acts on a well-vascularized tissue (5,6)
Used on intact bone marrow (5,7)
NACT may reduce postoperative micrometastasis progression (8)
Acts against local and distant subclinical metastasis (5,7)
Acts as a prognostic factor (9)
Acts as a radiation potentiator (10)
Increases radiosensitivity by improving size reduction and decrease ipoxic cell fraction (5,7,11)
Reduce pelvic distortion by tumor mass and facilitate subsequent RT (12,13)
Turn inoperable tumors into resectable (7)
Guide therapeutic itinere: identify chemosensitive tumors (7,10)

Table 1B Potential Drawbacks of Neoadjuvant Chemotherapy

Prolongation of treatment (7)
Delay of potentially curable treatment (7)
Possibility of tumor progression (7)
May determine replication rebounce (14,15)
Increase in toxicity of overall treatment (7)
Potential selection of drug resistant clones (7)
Increases radio resistance (15,16)
Transformation of clinically evident macroscopic metastasis in occult ones
Possible increase in postoperative complications
Increases tissue fibrosis (17)
Difficulty in understanding previous margins of the lesion
Increase in treatment costs

As far as surgical treatment is concerned, pelvic dissection should be tailored according to the initial pretreatment extension and volume of the tumor, removing all tissue invaded by the tumor prior to neoadjuvant chemotherapy (18). The identification of an accurate dissection margin may be difficult in previously treated and highly fibrotic tissue. On a theoretical basis, macrometastasis may also be reduced into occult metastasis, leaving unrecognized distant foci. When neoadjuvant chemotherapy is administered, the radicality of the hysterectomy should be tailored to the pretreatment conditions to remove all the neoplastic tissue. New specific, extended surgery has also been developed to obtain thorough parametrectomy for these advanced cases (19).

PILOT STUDIES

Cervical carcinoma had been considered a chemo-resistant cancer until 1983, and chemotherapy was only used after other treatment modalities failed. In 1983, Friedlander et al. (2) were the first to investigate the effect of chemotherapy in cervical cancer in previously untreated patients. This pilot study included 10 out of 33 assessable patients with locally advanced inoperable disease who underwent chemotherapy with 3 courses of Vinblastine, Bleomycin, and Cisplatin (VBP) as a first-line treatment. Six (60%) of these patients showed a partial response to chemotherapy; seven (70%) out of nine who continued treatment with radiotherapy exhibited a complete clinical response. Based on this preliminary report, the same group conducted the first pilot study to evaluate the role of neoadjuvant chemotherapy (NACT) before radical surgery in the treatment of locally advanced cervical carcinoma (FIGO stage IB–IVA) (3). This study confirmed the high proportion of clinical partial response and showed a 17% of complete clinical response rate with chemotherapy. In all patients with complete clinical response, microscopic foci of cervical cancer were found in pathological evaluation after surgery. Patients who enrolled in these studies manifested better survival rates compared with patients who submitted to the standard radiotherapy treatment (Table 2) (20–41).

Pilot studies have evaluated several factors; in particular, we grouped these results as drugs employed, pathological considerations, and survival.

Table 2 Neodjuvant Chemotherapy and Tumor Response: Pilot Studies

Author(s), year	No. of points	FIGO stage	CT schedule	Clinical response schedule (complete + partial)	Pathological complete response
Friedlander et al., 1983 (2)	10	IIb–IV	PVB	60%	0%
Friedlander et al., 1984 (3)	30	Ib–IIIb	PVB	67%	0%
Sardi et al., 1986 (12)	33	Ib–IIIb	POB	84%	3%
Muss et al., 1987 (10)	11	IIb–Iva	P	36%	—
Kirsten et al., 1987 (20) update of Friedlander, 1984	47	Ib–IIIb	PVB	66%	0%
Benedetti Panici et al., 1988 (21)	33	Ib–IIIb	PMB	75%	12%
Weiner et al., 1988 (22)	20	I–IV	POBM	72%	—
Kim et al., 1988 (23)	35	Ib–IIa > 4cm	POBM	89%	20%
Kim et al., 1989 (24), update of Kim 1988	54	Ib2–IIa > 4cm	PVB	94%	13%
Sardi et al., 1990 (7), update of Sardi 1986	151	IIb–IIIb	POB	85%	17%
Tobias et al., 1990 (25)	19	IIa–IV	PIB	68%	0%
Benedetti Panici et al., 1991 (26) update of BP 1988	75	Ib2–III	PMB	82%	13%

Benedetti Panici et al., 1991 (27)	26	Ib2–III	PB	88%	19%
Dottino et al., 1991 (28)	28	Ib2–IVa	POBM	100%	14%
Deppe et al., 1991 (29)	17	Ib2–IIIb	PM	76%	29%
Chang et al., 1992 (30)	33	Ib2–IIa	POB	85%	6%
Fontanelli et al., 1992 (31)	27	Ib2–IIb	PB	77%	7%
Zanetta et al., 1993 (32)	21	Ib2–IIIb	POB	76%	0%
Bloss et al., 1995 (33)	30	IIb2–IVa	POB	87%	0%
Eddy et al., 1995 (34)	34	Ib	PO	82%	0%
Leone et al., 1996 (35)	56	Ib	IP	54%	2%
Lacava et al., 1997 (36)	42	IIb–IVa	Vn	45%	2%
Serur et al., 1997 (37)	20	Ib	PMB	90%	5%
Giardina et al., 1997 (38)	23	Ib2–IIb	P	86%	14%
Zanetta et al., 1998 (39)	39	Ib2–IVa	TIP	84%	16%
Benedetti Panici et al., 1998 (9)	128	Ib2–III	PMB	83%	14%
Pignata et al., 1999 (40)	27	Ib–III	PVn	82%	19%
Vallejo et al., 2000 (41)	40	IIb–IVa	PIVn	60%	5%
Benedetti Panici, 2003[a]	24	Ib2–IIIb	PTN	75%	17%

PCR: pathological clinical response; CR: complete clinical response; PR: partial clinical response; SD: stable disease; Prog.: progression. A: Adriamicyn; B: bleomicyn; P: Cisplatinum; C: Cyclophosphamide; Cx: Cytoxan; E: Etoposid; F: Fluoruracil; I: Ifosfamide; M: Methotrexate; N: Navelbine; T: Paclitaxel; V: Vinblastin; O: Vincristine; Vn: Inorelbine.

[a] Unpublished data.

Chemotherapy Choice

Successive pilot studies have tried to verify the efficacy of different drugs, different overall dose, and different dose intensity regimens. Valle et al. (42) were obliged to reduce the overall drug dose from Adriamicyn 50 mg/mq, Bleomycin 10 mg/mq, and Cisplatin 100 mg/mq to Adriamicyn 50 mg/mq, Bleomycin 6 mg/mq, and Cisplatin 50 mg/mq because of unacceptable toxicity, but were somehow able to demonstrate good tumor response. In contrast, the experience reported by Sardi et al. (12) in 1986 was more encouraging. They used two different dose intensity schemes on patients with stages Ib–IIIb composed of 3 cycles of VBP. The conventional VBP scheme consisted of Vinblastine (1 mg/mq) and Bleomycin (15 mg/mq) on days 1–6, and Cisplatin (50 mg/mq) with an interval of 21 days between doses. The modified VBP scheme consisted of Vinblastine (1 mg/mq) and Bleomycin (25 mg/mq) on days 1–3, and Cisplatin (50 mg/mq) with 10-day interval between doses. The overall dose of Bleomycin was reduced from 90 to 75 mg/mq in every cycle, in preference to an increase in dose intensity in the modified regime. Tumor response in different sites was different for the two regimes: the conventional scheme achieved a moderate response in the cervix and vagina (62.5%), but elicited a poor response in the parametrium (28.5%) compared with the modified scheme, which obtained high response rate in all regions (92% and 94%, respectively). No major toxicity was observed in the high dose intensity group.

These observations allowed other authors to adjust doses and administration intervals. Our group was the first to apply dose intensity regimes as neoadjuvant treatment (27). The schedule adopted was Cisplatin (40 mg/mq) for five consecutive days, and Bleomycin (15 mg i.v. bolus) on days 1, 2, 8, and 9. This work demonstrated the feasibility of high dose intensity Cisplatin and Bleomicin regimes, with the advantage of a great reduction in time interval before definite treatment and a reduction of overall treatment duration.

Pathological Considerations

Pathological parameters have been frequently evaluated by pilot studies

The three most important points highlighted by phase II studies are as follows:

- Cervical cancer is a chemosensitive tumor.
- Response is dose-dependent, and possibly schedule-dependent.
- Different antitumor sites have different sensitivity to chemotherapy (vaginal and cervix lesions were more responsive compared with parametrial lesions) (9,12).

In 1987, Kirsten et al. (20) published the update of the first NACT pilot study, previously reported by Friedlander et al. (3) on patients with stage Ib to IVa, and the first survival data showing a median survival for all patients of 88 weeks and, in particular, ranging from 12 weeks in stage IVa patients, to stage II patients in which median survival had not yet been reached at the time this work has been published. This study also demonstrated the important role that central tumor (cervix) response plays as a prognostic factor. Compared with nonresponders, central tumor responders showed higher rate of disease recurrence (81% vs. 35%), radiotherapy failure (80% vs. 21%), and shorter median postchemotherapy survival (117 vs. 45 weeks). Other studies of the middle 1980s have also shown how NACT seem to affect the rate of

lymph node metastasis. Patients who have undergone NACT have a reduced rate of lymph node involvement (43). In particular, patients with better central response were less likely to have lymph node metastasis (21,23,24,44). It is therefore believed that tumors that respond on the cervix also respond in the lymph nodes (21,23,24,28,26,30). Important prognostic factors, such as depth invasion, parametrial invasion, and grading, influence chemotherapy response as well (19,26,30). Most of the above-mentioned studies have been conducted on squamous cell carcinoma but results on adenocarcinomas have demonstrated similar results (45,46).

Survival

In 1990, the update of the Argentinean pilot study was published (7). The extensive number of patients allowed some important consideration to be made even if the short follow up period was insufficient to draw any definite conclusion. Response rate to NACT is inversely proportional to tumor stage. Overall response rate was 92% in patients with stage IIB and 73% for those with stage IIIB. This is probably attributable to the different tumor size (30,35). The number of patients with no evidence of disease (NED) after 2 years was much higher for stage IIB compared with stage IIIB. This study included a historical control group treated with RT. The percentage of patients with NED after 2 years was significantly higher in the NACT group. This advantage of NACT in disease-free survival (DFS) rate was more important in stage IIB (79% vs. 47%, $p < 0.01$), but a significant difference was observed even in patients with stage IIIB disease (50% vs. 26%, $p < 0.01$) (7).

These premature results have been partially confirmed by the analysis reported on long-term survival that was conducted on 128 subjects who entered the NACT pilot studies conducted by our group between 1986 and 1990 (9). The estimated 10-year survival rates were 91%, 80%, and 34.5% for stages IB2–IIA bulky, IIB, and III, respectively ($p < 0.001$). The 10-year disease-free survival (DFS) estimate rate is 75%.

RANDOMIZED STUDIES

Based on numerous pilot studies mentioned above, most of which demonstrated the feasibility of NACT in terms of toxicity and tumor chemosensitivity, several different randomized trials were launched. The most important randomized studies compared the experimental group with traditional radiotherapy. Three different therapeutic techniques were examined with NACT: (1) NACT followed by RT, (2) NACT followed by RS, and (3) NACT followed by RS, then followed by RT.

Neoadjuvant Chemotherapy Before Radiotherapy

The first randomized study evaluating NACT followed by RT was performed by Souhami et al. (47), who analyzed the effect of NACT on patients with stage IIIB squamous cell carcinoma. Based on pilot studies, this subgroup of patients were less likely to respond to NACT compared to lower-stage tumors (7). In this study, 39 out of 91 randomized patients were assigned to the NACT–RT group. Although the clinical response (complete clinical response + partial clinical response) rate was higher in the NACT–RT group compared to the standard RT control group (72% vs. 59.5%,

respectively), survival in the NACT + RT groups was sufficiently low to have the study suspended prematurely. The 3-year overall survival rate among complete responders was 37.5% and 57% for the NACT–RT group and control group, respectively. Similar results were obtained by analyzing the partial responders. These results remain significant on the 5-year survival analysis, demonstrating an overall survival (OS) of 23% and 39% in the NACT–RT and RT control groups, respectively. Many patients who underwent the combined treatment also experienced acute toxicity in the form of severe nausea, vomiting, and skin hyperpigmentation, and in four patients Bleomycin fatal pulmonary toxicity occurred. It should be emphasized, though, that treatment-related deaths alone were not sufficient to justify these discouraging results. An important consideration that emerged from this study is the limits that tumor clinical response bears as a predictor of outcome in radiated patients.

Later, Kumar et al. (48) reported a second study that enrolled 94 patients in the experimental group and 90 in the control group. This randomized study included patients with FIGO stages IIB–IVA. In the RT control group, the complete clinical response rate was 69.3%. At the end of the chemotherapeutic treatment, analysis of results showed that, among the assessable patients, 4.5% had a complete clinical response rate and 67.5% had partial clinical response rate after NACT. After radiotherapy was completed, the complete response rate was 70%. Patients over 45 years and with Hb level greater than 10g/dL obtained a significantly better response rate. Chemotherapeutic responders obtained an 83% complete clinical response after RT vs. 33.3% complete clinical response obtained in chemotherapeutic nonresponders. The toxicity rate of both groups was tolerable. Although the Kumar study results were less discouraging compared to the previously described study of Souhami et al. (47), there was no statistical difference in the overall survival between the two groups: 38% vs. 43% in the NACT–RT and the RT groups, respectively. Sundford et al. (49) also failed to demonstrate DFS or crude survival benefit of NACT + RT vs. RT alone in a group of 94 patients with cervical carcinoma stages IIIB–IVA. Sardi et al. reported two randomized studies: one on stage IIIB (50) and one on stage IIB (51). The study on IIIB patients included three arms: NACT + RS + RT, NACT + RT, and an RT control arm. There was a trend but no significant difference in the OS and DFS in favor of patients treated using NACT (4-year OS NACT + RS + RT 63%, NACT + RT 53%, RT 37%). The study on IIB cervical cancer featured four arms: two control arms in which patients underwent RT or RS followed by RT and two experimental arms in which NACT was added to the previous treatments (51). Although after 7 years the NACT + RT group had a higher survival compared to the RT group (54% vs. 48%), this was not significant. What did emerge as significant was the OS rate of NACT + RT patients compared to RT alone with tumor exceeding 5 cm (66% vs. 36% $P < 0.005$).

A meta-analysis evaluating NACT + RT was recently carried out by Tierney (52). Results achieved from 18 randomized trials that globally enrolled 2074 patients were analyzed. When all trials were considered, there was no evidence of a benefit of NACT followed by RT compared to RT alone. This study shows poor survival rate in patients undergoing NACT regimens with low dose intensity cisplatin ($<25 mg/m^2$/wk) and prolonged cycle length (>14 days) chemotherapeutic treatment before radiotherapy. NACT followed by RT seems to be very effective when high dose intensity and short period is adopted.

In conclusion, the results of the above-mentioned studies and others show that, despite the significant response obtained using NACT + RT, OS and DFS are not

significantly better than the RT arm in the majority of cases. It is encouraging though that CT responders did have an improved survival rate as compared to CT non-responders.

Neoadjuvant Chemotherapy Before Radical Surgery

Concerning the use of NACT before radical surgery without routine adjuvant radiotherapy, few prospective randomized studies have been performed based on the promising results of the pilot studies described above. Only two studies have been performed using NACT + RS without routine adjuvant RT, one reported by Chang et al. in 2000 (53), and the other by Benedetti Panici et al. in 2002 (Table 3A) (13,53). The first one included 120 patients with stage Ib2 or bulky stage II disease randomly assigned to the experimental (NACT + RS) or the control arm (RT). Although the overall response and the toxicity in the experimental group were encouraging, analysis of disease-free survival (DFS) and overall survival (OS) showed no significant difference at 5 years. The OS was 70% and 62% in the NACT and control arm, respectively (31).

The second study was a multicenter randomized trial conducted by 14 Italian centers (13). Out of 409 patients, 210 were assigned to NACT followed by RS arm. Eligible patients were those with squamous cell carcinoma and disease stage Ib2, IIa > 4cm, IIb, and III. Survival analysis was conducted on intention to treat, eligible patients, and patients receiving treatment according to protocol. In all these groups, a significant increase in 5-year OS and DFS was observed. These results were confirmed in the analysis by FIGO stage for stages Ib2–IIa, but not for stages IIb and III. In particular, the 5-year survival analyses by FIGO stage showed significantly longer overall survival rate of 64.7% vs. 46.4% ($p = 0.005$) and progression-free survival rate of 59.7% vs. 46.7% ($p = 0.02$) for the stage Ib2–IIb patients in the NACT arm compared with the RT arm, respectively. Survival rate for stage III patients did not significantly differ in the two arms (OS: 41.6% vs. 36.7%, $p = 0.36$; PFS: 41.9% vs. 36.4% $p = 0.29$).

It should be noted that patients in the control group were treated with the RT regimen adopted at the time, and that at the present time, the best survival benefit seems to be achievable using concurrent chemo–radiotherapy, rather than by radiotherapy alone.

Other authors have investigated the use of NACT followed by RS, and routinely, additional adjuvant radiotherapy. Sardi et al. (54,55) reported three studies on NACT, followed by RS, then by RT (Table 3B). The effect of this mode of treatment was conducted on patients with stages IB, IIB, and IIIB of the disease (50,51,55,54). Concerning the IB tumors, NACT did not significantly affect the outcome in terms of 8-year OS (82% vs. 77% in the NACT and control group, respectively). It is interesting to note that in the experimental arm, there was a significantly higher resectability (100 vs. 85%, $p < 0.001$).

The investigation on stage IIB tumors included four arms: RT, RS + RT, NACT + RT, and NACT + RS + RT (51). The group treated with NACT followed by RS and RT included 76 patients. This group had the highest survival rate of the four arms and this difference was significant when compared to the two control groups (RT alone and RS + RT). In particular, survival was 41% and 48% in the RS + RT ($p < 0.01$) and RT ($p < 0.005$) arms, respectively, compared to 65% in the

Table 3A Neoadjuvant Chemotherapy Followed by Radical Surgery Vs. Radiotherapy: Randomized Trials

Author(s)	No. of points			FIGO stage	CT schedule (dose in mg mq)	No. of couses	Estimated overall survival (5 yr)		Conclusion
Chang et al. (53)	NACT + RS	120	68	Ib2 62; IIa 58	P 50 mg/mq p1q10; B 25 mg/mq p2,3,4q10; O 1 mg/mq p1q10	3	70%	95% C.I.	DFS and OS did not differ significantly
	RT		52				62%		
Benedetti Panici et al. (13)	NACT + RS	409	210	Ib2–IIa 174; IIb 148; III 87	P 80 mg/mq p1q21; B 15 mg/mq p1,8q21	2	58.9%	$P = 0.007$	Sequential NACT and RS was more effective than exclusive RT
	RT		199		P 50 mg/mq p1q7; B 30 mg/mq p1q7; O 1 mg/mq p1q7	6	44.5%		The increase was significant in IB2–IIB, but not in IIB tumors
					P 43 mg/mq p1q7; I 3.5 mg/mq p1q21	3			
					P 40 mg/mq p1q7	6			

Table 3B Neoadjuvant Chemotherapy Followed by Radical Surgery and Adjuvant Radiotherapy Vs. Radiotherapy: Randomized

Author	No. of points			FIGO stage	CT schedule (dose in mg mq)	No. of couses	Overall survival			Conclusion
Sardi (51)	NACT + RS + RT	149	76	IIb	P 50 mg/mq p1q10; O 1 mg/mq p1q10; B 25 mg/mq p1-3q10	3	7 yr	65%	$P < 0.005$	Survival was significantly increased compared to the RT group independent of tumor size.
	RT		73					48%		
Sardi (50)	NACT + RS + RT	107	54	IIIb	P 50 mg/mq p1q10; O 1 mg/mq p1q10; B 25 mg/mq p1-3q10	3	4 yr	63%	$P = 0.005$	OS and DFS were significantly better in the NACT group compared with the control group.
	RT		53					37%		
Sardi (54), update Sardi (55)	NACT + RS + RT	151	74	Ib1, Ib2	P 50 mg/mq p1q10; O 1 mg/mq p1q10; B 25 mg/mq p1-3q10	3	8 yr	81%	$P = 0.05$	There is no significant difference in OS in patients with Ib 1 tumors.
	RS + RT		72					66%		There is a significant benefit of NACT in patients with Ib2 tumors.

NACT + RS + RT group. Patients who underwent NACT had a significant increase in resectability and better pathological risk factors. The OS analysis in the two surgically treated arms demonstrated a benefit of NACT both followed by RS + RT vs. RS + RT without NACT in tumors with initial dimension greater (53% vs. 33%) and lesser (73% vs. 51%) than 5 cm.

Concerning the stage IIIB tumors, Sardi et al. demonstrated that OS was better in patients treated with NACT independently from the adjuvant treatment. The 4-year OS survival was 63%, 53%, and 37% for patients treated in the NACT + RS, NACT + RT and RT control groups, respectively. No significant difference was observed between the two experimental arms, but both had significantly better results compared to the control group ($p = 0.025$ for NACT + RS vs. RT, and $p = 0.005$ for NACT + RT vs. RT). Similar results were obtained for the DFS.

The above-mentioned meta-analysis (52) also examined the effect of neoadjuvant chemotherapy followed by surgery. Data were acquired on 872 patients from five different trials. Results showed an overall significant ($p = 0.0004$) increase in 5-year survival rate of 14%. This analysis failed to identify any subgroup of patients that could benefit or be damaged by such treatment. It should be noted that some of these patients received adjuvant RT as well.

INTRAARTERIAL NEOADJUVANT CHEMOTHERAPY STUDIES

In gynecologic malignancy, most chemotherapeutic regimes are intravenously infused. In recent years, some authors have evaluated the use of intraarterial chemotherapy (IACT). Drugs can be directly infused inside the uterine artery via insertion of a small catheter by passing through a 5 French catheter introduced from the controlateral femoral artery (Seldinger method). This procedure is carried out under local anesthesia, after a pelvic angiography has been performed. To improve safety, a computed tomography angiography may be performed before the chemotherapeutic immision (56). A recent retrospective study of 97 patients with locally advanced cervical carcinoma ranging from FIGO stage I to IV has shown positive results. The employed drugs were Cisplatin (60–70 mg/mq), Doxorubicin Hydrochloride (30–40 mg/mq), Mitomicycin (15 mg/mq), and 5 Fluoruracil (500 mg/body) infused via the bilateral internal iliac arteries. Complete pathological response was obtained in 29% of patients with stage I disease and in 20% of patients with stage IV disease. The 5-year survival rate of the operated patients was between 100% and 64% for stages I–IV of the disease (57). Good results appear to be confirmed in prospective randomized trials in patients who underwent surgical treatment. In the randomized trial conducted by Kigawa et al. in 1996 (58), 50 patients, FIGO stage IIB–IIIB, were equally enrolled in two arms, (a) the intraarterial neoadjuvant chemotherapy followed by RS experimental group and (b) the RT control group. Radical surgery was performed in 18 patients in the experimental group who were judged to be responsive to surgery, while inoperable patients underwent the same radiotherapy as the control group. The 3-year survival rate was 85.7% for operated patients, but only 42.9% for patients judged inoperable compared with 49.5% of the control group. In this study, neoadjuvant intraarterial infusion chemotherapy did not improve the prognosis of patients with advanced cervical cancer compared to radiation therapy alone, and only responders who underwent surgery showed improvement in survival (58). An innovative administration plan that has re-

cently been reported and is currently being studied is the i.a. and i.v. contemporary infusion associated with transcatheter arterial embolization. This trial used a combination of platinum-based drugs. The results obtained were 100% overall response rate, and 40% complete response (56).

In conclusion, intraarterial chemotherapy has not gained large diffusion worldwide: this can be ascribed to technical difficulties and the high cost of this procedure. At the moment, more studies are necessary to understand what role this technique may have in the treatment of locally advanced cervical cancer.

CONCLUSIONS

Cervical cancer is a chemo-sensitive tumor. Various regimes have been studied but there is no consensus as to which one is the gold standard, although most of the studies have adopted platinum-based regimen. Neoadjuvant chemotherapy has shown to be effective in decreasing tumor size and increasing the operability of large tumors. When used before radical surgery, this scheme gave better results than when RT was used alone, especially in IB2–IIB tumors. Results of the recent meta-analysis suggest that when surgery is adopted, a quick intensive burst of intensive platinum-based chemotherapy might improve 5-year survival rate by as much as 14% compared to RT. This observation has strong clinical implications, considering that chemoradiotherapy has achieved similar results (overall survival benefit of 12% at 5 years; see Green et al. (59)). This represents the rationale of the randomized EORTC trial (EORTC55994), which evaluated neoadjuvant chemotherapy followed by radical surgery vs. concurrent chemoradiotherapy in locally advanced cervical cancer patients. Neoadjuvant chemotherapy followed by surgery should be considered as the treatment of choice in countries or in conditions in which concomitant chemoradiotherapy cannot be delivered optimally in terms of doses, schedule, and time.

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Chemoradiation Therapy for Cervical Cancer

Peter Graham Rose
University MacDonald Women's Hospital, Case Western Reserve University, Cleveland, Ohio, U.S.A.

Cervical cancer is probably the most common female cancer in the world. Although the international statistics for cervical cancer rank it as the third most common cancer (1,2), the disease primarily occurs in countries without comprehensive or durable tumor registries. In these countries cervical cancer occurs at an epidemic proportion. Unfortunately, cervical cancer affects woman at a younger age than any other cancer that affects adult women (3). This results in an average of 28 years of life lost for every case (4). Cervical cancer usually occurs in patients who have not had regular Pap smear screenings. Due to the lack of screening, patients with cervical cancer often present with locally advanced stage disease. This extent of disease is beyond what can often be controlled with surgery alone. Radiation therapy is typically used in this setting. However as tumor size increases, reflected grossly in FIGO staging, survival decreases precipitously. In his classic paper, Fletcher described the relationship between the radiation dose required to control squamous cell cervical cancer based on the size of the primary tumor (5). When tumors exceed 6 cm, the dose of radiation required exceeds the tolerance of normal pelvic tissues. Because of the limitation on the dose that can be delivered, survivals with larger tumors are suboptimal. To overcome this a number of adjunctive therapies have been utilized. Three primary types of adjunctive therapies have included chemotherapy, hyperthermia and large particle radiation (6,7). However, because of the technical difficulties of cervical hyperthermia as well as the limited availability of large particle radiation therapy equipment, chemotherapy has emerged as the most common adjunct therapy to radiation.

Two primary schedules—neoadjuvant and concurrent chemotherapy and radiation—have been utilized. In the neoadjuvant schedule, chemotherapy is given before the radiation therapy. Since local disease volume is a significant prognostic factor in cervical cancer the concept of chemically debulking the tumor prior to radiation is attractive. Additionally, although chemotherapy has a relatively low response rate (20–25%) in recurrent disease, the response rate with neoadjuvant chemotherapy are significantly higher ranging from 60–100%. However, despite encouraging Phase I and II results, when this modality was tested in randomized trials, no benefit to neoadjuvant

chemotherapy was evident (8–16). Furthermore, in two trials the outcome was worse with the use of neoadjuvant chemotherapy. In the first of these two trials by Suhami et al. the regimen utilized included bleomycin, and pulmonary-associated deaths occurred in four patients (10). However, in a subsequent trial demonstrating an adverse outcome, the chemotherapy regimen utilized cisplatin and epirubicin (14). Again, a significantly poor survival rate was seen in the neoadjuvant chemotherapy arm. A number of theories including accelerated repopulation of resistant clones and poor treatment compliance may explain this poorer outcome (17,18).

In the concurrent schedule, chemotherapy is given during radiation therapy. This schedule limits the use of severely myeolsuppressive regimens due to the additional myelosuppression of pelvic radiation. The use of concurrent cisplatin-based therapy has become accepted as the new standard of care for women with cervical cancer who require radiation therapy. A clinical alert supporting this new standard was issued by the National Cancer Institute in February of 1999 (19) based on the results of five randomized cervical cancer trials (20–24). Collectively these studies comprised of more than 1,850 women who were treated with cervical cancer in a variety of clinical stages and settings.

These trials were similar in that all utilized cisplatin-based chemotherapy given concurrently during radiation therapy. However, some of the regimens used cisplatin in combination with 5-fluorouracil (5-FU) and one regimen utilized cisplatin, 5-FU and hydroxyurea (20,21,24). Additionally, the control arms for the trials are varied. Three of the trials used radiation alone as the control arm (21,23,24). Two of the trials utilized radiation with concurrent hydroxyurea as the control arm (20,22), based on two previous randomized trials by the Gynecologic Oncology Group (GOG) that had demonstrated improvement in progression-free survival and survival with radiation with concurrent hydroxyurea (25,26).

All of the five trials looked at patients who had varying degrees of locally advanced cervical cancer. In two of the trials, GOG 85 and 120, this was limited to patients with IIB, III, and IVA disease (20,22). GOG 85 compared radiation with cisplatin and 5-FU with radiation with hydroxyurea (20) (Table 1). Three hundred and eighty-six evaluable patients with stage IIB, III, and IVA cervical cancer who had undergone surgical staging to exclude paraaortic nodal metastasis were evaluated. Squamous cell carcinoma and adenocarcinoma were included in this trial, although the vast majority of patients, roughly 90%, had squamous cell carcinoma. A 30% improvement in progression-free survival and survival was noted for the chemo-radiation arm. The survival rate with radiation was 50.8% for cisplatin and 5-FU versus 39.8% with hydroxyurea. GOG 120 was a three-arm randomized phase III trial comparing radiation with weekly cisplatin/cisplatin, 5-FU and hydroxyurea; or hydroxyurea alone (22). The addition of hydroxyurea to cisplatin and 5-FU was to take advantage of hydroxyurea's inhibition of ribonucleotide reductase with tumor depletion of deoxyuridine monophosphate. Deoxyuridine monophosphate competes with the active metabolite of fluorouracil, fluorodeoxyuridine monophosphate, for the binding of thymidylate synthetase. This triple combination had been demonstrated to be effective in both head and neck and cervical cancer with concurrent radiation therapy (27,28). Five hundred and twenty-six patients with stage IIB, III, and IVA who had undergone surgical staging to exclude patients with paraortic nodal metastasis were evaluated. This trial demonstrated that both cisplatin-containing regimens improved both the progression free interval and survival. The survival rate

Table 1 Cisplatin-Based Chemoradiation Regimens in Included Clinical Trials

GOG 85:
cisplatin 50 mg/m^2 day 1&29 followed by
5-fluorouracil 1 gm/m^2/d as a 96 hr infusion day 1&29
RTOG 9001:
cisplatin 75 mg/m^2 day 1&29 followed by
5-fluorouracil 1 gm/m^2/d as a 96 hr infusion day 1&29
GOG 120:
cisplatin 40 mg/m^2 day 1, 8, 15, 22, 29, 35
or
cisplatin 50 mg/m^2 day 1&29 followed by
5-fluorouracil 1 gm/m^2/d as a 96 hr infusion day 1&29
hydroxyurea orally 2 gm/m^2 twice weekly
GOG 123:
cisplatin 40 mg/m^2 day 1, 8, 15, 22, 29, 35
SWOG 8797/GOG 109:
cisplatin 70 mg/m^2 day 1, 29, 50, 71 followed by
5-fluorouracil 1 gm/m^2/d as a 96 hr infusion day 1, 29, 50, 71
NCIC:
cisplatin 40 mg/m^2 day 1, 8, 15, 22, 29, 35

with radiation was 64% for weekly cisplatin and 66% for cisplatin, 5-FU and hydroxyurea versus 39% with hydroxyurea. Specifically, there was a decrease in local recurrence from 29% to 19% for both cisplatin-based regimens. The single agent cisplatin arm was associated with less hematologic and gastrointestinal toxicity than the three-drug combination and was felt to be the preferred regimen. RTOG 9001 also looked at patients with advanced stages IIB, III, and IVA, but included patients with bulky IB tumors or those with positive pelvic nodes (21). Patients were randomized between cisplatin and 5-FU with pelvic radiation or extended field (pelvic and paraaortic) radiation therapy alone (Table 1). The control arm for this trial, extended field radiation therapy, was based on 22% relative survival benefit seen in a previous trial of pelvic versus extended field radiation (29). Both the progression-free and overall survival was improved by addition of the use of chemoradiation. The survival rate with pelvic radiation with concurrent cisplatin and 5-FU was 73% for cisplatin and 5-FU versus 58% with pelvic and paraaortic radiation. Furthermore, chemoradiation resulted in both decrease in local recurrence and decrease in distant recurrence implying that control of local metastasis precluded further distant metastasis. The toxicities in this trial were divided into acute toxicity occurring in the first 60 days and late toxicity occurring after this time. While acute toxicities were increased, these were mostly hematologic with reversible myelosuppression and nausea and vomiting related to the chemotherapy. Serious chronic toxicities of radiation were not increased.

The next subset of patients that were studied with chemoradiation included those with bulky IB disease. By current FIGO definition, this would be patients with IB_2 disease. The optimal management of these patients is controversial and three primary management schemas have been pursued. First, initial primary surgery can consist

of radical hysterectomy followed by tailored radiation therapy with or without concurrent chemotherapy. The indications for treatment after initial surgery include high risk factors such as positive nodes, perimetrial extension or positive margins, or intermediate risk features such as deep myocervical invasion, vascular-lymphatic invasion or large tumor size. Second, radiation therapy can be delivered initially with or without concurrent chemotherapy followed with or without hysterectomy. Lastly, the initial use of neoadjuvant chemotherapy followed by radical hysterectomy in responding patients with tailored radiation therapy with or without concurrent chemotherapy has been studied. In a previous randomized trial, GOG protocol 71, pelvic and intracavitary radiation therapy was compared to pelvic and intracavitary radiation at slightly lower doses followed by adjuvant hysterectomy. Preliminary data favored the progression-free interval for the patients who received the adjuvant hysterectomy. In the subsequent trial (GOG 123) radiation plus hysterectomy was compared to radiation therapy with concurrent chemotherapy plus hysterectomy (23). The radiation and chemotherapy arm had a statistically significant improvement in progression-free interval and survival. The survival rate with pelvic radiation and weekly cisplatin was 84% versus 68% with pelvic radiation alone. There was significantly less residual invasive cancer found at hysterectomy, in the group who received chemoradiation. Transient side effects including hematologic and GI toxicity were increased with chemoradiation. However, these resolved without serious sequelae. The conclusion of the authors was that chemotherapy and radiation should be the new standard for bulky cervical cancer. This was based on the fact that long-term follow-up of GOG protocol 71 demonstrated no improvement in survival with the use of adjuvant hysterectomy.

Lastly, for the subgroup of high risk patients—those with positive nodes—perimetrial extensions or positive margins in a randomized trial were conducted (Southwest Oncology Group protocol 8797/GOG 109), which compared radiation therapy with concurrent cisplatin and 5-FU chemotherapy (4 courses delivered every three weeks) with a control arm of radiation therapy alone (24). Over all, significant improvement in the progression-free interval and survival was seen by the addition of chemotherapy during radiation therapy. The survival rate was 81% cisplatin and 5-FU with pelvic radiation versus 63% with pelvic radiation alone. An interesting finding was that patients with adenocarcinoma who received radiation therapy did significantly worse than patients with squamous cell carcinoma who received radiation therapy. When chemotherapy was added to the regimen, however, there was marked improvement in survival for both histologies and no difference in the outcome between adenocarcinoma and squamous cell carcinoma. This study was also different in that chemotherapy was administered for two cycles during radiation therapy and for two cycles after radiation.

Collectively, these 5 trials all showed significant increase in survival, by an order of 30-50% (20–24) (Figure 1). Since this announcement a sixth large randomized trial was reported by the National Cancer Institute of Canada (NCIC) (30). This compared radiation therapy with weekly cisplatin with radiation therapy alone. While all outcomes slightly favored chemoradiation, these were not significantly different. The primary difference between this and the other trials was that it was a significantly smaller trial, and the confidence interval of the results were much larger. Large differences in improvement of up to 39% could be missed by a trial of this magnitude (31).

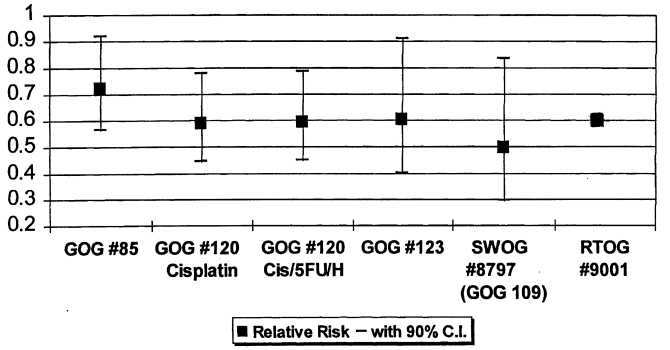

Figure 1 Relative risk estimate of survival from five chemoradiation clinical trials.

There were some important differences in this trial from the previous trials. The patients for this trial were evaluated only by abdominal/pelvic computerized tomography (CT) scans and excluded if paraaortic adenopathy was present. However, this modality has only a 34% sensitivity in detecting periaortic nodal metastasis in patients with locally advanced cervical cancer (32). Four of the 5 previous trials utilized surgical staging for some or all of the patients with locally advanced disease (20–22,24). This resulted in a better defined population of patients with disease limited to the pelvis. The only trial that did not use surgical staging used patients who had stage IB_2, where the likelihood of periaortic nodal metastasis was only 6% (23). It is estimated that 13% of the patients in the Canadian study had periaortic nodal metastasis which were not detected by CT scan imaging. By not excluding these patients, any benefit of localized therapy could be missed.

Anemia was also considerably more common in the cisplatin arm of the Canadian trial. Anemia, presumably as a result of greater tumor hypoxia, negatively impacts local control, disease-free survival, and overall survival for patients with cervical cancer undergoing radiation therapy (33). Grogan et al. in a large retrospective study reported statistically different 5-year survivals of 74%, 52%, and 45% for patients with average weekly hemoglobin levels $\geq$120 g/L, 110–119 g/L, and $<$110 g/L, respectively (33). Although information regarding transfusion was not prospectively collected, failure to correct this anemia may have accounted for an up to 10% decrement in survival for the chemoradiation arm (31).

The confidence interval of this sixth trial overlapped with the confidence interval of the pooled data from the 5 trials (31). It was the conclusion of the authors of the sixth trial that combined modality therapy with chemotherapy and radiation was probably beneficial. Furthermore, if one pools the data from all six trials, there remains a statistical risk reduction of 36% to the addition of chemoradiation (31) (Fig. 2).

The NCIC trial utilized an optimal schedule of radiation, 80 Gy delivered in a median of 51 days. The total treatment time has been increasingly recognized as having a profound impact on outcome (34,35). A total dose of 85 Gy to point A delivered in less than 56 days has been accepted as the optimal schedule (35). One of the criticisms of two of the trials in advanced stage cervical cancer (GOG 85 and GOG 120) is that the treatment times were "protracted" (20,22). Were the beneficial effects of radiation

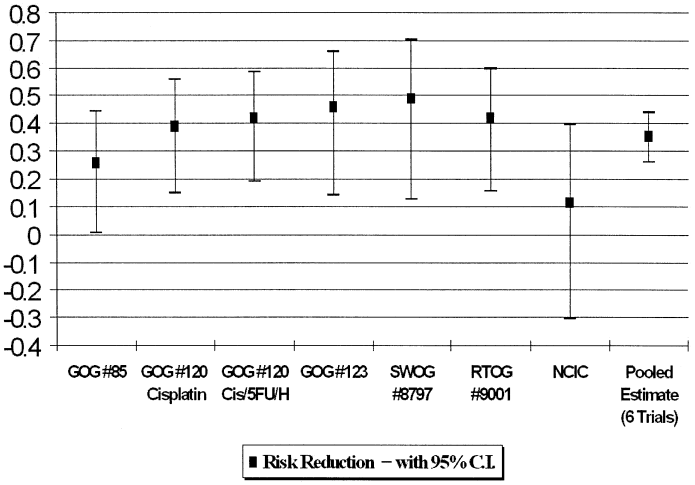

Figure 2 Reduction in the risk (1-rel. risk) of death from six chemoradiation clinical trials in cervical cancer.

only seen with suboptimal radiation dose and schedule? Both of these trials in question delivered 81 Gy, allowing up to 70 days for treatment; both trials had median treatment times of 63 days. The total treatment time in the arms of each study were the same, suggesting the benefit was the result of the intervention, cisplatin-based chemotherapy and not due to differences in treatment time. However, to further evaluate the significance of treatment time, patients in these trials were partitioned into those receiving optimal vs. protracted radiation (31). Optimal radiation therapy was defined as having received >85% of the prescribed dose without significant delay. The median treatment time for this cohort of optimal radiation patients was 57 days (range 39–65 days). Both optimal and protracted radiation treatment groups had similar risk reduction. Lastly, a significant benefit was seen in RTOG 9001 which utilized a more optimal radiation schedule (89 Gy in 58 days). Therefore, while

Table 2 Pelvis as Site of First Failure

	Cisplatin-based therapy		Non-cisplatin control	
	Total number	Number with pelvic failure	Total number	Number with pelvic failure
GOG 85	177	44	191	58
GOG 120	176	33	177	53
GOG 120	173	35		
RTOG 9001	193	37	193	68
GOG 123	183	29	186	73
SWOG 8797	127	11	116	20
NCIC	126	34	123	41
Total	1155	223(19.3%)	986	313(31.7%)

optimal radiation is desirable, this does not preclude benefit from concurrent cisplatin-based chemotherapy.

Prior studies have demonstrated an apparent improvement in local pelvic disease control (20–24). In the NCIC trial, a 6% difference in pelvic control (27% vs. 33%) was noted (31). This included one patient, randomized to chemotherapy and radiation, who refused all treatment. Despite including this patient, there was a 22% relative reduction in local recurrence with concurrent cisplatin chemotherapy and radiation in the Canadian trial. Furthermore, across all six studies a decrease in pelvic recurrence was noted (Table 2). Collectively, this represented a 12.4% decrease in the pelvis being the site of first failure (Odds Ratio 0.51 (95% CI .42–.63)). However, a potential flaw of this data set is that only the site of first failure was recorded in all six randomized studies, which does not exclude possible subsequent pelvic failure.

CONTROVERSIES

If we accept the benefit to the addition of concurrent cisplatin-based chemoradiation, a number of questions remain.

WHAT IS THE IDEAL PLATINUM DOSE AND SCHEDULE?

The ideal platinum dose and schedule has not been established clinically. Pre-clinical data suggest that the schedule and dose of platinum are critical. The data from Kalllman et al. suggest that if cisplatin is given as little as 6 hours after radiation, the therapeutic gain is negligable (36). Additionally, their data suggest that platinum given on a weekly schedule is as effective as a daily schedule and that, on a weekly schedule, a higher dose of platinum is more effective than a lower dose. Clinically, the doses of platinum utilized have been established to be tolerable. In lung cancer there are clinical data that the administration of cisplatin as a radiation sensitizer on a q three week schedule is less effective than a more frequent schedule (37).

WHAT IS THE ROLE OF OTHER AGENTS?

The use of multiple agents for chemoradiation in cervical cancer is historically based on the experience with radiation and chemotherapy with 5-FU and mitomycin C for anal carcinoma. When this regimen of 5-FU and mitomycin C was applied concurrently with radiation for cervical cancer significant responses were seen (38). However, in a retrospective analysis of patients who received chemoradiation for cervical cancer with 5-FU with or without mitomycin, Thomas et al. saw statistically a greater incidence of bowel complications in patients whose treatment included mitomycin C (39). Although discarded as an important agent due to concerns of increased toxicity, a recent randomized trial of radiation with mitomycin C vs. radiation alone demonstrated an improved four year disease free survival of 71% compared to 44% ($p = 0.01$) (40).

Byfield et al. demonstrated that in order for 5-FU to be effective as a radiation sensitizer, exposure must be maintained for at least 48 hours after radiation (41).

This has resulted in the development of prolonged infusion schedules of 96 and 120 hour. However, when tested as a single agent, 5-FU had only minimal and inconsistent radiation sensitization effects in cervical cancer. In a study by Thomas et al., in a four arm study, patients were randomized between daily- vs. twice-daily radiation therapy with or without 5-FU (42). The benefit of 5-FU radiation sensitization was only seen in patients with IB_2 tumors or IIB tumors involving only the unilateral perimetrium, but not for patients who had IIB disease involving the bilateral perimetrium or more extensive disease. Additionally, this benefit was only seen in patients who received daily but not twice daily radiation. Recently, to evaluate the role of continuous infusion 5-FU, a study comparing it to weekly platinum was conducted by the GOG. This study was closed on interim analysis when it was evident that the experimental arm, 5-FU infusion, had no likely chance of being superior to weekly platinum (31).

IS CHEMORADIATION EFFECTIVE IN ADVANCED STAGE DISEASE?

Questions regarding the efficacy of concurrent chemotherapy with radiation in advanced stage patients have been raised on the basis of two published studies (43). The first of these is the report by Thomas et al. that showed benefit only for early stage IB_2 tumors or IIB tumors involving only the unilateral perimetrium, but not for patients with more extensive disease (42). Additionally, in RTOG-9001, a survival benefit was reported only for patients with stage IB_2 and IIB but not patients with stage IIIB or IVA (21). This latter finding is felt to be due to the preliminary analyses and publication of these significant data (44). Although the trials by the GOG were not originally powered to allow substage analysis, in GOG-120 both stage IIB and IIB showed statistical benefit with the addition of concurrent chemotherapy. Therefore, on the basis of this evidence, concurrent cisplatin-based chemotherapy is advisable.

HOW SIGNIFICANT ARE THE ADDITIONAL COSTS?

An analysis of the five trials looking at costs demonstrated that the cost per treatment, cost per life saved, and cost per year of life saved was very reasonable with a cost per year of life saved ranging from $308–$3,712 (45). Weekly cisplatin outpatient administration was the least expensive.

WHAT IS THE ROLE OF ADJUVANT CHEMOTHERAPY FOLLOWING CHEMORADIATION?

To date no randomized trials have been designed to assess this question. Recently, Wong et al. reported the results of a randomized trial comparing radiation with concurrent epirubicin followed by five courses of adjuvant therapy with radiation alone (46). A significant survival benefit was seen with the addition of epirubicin leaving it unclear if this was the result or concurrent therapy, adjuvant therapy, or both. Adjuvant therapy is not supported by the preclinical data of Kallman et al., who

demonstrated no therapeutic gain when chemotherapy followed radiation therapy. In previous published clinical experience, the use of concurrent chemotherapy followed by adjuvant chemotherapy in patients with known metastatic disease has not improved cure rates (47). However, in SWOG 8797/GOG 109 patients who received 3-4 courses fared better than those receiving only 1-2 courses (24). Since the trial design called for 4 courses of therapy, this deviation may have resulted from numerous etiologies including poor performance status or greater non-compliance with both chemotherapy and radiation therapy.

CAN CHEMORADIATION BE UTILIZED WITH EXTENDED FIELD RADIATION?

Stehman et al. in a multivariate analysis of Gynecologic Oncology Group data, identified paraaortic nodal metastasis, as the most significant adverse prognostic factor in locally advanced cervical cancer (48). In patients with known paraaortic nodal metastases, curability with radiation therapy ranged from 25–50%, and depended in part on the extent of local pelvic tumor (49). However, the extent of paraaortic adenopathy was very significant with improved survival seen in patients with microscopic disease—presumably their disease was resected and the risk of more distant nodal metastasis decreased. Normal tissue tolerance, particularly the small bowel, limited the tolerable radiation therapy dose to 45 Gy. Efforts to exceed this radiation dose have resulted in significant and unacceptable toxicity (50).

The use of concurrent radiation therapy with extended field radiation has been studied for patients with known or at risk for paraaortic nodal metastasis. However, because of the greater amount of bone marrow irradiated with extended field radiation, myelosuppression was a more significant problem. In a study by the Gynecologic Oncology Group, the addition of hydroxyurea to extended field radiation therapy, there was unacceptable myelosuppression (51). Both the GOG and the RTOG have studied the use of cisplatin and 5-FU as a radiation sensitizer with extended field radiation therapy (52,53). The GOG study utilized daily radiation therapy, while the RTOG utilized twice daily radiation therapy. The use of twice daily radiation led to an apparent increase in gastrointestinal toxicity, with 31% versus 14% with daily radiation. Additionally, radiation therapy with weekly platinum has been studied with acceptable toxicity (54).

As demonstrated by Rotman et al. in an RTOG study, the use of extended field radiation therapy in locally advanced cervical cancer improved disease control over pelvic radiation therapy (29). Malfetano et al. reported the use of elective pelvic and paraaortic radiation with concurrent cisplatin for their patients with locally advanced disease (55). In their Phase II experience, a 75% survival and acceptable toxicity was reported. Positive emission tomography (PET) has also been studied for evaluating paraaortic nodal metastasis in patients with locally advanced disease (56). This is more sensitive than CT but is of limited availability and significant cost. Grigsby et al. recently reported that identification of paraaortic adenopathy by PET imaging accurately predicted long-term survival in patients with locally advanced cervical cancer (57). Whether extended field radiation therapy should be given routinely with concurrent chemotherapy, or whether this should be utilized only in patients who have disease detected by CT scan or other imaging modalities remains unresolved.

WHAT IMPROVEMENTS CAN BE MADE IN CISPLATIN-BASED CHEMORADIATION?

Anemia is common in patients with advanced cervical cancer and hemoglobin levels are prognostic of survival in patients undergoing radiation therapy (33). Anemia in cancer patients is associated with a blunted response to erythropoietin and erythropoietin levels are actually increased in patients with gynecologic cancer (58,59). The GOG is conducting a randomized trial of pelvic radiation therapy with concurrent weekly cisplatin chemotherapy with or without recombinant human erythropoietin to evaluate the incidence and significance of anemia during this therapy. However, this therapy may be significantly more costly, as much as four times as expensive, than transfusion (60).

Cytoprotection with glutathione has been utilized to increase cisplatin dose intensity in an effort to increase activity in an animal model and phase II trial (61). However, since glutathione increases cisplatin resistance in vitro, this raises a theoretical concern (62).

POTENTIAL NEW AGENTS

Until recently, for advanced and recurrent cervical cancer, no multiagent chemotherapy regimen was superior to single-agent cisplatin, although many were more toxic (63,64). However, a recent randomized trial demonstrated improvements in response rates and progression-free survival with the combination of cisplatin and paclitaxel compared to cisplatin alone (65). In addition to paclitaxel, a number of newer agents, including gemcitabine, topotecan, and tirapazamine, have demonstrated moderate activity in cervical cancer and/or have radiation-sensitization properties (66–68). Additionally, for each of these agents combination with cisplatin is tolerable and in some cases of metastatic disease apparently more active (69–71). In cervical cancer, Pattaranutaporn et al. studied the use of pelvic radiation therapy with gemcitabine 300 mg/m^2 weekly, with a 90% response rate (72). More recently phase I studies of weekly cisplatin and paclitaxel, gemcitabine or tirapazamine have been performed (73–75).

Carboplatin, while widely substituted for cisplatin in other areas of oncology, has not been as extensively studied as a radiation sensitizer in cervical cancer. A number of uncontrolled studies have looked at the use of carboplatin administered as a low-dose continuous infusion on a daily schedule for the first and fourth weeks of therapy (76–78). Studies of weekly schedules with carboplatin at an AUC = 2 are underway. The combination of carboplatin at an AUC of 2 and paclitaxel 90 mg/m^2/1 hr/week has been studied in a small number of patients with a 93% response (79). Evaluation of the role of these additional agents will require carefully planned randomized controlled clinical trials.

CONCLUSION

Due the limited radiocurability, based on dose limitations and normal tissue tolerance in the pelvis and in the paraaortic area, chemotherapy as an adjunct to radiation

therapy has emerged as a potential therapy for locally advanced cervical cancer. On the basis of carefully designed randomized clinical trials, the use of cisplatin-based chemotherapy has demonstrated persistent benefit in a large variety of clinical settings, and has been adopted as the new standard for women who require radiation therapy in the treatment of their cervical cancer. Experience with the use of chemotherapy with extended field radiation is increasing, but is not yet established on the basis of randomized trials. Numerous new agents are currently undergoing phase I development in combination with cisplatin.

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Chemotherapy for Recurrent and Advanced Cervical Cancer

Isabelle Cadron and Ignace Vergote
University Hospitals Leuven, Leuven, Belgium

ABSTRACT

Single-agent cisplatin remains the golden standard in the treatment of advanced or recurrent cervical carcinoma. However, other combination regimens have resulted in increased response rates compared with single-agent cisplatin, but no increased overall survival (OS) has been shown in phase III randomized trials. Future therapy will have to investigate the role of immunotherapy, gene therapy, and cellular therapy possibly in combination with chemotherapy.

INTRODUCTION

Cervical cancer is the second most frequent neoplasm worldwide and is the fourth most frequent cause of death from cancer in women. The widespread introduction of the Papanicolaou screening system has reduced the incidence and mortality of cervical carcinoma. This decline has mainly been confined to squamous cell carcinoma, which makes up to 85% of cervical cancers, whereas the incidence of nonsquamous cell carcinoma (adenocarcinoma, adenosquamous carcinoma, and small cell carcinoma), accounting for 10–15% of cervical carcinoma, is increasing (1). The improvement in overall survival reflects a trend toward early diagnosis rather than improvement in treatment because stage-specific 5-year survival rates remain unchanged.

Surgery and chemoradiation are the cornerstones of treatment of cervical cancer, but there remain a number of women with recurrent or advanced diseases or early-stage high-risk diseases who will not be cured with this approach. Treatment with cytotoxic agents can than be considered.

Chemotherapy has been limited for a long time to a palliative role in recurrent and advanced cervical cancer when surgery or irradiation is inappropriate or had failed. Response rates to chemotherapy in these settings are lower than when used as primary therapy. Recently, chemotherapy for cervical cancer has been used in several settings: neoadjuvant, concomitant, adjuvant, and second-line therapy.

This chapter will highlight the current use of chemotherapy for advanced and recurrent cervical cancer. First, we will discuss the current knowledge about treatment of advanced or recurrent cervical cancer. In the last part, we will discuss future topics for research and ongoing trials.

THE ROLE OF CHEMOTHERAPY IN RECURRENT AND ADVANCED CERVICAL CANCER

The optimal management of cervical cancer involves a careful assessment of the disease extent according to the "Fédération International de Gynécologie et Obstétrie" staging system (FIGO) for cervical cancer.

In consequence of this, we can divide advanced cervical cancers into two groups: locally advanced cancer (stages IIb–IVa) and metastatic disease (stage IVb).

The gold standard for locally advanced cervical cancer was, until recently, external and intracavitary radiotherapy. In February 1999, the U.S. National Cancer Institute (NCI) stated that concomitant chemotherapy and radiotherapy should be considered for all patients with cervical cancer. This announcement was based on the results of five large American randomized trials, which involved 1894 women with a wide variety of disease stages of cervical cancer in which radiation therapy was to be used (2–6). The results have been questioned by a Canadian NCI-sponsored trial (7). A meta-analysis reported by Green et al. (8), however, showed a potential absolute survival benefit of 12% attributable to the use of chemoradiotherapy. For more details, we refer to the chapter on concomitant chemotherapy.

Patients who have recurrent diseases or pelvic metastases have a poor prognosis, with a 1-year survival rate between 15% and 20% (9). Chemotherapy has a palliative role in patients with metastatic disease at presentation or recurrent disease following primary local treatment for whom salvage procedures, surgery, and/or irradiation are inappropriate or have failed. Since the mid-1970s, many of cytotoxic agents, alone and in combination, have been evaluated. The problem with chemotherapy in this setting is that there are several considerations to take into account. First, the blood supply to the tumor is impaired because it is postoperative or postradiotherapy. Second, for some patients, the bone marrow reserve decreases substantially after pelvic radiotherapy, resulting in increased bone marrow toxicity of dose-intensive cytotoxic chemotherapy. Third, recurrent and metastatic cervical cancer is frequently combined with poor renal function due to ureteral obstruction, with decreasing elimination of cytotoxic drugs that are excreted by the kidneys and an increasing effect of nephrotoxic drugs. Fourth, there is the likelihood that those recurrent or persistent foci of cancer are more resistant to chemotherapy. In function of previous irradiation, most investigators found that extrapelvic sites are much more responsive to chemotherapy than pelvic foci (10). Other important factors that can influence the disease outcome are: age, performance status, histology of cancer, duration of disease-free survival, the presence of a single lesion at recurrence, and primary treatment (risk of chemotherapy resistance) (11).

Cervical adenocarcinoma is histologically an uncommon type of cervical cancer with a worse prognosis and a greater recurrence rate compared with squamous cell carcinoma. Recurrent cervical adenocarcinoma has a poor outcome due to its lower radiosensitivity and chemosensitivity. Due to its rarity, randomized clinical trials about chemotherapy for adenocarcinoma are scarce.

Review of the literature shows an array of cytotoxic agents, combinations, doses, and response rates active for cervical cancer. During the past 25 years, both single-agent and combination chemotherapy have been used to treat patients in an attempt to improve survival.

As a consequence of current strategies for the treatment of high-risk early cervical cancer and locally advanced tumors, which more often include chemotherapy given concurrently with radiation or in neoadjuvant setting, the population of patients with adjuvant or recurrent cervical cancer who have not received prior chemotherapy becomes smaller. This makes it more difficult to enroll patients for the assessment of the efficiency of new chemotherapeutic regimens.

Single-Agent Chemotherapy

Cisplatinum is now considered as the most active single drug. Initial Gynecologic Oncology Group (GOG) data suggest that this agent produces objective responsive rates (RRs) of 50% in chemo-naïve women (dose, 50 mg/m^2) (12). A trial reported by Bonomi et al. (9) in 1985 involving 444 women revealed a response rate of 20–30% and complete remission (CR) occurred in only 10% of the cases. Although there appears to be a small but statistically significant increase in the RR with a doubling of the dose to 100 mg/m^2, this has not resulted in a detectable improvement in the rates of progression-free interval (PFI) or OS. Still, the duration of the objective responses with cisplatin remains disappointing, namely 4–6 months and an OS of 7 months. With other single-agent regimes, RRs have been reported to be in the range of 10–20%, but very few patients attain CR (13,14). Among the single agents with reported activity against cervical cancer are: methotrexate, 5-fluorouracil, vinca-alkaloids, mitomycin C, bleomycin, porfiromycin, epirubicin, doxorubicin (adriamycin), ifosfamide, cyclophosphamide, chlorambucil, melphalan, hexamethylamine, and dacarbazine (Table 1). Their activity is defined as an RR of $\geq$15%.

Other platinum regimens such as carboplatinum and iproplatinum showed an RR of 15% and 11%, respectively (42,43). Although their toxicity is less than with cisplatin, these compounds seem to be less active.

Ifosfamide, an alkylating agent, has produced RRs ranging from 14% to 33%, with a mild to moderate toxicity profile (27,36,37). Even in platinum-treated patients, the drug seems to be effective with an RR of 11% (47).

Regarding vinca-alkaloids, different results arise. Data on vincristine have been controversial (34,48,49) and data on vinblastine were disappointing, with an RR of 10% (35). Vindesine, a microtubule inhibitor that has shown anti-invasive and antimetastatic activity, showed more promising results, but the limiting factor was toxicity with leucopenia, and peripheral neuropathy was the most important criterion (19,24). One of the advantages of vindesine is that some studies suggest that it would be cleared from the plasma by an extrarenal mechanism. Drugs whose activity and toxicity are not compromised by renal function are of extreme importance because of frequent ureteral obstruction with cervical carcinoma (19). Vinorelbine, a semi-synthetic derivate of vinblastine with possible noncross resistance with other vinca-alkaloids, seems to have a comparable moderate activity and is better tolerated (23).

Paclitaxel is a natural product found in the bark of the western yew tree. It promotes assembly of microtubules and stabilizes them, preventing depolymerization, which in turn prevents cellular replication. Paclitaxel seems to be very active in

Table 1 Single-Agent Chemotherapy in Cervical Cancer

Drugs	Dose	PN (*n*)	RR (%)	PR (*n*)	CR (*n*)	MS (months)	PFI (months)	Reference
Alkylating agents								
Cisplatin	50 mg/m^2/3 weeks	25	44	8	3	4.5	2	(12)
	50 mg/m^2/3 weeks	150	21	16	15	7.1	3.7	(9)
	100 mg/m^2/3 weeks	166	31	31	21	7.0	4.6	(9)
	20 mg/m^2/3 weeks, days 1–5	128	25	21	11	6.1	3.9	(9)
Carboplatin	50 mg/m^2/3 weeks	454	18			—	3.2	(22)
	400 mg/m^2/4 weeks	175	15	17	10	6.2	2.7	(42)
Iproplatin	270 mg/m^2/4 weeks	177	11	12	7	5.5	3	(42)
Ifosfamide			33					(27)
	5 g/m^2/24 hr, iv, day 1	30	33	9	1	—	—	(91)
	1.5 g/m^2, iv, days 1–5	27	11	3	0	—	2.4	(37)
Cyclophosphamide	8 mg/kg/day, iv/4–6 weeks	76	20	15		—	—	(92)
Chlorambucil	0.2 mg/kg/day	26	27	6	1	—	—	(96)
Melphalan	1 mg/kg, iv/3 weeks or 0.2 mg/kg/day/4 weeks	20	20	4		—	—	(92)
CCNU	100–130 mg/m^2, po/6 weeks	5	20	1		—	—	(15)
Methyl-CCNU	220–225 mg/m^2, po/6 weeks	32	13	4		—	—	(15)
Antibiotics								
Adriamycin/ doxorubicin	60 mg/m^2, iv/3 weeks	18	39	6	1	—	—	(31)
4′-Epidoxorubicin	12.5 mg/m^2, iv/week	24	4	1	0	—	3.25	(20)
Bleomycin	15 mg/m^2	78	10	8		—	—	(15)
Mitomycin C	0.5 mg/kg/day, iv	18	22	4		—	—	(95)

Porfiromycin	7.5–10.5 mg/m^2	34	26	8	1	—	—	(15)
Piperazinedione	9 mg/m^2, iv/3 weeks	14	14	0	2	2	—	(39)
Epirubicin		23	36					(85)
Anti-metabolites								
5-FU	7.5–15 mg/kg/d iv	80	16	13		—	—	(93)
Methotrexate	60 mg/m^2 im/3 weeks	12	50	5	1	—	—	(31)
	500 mg-4g iv	7	29	2	0	—	—	
Hydroxyurea	40 mg/kg/d po	10	0	0		—	—	(15)
Plant Alkaloids								
Vindesine	2 mg/m^2 iv dl-2/ weeks	20	30	6	0	7	6.5	(19)
Vinorelbine	30 mg/m^2/20 hr/week	41	17	7	0	—	5	(23)
Vincrisine	50–75 μg/kg, iv/week	31	29	9		—	—	(49)
Vinblastine	1.4 mg/m^2/24 hr, days 1–5	20	10	2	0	—	—	(35)
Taxoids								
Paclitaxel	170 mg/m^2/24 hr, iv/3 weeks	52	17	7	2	—	—	(25)
	170 mg/m^2/24 hr, iv/3 weeks	42	31	9	4	—	4.8	(41)
Other								
Irinotecan	125 mg/m^2/90 hr, iv/week	42	21	8	1	6.4	3	(21)
Hexamethylamine	12 mg/kg/day	21	38	8		—	3.5	(94)
DTIC (dacarbazine)	Not given	12	25	3		—	—	(15)
Topotecan	1.5 mg/m^2, iv, days 1–5/ 4 weeks	43	19	5	3	—	2.4	(88)

PN = patient number; RR = response rate; PR = partial response; CR = complete response; MS = median survival; PFI = progression-free interval.

nonsquamous cell carcinoma of the cervix, with an RR of 31% in comparison with 17% for squamous cell cancer (25,41). This consideration has led to the development, by the GOG, of a randomized phase II trial comparing cisplatin with paclitaxel to cisplatin alone (see below) (73).

Dibromodulcitol acts as an alkylating agent with a reported RR of 29%, but, unfortunately, there is evidence of an association of this agent with the development of leukemia (38). Topotecan, a camptothecin derivate, is one of the newest agents and inhibits topoisomerase I, which may affect DNA function and synthesis (88). Irinotecan has a similar RR supporting the activity of topoisomerase I inhibitors (21).

Further studies will be necessary to identify new drugs with a high degree of activity.

Combination Chemotherapy

Numerous combinations of the reported active single chemotherapeutic agents have been used in an effort to improve RR and OS. Comparison of these studies is difficult because of a relatively small number of patients, inclusion of all histological types of cervical cancer, dose and scheme differences, and inclusion of patients with different prior therapies.

Several combinations have shown an increased RR in comparison with single-agent drugs, but as the toxicity profile increased also, OS remained equal and responses were mostly short in duration (Table 2).

Phase I and Phase II Trials

BMP Remarkable RRs were seen with the BMP regimen (bleomycin, methotrexate, and cisplatin), with an RR of 89% (51). The limiting factor was the dose of methotrexate causing nephrotoxicity. In answer to this, the same regimen with leucovorin was tested. Toxicity diminished to a great extent, but it had also a delirious effect on antitumor activity, with a decrease of RR to 53% and no benefit in survival (52).

In 1994, Chambers et al. (62) used an alternating regimen consisting of BMP–PFU. The RR was 35% (30.4% for those with recurrent disease and 41.2% for those with advanced disease), with 63.4% of responders having a CR (86% and 42.9%, respectively). Furthermore, this regimen was very well tolerated and 67% of patients achieved relief of pain. This study included 48 patients, of which only 40 were evaluable for response.

BVMiP or BOMiP (Bleomycin–Oncovin or Vincristine–Mitomycin C–Cisplatin) Vogl et al. (53) was the first to use the BOMiP regimen. They reported an RR of 78% and a median duration of response of 4 months. Chambers et al. (60) published an RR of 48% with the same regimen and also a median duration of response of 4 months because of pulmonary toxicity due to bleomycin and mitomycin C. In this study, they included not only patients with cervical cancer but also patients with cancer of the vulva and ovaries. Looking at the patients with cervical cancer only gave an RR of 40%. In 1987, the Southwest Oncology Group (SWOG) performed a randomized trial comparing cisplatin vs. cisplatin and mitomycin C vs. BVMiP (see below).

Vermorken et al. (74) also studied the BVMiP regimen, reporting an RR of 40% with 16% CR. Patients with only distant metastases had an RR of 54%, of which 31%

was CR, and patients with pelvic disease had an RR of 25%, of which all were partial. OS was 9.7 and 7.4 months, respectively. This suggests that patients with distant metastases only respond better than those with locoregional disease. However, most patients received prior radiotherapy. The results of Vermorken et al. have been corroborated by a phase II study performed by Wagenaar et al. (50) using mitomycin C and cisplatin. The RR was 42% with an OS of 11.2 months. These data suggest that the regimen has antitumor activity, but also that it is not superior to cisplatin only in terms of survival.

Vermorken et al. also conducted a randomized trial comparing BEMiP (bleomycin–vindesine (eldisine)–mitomycin C–cisplatin) with cisplatin only (see below).

5-FU Another combination deserving our attention is cisplatin + 5-FU, which has been reported to have an RR of 50% (11,61). A GOG trial shows only an RR of 22% in patients who received prior irradiation, which is identical to cisplatin only.

BIP–BIC BIP (bleomycin–ifosfamide–cisplatin) is a regimen that has been studied by different investigators, with RR ranging from 15% to 69%. Comparing the studies of Ramm et al. (58) and Blackledge et al. (27), we see that the only difference in admission is the duration of bleomycin infusion. Further studies, however, show no correlation between duration of bleomycin infusion and RR (77,81). Kumar and Bhargav (59), with a reported RR of 67%, gave a lower dose of bleomycin and divided the total dose of ifosfamide over 5 days. Buxton et al. (64) used the same schedule as Blackledge et al., and also had an RR of 69%. However, RR evaluation in previously irradiated tissues is extremely difficult, so instead of RR, it is preferable to look at OS. We see than that there is no difference among the four studies, with an OS ranging from 9 to 10.2 months.

Later, Murad et al. (65) substituted cisplatin of the BIP regimen with carboplatin. The dose of ifosfamide was augmented to 6 g/m^2 over 3 days. The RR was 60%, with 37% CR and a higher response in nonpreviously irradiated patients. Sixty-eight percent of the patients who used opioids before chemotherapy stopped using analgesics. The median OS for all patients was 11 months. Thus RR and OS are similar compared with the BIP regimen.

A Japanese study examined the combination of 254-S (a cisplatin analogue with less nephrotoxicity), ifosfamide, and peplomycin (a bleomycin analogue with an improved pulmonary toxicity profile) showing an RR of 83% in previously untreated patients and 61% in patients with recurrent disease. The dose-limiting factor was pulmonary toxicity (67).

Doxorubicin (Adriamycine) CAP (cyclophosphamide–adriamycin–cisplatin) combination did not prove to be more effective than single-agent cisplatin, with RR ranging from 10% to 20% with no survival or PFI benefit (55–57).

Paclitaxel The promising results with paclitaxel in phase I studies have led Zanetta et al. (72) to use the combination of paclitaxel, ifosfamide, and cisplatin (TIP). The RR was 67% (52% in patients who received prior radiotherapy and 75% in irradiation-naïve patients) and OS was, again, comparable to other studies (9.3 months).

The GOG also conducted a phase II study of paclitaxel and cisplatin as first-line therapy, with an RR of 46% (73). Because of this enhanced therapeutic benefit, the GOG performed a phase III trial comparing cisplatin only vs. cisplatin with paclitaxel. The preliminary results did not show any survival benefit for the combination regimen (75).

Table 2 Combination Chemotherapy in Cervical Cancer

Drugs	Dose	PN	RR (%)	PR (*n*)	CR (*n*)	MS (months)	PFI (months)	Reference
M + P	M: 100 mg/m^2, iv, day 3 P: 20 mg/m^2, iv, days 1–3	37	57	16	5	9	15	(32)
M + DX	M: 20 mg/m^2, iv, days 1 and 8/3 weeks DX: 50 mg/m^2, iv, day 1/3 weeks	9	89	2	6	4.8	—	(86)
BMV	B: 15 mg, iv/im, day 1 M: 10 mg/m^2, po, day 1 V: 1.5 mg/m^2, iv, day 1	17	53	8	1	8	2.5	(87)
BMP	B:10 U, im, days 1, 8, and 15 M: 40 mg/m^2, im, days 1 and 15 P: 50 mg/m^2, iv, day 4/3-weekly	9	89	8	0	8	4	(51)
BMP + L	L: 15 mg/m^2, im, 24 and 48 hr after M[a]	19	53	10	0	9	4	(52)
BMP–PFU	B: 10 U/m^2, iv, days 3–6 M: 150 mg/m^2, iv, days 15 and 22 + leucovorin P: 80 mg/m^2, iv, day 1 Alternated with: P: 100 mg/m^2, iv, day 1 5-FU: 1 g/m^2, iv, days 2–5, 4-weekly	40	35	5	9	11	10.5	(62)
BVMiP/BOMiP	B: 10 U, im, day 1/week O: 1 mg/m^2, iv, days 1, 8, 22, and 29 Mi: 10 mg/m^2, iv, day 1 P: 50 mg/m^2, iv, days 1 and 22, 6-weekly	13	77	7	3	8	4	(53)
	B: 30 U, iv, days 1–4[a] V: 0.5 mg/m^2, iv, days 1 and 4 Mi: on day 2	14	43	2	4	9	—	(54)
	B: 10 U, iv, day 1/week[a]	20	40	4	4	6 (for responders)	4	(60)

	B: 15 mg/d /48 hr, iv, days 1 and 2 (stop after cum dose of 300 mg) V: 1.4 mg/m^2, iv bolus, day 1 Mi: 6 mg/m^2, iv bolus, day 3 P: 50 mg/m^{2}3–4 hr, day 4, 4–weekly	50	40	12	8	9.25	5	(74)
Mi + P	Mi: 6 mg/m^2, iv, day 1 P: 50 mg/m^2, iv, day 1, 4-weekly	33	42	9	5	11.2	5 (10.5 for responders)	(50)
5-FU + P	5-FU: 1 g/m^2, iv, days 1–5 P: 100 mg/m^2, iv, day 1, 3-weekly	32	47	11	4	—	—	(11)
5-FU + DX + V + CTX	5-FU: 500 mg/m^2, iv, days 1 and 8 DX: 45 mg/m^2, iv, day 1 V: 1.4 mg/m^2, days 1 and 8 CTX: 100 mg/m^2, po, days 1–14, 4-weekly	31	58	14	4	13.5 (for CR)	—	(80)
BIP	B: 30 mg/m^2, iv/1 hr I: 5 g/m^2, iv/24 hr P: 50 mg/m^2, iv/2 hr, 4-weekly	20	15	3	0	9	4	(58)
	B: 30 mg/m^2, iv/24 hr[a]		69			9		(27)
	B: 15 mg iv bolus day 1 I: 1 g/m^2, days 1–5/2 hr, 3-weekly	21	67	10	4	—	—	(59)
	B: 30 mg/m^2, iv/24 hr, 3-weekly[a]	49	69	24	10	10.2	8.4	(64)
BIC	B: 30 mg/m^2, iv bolus, day 1 I: 2 g/m^2, iv/2 hr, days 1–3 C: 200 mg/m^2, iv bolus, day 1, 4-weekly	35	60	13	8	11	14	(65)
254-S + I + Pm	254-S: 80–100 mg/m^2, iv, day 1 I: 1.5 g/m^2, days 1–5 Pm: 5 mg, im, days 1–6	60	75	42	3	—	—	(67)
CTXAP	CTX: 600 mg/m^2, iv bolus A: 40 mg/m^2, iv bolus P: 50 mg/m^2, iv, 4-weekly	30	10	3	0	—	5.3	(55)
	CTX: 400 mg/m^2, iv bolus[a] P: 40 mg/m^2, iv/6 hr, 3-weekly	20	20	3	1	—	—	(56)

Table 2 Continued

Drugs	Dose	PN	RR (%)	PR (*n*)	CR (*n*)	MS (months)	PFI (months)	Reference
DX + MeCCNU	DX: 60 mg/m^2, iv, day 1/3 weeks; 45 mg/m^2, IV, day 21 MeCCNU:175 mg/m^2, po, day 1/3 weeks	31	45	5	9	9	—	(79)
B + P	B: 20 U/m^2, iv, days 1–3 P: 60 mg/m^2/2hr, day 1	42	38	16	16	—	—	(78)
Pe + P	Pe: 9 × 1600 mg, po/8 hr, start 1 hr before P P: 75 mg/m^2, 3-weekly	40	10	3	1	—	4.3	(70)
T + P	T: 135 mg/m^2/24 hr P: 75 mg/m^2/24 hr, 3-weekly	41	46	14	5	10	5.4	(73)
TIP	T: 175 mg/m^2/3 hr, day 1 I: 5 g/m^2, iv/24 hr, day 3 P: 50 (75) mg/m^2/60 hr, iv, day 2, 3-weekly	45	67	15	15	9.3	—	(72)
CPT-11 + P	CPT-11: 60 mg/m^2, iv/90 hr, days 1, 8, and 15 P: 60 mg/m^2, iv/90 hr, day 1, 4-weekly	10	60	4	2	—	—	(71)

PN = patient number; RR = response rate; PR = partial response; CR = complete response; MS = median survival; PFI = progression-free interval. P = cisplatin; Mi = mitomycin C; M = methotrexate, DX = doxorubicin; B = bleomycin; T = paclitaxel; V = vincristine; CTX = cyclophosphamide; I = ifosfamide; C = carboplatinum; CPT-11 = irinotecan; L = leucovorin; O = oncovin; A = adriamycin; Pe = pentoxifylline; Pm = peplomycin.

[a] If several investigators used the same regimen, only differences from the first scheme are given.

Irinotecan Sugiyama et al. conducted a phase II trial evaluating the efficacy and toxicity of irinotecan and cisplatin. Twenty-nine patients were included, of which 19 patients received the combination chemotherapy in neoadjuvant setting. Ten patients received the chemotherapy until disease progression, until unacceptable toxicity appeared, or until the patient desired to discontinue the therapy. They reported a median survival of 27.7 months, but this included patients in both settings. The RR for the group that received only chemotherapy was 60%; the OS of this group was not given. The most import factor regarding toxicity was a significant degree of myelosuppression (71). A randomized trial comparing this regimen with cisplatin only is necessary before making any firm conclusions.

New Drugs Despite the promising results of a phase I trial with pentoxifylline (RR of 46%), a phase II trial in combination with cisplatin was disappointing, with an RR of 10% only (70).

In the drug combinations without cisplatin, the RR varied but OS was not better than with the cisplatin-only regimen. However, the study performed by Guthrie and Way, using doxorubicin and methotrexate, suggested a survival benefit. Unfortunately, other investigators could not achieve this level of activity in comparable studies.

Phase III Randomized Trials

Recently, the European Organization of Research and Treatment of Cancer (EORTC) and the GOG conducted some phase III trials comparing the effectiveness of a combined regimen with the current standard of therapy, cisplatin only (Table 3).

A randomized trial performed by Omura et al. (22) compared cisplatin vs. cisplatin and mitolactol vs. cisplatin and ifosfamide. This showed an increase in RR and PFI in favor of the cisplatin–ifosfamide combination, but survival remains equal. Although toxicity increases in combination with ifosfamide, it is the first combination that shows an increase of PFI in comparison with cisplatin only.

A comparison of BEMiP (bleomycin–vindesine–mitomycin C–cisplatin) vs. cisplatin (66,76) showed a higher RR for BEMiP, but hematological toxicity increased and overall survival and PFI were similar.

A randomized trial, performed by the SWOG, compared BVMiP with cisplatin plus mitomycin vs. cisplatin only, showing no advantage of the combination regimen over cisplatin only. In contrast, with increasing drug combination, toxicity also increased (77).

The GOG also performed a randomized trial comparing cisplatin and ifosfamide vs. BIP (bleomycin–ifosfamide–cisplatin). An analysis of these data is in progress.

In conclusion, combination regimens increase the RR, although OS and PFI remain similar compared with single-agent cisplatin.

Intra-Arterial Chemotherapy

Intra-arterial drug administration has been studied in a variety of diseases including cervical cancer. These experimental approaches may achieve higher response rates but have not yet demonstrated an improvement in long-term survival. Complications reported include arterial thrombosis, wound problems, lymphedema, and osteonecrosis caused by the sharing of blood supply between the tumor and neighboring normal tissues (84).

Table 3 Randomized Studies of Combination Chemotherapy vs. Single-Agent Chemotherapy

Protocol	Drugs	Dose	PN	RR (%)	PR (*n*)	CR (*n*)	MS (months)	PFI (months)	Reference
EORTC 55863	P	P: 50 mg/m^2/3–4 hr, day 1/3 weeks	144	19	—	—	9.4	4.7	(76)
	vs.								
	BEMP	B:15 mg/m^2/72 hr, days 2–4 E: 3 mg/m^2, iv, days 1 and 8 M: 8 mg/m^2, iv, day 5 P: 50 mg/m^2/3–4 hr, day 1, 3-weekly	143	31	—	—	10	5.4	
SWOG 7936	P	P: 50 mg/m^2, iv/3 weeks	9	33	2	1	7	7.3	(77)
	vs.								
	P–Mi	P: 50 mg/m^2, iv, day 1/3 weeks Mi: 12 mg/m^2, iv, day 1/6 weeks	51	25	11	2	7	7.2	
	vs.								
	BVMiP	B: 30 mg, iv/24 hr, days 1–4 V: 0.5 mg/m^2, iv, days 2 and 4 Mi: 10 mg/m^2, iv, day 2 P: 50 mg/m^2, iv, days 1 and 22, 6-weekly	54	22	8	4	6.9	5.4	
SEG 264	DX-V–5-FU	DX: 50 mg/m^2, iv, day 1/3 weeks V: 1.4 mg/m^2, iv, days 1 and 8/3 weeks 5-FU: 500 mg/m^2, iv, days 1 and 8/3 weeks	31	10	2	1	7		(16)
	vs.								
	CTX	CTX: 1.1 g/m^2, iv, day 1/3 weeks	30	7	2	0	6		

GOG 110	P	P: 50 mg/m^2, iv/3 weeks	140	17.8	16	9	8	5.5	(22)
	vs.								
	P–Ml	P: 50 mg/m^2, iv, day 1 M: 180 mg/m^2, po, days 2–6, 3-weekly	147	21.1	17	14	7.3	7.7	
	vs.								
	P–I	P: 50 mg/m^2, iv, day 1 I: 5 g/m^2/24 hr, iv, day 1, 3-weekly	151	31.1	28	19	8.3	10	
GOG	DX	DX: 60 mg/m^2, iv/3 weeks	61	10	1	5	5.9	3.3	(18)
	vs.								
	DX–V	DX: 60 mg/m^2, iv/3 weeks V: 1.5 mg/m^2, iv/3 weeks	61	5	3	0	5.5	3.4	
	vs.								
	DX–CTX	DX: 50 mg/m^2, iv/3 weeks CTX: 500 mg/m^2, iv/3 weekly	52	6	1	2	7.3	3.9	
GOG 149	P–I	P: 50 mg/m^2/1 hr, iv, day 1 I: 5 g/m^2/24 hr, iv, day 1	Results not yet analyzed						
	vs.								
	BIP	B: 30 U/24 hr, iv, day 1 I: 5 g/m^2/24 hr, day 2 P: 50 mg/m^2/1hr, iv, day 2, 3-weekly							
GOG 169	P	P: 50 mg/m^2, day 1	Results not yet analyzed						(75)
	vs.								
	P–T	P: 50 mg/m^2, day 1 T: 135 mg/m^2/24 hr, day 1, 3-weekly							

PN = patient number; RR = response rate; PR = partial response; CR = complete response; MS = median survival; PFI = progression-free interval. P = cisplatin; I = ifosfamide; Mi = mitomycin C; T = paclitaxel; CTX = cyclophosphamide; DX = doxorubicin; V = vincristine; 5-FU = 5-fluorouracil; M = methotrexate; H = hydroxyurea; Ml = mitolactol.

FUTURE DIRECTIONS

The goals of any new cervical cancer chemotherapy protocol should include a decrease in toxicity of the combination regimen, palliation of symptoms with a concomitant improvement in quality of life, better distant and local control of disease, and prolongation of survival.

Future therapy will make use of immunological methods, gene therapy, and cellular therapy, possibly in combination with chemotherapy.

The current ongoing trials are searching for new active drugs and are testing known active regimens in phase III trials by comparing them with cisplatin only.

Some of the products that are being tested at this moment in phase II trials are gemcitabine (an antimetabolite) for NSSC, gemcitabine + cisplatin, topotecan + paclitaxel, capecitabine (an oral prodrug of 5-FU), antineoplastons A10 and AS 2-1 (inhibit cancer cell growth by arresting the cell cycle in the G1 phase and by reducing mitosis), arsenic trioxide (inhibit growth and induce apoptosis), bevacizumab (an anti-VEGF monoclonal antibody), DX-8951 (a novel camptothecin analog), SU 5416 (a receptor tyrosine kinase inhibitor), and bryostatin I (a protein kinase C inhibitor) + cisplatin.

One of the directions in the treatment of cervical cancer that is getting more attention is vaccination. Several institutions are performing phase II studies in patients with advanced or recurrent cervical cancer receiving vaccination with human papilloma virus 16 (HPV-16) peptides in order to stabilize the disease.

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Vulvar Cancer

Pierluigi Benedetti Panici and Filippo Bellati
University of Rome Campus Bio-Medico, Rome, Italy

Raimund Winter
University of Graz, Graz, Austria

INTRODUCTION

Vulvar cancer is a rare disease that usually involves the elderly. Even if tumors of the vulva arise in readily visible external body surfaces and frequently produce symptoms, delay in diagnosis is unfortunately still frequent. Historically, the treatment of this cancer has been extremely aggressive and therefore associated with a high rate of physical and psychological morbidity. During the past 20 years, improvement in the comprehension of this pathology has allowed the tailoring of treatment to the situation.

EPIDEMIOLOGY

Vulvar cancer is a relatively rare tumor. It accounts for 1% of all female cancers and 5% of all genital malignancies (1). In developed countries, it is the fourth gynecological malignancy after endometrial, ovarian, and cervical cancers. In the United States, 500 new cases are diagnosed and 500 deaths occur annually (2). Survival by stage is reported in Fig. 1. The classification of vulvar disease is reported in Table 1 (3a). Between 80% and 90% of vulvar malignancies are squamous cell carcinomas (3b). These can be divided into three distinct histological subtypes: basaloid carcinomas, warty carcinomas, and keratizing squamous carcinomas (4). Other malignancies that are rarely encountered on the vulva are melanoma, carcinoma of the Bartholin gland, Paget disease, basal cell carcinoma, soft tissue sarcoma, and malignant schwannoma (3). Due to the low frequency of these histotypes, in the following paragraph, we are going to discuss squamous cell carcinomas. More than 70% of vulvar cancers occur in patients above 60 years old, with a peak incidence between 70 and 80 years old (5). Probably due to the increase in female life expectancy, overall incidence has increased from approximately 5% in the 1960s to approximately 8% today (6). In recent years, there has been a trend for multifocal lesions associated with vulvar intraepithelial neoplasia (VIN) in younger premenopausal patients (7) and pregnant women (8).

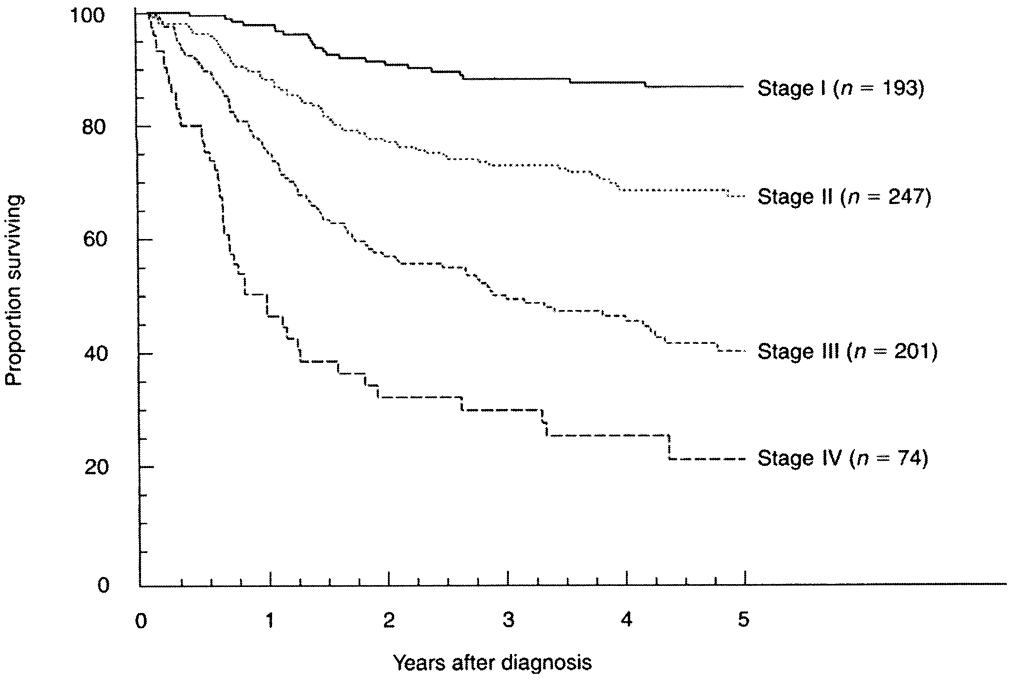

Figure 1 Epidermoid invasive cancer of the vulva: survival by FIGO stage ($n = 715$). (From Ref. 5.)

Many risk factors are in common with cervical cancer. These are smoking, higher number of sexual partners, previous genital warts, granulomatous infection, and human papillomavirus (HPV) infection (6,9). Patients who smoke and have a history of genital warts exhibit a 35-fold increase in the risk of carcinoma in situ and subsequent invasive carcinoma (9). Lichen sclerosus areas can be described in up to 30% of invasive squamous carcinoma specimens (10). HPV 16 DNA can be isolated in

Table 1 Classification of Vulvar Disease[a]

Neoplastic epithelial disorders
Intraepithelial neoplasia
VIN 1
VIN 2
VIN 3
Nonsquamous intraepithelial neoplasia
Paget's disease
Tumors of melanocytes (non invasive)
Invasive tumors

[a] Committee on Terminology, International Society for the Study of Vulvar Disease. Int. J. Gynecol Pathol 1989; 8:83.

70–80% of intraepithelial lesions and 10–60% of invasive lesions. (4,11,12). Association with HPV 6 and HPV 33 has also been identified (4,13). Other important risk factors are immunosuppression related to human immunodeficiency virus (HIV) infections or transplant medications and prior, concurrent, or subsequent neoplasia of the vagina and cervix (14). There is no evidence for the association with hypertension, diabetes, or obesity, which had been considered in the past (9,15,16). On the basis of a large epidemic, pathological, and virological analysis, it has been suggested that vulvar squamous cell carcinoma has two different etiologies (17). Two subtypes, basaloid and warty carcinomas, are associated with HPV (mostly HPV 16), whereas keratizing squamous carcinoma is not. As expected, basaloid and warty carcinomas are significantly associated with classical cervical cancer risk factors, whereas in keratizing squamous carcinoma, this link is less strong.

The prognosis of VIN differs fundamentally from that of cervical intraepithelial neoplasia (CIN). The risk of progression in young patients with HPV-associated VIN III (warty type) is 3–4% (18). In contrast, older women with VIN III have an approximately 19% risk of progression (19).

CLINICAL PRESENTATION

Common symptoms of VIN and invasive disease are pruritus, irritation, mass, pain, bleeding , ulceration, dysuria, and vaginal discharge (20,21). A biopsy is required in the presence of any vulvar lesion with warty appearance. Multifocal disease may cause difficulty in diagnosis; therefore, in these cases, it is advisable to directly perform a colposcopy (22).

PATTERNS OF SPREAD

Vulvar carcinoma has a propensity to remain locally confined (14). Most squamous carcinomas of the vulva occur on the labia majora and minora (60%), but the clitoris (15%) and perineum (10%) also may be primary sites. Approximately 10% of the cases are too extensive to determine a site of origin, and about 5% of the cases are multifocal (23).

Spread may occur through embolization to regional lymph nodes, direct extension to adjacent structures, or by the hematogenous route (6). The most frequent metastasis is to superficial inguinal nodes between Camper's fascia and fascia lata (1). From this point, the disease usually spreads to the femoral nodes. The most cephalad of the femoral node group is called Cloquet's node. The last lymph node station that can clearly be identified is the pelvic lymph node. Direct metastasis to the femoral and pelvic nodes without groin lymph node involvement is less frequent but has been reported (24–30).

SURGICAL STAGING

This neoplasia is surgically staged (5). FIGO (International Federation of Gynecology and Obstetrics) and tumor–node–metastasis (TNM) staging systems are reported in

Tables 2 and 3. The reason for such an aggressive attitude is that when compared with surgical staging, the percentage of error in clinical staging increases from 18% for stage I to 44% for stage IV disease (31). Staging emphasizes the definition of the primary tumor by size and location, including the involvement of structures contiguous with the vulva. Status of the nodes is based on surgical evaluation of the groins. The presence or absence of distant metastasis is also taken in consideration, including evaluation by cystoscopy or proctoscopy.

The prognosis of vulvar cancer is correlated with tumor stage and lymph node status. Five-year overall survival varies from 87% to 22% for stages I and IV, respectively, and from 81% to 50% for patients with no and one positive lymph node, respectively (5).

TREATMENT

The most important strategy adopted in vulvar cancer is surgery. More than 50% and >60% of patients are treated with surgery alone or in association with radiotherapy, respectively (5).

To reduce postoperative complications, surgical strategies have been modified in the last decades. En bloc radical vulvectomy, as proposed by Taussig (32) and Way (33), has been substituted by a more individualized approach. This more conservative approach consists of separation of the treatment of the primary lesion from the one of the regional lymph nodes in small lesions.

Treatment of the Primary Lesion

Microinvasive tumors (T1) and lesions that are less than 2 cm in diameter (T2) may be treated by wide local excision with low risk of groin lymph node or vulvar recurrence (34,35). A 1- to 2-cm lateral margin is recommended (36,37). Lesions that are larger or that involve the lower urethra, vagina, and anus (T3) require a radical vulvectomy, a partial resection of these organs, and bilateral inguinal and femoral lymphadenectomy. Tumor that have invaded the upper urethra, bladder, or rectal mucosa (T4) might also require pelvic exenteration. In addition, radiation therapy should be considered in larger lesions.

Treatment of Inguinal Lymph Nodes

Appropriate groin dissection is the most important factor in decreasing mortality for early vulvar cancer (23). Patients who develop groin lymph node recurrence have a >90% mortality (38). All patients with tumors with depth of invasion >1 mm should undergo an inguinal–femoral lymphadenectomy. When lymphadenectomy is performed, this should always include superficial and even deep lymph nodes (28), and should be bilateral in the presence of the bulky, central location of the primary lesions and multiple lymph nodes involvement (39). Even if, historically, pelvic lymphadenectomy has been considered part of the routine surgery, its role in the presence of groin involvement has been redimensioned. Finally, in favor of radiation therapy, many authors are now experimenting with the possible role of sentinel lymph nodes

Table 2 Interpretation of TNM Classification of Vulgar Cancer

T	Primary tumor	N	Regional lymph nodes	M	Distant metastasis
Tx	Primary tumor cannot be assessed		Regional lymph nodes are the femoral and inguinal nodes	Mx	Presence of distant metastasis cannot be assessed
To	No evidence of primary tumor	Nx	Regional lymph nodes cannot be assessed	Mo	No distant metastasis
Tis	Carcinoma in situ (preinvasive carcinoma)	No	No lymph node metastasis	M1	Distant metastasis (pelvic lymph node metastasis is M1)
T1	Tumor confined to the vulva and/or perineum 2 cm or less in greatest dimension	N1	Unilateral regional lymph node metastasis		
T1a	Tumor confined to the vulva and/or perineum 2 cm or less in greatest dimension and with stromal invasion no greater than 1.0 mm	N2	Bilateral regional lymph node metastasis		
T1b	Tumor confined to the vaginal and/or perineum 2 cm or less in greatest dimension and with stromal invasion no greater than 1.0 mm				
T2	Tumor confined to the vulva and/or perineum more than 2 cm in greatest dimension				
T3	Tumor involves any of the following: lower urethra, vagina, anus				
T4	Tumor involves any of the following: bladder mucosa, rectal mucosa, upper urethra, pelvic bone				

Table 3 FIGO (2001) and TNM Staging for Vulvar Cancer

FIGO stage	TNM	Clinical/pathological findings
Stage 0	Tis N0 M0	Carcinoma in situ, intraepithelial neoplasia grade 3
Stage I		Lesions ≤2 cm in size, confined to the vulva or perineum, no nodal metastasis
IA	T1a N0 M0	Lesions ≤2 cm confined to the vulva or perineum and with stromal invasion <1.0 mm[a], no nodal metastasis
IB	T1b N0 M0	Lesions ≤2 cm confined to the vulva or perineum and with stromal invasion >1.0 mm[a], no nodal metastasis
Stage II	T2 N0 M0	Tumor confined to the vulva and/or perineum, >2 cm in greatest dimension, no nodal metastasis
Stage III	T1 N1 M0 T2 N1 M0 T3 N0 M0 T3 N1 M0	Tumor of any size with adjacent spread to the lower urethra and/or the vagina, or the anus, and/or unilateral regional lymph node metastasis
Stage IV		
IVA	T1 N2 M0 T2 N2 M0 T3 N2 M0 T4 any N M0	Tumor invades any of the following: upper urethra, bladder mucosa, rectal mucosa, pelvic bone, and/or bilateral regional node metastases
IVB	Any T, any N, M1	Any distant metastasis including pelvic lymph nodes

(40). The role of pelvic adjuvant radiotherapy was examined by a randomized trial on 114 patients (39). The treatment arms were radiotherapy vs. pelvic node resection in patients with positive nodes. The radiotherapy arm received a 4500- to 5000-rad tumor dose in 5–6.5 weeks bilaterally to the groins and to the midplane of the pelvis. Acute and chronic morbidities were similar for both regiments. There was a significant benefit in survival in favor of the radiotherapy arm ($p = 0.03$).

Radiotherapy alone has little or no role in curative treatment of the primary lesion (41). Radiotherapy is usually adopted as neoadjuvant treatment to reduce tumor volume and therefore allow a less demolitive surgery (42,43), or more often as adjuvant treatment at the level of the inguinal and pelvic nodes (39).

Up to now, chemotherapy has not achieved sufficient success in neoplasia to justify standard use; its use is mainly limited to concomitant chemoradiation and as palliative therapy in advanced, metastatic, and recurrent diseases. Neoadjuvant chemotherapy treatment has also been proposed by some authors. The following chapter will review its application.

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Chemotherapy in Vulvar Cancer

Raimund Winter, Edgar Petru, and Hellmuth Pickel
University of Graz, Graz, Austria

INTRODUCTION

Early vulvar cancer is effectively treated with surgery alone or in combination with radiotherapy. Unfortunately, 5-year survival in patients with advanced and recurrent is still disappointing. Half of these patients die within 1–3 years. Most patients with lymph node involvement are treated with surgery with or without adjuvant radiotherapy (1). There is no evidence that chemotherapy alone has a curative role in this tumor. The possible role of chemotherapy in combination regimens is still to be defined. We are going to discuss the possible application of chemotherapy for the management of these tumors. In particular, we will discuss the role of neoadjuvant chemotherapy, neoadjuvant chemoradiotherapy, chemoradiotherapy as sole treatment, adjuvant chemoradiotherapy, and chemotherapy alone.

NEOADJUVANT CHEMOTHERAPY

Neoadjuvant chemotherapy has been initially adopted in bone (2) and head and neck tumors. At the beginning of the 1980s, it has been applied to the cancer of the cervix achieving good results (3). Based on these encouraging results, a pilot study on neoadjuvant chemotherapy followed by radical surgery was conducted at the end of the 1980s (4). This pilot study was carried out on 21 patients with advanced squamous cell carcinoma (FIGO stage IVa, TNM stages T2N2M0, T3N2M0, and T4N2M0). Patients underwent two to three cycles of cisplatin, bleomycin, and methotrexate. The tumor response rate was poor, no patients achieved complete response, and less than 10% achieved partial response. Inguinal lymph node clinical response was higher (66%) and significantly related to the primary tumor responsiveness. Surgery was feasible in 19 patients, but no evidence of significant distal disease control was obtained. Overall, 3-year survival was only 24%. Similar to cervical cancer, response to chemotherapy was a prognostic factor. The only apparent benefit that these patients achieved from this treatment was a relief from the symptoms in most cases. The Gynaecological Cancer Cooperative Group (GCCG) reported an EORTC trial (5) that included 18 previously untreated patients and 10 patients with recurrent disease. Response rate in primary tumors was 67% (12/18) and was 60% (6/10) for patients

with recurrent disease. All patients were initially judged not susceptible to surgical treatment. After chemotherapy with bleomycin, methotrexate, and lomustine, 8 (29%) patients were found to have resectable disease. Similar response rates have been recently reported by the same group using a modified regimen with a reduced dose of methotrexate (6). A prospective Italian phase II study using cisplatin, paclitaxel, and ifosfamide is presently ongoing to define an effective chemotherapy regimen to adopt before radical surgery.

NEOADJUVANT CHEMORADIOTHERAPY

This strategy should be considered only in patients with T3 and T4 vulvar carcinomas grossly involving the urethra and/or the anus or those who have fixed inguinal metastasis. In these patients, the attempt is to reduce the aggressiveness of surgery and therefore reduce complications and increase quality of life. Drugs that have been most frequently associated with radiotherapy were 5-FU, cisplatin, mitomycin, and bleomycin (Tables 1 and 2) (7–18). The association between radiotherapy and bleomycin was disappointing (18,19). In a study conducted on 15 inoperable patients, only 2 became susceptible to surgery and only 1 patient survived more than 4 years without signs of recurrence. In another study, which included 20 patients with primary disease, clinical response rate was high, but only 1 patient survived without signs of disease for more than 60 months. The association of radiotherapy with 5-FU and cisplatin or mitomycin has been more encouraging. Different studies have demonstrated the efficacy of these associations (8,9,12,20). Worth of notice for its size is the multi-institutional GOG trial conducted by Moore on 71 evaluable patients with stages III and IV disease (13). After chemoradiotherapy with cisplatin and 5-FU, 46% of the patients had no visible disease, only 3% had unresectable disease, and in only 4% of the patients urinary and/or gastrointestinal continence was not preserved. Neoadjuvant chemoradiotherapy also appears to be effective in the treatment of lymph node metastasis. A complete pathological regression in up to 55% of patients after RCT (9) has been demonstrated.

Table 1 Commonly Used Concomitant Radiochemotherapy Regimens in the Treatment of Advanced Vulvar Cancer

External radiotherapy	Anterior-posterior–posterior-anterior (AP–PA) fields 45 (−55) Gy (daily fractions of 1.5–1.8 Gy) to the vulva, the true pelvis, and the inguinal nodes administered over 4 to 6 weeks
Chemotherapy regimen I	Mitomycin C 15 mg/m^2/day day 1 (one cycle) 5-Fluorouracil 750 mg/m^2/day days 1–5 Every 4 weeks (2 cycles)
Chemotherapy regimen II	Mitomycin C 10 mg/m^2/day day 1 (one course) 5-Fluorouracil 1000 mg/m^2/day days 1–4 Every 4 weeks (2 cycles)
Chemotherapy regimen III	Cisplatinum 50 mg/m^2/day days 1 + 2 (one cycle) 5-Fluorouracil 1000 mg/m^2 days 1–4 (1–5) Every 4 weeks (2 cycles)

Table 2 Remission Rates in Patients Undergoing Radiochemotherapy (RCT) for T3 and T4 Vulvar Cancer

Authors	No. of patients	Agents	CR	PR	Remarks
Franzone et al. (7)	14	MMC, 5-FU	64%	21%	–
Landoni et al. (8)	41	MMC, 5-FU	31%	49%	72% underwent surgery; at least one death related to CRT
Lupi et al. (9)	24	MMC, 5-FU	CR + PR: 92%		13.8% mortality
Sebag-Montefiore et al. (10)	37	MMC, 5-FU	47%	34%	One toxic death
Thomas et al. (11)	9	(MMC), 5-FU	66%	n.a.	–
Wahlen et al. (12)	19	MMC, 5-FU	53%	37%	5/19 (26%) patients had local failures within 6 months
Russell et al. (13)	18	(Cispl.), 5-FU	89%	5%	–
Berek et al. (14)	12	Cispl., 5-FU	67%	25%	exenteration: $n = 1$
Cunningham et al. (15)	14	Cispl., 5-FU	64%	28%	–
Moore et al. (16)	73	Cispl., 5-FU	46%	–	5/38 (13%) patients had positive resection margins; colostomy: $n = 1$
Eifel et al. (17)	12	Cispl., 5-FU	42%	50%	–
Scheistroen and Trope (18)	20	Bleo	25%	50%	–

Legend: CR = complete remission; PR = partial remission; MMC = mitomycin C; 5-FU = 5-fluorouracil; Cispl. = cisplatinum; Bleo = bleomycin; MTX = methotrexate.

As expected, local and systemic side effects are common. In most studies, after 3 to 5 weeks, RCT has to be interrupted for about 1 week (10,14,15). Wound complications following secondary surgery after initial RCT are common (16).

Therefore sole radiotherapy or chemoradiotherapy treatment without subsequent radical surgery is often preferred.

CHEMORADIOTHERAPY AS SOLE TREATMENT

It has been proposed by different authors that patients who undergo primary chemoradiotherapy who achieve a complete response may not require surgery. Even in patients with FIGO stages III and IV disease, chemoradiotherapy can lead to complete response in a good proportion of patients. Berek et al. (14) achieved clinical complete response in more than two-thirds of these patients (15). A study was conducted on 33 patients of which 9 did not receive any previous treatment (11). These patients underwent radiation therapy with concurrent infusional 5-fluorouracil with or without mitomycin C. Of these 9 patients, 6 achieved a complete clinical response, but half of them relapsed with a median follow-up of 16 months. Russell et al. (13) reported the results of 18 patients affected by primary vulvar carcinoma treated with 5-fluoruracil with or without cisplatin or mitomycin C with concurrent radiotherapy. Clinical complete response was obtained in 16 patients and, at the time of the report, 12

patients were NED with a median follow up of 24 months (2–52 months). Promising results have also been obtained by Wahlen et al. (12) on 19 patients with FIGO stages II and III disease. Overall clinically CR response was obtained in 10 (53%) patients. Of these 10 patients, only 1 patient experienced recurrent disease both locally and distantly. The other 9 patients remained NED with a median follow up of 18.5 months (range 3 to 56 months). More recently, Cunningham et al. (15) reported a study on 14 patients in whom the location and the extent of the disease made pelvic exenteration the only surgical option. The regimen adopted was two cycles of chemotherapy with cisplatin (50 mg/mq) and 5-FU (1000 mg/mq/24×96 hr) in addition to radiation therapy. Total radiation doses to the vulva and groins ranged from 50 to 65 Gy, with pelvic doses of 45 to 50 Gy. In this study, 9 (64%) patients obtained a complete clinical response and did not undergo surgery. Of these, only 1 patient relapsed with follow-up of 7–81 months, mean 36.5. Considering these satisfactory results, this type of treatment is the most commonly used for unresectable advanced disease.

ADJUVANT CHEMORADIOTHERAPY

Postoperative RT has been considered for many years as the standard adjuvant treatment after surgery in patients with unfavorable prognostic factors. Postoperative

Table 3 Combination Chemotherapy for Advanced/Recurrent Squamous Cell Carcinoma of the Vulva

Author	Chemotherapy regimen	No. of patients	Complete response	Partial response	Response rate (%)	Operability rate postchemotherapy (%)
Mosher, 1972	BM	1	1	–		
Morrow, 1974	AP	1	–	–		
Forney, 1975	7-drug polychemotherapy[a]	1	–	1		
Vogl, 1976	MHO	2	–	–		
Guthrie, 1978	MOB + VB	3	–	3		
Hakes, 1979	MO	2	–	–		
Trope, 1980	BMc	9	1	4	56	
Belinson, 1985	BOMcP	3	–	–		
Chambers, 1989	BOMcP	2	–	1		
Shimizu, 1990	BOMcP	1	1	–		
Benedetti Panici, 1993	PBM	21	–	2	10	90
Behbakht, 1996	BIP	1	–	–		
Durrant, 1990, EORTC	BMC	28	3	15	64	29
Wagenaar, 2001, EORTC	BMC	25	2	12	56	40

Abbreviations used: A = adriamycin (doxorubicin); B = bleomycin; C = cyclophosphamide; H = hydroxyurea; I = ifosfamide; M = methotrexate; Mc = mitomycin C; O = vincristine (oncovin); P = cisplatin; V = vinblastine.
[a] Cyclophosphamide/5-fluorouracil/actinomycin-D/vincristine/cytosine arabinoside/methotrexate/bleomycin.
Source: Ref. 6.

combined chemoradiotherapy has been recently used in view of the excellent results obtained in patients with cervical cancer. Han et al. (21) reported the results of 6 patients with vulvar cancer FIGO stages III and IV who underwent adjuvant chemoradiotherapy. This group of patients was compared to patients undergoing adjuvant RT. The comparison between these two groups appeared in favor of the primer even if the difference was not statistically significant due to the limited number of patients.

CHEMOTHERAPY FOR DISTANT RECURRENT AND METASTATIC DISEASE

Unfortunately, no large studies using chemotherapy alone to treat vulvar cancer patients has been published (Table 3) (6). Many physicians adopt regimens that are used in squamous cell carcinoma of the cervix. Others continue the chemotherapeutic regimen used during the concomitant chemoradiotherapy treatment with cisplatin and

Table 4 Combination Regimens Most Frequently Adopted

Author	Dose and schedule		No. of patients	Clinical response	%
Belinson et al. (22)	Bleomycin	15 mg/m^2 cont. IV days 1–3	3	0	0
	Vincristine	1.4 mg/m^2 IV day 3			
	Mitomycin C	10 mg/m^2 IV day 3			
	Cisplatin	60 mg/m^2 IV day 3			
Durrant et al. (5)	Bleomycin	5 mg IM days 1–5	28	18	64
	Methotrexate	15 mg PO days 1 and 4			
	CCNU	40 mg PO days 5–7			
Shimizu et al. (23)	Bleomycin	5 mg IV days 1–6	Case report		Complete clinical response
	Vincristine	1 mg IV day 6			
	Mitomycin C	10 mg IV day 6			
	Cisplatin	100 mg IV day 6			
Wagenaar et al. (6)	Week 1		25	14	56
	Bleomycin	5 mg IM days 1–5			
	Methotrexate	15 mg PO days 1 and 4			
	CCNU	40 mg PO days 5–7			
	Weeks 2–6				
	Bleomycin	5 mg IM days 1 and 4			
	Methotrexate	15 mg PO day 1			

5-FU even if little or no scientific evidence is present in favor of this strategy. Considering that no study has analyzed the different regimens in these patients, the treatment choice should fall on drugs that have demonstrated some efficacy in other conditions. When the patients' clinical condition allows an aggressive systemic therapy, combined regimens should be preferred. The most frequently adopted regimens are reported in Table 4 (5,6,22,23). Most regimens adopt combination that includes bleomycin and methotrexate and/or vincristine. The two largest series reported by the EORTC have used the association between bleomycin, methotrexate, and cyclophosphamide (5,6). If the patients' condition allows only a single agent, bleomycin, methotrexate, and adriamycin have proved some efficacy in terms of response, even if duration of response is usually short (24,25).

CONCLUSION

Surgery remains the gold standard in patients with primary vulvar cancer. Patients with advanced tumors are usually elderly and debilitated. In recent years, physicians have understood the fundamental importance of quality of life and have tried to reduce permanent morbidity by tailoring surgery and attempting alternative treatments. Chemotherapy alone has not yet acquired sufficient evidence to be adopted outside clinical trials. More promising appears to be the role of concomitant chemoradiation therapy in unresectable tumors. It is our opinion that, in the future, the trend will be to adopt more frequently such procedure in a neoadjuvant setting in order to reduce surgical aggressiveness and therefore reduce postoperative morbidity and increase the quality of life of these patients. The role of sole chemotherapy will probably remain confined to palliative treatment of metastatic and recurrent tumors.

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Vaginal Cancer

Roberto Angioli, Innocenza Palaia, and Filippo Bellati
University of Rome Campus Bio-Medico, Rome, Italy

INTRODUCTION

Primary vaginal cancer without involvement of the vulva or cervix is a rarity, accounting for only 1–2% of gynecological malignancies (1).

Between 80% and 90% of vaginal tumors are secondary lesions, most frequently from the cervix, endometrium, and vulva, or, less commonly, from the rectum, colon, and ovary.

In recent years, there has been a decline in the incidence of vaginal cancer: possible explanations can be the increase of cervical cytology screening and the introduction of a standardization of diagnostic criteria. The incidence of invasive vaginal cancer is 0.42/100,000 women (2); it represents between 1% and 2% of all tumors of the female genital tract. Grade 3 vaginal intraepithelial neoplasia (VAIN III) is considered a precursor of invasive vaginal cancer. Between 3% and 9% of VAIN lesions progress to invasive disease (3–5). More than 90% of the primary tumors are squamous cell carcinomas. The peak incidence of the disease is between 50 and 70 years in women and the mean age is between 60 and 65 years (2). Low social economic level, history of genital warts, human papillomavirus (HPV), vaginal discharge or irritation, early hysterectomy, and vaginal trauma are the most studied risk factors for vaginal cancer (6,7); even if pelvic radiotherapy was thought to be a possible risk factor (8) for epithelial vaginal cancer, more recently, reports were not able to confirm this observation (9).

Primary adenocarcinomas represent only 9% of primary tumors of the vagina and affect a younger population of women. A strong correlation between in utero exposure to diethylstilbestrol (DES) and vaginal clear cell adenocarcinoma was noted by some authors since the earlier 1970s (10). This synthetic estrogen has been widely prescribed to pregnant women during the 1950s and 1960s, and its use was discontinued only in 1971. Nowadays, a continued surveillance of the group of women prenatally exposed to this estrogen is still warranted.

Among nonepithelial tumors, malignant melanoma is the second most common cancer of the vagina, accounting for 2.8–5% (11). The average age of these patients is 58 years; the most common location of these tumors is the lower third of the vagina. Because the disease is deeply invasive, hematogenous spread is the most common lethal recurrence.

The most frequent malignant mesenchymal tumors of the vagina in adult women are smooth muscle tumors (sarcomas).

In infants and children younger than 5 years old, the botryoid variant of embryonal rhabdomyosarcoma is the most frequent mesenchymal vaginal neoplasm.

As to malignant germ cell tumors, endodermal sinus tumor has been reported to be a rare primary tumor of the vagina.

The last FIGO Annual Report shows that the 5-year overall survival remains at 50% for all stages (12). The dramatical drop in 5-year survival among patients beyond stage II reflects the lack of adequate methods of detection and treatment of subclinical metastatic diseases. Malignant melanoma is the worst histological type suggesting early dissemination in clinically early stages.

Because of the rarity of vaginal cancer, these patients should be treated in centers that are familiar with the complexity of the treatment and modalities of therapy.

PATTERN OF SPREAD

Vaginal cancer frequently occurs in the posterior wall of the upper third of the vagina (2). It frequently spreads by direct extension to the vulva and/or cervix. The absence of an anatomical barrier allows vaginal tumors to extend to the surrounding tissues and other pelvic organs. Tumors of the anterior vaginal wall may involve the vesicovaginal septum; on the other hand, lesions of the posterior wall may invade the deep rectovaginal layers. Laterally, the disease may reach the obturatory fossa and the pelvic wall through the paraculpo and uterosacral ligaments. Concerning lymphatic spread, some authors demonstrated that, independently from the site of the primary lesion, any pelvic lymph node group may be involved (13). The incidence of positive pelvic nodes ranges between 5% and 20% in different series (14). Inguinal lymph nodes metastases have also been reported, particularly in patients with lesions of the distal third of the vagina (15). In patients with advanced disease, distant metastasis can occur (lungs, liver, and bone): in particular, clear cell vaginal adenocarcinoma is more frequently associated with distant metastasis when compared with squamous cell carcinoma (16).

CLINICAL PRESENTATION

The presentation of this disease is similar to that of cancer of the cervix. The most frequent sign is abnormal vaginal bleeding; this may be a dysfunctional bleeding, or a postcoital spotting. In locally advanced diseases, urinary or gastrointestinal symptoms may occur. In particular, tumors that have evolved anteriorly may cause urgency, urinary retention, or hematuria. Tumors that have developed toward the rectum may cause tenesmus, constipation, or rectal bleeding.

STAGING

For a lesion to be classified as a primary vaginal tumor, it is essential that at diagnosis, the cervix and the vulva are not involved. Tumors that involve the vagina but also the

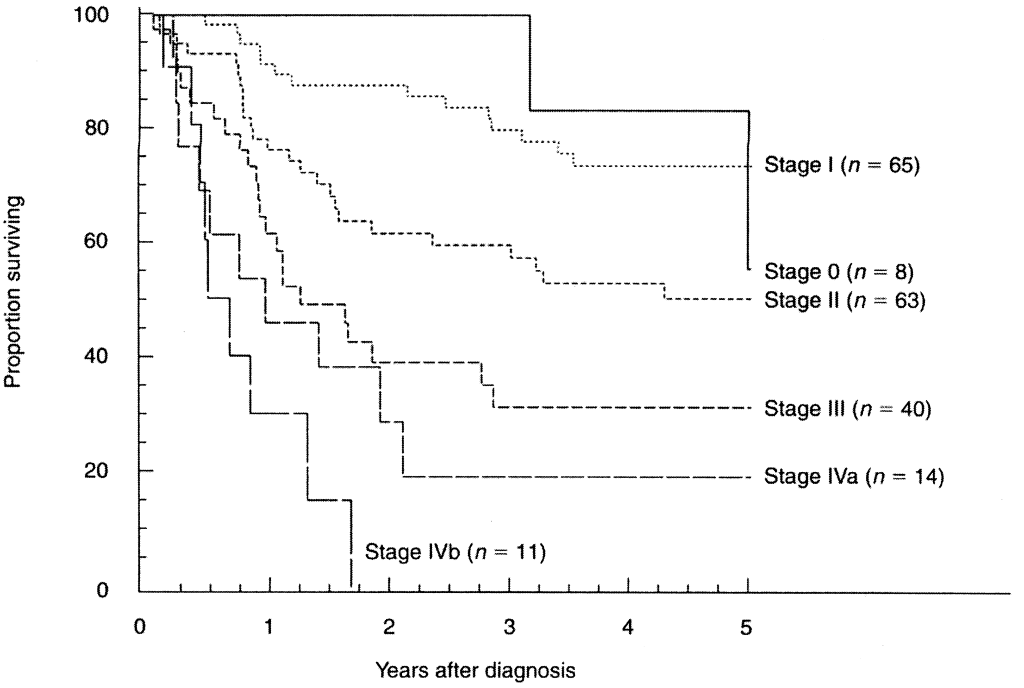

Figure 1 Carcinoma of the vagina: survival by FIGO stage, (n = 201). (From Ref. 12.)

vulva, urethra, or cervix should be classified as primary tumors of the latter organs. In dependence on the site of the lesion, a histological verification of these close organs should be performed to reduce mistakes in diagnosis (17).

In analogy to the cervix, vaginal cancer is clinically staged. Staging procedures include: clinical examination, cystoscopy, proctoscopy, chest x-ray, and skeletal x-ray. Information derived from computed tomography (CT) scan, magnetic resonance imaging (MRI), and lymphangiography may be useful in tailoring the subsequent treatment (24).

Table 1 Carcinoma of the Vagina: Figo Staging

Stage 0	Carcinoma in situ; intraepithelial neoplasia, grade 3
Stage I	The carcinoma is limited to the vaginal wall
Stage II	The carcinoma has involved the subvaginal tissues but has not extended to the pelvic wall
Stage III	The carcinoma has extended to the pelvic wall
Stage IV	The carcinoma has extended beyond the true pelvis, or has involved the mucosa of the bladder or rectum; bullous edema as such does not permit a case to be allotted to stage IV
IVa	Tumor invades the bladder and/or rectal mucosa, and/or direct extension beyond the true pelvis
IVb	Spread to distant organs

The FIGO staging system for vaginal cancer is based on clinical findings and is analogous to the staging system for cervical cancer (Fig. 1, Table 1).

TREATMENT

Treatment of cancer of the vagina depends on the stage of the disease, the type of disease, and the patient's age and overall condition.

Radiotherapy is the treatment of choice for most carcinomas of the vagina. However, therapeutic alternatives depend on stage and histotype. The following describe the different approaches used:

(a) VAIN: In recent years, the treatment of VAIN has undergone a significant evolution: the selection of treatment depends on patient factors and local expertise. Therapeutic options are: wide local excision (18), partial or total vaginectomy (19), intravaginal chemotherapy with 5% fluorouracil cream (20), laser therapy (21,22), and intracavitary irradiation (23). All these treatments produce similar cure rates.

(b) Early disease (stage I): Stage I disease is usually treated with intracavitary radiation therapy (23,24). However, surgery may have a role in this setting of patients: young women in whom there is a desire to preserve ovarian function, treatment of radiation failures, and nonepithelial tumors. Surgical procedures for stage I invasive vaginal carcinoma consist of radical hysterovaginectomy and pelvic lymph node dissection.

(c) Stages II and III: Concerning stage II–III vaginal carcinomas, data suggest that most patients require treatment with a combination of external beam and brachytherapy (25). Selected cases may be cured with radical surgery, but to remove the tumor, total pelvic exenteration is often required. Combined techniques (radiotherapy plus surgery) have been suggested by few authors, but more complications may be seen (26,27).

(d) Nonepithelial tumors: Rhabdomyosarcoma, melanoma, leiomyosarcoma, and endodermal sinus tumor of the vagina may benefit from surgery and radiotherapy as well. However, chemotherapy has some applications in this setting.

Chemotherapy regimes are described in the following chapter.

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Vaginal Cancer Chemotherapy

Raimund Winter, Edgar Petru, and Hellmuth Pickel
University of Graz, Graz, Austria

INTRODUCTION

Vaginal cancer without involvement of the vulva or cervix is a rarity, accounting for only 1–2% of gynecological malignancies (1). About 50% of these lesions arise in the upper third of the vagina and 57% are located on the posterior wall of the vagina (2). Overall, 80–90% of vaginal neoplasias are secondary lesions of primary tumors of the cervix, endometrium, colon and rectum, ovary, or vulva.

Most vaginal cancers are squamous epithelial carcinomas. The mean age of the patients is 60 years and 76% are older than 50 years (3). Rarely, vaginal cancers can develop in women between 20 and 40 years of age (4–6).

The main treatment modalities for primary vaginal cancer, similar to cervical cancer, are surgery and radiotherapy. Considering that concomitant chemoradiation has become the standard treatment for locally advanced cervical carcinoma (7), radiotherapy for primary cancer of the vagina might be replaced by chemoradiation in the future.

SQUAMOUS CELL CARCINOMA

Similar to vulvar cancer, the role of chemotherapy alone for the management of vaginal carcinoma is limited. Moreover, the rarity of this neoplasm did not allow adequate phase II testing of cytotoxic agents because no single institution has sufficient patients.

Some authors have proposed the use of neoadjuvant chemotherapy followed by radiotherapy to treat advanced vaginal cancer; in particular, Patton et al. (8) reported a 5-year survival rate of 30% in patients with bulky disease who underwent intra-arterial chemotherapy with cisplatin, bleomycin, and cisplatin followed by radiotherapy. However, no authors have subsequently confirmed these data.

Concomitant chemoradiation therapy in patients with locally advanced vaginal cancer (9,10) has been evaluated as well. Although the number of patients studied is limited, interesting results have been reported by Evans et al. (11), who studied 25 patients with advanced squamous carcinomas of the lower genital female tract (cervix, 14 patients; vulva, 4 patients; vagina, 7 patients); all patients were found to have

extensive disease not amenable to standard therapy (stages II and III). Patients were treated with a combined modality approach using 1 g/m^2 5-fluorouracil given as a continuous infusion for 4 days, 10 mg/m^2 mitomycin C, IV push, on day 1, and concomitant radiotherapy starting on day 1. With a median follow-up time of 28 months, the reported survival by site was 70% for the cervix, 100% for the vulva, and 66% for the vagina. Among patients with vaginal cancer, four patients (57%) achieved complete response and were without disease at 8 and 39 months (11). Concerning the use of chemotherapy for advanced and/or recurrent disease, only anecdotal data are available. Concerning single-agent chemotherapy, poor response was noted with etoposide (12), mitoxantrone (13), cisplatin (14), and nitrosoureas (15). Only Piver et al. (16) in 1978 reported a 14% response with adriamycin when used as a single agent or in combination with 5-fluorouracil and cyclophosphamide. However, from these data, no conclusion can be drawn about the efficacy of chemotherapy in those patients who are unfortunate enough to develop advanced or recurrent diseases. In 1986, the Gynecologic Oncology Group conducted a phase II trial in patients affected by advanced or recurrent vaginal cancer treated with 50 mg/mEq cisplatin every 3 weeks. Only one complete response was observed among the 16 patients with squamous cell carcinoma (17). These results suggest that cisplatin has poor activity in treating advanced or recurrent vaginal carcinomas, at least at the dose and schedules tested.

In conclusion, data regarding the use of chemotherapy for the management of vaginal squamous cell carcinoma are lacking. Nowadays, chemotherapy is used only as salvage therapy for patients affected by recurrent and/or metastatic vaginal cancer.

SARCOMAS

Therapy for vaginal sarcoma consists of surgery with or without adjuvant radiotherapy. Considering the poor outcome of patients affected by vaginal sarcoma, some authors have proposed a multimodal approach using chemoradiation to avoid aggressive surgical procedure (i.e., total pelvic exenteration).

The use of chemotherapy for the management of vaginal sarcoma has been suggested by some authors who first achieved good results using cisplatin, ifosfamide, and doxorubicin for the management of similar tumors arising from the uterus.

Several authors have subsequently proposed a chemotherapeutic approach for the management of vaginal sarcomas. In particular, Hays et al. (18) have studied 24 children, aged between 1 and 4 years, affected by primary vaginal sarcoma, including botryoid sarcoma ($n = 15$). The largest group of patients with vaginal lesions was treated with multiple courses of preoperative vincristine sulfate, actinomycin D, and cyclophosphamide (VAC) and delayed hysterectomy–vaginectomy. Only eight patients required postoperative radiotherapy. This group had a high rate of response to these chemotherapy regimens and was managed without exenterative surgery (18).

Subsequently. Andrassy et al. (19) have reviewed the results of four sequential prospective clinical trials conducted by the Intergroup Rhabdomyosarcoma Study Group to assess the validity of surgery, radiotherapy, and chemotherapy in the management of these patients. The conclusion of these authors was that primary chemotherapy (VAC or VAC plus doxorubicin and cisplatin) provides excellent tumor control. After chemotherapy, local resection was appropriate in most of the patients, whereas removal of organs (i.e., vaginectomy and hysterectomy) was not necessary,

except in patients with persistent or recurrent disease. Surgical management of vaginal rhabdomyosarcoma has, therefore, changed dramatically, and more space is given to primary chemotherapy in the contemporary management of this disease.

ENDODERMAL SINUS TUMOR

Before the routine use of adjuvant chemotherapy, patients affected by endodermal sinus tumor of the vagina have a generally a poor prognosis, with fewer than 25% surviving 5 years after the first diagnosis. In 1984, Young and Scully (20) reported a series of nine cases of endodermal sinus tumor of the vagina diagnosed in children aged between 6 months and 6 years. Among these patients, three were treated with surgery alone and died after 6–13 months despite surgical complete resection. Six patients who were treated by surgical procedure plus adjuvant chemotherapy (vincristine, cyclophosphamide, and actinomycin D) were alive and free of disease from 2 to 9 years postoperatively. Subsequently, many authors confirmed the validity of this chemotherapeutic regimen (21–25) for the treatment of this disease.

CONCLUSION

Generally, the role of chemotherapy alone in epithelial vaginal cancer is limited. In recent years, chemoradiation has been increasingly used in patients with advanced diseases and has led to tumor reduction in a substantial proportion of patients. However, more studies are needed to confirm these data.

Palliative chemotherapy can be used for patients affected by advanced or recurrent disease. Concerning sarcomas and endodermal sinus tumor of the vagina, chemotherapy has a definite management role in this setting, and VAC is the treatment of choice with an optimal response rate.

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Management of Hydatidiform Mole

John Tidy and B. W. Hancock
University of Sheffield, Sheffield, England

INTRODUCTION

Hydatidiform mole is an abnormal conceptual event. There are two forms of hydatidiform mole: complete hydatidiform mole and partial hydatidiform mole. These two entities are quite distinct in many ways such as in their etiology, epidemiology, presentation, and management.

FACTORS INFLUENCING THE INCIDENCE OF HYDATIDIFORM MOLE

Establishing the true incidence of this disease is problematical. Most studies base the figures of incidence as a proportion of the number of births, as there is no way of estimating the total number of conceptions that take place in a given year. Factors that therefore affect the incidence of this condition include the reliability of the diagnosis and the reporting of the disease, and the ability to collect verifiable data on the live birth rate. Therefore, some series are able to publish incidence rates based on national data, whereas other series are confined to regional data or even local hospital information. This may explain, to some degree, the geographical variation of the incidence of this disease. However, it is generally held to be true that there is a variation in the incidence within different ethnic populations. The incidence in Caucasian populations has been reported to be as low as 0.7/1000 births in Australia, and as high as 4.6/1000 births in Hawaii (1). The incidence of hydatidiform mole registered in the UK, which has both a national program for the registration of pregnancy and national statistics for delivery rates, was 1.54/1000 live births in 1983 (2).

The incidence of this disease in various ethnic groups is unclear. A recent report from Korea has shown a reduction in the incidence of this disease, and it has been speculated that the cause for this may be reduction in the number of pregnancies per woman but also the possibility of the adoption of a more westernized lifestyle (3). Recent data from our department have shown a gradual increase in the incidence of cases reported over a 10-year period from 1.26/1000 deliveries to 1.63/1000 deliveries. Interestingly, a subanalysis of the ethnicity of patients registered at our center shows that women of Asian descent have an average risk 1.9 times greater than that of non-

Asians. The data within the Asian population also indicated an increasing incidence of cases as well.

The above incidence figure may be an underestimate of the true incidence of hydatidiform moles, as it is believed that many partial moles may avoid detection and registration. Partial molar pregnancies often present with symptoms and signs suggestive of miscarriage, and the ultrasound features of partial molar change are less reliable. As it is inevitable that many of the products of these miscarriages will not undergo histological examination, the true number of partial moles may be under-recorded.

Age has a significant influence on the incidence of hydatidiform moles. Women at either end of their reproductive lives show an increased incidence, and this is true for all ethnic groups. The relative risk for women under the age of 15 years is 6.04, and that between the ages of 40 and 45 years is 2.97, whereas it rises to 411 in women over the age of 50 years. The influence of paternal age is variably reported.

PAST REPRODUCTIVE HISTORY

Although there appears to be no evidence that the previous number of viable pregnancies influences the incidence of hydatidiform moles, there is a strong link between a past history of molar pregnancy and a subsequent risk of further molar pregnancies. The majority of women after a single molar pregnancy will proceed to a normal pregnancy and vaginal delivery; the increased risk of a second hydatidiform mole per patient is 1 in 52 and this rises to a risk of 1 in 4.75 for the risk of a third molar pregnancy if it has been preceded by two molar pregnancies.

GENETICS OF MOLAR PREGNANCIES

The genetic constitution of a complete mole is different from that of a partial mole (4). Complete moles are diploid in genetic constitution and the chromosomal content is entirely paternally derived. Most complete moles arise either because of the fertilization of an empty egg by a diploid sperm, or by the fertilization of an empty egg by a haploid sperm, which then undergoes spontaneous duplication. The karyotype in these cases is always 46,XX, as duplication of the Y chromosome is presumed to be nonviable. A small percentage of cases arises because of the dispermic fertilization of an empty egg and, in these cases, the karyotype may be either 46,XY or 46,XX.

Partial hydatidiform moles are triploid in their karyotype and usually have one set of maternally derived chromosomes. Studies have suggested that the most likely origin is by dispermic fertilization of a normal egg. There is usually evidence of fetal tissues in partial moles, whereas complete moles have no associated fetal tissues.

PRESENTATION OF HYDATIDIFORM MOLE

Complete Moles

The classical presentation of complete moles in pregnancies has become increasingly rare in the developed world as a result of the routine use of ultrasound examination in

early pregnancy. However, in developing countries where these resources may not be available, women may still present with marked abnormalities of early pregnancy (Table 1). Presentation with excessive vaginal bleeding due to a large uterus with molar tissues may be life-threatening, as is the early onset of pre-eclampsia, if not treated appropriately.

Women who now present to the gynecologist in early pregnancy with a history of vaginal bleeding or abdominal pain routinely undergo ultrasound examination as part of their management. This has led to the earlier diagnosis of complete molar pregnancies. The classical appearance of a complete mole on ultrasound demonstrates vesicular tissues within the uterine cavity with no evidence of any fetal material. In women who have no symptoms in early pregnancy, the diagnosis of complete molar pregnancy is sometimes made as part of the routine use of ultrasound in early pregnancy to confirm the dates of gestation.

Partial Hydatidiform Molar Pregnancy

The presentation of these pregnancies is less distinct. Most will present as either an incomplete miscarriage or a delayed miscarriage. The diagnosis may only be made on histological examination of the products of conception.

Dilemmas in Early Pregnancy

Two clinical scenarios, which lead to an increased level of anxiety both for the pregnant woman and for the obstetrician and gynecologist, occur in early pregnancy. The use of ultrasound is associated with the reporting of more subtle abnormalities of the placental bed. In some circumstances, the ultrasound may show cystic changes within the placenta along with a viable fetus. In this situation, the concern over the potential for a partial mole is raised. Studies, however, are reassuring and the recommendation would be that the pregnancy should be allowed to proceed. There is no evidence that women who may have suspected partial molar change coexistence with a normal fetus are at any increased risk of the subsequent need for chemotherapy after delivery.

Ultrasound examination may also reveal a coexisting normal pregnancy with a coexisting complete molar pregnancy. In this situation, the mother needs to be counseled over the risks and benefits of proceeding with the pregnancy. The probability of delivering a viable baby is no higher than 25%, and there is a significant risk of

Table 1 Late Presentation of Hydatidiform Moles

Excessive vaginal bleeding
Excessive uterine enlargement
Ovarian thecal luteal cysts
Early-onset pre-eclampsia
Thyroid crisis
Central nervous system involvement
Respiratory failure

complications such as vaginal bleeding and pre-eclampsia. However, if the pregnancy is successful and a delivery occurs, then there is no increased risk for chemotherapy.

SURGICAL MANAGEMENT OF MOLAR PREGNANCIES

Complete Moles

There is debate over the appropriate way to surgically manage complete molar pregnancies. There are some retrospective data suggesting that the use of agents that may ripen the cervix, such as prostaglandins, may lead to uterine activity, which may cause embolization of trophoblastic tissues to the rest of the body, and this is held to be true for the use of oxytocin infusions at the time of surgical evacuation (2,5,6). Oxytocin leads to the rhythmic contraction of the uterus and may result in increased intrauterine pressure, again leading to embolization of trophoblastic tissues. Occasionally, some patients do require the use of this infusion prior to surgical evacuation, but it should be limited only to those women who have excessive vaginal bleeding when oxytocin is necessary to control significant hemorrhage. The ideal method of evacuation is dilatation and suction curettage of the uterine cavity. This method can be used to evacuate a uterus of any size because there is no fetal tissue present and the vesicles can easily be evacuated through the suction curettage. Once the uterine cavity has been evacuated, then oxytocin infusions may be used if hemorrhage is a problem (7).

There has been considerable revolution in the medical management of early pregnancy loss with the use of systemic progesterone medication along with vaginal prostaglandin preparations. However, there is very little to suggest that these are safe to use in the management of complete moles.

The use of the nonsurgical methods described above appears to increase the subsequent need for chemotherapy. This may be due, in part, to the embolization of trophoblastic tissues but also to the possibility that the medical methods are less effective in molar pregnancies in producing complete evacuation of the uterus.

Partial Moles

Partial molar pregnancies are best evacuated by surgical methods, if this is technically possible. However, if the presence of fetal tissue precludes this, then medical methods should be used. Because of the low risk for the need for chemotherapy in partial molar pregnancies, the increased risk following medical evacuation does not appear to be significant (7).

Role of Repeat Uterine Evacuation

The role of repeat uterine evacuation in the management of gestational trophoblastic disease is unclear. Repeat evacuation is often performed by gynecologists without consultation with expert centers as to its necessity. Many patients continue to have vaginal bleeding, and it is felt that further evacuation may lead to a resolution of this problem. Analysis of the data from the Sheffield Center has shown that repeated evacuations may be of value in resolving persistent uterine disease, but only if the woman has a urinary human chorionic gonadotropin (hCG) level of <5000 IU at the time of the repeat evacuation. Repeat evacuation in levels above 5000 IU is less

effective and, usually, the woman will require chemotherapy. There appears to be no indication for more than one repeat evacuation of the uterus.

MONITORING HCG LEVELS POSTUTERINE EVACUATION

It is vital that, as part of the management of patients with hydatidiform molar pregnancies, regular postevacuation monitoring of hCG levels is performed. This monitoring may be either by estimation of serum levels of hCG, or by monitoring of urinary hCG levels.

Human chorionic gonadotropin is a complex molecule, which may exist in various forms that can be detected, particularly in serum samples. These include nicked hCG, hyperglycosylated hCG, and free β-subunits. Because of these great variations in the structure of the hCG present in trophoblastic disease, it is essential that assays being used to assess persistent diseases recognize all main forms of hCG and its β-subunits. Failure to do this may result in missing diseases. However, falsely elevated levels of hCG may occur, with some assays resulting in the clinical scenario of phantom hCG production (8).

Ectopic Molar Pregnancies

Molar pregnancies may occur in any ectopic site within the reproductive tract; however, these pregnancy events are very rare (9,10). The management of ectopic molar pregnancies in the past has been through surgical excision. With the recent introduction of a more conservative laparoscopic surgery, it is unclear if this will lead to a higher rate of persistent disease. There is also a concern that the use of a single dose of methotrexate in the management of ectopic pregnancies may be associated with the same limitations as those of conservative laparoscopic surgery and again lead to a higher rate of persistent disease that will require treatment.

Hysterectomy

Hysterectomy may be used in the management of hydatidiform mole. Indications are varied and include the initial management of the presenting pregnancy through the management of chemotherapy-resistant diseases (11). Hysterectomy in the initial management of molar pregnancy may be considered if a woman has other gynecological morbidities and/or is desirous of a hysterectomy. Although hysterectomy will lead to a total removal of the uterine molar pregnancy, it does not completely reduce the need for subsequent chemotherapy. The patient must be warned that although hysterectomy may help the initial management, there is still a 10% risk of requiring subsequent chemotherapy and therefore must be followed up with serial hCG monitoring.

Long-Term Follow-Up of Patients with Molar Pregnancies

The introduction of central registries and centers of excellence has led to a reduction in mortality and morbidity associated with this disease. The development of problems associated with molar pregnancies is at its greatest during the first 12 months following

Table 2 Risk Scoring for Persistent Trophoblastic Disease

	Score			
	0	1	2	4
Age	<39	>39		
Last pregnancy	Mole	Abortion/ unknown	Term	
Interval to treatment from evacuation (months)	<4	4–7	7–12	>12
Serum hCG (IU/L)×	$<10^3$	10^3–10^4	10^4–10^5	$>10^5$
Number of metastasis	Nil	1–4	4–8	>8
Site of metastasis	Lung, vagina	Spleen, kidney	GI tract	CNS, liver
Largest metastasis (cm)	<3	3–5	>5	
Previous chemotherapy	Nil		Single	Multiple

Source: Ref. 17.

diagnosis. Patients can potentially develop recurrence from their original pregnancy, or even develop second molar pregnancies. As it is impossible to distinguish these two events unless by complicated genetic analysis, it is usually advised that patients with molar pregnancies not become pregnant for 6–12 months following diagnosis. However, some women have become pregnant during this routine follow-up period and fetal outcome is generally good.

Advice on the use of the oral contraception following the diagnosis of molar pregnancy is controversial. Evidence from a UK center suggests an increased risk for the need for chemotherapy if the oral contraceptive pill is started before normal hCG levels are obtained (5). However, many studies from elsewhere have not shown this to be a problem. The current advice in the UK is to avoid the combined oral contraceptive pill until levels of hCG have returned to normal, although many centers in the United States allow women to use the oral contraceptive pill earlier because of the belief that the risk of a subsequent pregnancy bears a greater risk to the woman (12–14). The use of hormone replacement therapy is less well understood but is probably safer to use than the combined oral contraceptive pill.

Treatment of Persistent Gestational Trophoblastic Disease

Not all complete and partial molar pregnancies resolve. Some will require treatment with chemotherapy. The percentage of women requiring such treatment is between 6%

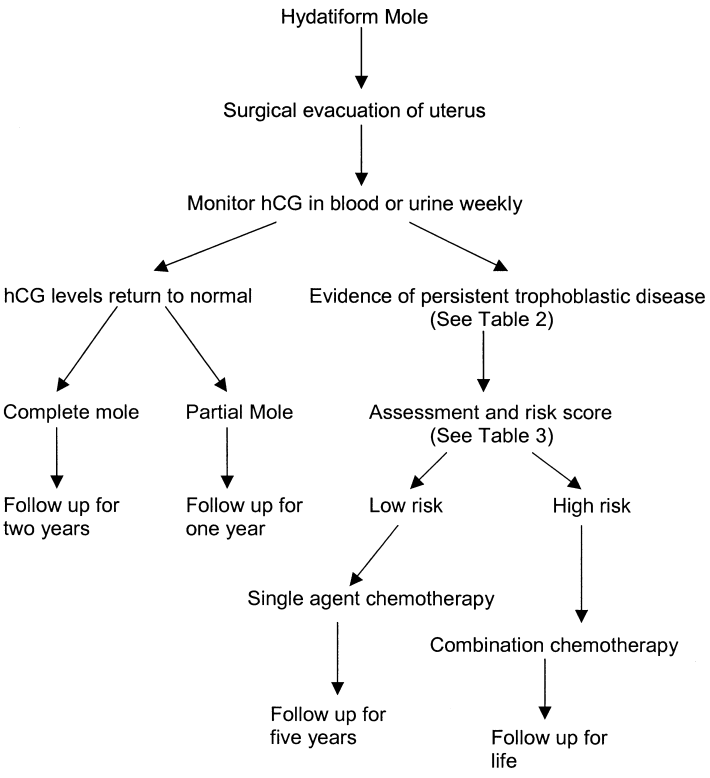
Table 3 Criteria for Chemotherapy in Persistent Trophoblastic Disease

- hCG levels greater than 20,000 IU/L after one or two uterine evacuations
- Static or rising hCG levels after one or two uterine evacuations
- Persistent hCG elevation 6 months postuterine evacuation
- Persistent uterine hemorrhage with raised hCG levels
- Pulmonary metastases with static or rising hCG levels
- Metastases in liver, brain, or GI tract
- Histological diagnosis of choriocarcinoma

Table 4 Chemotherapy Regimens Used in the Treatment of Persistent Trophoblastic Disease

Low-risk chemotherapy regimen (score of six or less in Table 2)
Methotrexate: 50 mg, im, on alternate days, four doses per treatment cycle
Folinic acid: 15mg, orally, 24 hr after each methotrexate injection
7-day rest between cycles
High-risk chemotherapy regimen (score of seven or more in Table 2)
Arm A
Methotrexate 100 mg/m^2, iv, 30-min infusion in 250 mL of normal saline followed by 200 mg/m^2, iv, 12-hr infusion in 1 L of normal saline; an additional 1 L of normal saline is then infused over 6 hr
Folinic acid: 15 mg, six hourly starting 24 hr after methotrexate; eight doses are administered, the first four being im or iv
7-day interval
Arm B
Dactinomycin: 0.5 mg, iv, 1-hr infusion in 250 mL of normal saline
Etoposide: 100 mg/m^2, iv, 1-hr infusion in 500 mL of normal saline
Arm A is repeated after seven rest days

Table 5 Algorithm for the Management of Hydatidiform Mole



and 20% throughout the world (15). This variation is not a consequence of differences in the aggressiveness of molar pregnancies, but is more a reflection of different methods of clinical practice. In the UK where there is central registration available and close monitoring of patients, the rate of chemotherapy use is between 6% and 10% (16). However, in other centers in the United States where follow-up has been cited as a great difficulty, chemotherapy rates of 20% are not uncommon. The indications for chemotherapy at our center in Sheffield are listed in Table 2. Patients who fulfill the criteria are admitted to our center for full clinical and radiological evaluation. Each woman is assessed against the current World Health Organization (WHO) scoring system (Table 3) (17). Women who score six or less are considered low-risk and receive a course of low-dose intramuscular methotrexate with folinic acid rescue (Table 4). Women who score seven or more fall into the high-risk category and are treated with a combination regimen of intravenous methotrexate, etoposide, and dactinomycin. Chemotherapy for both groups is continued until hCG levels are normal for six consecutive weeks.

Following completion of chemotherapy, monitoring of serial serum hCG levels and urinary hCG levels follows. Women in both groups are advised not to become pregnant for the first 12 months following completion of chemotherapy, and women who are treated with low-risk chemotherapy are followed-up for 5 years and those who receive high-risk chemotherapy are followed up for life (Table 5).

CONCLUSION

Hydatidiform molar pregnancies are uncommon events, but the incidence varies throughout the world according to ethnicity. The majority of these pregnancies are dealt with by evacuation of the uterus with no significant long-term problems. However, because of the risk of persistent disease, careful follow-up and, ideally, registration at specialist centers are advisable. Should women develop persistent disease, then chemotherapy regimens are advised in this situation, with cure rates approaching 100%.

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Trophoblastic Disease

Edward Newlands
Charing Cross Hospital, London, England

INTRODUCTION

Gestational trophoblastic disease (GTD) has a broad spectrum of biological behavior of the abnormal trophoblast from hydatidiform moles that remit spontaneously following evacuation of the uterine cavity to highly aggressive tumors of widely metastasising potential, which are usually pathologically choriocarcinoma. GTD can follow any form of pregnancy including normal pregnancy, but the most common antecedent conception is a hydatidiform mole. The incidence of GTD following a normal pregnancy is of the order of 1 in 40,000–50,000 pregnancies, but complete hydatidiform moles have an incidence in the United Kingdom of approximately 1 in 1200 pregnancies. GTDs are clearly uncommon conditions and, in the United Kingdom, there is a national service for women with this condition. Under the auspices of the Royal College of Obstetricians and Gynaecologists and the Supraregional Specialties run by the Department of Health, there are three reference centers for registering patients for serial human chorionic gonadotrophin (hCG) estimations, and these are based at Dundee, Sheffield, and the Charing Cross Hospital in London. At present, approximately 1400 women are registered at the three centers per annum and around 120 patients will need chemotherapy to eliminate their GTD at the two treatment centers, which are based at the Charing Cross Hospital in London and Weston Park Hospital in Sheffield. This national service allows the accumulation of great expertise and experience in treating this rare group of diseases and with proper management it is uncommon for any woman to die of her GTD in the United Kingdom (1).

PATHOLOGY AND GENETICS

There are four main pathological entities covered within the term GTD and their biological behavior is very different.

Complete Hydatidiform Mole (CHM)

CHM are pathologically multivesicular masses with diffuse hydropic villi and variable degrees of trophoblasfic proliferation. Usually, there is no evidence of a fetus, but with

earlier diagnosis, which is now possible with ultrasound so that these pregnancies are evacuated commonly at between 6 and 8 weeks of gestation and evidence of fetal red cells can be seen in CHM (2). With the earlier diagnosis of CHM on ultrasound, the fully developed mole is now uncommonly seen pathologically and the degree of hydrops in the villi is considerably less than is seen in molar pregnancies evacuated at 12+ weeks. Genetically, complete moles are androgenetic and the maternal genes are not expressed. Molecular genetics can identify whether the CHM is the result of mono- (approximately 75% of CHM) or di-(approximately 25% of CHM) spermic fertilization of the ovum. Pathologically, all trophoblastic tissue stimulates marked angiogenesis in the myometrium. It is common for molar tissue to invade the myometrium, and this can frequently be visualized on ultrasound. Pathologically, invasive mole is a term that has been used to describe myometrial invasion by molar tissue. As the management of these patients is essentially by suction evacuation of the uterine cavity, myometrial tissue is rarely available to the pathologist unless a hysterectomy has been performed.

Partial Hydatidiform Mole (PHM)

Szulman and Surti (3,4) identified a separate pathological entity in the 1970s. PHM produce much less florid hydropic change in the trophoblast, which is usually focal and there is also usually less trophoblastic proliferation. Fetal parts may be present in a PHM and may be apparent macroscopically. PHM are genetically distinct from CHM in that they are triploid conceptuses with two paternal haplotypes and one maternal haplotype. PHM are biologically less aggressive that CHM and a much smaller proportion require chemotherapy. Because the diagnosis of PHM can be easily confused with hydropic change in a normal conceptus, it is likely that the incidence of PHM is still underdiagnosed.

Choriocarcinoma (CC)

CC can occur both after a CHM and a full-term normal pregnancy (5). This is not a premalignant condition, but a frank cancer that is commonly biologically aggressive. The tumor is composed of both cyto- and syncytio-trophoblastic cells. CC is unusual in human malignancies in that it stimulates virtually no stromal reaction, with the tumor essentially growing intravascularly. This explains the clinical complications in patients with CC in that they can either have local hemorrhage or hemorrhage at sites of metastases. CC commonly metastasizes to the lungs, less commonly to the brain, liver, kidneys, gut, and other sites. CC genetically reflects the antecedent pregnancy that gives rise to it: if it arises from a CHM, then it is an androgenetic tumor without maternal genes, and if it arises from a full-term pregnancy, then genetically it has both maternal and paternal haplotypes in the tumor.

Placental Site Trophoblastic Tumor (PSTT)

PSTT is a rare variant of GTD that has been pathologically identified over the last two decades as biologically and pathologically distinct from typical CC (5). PSTT are dominantly cytotrophoblastic tumors that produce less hCG than CC, and on immunostaining only some of the cells stain for hCG, but there is more staining of

the celis for human placental lactogen. PSTT can arise both from a normal pregnancy and from a CHM and the genetics within the tumor reflect the genetics of the conception that gave rise to the tumor. PSTT are locally invasive and, unlike CC, can spread via the lymphatics and are the only form of GTT that reasonably commonly spread by this route. The management of patients with PSTT is different from those patients with CC, as PSTT is quite commonly localized to the uterus and its chemosensitivity is variable. Therefore, hysterectomy is the treatment of choice for patients presenting with localized disease.

EPIDEMIOLOGY AND TUMOR MARKERS

The incidence of CHM does vary worldwide. The incidence in Europe and North America is typically 1 in 1000–1200 pregnancies. In contrast, in the Far Eastern countries such as Korea, Japan, and the Philippines the incidence is of the order of 1 in 500–700 pregnancies. This is shown by the work of Jacobs, who studied the incidence of molar pregnancies in Hawaii (6). While the native Hawaiians had an incidence very similar to the recent European immigrants, patients from Japan and the Philippines had roughly twice the incidence of molar pregnancies. Recent data from Korea and Japan indicate that over the last decades, the incidence of molar pregnancies is decreasing and could well be approaching the incidence in Europe and North America over the next decade or so (7). The reason for this decrease in incidence of molar pregnancies is unclear but given its rapidity, it is likely to reflect an environmental change. The most likely change that has happened over the last few decades is the rapid change from traditional diets to a more westernized diet in countries such as Japan, Korea, and the Philippines.

The incidence of CHM varies with maternal age and therefore there is clearly a maternal factor predisposing to molar pregnancies. If the incidence of molar pregnancy as determined by maternal age is standardized in patients aged 25–29 as 1, the incidence of patients becoming pregnant less than 15 years is six times greater. For patients becoming pregnant at greater than 50 years, it is 411 times greater (8).

At present, we do not understand why some patients develop GTD. Occasionally, patients can have repeated moles with each subsequent pregnancy and if a patient has had one molar pregnancy, then the chances of her having a subsequent second molar pregnancy is 1 in 70. However, the vast majority of these women succeed in completing their families normally.

The trophoblast for all variants of GTD, like the normal placenta in a pregnancy, produces hCG. GTD do not reach clinically detectable sizes without producing hCG that can be monitored in the patients serum and urine. Many assays are now available for measuring hCG for a normal pregnancy. However, there are differences between the hCG production in a normal pregnancy where the bulk of the hCG produced is intact hCG early on in the pregnancy, and in the second and third trimester an increasing proportion of this hCG is nicked (nicked hCG is biologically much less active than intact hCG). In contrast, in GTD, the hCG produced is considerably more degraded with less intact hCG than is produced in a normal pregnancy (9). The degradation products of hCG include nicked hCG, hCG missing the carboxy terminal portion, free α-subunit, free β-subunit, and core α-fragment. In addition, the glycosylation pattern of hCG produced by GTD is different from pregnancy hCG. Assays

detecting only intact hCG which are designed as pregnancy tests are, in general, satisfactory for detecting a raised serum level of hCG but will not detect all the fragments of hCG when monitoring patients with GTD. For this clinical application, an assay, which detects all the variants of hCG described above, needs to be used. We continue to use a radioimmunoassay, which detects intact hCG and its degradation products.

MANAGING GTD

Serial measurements of hCG are crucial and are used in the following ways:

1. To detect whether the trophoblastic disease is dying out or growing;
2. To monitor response or resistance to therapy;
3. To confirm remission of the tumor;
4. To monitor patients after the completion of their treatment to ensure that they remain in remission.

hCG in the management of GTD comes close to being the ideal serum tumor marker for monitoring a human malignancy (Table 1). Although PSTT produce less hCG than the other varieties of GTD, there is detectable hCG in the serum of these patients with clinically active disease.

Although hCG is the molecule that is used for monitoring patients with GTD, the trophoblast does produce a range of other hormones including estrogens and progestogens, and there is no doubt that some women with GTD can subjectively detect a different hormonal profile than is produced in a normal pregnancy. Patients commonly have more nausea and vomiting and malaise when they have GTD. The abnormal trophoblast in GTD can be stimulated in vitro by estrogens and progestogens and we advise that patients with a raised hCG are not put on the oral contraceptive or given exogenous hormones. On a database of more than 10,000 patients registered with molar pregnancies, 30% of patients who were put on exogenous hormones before their hCG reached the normal range required chemotherapy. This is a statistically higher incidence from the rest of the patients who had not received exogenous hormones, where only 7–8% required chemotherapy (1). This is a controversial area in the management of patients with molar pregnancy where North America and the UK differ. In North America, if the hCG is raised at 8 weeks

Table 1 Charing Cross Hospital—Hydatidiform Mole Follow-up

Serum samples for hCG	2-weekly until normal,
Then urine samples for hCG	4-weekly until 1 year postevacuation,
Then urine samples for hCG	3-monthly until 2 years postevacuation.

1. hCG follow-up will range from 6 months to 2 years after evacuation of hydatidiform mole
2. If the patient's hCG values reach normal range within 8 weeks of evacuation, follow-up will be limited to 6 months
3. Patients who do not have normal hCG values within 8 weeks of evacuation should have 2-year follow-up
4. Further estimations of hCG 6 and 10 weeks after any future pregnancies are requested because of a small increase in risk of choriocarcinorna developing in such patients

following evacuation of the molar pregnancy, patients are started on chemotherapy, which results in approximately 25% of these patients receiving chemotherapy. In the UK, we take a more conservative view of exposing patients to chemotherapy and we are prepared to wait longer for the molar pregnancy to die out. This results in treating 7–8% of patients in UK who have bad molar pregnancies with chemotherapy (Figure 1). The suspicion is that those patients whose abnormal trophoblast is dying out more slowly beyond the cut-off point used in North America are those whose disease can be stimulated by exogenous hormones.

That abnormal rests of molar trophoblast can be stimulated by subsequent pregnancies has been suspected for some time, and we have been able to prove genetically that this does in fact happen (10). We have confirmed in several patients, who have had normal pregnancies after a previous molar pregnancy, that the choriocarcinoma developing after that subsequent pregnancy is genetically identical to the original molar pregnancy. The longest interval from the molar pregnancy to developing choriocarcinoma is 7 years. This patient had a molar pregnancy in 1990 that remitted spontaneously. This was followed by two normal-term deliveries and then a Down's syndrome pregnancy, which was terminated. The choriocarcinoma that developed in 1998 was genetically identical to the molar pregnancy in 1990. This case

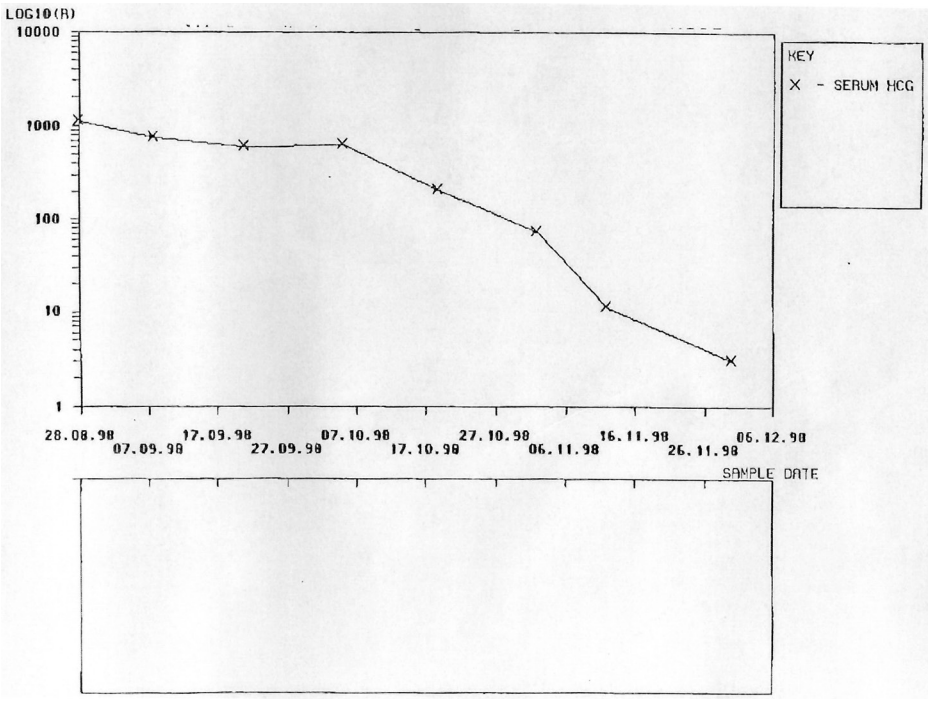

Figure 1 Patient who had a complete hydatidiform mole evacuated and her hCG has fallen slowly to normal over 14 weeks. In North America, she would have been treated 8 weeks after evacuation of the hydatidiform mole. Her hCG follow-up will continue for a total of 2 years, but it will be safe for her to start a further pregnancy after the hCG has been normal for 6 months.

emphasizes the importance of monitoring these patients to confirm that the hCG returns to normal after each subsequent pregnancy.

CLINICAL PRESENTATION AND REGISTRATION

The most common presentation of GTD is a patient with either a PHM or CHM and the patient presents with varying degrees of vaginal bleeding. The differential diagnosis is between a threatened abortion and obviously the less common event of a GTD. Ultrasound now usually allows the distinction to be made on the basis of the presence of the hydropic villi and usually in GTD, the absence of any evidence of a fetus. The initial management of these patients is evacuation of the uterine cavity, usually by suction evacuation, because molar tissue commonly invades the myometrium and it can be easy to perforate the uterus with a metal curette. Following evacuation of the uterine cavity, patients should be registered at a trophobiastic disease center which, in the UK, means Dundee in Scotland, Sheffield for Northern England, and Charing Cross Hospital in London for the rest of the UK. Following registration, patients are monitored with serial hCG estimations to determine whether the molar tissue is dying out, or is going to persist, or grow as reflected in either a plateau of the hCG values or rising values if the disease is growing. In some patients where there is vaginal bleeding and ultrasound shows persistent molar tissue in the uterine cavity, a second evacuation of the uterus may be needed but this should only be performed in selected cases (1). Further evacuations are not in the patient's interest because most of these patients will need chemotherapy. Irregular bleeding in the postnatal period can occasionally be the presenting symptom of CC and, of course, these patients will have elevated hCG values if these are carried out. As CC is an aggressive disease, a significant proportion of these patients will present with symptoms of metastatic disease and it is important in women of childbearing age presenting with widely metastatic disease that an hCG value is checked to exclude the occasional patient presenting with metastatic GTD.

It is important that the minimum number of women are exposed to cytotoxic chemotherapy, and the indications that are used in the UK for selecting patients for treatment for their GTD are shown in Table 2.

PROGNOSTIC FACTORS AND STAGING

All gynecological tumors are included in the FIGO Staging System. This is essentially an anatomical system, which works well for a range of gynecological tumors but is

Table 2 Indications for Chemotherapy

Serum hCG above 20,000 U/L more than 4 weeks after evacuation, because of the risk of uterine perforation. Histological evidence of choriocarcinoma
Evidence of metastases in brain, liver, or gastrointestinal tract, or radiological opacities greater than 2 cm on chest X-ray
Long-lasting uterine hemorrhage
Rising hCG values
HCG in body fluids 4–6 months after evacuation

Table 3 Charing Cross Hospital Scoring System for Gestational Trophoblastic Disease

Variable	Charing cross	Scoring system		
	0	1	2	6
Age (yr)	<39	>39		
Antecedent pregnancy (AP)	Mole	Abortion or unknown	Term	
Interval (end of AP to chemotherapy at Charing Cross Hospital (months))	<4	4–7	7–12	>12
hCG (U/L)	10^3–10^4	<10^3	10^4–10^5	>10^4
ABO (female × male)		A × O O × A 0 or A X unknown	B × A or 0 AB × A or 0	
Number of metastases	Nil	1–4	4–8	>8
Site of metastases	Not detected, lungs, vagina	Spleen, kidney	Gastrointestinal tract, liver	Brain
Largest tumor mass	<3 cm	3–5 cm	>5 cm	
Previous chemotherapy	Nil	Nil	Single drug	2 or more drugs

Low risk: 0–5, medium risk: 6–9, high risk: >9.
Source: Ref. 4.

unsatisfactory for selecting treatment in patients with GTD. There are other more significant prognostic factors for GTD (which are well recognized) that determine the selection of treatment and outcome for the patient more accurately than FIGO staging (10). These are shown in Table 3. Up to now, we have continued to use the Charing Cross System devised by Bagshawe in 1976, which has had only minor modifications since then. This divides patients into low-, medium-, and high-risk categories, depend-

Table 4 Proposed Changes to WHO Prognostic Scoring System, 1999

	Score			
Prognostic factors	0	1	2	4
Age (yr)	≤39	>39		
Antecedent pregnancy (AP)	Mole	Abortion	Term	
Interval (months)	<4	4–6	7–12	>12
hCG (UIL)	<10^3	10^4–10^5	10^4–10^5	>10^5
Largest tumor mass (cm)		3–5	>5	
Site of metastases		Spleen, kidney	Gastrointestinal tract	Brain Liver
Number of metastases identified		1–4	5–8	>8
Prior chemotherapy failed			Single drug	2 or more drugs

Low risk: 0–6, high risk: >6.

ing on how many adverse prognostic variables are present at the time of presentation. The most important adverse prognostic variables in Table 3 are: (1) interval from the last known antecedent pregnancy of >12 months; (2) initial hCG concentration $>10^5$ IU/L; (3) metastases in brain and liver; (4) antecedent pregnancy is a term delivery; and (5) failure of prior chemotherapywith two or more drugs. Using the FIGO anatomical staging alone, some patients would be undertreated, and others overtreated (11). In the future, we plan to use the proposed update of the WHO prognostic scoring system (Table 4).

TREATMENT

Patients in the low-risk category of GTD are treated with methotrexate and folinic acid on a well-established schedule shown in Figure 2 and Table 5. Methotrexate has a number of advantages for these patients in that it does not induce alopecia, it is rarely myelosuppressive, and, apart from mucositis in some patients, is generally well tolerated. With up to 40 years of follow-up, there is no evidence that methotrexate, when used in this schedule, induces second tumors (12). However, it has to be recognized that, in up to 30% of patients in the low-risk category, their disease will become resistant to methotrexate, or the patient will not tolerate methotrexate (usually

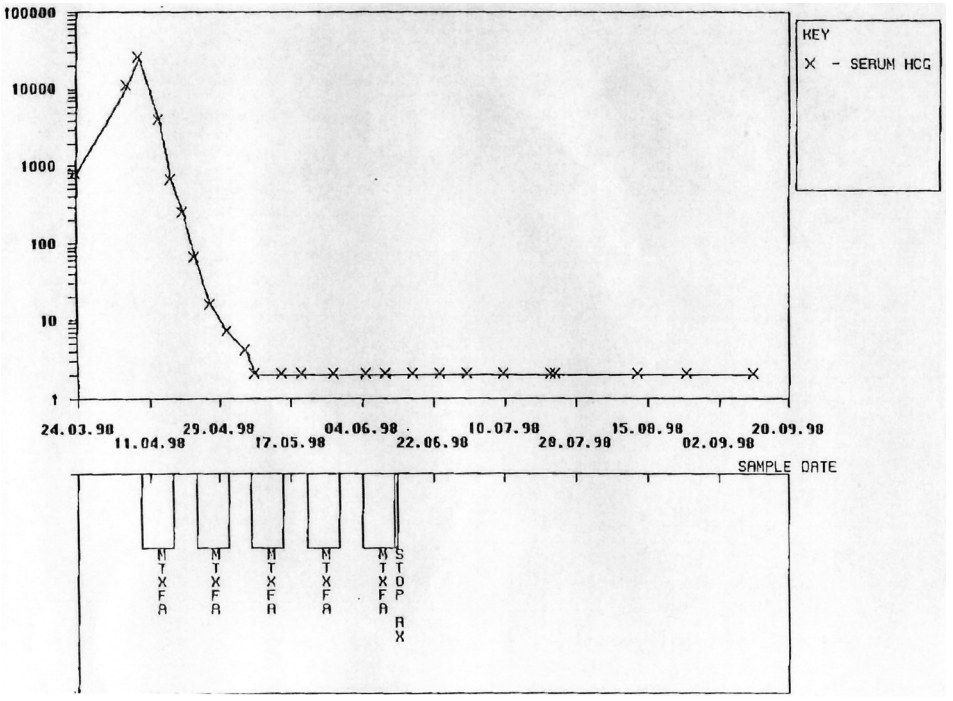

Figure 2 Patient whose hCG rose after evacuation of a hydatidiform mole. There were no adverse prognostic factors (Table 3) and her disease responded promptly to simple chemotherapy with methotrexate and folinic acid.

Table 5 Charing Cross Hospital Treatment Schedules for GTT

LOW RISK

1. Methotrexate/folinic acid
   - Day 1 Methotrexate, 50 mq (i.m.) at 1200 h
   - Day 2 Folinic acid, 15 mg (i.m. or p.o.) at 1800 h
   - Day 3 Methotrexate, 50 mq (i.m.) at 1200 h
   - Day 4 Folinic acid, 15 mq (i.m. or p.o.) at 1800 h
   - Day 5 Methotrexate, 50 mq (i.m.) at 1200 h
   - Day 6 Folinic acid, 15 mq (i.m. or p.o.) at 1800 h
   - Day 7 Methotrexate, 50 mg (i.m.) at 1200 h
   - Day 8 Folinic acid, 15 mg (i.m. or p.o.) at 1800 h
   - Cycles are repeated after a 6-day drug-free interval
2. Actinomycin D
   - Actinomycin D, 0.5 mq (i.v.). Total days 1–5 repeated on 2-week cycle

HIGH RISK

1. EMA-CO
   - *Week 1*
     - Day 1
       - Actinomycin D, 0.5 mg (i.v.) bolus
       - Etoposide, 100 mq/m^2 (i.v), in 500 mL N saline over 30 min
       - Methotrexate, 300 mg/m^2 (i.v.), in 1 L N saline over 12 h
     - Day 2
       - Actinomycin D, 0.5 mg (i.v.) bolus
       - Etoposide, 100 mg/m^2 (i.v.), in 500 mL N saline over 30 min
       - Folinic acid, 15 mq (oral/i.m.) 12-hourly × 4 doses starting 24 h after commencing methotrexate
   - *Week 2*
     - Vincristine 1.4 mg/m^2 (i.v.) bolus (max. 2 mg)
     - Cyclophosphamide 600 mg/m^2 (i.v.), in 500 mL N saline over 30 min
2. RELAPSED (high risk)

EP/EMA regime for patients with disease resistant to EMA/CO

Etoposide and cisplatin alternating weekly with methotrexate, actinomycin D and etoposide

- *Week 1*
  - Day 1 (EP)
    - Etoposide, 100 mg/m^2 (i.v.) in 500 mL N saline over 30 min
    - Cisplatin, 25 mg/m^2 (i.v.) over 4 h
    - Cisplatin, 25 mg/m^2 (i.v.) over 4 h
    - Cisplatin, 25 mg/m^2 (i.v.) over 4 h
- *Week 2*
  - Day I (EMA)
    - Etoposide, 100 mg/m^2 (i.v.) over 30 min
    - Methotrexate, 300 mg/m^2 (i.v.) over 24 h
    - Actinomycin D, 0–5 mq (i.v.) bolus
  - Day 2
    - Folinic acid, 15 mq (p.o.) 12-hourly for four doses to start 24 h after starting methotrexate

because of severe mucositis and occasionally because of severe pleurisy or hepatic damage).

Although the Charing Cross Prognostic Scoring System divides the patients into three groups of low, medium and high risk, we feel confident now that patients presenting with disease in the medium-risk category can be safely treated initially with methotrexate and folinic acid, while accepting that a higher proportion of these patients will become resistant to methotrexate than true low risk patients. In a recent analysis, we identified that patients who become resistant to methotrexate and folinic acid will still respond well to the more intensive schedule that we have used for the high-risk patients and that their short- and long-term outlook is not compromised by this policy. This also simplifies the management of these patients into two groups of low and high risk. Patients in the high-risk group (Table 5 and Figure 3) have been treated with an intensive weekly schedule, the EMA/CO [etoposide, methotrexate, actinomycin D)/[cyclophosphamide, vincristine (Oncovin)] schedule, which we have used since 1979. This schedule has the advantage of relative dose intensity and convenience for a patient only having to be admitted to the Trophoblastic Disease Center for one night per 2 weeks. With modern antiemetics, this schedule is generally well tolerated, although it will induce temporary alopecia in all patients. As the

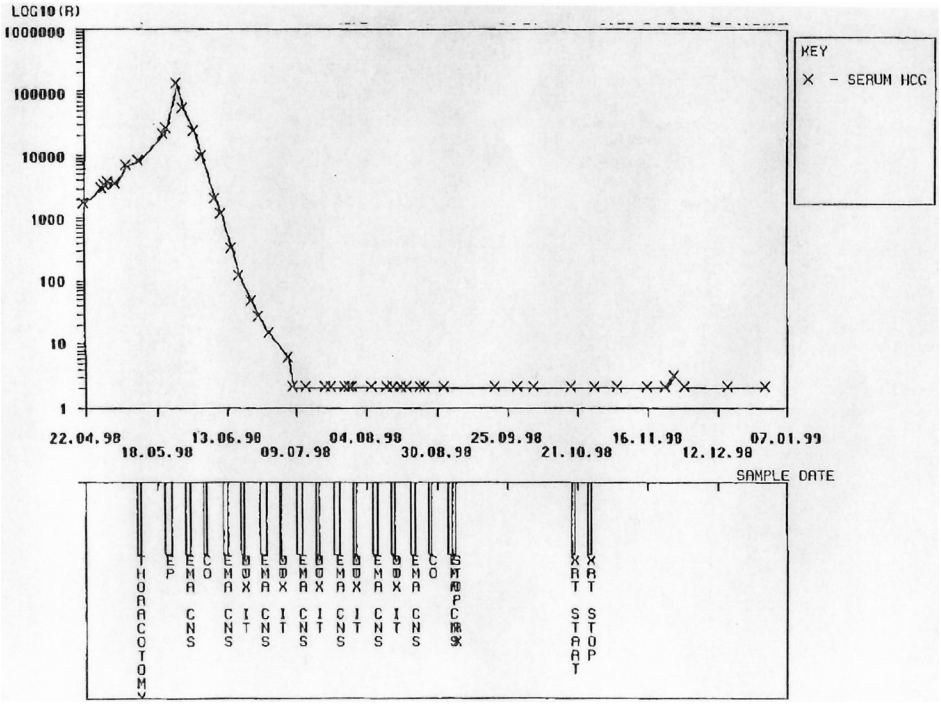

Figure 3 Patient presenting with high-risk disease with metastases in lungs and brain. Genetic analysis confirmed that the choriocarcinoma in her lungs was androgenetic and identical to the hydatidiform mole she had in 1990. She had three intervening pregnancies (see text) before presenting with irregular vaginal bleeding and a raised hCG. She had EMA/CO chemotherapy followed by stereotactic radiotherapy to the deep inoperable lesion in the brain.

chemotherapy is quite intensive, some patients will need granulocyte colony stimulating factor (Neupogen or Granocyte), which is given subcutaneously for 2–4 days between each weekly cycle of chemotherapy. In 1997, we reported results using the EMA/CO schedule in 272 consecutive patients, and the overall survival at 5 years was 86% (13). No deaths from GTD occurred later than 2 years after the start of EMA/CO chemotherapy. However, in a multivariate model, we did identify that there were still adverse prognostic factors for which current treatment did not completely compensate. These were: liver metastases ($p < 0.0001$), interval from antecedent pregnancy ($p < 00001$), brain metastases ($p = 0.0008$), and term delivery of antecedent pregnancy ($p = 0.045$). The EMA/CO schedule of chemotherapy has been widely adopted worldwide for treating high-risk patients with GTD.

For patients whose disease becomes resistant to EMA/CO or relapses after EMA/CO chemotherapy, the outlook is still surprisingly good. Salvage surgery is important in these patients if the main site of disease is known. A combination of salvage surgery with a limited amount of additional chemotherapy, usually introducing cisplatin EP (etoposide, cisplatin) EMA (day 2 of actinomycin D and etoposide is omitted from this schedule) (Table 5) is again given on an alternating weekly schedule, which is effective in the majority of these patients. This approach was followed for patients who have failed on EMA/CO chemotherapy. Out of 47 patients, 33 (70%) were salvaged, usually by the combination of surgery and EP/EMA chemotherapy (13).

PSTT behave differently from other GTDs. They tend to be locally infiltrating and if the disease is limited to the uterus, the treatment of choice is hysterectomy. Where the patient has metastatic disease, the chemosensitivity of PSTT is rather variable. There is the interesting phenomenon of the age of the tumor being a major prognostic variable in patients with PSTT (14). These tumors are rare and in an analysis of 17 patients treated at the Charing Cross Hospital, the 5-year survival is 80%. However, for patients whose last known antecedent pregnancy is less than 2 years from the time of presentation, all 12 patients are alive and in remission with either hysterectorny alone or hysterectomy plus chemotherapy (usually with the EP/EMA schedule). In contrast, in patients presenting greater than 2 years from the last known pregnancy, only 1 (20%) out of 5 is alive.

POTENTIAL FUTURE DEVELOPMENT IN THERAPY

A range of new cytotoxic agents have entered the clinic over the fast decade, but because of the good results in managing patients with GTD with the established agents identified above, there is limited experience of how active they are in patients relapsing after standard treatment. Paclitaxel has some activity in the small number of patients that have been treated. Docetaxel has no documentation so far. Gemcitabine shows activity in the small number of patients treated so far when used in combination with cisplatinum. The role of high-dose chemotherapy with autologous bone marrow support probably has a role in the management of patients with relapsed germ cell tumors not amenable to salvage surgery. It seems probable that in individual patients with relapses from their GTD, high-dose chemotherapy with autologous bone marrow support may be a further option for therapy and there are a few cases where long-term remissions have been induced using this approach.

FOLLOW-UP AND POSTCHEMOTHERAPY SEQUELAE

After completing their chemotherapy for GTD, patients are put on long-term follow-up initially with serum and urine hCG measurements and, in due course, only urine samples are measured. Because GTD cannot grow clinically without producing hCG, these patients are not normally seen for follow-up in the clinic after one initial posttreatment clinic visit. Patients are advised not to try to get pregnant for 12 months after completing their chemotherapy, so that a reasonable length of follow-up has passed to ensure that their tumor remains in remission and also to minimize the potential teratogenetic effect of the chemotherapy on subsequent pregnancies. In patients who have a subsequent pregnancy, hCG follow-up is stopped during the pregnancy, but it needs to be reconfirmed that the hCG returns to normal after the delivery of each subsequent child (Table 1). We have analyzed the posttreatment fertility in patients treated at the Charing Cross center (15). In this analysis of 1211 patients treated, the survival rate was 96%. A total of 728 patients had tried to become pregnant and 607 (83%) reported at least one live birth. Interestingly, there was no difference in the incidence of subsequent successful pregnancies in the 392 women who received only methotrexate therapy and the 336 patients treated with multiagent chemotherapy.

However, chemotherapy is not without long-term risk for patients. We analyzed 1377 patients treated at the Charing Cross who had been followed up for a total of 15,279 person years. Therapy with methotrexate and folinic acid showed no increase in second tumors. However, there was an excess of second tumors in the population treated with combination chemotherapy (16). When compared with age-matched controls from the London region, there was a significant increase in second tumors to 37 when 24 were expected ($p < 0.011$). The tumors that were of increased incidence in this population were myeloid leukemia (relative risk = 17), colon (relative risk = 4–6), and breast cancer, where the survival exceeded 25 years (relative risk = 5.8). These results emphasize that women should not be exposed to chemotherapy unless there is a clear clinical indication and that the small risk of a second tumor has to be accepted in patients with high-risk disease until equally effective and less toxic treatment becomes available.

We have analyzed the influence of chemotherapy on the age of menopause in patients treated at the Charing Cross Hospital. We compared these patients with controls who were women who had had molar pregnancies and did not require chemotherapy. The median age of menopause in the controls was 53 (range 40–57 years) (17). Even treatment with single agent methotrexate brought forward the age of menopause to a median of 51 (range 25–56 years, $p = 0.004$). Combination chemotherapy brought forward the age of menopause even further to a median of 49 (range 25–56 years, $p = 0.004$). Our recommendation is that patients who have been treated with chemotherapy for their GTD should have hormone replacement therapy at least until the median age of menopause in the controls, i.e., 53 years.

CONCLUSION

Trophoblastic disease forms a spectrum from the spontaneously regressing molar pregnancies to the highly aggressive tumors of CC and PSTT. All patients at risk

should be registered with a trophoblastic disease center and monitored with serial hCG values to determine whether they need chemotherapy. With appropriate treatment, few of these patients should succumb from their disease and most should be able to complete their families in due course with the only small but significant side effects of treatment being: (a) a small risk of induction of second tumors in patients receiving combination chemotherapy and (b) bringing the menopause forward by a few years.

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Rare Tumor: *Melanoma—Lymphoma—Sarcoma*

Pissamai Yuenyao and John J. Kavanagh
The University of Texas M.D. Anderson Cancer Center, Houston, Texas, U.S.A.

MELANOMA

Gynecologic melanomas are rare, accounting for fewer than 1% of all gynecologic cancers and only 2–3% of all melanomas (1). Melanomas are common in women who have had excessive exposure to the sun and may also occur in areas of the body not exposed to the sun in white women with a history of excessive sun exposure. The mechanism is unclear. It may be related to sun-induced circulatory melanocyte-stimulating factors such as melanocyte-stimulating hormone. Usually, melanocytes are derived from the neural crest. Most melanomas arise in the skin, but they may also arise from mucosal surfaces or at other sites to which neural crest cells migrate. Abnormal melanocytes may produce growth factors that upregulate melanoma growth. However, spontaneous regression of melanomas may be related to the immune system (1).

Cellular Classification

Clinicopathologic cellular subtypes of malignant melanoma include the following (2).

1. Superficial spreading is the most common type and tends to remain relatively superficial early in its development. Prognosis, both long term and short term, is excellent.
2. Nodular type is the most aggressive lesion. This raised lesion penetrates deeply and may metastasize widely, so prognosis is very poor.
3. Lentigo is a flat freckle that may become quite extensive but also tends to remain superficial.
4. Acral-lentiginous is common lesion in palm, plantar, and subungual areas.

Staging

Melanomas are staged according to one of three available microstaging systems, which base prognosis on either depth of local invasion or tumor thickness. The FIGO staging used for squamous lesions is not applicable to melanomas because the melanoma

lesions are usually smaller and the prognosis is related to depth of penetration rather than to diameter (1,3). The Clark's level system used for cutaneous melanoma is less readily applicable to vulvar melanoma because of the lack of a well-defined papillary dermis in vulvar skin and the mucous membrane of the labia (4). Breslow's classification is believed to be more accurate and can predict lymph node metastases (5), but it fails to predict survival (6,7). Chung's level is more predictive because it determines the depth of invasion by measuring depth with a micrometer in relation to the epidermis (2). Most authors prefer to use Chung's modification (2,6,7).

Microstaging

	Clark's level (4)	Chung modification (3)	Breslow system (5)
I	Intraepithelium	Intraepithelium	<0.76 mm
II	Into papillary dermis	≤1 mm from granular layer	0.76–1.50 mm
III	Filling dermal papillae	1.1–2 mm from granular layer	1.51–2.25 mm
IV	Into reticular dermis	>2 mm from granular layer	2.26–3.0 mm
V	Into subcutaneous fat	Into subcutaneous fat	>3 mm

Melanoma of the Vulva

Melanoma is the second most common malignant tumor of the vulva (1). Based on a report from the United States, most of vulvar melanoma patients are older than 50 years old (8), whereas a study from Sweden reported that the majority were at least 60 years old (9). Morrow and Rutledge (10) evaluated 30 women with vulvar melanoma, of which 78% were white, 6.7% were black, and the rest were Hispanic. The most common sites of vulvar melanoma are the labia minora and the clitoris (2). Melanoma should be suspected in any pigmented lesion or any mucosal lesion that changes in size or color, becomes itchy or bleeds spontaneously (10,11). Biopsy should be considered. Women at increased risk of developing melanoma include those with a family history of melanoma and those with dysplastic nevi elsewhere in the body; the family history of other nonmelanoma cancer can also increase the risk of vulvar melanoma (10).

Treatment and Prognosis

The most widely used treatment modality for vulvar melanoma is surgery. Most surgeons have abandoned radical vulvectomy with bilateral inguinofemoral lymphadenectomy as the treatment of choice over the last 20 years (3,10,12), because the procedure is associated with multiple complications and has failed to improve survival rates. Most recent reviews have recommended some form of partial vulvectomy or radical wide excision, with or without inguinal lymphadenectomy (11,13). Systemic chemotherapy in metastatic melanoma remains palliative. Dacarbazine and cisplatinum have been reported to have activity, with a response rate of 20% when evaluated as single agent (14). Interferon alfa-2b is the first agent to show significantly prolonged relapse-free and overall survival when given as adjuvant therapy in a randomized controlled trial in patients whose tumor invaded to a depth of more than 4 mm, or who

had regional metastases (15). Estrogen receptors have been observed in human melanomas, and occasional responses to tamoxifen have been reported (16,17). Extensive studies have been activated for evaluation of the reliability and accuracy of sentinel node detection by radiopharmaceutical or blue dye mapping techniques, which may improve surgical outcome (18).

The overall survival rate in vulvar melanoma is approximately 50% (2,10). Patients with lesions invading to 1 mm or less have an excellent prognosis, but as depth of invasion increases, prognosis worsens. Pelvic nodal metastases do not occur in the absence of groin node metastases (10,12). If the melanoma is associated with pelvic node metastases, the prognosis is always poor. The survival rate after recurrence is only approximately 5% (2).

Melanoma of the Vagina

Malignant melanoma is the second most common cancer of the vagina. Most lesions occur in the lower third, particularly on the anterior wall. Vaginal melanomas also arise from nevi and occasionally from melanoses, which are areas of benign melanocytes in the basal layer of the vagina. A majority of patients are older than 60 years. Primary vaginal melanomas are nodular or polypoid, gray or black, soft masses. The overlying epithelium is frequently ulcerated (19). Vaginal bleeding is the most common clinical presentation, followed by vaginal discharge and presence of a mass (20). Microscopically, these tumors may be composed of spindle, epithelioid, or small lymphocyte-like cells. The cells may not be pigmented. The poorly differentiated lesions are difficult to distinguish from sarcoma or squamous cell carcinoma. Approximately 69% of melanocytes may spread into the adjacent epithelium (19).

Treatment and Prognosis

Treatment of primary vaginal melanoma continues to be radical surgery. Results of treatments are poor because only 5% of the patients have lesions less than 2 mm thick (19). Reid and associates (21), in a meta-analysis of different modalities of treatment, showed that there was no significant difference in survival or disease-free interval for radical vs. conservative surgery. Patients who underwent radical surgery had a better 2-year survival rate than those who underwent conservative treatment (22). Inguinal lymph node recurrence and distant metastases were the most common sites of treatment failure in patients treated with conservative surgery or radiotherapy (23,24). Chemotherapy has shown no benefit in the therapy for vaginal melanoma (19). The overall 5-year survival rate was only 5%, and even extended radical operations produce poor outcome (25). The initial recurrence site is the vagina (19). Size of the lesion was the best prognostic factor (26). Interferon alfa-2b has been shown to improve relapse-free and overall survival rate in high-risk cutaneous melanoma (15).

Melanoma of the Cervix

Most melanomas of the cervix are metastases, rather than primary tumors. A review of literature revealed only 27 cases of primary melanoma of the cervix. Most patients are older than 55 years. The most common presenting symptom is abnormal vaginal

bleeding (27,28). The lesions appear macroscopically as strongly colored, polypoid masses, either pigmented or nonpigmented. Microscopic examination reveals are bizarre, pleomorphic cells. Because the cervix is a very unusual site for melanoma, the FIGO system, rather than that of Clark or Breslow, has been recommended for staging. Most patients have FIGO stage I or II disease at the time of diagnosis (27).

Treatment and Prognosis

Radical hysterectomy, either with or without pelvic lymphadenectomy, has been recommended (27,29). Radical hysterectomy for a lesion that is confined solely to the cervix has been recommended (1). Vaginectomy should be performed to assure clean surgical margins of at least 2 cm (30). Patients who underwent elective lymphadenectomy had no better survival rate than those who did not (31). Adjuvant radiotherapy may improve local control if the surgical margins are close. The 5-year survival rate is poor, not exceeding 40% for stage I disease (28).

LYMPHOMA

Genital tract lymphoma is a rare disease, and information on diagnosis, treatment, and outcome is limited. The majority of these tumors are non-Hodgkin's lymphomas, most commonly in lower genital tract involving the cervix (32). For staging of lymphomas of the genital tract, either the Ann Arbor classification or the FIGO classification has been recommended, although their utility depends on histologic accuracy. The most common used chemotherapy agents include the combination of cyclophosphamide, doxorubicin, vincristine, and prednisolone (33).

Lymphoma of the Vulva

Primary extranodal lymphoma of the vulva seems to be quite unusual. Most patients are in their third to sixth decade of life (32). The most common presenting symptom is vulvar mass (32,34). The other symptoms include vaginal bleeding, postcoital bleeding, and urinary symptoms (32). Biopsy of the lesion should be considered. Fine-needle aspiration of the tumor may be part of the diagnosis (35).

Treatment and Prognosis

Treatment is by surgical excision, followed by chemotherapy and/or radiation (33). Delayed diagnosis and inappropriate management may lead to widespread destruction of lower genital organs (36).

Lymphoma of the Vagina

Most primary lymphomas involving the vagina are diffuse large-cell type, accounting for 1% of primary extranodal lymphomas. Localization of lymphoma in the vagina is very rare (37). Diagnosis is frequently delayed by the lack of specific symptoms; common symptoms include abnormal vaginal bleeding, abnormal vaginal discharge, and perineal discomfort. The tumor is usually infiltrative, and biopsy under colposcopy may yield a false-negative result because these tumors can present at any age and

may mimic other diseases of the vagina clinically and pathologically (38). Intact endothelium is present (37).

Treatment and Prognosis

In the past, most patients were treated with radical surgery, either alone or in combination with radiation therapy. A recent study showed the effectiveness of chemotherapy followed by localized radiation therapy; this combined modality regimens replaced early surgery. In standard management of lymphoma of the vagina, only stage I and, depending on grading and histologic subtype, stage II are exclusively treated with radiotherapy, whereas chemotherapy alone or in combination with radiation is used in all other stages. Chemotherapy should be considered in young women to preserve reproductive function (38,39).

Lymphoma of the Cervix

Primary lymphoma of the cervix was reported to constitute approximately 0.06–0.12% of the non-Hodgkin's lymphomas (40). Abnormal vaginal bleeding is the most common presenting symptom (41–44). The cervix becomes diffusely enlarged with tumor infiltration. Biopsy can give a false-negative result. Differential diagnosis should include infection, sarcoma, and small-cell carcinoma of the cervix (41,43). Immunohistochemical studies useful in making the diagnosis include leukocyte-common antigen, B-cell and T-cell antigens, and cytokeratin (45).

Treatment and Prognosis

The therapeutic approach to primary lymphoma of the cervix is still limited. The majority of patients has been treated with radiation. Chemotherapy seems to be appropriate in more advanced disease or in patients with a recurrence (41–44). Neoadjuvant chemotherapy followed by surgery has advantages such as reduction of tumor volume, which makes the subsequent surgery simple, and may help prevent micrometastases and preserve ovarian function in young women (44). Irinotecan (46) and paclitaxel (47) have been shown to induce modest antitumor activity in lymphomas. The histologic grading correlates with the prognosis (37). The combination of chemotherapy and irradiation may be the most effective treatment regimen for cervical lymphoma (48).

SARCOMA

Sarcomas of the genital organs, fortunately, are rare, because the prognosis is quite often poor. Abnormal vaginal bleeding is the common symptom, which alerts physicians into thinking about the possibility of a rare genital neoplasm, especially in childhood, because early detection may lead to cure and preservation of future fertility.

Sarcoma of the Vulva

Primary sarcomas of the vulva are rare. Generally, sarcomas appear morphologically as comprising spindle-shaped, round, or pleomorphic cells, which do not seem to be of

epithelial origin. These tumors are often positive for specific stains such as reticulum or immunoperoxidase. Biopsy reveals the lesion that contains normal skin, which is useful for diagnosis. The lesion tends to occur in younger women (49).

Leiomyosarcoma is the most frequent primary vulvar sarcoma. It commonly arises in the labia majora or Bartholin's gland region. The tumors are usually larger than 5 cm in diameter when detected, and may be deep within the subcutaneous tissue. Leiomyosarcoma usually appears as a painful mass; lymphatic metastases are uncommon (50). Primary treatment is wide surgical excision. Adjuvant radiation may be helpful for high-grade and locally recurrent low-grade lesions (51). The recurrent disease was associated with three main determinants: diameter greater than 5 cm, infiltrating margins, and five or more mitotic figures per 10 high-power fields (50). Local recurrence atypically appears within 1–2 years.

Malignant fibrous histiocytoma (MFH) is the second most common sarcoma of the vulva, usually occurring in middle-aged women. Histologic findings may confuse these tumors with liposarcoma, pleomorphic rhabdomyosarcoma, or poorly differentiated sarcoma. Presentation varies from an asymptomatic lump to a painful, ulcerated mass, depending on lesion size. Local recurrence and lymphatic and hematogenous metastases often occur (52). Adjuvant radiation therapy reportedly reduces the rate of local recurrence (53). Radical local excision is the treatment of choice and ipsilateral groin node dissection is recommended for treatment of large, deeply invading lesions (54).

Epithelioid sarcoma is a malignancy of uncertain histogenesis. It commonly occurs in the lower extremities of young adults. In the few patients reported to have tumors in the vulvar area, this tumor was more malignant than the extragenital variant. Both local failure and distant metastases are common. These sarcomas can be misdiagnosed as malignant rhabdoid tumor or a Bartholin's cyst, leading to inadequate treatment (55).

Rhabdomyosarcomas are the most common soft-tissue sarcomas of childhood. In the Intergroup Rhabdomyosarcoma Study I and II with primary tumors of the female genital tract, all patients were managed with combination chemotherapy, comprising vincristine and dactinomycin or these drugs with cyclophophamide, with or without radiation therapy. Wide local excision of the tumor, with or without inguinofemoral lymphadenectomy, was carried out before or after the chemotherapy, and patients were in long-term remission (56).

Sarcoma of the Vagina

The most common form in infants and children is sarcoma botryoides, while the most common variant in adult is leiomyosarcoma (57).

Leiomyosarcomas are usually bulky and occur in the upper vagina, where they may cause disturbances in micturation (58). Curative rate is high in patients who have tumor with low malignant potential. The benefit of adjuvant radiotherapy is uncertain, but it should be considered for patients with a high-grade lesion (51).

Rhabdomyosarcoma is a malignant tumor of the rhabdoblasts. Diagnosis follows the discovery of a vaginal mass, which resembles a bunch of grapes (hence the term botryoides). Other common symptoms include abnormal vaginal bleeding and discharge. Sarcoma botryoides is usually found in the vagina during infancy and early childhood, in the cervix during the reproductive years, and in the corpus uteri

during the postmenopausal period. The peak incidence of vaginal sarcoma botryoides is at approximately 3 years of age, and the lesions may rarely be present at birth (59). The characteristic microscopic feature is the presence of cross-striated rhabdomyoblasts (strap cells). Exenteration was usually performed for these tumors in the past, but the associated survival rate is poor. Recently, conservative surgery has been performed in conjunction with preoperative or postoperative chemotherapy and radiation, with significantly prolonged survival. The usual chemotherapy regimen has consisted of vincristine, actinomycin D, and cyclophosphamide (60). The pelvis is the first site of recurrence in all treatment failures (61).

Sarcoma of the Cervix

Sarcoma is one of the least common primary neoplasms of the cervix, with a 0.5% incidence rate of cervical cancers. The overall prognosis is poor, except for the adenosarcoma subtype (62). With leiomyosarcoma of the cervix, the presenting symptoms may include abnormal menstruation, such as hypermenorrhea, and abdominal distention. Adenosarcoma are soft, tan, polypoid or papillary masses. Microscopic examination showed a biphasic pattern with mesenchymal and epithelial component (63,64). Sarcoma botryoides of the cervix is extremely rare.

Treatment of cervical sarcoma has consisted of hysterectomy. In adenosarcoma, platinum-based chemotherapy administered up front in inoperable cases has definite efficacy. In localized sarcoma botryoides in the cervix, surgical resection is not an adequate therapy; adjuvant chemotherapy should always be given, even at a very early stage (65). Conservative surgery such as simple hysterectomy or local excision, often performed after neoadjuvant chemotherapy vincristine, doxorubicin, and cyclophosphamide (66), or doxorubicin and ifosfamide (67), has been reported. The role of radiation is unclear.

Sarcoma of the Ovary

Malignant mixed mesodermal sarcoma is the most common type of ovarian sarcoma, but only 100 cases have been reported. Most lesions occur in nulliparous and menopausal women. The presenting symptoms are similar to those of other ovarian malignancies. The lesions are biologically aggressive, and most patients have evidence of metastases (68). Surgery is the mainstay primary treatment, as in epithelial ovarian carcinoma. Combination of radiotherapy with vincristine, dactinomycin, and cyclophophamide showed effectiveness, but chemotoxic effects should be observed and treatment modifications recommended (69). In a group treated with a similar protocol as part of a Gynecologic Oncology Group study, there was no significant difference in survival or stage distribution among the patients with carcinosarcoma and those with mixed mesodermal sarcoma (70). No significant survival advantage was observed in patients who underwent optimal cytoreduction compared to patients who did not (71,72). Combinations of cisplatin, doxorubicin, and cyclophosphamide or cisplatinum and doxorubicin has been reported to yield response rates of 85% (71). A recent study showed that the mean survival duration of patients whose tumors were positive for estrogen receptor was significantly longer than for patients whose tumors were not positive (73).

Other ovarian sarcomas that have been reported include rhabdomyosarcoma and leiomyosarcoma in both perimenarchal and postmenopausal women. Aggressive combination therapy may improve survival rate (74).

Sarcoma of the Fallopian Tube

Primary sarcoma of the fallopian tube is very rare: fewer than 50 cases have been reported. Clinical signs and symptoms are usually nonspecific and include lower abdominal pain, fever, and vaginal bleeding. The age at diagnosis varies from 14 to 76 years, with a mean of 55 years (75). Treatment of rhabdomyosarcoma has been reported by The Intergroup Rhabdomyosarcoma Studies. Standard of treatment is multimodal therapy consisting of combined surgical resection, chemotherapy, and radiotherapy (76). The most widely used chemotherapy regimen includes vincristine, dactinomycin, and cyclophosphamide. Important prognostic factors appear to include the extent of disease at the time of diagnosis and site of the primary tumor, with sites that produce symptoms earlier having a better prognosis (77).

Other rare primary sarcomas of the fallopian tube, leiomyosarcoma and adenosarcoma, have been reported. Surgical resection followed by adjuvant doxorubicin and cisplatinum may prolong life by 2 years. Combination of chemotherapy include doxorubicin, cyclophosphamide, and with or without cisplatin, after initial treatment has been shown to increase the rate of survival (78,79).

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