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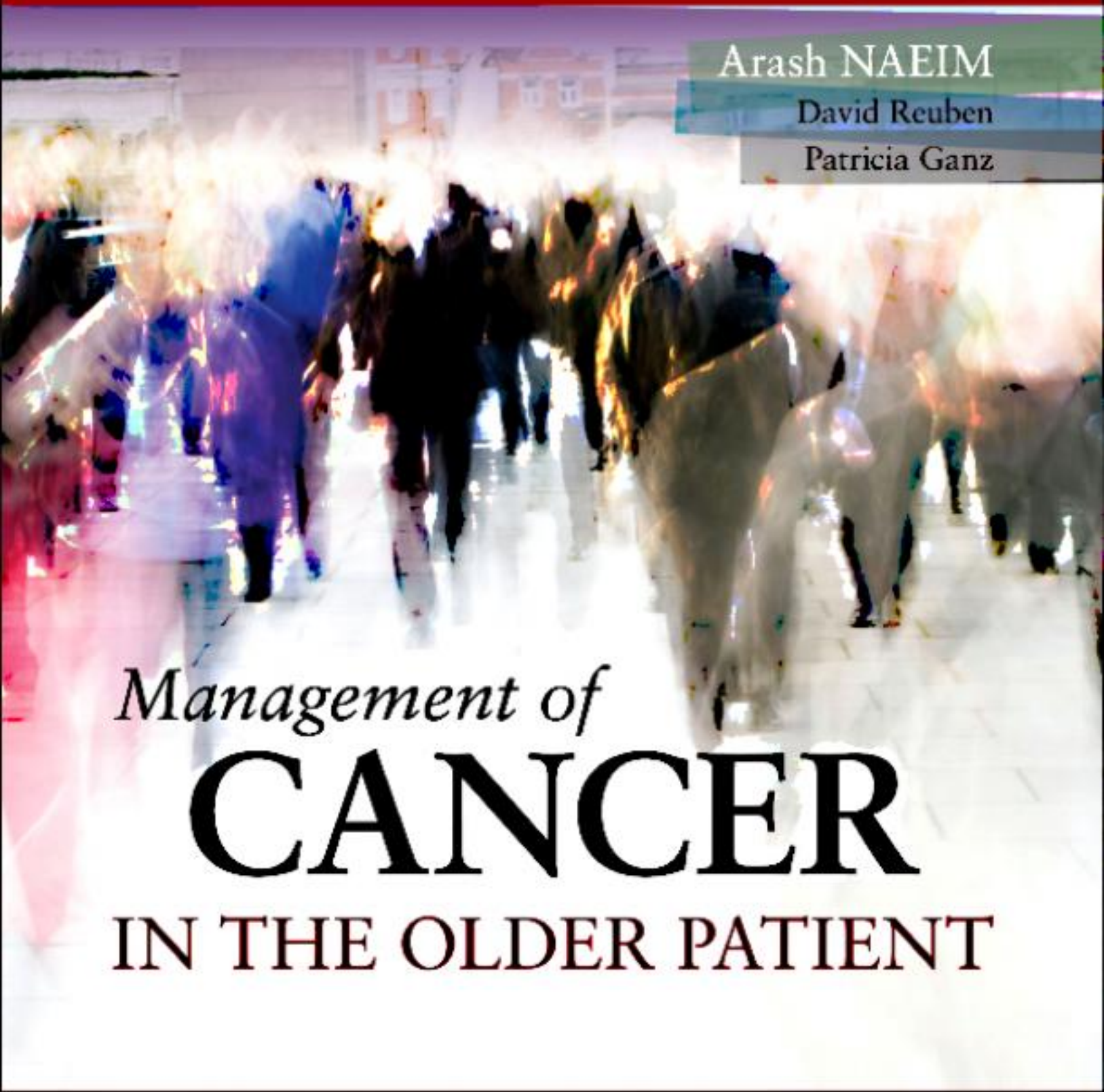

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Management of CANCER IN THE OLDER PATIENT

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To Arya and Shayan for their inspiration. My hope is that I can be nearly as good a father to you as my dad is to me.

To all those older individuals with cancer who have taught me that life is richer when living with dignity, quality, and passion.

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For all my older patients, friends, and family members who have fought their battles with cancer.

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Patricia Ganz

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PREFACE

The population is aging. It is estimated that 1 in 5 individuals will be older than 65 years by the year 2030. The risk of cancer increases with age, with persons older than age 75 having the highest risk. Individuals older than age 65 also account for greater than two thirds of all cancer deaths. The demand for cancer care will steadily grow, but workforce projections for the next decade demonstrate that the supply of oncologists will not meet this demand. Therefore it is critically important for primary care providers (general practitioners, family practitioners, internists, and nurse practitioners) to become more familiar with the *Management of Cancer in the Older Patient*.

A frequent comment among general oncologists is that they mostly see older individuals, a viewpoint supported by the epidemiologic data. It is important to note that most of the evidence supporting treatment recommendations in oncology is derived from clinical trials where older individuals were significantly underrepresented. Moreover, those older individuals who did participate in clinical trials usually represented a healthy cohort with minimal competing comorbid conditions and little impairment in physical functioning. As a result, it is often hard to know how to generalize the evidence base to everyday practice or apply it to the average older patient with cancer.

Older individuals tend to be a more heterogeneous population. Although only 1 in 10 individuals has a functional impairment between the ages of 65 and 74, this number increases to almost half for patients over the age of 85. Similarly, as individuals age, the number of other co-existing conditions (comorbidity) increases as well, with individuals over the age of 75 having, on average, 5 other health conditions. Age, functional status, and comorbidity alter the lens through which providers view the older patient with cancer. These perceptions affect their approach to screening and prevention, diagnosis, treatment, supportive care, and survivorship care. In these areas, the role of the primary care provider extends beyond just screening, diagnosis, and referral to also include comanagement, aftercare, and long-term surveillance.

In parallel to the clinical practice of cancer care, the field of oncology is quickly being transformed. There is a large growth of research in molecular and cell biology, as well as immunology. Over the last decade, numerous new targeted therapies have received approval from the Food and Drug Administration. These newer therapies often have a more pronounced therapeutic effect but have different side effect profiles than traditional chemotherapy. There is an increasing trend toward personalizing or individualizing treatment based on the underlying biology of the individual and/or the tumor. In older patients with cancer, it will be important to combine these advances with the recognition that host factors that are markers for frailty also need to be factored into the process of individualizing care. The drug advances in cancer care are also associated with the high cost of treatment, which, when combined with increasingly large numbers of elderly patients, will put a strain on the resources allocated to health care.

The *Management of Cancer in the Older Patient* examines the key issues that a primary care provider would encounter in providing and supporting the care of an older patient. The book is divided into six sections. Section I, Screening/Prevention, examines key guidelines for screening and discusses populations for which screening may be underutilized or overutilized. Section II, Diagnosis/Assessment, examines diagnostic workup, assessment (geriatric assessment, functional assessment, and comorbidity), as well as the value of a second opinion. Section III, Treatment, examines modalities of treatment (surgery, radiation, and chemotherapy) with special chapters on novel and targeted therapies, clinical trials in the elderly, and shared treatment decision making. Section IV is focused entirely on supportive care with special chapters on insomnia and complementary and alternative care. Section V focuses on rehabilitation, surveillance, and survivorship. Section VI, the last section, examines important issues including home care, caregiver burden, communication, end of life and hospice, ethical issues, and economic issues important to managing the older cancer patient.

Most of the chapters in *Management of Cancer in the Older Patient* are case based with the use of summary and key tables to help synthesize the information. Whenever possible, we have included a suggested reading list that may be valuable to the reader. The goal of this book is to take a multidisciplinary approach to traditional topics such as prevention, screening, diagnosis, treatment, and survivorship while applying a geriatric lens to these issues, focusing on functioning, assessment, frailty, quality of care, quality of life, caregivers, and cost. Our hope is that this book makes a very practical contribution to improve the decision-making process of primary care providers, who often serve as the central resource or "quarterback" in the care of older complex patients. The editors are excited to contribute to a field that will be increasingly important as the number of older Americans with cancer rises dramatically in the coming decades.

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Arash Naeim

CHAPTER

1

The Epidemiology of Cancer and Aging

Kerri M. Clough-Gorr and Rebecca A. Silliman

Aging, a highly individualized process, is known to be related to changes in the physical, cognitive, emotional, social, and economic status of older adults. Increasing age is primarily associated with negative changes in these areas (e.g., increased comorbidity, decreased function, limited social support). These age-associated changes may occur singly or in combination, with broad variation among older adults. Moreover, they often result in considerable consequences not just for aging individuals themselves but simultaneously for health care systems, families, and caregivers.

A common late-life experience is a cancer diagnosis. According to the National Cancer Institute (NCI), aging is the most important risk factor for cancer, with most cancers occurring in persons aged 65 years and older. Over the last several decades, cancer trends have been changing contemporaneously with our knowledge of aging. Because of the increased heterogeneity of older populations, treating older cancer patients seldom means treating only the cancer. Furthermore, with improved screening and treatments, larger numbers of older cancer patients are experiencing longer-term survival. Unfortunately, even though older adults make up the largest segment of the cancer population, they are often undertreated and are seldom included in clinical trials. Few clinical trials are even designed to identify optimal treatments for them.

The combined effects of cancer and aging are of concern because of graying populations worldwide (a larger proportion aging in industrialized countries; greater numbers aging in developing countries). Although we cannot truly anticipate the changes that rapid population aging will bring, we can attempt to understand the epidemiological patterns of aging and cancer, where they intersect, and their potential implications. Such understanding will provide a frame of reference to address age-related disparities in research, education, and treatment in the older adult cancer population. Because of growing numbers alone, it is certain that management of cancer in older adults will continue to be a complex, resource-intensive, and increasingly common problem.

What follows herein is an overview of topics pertaining to the epidemiology of cancer and aging. Trends in cancer incidence and mortality are examined, and the specific characteristics and unique issues related to older cancer patients are described. Special attention is provided to the survivorship experience of older cancer patients, along with a summary of the challenges associated with studying them.

INCIDENCE AND MORTALITY: THEN AND NOW

There have been remarkable changes in the United States population over the last century. One hallmark of these changes is the expansion of the older (65 years and older) population (Figure 1-1).[1] U.S. Census Bureau estimates show that the percentage of Americans 65 years and older has more than tripled (from 4.1% in 1900 to 12.8% in 2008). The older population itself is getting older; in 1940, 4.1% of the older population was 85 years or older (the "oldest old"), whereas in 2008, 14.7% was in this group. This trend toward greater longevity is reflected by tremendous growth in the centenarian population (approximately 120% from 1990 to 2008) and the current life expectancy estimates of older adults (Figure 1-2).[5,7] After the middle of the twentieth century, life expectancy at age 65 years increased moderately (5 years for men, 8 years for women) relative to life expectancy gains at birth. In recent years (1990 to 2005), the gap in life expectancy between older white and black people has been stable and narrower than at birth (difference at age 65 years approximately 2 years for men and 1 year for women).[8]

These aging trends will hasten with the senescence of the Baby Boom generation, but, on the basis of previous life expectancies, not necessarily uniformly across sex and race/ethnicity. The number of older Americans is expected to more than double by 2050 (increasing from 39 million in 2008 to 89 million) with substantial growth in older minority segments (Figure 1-3) and increasingly in female "oldest-olds."[2] The U.S. Census

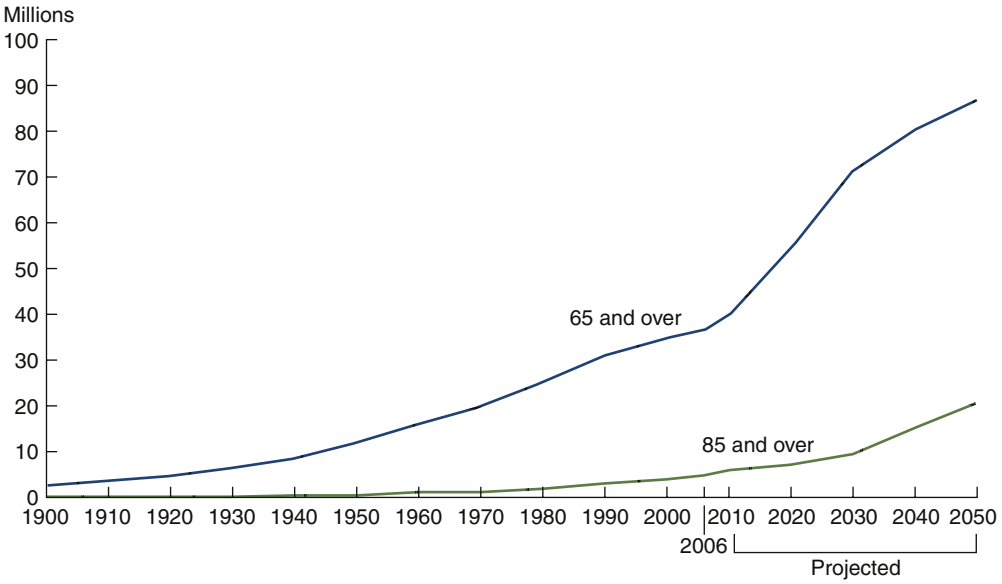

FIGURE 1-1 Number of people age 65 and older in the United States, by age group, selected years 1900-2006 and projected 2010-2050. *(Adapted from U.S. Department of Health and Human Services: A Profile of Older Americans: 2008. Washington, DC: Administration on Aging, 2008.)*

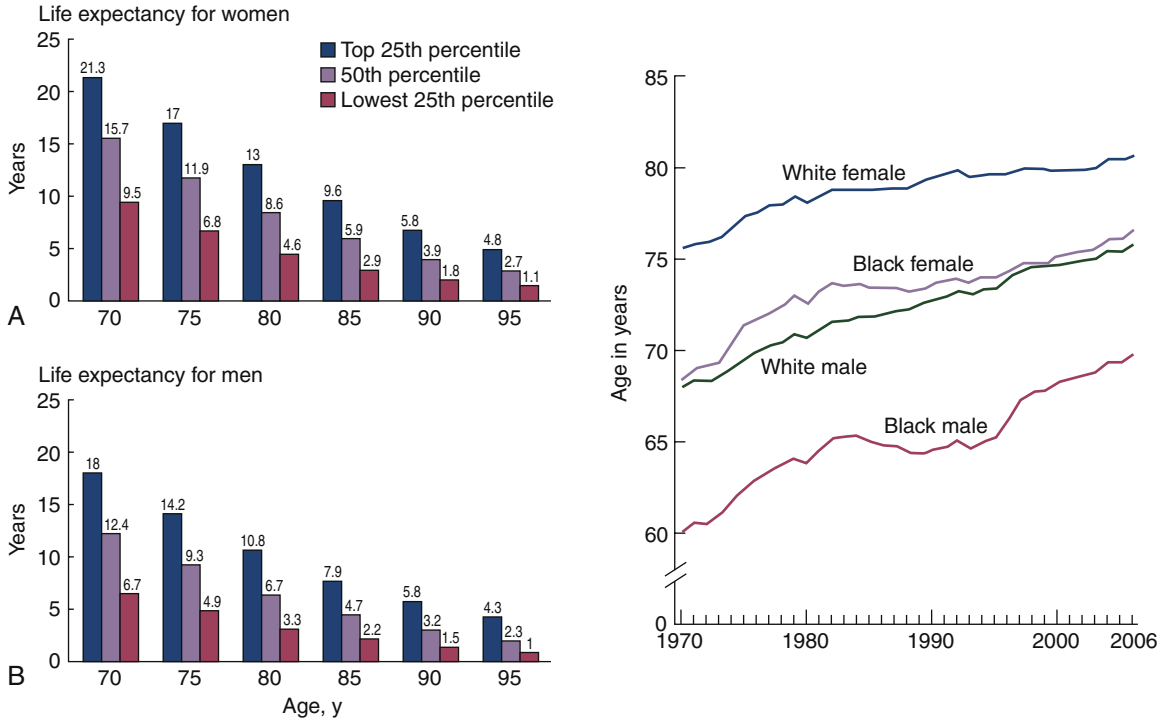

FIGURE 1-2 Life expectancy of older adults in the United States **A,** Upper, middle, and lower quartiles of life expectancy by sex at selected ages. *(Adapted from Walter LC, Covinsky KE. Cancer screening in elderly patients: a framework for individualized decision making. JAMA 2001;285:2750-6.)* **B,** Life expectancy for women and men by race 1970-2006. *(Adapted from Heron et al. Deaths: final data for 2006. National Vital Statistics Reports; Vol 57, No 14. Hyattsville, MD: National Center for Health Statistics; 2009.)*

Bureau also projects by 2050 a nearly 225% increase in persons aged 100 years and older (from 2008) and that, for the first time in United States history, the population older than 65 years will outnumber the population younger than 15 years. Figure 1-4 shows the overall projected age shift in the U.S. population pyramid from 2000 to 2050.[2]

As older Americans live longer than ever before, the inevitable shift in the population age structure foreshadows many challenges. Importantly, whether or

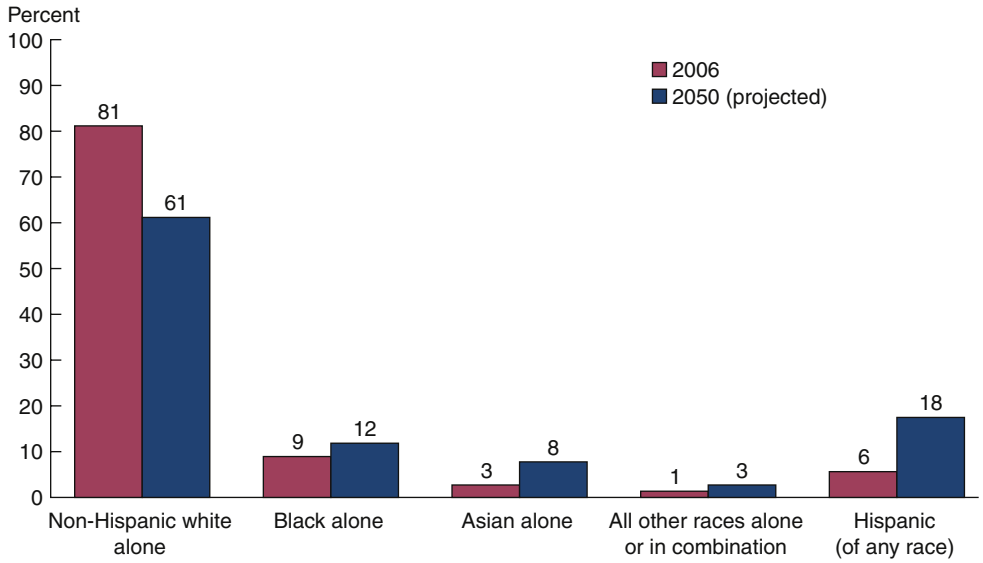

FIGURE 1-3 United States population age 65 and older by race and Hispanic origin, selected years 2006 and projected 2050. *(Adapted from U.S. Department of Health and Human Services: A Profile of Older Americans: 2008. Washington, DC: Administration on Aging, 2008.)*

not years added later in life are healthy, enjoyable, and productive depends in large part on prevention and control of potentially debilitating and sometimes fatal chronic diseases such as cancer. Figure 1-5 shows that cancer is the fourth most common chronic disease and the second leading cause of death in older adults in the United States.[1] Cancer is a disease that disproportionately affects older adults. Over the past decades, cancer incidence and mortality trends in the oldest population showed a greater burden than for those in the so-called young-old (65 to 74 years) and younger populations (Figure 1-6).[3]

The increased risk of cancer in older adults is proposed to be related to two main age-linked processes. Because cancer is a multistep process, over the course of longer lives there is both increased opportunity for DNA damage and longer exposure to potential carcinogens. Older adults, therefore, may have greater potential for accrued molecular damage coexisting with age-related decreased cellular repair activity leading to malignancies. This is supported by the epidemiological evidence, which consistently shows at least twofold or higher all-cause cancer mortality and incidence rates in older adults since SEER reporting began in 1975. From 2002 to 2006, the median age at diagnosis for cancer of all sites was 66 years.[9] However, looking at more finely stratified older age groups during the same period, approximately 24.9% of all cancers were diagnosed between 65 and 74 years, 22.2% between 75 and 84 years, and 7.6% at 85 years of age and older. These patterns hold across most primary cancer types. Within the older age groups, controversies exist over evidence pointing to a potential drop of cancer incidence and mortality in the oldest-old group. These data raise unresolved questions as to whether the effect is real and, if so, whether it is due to selective survival, an interaction with late-life biology, or both.

Trends in recent years in the older U.S. population show decreases in age-adjusted all-cause cancer mortality and incidence (–1.1 and –1.2 annual percent change 1997 to 2006, respectively).[3,6] However, trends and risks vary considerably by primary cancer site and sex (Figure 1-7 and Table 1-1).[6,10] In people 65 years of age and older, lung cancer incidence and mortality increased for women and decreased for men. Nonetheless, it was the second leading cancer site and the most fatal cancer (approximately 30% of all cancer deaths) in both women and men. The second- and third-ranked fatal cancers were breast and colorectal cancers in women and colorectal and prostate cancers in men. All showed varied but decreased mortality and incidence over time. The risk of colorectal cancer rose precipitously with age, with 91% of cases diagnosed in individuals aged 50 years of age and older, with moderate decreases in mortality and incidence (–2.9 and –3.0 annual percent change 1997 to 2006, respectively).[6,9,10]

There are also considerable differences in cancer burden and survival across race and ethnic populations (Figures 1-8 and 1-9).[4,6] All-cause cancer incidence and mortality rates have been higher, and relative survival rates lower, for African-Americans in comparison to whites. Hispanic, Asian, Pacific Islander, American Indian, and Alaska Native persons generally have lower incidence rates than whites, except for several specific cancers (e.g., stomach, liver, cervix, kidney, and gallbladder). This general pattern of lower incidence among racial and ethnic minorities has been attributed to younger age structures. However, cancer disparities in incidence, mortality, and late-stage presentation also exist within these groups by geography, national origin, economic status, and other factors. By 2050 and beyond, these disparities are expected to transition into the older age groups as demographic changes (i.e., growth in older

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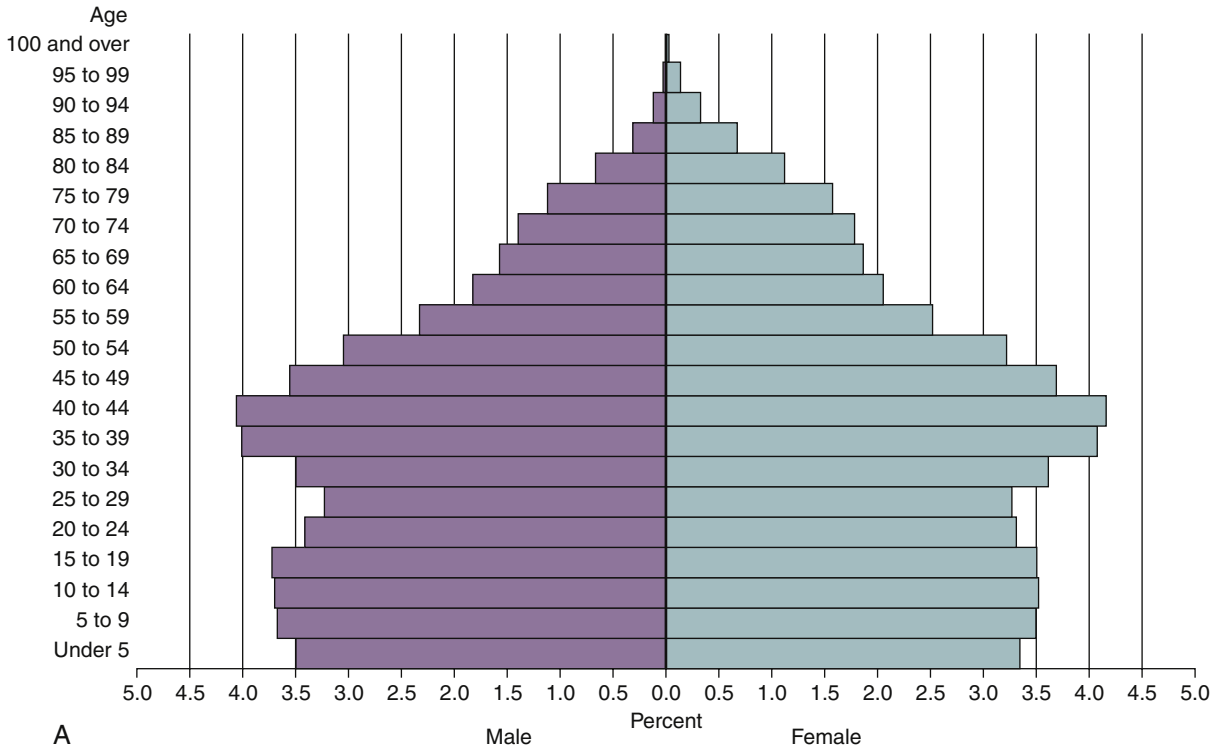


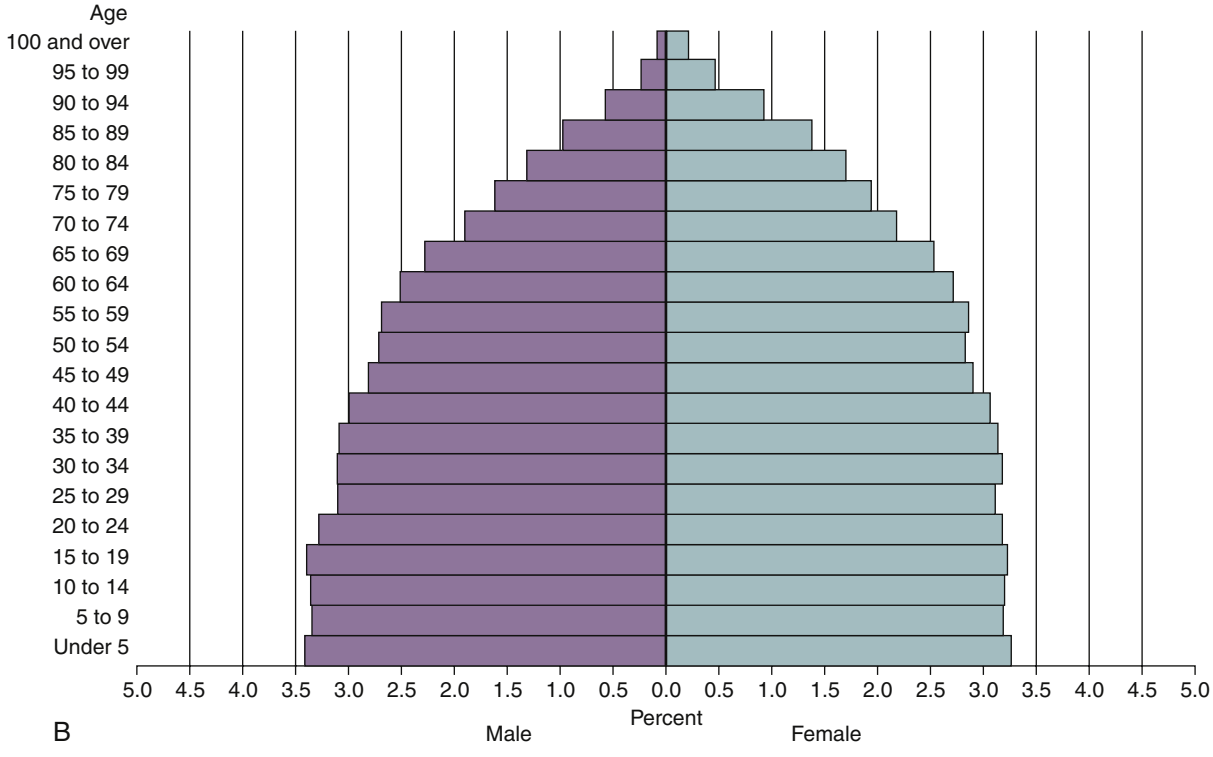
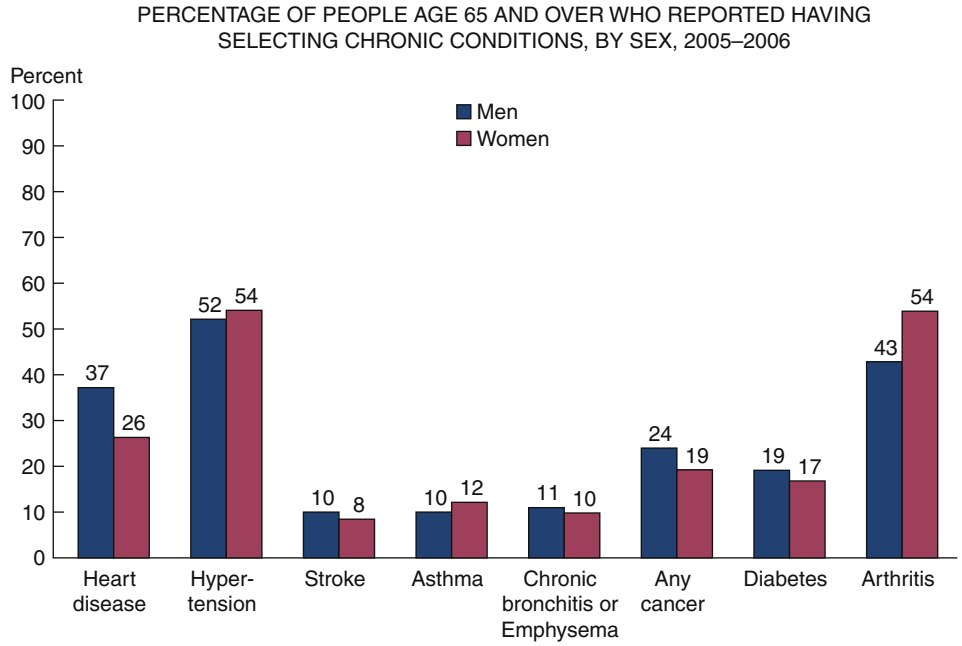
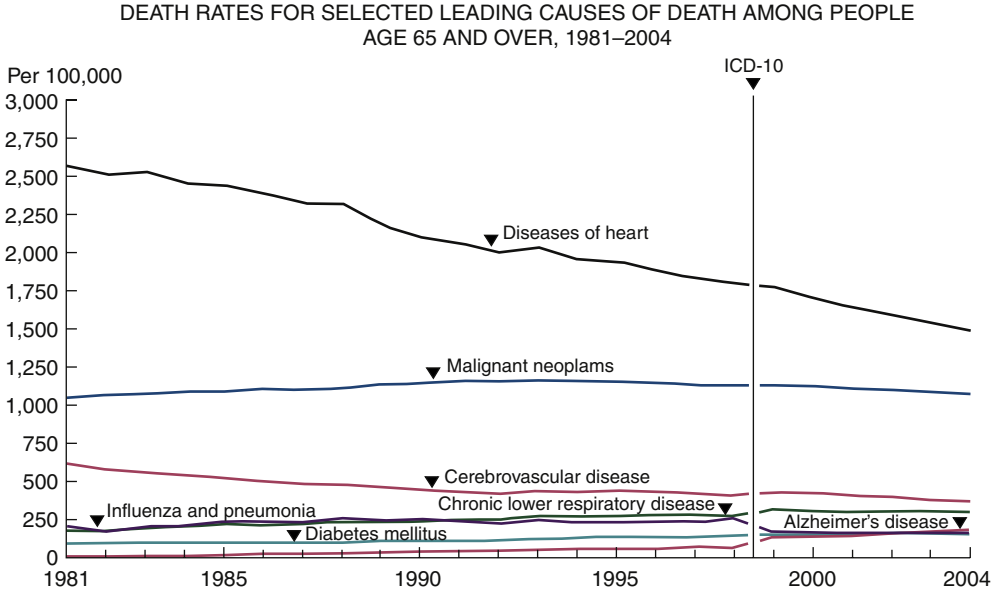


FIGURE 1-4 Population pyramids of the United States (*left*) 2000 and (*right*) projected 2050. *(Adapted from U.S. Census Bureau: Projections of the Population by Age and Sex for the United States: 2010 to 2050 (NP2008-T12). Washington, DC: Population Division, U.S. Census Bureau; 2008.)*

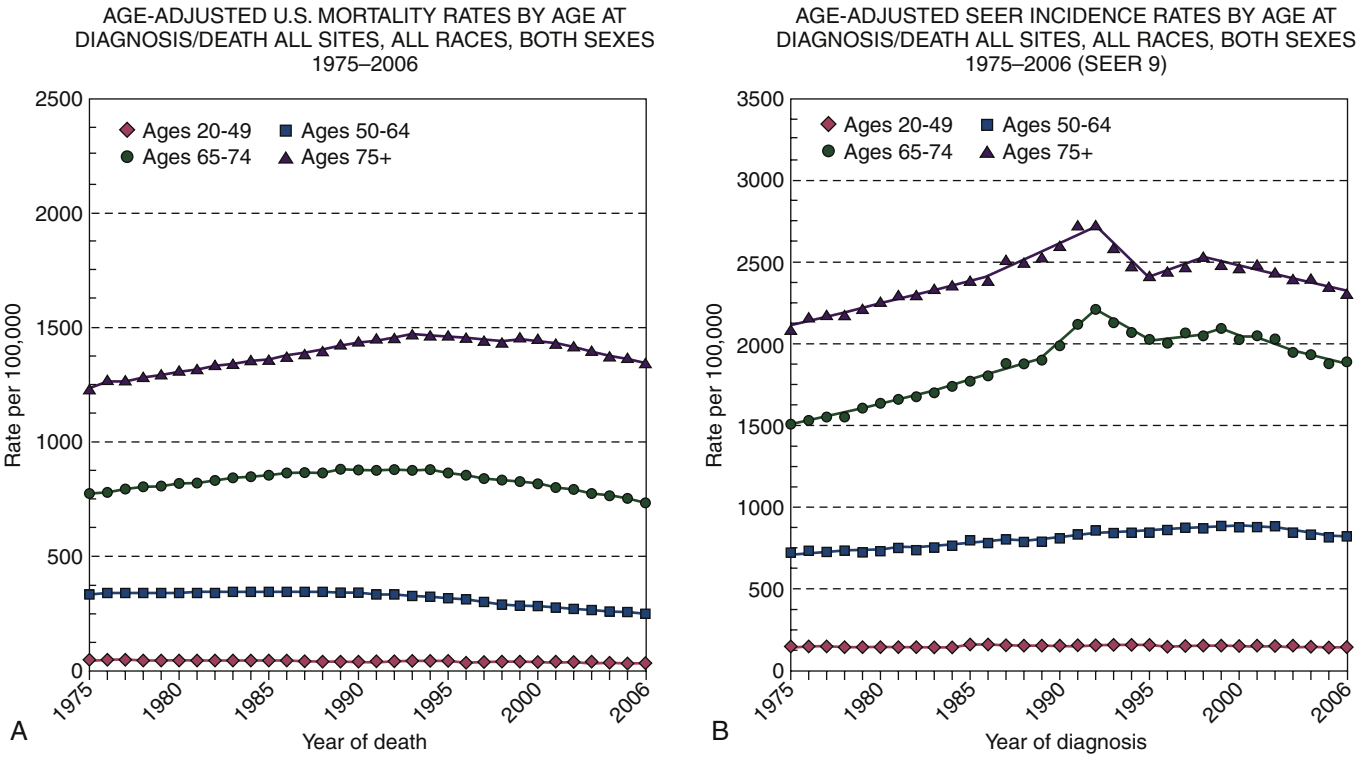


Note: Data are based on a 2-year average from 2005–2006.
Reference population: These data refer to the civilian noninstitutionalized population.
A Source: Centers for Disease Control and Prevention, National Center for Health Statistics, National Health Interview Survey.



Note: Death rates for 1981–1998 are based on the 9th revision of the *International Classification of Diseases* (ICD-9). Starting in 1999, death rates are based on ICD-10 and trends in death rates for some causes may be affected by this change.[11] For the period 1981–1998, causes were coded using ICD-9 codes that are most nearly comparable with the 113 cause list for the ICD-10 and may differ from previously published estimates. Rates are age adjusted using the 2000 standard population.
Reference population: These data refer to the resident population.
B Source: Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System.

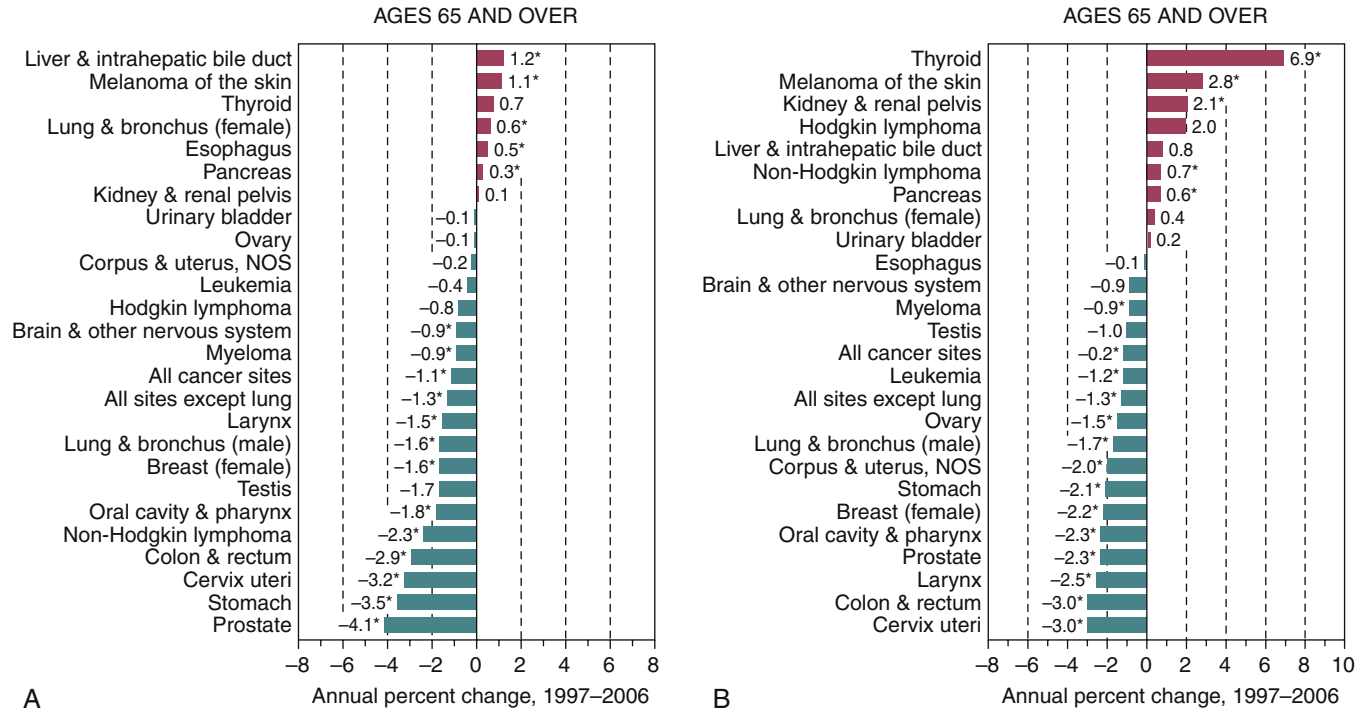
FIGURE 1-5 Incidence and mortality of chronic conditions in the population aged 65 and older in the United States. **A,** Percentage of population 65 years and older, by chronic condition and sex, 2005-2006. **B,** Mortality rates in population 65 years and older, by leading causes of death, 1981-2004. *(Adapted from U.S. Department of Health and Human Services: A Profile of Older Americans: 2008. Washington, DC: Administration on Aging, 2008.)*



Cancer sites include invasive cases only unless otherwise noted.
Mortality source: US Mortality Files, National Center for Health Statistics, CDC.
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 3.3.2, June 2008, National Cancer Institute.

Cancer sites include invasive cases only unless otherwise noted.
Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah and Atlanta).
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 3.3.2, June 2008, National Cancer Institute.

FIGURE 1-6 Trends of age-adjusted all-cause cancer mortality (*left*) and incidence (*right*) rates for the United States population, by age group, 1975-2006. *(Adapted from FastStats: An interactive tool for access to SEER cancer statistics. Bethesda, MD, National Cancer Institute, 2009.)*



Source: US Mortality Files, National Center for Health Statistics, Centers for Disease Control and Prevention. For sex-specific cancer sites, the population was limited to the population of the appropriate sex.
* Underlying rates are per 100,000 and age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1103). The Annual Percent Change is significantly different from zero (p<.05).

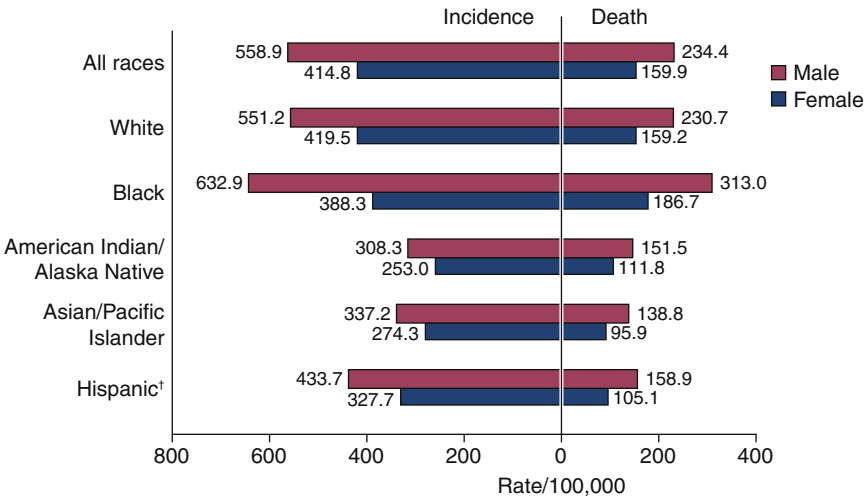
Source: US Mortality Files, National Center for Health Statistics, Centers for Disease Control and Prevention. For sex-specific cancer sites, the population was limited to the population of the appropriate sex.
* Underlying rates are per 100,000 and age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1103). The Annual Percent Change is significantly different from zero (p<.05).

FIGURE 1-7 Change in trends of age-adjusted all-cause cancer mortality (*left*) and incidence (*right*) rates for the population aged 65 and older in the United States, by primary cancer site, 1997-2006. *(Adapted from SEER Cancer Statistics Review, 1975-2006. Bethesda, MD, National Cancer Institute, 2009.)*

TABLE 1-1 Probability of Developing Cancer for Selected Age Groups in the United States,* by Sex, 2003 to 2005

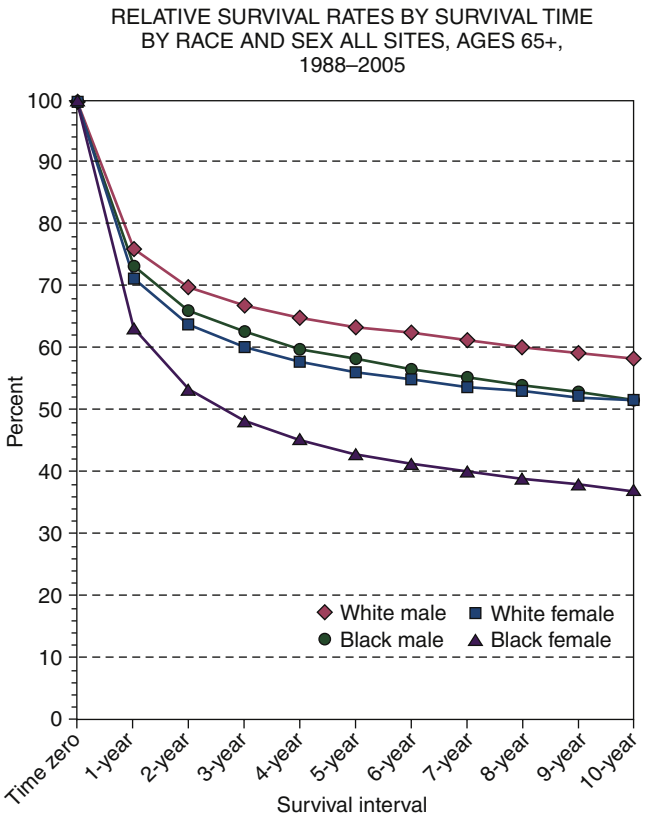
		Age Group				
Cancer Site	Sex	Birth to 39 Years (Percentage)	40 to 59 Years (Percentage)	60 to 69 Years (Percentage)	70 Years and Older (Percentage)	Birth to Death (Percentage)
All sites†	Male	1.42 (1 in 70)	8.44 (1 in 12)	15.71 (1 in 6)	37.74 (1 in 3)	43.89 (1 in 2)
	Female	2.07 (1 in 48)	8.97 (1 in 11)	10.23 (1 in 10)	26.17 (1 in 4)	37.35 (1 in 3)
Urinary bladder‡	Male	0.02 (1 in 4448)	0.41 (1 in 246)	0.96 (1 in 104)	3.57 (1 in 28)	3.74 (1 in 27)
	Female	0.01 (1 in 10,185)	0.12 (1 in 810)	0.26 (1 in 378)	1.01 (1 in 99)	1.18 (1 in 84)
Breast	Female	0.48 (1 in 208)	3.79 (1 in 26)	3.41 (1 in 29)	6.44 (1 in 16)	12.03 (1 in 8)
Colon and rectum	Male	0.08 (1 in 1296)	0.92 (1 in 109)	1.55 (1 in 65)	4.63 (1 in 22)	5.51 (1 in 18)
	Female	0.07 (1 in 1343)	0.72 (1 in 138)	1.10 (1 in 91)	4.16 (1 in 24)	5.10 (1 in 20)
Leukemia	Male	0.16 (1 in 611)	0.22 (1 in 463)	0.35 (1 in 289)	1.17 (1 in 85)	1.50 (1 in 67)
	Female	0.12 (1 in 835)	0.14 (1 in 693)	0.20 (1 in 496)	0.77 (1 in 130)	1.07 (1 in 94)
Lung and bronchus	Male	0.03 (1 in 3398)	0.99 (1 in 101)	2.43 (1 in 41)	6.70 (1 in 18)	7.78 (1 in 13)
	Female	0.03 (1 in 2997)	0.81 (1 in 124)	1.78 (1 in 56)	4.70 (1 in 21)	6.22 (1 in 16)
Melanoma§	Male	0.16 (1 in 645)	0.64 (1 in 157)	0.70 (1 in 143)	1.67 (1 in 60)	2.56 (1 in 39)
	Female	0.27 (1 in 370)	0.53 (1 in 189)	0.35 (1 in 282)	0.76 (1 in 131)	1.73 (1 in 58
Non-Hodgkin lymphoma	Male	0.13 (1 in 763)	0.45 (1 in 225)	0.58 (1 in 171)	1.66 (1 in 60)	2.23 (1 in 45)
	Female	0.08 (1 in 1191)	0.32 (1 in 316)	0.45 (1 in 223)	1.36 (1 in 73)	1.90 (1 in 53
Prostate	Male	0.01 (1 in 10,002)	2.43 (1 in 41)	6.42 (1 in 16)	12.49 (1 in 8)	15.78 (1 in 6)
Uterine cervix	Female	0.15 (1 in 651)	0.27 (1 in 368)	0.13 (1 in 761)	0.19 (1 in 530)	0.69 (1 in 145)
Uterine corpus	Female	0.07 (1 in 1499)	0.72 (1 in 140)	0.81 (1 in 123)	1.22 (1 in 82)	2.48 (1 in 40)

Adapted from Jemal et al. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225-49.
*For people free of cancer at beginning of age interval.
†All sites exclude basal and squamous cell skin cancers and in situ cancers except urinary bladder.
‡Includes invasive and in situ cancer cases.
§Statistics for whites only.



*Rates are age-adjusted to the 2000 U.S. standard population. Incidence rates cover 91% of the U.S. population; death rates are for 100% of the U.S. population.
†Hispanic is not mutually exclusive from (white, black, Asian/Pacific Islander, American Indian/Alaska Native).

FIGURE 1-8 All-cause age-adjusted cancer incidence and mortality rates in the general United States, by sex, race, and ethnicity, 2001-2005. *(Adapted from Centers for Disease Control and Prevention: Health Disparities in Cancer. Atlanta, GA, National Center for Chronic Disease Prevention and Health Promotion, Division of Cancer Prevention and Control, 2008.)*



Cancer sites include invasive cases only unless otherwise noted.
Survival source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).
Survival rates are relative rates expressed as percents. The annual survival estimates are calculated using monthly intervals.

FIGURE 1-9 Relative all-cancer-site survival rates by survival time, race, and sex in the population age 65 and older in the United States, 1988-2005. *(Adapted from SEER Cancer Statistics Review, 1975-2006. Bethesda, MD: National Cancer Institute; 2009.)*

and minority populations) intersect to drive increases in cancer incidence.

CHARACTERISTICS OF OLDER PATIENTS WITH CANCER

As has been noted, age is the single most important risk factor for the development of cancer; yet, many risk factors that affect the general population are also contributors to cancer risk in older adults. These same risk factors are often associated not only with cancer, but also with common diseases and disabilities of aging (e.g., chronic diseases such as heart disease or hypertension, limitations in physical function). In turn, these risk factors and associated conditions can greatly affect treatment decision making, responses to treatment, and outcomes. Some risk factors such as smoking, diet, and physical exercise are modifiable, whereas others such as family history and race are not (for example, genetic factors are estimated to account for up to 10% of prostate, breast, and colorectal cancers).[11-13] The World Health Organization estimates that more than 30% of cancer deaths in the general population can be prevented by modifying risk factors (Table 1-2).[14] The effect of these factors may be magnified in older adults because of their association not just with cancer but with other common causes of morbidity and death as well. What follows is an examination of some common modifiable risk factors and their impact in relation to cancers and treatment-related issues in older adults. Genetic risk factors are not addressed because of their tendency to be less age-specific, nor are environmental risk factors addressed because of their overall variability in older adults.

TABLE 1-2 Number of Attributable Deaths and Population Attributable Fractions (PAF) Estimating Individual and Joint Contributions of Selected Modifiable Risk Factors by Cancer Site, Worldwide and in High-Income Countries

	Total Deaths	PAF (%) and Number of Attributable Cancer Deaths (Thousands) for Individual Risk Factors	PAF Due to Joint Hazards of Risk Factors
Worldwide			
Mouth and oropharynx cancers	311 633	Alcohol use (16%; 51), smoking (42%; 131)	52%
Esophageal cancer	437 511	Alcohol use (26%, 116), smoking (42%; 184), low fruit and vegetable intake (18%; 80)	62%
Stomach cancer	841 693	Smoking (13%; 111), low fruit and vegetable intake (18%; 147)	28%
Colon and rectum cancers	613 740	Overweight and obesity (11%; 69), physical inactivity (15%; 90), low fruit and vegetable intake (2%; 12)	13%
Liver cancer	606 441	Smoking (14%; 85), alcohol use (25%; 150), contaminated injections in health-care settings (18%; 111)	47%
Pancreatic cancer	226 981	Smoking (22%, 50)	22%
Trachea, bronchus, and lung cancers	1 226 574	Smoking (70%; 856), low fruit and vegetable intake (11%; 135), indoor smoke from household use of solid fuels (1%; 16), urban air pollution (5%; 64)	74%
Breast cancer	472 424	Alcohol use (5%; 26), overweight and obesity (9%; 43), physical inactivity (10%; 45)	21%
Cervix uteri cancer	234 728	Smoking (2%; 6), unsafe sex (100%; 235)	100%

TABLE 1-2 Number of Attributable Deaths and Population Attributable Fractions (PAF) Estimating Individual and Joint Contributions of Selected Modifiable Risk Factors by Cancer Site, Worldwide and in High-Income Countries—cont'd

	Total Deaths	PAF (%) and Number of Attributable Cancer Deaths (Thousands) for Individual Risk Factors	PAF Due to Joint Hazards of Risk Factors
Corpus uteri cancer	70 881	Overweight and obesity (40%; 28)	40%
Bladder cancer	175 318	Smoking (28%; 48)	28%
Leukemia	263 169	Smoking (9%; 23)	9%
Selected other cancers	145 802	Alcohol use (6%; 8)	6%
All other cancers	1 391 507	None of selected risk factors	0%
All cancers	7 018 402	Alcohol use (5%; 351), smoking (21%; 1493), low fruit and vegetable intake (5%; 374), indoor smoke from household use of solid fuels (0·5%; 16), urban air pollution (1%; 64), overweight and obesity (2%; 139), physical inactivity (2%; 135), contaminated injections in health-care settings (2%; 111), unsafe sex (3%; 235)	35%
High-Income Countries			
Mouth and oropharynx cancers	40 559	Alcohol use (33%; 14), smoking (71%; 29)	80%
Esophageal cancer	57 752	Alcohol use (41%; 24), smoking (71%; 41), low fruit and vegetable intake (12%; 7)	85%
Stomach cancer	146 267	Smoking (25%; 36), low fruit and vegetable intake (12%; 17)	34%
Colon and rectum cancers	256 791	Overweight and obesity (14%; 37), physical inactivity (14%; 36), low fruit and vegetable intake (1%; 3)	15%
Liver cancer	102 033	Smoking (29%; 29), alcohol use (32%; 33), contaminated injections in health-care settings (3%; 3)	52%
Pancreatic cancer	110 154	Smoking (30%; 33)	30%
Trachea, bronchus, and lung cancers	455 636	Smoking (86%; 391), low fruit and vegetable intake (8%; 36), indoor smoke from household use of solid fuels (0%), urban air pollution (3%; 12)	87%
Breast cancer	155 230	Alcohol use (9%; 14), overweight and obesity (13%; 20), physical inactivity (9%; 15)	27%
Cervix uteri cancer	16 663	Smoking (11%; 2), unsafe sex (100%; 17)	100%
Corpus uteri cancer	26 955	Overweight and obesity (43%; 12)	43%
Bladder cancer	58 636	Smoking (41%; 24)	41%
Leukemia	73 110	Smoking (17%; 12)	17%
Selected other cancers	57 095	Alcohol use (8%; 5)	8%
All other cancers	509 507	None of selected risk factors	0%
All cancers	2 066 388	Alcohol use (4%; 88), smoking (29%; 596), low fruit and vegetable intake (3%; 64), indoor smoke from household use of solid fuels (0%; 0), urban air pollution (1%; 12), overweight and obesity (3%; 69), physical inactivity (2%; 51), contaminated injections in health-care settings (0·5%; 3), unsafe sex (1%; 17)	37%

From Danaei G, Vander Hoorn S, Lopez AD et al. Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. Lancet 2005;366:1784-93.
PAF, Population Attributable Fraction

Smoking is considered the leading cause of preventable death in the United States, accounting for nearly one of five deaths each year.[15,16] Regardless of age, smoking is by far the most important risk factor for the development of lung cancer (about 90% of lung cancer deaths in men and 80% in women are due to smoking).[9] The longer one smokes, and the greater amount smoked daily, the more lung cancer risk increases. Thus, older smokers are at particularly high risk, as evidenced by their having the highest probabilities of having lung cancer overall (Table 1-1). According to the U.S. Surgeon General, smoking is also associated with an increased risk of at least 14 other types of cancer (nasopharynx, nasal cavity and paranasal sinuses, lip, oral cavity, pharynx, larynx, esophagus, pancreas, uterine cervix, kidney, bladder, stomach, and acute myeloid leukemia).[16] Although the U.S. Surgeon General does not currently recognize smoking as a risk factor for colorectal cancer, there is evidence that it is.[17-20] The increased colorectal cancer risk among smokers is hypothesized to be due to cancer-causing substances in tobacco and/or the relation between smoking and alcohol use (colorectal cancer has been linked to alcohol

use). Smoking is also known to be a major cause of other chronic conditions commonly affecting older adults, such as heart disease, cerebrovascular disease, and chronic lower respiratory disease (Figure 1-5), all of which can greatly complicate cancer treatment options and tolerance. Although older adults have the lowest current smoker rates (under 10%), older former smokers may represent considerable past exposures.[21] With the actual number of older adults increasing and the higher smoking rates in minorities, interactions of smoking-related health problems in the older population will continue to be of serious concern.

Obesity is a growing epidemic in the United States and is not limited to younger populations. The Centers for Disease Control (CDC) estimates that nearly 30% of the 65-and-older population is obese, with even higher rates in minority populations. There are many negative health outcomes associated with obesity. It is associated with excess mortality, as well as with increased risk of heart disease, diabetes, osteoarthritis, cancer, and disability.[22-29] In the case of cancer, studies have estimated that obesity may contribute to up to 6% of U.S. incident cancer cases.[30, 31] It has been linked to cancers of the colon, breast (postmenopausal), endometrium, kidney, esophagus, gallbladder, ovaries, and pancreas.[22] Furthermore, obesity has been associated with a worse prognosis for certain cancers (e.g., breast, colon, lymphoma, and prostate) and a greater risk for disease recurrence.[22,32,33] Unfavorable survival rates in obese cancer patients may be related to the higher likelihood of associated comorbid conditions or unfavorable tumor characteristics.[34] Detection of breast tumors is more difficult in obese than in lean women and may explain findings that higher body mass is associated with advanced stage breast cancer and, in turn, poorer prognosis.[35] In addition, studies demonstrating systematic underdosing of chemotherapy in overweight and obese breast cancer patients suggest another potential factor in poorer survival rates.[34,36-38] The unique challenges and increased complications associated with older obese cancer patients directly influence planning, delivery, and tolerance of cancer treatments. Current demographics predict a rise in the risk of morbidity and death from obesity-related cancers common in older adults, resulting from the burgeoning numbers of older Americans (especially minorities), the increasing prevalence of obesity, and persistent racial differences in obesity.

Diet and physical activity are two other important modifiable risk factors for common cancers in older adults.[14] As with smoking and obesity, diet and physical activity are closely related to some cancers (e.g., prostate, colorectal, breast) and to other diseases and conditions of aging. For instance, eating well and exercising may reduce the risk not only of cancer but also of heart disease, stroke, type 2 diabetes, bone loss, and anemia. Diet and exercise are, obviously, also related to obesity and being overweight, as discussed previously. Importantly,

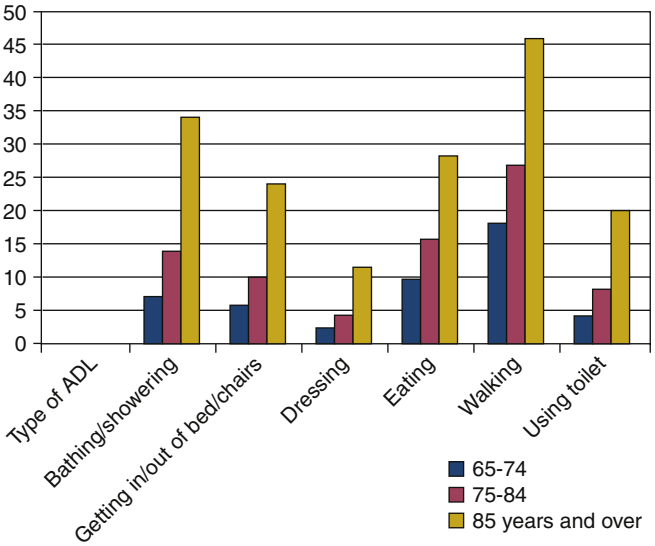


FIGURE 1-10 Percent of community-dwelling older adults reporting a limitation in activities of daily living, by age, 2006. *(Adapted from U.S. Department of Health and Human Services: A Profile of Older Americans: 2008. Washington, DC: Administration on Aging, 2008.)*

this constellation of health-related factors may play a key role in cancer treatment decision making and tolerance. Unfortunately, physical activity may be less modifiable in older adults than in younger populations because a sedentary lifestyle in older adults may not actually be a choice but a consequence of coexisting functional limitations. Figure 1-10 shows how age is associated with a decreased ability to accomplish daily activities in community-dwelling older adults.[1] Older minorities, especially African-Americans and Hispanics, have an even greater number of functional disabilities than their white counterparts.[39,40] In general, older adults who are functionally dependent have a lower life expectancy and stress tolerance, including tolerance for the stress of cancer treatment.[41] Difficulty shopping, preparing meals, or eating can greatly affect the diet of older adults, for whom nutrition is a health concern that directly affects cancer treatments and tolerance. Even though regular physical activity, maintenance of a healthy body weight, and a healthy diet are widely considered to reduce cancer risk, the lifestyle changes required to achieve them may not be feasible in older adults.

The issues surrounding modifiable risk factors previously outlined are by no means the only matters of concern in the treatment of older cancer patients. Studies show documented undertreatment of older cancer patients across cancer types. Common reported reasons for undertreatment are the high prevalence of comorbidities, lower life expectancies, limited data on treatment efficacy from clinical trials, and increased adverse effects of treatment.[42] Paradoxically, undertreatment persists even though studies have shown that older adults are prepared to receive cancer treatments just as readily as younger patients and most appear to benefit from

treatment to a similar extent as younger patients.[43-48] Likewise, treatments such as surgery and adjuvant therapy are well tolerated, effectively decrease relapse, and improve survival in many older cancer patients.[42,49-59] Defining treatment strategies specific to older adults is hampered by limited age-specific evidence and the fact that treating older adults for cancer seldom means treating their cancer alone. Chronological age is a poor indicator of future life expectancy, functional reserve, or the risk of treatment complications.[60,61] Because aging is so highly individualized, recent guidelines suggest that clinical decision making for cancer treatments based on geriatric assessment is most likely to result in positive outcomes in older cancer patients.[52,60,62] The key to managing older cancer patients is the ability to accurately assess whether the expected benefits of treatment will outweigh the risks.[63] In fact, once they are adequately evaluated, fewer older patients should have to be excluded from treatment because of reduced tolerance.[64] To date, the lack of systematic comprehensive evaluation and age-specific evidence restricts treatment-modification decision making to factors such as chronological age and slows the development of interventions to optimize cancer treatment in older adults. Our expanding knowledge and understanding of the aging process will eventually allow us to accurately identify older cancer patients who will benefit from prevention and treatment options and distinguish them from those who are not candidates for treatments with curative intent. Future research will provide a more robust foundation for targeting treatments to older cancer patients for the purpose of maximizing clinical benefit and cost-effectiveness, as well as eliminating undertreatment.

UNIQUE ISSUES OF CANCER AND AGING

The prospect of a longer life span is generally considered desirable, as long as one is healthy. With longer life, though, the biological changes, diseases, and conditions known to be associated with aging become precipitously more prevalent. Older adults face many more health care concerns than do younger adults. In 2006, only 39% of community-dwelling older adults in the United States assessed their health as excellent or very good, compared with 65% of persons younger than 65 years, and most older Americans reported having at least one chronic condition.[21] African-American and Hispanic Medicare beneficiaries are both more likely than whites to have serious health problems and long-term care needs.[39] As previously discussed, cancer incidence and mortality trends in the older population differ from those in the younger population and also by race (e.g., consistently higher rates in persons 65 years and older and certain types of cancer consistently higher in minority groups, such as prostate cancer in African-Americans).[6] This may be due to the influence of age on cancer biology, prolonged exposures, systemic effects of aging, or quality of care. In addition, older adults with cancer and their families often have different needs than younger adults. For example, they may not always have access to transportation, social support, or the financial resources required to successfully undergo cancer treatments. The nexus of cancer and aging presents some unique issues for older cancer patients and their caregivers (familial and professional) alike.

There is evidence indicating that cancers may behave differently depending on the age of the patient.[62,65,66] It is hypothesized that, basically, two types of mechanisms are involved: (1) changes in the intrinsic biology of the tumor cells and (2) changes in the ability of an older host to sustain and stimulate tumor growth. The biology of aging and its interactions with cancer are not completely understood and are further complicated by their heterogeneity across cancer type. Table 1-3 shows how the biology of certain tumors changes with increasing age, and Table 1-4 lists some of the biological interactions of cancer and aging.[67, 68] With increased age, some cancers become more aggressive (e.g., leukemias, lymphomas, ovarian), and others become more indolent (e.g., breast, lung). As an example, in the case of breast cancer, age-specific incidence profiles differ between

TABLE 1-3 Age-Related Changes in Tumor Biology by Selected Cancer Type and Hypothesized Mechanism

Neoplasm	Change with Increasing Age	Possible Mechanism
Acute myeloid leukemia	Resistance to chemotherapy	Tumor cells show increased expression of the multidrug resistance protein (MDR1) and unfavorable cytogenetic changes
Non-Hodgkin lymphoma	Reduced response to chemotherapy Reduced duration of response and survival	Stromal cells show increased concentration of interleukin-6 in the circulation, stimulating lymphocyte proliferation; Immune senescence and increased growth rate of highly immunogenic tumors is also evident
Breast cancer	More indolent	Tumors show higher concentrations of well-differentiated hormone-receptor–rich neoplastic cells and decreased tumor growth fraction; Stromal cells exhibit endocrine senescence; Immune system senescence
Non-small cell lung cancer	More indolent	Development of cancer in elderly ex-smokers
Ovarian cancer	Decreased response to chemotherapy and reduced survival	Unknown

From Balducci L, Aapro M. Epidemiology of cancer and aging. Cancer Treat Res 2005;124:1-15.

TABLE 1-4 Biological Interactions of Cancer and Aging

Molecular Changes of Aging That Could Favor Carcinogenesis
• Accumulation of DNA adducts, DNA hypermethylation, and point mutations, which prime the cells to "late-stage" carcinogens
• Higher concentration of cells in advanced carcinogenesis; therefore more likely to be hit "at random" by environmental carcinogens
• The exposure of tissues from young and old rodents to the same dose of carcinogen results in higher numbers of tumors in the older tissues.
Molecular Changes of Aging That Could Inhibit Carcinogenesis
• Progressive telomere shortening, leading to senescence
• Activation of genes that oppose cell replication, such as the gene encoding ARF, the cyclin-dependent kinase inhibitor
Cellular Changes of Aging That Could Favor the Development of Cancer
• Premature senescence of fibroblasts associated with production of tumor growth factors and metalloproteinases that favor metastatic spread
• Premature senescence associated with loss of apoptosis and development of immortal cells. A possible mechanism to explain some slow-growing malignancies in older individuals, such as follicular lymphomas.
Physiological Changes of Aging That Could Influence Tumor Growth
• Endocrine senescence might cause slower growth of endocrine-dependent tumors (such as breast, prostate and endometrial cancer).
• Immune senescence might favor the growth of highly immunogenic tumors, such as large cell lymphomas, renal cell carcinomas, and aggressive sarcomas. Alternatively, the growth of less immunogenic tumors might be slowed in older patients, owing to a reduced immune cell infiltrate and decreased inflammatory cytokine expression.
• Premature senescence of stromal cells associated with increased production of growth factors and metalloproteinases
• Increased concentration of catabolic cytokines in the circulation, which might lead to muscle loss and oppose the growth of highly proliferative tissues and neoplasias

From Balducci L, Aapro M. Epidemiology of cancer and aging. Cancer Treat Res 2005;124:1-15.

early- and late-onset breast cancers.[69] Early-onset breast cancers are thought to be primarily due to inherited or early-life cellular damage of immature breast tissue, whereas late-onset breast cancers are considered to be due to extended exposures and age-related cellular damages. Clinical observations and biomarker studies indicate that late-onset breast cancers grow more slowly and are biologically less aggressive than early-onset breast cancers, even when hormone and growth factor receptor expression are taken into account.[70] In general, some cancers in older adults have a worse prognosis than in younger adults (e.g., non-Hodgkin lymphoma), whereas others have an improved prognosis (e.g., breast, lung); this may be confounded by the fact that older adults tend to be diagnosed at more advanced stages than do young persons.[67,71] Age-related physiological changes due to both genetic (e.g., organ and systems functional reserve) and environmental influences (e.g., disease, physical and emotional stresses, lifestyle, and carcinogenic exposures) involve a progressive loss of the body's ability to cope with stress.[72,73] Age-related physiological changes may be particularly relevant to cancer biology and treatment. They may affect the growth rate of the tumor, the pharmacokinetics of drugs, and the risk of drug-related toxicity.[73] There is little doubt the mechanisms and pathways of cancer and aging are interrelated.[68] Their interactions can have an impact on cancer risk, tumor activity, and older patients' responses to treatment.[73-75] Moreover, evidence must be cautiously interpreted and translated because our ability to understand the effects of underlying aging biology may be obscured by age discrepancies between study populations and general cancer populations.[70] This may be particularly problematic for older cancer patients, for whom treatment complications can have a serious ripple health effect.

As previously described, the diseases most commonly associated with aging (Figure 1-5) are chronic, are usually progressive in nature, often negatively affect physical health, and are related to modifiable cancer risk factors, as well as to outcomes (e.g., functional reserve, morbidity, mortality). Because age is considered the most important risk factor for cancer and is associated with increasing comorbidity, coexisting diseases are of substantial concern in older cancer patients. Indeed, cancer patients 70 years and older have, on average, three comorbidities.[76,77] The consequences of coexisting illnesses are related to pathophysiology, prognosis, diagnosis, treatment, and etiology and may have broad-ranging serious implications in the lives of older adults, especially for those with cancer.[78] Table 1-5 shows the biomedical framework for interactions of comorbidities as outlined in the report of the National Institute on Aging Task Force on Comorbidity.[78] The framework highlights the substantial potential for synergism between concomitant diseases. It emphasizes that health issues related to cancer and its treatment should not be considered in isolation but in relation to other prevalent diseases. There is evidence suggesting that a primary cancer diagnosis interacts with comorbidity, that survival is inversely related to the number of comorbidities, and that death more commonly results from comorbidity, rather than from cancer, with advancing age.[79-85] However, cause of death varies according to the aggressiveness of the cancer (i.e., cancer-specific cause of death for aggressive cancers and comorbidity-related cause of death for less aggressive cancers). It is difficult to fully isolate the individual contributions of comorbidity, functional status, and treatment modification to prognosis.[76,81,85] Interactions of comorbidity and cancer may also result in more severe

TABLE 1-5 Biomedical Framework for Interaction of Comorbidity

Pathophysiology and Prognosis
1. One condition worsens another (faster progression, poorer outcomes, more disabling).
2. One condition increases risk for another.
3. Combination of two conditions has synergistic effects on other poor outcomes.
Diagnosis
4. One condition creates problems for diagnosing or assessing another.
Treatment
5. A treatment for one condition worsens or causes another condition.
6. Response to a treatment for one condition is affected by another condition.
7. The combination of treatments for more than one condition creates new problems.
Etiology
8. Two or more conditions combined occur more frequently than expected (common cause?).

From Yancik et al. Report of the national institute on aging task force on comorbidity. J Gerontol A Biol Sci Med Sci 2007;62:275-80.

morbidity, disability, or both, with subsequently higher levels of dependence on family, friends, and local services. Some of the latter issues in relation to survivorship will be addressed later in the chapter.

Because each person ages at a different rate and with actual age being a poor mirror of physiological age (an estimation of age based on how a person functions), the evaluation of function and coexisting illnesses is essential, especially when evaluating older adults for cancer treatment. The specific issues of cancer and aging beg important and unique questions that should be considered whenever managing older adults with cancer: Will the patient die of or with cancer? Will the cancer compromise the function and the quality of life of the patient? Will the patient be able to tolerate complications of treatment?[71,74] Unlike younger patients, the main determinants of outcomes (including survival) in older cancer patients are not age or tumor characteristics alone but also comorbidities and functional reserve.

SURVIVORSHIP OF OLDER CANCER PATIENTS

With improvements in cancer screening and treatment over the past several decades, the risk of death from cancer following diagnosis has steadily decreased. This has resulted in the number of cancer survivors in the United States increasing to nearly 11.4 million, most (60%) of whom are 65 years of age and older.[86] An important aspect of cancer survivorship is that cancer survivors of all ages are at greater risk for recurrence and for developing multiple primary malignancies (MPMs). In fact, one of the most serious events experienced by cancer survivors is the diagnosis of a new cancer. The National Cancer Institute estimates that the risk of developing a second primary or multiple primaries varies from 1% to 16%, depending on the primary cancer site, and this risk is increasing.[87-89] As with first primary cancers, the incidence of multiple primaries increases with age, and nearly 7% of older cancer survivors are affected[90-93]; yet, in this largest group of cancer survivors (65 years and older), multiple primary malignancies and their consequences remain understudied. Multiple primary cancers in older survivors may reflect late sequelae of treatment, as well as the effects of aging, lifestyle factors, environmental exposures, host factors, and combinations of influences, including gene-environment and gene-gene interactions.[94-96]

Breast cancer survivors represent one of the largest groups of survivors with multiple primary malignancies, the most common site being contralateral breast cancers, followed by prostate and colorectal cancers.[90,97] This ranking may reflect both the high incidence and survival rates for the first primary cancer but not necessarily greater risks for a subsequent cancer. Cross-sectional studies of MPM suggest that their prevalence peaks in the seventh or eighth decade; longitudinal studies indicate that the incidence of MPM increases with survival after the diagnosis and treatment of the first malignancy.[93] Despite documented disparities in cancer treatment and survival related to age, race/ethnicity, residence, and socioeconomic status, the impact of these characteristics on MPM risk has not been well studied.[98-106] Radiation therapy has been linked to excess risk for contralateral breast cancer, lung cancer, soft tissue sarcoma, and esophageal cancer.[91,107-113] Excess endometrial cancer is considered to be related to previous tamoxifen therapy.[114,115] An increased risk of leukemia after a primary cancer has been associated with both chemotherapy and radiation therapy.[97,116-119] The few studies that have examined nontreatment and multiple primaries that are not cancer-site specific are inconsistent.[120-123] The American Cancer Society recommends primary prevention (i.e., tobacco avoidance and cessation, healthy diet, weight control, physical activity) as the main strategy to reduce the burden of multiple primary cancers related to lifestyle factors.[97]

CHALLENGES OF EPIDEMIOLOGICAL STUDY OF OLDER PATIENTS WITH CANCER

Older adults remain understudied in general, and this is particularly true in cancer research.[39,124] Unfortunately, the lack of participation of older adults in research studies reduces opportunities for discoveries that may be particularly relevant to their care.[125] There are many challenges in the study of older adults that are unique and must be considered to ensure validity and reliability of the evidence. Some of these challenges are reviewed,

and their consequences for research and for the care of older adults with cancer are considered.

Although most new cancer cases occur in older adults and it is accepted that well-conducted randomized controlled trials (RCTs) provide the highest level of evidence to guide clinical management, relatively few older cancer patients participate in RCTs of new cancer treatments. Conducting RCTs in vulnerable patient populations is challenging, and oncology treatment trials have documented low participation rates among older adults.[39,71] Barriers to participation and retention include study design; physician, patient, and logistic issues (e.g., availability of caregivers, travel constraints); and financial costs.[125] By design, RCTs enroll participants with similar characteristics to ensure results of the trial are due to the intervention and not to other factors. Eligibility criteria are implemented to achieve accurate and meaningful results. Age-based criteria, common in cancer trials, are a means to exclude the inherent variability of older cancer patients and to minimize the risk of other comorbidities worsening by study participation. Notably, evidence is accumulating that persons older than 65 years who are reasonably fit tolerate aggressive chemotherapy treatments as well as younger persons.[125,126] According to these studies, age alone should not be a barrier to participation in clinical trials of new cancer treatments.[124,125] However, the heterogeneity of older cancer patients necessitates large samples or increased duration of observation to achieve adequate study power. Nevertheless, RCTs of older cancer patients are feasible.

Longitudinal studies—of any design—can play a major role in understanding the natural history, the analysis of change of disease, and the impact of treatment on older patients.[127] However, the validity and integrity of studies in which data are collected from participants over time can be severely compromised by attrition.[128,129] Longitudinal studies of older adults are particularly challenging to conduct because of age, disease, and functional status of the study population. Older, sicker, more disabled persons are less likely to enroll in studies, and these characteristics similarly affect the likelihood of continued study participation.[130,131] Common reasons for loss to follow-up in longitudinal studies of older adults include illness, being hospitalized, and moving to nursing homes. In most studies of older adults, dropouts differ from completers in demographic characteristics, physical and mental health indices, and extent of social support.[132-135] These realities are magnified in the setting of a cancer diagnosis, and the attrition of respondents can create methodological challenges (e.g., bias in data analysis) and must be seriously considered in study design.[136-138] On the other hand, outcome-based retrospective cohort and case-control studies evaluating the effectiveness of cancer-related care can be alternatives to RCTs. Retrospective studies circumvent the challenges of enrollment, retention, and attrition, as well as the high costs of prospective studies, with the use of existing data sources. However, if not properly designed, they can be more prone to confounding and bias.

Translation of evidence to evidence-based practice requires a specific and adequate knowledge base. Because older patients and minorities continue to be underrepresented in studies, there is limited evidence about the efficacy and tolerability of standard treatments in these patients. In the not so distant future, the older populations in the U.S. will more than double, with sizeable increases in the minority segments. It is estimated that by 2030, a 67% increase in cancer incidence for older adults will occur, accompanied by a 99% increase in minorities compared with 31% in whites.[139] It is essential to expand and accelerate our production of cancer-related evidence in this growing and changing population, regardless of study design. The current lack of efficacy data restricts the basis of treatment choice and modifications, and has retarded the development of interventions to optimize cancer treatment in older adults.

Summary

The aging of the U.S. population and the consequence of increased cancer incidence with longer life spans require physicians to develop a better understanding of the epidemiology of cancer, aging, and their intersection. Today, a person 65 years old can expect to live an average of 18.5 additional years, and a person 85 years old, 6.4 more years. These represent a considerable number of years at the end of the life course, which has become progressively more entwined with cancer. Thus, the treatment of older adults with cancer should be focused on maintaining or strengthening the quality of those years.

As has been discussed in this chapter, aging and cancer share pathways and interact to form a complex setting, full of challenges for identifying risk and devising optimal care for older cancer patients. The consequences of cancer and its treatment have a greater impact in older patients, particularly because of the interaction of cancer treatment effects, comorbidities, and age-related disabilities. Comorbidity is of particular concern in older cancer patients because of its prevalence and because it may be affected by cancer and, in turn, affect cancer and its treatment. Although primary prevention through lifestyle changes is promoted as the primary means to reduce cancer burden, some of these changes cannot be achieved in older adults. A greater understanding of cancer and aging will provide valuable opportunities to devise treatment strategies that maximize survival, minimize morbidity, and maintain quality of life in older cancer patients. Development and cogent use of cancer treatments in the complex setting of the older cancer patient require an understanding of the epidemiology of cancer and aging.

See expertconsult.com for a complete list of references and web resources for this chapter

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CHAPTER

2

Cancer Screening and Prevention in the Older Patient

Jennifer M. Croswell and Barnett S. Kramer

CASE 2-1 CASE DESCRIPTION

A husband and wife, aged 76 and 77, respectively, are new patients to a medical practice. The wife mentions that along with having seen multiple direct-to-consumer promotions emphasizing the importance of "healthy living" and the role of early detection in cancer, they recently watched a close friend die of prostate cancer. The wife mentions that she has had "about seven or eight mammograms" in her life, starting when she was 44 years old, but her last test was several years ago, and she is now very worried that she has not been sufficiently proactive about her health. She has come to schedule a mammogram. She would also like to get a prescription for raloxifene, after seeing an advertisement about its bone and breast health benefits in *Ladies Home Journal*. She states that her husband has "never liked going to the doctor," and has never previously had a serum prostate-specific antigen (PSA) test, but she has decided, on the basis of their friend's experience, to "put her foot down." She also would like to schedule both of them for colonoscopies. Both are now retired; the husband was a construction worker, and the wife, an elementary school teacher. The husband states that except for an incarcerated hernia requiring surgical intervention and a traumatic crush injury to his left shoulder caused by an on-the-job accident, he has no significant medical history. Her medical history is significant for mild hypertension, controlled with the use of a thiazide.

Public health messaging about the power of prevention and early detection has been both pervasive and persuasive. However, given its intuitive, "common sense" appeal, it is also frequently presented in an overly simplistic manner that belies the true complexity of decision making in this field, particularly in the elderly. Benefits may be overstated, and potential harms unrecognized or unconsidered. This chapter is intended to provide a review of the general principles of cancer screening and prevention, as well as a focus on the specific issues unique to older adults; these concepts should facilitate informed, individualized discussions with patients.

First and foremost, it is essential to realize that screening and prevention are fundamentally different activities from treatment of established disease. In the case of treatment, the baseline status of the population is one of symptomatic illness; individuals are actively seeking relief from a specific problem. Screening and prevention, however, deal with a population not overtly affected by the condition of interest and in whom the vast majority will never go on to acquire the disease. It is difficult to make an essentially healthy person better off than he or she already is; as such, the level of acceptable harm due to screening and prevention is lower than for a treatment scenario. The concept of *primum non nocere* is of particular relevance in the arena of prevention and screening, where the potential for the balance of benefits and harms to tip in the wrong direction rests at a different baseline than with treatment.

ANALYTIC FRAMEWORK: REJECTING INTUITIVE THINKING IN SCREENING AND PREVENTION

One of the most efficient tools developed to help clinicians and researchers sort through the salient elements related to the utility of a screening or prevention intervention is the analytic framework. Figure 2-1 depicts sample analytic frameworks (adapted from the U.S. Preventive Services Task Force) for prevention and screening activities, respectively.[1]

The analytic framework demands that attention be paid to (1) the population under consideration for the intervention (different groups might benefit more or less from a given screening or intervention practice, and proof of efficacy in one group does not automatically equate to utility for all populations); (2) the specifics of the intervention in question; (3) potential harms generated by the application of screening test or preventive agent; (4) potential harms generated by diagnostic follow-up or treatment of a disease; and (5) the precise nature of the potential beneficial outcomes of the intervention. The framework makes a point of explicitly delineating the difference between an intermediate outcome and a true health outcome. This is a useful reminder in screening and prevention efforts because a change in a laboratory value or radiographic examination does not necessarily equate to a decrease in deaths or a clinically meaningful

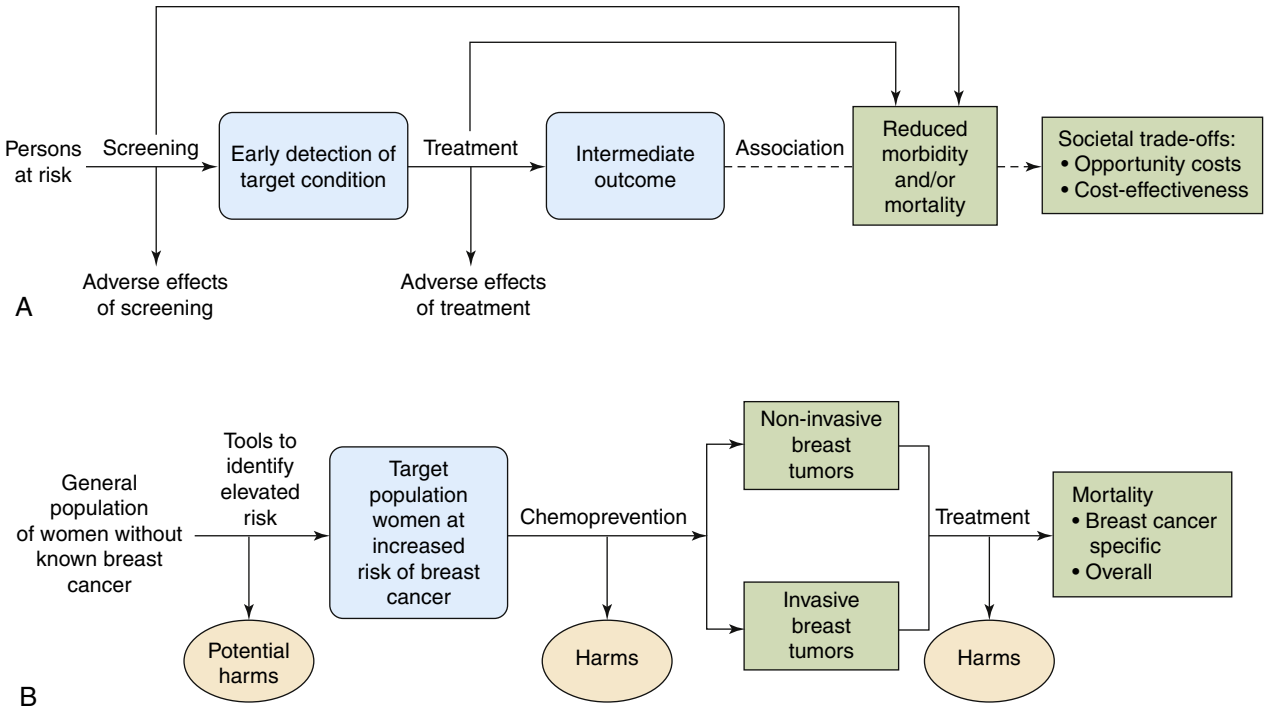

FIGURE 2-1 Sample analytic frameworks developed by the U.S. Preventive Services Task Force for both screening and preventive interventions. The analytic framework is a useful tool when evaluating the overall net benefit to harm ratio of an intervention, because it makes explicit each of the necessary links of the chain of evidence proving an intervention's efficacy, and also demands careful consideration of potential harms. **A,** Screening Analytic Framework. **B,** Prevention Analytic Framework. *(From Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 20(3 Suppl):21-35, 2001. Used with permission.)*

reduction in morbidity for the patient. Although intermediate outcomes are quicker and easier to obtain in studies of screening and prevention interventions because they occur with far greater frequency in an asymptomatic population than "hard" outcomes such as death, it is frequently difficult if not impossible to project with confidence how well they truly predict for endpoints with more clinical impact.

The framework's careful elucidation of the possible burdens associated with a given screening or prevention behavior is also of great importance: because these practices generally appear essentially innocuous (e.g., a blood draw, an x-ray, or ingestion of a substance already found in other foods) in an asymptomatic population, any associated potential harms are frequently overlooked or discounted. As the framework shows diagrammatically, any benefit of screening or prevention is linked to resulting therapy, so both the benefits and harms of therapy must be considered. Even if an intervention has been demonstrated to reduce disease-specific mortality in some individuals, the practice could still potentially be of net harm to a population, depending on the frequency and severity of associated complications that its use generates.

Finally, the framework is also useful in that it rejects mental shortcuts and a reliance on personal experience, opinion, or assumptions in favor of a series of defined links in a chain of evidence to prove the final net utility of an intervention. This is absolutely critical in the realm of prevention and screening activities because there are strong obfuscating biases operating that can mislead even the most astute clinician, if he or she relies on experience, personal observation, or logical deduction to evaluate the worth of these practices.

BIASES IN SCREENING AND PREVENTION STUDIES

The first of these biases is known as the *healthy volunteer effect*. This bias occurs because there are fundamental differences between people who are interested in and choose to participate in screening and prevention activities, and those who do not. Persons who participate in early detection or preventive efforts are often more attuned to health messages (e.g., exercise more, smoke less), come from higher educational and socioeconomic strata, are more likely to be compliant with medical advice, and have a generally superior baseline health status, as compared with those who are not interested in such activities. The healthy volunteer effect has been documented in a range of screening and prevention studies: for example, in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer screening trial, investigators found that participants in both the screening and control arms consistently showed lower-than-expected mortality rates (when compared with the general population) for cardiovascular, respiratory, and digestive diseases, diabetes, and all cancers other than those screened for in the study. Even injuries and poisonings occurred about half

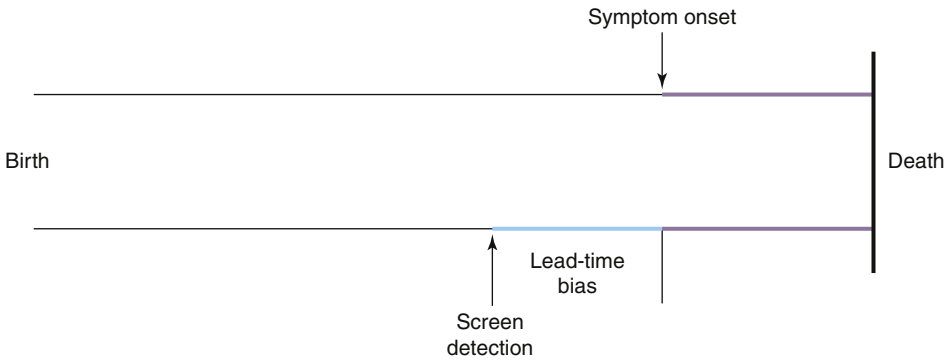

FIGURE 2-2 Lead-time bias. Early detection will advance the date of cancer diagnosis compared with symptomatic detection; however, in this case, although the individual lives longer with the diagnosis of cancer, there is no change in the ultimate time of death.

as frequently as would be expected. An intervention's apparent success may be entirely attributable to other confounding characteristics that track with the desire to be screened or engage in preventive activities.

A second confounding factor related to screening is known as *lead-time bias*. Any early detection tool will advance the date of diagnosis forward in time from that of symptomatic presentation. However, it does not automatically follow that a person will live longer as a result of this activity. Figure 2-2 depicts this concept. In this case, it can be seen that although early detection, by definition, shifts the date of diagnosis to an earlier point of time and, as a result, lengthens the period of life during which the person is known to have disease, it has no impact on the time of death. She simply spends more of her life as a cancer patient.

Lead-time bias explains why survival is a particularly misleading endpoint in screening trials, as opposed to disease-specific mortality. To demonstrate this conceptually, take as a hypothetical example a disease that kills 100% of people 4 years after the onset of physical symptoms. The 5-year survival rate is therefore 0%. A new screening test is developed that can diagnose the disease 5 years before symptom onset. The 5-year survival for screen-detected disease therefore rises to 100%, even though nothing has been done in this scenario that will affect the outcome of the disease. Mortality rates are not subject to lead-time bias because they deal with an entirely different denominator: whereas 5-year survival is the number of individuals with the disease alive after 5 years divided by the number of individuals diagnosed with the disease, mortality is the number of individuals who have died from the disease divided by the total population at risk for the disease.

This highlights an important difference between trials of screening and prevention: the usual endpoint used to evaluate efficacy. In the case of cancer screening, as noted previously, the primary endpoint should be *cause-specific mortality*. However, in prevention trials, the primary endpoint is generally cumulative cancer *incidence*. The ultimate goal of primary disease prevention is to decrease mortality. Practically speaking, however, few if any cancer prevention trials are large enough or long enough in duration to detect a difference in cancer mortality. In fact, none of the chemoprevention trials that are discussed in this chapter have shown an improvement in cause-specific or overall mortality. In the case of the elderly, a reduction in cancer incidence may never translate into improved cancer mortality because of limited life expectancy. However, the diagnosis of cancer is important in and of itself as a health outcome because it has such a major impact on overall health and because treatments triggered by the diagnosis can be so morbid, particularly in the elderly.

Length-biased sampling is a third form of bias inherent in screening programs. Early detection tools are more effective at identifying slower-growing, less lethal lesions than rapidly progressing ones. This occurs because although every tumor has a given window of time between the threshold of detectability and the appearance of symptoms (the target period of early detection efforts), less aggressive cancers will have a longer preclinical period of growth than more rapidly fatal cancers. As such, a screening tool applied at set intervals has a greater likelihood of detecting these slowly progressive, more favorable lesions than those tumors that quickly advance to a symptomatic state. This does not automatically mean that early detection has had a beneficial impact on the course of the disease; screening programs may simply "stack the deck" with more indolent lesions.

The most extreme form of length-biased sampling is a highly counterintuitive concept termed *overdiagnosis*. Overdiagnosis occurs when a cancer is detected that would never have gone on to cause problems for the individual. This can occur for two reasons: (1) despite its histological appearance, the lesion is essentially indolent and has no malignant potential or (2) the lesion is so slow growing that the individual would die of another competing cause of death before the cancer would have ever become a health concern. This second mechanism is particularly of concern in older persons; cancer is largely a disease of aging and, even in those who coincidentally have slow-growing cancers, competing causes of death can account for a large proportion of deaths.

Overdiagnosed individuals cannot, by definition, benefit from the treatment(s) received, but they are exposed to all of the potential morbidities and even mortality that may accompany the therapy. Table 2-1 provides a summary of these important biases.

The potential benefits of screening are a reduction in mortality (overall or disease-specific), or, at minimum, clinically important morbidity associated with the cancer. As effective screening is applied to older populations, because all causes of death become more common with age, it becomes less likely that overall mortality rates will be affected and more probable that only disease-specific mortality will change.

TABLE 2-1 Key Clinical Pearls

Important biases in cancer screening	Healthy volunteer bias: There are fundamental differences between people who choose to participate in screening and those who do not; persons that participate may tend to be more attuned to health messages, come from higher educational and socioeconomic strata, and have a generally superior baseline health status Lead-time bias: The interval between diagnosis at the asymptomatic stage (by screening) and by symptoms; by advancing the date of diagnosis, screening adds apparent survival time compared with symptomatic detection, but this may not translate into a longer life span Length-biased sampling: Screening tools disproportionately detect slower-growing, more latent cancers compared with symptomatic detection Overdiagnosis: A situation where, despite its pathological appearance, a cancer either has no malignant potential or will not affect remaining life span as the person will die of another cause first
Important considerations for screening and prevention in the older patient	Limited life expectancy and presence of comorbidities: Can increase probability of overdiagnosis and overtreatment, as absolute potential for benefit of screening and prevention decreases with age Increasing likelihood of harm from preventive agents, treatments: Older populations may not be as resilient to the toxic effects of chemopreventive agents or the stresses of surgical interventions Limitations of most screening and prevention efficacy trials in the older population: Most trials have excluded older patients, meaning that evidence of benefit is extrapolated/assumed to be true in this group

COMMONALITIES BETWEEN CANCER SCREENING AND PREVENTION IN THE ELDERLY

Some of the core principles in making the personal decision about preventive interventions are similar to those involved in screening decisions. Just as with screening, the target population for cancer prevention is generally healthy; hence, careful consideration must be given to both benefits and harms. The absolute benefits often diminish in the very elderly, whereas the absolute rate of harms may increase. The harms associated with screening and related diagnostic follow-up and treatment often increase with age. For example, advancing age has an adverse effect on postoperative mortality for a range of surgical procedures and associated complication rates. In the case of cancer prevention, strategies frequently involve pharmacologic interventions, which may have unfavorable toxicity profiles in the elderly compared to the young. These considerations may even reverse the benefit-harm balance of screening tests or preventive interventions in the elderly.

Just as with screening, powerful biases can confound the interpretation of prevention studies, leading to overestimation of benefits. "Healthy volunteer" bias is particularly important in prevention studies because adherence to (and interest in) preventive interventions is often associated with underlying robust health and favorable outcomes independent of the actual effect of the intervention. Healthy volunteer bias in clinical screening and prevention trials may therefore make accurate generalization of both benefits and harms to the very elderly difficult.

UNIQUE ASPECTS IN JUDGING BENEFITS AND HARMS OF CANCER PREVENTION IN THE ELDERLY

There are also important differences between screening and primary prevention interventions in the elderly. As previously discussed, limited life expectancy may amplify overdiagnosis in screening because even progressive tumors may not grow quickly enough to cause medical problems before the individual dies of competing causes. Delay in time to benefit can also represent an important difference between screening and prevention strategies. "Lead time" before a cancer screening test confers benefit may be on the order of 3 to 15 years. However, the delay in benefits from certain preventive interventions could, in some cases, be far longer if the intervention acts at early stages of carcinogenesis and may be even more likely than screening interventions to fall beyond the remaining life expectancy of an elderly person considering, for example, difficult changes in lifestyle. In contrast, risk for lung cancer begins to drop within a few years after quitting smoking, so tobacco cessation programs are likely to produce benefits even in the elderly.

With some exceptions, such as episodic single cervical cancer or colon cancer screening tests to detect and remove preneoplastic lesions, preventive interventions are usually long term and require prolonged effort. This is particularly true of dietary change and exercise but also applies to the need to take pharmacologic agents for years. These long-term interventions can be especially challenging in a cognitively impaired person or in someone with the physical limitations of advancing age that limit exercise. This stands in contrast to screening interventions, which are repeating but episodic in nature, and although they may cause distress in a cognitively impaired person (who might not understand what is being done), are usually brief, time-limited encounters.

Case Study: Screening Interventions

The Husband: Prostate Cancer Screening. Although this female patient firmly believes in the power of PSA screening to avert prostate cancer death in her husband, experts strongly disagree over the utility of this modality. Despite explosive uptake of this technology in the United States, for many years only observational studies existed to guide practitioners' judgement, and such studies are particularly prone to the biases previously mentioned. In 2009, the publication of two randomized controlled trials shed new light onto the issue. The first trial was the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial. It assigned approximately 77,000 men, aged 55 to 74 years, at 10 U.S. study sites to receive annual PSA testing for 6 years or to usual care. After 7 to 10 years of follow-up, no statistically significant difference in prostate cancer mortality rates was observed, with a trend toward *increased* death in the screened group (rate ratio 1.13; 95% CI, 0.75-1.7). Between 40% and 50% of participants in the control group did receive PSA screening at least once outside the confines of the trial, which may have had an impact on the observed effect size, although any potential benefit would remain small.[2]

The second trial, the European Randomized Study of Screening for Prostate Cancer (ERSPC), was a multinational study that randomized approximately 162,000 men between ages 50 and 74 years (with a predefined "core" group of 55 to 69 years) to receive PSA testing (at varying intervals, and with digital rectal examination and transrectal ultrasound, depending on screening center, or no screening). There was about a 20% relative reduction in the risk of prostate cancer death in the "core" screening group after a median follow-up of 9 years. Of note, no statistically significant difference in prostate cancer mortality was observed in the overall study population, and, again, there was a trend toward *increased* mortality in the oldest enrolled subgroup (70 to 74 years) (rate ratio 1.26, 95% CI, 0.80-1.99). The trial also raised considerable concerns about resulting overdiagnosis; it found that 48 cases of prostate cancer needed to be treated to avert one death from the disease.[3]

Neither of these trials provides direct evidence concerning the efficacy of PSA screening for men—such as this patient—who are 75 years and older. Additionally, because most men 75 years and older have a reduced life expectancy, few would be expected to live long enough to experience a mortality benefit from screening. There is also evidence to suggest that any net benefit of treatment with radical prostatectomy for diagnosed prostate cancer may be largely limited to men younger than 65 years.

As stated previously, potential harms must always be weighed against likelihood of benefit when deciding the worth of a clinical intervention. In the case of PSA testing, important possible harms to the individual besides the documented potential for overdiagnosis and overtreatment of latent disease include false-positive results and resulting unnecessary diagnostic procedures (including repeat biopsies). Analysis of the PLCO trial has shown that the cumulative probability for a man to receive at least one false-positive PSA test is 13%, and the probability of undergoing resulting invasive testing is 6%, after four rounds of testing.[4] False-positive tests have been shown to have an impact on men's mental health. Multiple studies have shown that men with false-positive PSA screening test results are more likely to worry about prostate cancer, have an inaccurately elevated perceived risk for the disease, and have sexual function issues compared with those with normal results. These psychological findings have been documented to persist for at least 1 year after the false-positive test, despite diagnostic resolution of the issue (a normal biopsy).

Finally, potential harms associated with therapy for the disease must also be factored into the overall risk-benefit profile of a screening test because the test can confer no benefit without resulting treatment. In the case of prostate cancer, the harms of treatment can be considerable. A study of quality of life among survivors of localized prostate cancer after treatment with radical prostatectomy, brachytherapy, or external-beam radiotherapy found that at 1 year after treatment, depending on choice of therapy, 54% to 75% could not maintain erections for intercourse, 3% to 14% experienced bowel urgency described as "a moderate or big problem," and 6% to 16% had urinary incontinence at least once a day.[5] Multiple studies have also shown that the postoperative mortality from radical prostatectomy increases with age; as noted previously, this may occur in the context of absence of potential for benefit from the therapy.

This careful review of the uncertainty of benefits, along with the potential harms of screening and therapy, convinces this patient and his wife that he should forgo PSA screening.

The Wife: Breast Cancer Screening. The wife remains concerned that she has not been getting regular mammograms. There have been a number of randomized controlled trials of mammography performed; however, most of these trials are older (approximately 30 years) (which could reduce the true importance of screening

relative to treatment, as new therapies have emerged over time) and have important methodological limitations. Several meta-analyses of these trials have estimated an approximate 15% relative reduction in breast cancer deaths after 10 to 14 years of regular mammography screening in women aged 39 to 74 years.[6] However, age is a critical factor affecting the magnitude of risk reduction. The most recent systematic review performed for the U.S. Preventive Services Task Force found that for women ages 50 to 59, the relative risk was 0.86 (95% CrI [credible interval], 0.75-0.99); for women 60 to 69, 0.68 (95% CrI, 0.54-0.87); and for women 70 to 74, there was a (not statistically significant) trend towards *increased* breast-cancer mortality with screening (RR, 1.12, 95%; CrI, 0.73-1.72).[7] Importantly, of all of the studies, only the Swedish Two-County trials included women between the ages of 70 and 74 years, and no trial has directly evaluated the efficacy of mammography in women aged 75 years and older.

As with prostate cancer screening, potential harms of mammography screening include the risk of overdiagnosis and overtreatment, adverse effects of treatment, and false-positive results, with resulting psychological effects and unnecessary diagnostic procedures. The potential for radiation-induced breast carcinogenesis has also been cited as a concern, although younger populations (e.g., 40 to 49 years) would be at greatest risk for this outcome. Rates of overdiagnosis associated with the use of screening mammography have been estimated at 10% to 30% of all breast cancers diagnosed.[8] Another way of framing these findings is that for every 2000 women screened regularly for 10 years, 10 women will be treated unnecessarily and 1 death from breast cancer will be averted (the latter after a delay of about 5 to 10 years). Importantly, because overall mortality rates (competing causes of death) rise with increasing age, the probability of overdiagnosis and overtreatment in women 70 years and older is likely higher than for other age groups.

False-positive test results are common with screening mammography. One analysis found that after 10 years of regular screening, nearly 50% of women would have at least one false-positive test, and 20% a resulting biopsy.[9] However, the frequency of false-positive results is thought to decrease with increasing age. Screening also may increase the overall frequency of mastectomies. A pooled analysis of randomized trials found that the relative risk of mastectomy after mammography compared with no screening was 1.35 (95% CI, 1.26-1.44).[8]

Psychological distress associated with false-positive mammography screening has been documented as well. A systematic review of the long-term effects of false-positive mammograms found that, compared with women who had received normal results, women with false-positive test results used mental health care professionals more frequently and had higher levels of anxiety, apprehension, and intrusive thoughts specific to breast cancer.[10] False-negative tests (that is false reassurance that the woman does not have breast cancer) can also be of concern; mammography is estimated to miss 1 breast cancer per 1000 women screened per screening round.[7]

After a careful discussion regarding the unavailability of high-quality evidence about the efficacy of mammography for women in this patient's age range, along with a review of the important potential associated harms—particularly overdiagnosis and overtreatment—the wife decides that she would like to take some time to further consider the information before deciding on whether to be screened for breast cancer.

The wife is also interested in pursuing colonoscopy screening for colorectal cancer for both herself and her husband. She notes that neither has previously received a colonoscopy, although her gynecologist had occasionally performed an in-office guaiac smear; the results of these have always been negative. Her physician points out to her that in-office guaiac smears are not considered an acceptable form of colorectal cancer screening, having never been tested in prospective studies.

Husband and Wife: Colorectal Cancer Screening. Until recently, only the home based fecal occult blood test (FOBT) had randomized, controlled evidence available to demonstrate reductions in colorectal cancer deaths. Several trials of FOBT have consistently shown relative reductions in colorectal cancer mortality of between 15% and 33%, depending on whether the test was administered annually or biennially; this translates into an absolute risk reduction of about one to five deaths per 1000 participants.[11] Of note, most trials only included individuals up to 74 years of age; a single study provides evidence for up to 80 years. Newer fecal immunochemical tests have demonstrated improved sensitivity and specificity compared with guaiac-based tests and have been recommended for use by the U.S. Preventive Services Task Force (Table 2-2).

Flexible sigmoidoscopy (which can evaluate the left side of the colon up to the splenic flexure) is another screening option for the couple to consider. A recently published randomized, controlled trial of one-time flexible sigmoidoscopy versus usual care in 170,000 men and women ages 55 to 64 years demonstrated a statistically significant 30% relative reduction in colorectal cancer mortality.[12] Although colonoscopy has the least evidence available to directly demonstrate its efficacy in reducing colorectal cancer mortality, because the procedure is integral to diagnostic follow-up and polyp removal for the other screening options (and, as such, is a necessary step in colorectal cancer screening programs), this has been thought to represent sufficient indirect evidence of efficacy to support its use as a stand-alone screening option. Colonoscopy generally allows for visualization of the entire colon (to the cecum). On the other hand,

TABLE 2-2 Age-Specific Recommendations for Screening and Prevention from the U.S. Preventive Services Task Force*

Intervention	Modality	Recommendation
Prostate cancer screening	PSA	Men, <75 years: the current evidence is insufficient to assess the balance of benefits and harms ("I") Men, 75+ years: Recommends against screening ("D")
Breast cancer screening	Mammography	Women, 50-74 years: Recommends biennial screening ("B") Women, 75+ years: The current evidence is insufficient to assess the balance of benefits and harms ("I")
Colorectal cancer screening	Fecal occult blood testing, annually Flexible sigmoidoscopy, every 5 years Colonoscopy, every 10 years	Men and women, 50-75 years: Recommends screening ("A") Men and women, 76-85 years: Recommends against routine screening; there may be considerations that support screening in an individual patient ("C") Men and women, 86+ years: Recommends against screening ("D")
	CT colonography Fecal DNA testing	The current evidence is insufficient to assess the balance of benefits and harms ("I")
Breast cancer chemoprevention	Tamoxifen Raloxifene	Women, any age, low to average risk for breast cancer: Recommends against routine use ("D") Women, any age, high risk: Recommends clinicians discuss chemoprevention ("B")
Colorectal cancer prevention	Aspirin/NSAIDs	Men and women, all ages: Recommends against routine use ("D")
Cancer chemoprevention, general	Vitamins A,C, E Multivitamins with folic acid Antioxidants	Men and women, any age: The evidence is insufficient to recommend for or against use ("I")

*For more detailed information regarding these recommendations, go to: http://www.ahrq.gov/clinic/uspstf/uspstopics.htm

two recent epidemiologic studies have suggested that the benefits of colonoscopy may be restricted to the left side of the colon. Other screening options under development include computed tomography (CT) colonography and fecal DNA testing; however, evidence regarding the effectiveness of these modalities is still being acquired.

Harms associated with screening vary by the modality used. FOBT in and of itself appears to have the lowest risk of associated adverse events, although its associated false-positive rate (2% to 10%, depending on whether rehydration is used) is of concern because each positive test leads to further evaluation with colonoscopy, which has higher rates of complications.[11] In the most recent systematic evidence review performed in support of the U.S. Preventive Services Task Force, flexible sigmoidoscopy was found to have a rate of serious complications of about 3.4 per 10,000 procedures (including perforation, major bleeding, diverticulitis, and cardiovascular events requiring hospitalization, as well as death). Colonoscopy appeared to have the highest rate of associated serious complications, at 25 per 10,000 procedures. Perforations alone accounted for about 4 per 10,000 procedures.[13]

Although the relative frequencies of harm by age have not been well studied, at least two trials have shown increased risks of perforation with colonoscopy in older adults (older than 60 years). A modeling study performed by two groups from the Cancer Intervention and Surveillance Modeling Network (CISNET) found that although colorectal adenoma incidence does increase with advancing age, for individuals between the ages of 75 and 85, any gains in life-years acquired through screening were small in comparison to the risks of associated complications. Furthermore, as was true for prostate and breast cancer, the increasing frequency of important comorbidities and competing causes of death in this population reduces the likelihood that any benefits of screening (which may take up to a decade or more to appear) will be actualized.

After reviewing the limitations of the evidence for persons aged 75 and older, and after careful discussion of the variable risks associated with each of the colorectal cancer screening strategies, the husband decides he is not interested in pursuing any type of screening. The wife decides that she is uncomfortable with pursuing colonoscopy as a primary screening test, given the review of potential harms, but, as she feels she is in essentially good health, she is interested in at-home FOBT testing.

Case Study: Prevention Interventions

The Husband: Prostate Cancer Prevention

The husband has chosen not to receive prostate cancer screening. However, his friend informed him that a drug that is used to treat benign prostatic hyperplasia (BPH) and baldness has been shown to decrease the risk of developing prostate cancer and that the side effects are relatively mild. This appeals to him, and he wants to know whether he should take it for cancer prevention.

Although not approved by the Food and Drug Administration (FDA) for prostate cancer prevention, a large randomized placebo controlled trial of the 5-alpha reductase inhibitor finasteride (the Prostate Cancer Prevention Trial [PCPT]) does provide good evidence that finasteride at a dose of 5 mg orally per day decreases the risk of prostate cancer.[14] In the trial, 18,882 men aged 55 and older were randomly assigned to take finasteride or placebo for up to 7 years. Over the 7-year period, the rates of prostate cancer diagnosis were 18% and 24% in the finasteride and placebo arms, respectively, for a relative reduction of 25%. Because the study design mandated an end-of-study prostate biopsy in all men who had not previously been biopsied, the high rates of cancer in each study were due to both clinically relevant cancers and those that would not have been detected had it not been for per-protocol biopsy. A subsequent systematic review of the use of 5-alpha reductase inhibitors for prostate cancer prevention estimated the number needed to treat (NNT) to prevent one diagnosis of prostate cancer after about 7 years of finasteride use was about 71.[15]

Side effects of finasteride were modest and included a decrease in volume of ejaculate, a small decrease in libido, and slight increases in erectile dysfunction and gynecomastia. The effects on sexual function were generally reversible. On the plus side, problems associated with urinary obstruction (including urinary urgency, frequency, and retention) were lower in the finasteride arm compared with placebo.

However, the initial report of the PCPT showed a potentially worrisome increase in diagnoses of high-grade (Gleason score 7-10) tumors associated with finasteride (6% compared with 5%). Even though the number of deaths from prostate cancer was the same in each arm, the fear was that the increase in high-grade tumors might ultimately translate into a higher risk of death from prostate cancer. Subsequent analyses have provided evidence that the increase in high grade tumors in men taking finasteride is likely to be spurious because finasteride decreases the size of the prostate gland, leading to an increase in sensitivity of PSA in the detection of high grade tumors.[15] As part of the study design, all men were being routinely screened annually with PSA and digital rectal examinations.

The routine screening of all men in the PCPT brings up a key issue in counseling this patient. Because of the study design, the impact of finasteride on prostate cancer risk is only known in men who are being regularly screened for prostate cancer. PSA testing is known to increase the risk of being diagnosed with prostate cancer by about 100%. Many of these screen-detected cancers are indolent and would never have come to attention had it not been for screening. Therefore finasteride does not bring the risk of being diagnosed with prostate cancer down to the level of risk in a man who is not being screened at all. It is also not known how effective finasteride is in preventing cancers not detected by screening. Because this man declined prostate cancer screening, finasteride may be of little or no benefit.[15]

Given this caveat, he asks whether a specific diet, dietary supplements, or vitamins are known to prevent prostate cancer. Unfortunately, there are no known dietary interventions known to decrease prostate cancer risk. In a randomized trial, selenium and vitamin E did not decrease prostate cancer risk.[16] Evidence regarding most other nutrients and supplements is inconsistent, and there are no randomized trials to inform decisions.

The wife has heard about the use of the selective estrogen receptor modulators (SERMs) tamoxifen and raloxifene to lower breast cancer risk and would like to know if she should take one. As in the case of counseling on prostate cancer chemoprevention, treatment decisions are complex and must be individualized. The risk-benefit ratio changes with age and also depends on the underlying absolute risk for breast cancer. As in the case of prostate cancer chemoprevention, there is evidence from randomized controlled trials to help guide the decision.

The Wife: Breast Cancer Prevention. In the Breast Cancer Prevention Trial (BCPT), 13,388 women at increased risk of breast cancer were randomly assigned to take tamoxifen (20 mg per day for up to 5 years) or a placebo.[17] In the subsequent Study of Tamoxifen and Raloxifene (STAR), 19,747 women were randomly assigned to take tamoxifen (20 mg per day) or raloxifene (60 mg per day), a SERM that is FDA-approved for the management of osteoporosis of menopause.[18] Both trials required an estimated 5-year absolute breast cancer risk of at least 1.66%, calculated by a validated statistical model (the "Gail model"; see http://www.cancer.gov/bcrisktool/). The model was based on several risk factors: age, race/ethnicity, family history, age at menarche, age at first live birth of a child, and prior biopsy history. Because the average 5-year risk of breast cancer for an American woman is about 1.66% once she reaches the age of 60 years, this patient may meet the criterion for a discussion about chemoprevention with a SERM. However, since 1.66% is the *average* risk for a 60-year-old woman, many elderly women have a risk level lower than this threshold, and the Gail model estimate should be obtained on the basis of the specific additional risk factors of this patient.

In the BCPT, tamoxifen reduced the relative risk of both invasive and noninvasive breast tumors by about 40% after 7 years of follow-up compared with placebo. The number of women at elevated risk of breast cancer needed to treat to avert an invasive breast cancer was about 60 to 65 and about 175 to avert a noninvasive tumor. The preventive effects were limited to estrogen receptor (ER)–positive tumors. Several other randomized trials (the International Breast Intervention Study;

the Royal Marsden Tamoxifen Trial; and the Italian Randomized Tamoxifen Prevention Trial) have demonstrated similar results for invasive cancer.

Tamoxifen has been shown to cause a number of life-threatening side effects, and several of these increase with age. These include endometrial cancer, stroke, and thromboembolic events (e.g., pulmonary embolism). It is therefore important that elderly women explicitly discuss the possible life-threatening toxicities in considering the use of tamoxifen. Tables have been published that show estimates of the benefits and harms of tamoxifen according to a woman's baseline risk of breast cancer, her age, and the presence of a uterus. Those tables show, for example, that women over age 70 who have a uterus do not generally have a favorable benefit-risk balance unless their estimated 5-year risk of breast cancer is at least 6.5%.

Raloxifene, another SERM, has been shown to decrease the risk of invasive breast cancer in placebo-controlled trials for prevention of osteoporotic fractures and cardiovascular events in postmenopausal women at elevated risk for these outcomes. Unlike tamoxifen, raloxifene does not appear to increase the risk of endometrial cancer in women with a uterus. Because of these observations, raloxifene was directly compared with tamoxifen in the previously mentioned STAR trial. The effects of raloxifene on the risk of invasive cancers observed in the STAR trial were similar to tamoxifen and restricted to ER-positive tumors. However, unlike tamoxifen, raloxifene appeared to have little or no preventive effect on noninvasive tumors.

The toxicity profiles between the two drugs differ in important ways. Raloxifene has a lower incidence of thromboembolic events and tends toward fewer endometrial cancers in women with uteri. Taking all of this evidence into account, it is likely that raloxifene would have a more favorable benefit-risk profile in this patient, if she has a high enough risk of developing breast cancer and wishes to use a chemopreventive agent.

This patient is also curious about other potential breast cancer prevention options. Although prophylactic mastectomy has been shown to be associated with a reduced risk of breast cancer in women with highly penetrant predisposing inherited mutations in genes such as BRCA1 and BRCA2, it is reserved for women at extremely high risk, and thus is not a consideration for this 76-year-old woman with no prior history of cancer. Finally, no lifestyle or dietary changes and no vitamins or dietary supplements have been proven to decrease the risk of breast cancer (and certainly not in the very elderly). It is true, however, that the well-established risk of breast cancer associated with combined postmenopausal hormone therapy with estrogen plus progestin decreases rapidly if the hormones are stopped. Therefore this would be a serious consideration if the patient had been taking hormone therapy.

The third area of particular interest to this couple is colorectal cancer prevention. The hormone therapy component of the randomized Women's Health Initiative (WHI) provided evidence that postmenopausal hormone therapy with combined estrogen plus progestin, but not estrogen alone, lowers the risk of colorectal cancer.[19] This protective effect is supported by observational evidence. However, the WHI combined hormone therapy study was halted because of a net unfavorable balance in health outcomes. Therefore, hormone therapy should not be considered a standard option for colorectal cancer prevention in this female patient.

Husband and Wife: Colorectal Cancer Prevention. On the basis of the fact that colorectal cancers overexpress cyclooxygenase-2 (COX-2) and observational evidence that use of the COX-2 inhibitors such as celecoxib and rofecoxib are associated with a lower risk of colorectal cancer, there was strong interest several years ago in the use of COX-2 inhibitors for cancer prevention. However, several randomized trials were launched and then stopped because of an increased risk of several life-threatening toxicities, including myocardial infarction, stroke, and heart failure. Such adverse outcomes would be particularly important in the elderly, who are at increasing risk for them by virtue of their age.

Aspirin, a nonspecific anti-inflammatory drug, is also of interest, and it is often used in low doses (e.g., one "baby aspirin" of about 81 mg per day) to prevent myocardial infarction in men at elevated risk and stroke in women at elevated risk. However, the doses tested for colorectal cancer have generally been far higher than those used to prevent cardiovascular disease. Randomized trials, supported by observational evidence, suggest that taking at least 300 mg of aspirin per day for at least 5 years can prevent colorectal cancer after a latency period of 10 years or more.[20] However, it is likely that the bleeding risks combined with the long latency before the onset of benefit in this elderly couple would weigh strongly against the use of aspirin in the doses needed to prevent colorectal cancer.

Lifestyle changes such as exercise, increased dietary fiber, lower meat intake, high fruit and vegetable intake, or use of vitamins, minerals, or dietary supplements have been of interest for many years for colorectal cancer prevention. Most of the interest arose from retrospective case-control studies. However, prospective cohort studies that are less subject to recall biases are far less supportive of these associations. There may be reasons to recommend dietary and lifestyle changes for prevention of other chronic diseases, but the evidence is too weak and inconsistent to suggest that the changes will lead to reduction in risk of colorectal cancer.

Finally, polyp removal as a result of colorectal cancer screening is a form of primary cancer prevention. Screening has been covered earlier in this chapter.

CONCLUSION

Discussions about cancer screening and prevention are particularly complex in the elderly (Table 2-3). If the adage that it is very difficult to make a healthy person better off than he already is applies to cancer screening and prevention in general, it is of particular relevance to the elderly. Harms of screening and prevention often occur relatively quickly, and benefits, if any, are often delayed by years or decades. Moreover, what evidence that exists to inform personal decision making is often either observational in nature (and therefore subject to strong study biases) or particularly sparse in the elderly; most randomized trials in healthy volunteers attract a relatively young population. Therefore extrapolations of existing evidence to the elderly can be difficult. Some of the tools provided in this chapter can facilitate the discussion with patients, but individualization will always play an important role. Across-the-board recommendations in the elderly are usually overly simplistic.

TABLE 2-3 Controversial Issues

Need for randomized trials in screening and prevention	Because the outcome of interest (death from cancer or cancer incidence) in a healthy population is relatively rare, randomized trials of screening and prevention must often be large, and may require many years of follow-up along with considerable resources. However, because of fundamental biases inherent in observational studies of screening and prevention trials (see Table 2-1), RCTs are the only method by which one can definitely evaluate the efficacy of a given preventive agent or early detection method.
Overdiagnosis	Although counterintuitive, the concept of overdiagnosis itself is now accepted as a harm of screening for most if not all cancers, including prostate, breast, and colorectal. For a given cancer, estimates regarding the magnitude of overdiagnosis (as a proportion of all detected disease) remain areas of debate.
Universal upper age boundaries for screening and preventive interventions	Some guidelines organizations (including the USPSTF) have begun to establish lower and upper age boundaries for screening practices, on the basis of clinical trial evidence and modeling approaches. This has arisen out of the recognition that different age subpopulations are likely to experience different balances of net benefits and harms. However, as individuals may vary in terms of associated comorbidities and life expectancies, not all groups agree with this approach.

SUMMARY

Prevention and early detection interventions hold immense intuitive appeal; however, public health messages around these issues have often understated the true complexity of decision making in this field. This is particularly true regarding the unique considerations in screening and prevention for older populations. This chapter begins with a review of general principles of cancer screening and prevention. It introduces the analytic framework, a tool to assist researchers and clinicians in basing decisions about the utility of a given preventive or early detection intervention on an explicit chain of evidence that highlights the net balance of benefits and harms for a given population, rather than a reliance on assumptions or simple intuitive reasoning. Major biases associated with screening and prevention studies (particularly observational studies), including the healthy volunteer effect, lead-time bias, length-biased sampling, and the concept of overdiagnosis, are discussed. Important similarities and key conceptual differences between screening and prevention trials and activities are highlighted.

A critical discussion of the specific considerations for screening and prevention activities in older adults in the areas of prostate, breast, and colorectal cancer follows. Unique factors to bear in mind for older populations include (1) a paucity of direct evidence supporting the use of screening and prevention interventions in this subgroup (as most older adults have been excluded from efficacy trials); (2) the impact that limited life expectancy and the presence of comorbid conditions can have on the probability of overdiagnosis and overtreatment; (3) the differential effect that toxicities of chemopreventive agents or treatments may have on older populations; and (4) the fact that the overall potential for benefit from screening or preventive actions will generally decline with age. The concepts presented in this chapter should help to facilitate informed, individualized discussions with patients.

See expertconsult.com for a complete list of references and web resources for this chapter

CHAPTER

3

Approach to Cancer Diagnosis: Use of Radiology, Pathology, and Tumor Markers

Sunil Amalraj and Arash Naeim

In 1947, the American Cancer Society began a public education campaign about the signs and symptoms of cancer, describing them as "Cancer's Danger Signals," ranging from "unusual bleeding or discharge" to "nagging cough or hoarseness." This approach has evolved over the decades, with the improvement in diagnostic techniques that has made it possible to rapidly diagnose cancer in patients with minimal symptoms or none at all. The primary care physician and geriatrician are on the front lines of diagnosing cancer, especially in its earliest and most treatable stages.[1]

The number of individuals older than 65 years in the United States is expected to more than double over the next 30 years, with the largest increase occurring in the subsegment of individuals aged 75 to 84. More than 60% of new cancers and 70% of cancer deaths occur in people older than 65 years.[2] The primary care physician or geriatrician must not only manage the chronic comorbid medical conditions of older patients, but also display vigilance in the medical examination of this high-cancer-risk population. The evaluation can often be complex, involving multiple imaging modalities, specialized blood tests, and biopsy procedures, and has the potential to be an emotionally distressing experience for the patient. When cancer is suspected in an older patient, a logical and targeted plan of medical tests must be constructed that takes into consideration the impact on the patient's current performance status, his or her goals of care, and the associated financial costs.

Cancer is one of the most common diseases that drastically diminish quality of life and life expectancy. According to the American Cancer Society, over 1.4 million new cancer diagnoses will be made in the United States in 2009. This number does not include basal and squamous cell skin cancers or in situ carcinoma (except bladder). Cancer is the second most common cause of death next to heart disease and accounts for nearly one of every four deaths. The most common sites of new cancer cases for men are prostate (25%), lung/bronchus (15%), and colorectal (10%). For women, they are breast (27%), lung/bronchus (14%), and colorectal (10%). The leading cause of cancer deaths for both men and women was lung cancer, which accounted for 30% of male cancer deaths and 26% of female cancer deaths.[3] Aging and cancer are complex processes that are regulated by multiple factors. Extensive research into the molecular mechanisms of both aging and cancer has demonstrated the convergence of many common biological pathways. The most critical of these pathways are those activated by DNA damage, inflammation, depletion of stem cells, and oxidative stress.[4-7] Hence, cancer can be truly thought of as a disease of aging. The National Cancer Institute, Surveillance Epidemiology and End Results program has found, from data collected between 2003 and 2007, that the median age for cancer diagnosis for prostate is 67 years; for breast, 61 years; for colon/rectum, 70 years; for lung, 71 years; and for leukemia, 66 years. Furthermore, 68.4% of lung cancer diagnoses and 63.4% of colorectal cancer diagnoses were made in patients older than 65 years.[8]

MAJOR IMAGING MODALITIES IN CANCER DIAGNOSIS

Cancer imaging studies have a fundamental role in the diagnosis and management of many types of cancers. Computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound are widely used to help distinguish between malignant and benign lesions, to accurately stage a newly diagnosed cancer, and to provide objective information on tumor size that can be used to determine the response to treatment. Specialized plain film x-ray imaging such as mammography has been established as an important screening method and post-treatment surveillance program for breast cancer.[9] The recent improvements in functional imaging, such as PET-CT scanning, have made it possible to obtain important additional information for treatment decisions.

CASE 3-1

A.J. is a 78-year-old widowed man with a past medical history of coronary artery disease, hypertension, and glaucoma who presents to his geriatrician with 4 months of epigastric abdominal pain that radiates to the back, along with episodes of nausea. He also reports an 8-pound weight loss over the past 2 months. On physical examination, he has no signs of ascites or gastrointestinal obstruction. Laboratory studies disclosed the following values: hemoglobin, 10.5 g/dL; white blood cell count, 10,500/μL; platelet count, 330,000/μL; total bilirubin, 2.50 mg/dL; direct bilirubin, 1.50 mg/dL; aspartate aminotransferase, 109 U/L; alanine aminotransferase, 115 U/L; alkaline phosphatase, 467 U/L; lactate dehydrogenase, 503 U/L; and CA 19-9, 82 U/mL. The patient's geriatrician orders an upper endoscopy, which is within normal limits.

Continued

Plain X-rays

Traditional plain film x-rays are widely used for the detection of lung cancers and bone cancers. This form of imaging provides high resolution, but with only limited contrast if there are no calcifications located in the tumor. Chest x-ray screening has not been demonstrated to be effective at reducing mortality from lung cancer. A solitary pulmonary nodule 8 mm or larger in diameter requires further evaluation, including repeat chest x-ray, computed tomography, and possibly biopsy.[10] The skeletal survey, which includes plain x-ray films of the skull, axial skeleton, pelvis, and bilateral extremities, has a key role in the evaluation of patients suspected of having osseous involvement from multiple myeloma.[11]

Mammography

Mammography is the main imaging modality used for the early detection of breast cancer. Mammographic screening programs have been shown to save lives when compared with unscreened populations. Mammography has an overall sensitivity of less than 50%, and efforts are underway to improve its effectiveness as a screening tool.[12] Most mammography performed today is based on newer digital imaging systems. A recently completed trial involving over 50,000 women (Digital Mammographic Imaging Screening Trial) found comparable efficacy compared to plain x-ray mammography. Digital mammography is superior for woman with radiodense breasts and those younger than age 50. The sensitivity for digital mammograms is 41%, with 98% specificity and a positive predictive value of 12%.[13] A newer mammographic imaging technique, tomosynthesis, which generates a number of "slices" of the breast for analysis, has shown encouraging results.[14]

Ultrasound

Ultrasound produces high-resolution images from high-frequency sound waves, and its use has many applications in cancer diagnosis. This form of imaging avoids ionizing agents and contrast agents. It is very effective in distinguishing solid from cystic masses, and is an important tool for evaluating breast abnormalities. It is also helpful in locating and evaluating palpable lesions that are not visible with mammography. MRI with ultrasound can also provide accurate imaging guidance for biopsy procedures and information regarding blood flow intensity and direction in affected vascular structures. Ultrasound images are most widely used for the detection of gynecological, liver, and neck malignancies.[15] Endoscopic ultrasound (EUS), also known as echoendoscopy, combines the techniques of endoscopy with ultrasound imaging technologies and is useful for the diagnosis of esophageal cancer, pancreatic cancer, and rectal cancer.[16] High-intensity focused ultrasound has been utilized as a therapeutic option for ablation of localized breast and prostate cancer.

Computed Tomography

CT scans today have a central role in the diagnosis, staging, and surveillance of cancer because of their ability to offer cross-sectional imaging. This technology has rapidly evolved, with increasing simultaneous imaging slices up to 256, and rotational speeds that allow a whole body scan with a single breath hold. Additional advancements have led to three-dimensional reconstruction and angiography. While CT scans can demonstrate detailed measurements of tumor size and location, intravenous and oral contrast must be used in a coordinated function to obtain optimal images. Some major disadvantages of CT include total radiation dose, renal toxicity and allergic reactions to intravenous contrast, and high financial cost.[17] Triphasic CT scanning (arterial phase, portal venous phase, venous phase after a delay) of a suspicious liver lesion greater than 2 cm and demonstrating classic arterial enhancement is sufficient for making the diagnosis of hepatocellular carcinoma.[18] There has been increasing concern about the carcinogenic potential of multiple diagnostic CT scans. Results from epidemiological studies of medical diagnostic radiation exposure have found that cancer risk from all forms of ionizing radiation is cumulative. The only consistently established link involves exposure to medical radiation during pregnancy and the subsequent risk of pediatric cancer in these children.[19] Thus for the geriatric patient, the risk to the individual patient is minimal, and the benefit/risk balance favors the older patient. The current research evaluating the cancer risk of CT scans when used for symptomatic screening has yet to establish any evidence-based guidelines.

Magnetic Resonance Imaging

MRI scanning offers another form of anatomic imaging without ionizing radiation, and provides superior soft tissue contrast and spatial resolution. MRI is the imaging

modality of choice for primary and metastatic tumors of the brain and spinal cord, as well as for musculoskeletal tumors. It also plays an important role in the detection of breast cancer in women with dense breast tissue, and in the diagnosis of soft tissue sarcoma and hepatocellular carcinoma. Today's MRI machines, at a strength of 1.5 to 3 Tesla units (T), are capable of rapid-pulse sequences and gating of images, allowing the visualization of blood with the use of contrast materials such as gadolinium. As the speed of MRI image acquisition improves and better contrast enhancement is developed, the applications for cancer imaging will only increase.[20] Absolute contraindications for MRI scanning that are especially common in the elderly include cardiac pacemakers, ocular metal, and significantly reduced creatinine clearance. Nephrogenic systemic fibrosis (NSF) has recently been linked to gadolinium-based contrast agents (GBCA). The practitioner should avoid use of these agents in patients whose glomerular filtration rate is less than 30 mL/min/1.73 m^2 unless the diagnostic information is essential and cannot be obtained with noncontrast MRI or other imaging modalities.[21] The technique of diffusion MRI images, used widely for strokes, has showed promise in measuring the response to treatment of brain tumors. This imaging method, which can distinguish between dead and living brain tumor cells, allows assessment of the cancer for therapeutic effectiveness without relying on measurable changes in tumor size.[22]

Nuclear Medicine

Radionuclide bone scans are commonly used to detect bone metastases from such primary malignancies as breast and prostate cancers. The most commonly used isotope for single-photon imaging is technetium-99m, which can be used to image bone (bone scan with ^{99m}Tc-diphosphonate) or thyroid (technetium pertechnetate). In multiple myeloma, the radionuclide bone scan may be falsely negative because of purely osteolytic lesions.[23] Neuroendocrine tumors of the gastrointestinal tract are often located using radiolabeled somatostatin analogues. Metaiodobenzylguanidine (MIBG), which is structurally similar to noradrenaline, can be radiolabeled with radioiodine (^{123}I) and has a sensitivity of approximately 90% for the detection of pheochromocytoma.[24]

The detection of sentinel nodes has an important role in breast cancer and melanoma. Lymphoscintigraphy involves injection of a radiopharmaceutical such as ^{99m}Tc-labeled colloid particles and use of a handheld gamma probe to localize a focus of increased radioactivity. This technique is highly effective in detecting involved local regional lymph nodes.[25] Therapeutic isotope applications include iodine-131 for the treatment of thyroid cancer, and a CD20 monoclonal antibody linked to the radioactive isotope yttrium-90 (Zevalin) used in refractory B-cell non-Hodgkin lymphoma.[26]

TABLE 3-1 Diagnostic Performance of PET-CT and CT with Contrast[33-40]

Tumor	CT (Contrast) Staging Accuracy	PET-CT Staging Accuracy	PET-CT Staging Sensitivity/ Specificity
Lymphoma	67%	93%	93/100
Lung Cancer/ Solitary Lung Nodule	85%	93%	96/88
Head and Neck Cancer	74%	94%	98/92
Colorectal Cancer	65%	89%	86/67
Thyroid Cancer	75%	93%	95/91
Breast Cancer	77%	86%	84/88
Melanoma	86.3%	98.4%	94.9/100

Positron Emission Tomography

Positron emission tomography (PET) allows functional imaging by using intravenous radiolabeled metabolic tracers such as 18-fluorodeoxyglucose (FDG). PET imaging is most sensitive in fast-growing tumors with strong metabolic activity such as head and neck and colon cancers, melanoma, and aggressive lymphoma. When PET scan is performed with concurrent CT scanning, functional and anatomic information can be obtained rapidly, allowing for more accurate decision making.[27] Initial evaluation of both Hodgkin and non-Hodgkin lymphoma is increasingly performed with PET-CT scanning because of its increased sensitivity, with the ability to detect 20% more malignant lesions, including bone marrow and splenic involvement.[28] It also has an important role in determining whether complete response has been achieved for those lymphomas that were PET-avid at the time of diagnosis.[29] There is also substantial evidence that PET-CT is superior to CT alone for colon cancer patients in recurrent cancer is suspected after previous surgical resection.[30] An increasing amount of research supports the use of PET-CT in determining the need to pursue invasive testing for a solitary pulmonary nodule suspected of cancer. In a recent retrospective meta-analysis, PET-CT showed a sensitivity of approximately 96% and a specificity of approximately 80% for detecting cancer in solitary pulmonary nodules (predominantly ≥1 cm in diameter).[31-32] (Table 3.1).

CANCER PATHOLOGY

The treatment of cancer is almost always based on analysis of tissue pathology. With the exception of hepatocellular carcinoma and emergent situations such as acute leukemia with leukostasis, the first step after detection

CASE 3-1 CONTINUED

CT scan of the abdomen with/without intravenous contrast showed dilatation of the gallbladder and the intrahepatic and extrahepatic biliary tree, with a 5 cm mass in the head of the pancreas. A histological diagnosis of adenocarcinoma of the pancreas was made by CT-guided fine needle aspiration (FNA) biopsy.

Pancreatic cancer is the fourth most common cause of cancer-related death for men in the United States. Its peak incidence occurs in the seventh and eight decades of life. When the index of suspicion for pancreatic cancer is high, CT scan should be performed with the "pancreas protocol" (triphasic cross-sectional imaging and thin slices). Endoscopic ultrasound (EUS) is frequently used to further evaluate pancreatic masses and determine the degree of periampullary invasion. Endoscopic ultrasound also provides useful staging information such as the assessment of vascular invasion.[16] Reviews of surgical studies have found that curative pancreaticoduodenectomy (Whipple procedure) can be performed safely in selected patients younger than 80, with morbidity rates, mortality rates, and cost analysis similar to those achieved with younger patients.[41]

of a possible malignancy is coordinating a procedure to obtain a tissue sample for initial confirmation of the diagnosis and future treatment planning. This involves close cooperation between the primary care provider and the radiology or surgical consultant to pursue the lowest-risk approach for the older patient, who often comes with several comorbidities. The pathology report always includes such information as tumor size, histological classification, tumor grade, and pathologic staging. These anatomic features are augmented by immunohistochemical, cytogenetic, and molecular biologic testing, as indicated, to allow detailed tumor classification and to guide the best therapeutic treatment plan.[42]

CASE 3-2

K.T. is an 80-year-old married woman, with a past medical history of insulin-dependent diabetes mellitus, chronic renal insufficiency, and atrial fibrillation, who presents to her geriatrician for further evaluation after noticing persistent right cervical adenopathy, which is painless. She reports increased fatigue and a low grade fever. Her hemoglobin level is 11.5 g/μL, with a white blood cell count of 6,500/μL, and a platelet count of 330,000/μL. The serum lactate dehydrogenase level is 720 U/L. Renal and liver function are normal. Her physical examination is unremarkable and her weight has been stable.

Fine Needle Aspiration/Image Guided Biopsy

The technique of fine needle aspiration (FNA), which utilizes a fine-gauge needle to obtain a sample of cells from a suspicious mass, has been a cornerstone of diagnosis for many cancers, such as carcinoma of the thyroid. It

CASE 3-3

P.M. is a 72-year-old married woman, with a past medical history of insulin-dependent diabetes mellitus, hypertension, gout, and nephrolithiasis, who presents to her geriatrician for further evaluation after a routine complete blood count (CBC) found a significant white blood cell count: leukocytes 35,000/μL with 88% lymphocytes. The hemoglobin level is 12.5 g/dL, and the platelet count is 320,000/μL. She is feeling well and denies weight loss, night sweats, fatigue, shortness of breath, skin changes, or recent infection. Her physical examination is positive for mild splenomegaly (spleen palpable 2 to 3 cm below the costal margin), but is otherwise unremarkable. She has no clinical evidence of lymphadenopathy, or of abnormal bruises.

is cost-effective, poses minimal risk for complications, and avoids the need for general anesthesia. These factors make FNA especially appropriate for use with older patients. Although accuracy rates range from 90% to 95%, FNA is limited to cancer diagnoses that are dependent on cell features rather than tumor architectural patterns, which require larger tissue samples. Thus, FNA is insufficient in making a diagnosis of lymphoma or testicular cancer. Percutaneous image-guided biopsies are the most common way of making a tissue diagnosis of cancer today. Real-time imagery provided by ultrasound, CT scan, and MRI has advanced the biopsy procedure, allowing for acquisition of larger samples of suspicious tissue. Hence, they usually result in adequate tissue to complete immunohistochemical staining, flow cytometry testing, cytogenetic evaluation, and molecular studies.[43] Image-guided biopsy is most often performed under local anesthesia, and has a relatively low complication rate when performed by an experienced radiologist. A recent retrospective analysis performed at the Mayo Clinic found image-guided biopsy in elderly patients did not carry a greater risk of any major complication as compared with younger patients.[44]

Immunohistochemistry

Light microscopy utilizing conventional hematoxylin-eosin (HE) staining is central to determining the gross structure of the tumor, such as distinguishing between adenocarcinoma and neuroendocrine solid tumors and evaluating important parameters such as the nuclear/cytoplasmic ratio of lymphoma tumor cells. Immunohistochemical staining (IHC) is a technique for identifying and classifying malignant cells by means of antigen-antibody interactions used in conjunction with standard light microscopy. IHC is widely used to analyze the distribution and localization of biomarkers and differentially expressed proteins in tumor biopsy samples. The site of antibody binding can be identified either by direct labeling of the antibody, or by a secondary labeling method.[45] Its most common use is

in immunoperoxidase staining, wherein an antibody is conjugated to the enzyme peroxidase, producing a colored chemical reaction. Although not always able to provide a specific diagnosis, these stains can often aid in the differential diagnosis of carcinomas, lymphomas, melanoma, and certain sarcomas when used in conjunction with routine histological examination.[46] Immunofluorescence is an antigen-antibody reaction in which the antibodies are tagged with a fluorescent dye such as such as fluorescein or rhodamine, and the antigen-antibody complex is visualized using an ultraviolet (fluorescent) microscope. Specific cytokeratin proteins that are components of the cytoskeleton of epithelial cells found on certain cancer cells are often identified this way and play an important role in diagnosis. One example of this is discriminating between the diagnosis of primary lung acinar adenocarcinoma and lung metastasis of colorectal cancer. Positive staining of CK7 was observed in most of the primary lung adenocarcinoma samples and positive staining of CK20 was observed in most lung metastases of colorectal cancer.[47]

Flow Cytometry, Cytogenetics, Molecular Testing, and Cancer Diagnosis

Flow cytometry is a method of measuring the number of cells in a sample, and certain characteristics of cells, such as size, shape, and the presence of tumor markers on the cell surface. The cells are stained with a light-sensitive dye, placed in a fluid, and passed in a stream before a laser or other type of light. The measurements are based on how the light-sensitive dye reacts to the light. Among the most common clinical uses of flow cytometry in cancer diagnosis is the classification of chronic lymphoproliferative disorders and acute hematological malignancies.[48] Acute and chronic leukemia display characteristic patterns of surface antigen expression (CD antigens), which facilitate their identification and proper classification and hence play an important role in instituting proper treatment plans. For example, flow cytometry plays a decisive role in distinguishing acute promyelocytic leukemia (APL) from other forms of acute myeloid leukemia (AML), and therefore is critical to determining the initial treatment.[49] Cytogenetic testing involves examining the chromosomes in a cell to detect any abnormality characteristic of a malignancy, such as translocation, inversion, deletion, or duplication. The development of a newer cytogenetic process called fluorescence in situ hybridization (FISH) has expanded molecular diagnostic capabilities. FISH uses special fluorescent dyes to recognize specific chromosome changes in certain types of cancer. The DNA from a biopsy sample is combined with a fluorescently-labeled probe, such as the one for HER-2/neu-positive breast cancer, that is visible under fluorescent microscopy.[50-51] Another DNA analysis technique, called polymerase chain reaction (PCR), which makes possible the rapid amplification of DNA, is used to detect the bcr-abl oncogene in blood or bone marrow when the myeloproliferative neoplasm (MPN) chronic myeloid leukemia (CML) is suspected.[52] (Tables 3.2 and 3.3).

TABLE 3-2 Recurrent Molecular Abnormalities Associated with Myeloproliferative Neoplasms

Genetic Abnormality	Disease	Frequency
BCR-ABL	Chronic myelogenous leukemia	≈99%
JAK2V617F	Polycythemia vera	>95%
	Essential thrombocytosis	≈60%
	Primary myelofibrosis	≈60%
JAK2 exon 12	Polycythemia vera	≈2%
PDGFRA	Myeloid neoplasm +eosinophilia	Undetermined
	Mast cell disease	
PDGFRB	Myeloid neoplasm +eosinophilia	Undetermined
KIT (D816V)	Mast cell disease	Undetermined

From Vannucchi AM, Guglielmelli P, Tefferi A. Advances in understanding and management of myeloproliferative neoplasms. CA Cancer J Clin 2009;59(3):171-91.

CASE 3-2 CONTINUED

The patient was referred to a head and neck surgeon who performs fine needle aspiration (FNA). Cytology studies demonstrate small cleaved lymphocytes and flow cytometry shows a CD5-negative, CD10-positive, CD20-positive monoclonal population suspicious for non-Hodgkin lymphoma (NHL). However, FNA is not adequate to make a diagnosis of lymphoma. The presence of a monoclonal cell population with a CD10-positive immunophenotype is highly suggestive of follicular lymphoma, but an accurate diagnosis cannot be made without lymph node architecture. Furthermore, FNA cannot determine the histological grade of the follicular lymphoma, which strongly influences treatment choice. NHL is the ninth leading cause of cancer deaths among men and the sixth among women.[55] The incidence of NHL has increased significantly in the past three decades, especially in patients in the sixth and seventh decade of life.[56]

Clinical Applications for Biomarkers in Cancer

Since the discovery of the first tumor markers over a century ago (Bence-Jones proteins), numerous molecules have been identified as being associated with various cancers. Tumor markers are biochemical substances produced by malignant cells or by other cells of the body in response to cancer or certain noncancerous conditions. They can be found in the blood, in the urine, in

TABLE 3-3 Immunophenotype for Selected Cancers[54]

Disorder	Positive	Negative
Large B-cell lymphoma	CD19, CD20, CD22, CD79a,	CD2, CD3, CD5, CD7
Follicular small cleaved cell lymphoma	CD10, CD19, CD20, CD21, CD22, CD24,	CD2, CD3, CD4, CD5, CD7, CD8, CD11c, CD23, CD25, CD43
Mantle cell lymphoma	CD5, CD19, CD20, CD22, CD24, CD43,	CD11c, CD23, CD5/CD19 or CD5/CD20
Hairy cell leukemia	CD11c, CD19, CD20, CD22, CD25, CD79a, CD103	CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD23
Acute promyelocytic leukemia, M3	CD13, CD15, CD33	CD2, CD3, CD5, CD7, CD11b, CD14, CD41, CD42, CD61, CD71
Acute mega-karyoblastic leukemia, M7	CD33, CD41, CD42, CD61	CD2, CD3, CD5, CD7, CD11b, CD13, CD14, CD15, CD71
ALL (T-cell precursor)	CD3, CD7	CD10, CD19, CD20, CD22
ALL (pre-B)	CD10, CD19, CD22, CD79a	CD3, CD4, CD5, CD7, CD8
Sézary syndrome (mycosis fungoides)	CD2, CD3, CD4, CD5	CD1, CD7, CD8, CD10, CD11c, CD16, CD19, CD20, CD22, CD25, CD56, CD57

From Nguyen AN, Milam JD, Johnson KA, Banez EI. A relational database for diagnosis of hematopoietic neoplasms using immunophenotyping by flow cytometry. Am J Clin Pathol, 2000. 113(1): p. 95-106.

CASE 3-3 CONTINUED

A CT scan of the chest, abdomen, and pelvis shows bilateral 1.5 cm axillary lymphadenopathy. A review of the peripheral blood smear shows small, mature-appearing lymphocytes with dense nuclei and a small amount of cytoplasm. Flow cytometry of the peripheral blood reveals a clonal B-cell population that is CD5-positive, CD19-positive, CD23-positive, and, CD10-negative. Cytogenetic studies are remarkable for 13q- and 12q- chromosomal abnormalities. Based on the CBC, flow cytometry, and cytogenetics, early-stage chronic lymphocytic leukemia (CLL) is diagnosed. A bone marrow biopsy is not required. Chronic lymphocytic leukemia is one of the most common hematological malignancies in the United States, with an incidence of 3.5 per 100,000. The median age at diagnosis is 70 years for men and 74 years for women.[57]

the tumor tissue, or in other tissues. Tumor markers can be broadly classified into tumor-specific antigens and tumor-associated markers. The vast majority of tumor markers are tumor-associated antigens that can also be found in normal tissue.[58]

There are few specific situations where tumor markers play an important role in the screening and initial diagnosis of a malignancy; however, in clinical practice, tumor markers are most frequently used in evaluating the progression of disease status after the initial therapy and in monitoring the effectiveness of treatment. Tumor marker use in the United States is influenced by the requirement for their approval by regulatory agencies such as the U.S. Food and Drug Administration (FDA), which affects eventual reimbursement from insurance companies. Recommendations for the use of tumor markers are published by the American Society for Clinical Oncology and the National Comprehensive Cancer Network Practice Guidelines in Oncology.[59]

CASE 3-4

J.B. is a 70-year-old married man, with a past medical history of rheumatoid arthritis, hypertension, and hepatitis B with compensated cirrhosis, who presents to his primary care physician for further evaluation of an elevated serum alkaline phosphatase at 655 U/L. He underwent ultrasonography and was found to have a 4.8 cm hypoechoic tumor in the right lobe of the liver. Serum total bilirubin, alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transpeptidase levels were within normal limits, as were coagulation studies. The serum α-fetoprotein concentration was elevated, at 800 ng/mL (normal <20 ng/mL). Serum carcinoembryonic antigen (CEA), and carbohydrate antigen (CA) 19-9 levels were normal. Computed tomography of the liver displayed a tumor in the right lobe, 5.8 cm in diameter, showing a broad zone of peripheral enhancement after administration of intravenous contrast material, and a central low-density area in the arterial-dominant phase. The border of the lesion was irregular and indistinct, and the radiodensity of the tumor was lower than that of the surrounding liver parenchyma.

SCREENING AND EARLY DETECTION

Screening refers to evaluating an asymptomatic patient for the purpose of early detection of cancer. Clinical sensitivity and specificity, in addition to the prevalence of the cancer in the population, will determine the positive predictive value of the screening marker, Although tumor markers were originally developed for identifying a malignancy in a patient without have any focal physical complaints, the only serum tumor marker that is part of any screening program today is prostate-specific antigen (PSA). Other identified tumor markers lack sufficient sensitivity and specificity for widespread use in screening.[60]

The American Cancer Society (ACS) and the American Urological Association recommend PSA and digital rectal examination annually, beginning at age 50, for men who have a life expectancy of at least 10 years. The U.S. Preventive Services Task Force (USPSTF) and American Academy of Family Physicians do not recommend routine

prostate cancer screening with PSA, based on insufficient evidence that early detection by PSA improves health outcomes. Furthermore, PSA is organ-specific but not prostate cancer-specific. Elevated PSA levels (>4 ng/mL) can be found in men with benign prostatic hyperplasia (BPH) and prostatitis. Also, a normal PSA level does not exclude a diagnosis of prostate cancer.[61] Age-specific reference ranges for PSA have been developed (0 to 2.5 ng/mL, 3.5 ng/mL, 4.5 ng/mL, and 6.5 ng/mL for age ranges 40 to 49, 50 to 59, 60 to 69, and 70 to 79 years, respectively) in an attempt to produce increased sensitivity of the test in younger men, so that localized tumors can be detected earlier, when surgical cure is still possible, and improved specificity of the test in older men, who are more likely to have benign elevations in PSA. PSA velocity and analysis of free and complexed PSA levels offer methods of improving PSA specificity. At least three PSA measurements 12 to 18 months apart are needed to accurately calculate PSA velocity. A PSA velocity rate (rate of change) greater than 0.75 ng/mL per year is highly suggestive of cancer. Patients with prostate cancer have a lower percentage of free PSA (free PSA/total PSA) compared with men with benign disease.[62–63]

Tumor Markers in Cancer Diagnosis

Hepatocellular carcinoma is the fifth most common cancer in the world, and the third most important cause of cancer mortality. Prognosis for this disease is poor, since hepatocellular carcinoma (HCC) is usually diagnosed at an advanced stage. Alpha-fetoprotein (AFP) is effective as a tool for confirming a diagnosis of HCC in high-incidence populations such as patients with hepatitis and cirrhosis. An elevation in AFP above 20 ng/mL has been shown to have a sensitivity of between 60% and 90% and a corresponding specificity of 70% to 80% for HCC. An AFP level over 200 ng/mL or the presence of classical arterial enhancement on triphasic CT or MRI is considered to be diagnostic of HCC when a liver mass is greater than 2 cm in size.[64-65]

AFP and β-human chorionic gonadotropin (hCG) have an important role in the classification of germ cell tumors. Usual reference values for AFP are 10-15 mg/L, and for hCG 0-5 IU/L in evaluation for testicular cancer. In seminoma (one form of testicular cancer), AFP is not elevated, but hCG is present in 10% to 30% of cases. Either hCG or AFP or both are produced by 60% to 90% of nonseminomatous germ cell testicular tumors at the time of diagnosis. Both hCG or AFP are elevated in embryonal carcinoma (hCG > 65%; AFP >70%) and AFP is elevated in yolk sac tumors. Also, hCG is elevated in choriocarcinomas and hence useful in diagnosing gestational trophoblastic tumors.[66]

The tumor marker CA-125, developed for epithelial ovarian cancer, is useful in distinguishing benign from malignant disease in postmenopausal women who present with ovarian masses and elevated concentrations of CA-125. One study found a CA-125 greater than 95 U/mL has a positive predictive value of 95% in a postmenopausal woman with a pelvic mass.[67-68] A two-stage strategy in which ultrasonography is performed only if CA-125 concentrations are elevated has shown promise in detecting ovarian cancer. In a study of 4000 women, the specificity of CA-125 plus ultrasound was 99.9% compared with 98.3% for CA-125 alone.[69]

Neuroendocrine tumors constitute a heterogeneous group of rare cancers that originate from endocrine glands in various tissues such as the pituitary, parathyroid, and adrenal glands; the pancreas; and the respiratory tract.[70] Tumor markers often play an important role in the detection of these tumors. For example, the diagnosis of pheochromocytoma usually is established by finding an increase in the urinary excretion of catecholamines or catecholamine metabolites such as vanillylmandelic acid (VMA) and homovanillic acid (HVA).[71] The urinary serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) is the primary test for determining the overproduction of serotonin that is characteristic of carcinoid tumors.[72]

CASE 3-4 CONTINUED

Elevation of the tumor marker α-fetoprotein (AFP) to 800 ng/mL, in the presence of a liver lesion greater than 2 cm in diameter, is sufficient for the diagnosis of hepatocellular carcinoma (HCC). The presence of classical arterial enhancement on triphasic CT further confirms this diagnosis. Tissue biopsy is not required to confirm the diagnosis in this case.[64] The median age at diagnosis for HCC is 64, with 48% of cases occurring in people older than 65 years. The overall 5-year survival for the period 1999 to 2006 was 13.8%.[3] Treatment options for this patient include liver transplantation, surgical resection, ablation (radiofrequency, cryoablation, microwave) and chemoembolization. Short- and long-term results for liver transplantation in patients older than 65 have found outcomes to be comparable to those younger than 65, if older candidates are carefully selected.[73] (Table 3.4).

Summary

Men in the United States have a one in two lifetime risk of developing cancer and women have a one in three lifetime risk of developing cancer. During the last 3 decades there has been steady improvement in the relative 5-year survival rate for all cancers, with a 50% survival from 1975-1977 improving to a 66% survival from 1996-2004.[3] There has also been an increase in the incidence of certain cancers, such as breast cancer (4.3%) and prostate cancer (7.6 %), since 1975.[8] The factors behind these two trends include advances in treatment, the aging population, and significant improvements in our ability to detect cancer at a less advanced stage. As a result of increasing life expectancy, the incidence of cancer is elevenfold higher in persons older than 65 years compared to those younger than 65.[76] The development of imaging

TABLE 3-4 Malignancies Associated with Elevated Tumor Marker Levels

Tumor Marker	Primary Tumor	Diagnosis	Screening	Normal Value	Benign disease unlikely	Benign conditions
PSA	Prostate cancer	Adenocarcinoma of unknown primary	Yes	<4 ng/mL	>10 ng/mL	Prostatitis, BPH
CA=125	Ovarian cancer	Pelvic mass in postmenopausal women	No	<35 units/mL	>200 units/mL	Menstruation, pregnancy, fibroids, ovarian cysts
AFP	Hepatocellular cancer	Liver mass and cirhosis	No	<5.4 ng/mL	>500 ng/mL	Cirrhosis, hepatitis, pregnancy
β-hCG	Germ cell tumor	Adenocarcinoma of unknown primary	No	<5 mIU/mL	>30m mIU/mL	Hypogonadal states, marijuana use
CA 19-9	Pancreatic cancer	Selected pancreatic masses	No	<37 units/mL	>1000 units/mL	Pancreatitis, biliary diease, cirrhosis
CEA	Colorectal cancer	No	No	<2.5 ng/mL <5.0 ng/mL	>10 ng/mL	Cigarette smoking, pancreatitis, peptic ulcer disease, cirrhosis
CA 27.29	Breast cancer	No	No	<38 units/mL	>100 units/mL	Breast, liver, kidney disorders, ovarian cysts

From Perkins GL, Slater ED, Sanders GK, Prichard JG. Serum tumor markers. Am Fam Physician, 2003. 68(6): p. 1075-82; and Manne U, Srivastava RG, Srivastava S. Recent advances in biomarkers for cancer diagnosis and treatment; Drug Discov Today 2005;10(14):965-76.

modalities such as PET-CT, biomarker assays, histological staining techniques, and molecular testing has made possible the earlier diagnosis and treatment of many solid tumors and hematological malignancies.

A multidisciplinary health care team should be involved with planning from the earliest stage of the cancer evaluation, but a single physician should assume the lead role in communicating with the patient. The primary care physician or geriatrician is often in the best position to assess the severity of the patient's comorbid conditions and understand the patient's goals of care. A geriatric oncology tumor board format adapted from those frequently used in medical oncology for specific cancer types and involving the primary care physician could be an effective tool to develop a personalized diagnostic plan for each older patient. The decision to utilize all the medical technology available to prove the final diagnosis of a suspected cancer must be balanced with an individualized assessment of the patient's capacity to tolerate the toxicity of the likely treatment options. Diagnostic decision making in modern oncology continues to strive to integrate the application of technological advances and patient autonomy with the best understanding of the probability of enhancing patient quality of life when cure is not possible.

See expertconsult.com for a complete list of references and web resources for this chapter

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CHAPTER

4

Assessment

Jeffrey Mariano and Lillian C. Min

Our nation is aging. By 2030, 20% of the population will be over the age of 65. It is estimated that 1.5 million new cases of cancer were diagnosed in 2009 and over 500,000 cancer-related deaths occurred. Of these, approximately 60% of cancer cases and 70% of cancer-related deaths will occur in individuals aged 60 years and older.[1] As the population ages, it is increasingly important that doctors and oncologists characterize the "functional age" of older patients with cancer in order to tailor treatment decisions and stratify outcomes on the basis of factors other than chronologic age, and develop interventions to optimize cancer treatments.[2,6,7]

CASE 4-1 CASE STUDY: Mrs. S

Mrs. S is an 80-year-old woman with a history of hypertension presenting to her primary care provider. She was recently hospitalized and discharged from a skilled nursing facility due to an ankle fracture received as a result of a car accident in which she was the driver. She completed rehabilitation and has since returned home. Prior to the accident, she was living alone. However, her son now checks in on her more frequently and calls her twice a day. At this point, she is also afraid of driving and has been relying on public transportation and family members.

Over the next year, Mrs. S becomes increasingly anxious and depressed. She describes "not feeling well" and weight loss. Lab tests are unremarkable. Her son brings concerns of depression to her primary doctor's attention and she is started on Citalopram. Repeat clinical breast exams reveal bilateral breast masses, the right greater than the left.

WHAT INFORMATION FROM A GERIATRIC ASSESSMENT WOULD HELP GUIDE TREATMENT?

Physiologic reserve, functional status, cognition, and comorbidity vary considerably among older adults as a result of the aging process. Given this heterogeneity of factors, a geriatric assessment (GA) may help in managing the older patient with cancer.[2,3,7]

OVERVIEW OF THE GERIATRIC ASSESSMENT

A geriatric assessment includes an evaluation of an older individual's functional status, medical conditions (comorbidities), cognition, nutritional status, psychological state, and social support, as well as a review of the patient's medications (Table 4-1). A meta-analysis of 28 controlled trials demonstrated that Comprehensive Geriatric Assessment (CGA), if linked to geriatric interventions, reduced early rehospitalization and mortality in older patients through early identification and treatment of problems.[74] The components examined in GA can predict morbidity and mortality in older patients with cancer, and can uncover problems relevant to cancer care that would otherwise go unrecognized.[2,8] This approach to cancer care can facilitate individualizing the options for cancer management, quality of life, and prognosis.[8,74]

Three fundamental concepts guide geriatric assessment and the resulting medical management. At the core of geriatric assessment is functional status, both as a dimension to be evaluated and as an outcome to be improved or maintained. The maintenance and restoration of functional status is an essential overriding objective of good geriatric and geriatric oncologic care.[2,5,6,7] A second overarching concept guiding geriatric assessment is prognosis, particularly life expectancy. Finally, geriatric assessment must be guided by patient goals.[2]

PHYSICAL FUNCTION

Functional Status

Functional status and disability reflect the interactions among multiple medical conditions, physiologic aging, psychosocial support, cognitive impairment, and the overall health and vitality of the individual.[4] Functional evaluation can add a dimension beyond the usual medical assessment, providing information on patient care needs and prognosis.[6,4]

The choice of functional assessment tool depends upon the characteristics of the population (community-dwelling, hospitalized, nursing home residents) and the level of function being assessed. Function can be assessed

TABLE 4-1 Components of the Geriatric Assessment

Functional Evaluation (Physical Function)
Self report
Performance-based
Gait and balance evaluation
Comorbidity
Cognitive Function
Psychological State (Affective Assessment)
Social Support
Polypharmacy
Nutrition
Symptoms
Selected Geriatric Syndromes
Advanced Care Planning

by self-report, proxy report, performance-based testing, or a combination of these approaches.[1,3,5]

Self-Reported Tools to Measure Functional Status

Activities of Daily Living (ADLs and IADLs, Tables 4-2 and 4-3) [73]. Most commonly, older adults' functional status is assessed at two levels: activities of daily living (ADLs) and instrumental activities of daily living (IADLs). ADLs are self-care tasks, such as:

- bathing
- dressing
- toileting
- maintaining continence
- grooming
- feeding
- transferring

Questions about functional ability may be valuable if posed in reference to recent activities: for example, "Did you dress yourself this morning?" rather than "Do you dress yourself?"

An inability to perform basic ADLs alone implies a higher risk for functional decline, hospitalization, and poor outcomes leading to delirium and or death. Dependency in these tasks, which is present in up to 10% of persons aged 75 years or older, usually requires full-time help at home or placement in a nursing home.[72]

IADLs are tasks that are integral to maintaining an independent household, such as:

- using the telephone
- shopping for groceries
- preparing meals
- performing housework
- doing laundry
- driving or using public transportation
- taking medications
- handling finances

Asking "Did you drive here today?" or "When did you last drive? (rather than "Do you drive?") may elicit a more useful answer. IADLs are more likely than ADLs to be influenced by factors other than capacity, such as cultural and gender roles and learned skills.

Basic ADLs (BADLs) and IADLs are commonly reported as total scores (see Tables 4-2 and 4-3). The total score for BADLs is 0 to 6; for IADLs it is 0 to 8. In some categories of IADLs, only the highest level of function receives a 1; in others, two or more levels have scores of 1 because each describes competence at some minimal level of function. When these screens are used over time, they serve as documentation of a person's functional improvement or deterioration. It is worth noting that the description of the functional capabilities is more important than the number total score, especially when monitoring function over time.[73]

A longitudinal analysis of older adults that characterized functional states between independent in ADLs and mobility, dependent on mobility but independent in ADLs, and dependent in ADLs translated to diminished survival and more of that survival spent in disabled states. For example, the life expectancy of an ADL-disabled 75-year-old is similar to that of an 85-year-old independent person; thus the impact of the disability approximates being 10 years older with much more of the remaining life spent disabled.[30a]

Advanced Activities of Daily Living (AADLs). Advanced activities of daily living represent the highest level of function and are comprised of vocational, social, or recreational activities that reflect personal choice and add meaning and richness to a person's life. The AADLs include employment, attending church, volunteering, going out to dinner or the theater, participating in physical recreational activities, and the like. Changes in these activities may reflect a precursor to IADL or ADL dysfunction.[72]

Karnofsky and Eastern Cooperative Oncology Group (ECOG) Performance Status (PS). Traditionally, the oncologist's assessment of functional status includes an evaluation of Karnofsky or Eastern Cooperative Oncology Group (ECOG) performance status (PS), Table 4-4. In older adults, particularly those with multiple chronic diseases, the prognostic ability of ECOG-PS may not relate to the specific impact of cancer [2,6,8] and may be insensitive to functional impairment. Although 70% to 80% of older adults with cancer present with ECOG PS of 0 to 1 (normal or symptomatic but ambulatory), greater than half require assistance with IADLs.[5,21] Furthermore, studies have shown that physicians', nurses', and patients' assessments of performance status using these measures may be discordant.[10]

Use of Self-Reported Functional Status Measures in Cancer Patients

Older patients with cancer, both during initial diagnosis and as cancer survivors, are more likely to require functional assistance than those without cancer.[13,15] Functional

TABLE 4-2 Activities of Daily Living (ADLs)

In each category, circle the item that most closely describes the person's highest level of functioning and record the score assigned to that level (either 1 or 0) in the blank at the beginning of the category.

A. Toilet	_____
1. Care for self at toilet completely; no incontinence	1
2. Needs to be reminded, or needs help in cleaning self, or has rare (weekly at most) accidents	0
3. Soiling or wetting while asleep more than once a week	0
4. Soiling or wetting while awake more than once a week	0
5. No control of bowels or bladder	0
B. Feeding	_____
1. Eats without assistance	1
2. Eats with minor assistance at meal times and/or with special preparation of food, or help in cleaning up after meals	0
3. Feeds self with moderate assistance and is untidy	0
4. Requires extensive assistance for all meals	0
5. Does not feed self at all and resists efforts of others to feed him or her	0
C. Dressing	_____
1. Dresses, undresses, and selects clothes from own wardrobe	1
2. Dresses and undresses self with minor assistance	0
3. Needs moderate assistance in dressing and selection of clothes	0
4. Needs major assistance in dressing but cooperates with efforts of others to help	0
5. Completely unable to dress self and resists efforts of others to help	0
D. Grooming (neatness, hair, nails, hands, face, clothing)	_____
1. Always neatly dressed and well-groomed without assistance	1
2. Grooms self adequately with occasional minor assistance, e.g., with shaving	0
3. Needs moderate and regular assistance or supervision with grooming	0
4. Needs total grooming care but can remain well-groomed after help from others	0
5. Actively negates all efforts of others to maintain grooming	0
E. Physical Ambulation	_____
1. Goes about grounds or city	1
2. Ambulates within residence on or about one block distant	0
3. Ambulates with assistance of (check one) a ( ) another person, b ( ) railing, c ( ) cane, d ( ) walker, e ( ) wheelchair 1.__Gets in and out without help. 2.__Needs help getting in and out	0
4. Sits unsupported in chair or wheelchair but cannot propel self without help	0
5. Bedridden more than half the time	0
F. Bathing	_____
1. Bathes self (tub, shower, sponge bath) without help	1
2. Bathes self with help getting in and out of tub	0
3. Washes face and hands only but cannot bathe rest of body	0
4. Does not wash self but is cooperative with those who bathe him or her	0
5. Does not try to wash self and resists efforts to keep him or her clean	0

Scoring Interpretation: *For ADLs, the total score ranges from 0 to 6.* In the above-mentioned categories, only the highest level of function receives a 1; These screens are useful for indicating specifically how a person is performing at the present time. When they are also used over time, they serve as documentation of a person's functional improvement or deterioration.

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status may be dependent on cancer stage, with observational studies showing this dependency is more commonly found in hospitalized patients with metastatic disease as compared with patients with nonmetastatic disease. IADL impairment predicted postoperative complications (P = .043) in a series of older adults undergoing cancer-related surgery[16] and functional status predicted risk of treatment-related toxicity in studies of ovarian cancer patients receiving standard cytotoxic chemotherapy.[28] In addition, the need for assistance in IADLs has been reported to correlate with psychological distress in older adults with cancer.[26]

The need for assistance with IADLs has been shown to have the same predictive capability for mortality among older adults with cancer.[11,12] Functional limitations in cancer survivors also persist.[11,13,14,19]

Because functional status changes over time and is affected by other conditions as well as cancer and by the patient's social needs, accurate assessments at multiple time points over the course of the cancer patient's life are valuable in monitoring response to treatment and can provide prognostic information that is useful in short- and long-term care planning. Acute or

TABLE 4-3 Instrumental Activities of Daily Living Scale (IADLs)

In each category, circle the item that most closely describes the person's highest level of functioning and record the score assigned to that level (either 1 or 0) in the blank at the beginning of the category.

A. Ability to Use Telephone	_____
1. Operates telephone on own initiative; looks up and dials numbers	1
2. Dials a few well-known numbers	1
3. Answers telephone but does not dial	1
4. Does not use telephone at all	0
B. Shopping	_____
1. Takes care of all shopping needs independently	1
2. Shops independently for small purchases	0
3. Needs to be accompanied on any shopping trip	0
4. Completely unable to shop	0
C. Food Preparation	_____
1. Plans, prepares, and serves adequate meals independently	1
2. Prepares adequate meals if supplied with ingredients	0
3. Heats and serves prepared meals or prepares meals but does not maintain adequate diet	0
4. Needs to have meals prepared and served	0
D. Housekeeping	_____
1. Maintains house alone or with occasional assistance (e.g., domestic help for heavy work)	1
2. Performs light daily tasks such as dishwashing, bed making	1
3. Performs light daily tasks but cannot maintain acceptable level of cleanliness	1
4. Needs help with all home maintenance tasks	1
5. Does not participate in any housekeeping tasks	0
E. Laundry	_____
1. Does personal laundry completely	1
2. Launders small items; rinses socks, stockings, etc.	1
3. All laundry must be done by others	0
F. Mode of Transportation	_____
1. Travels independently on public transportation or drives own car	1
2. Arranges own travel by taxi but does not otherwise use public transportation	1
3. Travels on public transportation when assisted or accompanied by another	1
4. Travel limited to taxi or automobile with assistance of another	0
5. Does not travel at all	0
G. Responsibility for Own Medications	_____
1. Is responsible for taking medication in correct dosages at correct time	1
2. Takes responsibility if medication is prepared in advance in separate dosages	0
3. Is not capable of dispensing own medication	0
H. Ability to Handle Finances	_____
1. Manages financial matters independently (budgets, writes checks, pays rent and bills, goes to bank); collects and keeps track of income	1
2. Manages day-to-day purchases but needs help with banking, major purchases, etc	1
3. Incapable of handling money	0

Scoring Interpretation: *For IADLs, the total score ranges from 0 to 8.* In some categories, only the highest level of function receives a 1; in others, two or more levels have scores of 1 because each describes competence at some minimal level of function. These screens are useful for indicating specifically how a person is performing at the present time. When they are also used over time, they serve as documentation of a person's functional improvement or deterioration.
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subacute changes in functional status are important to elicit as they may be a marker of underlying medical illness, including recurrence of cancer, cognitive losses, or other psychosocial issues.[3,6] Health care providers can promote their patients' autonomy by mobilizing appropriate medical, social, and environmental supports.

Performance-Based Instruments of Physical Function

Performance-based instruments can provide additional information beyond an older adult's self-reported perception of difficulty.[2,72]

Get-up-and-Go Test. Ambulation is an essential prerequisite for completing many of the activities of daily

TABLE 4-4 Karnofsky and Eastern Cooperative Group Performance Scales

Percentage (%)	Karnofsky Performance Scale	Score	ECOG Performance Scale
100	Normal, no complaints, no evidence of disease	0	Normal activity; asymptomatic
90	Able to carry on normal activity; minor signs or symptoms of disease	1	Symptomatic; fully ambulatory
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	Symptomatic; in bed <50% of time
60	Requires occasional assistance, but is able to care for most of his/her needs		
50	Requires considerable assistance and frequent medical care	3	Symptomatic; in bed 50% of time; not bedridden
40	Disabled, requires special care and assistance		
30	Severely disabled, hospitalization indicated; death not imminent		100% bedridden
20	Very sick, hospitalization indicated; death not imminent	4	
10	Moribund, fatal processes, progressing rapidly		
0	Dead	5	Dead

living and slowing of gait speed is an indicator of future morbidity. For example, gait speeds of 1 m/s or less, and especially those less than 0.6 m/s, predict hospitalization, cognitive impairment, and mortality.[70,71]

The "Get-up and Go Test" has been recommended.[3,5,6,7,8,9] This assessment tool does not require specialized equipment, but uses an armless chair and has the individual stand up from the chair, walk 3 meters and sit back down. (Table 4-5) It can be performed by the physician, nurse, or other trained health care provider. Severe abnormalities are considered present if the subject appears at risk for a fall at any time during the test. The time needed to complete this task is used to score the test; greater than 15 seconds is considered a positive screen. Also, ranges of times required to complete the task correlate with independence in some functional tasks. (Table 4-5)

TABLE 4-5 Timed Get-Up and Go Test*

Examiner asks the patient to:
- Stand up from a chair (without use of armrests, if possible)
- Stand still momentarily
- Walk 10 feet (3 meters)
- Turn around and walk back to chair
- Turn and be seated

Factors to note:
- Sitting balance
- Imbalance with immediate standing
- Pace (undue slowness) and stability of walking
- Excessive truncal sway and path deviation
- Ability to turn without staggering
- Observe and time the patient

Positive screen:
- Time of >15 seconds to complete test

		Timed Get Up and Go (secs)		
		10-19	20-29	30+
Tub or shower transfers	Self	59%	60%	23%
Climbs stairs	Self	77%	60%	4%
Goes outside alone	Yes	82%	50%	15%
Chair transfer	Self	100%	93%	62%

Adapted from Podsiadlo D, Richardson S. J Am Geriatrics Soc 1991;39:142-148 and from Susan Friedman, MD, MPH, University of Rochester.
*Proportion able to complete mobility tasks, according to "Timed Get Up and Go" times

COMORBIDITY

Survival rates from the 15 most prevalent invasive cancers have improved over the past 10 years,[79] with declining deaths due to colorectal cancer attributable to improvements in detection, risk-factor reduction, and treatment.[79] The Surveillance, Epidemiology, and End Results (SEER) study has shown that over one quarter of older patients with colon cancer have three or more chronic conditions, and over half of older patients have at least one chronic condition.[80] Furthermore, concurrent aging of the population is expected, many of whom survive into their oldest decades with a greater burden of chronic medical comorbidities. Having two or more chronic conditions is prevalent in two-thirds of older patients (age ≥65) in the general United States population; while the prevalence increases to three-fourths of the oldest patients (age ≥80).[81,82] These trends suggest that clinicians will face the increasing challenge of managing older cancer survivors with multiple comorbidities, each of which may be considered for recommended clinical guidelines, care processes, and medication regimens.[83-85]

There are no clinical guidelines that address specific combinations of malignancies and common noncancer comorbidities of aging. Rather, guidelines for the care of older cancer patients focus on determining overall life expectancy on the basis of functional status and the index malignancy.[86] The National Comprehensive Cancer Network (NCCN)[86] suggests that supportive, rather than curative, care be recommended for older patients with a serious comorbidity and at least one functional impairment.

In the absence of a guideline for this geriatric patient that addresses all of Mrs. Z's comorbidities in

CASE 4-2 CASE STUDY: Mrs. Z

Mrs. Z is a 76-year-old woman with rectal cancer (T1N1M0) who presents with a fall and a new compression fracture. She was diagnosed with rectal cancer 12 months ago, when she presented with rectal bleeding. She was treated initially with capecitabine and radiation because her oncologist felt she was frail and looked more like an 85-year-old. Her other past medical history is significant for essential hypertension and osteoarthritis of the knees. Last year, during the workup of her cancer, mild type 2 diabetes was discovered. She continues to have mild insulin resistance, which she has managed through diet modification resulting in some weight loss. Last week, she fell while reaching overhead in her kitchen, and landed on her right buttock. In the emergency room she was found to have a new compression fracture of S2 and a stable hairline fracture of the right ala. MRI of the spine and pelvis was negative for bony lesions. She was discharged with an abdominal brace and pain medications. She has had an excellent response to her cancer treatment and is being evaluated for definitive surgical treatment.

In light of Mrs. Z's cancer and comorbidities, what is her life expectancy?

combination (i.e., someone with rectal cancer, diabetes, hypertension, osteoarthritis, and a new fragility fracture), the challenge is to weigh the relative risks and benefits of recommended care for these conditions, the expected benefits of the care, and this patient's goals and preferences. The patient's overall life expectancy should be considered in light of the time required for the expected benefit to be gained ("time to benefit"). This approach has been suggested by diabetes guidelines from the American Diabetes Association,[87, 88] as well as by other authors.[83,89-91] Braithwaite et al.[92] have proposed a general (noncancer) framework to further consider the "payoff time," which is the time frame over which a recommended treatment's cumulative benefits exceeds its harms, and whether or not the patient's life expectancy according to his or her most serious condition exceeds this payoff time.

In this case of Mrs. Z, the decision whether to recommend treatment of her osteoporosis, hypertension, and diabetes depends on whether or not she will survive long enough to realize those benefits. A list of some of the instruments for assessing comorbidity is shown in Table 4-6.

Estimating Life Expectancy with Respect to Cancer

The SEER provides an online calculator (http://seer.cancer.gov/canques/survival.html) to estimate the life expectancy for many cancers. Specifically for this patient with colorectal cancer (variables entered were: race = white, site = colon and rectum, year of diagnosis 1999-2006, age at diagnosis = 75+, stage at diagnosis = regional), mortality risk over the next 5 years was estimated at 65%. This estimate did not take into account her chemotherapy and radiation, nor her comorbid conditions.

TABLE 4-6 Comorbidity Scales

Charlson Comorbidity Index (CCI)	A weighted index that takes into account the number and the seriousness of comorbid disease; a score over 5 is considered high and is usually associated with poor prognosis
Cumulative Illness Rating Scale-Geriatric (CIRS-G)	Classifies comorbidities by organ systems (13 or 14 according to the version) and grades each condition from 0 (no problem) to 4 (severely incapacitating or life-threatening condition)
The Adult Comorbidity Evaluation (ACE-27)	Measures the severity of comorbidity based on 26 disease systems; each condition is graded with a three-category severity system (mild, moderate, severe)

From References 75, 76, 41.

Estimating Life Expectancy by Age and Comorbid Conditions

Because this patient has a number of comorbidities, using age alone in this patient overestimates her life expectancy. Simple life tables based on age and gender available from the United States National Vitals Statistics[93] approximate this patient's life expectancy at approximately 10 years. A simple online life expectancy estimator on the basis of age alone is available at the American Association of Retired Persons website (http://www.ssa.gov/OACT/population/longevity.html).

One approach suggested by Walter et al. for decisions related to cancer screening in older patients is to first estimate whether a patient falls into the healthiest or sickest quartile of health in comparison to other similarly-aged patients.[91] Under the assumption that Mrs. Z is in the bottom quartile of health compared to other women in her age group, her life expectancy is only 4.6 years.[91]

One study of older colorectal cancer patients has considered the effect of common comorbid conditions on survival.[80] The comorbidities considered were chronic obstructive pulmonary disease, heart failure, diabetes, atrial fibrillation, cerebrovascular disease, myocardial infarction, peripheral vascular disease, hip fracture, ulcers, dementia, rheumatologic disease, chronic renal failure, paralysis, liver disease, and AIDS. Given that Mrs. Z had one of these conditions (diabetes) and that her rectal cancer was stage III, applying the results of this study would result in a predicted life expectancy of 5.8 (95% CI 5.5-6.2) years.

When a comorbid disease, rather than the cancer, is severe and life-threatening, it may dominate the life expectancy calculation. In the case of heart failure patients, an online calculator based on the Seattle Heart Failure Model can be found at: http://depts.washington.edu/shfm/. For liver disease, the Mayo Clinic has published the End Stage Liver Disease (MELD) Score availableat:www.mayoclinic.org/meld/mayomodel7.html.

For chronic kidney disease in older adults, annual risks can be found by age group and disease stage.[94] For type 2 diabetes, the Cleveland Clinic has developed a multivariable calculator for 6-year risk at: www.lerner.ccf.org/qhs/risk_calculator. Predicted life expectancy for dementia patients has also been studied.[95] A palliative care website has been developed to provide various disease-specific and general calculators at www.pallimed.org/2007/05/prognosis-links.html.

Other Considerations

Although comorbidity is most commonly used to estimate survival, older patients' functional status plays a central role in predicting mortality and making medical decisions.[96,97] One screening tool, the Vulnerable Elders-13 Survey (VES-13),[98] is based on functional status and age, rather than comorbidities. It provides risks for both death and functional decline over specific time intervals.[99,100] The VES-13 estimates life expectancy of less than 5 years for older (age ≥ 75) patients with scores of 8 or less.[100] Expectation of further functional decline within 5 years can be predicted for older patients with scores of 4 or less.[100] For patients who value preservation of functional status, this tool might be more useful than using life-expectancy alone.

Recommended Care of Comorbidities In Older Patients with Limited Life Expectancy

Two geriatric-specific clinical guidelines and quality indicators that address broad areas of medical care across multiple comorbidities were published in 2007. Quality indicators from the Assessing the Care of Vulnerable Elders Study (ACOVE-3)[101] define the level of care performance below which quality of care is considered to be poor. These indicators were tailored to older patients' limited life expectancy and individual care preferences. Better performance on the ACOVE indicators has been shown to be associated with improved survival.[102] The Screening Tool to Alert Doctors to the Right Treatment (START)[103] uses chronic conditions to remind clinicians to recommend 22 medications that are commonly omitted in the care of older patients.

COGNITIVE

Cognitive impairment increases with age and confers an increased risk for all cause mortality.[37] Frequently, especially in its early stage, it goes unrecognized.[38] Studies that included a screening cognitive exam as part of the GA for older patients with cancer have found that up to 25% to 50% had abnormalities that warranted further evaluation.[5,26a] Assessment of cognitive status is essential to provide a basis for comparison in future encounters. Studies have shown that cognitive impairment affects diagnosis and treatment options and can affect decision-making in the older cancer patient (both in accepting treatment and in prognosis).[40,41,42,43] Specifically, cognitive impairment is an important risk factor for the development of delirium.[39]

Mini-Mental Status Exam (MMSE) and Montreal Objective Cognitive Assessment (MOCA)

The MMSE is a brief quantitative measure of cognitive status in adults. It can be used to screen for cognitive impairment and to aid in estimating its severity. It is composed of tests of orientation, registration, calculation, recall, language, and visual-spatial skills. It is helpful in establishing a diagnosis of dementia (cognitive impairment severe enough to affect functional status). It can be used serially to follow the course of cognitive changes in an individual over time or to compare mental status in certain situations (for example, when hospitalized or after chemotherapy) with baseline. The Montreal Objective Cognitive Assessment (MOCA) is another screening tool that has been developed, and has been found to be more sensitive than the MMSE in detecting mild cognitive impairment in brain metastasis patients.[77,78] Abnormal scores in either screen may herald the need for more testing or for functional reevaluation to mobilize more care (medication management, caregiving).

Mini-Cog. This test involves a three-item recall and a clock drawing test. These scales are designed as screening tools; further evaluation is warranted when a screen is positive.[6,8]

Delirium and the Confusion Assessment Method (CAM)

Delirium is a geriatric syndrome that should be considered with any change in mental status and cognition. The hallmarks of delirium are acute onset, fluctuating course, impaired attention, and cognitive changes. It can be mistaken for dementia, depression, or another psychiatric problem. The onset of delirium in any cancer patient is important, as multiple causes that are more common in cancer, including brain metastasis or metabolic issues like hyponatremia or hypercalcemia, can predispose the already at-risk individual to develop delirium.

The Confusion Assessment Method (CAM) is an easy to assess, four-step diagnostic test (Table 4-7).[39]

Because dementia and cognitive impairment increase with age, if cognitive screening is abnormal, the physician should fully assess cognition or refer the patient for more detailed neuropsychologic assessment.[8]

AFFECT (AFFECTIVE ASSESSMENT)

An estimated 12% to 20% of community-dwelling persons aged 65 years and older experience significant depressive symptoms.[45] These patients present with weight loss, insomnia, memory loss, and functional decline. In older

TABLE 4-7 Confusion Assessment Method

Confusion Assessment Method (CAM)

Step 1: Administer a formal cognitive test that also tests attention, e.g.:

- A-test
- Digit Span
- Serial 7's, WORLD backwards, days of week backwards
- Mini-cog or MMSE

Step 2: Consider ancillary information re fluctuating cognitive status (nursing, family, your own observations).

1a. Acute change in mental status from baseline — ☐ Yes ☐ No

1b. Fluctuating course throughout day or interview (attention, organization, or consciousness) — ☐ Yes ☐ No

2. Poor attention (easily distracted) — ☐ Yes ☐ No

3. Disorganized Thinking (rambling, illogical) — ☐ Yes ☐ No

4. Altered level of consciousness (e.g., vigilance, lethargy, stupor, coma) — ☐ Yes ☐ No

☐ "Yes" to all three questions (1a,1b, & 2)

☐ "Yes" to either questions (3 or 4)

☐ Positive CAM
(BOTH dotted boxes are checked
Your patient may be delirious

Adapted from Inouye SK. The Confusion Assessment Method (CAM): Training Manual and Coding Guide 2003. Yale University School of Medicine. Accessed on 9/4/07 from http://elderlife.med.yale.edu/pdf/The%20Confusion%20Assessment%20Method.pdf

adults with depressive symptoms, 90% exhibit weight loss, compared to 60% of younger adults.[2,8] Cultural variation and overlap with major medical illness may influence how emotional states are expressed.[44] Affective assessment is particularly important in older adults with cancer; for example, symptoms of depression were associated with poorer progression-free survival, overall survival, and increased toxicity in older women with ovarian cancer treated with platinum-based regimens.[28] Some studies have shown that women diagnosed with depression and breast cancer receive less than definitive treatment and worsened survival.[2,8] Although cancer can elicit normal grief and bereavement, a suspicion of underlying depression should be considered by all members of the health care team. The GDS (Geriatric Depression Scale) and PHQ-9 are recommended as a depression screen in cancer patients.[46]

In one study, 20% of cancer patients were found to be depressed and in half of those, depression would have been missed without using the GDS. Given the consequences of depression and the options for treatment and support, screening for depressive symptoms should be part of the assessment in caring for older adults with cancer.[8,20,22]

Other elements of geriatric assessment account for issues that are rarely abnormal in younger adults (e.g., hearing, nutrition) but which may cause substantial morbidity in older persons and which are described later in this chapter. These geriatric issues are important in the management of older adults with cancer and are covered in other parts of this book. If these issues are present, they are often directly or indirectly worsened by the treatment and progression of cancer.[3] Affective disorders are discussed in greater detail in Chapter 15.

SOCIAL (SOCIAL ASSESSMENT)

Performance status, as measured by the ECOG-PS, represents a clinician's viewpoint and does not take into account the subjective psychosocial aspects of life that assume greater importance as one ages.[2,6] For cancer patients, the periodic assessment of social support allows the health care team to detect changes in care needs and prevent caregiver burnout. Informally, clinicians can probe systematically by themselves or with other members of the team (e.g., social workers or nursing staff).[48,49] For frail older cancer patients, the availability of assistance from family and friends may help inform the decision about cancer treatment strategy, including surgery or certain chemotherapies.[51]

CAREGIVER BURDEN

For many caregivers, there is value in the caregiving role, but it is a reality resulting in emotional and physical sacrifice, as well as profound economic difficulties. In one study, over half of caregivers reported not getting training they perceived as necessary in the management of treatment side effects; in helping manage pain, nausea, or fatigue; or in wound care. Twenty-five percent reported poor or fair health and low confidence in the quality of the care they provided. The inability of caregivers to meet the patients' needs for daily assistance

may compromise patient well-being and result in hospitalization.[50,51]

The Zarit Caregiver Burden Index, a 22 item instrument, assesses the reaction of family members caring for older adults with chronic diseases, including cancer.[48,49] Shorter versions, including the Zarit-12, have been studied in breast cancer patients for evaluation and screening.[49] Studies are needed to determine how caregiver burden affects the pattern of health care resource utilization and older cancer patient outcomes, including adherence to treatment, survival, and quality of life.[50] Caregiver burden is discussed in more detail in Chapter 26.

POLYPHARMACY

Community-dwelling older Americans take an average of 2.7 to 6 prescription medications and 1 to 2.4 over-the-counter medications. Studies have shown that polypharmacy is associated with an increased risk of adverse drug reactions and falls.[8] Studies have shown that the number of drug-related problems is associated to the total number of prescriptions. These drug-related problems include drug-drug interactions, drug-disease interactions (NSAIDs and renal insufficiency), drug-nutrient interactions, or malnutrition caused by side effects causing anorexia, nausea, vomiting, altered taste, or mucositis. A complete review of prescription and nonprescription medications, vitamins, and supplements is important in all cancer patients.[52,53]

NUTRITION

Nutritional Screen and Malnutrition

Malnutrition is among the most serious manifestations of cancer and its treatment. Cancer-induced malnutrition may be more severe in older adults that have associated impaired body energy regulation, altered body composition and cell function with changes in body water and fat, and diverse dietary behaviors coupled to changes in taste and smell, medications, and multiple chronic illnesses. Cancer patients with a weight loss greater than 5% have a shorter median survival rate than cancer patients with stable weight.[54] Cancer and nutrition are discussed in greater detail in Chapter 20.

HEARING AND VISION

Both vision and hearing loss restrict activity, predict functional disability, foster dependency, diminish the sense of well-being, and increase stress in older adults.

Visual impairment is related to increased morbidity and increases risk for falls, hip fractures, and depression.[8]

Given that some vision and hearing impairment is treatable, a screen should be undertaken. For vision, this can be accomplished by use of a Snellen eye chart, and for hearing, with a whisper test.

SYMPTOMS

Pain and Nonpain Symptoms

Pain is one of the most frequent and disturbing symptoms associated with cancer. Older adults are more likely to experience pain, less likely to complain of pain, and more likely to have pain go unrecognized.[56,57,60,61] Pain may be minimized for various reasons, including expectations with aging,[58] its impact on increased family and caregiver involvement, and its being interpreted as a metaphor of death.[55]

Patient self-report is the most accurate and reliable way of reporting pain. Pain scales are usually used in the clinical setting. Numeric 0-10 scales, face pain scales, verbal scales in English and other languages can all be utilized. Furthermore, attaching pain to a functional outcome (e.g., how pain affects ambulation, sleep, or mood) adds value to the assessment. The American Geriatrics Society has guidelines on the management of persistent pain in older adults with cancer.[56] In addition to pain, the palliation of nonpain symptoms, including nausea, anorexia, insomnia, pain, dyspnea, and constipation, is critical in the management of cancer patients. Pain and nonpain management are discussed in greater detail in Chapters 16, 17, 18, and 19.

ADVANCED CARE PLANNING

Advance directives is a general term that describes legal documents (e.g., living wills and durable power of attorney for health care). These documents allow a person to give instructions about future medical care if an individual is unable to participate in medical decisions because of serious illness or incapacity.[63] Clinicians treating cancer patients need to make it clear that discussions of advance directives do not equate to stopping treatment.[2] Preferences for how aggressive to be in treating cancer are separate issues. As such, discussions regarding advance directives need to begin early in the course of treatment rather than in the days when incapacity or death is imminent. Clinicians should begin discussions with older patients about preferences for specific treatments while they have the cognitive capacity to make these decisions.[63] Patients should be asked to identify a spokesperson to make medical decisions if the patient cannot speak for herself or himself. This information should be conveyed through a durable power of attorney for health care (DPAHC), which also allows patients to specify treatments that they do not want. Many states have allowed the use of Physician Orders for Life-Sustaining Treatment (POLST), a specific advance directive that documents a patient's end-of-life treatment preferences and serves as an order sheet. The standardized form is signed by both the physician and the patient and must be honored across all settings of care. (See Chapters 28 and 29.)

PATIENT PREFERENCES AND GOALS

The creation of patient goals is instrumental in decision making. As people age, their current and future health may enter prominently into determining and achieving their life goals. Among the very old, the patient's goals may be limited to achieving a functional or health state (e.g., being able to walk independently), controlling symptoms (e.g., control of pain or dyspnea), maintaining his or her living situation (e.g., remaining in one's home), or short-term survival (e.g., living long enough to reach a personal milestone such as an upcoming holiday). Sometimes, patient and physician goals differ. For example, a patient may want a cure when the physician believes that only symptom management is possible, especially with cancer. Conversely, the physician may believe that a better outcome is possible but the patient declines to pursue the recommended path (e.g., mastectomy).

A STRATEGIC APPROACH TO ASSESSMENT IN THE OLDER PATIENT WITH CANCER

Typically, geriatric assessment is conducted in two stages: screening and further assessment of positive screens. Because of time constraints in the busy primary care and oncology practices, screening can be delegated to office staff and patients and their families through standing orders and forms for staff, as well as by previsit questionnaires.

Studies have shown that these screening questions and assessments, e.g., ADL or GDS/PHQ-9, can be applied to older cancer patients.[2]

In ambulatory clinical settings, self- or proxy-reported functional status is collected by questionnaires or by interview with patients or family. A functional status assessment that indicates a patient's ability to perform specific functional tasks *and* provides information about who provides help, if needed, is more valuable than merely assessing ability. An example is the pre-visit questionnaire used in the UCLA outpatient geriatric practice (http://www.geronet.ucla.edu/images/stories/docs/professionals/Geri_Pre-visit_Questionnaire.pdf). Another is proposed by the National Comprehensive Cancer Network (http://www.nccn.org).[2,5]

These questionnaires gather information about:

- past medical and surgical history
- medications/allergies
- social history, including available social support resources
- preventive services
- ability to perform functional tasks and need for assistance
- home safety
- advance directives.

In addition, the pre-visit questionnaire can include specific questions assessing:

- vision
- hearing
- falls
- urinary incontinence
- depressive symptoms.

CASE 4-1 COMPREHENSIVE ASSESSMENT CASE. PART 1

Mrs. S was subsequently diagnosed with ductal carcinoma in situ and lobular adenocarcinoma and was referred to an oncologist. Mastectomy was recommended, as well as chemotherapy and radiation.

Geriatric Assessment Results

Functional Status

ECOG: 0-1, Karnovsky score: 80-90

5/6 BADL (Patient needs assistance in getting into tub to bathe.)

4/8 IADL (Patient uses phone, still able to use stove, takes medication by setting it in her bathroom.)

Timed Get-Up and Go: 13 seconds (<15 seconds normal); no history of fall

Comorbidity

Hypertension, no renal insufficiency

Cognition

2/3 recall with a normal clock, with ability to extrapolate hands at 10 minutes after 11.

Affective

Negative PHQ-9

Social

Good family support and good perception of care with 4-hour caregiver and son

Nutrition

BMI 23

Pain and Nonpain Syndromes

None

Hearing/Vision

Wears glasses for reading, denies hearing loss

Advanced Care Planning

Son established as DPOAHC. Functional goals of intact cognition and ambulation were important. Did not want to be a burden to her family and cherished her independence.

Clinical Course

The patient underwent mastectomy, with her family being informed about delirium risk, given the abnormal screening. The family anticipated the need for increased caregiving postoperatively as well. Postoperative day 2, she had a positive CAM (Confusion Assessment Method) and perseverated about needing to take care of her cats. She was found to have some urinary retention and UTI. She recovered and was sent to a skilled nursing facility, at which time she was able to ambulate with a walker >200 ft. She had outpatient physical therapy and graduated to a cane. She was treated with erlotinib (Tarceva) and did well.

CASE 4-1 COMPREHENSIVE ASSESSMENT CASE. PART 2

After 3 years of follow-up, she presents to the emergency department with a 1-month history of worsening mental status. Her son notices that her medications are not taken correctly and that she has been having episodes of insomnia, as well as a trip and near fall. He now visits her daily and has hired a caregiver to be with her during the nights. Lab workup reveals a sodium level of 125 and imaging reveals new metastatic lesions to the brain.

Functional Status
ADL survey filled out by son.
2/6 BADL (Patient with all ADLs except feeding and transferring)
0/8 IADL (Son has moved in to assist her)

Timed Get-up and Go Test
With walker, 25 seconds (<15 seconds normal) with nearby assistance of son. Two falls over past 1 month; no injuries, no syncope or seizure.

Comorbidity
Renal insufficiency, orthostatic hypotension

Cognitive Status
0/3 recall with an abnormal clock, with inability to place the numbers in the clock, perseverating on the number 12.

Affective
Unable to conduct GDS or PHQ-9 (deferred)

Social
Positive caregiver burden, as seen on 12-point Zarit Caregiver Burden Scale, also a financial burden.

Nutrition
Weight loss of 8 pounds

Pain Symptoms
Complains of dizziness and headache

Nonpain Symptoms
Constipation

Hearing/Vision
No change

Advanced Care Planning
Son decides, on the basis of prior discussions, that pursuing palliation of symptoms was more important than continuing treatment.

Plan
Patient transitioned to hospice at home with 24-hour care in light of prior goals of care.

Ongoing monitoring for caregiver burden assisted by hospice social worker, volunteers, and health aide.

Summary

Geriatric oncology is defined by the multidimensional and multidisciplinary approach of the elderly cancer patients. Autonomy, beneficence, nonmaleficence, and justice are the four fundamental principles on which are based the treatment objectives and practical management of these patients. Studies have also shown that decisions on curative treatment, palliative chemotherapy, and surgery can be affected by the patient's chronologic age.[10,19,27] Furthermore, studies have shown that cancer and its treatment precipitate geriatric syndromes such as falls, malnutrition, and delirium both as a direct effect or indirect effect mediated by other comorbidities.[67,68] By using a geriatric evaluation, characterizing functional status (physical, cognitive, psychosocial) and comorbidities, and taking into account the patient's wishes, a more meaningful and proactive approach can be used to manage the patient's cancer.

Functional status and a geriatric evaluation also help in *prioritizing individual patient problems and deciding on the intensity and effectiveness of treatment*. Functional assessment should be accurately recorded so that the **degree of change** and the **speed of change** can be monitored. When multiple medical, psychosocial, and cognitive comorbidities are present, the control of chronic diseases like hypertension and diabetes is frequently less important than managing the symptoms of cancer, particularly in the more functionally frail. When there are ongoing declines in physical, cognitive, or psychosocial functioning, continuation of palliative chemotherapy or other options in the management of their cancer should be reevaluated.

CASE 4-1 COMPREHENSIVE ASSESSMENT CASE. CASE SUMMARY

In this case, a geriatric assessment characterized changes in Mrs. S's functional status that were associated with loss of independence, increased caregiver burden, and greater financial expenditures. At several time points, *changes in functional status* were an important *presenting symptom of illness, in this case of her breast cancer.*

For ongoing cancer treatment, prognosis for functional status improvement or decline become important factors *in determining treatment options and further transitions of care* (e.g., hospital to home with increased care vs. Skilled Nursing Facility). For the former, if the prior functional status is not known, how can recovery be framed after a major catastrophic event such as a new diagnosis of breast cancer? The primary care physician, oncologist, or other members of the health care team (i.e., physical therapist, nurse) must be able to convey specific knowledge of the person's previous level of function to assist in setting reasonable targets for recovery. For example, because Mrs. S's functional status was preserved at the time of her presentation with breast cancer, mastectomy and chemotherapy were appropriate and acceptable options.

Throughout patients' cancer care, establishing a "safe" environment that supplements their functional status is critical. This can be achieved by additional caregivers or other supported care settings (assisted living, nursing home, rehabilitation center). In this case, the family was informed of the need to anticipate increased care.

For the busy medical practice, the use of a modified geriatric evaluation specifically focusing on physical function, self-reported (ADLs) with ECOG and Karnofsky PS as well as performance-based, is recommended; cognitive evaluations, and more in-depth psychosocial

evaluations should be pursued. Delegation of screening tests to other members of the healthcare team is important. As the cancer population ages, this approach will take on more importance as health care professionals move to describing a person's "functional age" rather than his or her "chronologic age."

Conducting careful, comprehensive, and periodic geriatric and functional assessments (initial, after treatments, and at other times), primary care and oncology providers can promote their patients' autonomy and mobilize appropriate medical, social, and environmental supports on their behalf.

See expertconsult.com for a complete list of references and web resources for this chapter

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CHAPTER

5

Choosing the Right Oncologist and the Value of a Second Opinion

Melissa Cohen

CASE 5-1 CASE STUDY

The patient is a 77-year-old woman with a history of myocardial infarction, diabetes, and hypertension who presents with newly diagnosed breast cancer. She has a hearing impairment and mild cognitive dysfunction, and has several well-educated children involved in health care. She has a 5.1 cm hormone receptor-positive tumor but no lymph node involvement (i.e., a stage III breast cancer). After surgery, she was referred to an oncologist.

CASE 5-1 CASE UPDATE

The patient's daughter, who is a PhD immunologist, drives her mother 60 miles for their first consultation to see a breast cancer specialist at the closest academic center. It takes 2 hours with traffic to make the trip.

A diagnosis of cancer is an overwhelming experience for patients and their family members; therefore choosing the "right" oncologist is often the most important decision they make. The oncologist has many roles, being involved in diagnosis, counseling, treatment, administration, support, and coordination of care. Often a patient is limited in his or her choice by location or insurance plan. Even within these limitations, there are still many decisions to make: tumor-specific versus general oncologist, oncologists associated with teaching hospitals versus those in the community, as well as a variety of personal characteristics. Ultimately, the patient and family will select an oncologist they feel comfortable with for a balance of reasons. Frequently, making such a decision requires meeting several doctors (first through third opinions) or whatever else is required until they find a doctor with the personality and clinical characteristics with which they are content.

The first step in choosing the right oncologist is finding one who has experience treating the type of cancer with which a patient has been diagnosed. The comparison of outcomes among general medical oncologists and tumor-specific oncologists remains a matter of considerable debate. In the oncology literature, there is little literature comparing outcomes between general versus tumor-specific oncologists. Who delivers the "best" care is more likely to be based on a number of factors such as patient volume, personal preferences, and differences between academic and community setting. Oncologists who specialize in a particular tumor are more likely to be affiliated with large hospitals or academic teaching hospitals that may not be located in proximity to the patient's home and which can make receiving treatment involve considerable logistics and travel time. In a recent survey, specialist oncologists who practiced in a university setting were more likely to be aware of clinical trials and to enroll patients into them than oncologists who practiced alone or in private groups in the community by a ratio of 56:1.[1] In addition, academic oncologists were simultaneously more likely than community oncologists to report providing off-protocol therapy.[2] On the other hand, general medical oncologists can provide excellent care and achieve excellent outcomes. An advantage to community oncologists may be their increased availability to patients. Studies that show a benefit of one over the other usually use intermediate outcomes and there are many confounding factors, including referral biases, shared care, and illness burden.

ACADEMIC VERSUS COMMUNITY SETTING

Teaching hospitals are responsible for training medical residents and fellows in the United States. There are many studies that examine outcomes in teaching hospitals versus those in a community setting. Superior outcomes have been reported in some studies, but others claim the

opposite. A systematic review of the literature demonstrated a great deal of variability, but overall there was no major difference in the effectiveness of treatment provided by teaching hospitals or nonteaching hospitals.[3] The most convincing arguments in favor of outcomes in teaching hospitals pertain to cancer patients undergoing complex surgical procedures who benefit from board-certified specialty surgeons, multidisciplinary teams, availability and use of sophisticated clinical amenities, and highly trained personnel.[4–6] A study of over 24,000 cases of breast cancer, comparing outcomes, suggests that patients with infiltrating ductal carcinoma treated at teaching hospitals had significantly better survival than those treated at high-volume centers or community hospitals, particularly in the setting of advanced disease.[7] A study in Great Britain of nearly 3000 women also suggests this trend, demonstrating that breast cancer patients treated in specialist units had 57% lower local recurrence rate and 20% lower risk of death.[8] However, the literature also highlights some less optimal aspects of receiving care in teaching hospitals. Often teaching or academic centers are not in proximity to the cancer patient's home, and travel may be a burden; this may be more significant as the condition deteriorates or if the treatment plan is quite intense. In addition, if patients do not live near the treating hospital, it is likely that in an emergency they will be hospitalized close to home, where their records may not be available and they will not be under the care of their primary oncologist or team. In addition, physicians in academic centers have additional responsibilities other than patient care that may make them less "available." There are many reasons why obtaining care in the community setting may be preferable. For instance, a community hospital is more likely to be close to a patient's home and convenient for emergencies. The doctor treating the patient's cancer is most likely going to be the one treating him or her on inpatient admissions and returning phone calls and answering questions. The doctors, nurses, and office staff are generally more available and have more flexible hours than those provided in a teaching hospital setting.

The optimal type of personality for an oncologist depends on who the patient is and what qualities are important to him or her.[10] For the most part, it is agreed upon that "effective" care requires a match between health care provider skills and the needs and expectations of the patient.[9] Table 5-1 lists many of the characteristics that oncologists, ideally, should possess.

One of the most important characteristics of an oncologist is that he or she be an effective communicator (understandable, direct, and simple). When 100 patients at an Israeli cancer center were asked about doctor-patient communication, nearly 90% of patients felt strongly that eye contact was important.[10] Trust is a central element in the patient-physician relationship. Patients base this trust on physician behaviors such as competence, compassion, dependability, confidentiality, and communication.[11-13]

TABLE 5-1 Potentially Important Characteristics of an Oncologist

Effective communicator
Trust
Compassionate
Patient
Experienced
Gender (if patient has a preference)
Same cultural/language background

- Compassionate ("touchy-feely") or more reserved ("hands off")
- Experienced (young and with recent training, older and seasoned with more experience)
- Gender: Some patients feel that to have a physician of a specific gender will improve their ability to communicate.
- Culture: Just as with gender, a patient and his/her family concentrate their efforts on finding a physician with a similar cultural background, so that the diagnosis, prognosis, and treatment plan can be communicated in a culturally acceptable fashion.

CASE 5-1 CASE UPDATE

Not only did it take 2 hours to drive to the initial consultation, but the physician was running behind, spoke abruptly, and strongly argued for an aggressive treatment plan with combined hormone and chemotherapy. The daughter was hoping for a more informative encounter that would allow more discussion and more involvement with decision making.

VALUE OF A SECOND OPINION

Second opinions in oncology are common.[14-16] In 1992, 56% of 1500 cancer survivors in the United States reported to have obtained at least one second opinion.[17] It has been shown that a process of second opinion is of great value for the staging of tumors, which is the foundation for individual treatment decisions.[18,19] Second opinions are sought for many reasons. (Table 5-2.)

Denial/ Need for More Information

Denial occurs relatively frequently in patients with cancer, because of the life-threatening character of the disease. As stated by Bayliss, "Often the patient or patient's relatives are concerned at the diagnosis and

TABLE 5-2 Reasons for a Second Opinion in Oncology

Denial/Need for more information
Treatment is too aggressive or not aggressive enough
Interpersonal difficulties
Treatment failure

potential prognosis that the first opinion is unacceptable or not fully comprehended until confirmed by another expert."[20] Most patients report the reason for seeking a second opinion is their need for more information. This does not necessarily mean that the first specialist did not provide the patient with enough information. A plethora of research has shown that recall of clinical information and treatment in the medical encounter is suboptimal.[21-23] It has been hypothesized that the ability to recall this information predicts patient satisfaction.[24] Many studies suggest there are many factors that influence this ability such as age, gender, educational status, and prognosis, among others.[24]

Treatment

Cancer treatment is usually toxic and/or potentially disfiguring. The treatment offered by the first oncologist may be deemed too radical, or often, in the case of the older cancer patient, not radical enough, and some alternative treatment plans are hoped for in the second consultation.[20] Another reason for seeking a second opinion is when interpersonal difficulties occur. Dissatisfaction with the first specialist was observed in one third of cancer patients questioned regarding their motives for seeking a second surgical opinion, in a study in the Netherlands.[25] Treatment failure and clinical trial availability is a very common reason for a second opinion.

There are several important things to review in a second opinion. Patients usually have high expectations for this consultation. Asking at the outset of the visit for the patient's specific agenda and questions they want answered can improve patient and physician satisfaction.[26-28] The basis of the second opinion is a thorough reevaluation of the patient's case, including a review of diagnostic material such as diagnostic history, sequence of events, surgical record, radiographic images, pathology report, and, at times, the tissue itself.

In oncology, perhaps more than in other fields of medicine, diagnostic and treatment guidelines and protocols are well defined for most tumor types.[29] The variability of interpretation and weighing of older patients' clinical and personal characteristics, however, leads to considerable variability in the advice they receive, and therefore a second opinion may be more important.

TABLE 5-3 Goals/Benefits of Multidisciplinary Team Cancer Meetings

Improved consistency, continuity, coordination, and cost-effective care
Improved communications between health professionals
Improved clinical outcomes
Increased recruitment into clinical trials
Educational opportunities for health professionals
Support in a collegial environment
Increased job satisfaction and psychological well-being of team members

From Fleissig A, Jenkins V, Catt S, Fallowfield L. Multidisciplinary teams in cancer care: are they effective in the UK? Lancet Oncol. 2006 Nov;7(11): 935-43.

CASE 5-1 CASE UPDATE

The family decides to get a second opinion. The second oncologist they consult offers a different opinion. Given her comorbid conditions, the oncologist believes that the addition of chemotherapy to hormone therapy would add less than 1% in overall 10-year survival. The patient had a strong preference against chemotherapy and feels reassured after the conversation that hormone therapy alone is the best choice for her, personally.

THE ROLE OF CASE CONFERENCES AND TUMOR BOARDS

Caring for most cancer patients is a complex process utilizing multiple modalities of treatment that can be provided by a number of health care professionals; it therefore necessitates good coordination and communication throughout the entire process. Multidisciplinary team meetings are regularly scheduled meetings designed to review individual cancer patients prospectively, and form appropriate management plans using evidence-based medicine from multimodality input.[30] Global acceptance and implementation of multidisciplinary teams (MDTs) has been seen; they are standard of care in the United Kingdom, United States, continental Europe, and Australia. Participants at such meetings usually consist of medical oncologists, radiation oncologists, surgical oncologists, radiologists, nurses, and social workers. The main purpose of these meetings is to ensure all appropriate tests and treatment options are considered for each patient (Table 5.3)

Theoretically, MDT cancer meetings should increase adherence to guidelines, aid in decision making, and improve outcomes by ensuring a high-quality diagnosis, evidence-based decision making, optimal treatment planning, and timely delivery of care. It is felt that by bringing together multiple practitioners with diverse experience, knowledge, and skills, holistic evaluation of patients can occur and the most appropriate treatments will be considered. According to the literature, specific tumor types

such as breast, rectal, head and neck cancers, and inoperable non-small cell lung cancer are the most common specialties within oncology wherein multidisciplinary team meetings occur.[31] This approach becomes exceptionally important when dealing with complex cases such as making treatment decisions for patients where there is little evidence to guide treatment. Elderly patients are a heterogeneous group, with multiple comorbidities and widely varying functional status, all of which make predicting their response to treatment difficult. This is where the strength of the MDT cancer meeting can be utilized, as decision making needs to combine the existing evidence, the available treatment options, and consideration of geriatric principles. Less obvious benefits to MDT cancer meetings include the opportunity to improve the coordination of services, as well as the learning opportunities they provide for participants. MDTs provide the opportunity for team members to learn from each other. However beneficial MDT cancer meetings seem, there are many obstacles that make their coordination difficult. MDTs require substantial administrative, human, and technical resources in order to run successfully. They require consistent participation by physicians, which can take away from patient care. For instance, radiologists may work in many tumor types, making attendance at each specialty MDT difficult. Further critiques argue that participation in MDT cancer meetings may increase the time needed to process patients, and that they increase costs.

See expertconsult.com for a complete list of references and web resources for this chapter

CHAPTER

6

Overview of Cancer Surgery in the Elderly

M. Margaret Kemeny and David M. Heimann

In the next 50 years, the number of Americans older than 65 is expected to double[1] from 35 million to 70 million. Because the incidence of cancer increases exponentially with advancing age, there will be a significant rise in the number of elderly patients diagnosed with cancer. It is projected that by the year 2050, the number of cancers in the elderly will reach 2.6 million.[1] Currently, people older than 65 account for 60% of newly diagnosed malignancies and 70% of all cancer deaths.[2]

Knowing that the life expectancy of a girl born in 2005 is 80.4 years, that for a boy it is 75.2 years,[3] and that life expectancies of a 75-year-old woman and man are 12.8 and 10.8 years, respectively,[3] should lead the cancer surgeon to be appropriately aggressive in the endeavor for 5-year survival in the elderly cancer patient.

Because surgery is the mainstay of treatment for solid tumors, the greatest dilemma for the oncologic surgeon is whether the use of radical surgery, with its accompanying morbidities, is justified in the very elderly. With advances in modern medicine, it is understood that any patient up to age 70 is eligible for the same degree of surgical intervention as a younger patient would be, unless the patient has very severe comorbidities. This chapter is dedicated to the discussion of treatment strategies for the patient age 70 or older. Unfortunately, scientific data from randomized studies is often not readily available for older populations because they are more likely to be excluded from clinical trials. Studies that are available are retrospective and often display considerable bias in the patients chosen for certain treatments, especially surgical procedures. Prejudices can arise from what is perceived as limited life expectancy, the presence of comorbid diseases, assumed decreased functional or mental status, limitations in economic resources, and assumed inability to tolerate treatment. The influences of these biases have affected the enrollment of patients into protocols and the treatment, and probably the survival, of elderly patients with cancer.

A study evaluating survival up to 10 years after the diagnosis of cancer in patients older than 65 years with various cancers revealed that not receiving definitive therapy for the patient's cancer was associated with a threefold greater death rate.[4] Inadequate treatment remained a significant factor, even after controlling for stage at diagnosis, socioeconomic factors, comorbidity, and physical functioning. Thus the evidence suggests that the withholding of appropriate treatment because of age will result in inferior survival.

The idea that the elderly, as a group, cannot tolerate extensive surgery has not been supported by the data. Over the past 30 years numerous publications have shown that surgical procedures can be performed safely in the elderly.[5-15] The balance between operative risk and expected cure or palliation is important when treating any patient with cancer. The elderly patient's age alone should not be an automatic contraindication to extensive surgery. The impact of treatment on the quality of life is extremely important and should always be kept in mind.

Data supports the rule that surgical morbidity and mortality rise with advanced disease states and emergency surgery. Because there is often a delay in cancer diagnosis in elderly patients, this can lead to more advanced cancers and a greater number of emergency presentations with the associated worse outcomes. Thus early diagnosis and treatment in the elderly should be encouraged. Not performing surgery in the elective setting may result in the same patient's need for life-saving emergency surgery several months later.

This chapter reviews the role of surgery in the management of elderly patients with the following common solid organ cancers: (1) breast cancer; (2) colon cancer; (3) liver metastases; (4) gastric cancer; (5) pancreatic cancer; (6) melanoma.

BREAST CANCER

CASE 6-1

A 79-year-old woman presented to her physician with a large palpable breast mass. She had a past medical history of congestive heart failure, poorly-controlled hypertension, poorly-controlled diabetes, morbid obesity, and bipolar disorder. She was a widow and lived by herself. Because of her significant comorbidities and the perceived risk of general anesthesia, she underwent a lumpectomy

and sentinel lymph node biopsy under local anesthesia. Her pathology revealed a T3 lesion, 6 cm in size with clear margins and negative sentinel lymph node. The tumor was positive for both estrogen receptor (ER) and progesterone receptor (PR) and negative for HER-2/neu. After recovering from her surgery, the patient was able to receive standard postlumpectomy radiation by having transportation arranged for her by social services. She remains disease-free at this time on daily tamoxifen.

This case illustrates several points about breast cancer in the very elderly. Patients are often not screened after the age of 75 and can present with very large and sometime locally advanced cancers, like this woman. There are many elderly who are actually too frail to receive general anesthesia, yet for breast cancer these procedures can be done safely under local anesthesia. With the proper transportation support, the elderly, even those who live alone, can receive appropriate radiation. Tumors are overwhelmingly hormone-positive and hormonal therapy can be given safely to most of these patients.

The incidence of breast cancer rises with age. Nearly one third of breast cancers occur in women older than 70 years[16] and half the deaths are in women older than 65 years of age.[17]

Should the surgical treatment of breast cancer in the elderly be different than for younger women? Although the morbidity and mortality for breast surgery in the elderly is very low,[18] the fear of treatment morbidity and mortality sometimes prompts a minimalist approach in the elderly, whereas, paradoxically, at other times, mastectomy is offered with little if any discussion about the possible desire for breast conservation. In addition, reconstruction is rarely offered to elderly patients.

Despite the fact that the National Institutes of Health consensus conference found breast-conserving therapy (BCT) to be the preferable method of treating early-stage disease[19] it is still underutilized for all ages and particularly in the elderly. The elderly have also been found to have a lower rate of BCT in the treatment of ductal carcinoma in situ (DCIS).[20]

Hurria et al.[21] performed a retrospective study examining the factors influencing treatment patterns for women aged 75 and older with breast cancer. The goal of the study was to determine local and systemic treatment patterns for these patients. Even in this advanced age cohort, there was a difference in treatment seen between those patients aged 75 to 79 and those who were older. However, there was no difference in receiving hormonal therapy, which is generally viewed as a "less-toxic" treatment. Chemotherapy, radiation therapy, and axillary lymph node dissection, which are generally viewed as more "toxic" therapies were less likely to be used in the armamentarium for patients older than 80.

Patients with increased comorbidities were significantly less likely to receive radiation therapy, despite the findings of the Cancer and Leukemia Group B (CALGB) study that radiation is beneficial in preventing locoregional disease in women, age 70 and older, who have undergone partial mastectomy. Other studies have also demonstrated that when breast conservation is performed, it is often done without axillary dissection or the use of postoperative radiation, as would be the standard for younger women.[18,22] In one retrospective series, the survival of elderly women was found to be lower for those treated with less-than-standard protocols.[22]

The relatively recent implementation of sentinel lymph node (SLN) biopsy instead of a full axillary dissection has resulted in decreased operative morbidity. Overall, SLN biopsy has been shown to be a safe procedure, with accuracies of 97% in randomized studies of all age groups.[23,24] Looking specifically at the older patient, one series of 241 patients 70 years or older identified the SLN in every one, with no major complications.[25] Another study of 730 breast cancer patients compared the rate of identification of SLN in the younger patients and the 261 (36%) patients who were at least 70 years of age. The overall sentinel node identification rate was statistically equivalent in the group younger than 70 (98.8%) versus the older group (97.1%).[26] These kinds of data support the dictum that SLN biopsy should be offered to all women diagnosed with invasive breast cancer who do not have palpable axillary disease, regardless of age. The combination of lumpectomy with SLN biopsy, which is now considered the standard of care, can be done as an outpatient procedure with limited if any morbidity and there should be no reason to deny this definitive treatment to the elderly.

Radiation therapy to the breast after BCT is considered standard therapy, yet radiation is often omitted in many elderly patients. In one series, only 41% of women older than 75 years had radiation, in contrast to 90% of women younger than 65 years and 86% of women between the ages of 65 and 74 years.[27] Concerns have been expressed about whether the elderly will tolerate radiation, whether they will have difficulty completing therapy because of physical restraints in getting to radiation facilities, and whether long-term outcomes are the same as in younger patients. However, many studies have provided evidence to refute these concerns.[28,29] Furthermore, studies show that local recurrence rates for breast cancer have been reported as high as 35% in the elderly when radiation is not given,[30] contradicting the theory that those patients will not benefit from radiation therapy. A randomized study from the CALGB compared 647 women older than 70 years with stage I estrogen-positive breast cancer that were randomized to receive lumpectomy plus tamoxifen or lumpectomy followed by tamoxifen and radiation therapy. The group given radiation had a significantly lower risk of locoregional recurrence (1% versus 7%; $p<0.001$) at a median follow-up of 7.9 years.[31] Surgeons who believe that radiation therapy is not possible in the elderly will not offer them the choice of lumpectomy, moving straight to mastectomy. Again,

evidence has shown that this is not the correct way to treat these elderly patients, who should have the same choice for breast-conserving therapy as younger patients.

In the elderly patient who undergoes a mastectomy, very rarely is breast reconstruction performed or even offered. In one study, the single greatest predictor for a surgeon to recommend breast reconstruction was patient age younger than 50.[32] Yet experience with breast reconstruction in patients older than 60 demonstrates that it is safe, provides good long-standing results, and has acceptable complication rates when compared to younger patients. Age alone should not be a determining factor in selecting women for breast reconstruction, but this should be a discussion between the patient and physician.

In summary, surgical treatment of breast cancer in the elderly should follow the standard of care used for all women. Breast-conserving surgery and SLN biopsy with radiation has been shown to be safe and effective in treating breast cancer, with low morbidity and mortality in all age groups.

COLON CANCER

CASE 6-2

A 77-year old- man presented to the emergency department with acute onset of abdominal pain. A CT scan revealed a partial small bowel obstruction with a cecal mass. The patient had never had a colonoscopy and was not followed by a primary care physician. On follow-up abdominal films the next day, the oral contrast from the CT scan was noted in the left colon. Thus after a bowel prep, a colonoscopy revealed a near-obstructing large cecal adenocarcinoma. He was taken to the OR on the next day for a right hemicolectomy. Pathology showed a T3N2 (12/25LN+) stage IIIC colon cancer. Postoperatively, an abdominal fluid collection in the right lower quadrant developed, which required drainage by interventional radiology. After drainage, he did well. He received adjuvant chemotherapy, is doing well more than 1 year postoperatively, and is free of disease on radiographic studies.

This case illustrates three points about colon cancer in the elderly: (1) right-sided lesions are more common; (2) lesions are detected at more advanced stages; (3) emergency operations are often necessary at presentation, with increased morbidity.

The incidence of colorectal cancer increases with age, as 90% of patients are diagnosed after age 55.[33] Several studies report a difference in tumor location between the more elderly and the younger patients, with more right-sided lesions and fewer rectal lesions in the elderly.[34-38] Because patients with right-sided lesions are more likely to present later, due to fewer signs and symptoms compared to left-sided or rectal cancers, the older patients are more likely to fall into the late presentation category.

Several studies show that elderly patients are more likely to undergo emergency surgical procedures compared to a younger population. In one study from the British Colorectal Cancer Collaborative Group (CCCG), the incidence of undergoing an emergency operation more than doubled for patients 85 or older (11% for younger than 65 years vs. 29% for 85 years or older, $p<0.0001$).[39] The same study also revealed differences in both stage at presentation and the rate of curative surgery within the elderly population, with the "older of the old" presenting with more advanced disease and being less likely to undergo curative surgery.

Because of recent data from a number of studies demonstrating improved survival when at least 12 lymph nodes are examined in resection specimens for colon cancer, this number is now considered the gold standard for node removal. The data revealed a benefit in resecting at least 12 lymph nodes irrespective of the patient's age. The adequacy of number of lymph nodes removed in elderly patients was recently examined,[38] revealing that as age increased the number of nodes removed decreased. This might reflect a less extensive operation, possibly accounting for decreased survival in the elderly.

The mainstay of curative therapy for all nonmetastatic colon cancer is adequate surgical resection. It may even be required in many cases in the presence of disseminated disease to avoid or treat the complications of obstruction and bleeding. A number of retrospective series examined the influence of advanced age on the morbidity of colon cancer surgery. The risk of perioperative complications is generally reported to be higher in the elderly than in younger patients. In a meta-analysis, the cardiovascular complications were statistically significantly increased ($p<0.001$) in one series from 0.8% in patients older than 65 to 4% in patients older than 75.[39] Pneumonia and respiratory failure was seen in 5% of patients younger than 65 years, compared to 15% in those at least age 85 ($p<0.001$). However, the anastomotic leak rates in the meta-analysis were not statistically different in young versus elderly patients. A large study from the United Kingdom of more than 2500 patients 80 years old or older showed an increased mortality, but colectomy-specific complications, such as anastomotic leaks, were no different in the elderly versus younger patients. The 30-day overall mortality rate was 15.6%, but increased to 27.5% for those at least age 95. Multivariate analysis for this group of very elderly patients revealed the following independent risk factors for 30-day mortality: age; operative urgency; ASA grade; resection versus no resection; metastatic disease. Other studies support these conclusions that comorbid factors in the very elderly may increase multisystem-related complications, which are further exaggerated in the emergent situation, but there is no increase of anastomotic leaks due to advanced age.

Emergency operations are clearly associated with an increased mortality rate. Elderly patients presenting with malignant bowel obstructions are a high-risk cohort with increased postoperative complications and mortality. In the previously mentioned British study, approximately

25% of patients that underwent either a palliative stoma or a Hartmann procedure died within 30 days postoperatively.[40] These procedures are often done as an emergency in an end-stage patient, two factors known to contribute to an increased risk of morbidity and mortality.[7,41] Early intervention with semi-elective surgery would often avoid situations such as bleeding, perforation, and obstruction that require emergency surgical intervention.

Overall cancer-related survival was comparable when comparing patients aged 75 and older to those under 75, despite an increase in operative mortality for the older population.[42] One study showed that although the physical status and operative mortality were worse in the elderly undergoing surgery for colorectal cancer, for those elderly who were fit for surgery, who underwent curative resection, and who survived more than 30 days, the 5-year survival was comparable to younger patients by multivariate analysis.[36]

Age alone should never be a contraindication for colectomy, and whenever possible, the full curative treatment including adjuvant chemotherapy should be utilized as indicated by pathologic and operative findings.

LIVER METASTASES FROM COLON CANCER

CASE 6-3

An 85-year-old man who had a colon resection for a stage III colon cancer 7 years prior was noted on routine blood work to have an elevated CEA level at 7.1 ng/mL (normal <2.5). A CT scan showed a solitary lesion in the left lobe of the liver. These findings were confirmed by PET scan which revealed only the lesion in the left lobe of the liver. Treatment options were discussed with the patient and he opted to undergo a liver resection, a left lateral lobectomy. The patient required no blood transfusions. He was discharged home 5 days after surgery and has done well since.

Metastatic disease from colorectal cancer is predominantly (80%) found in the liver and often confined to the liver on presentation. For patients with liver-only disease that is deemed operable, liver resection can lead to a 21% to 48% 5-year survival.[43-48] The safety of performing liver resections has greatly improved in recent years owing to improvements in techniques of resection and intraoperative and postoperative care. Liver resections are now being routinely performed with mortality rates of less than 5%.[43,45,47-49]

Liver resections can also be performed safely in elderly patients. A number of series have looked at morbidity and mortality rates for older individuals. A study from Memorial Sloan-Kettering Cancer Center reviewing liver resections for colorectal metastases in 128 patients older than 70[13] found the perioperative mortality rate and the morbidity rate were the same as for patients younger than 70. In multivariate analysis, the three factors that were found to be important in predicting complications (male sex, resection of at least one lobe of the liver, and an operating time of greater than 4 hours) did not include age. Median hospital stay for patients aged 70 years and older was only 1 day longer than for patients younger than 70 years.

TABLE 6-1 Predictors of Survival from Liver Resection

Variable	Zero Points	One Point
Age	≤60	>60
Tumor size	<5 cm	≥5 cm
Nodal involvement of primary tumor	No	Yes
Disease-free interval	≥2 years	<2 years
Number of liver lesions	<4	≥4
Resection margins	Negative	Positive
CEA level	<5	≥30
	Total Points	**Survival Rate**
2-year survival	0-2	79%
	3-4	60%
	5-7	43%

From Nordlinger B, Guiguet M, Vaillant JC et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. Cancer 77(7): 1254, 1996.

There are several prognostic scoring systems to estimate the prognosis after liver resection, and none of them has age as one of the significant prognostic variables. When deciding on the usefulness of a liver resection in an elderly patient one of these systems should be employed. The clinical risk score devised by Memorial Sloan-Kettering[50] used 5 factors to compute survival. They were: (1) nodal status of primary disease; (2) disease-free interval of less than 12 months between primary and metastases; (3) more than one hepatic tumor; (4) CEA level greater than 200 ng/mL; and (5) size of metastases greater than 5 cm. If all of the factors are good, then the projected 5-year survival is 60%. If a patient has all the negative factors, the survival drops to 14%. Another scoring system from France uses seven variables (Table 6-1) and computes 2-year survival. These systems should be used for all patients, including the elderly, because elderly patients can benefit from liver resection equally to younger patients.

GASTRIC CANCER

CASE 6-4

A 76-year-old man with a history of alcohol and tobacco abuse reported dark tarry stools and was noted by his primary care physician to be anemic. He underwent upper and lower enodoscopy and was noted to have a large ulcer along the greater curvature of the stomach. A biopsy was performed, which revealed adenocarcinoma. The patient reported neither weight loss nor early satiety. He had a

history of diabetes mellitus, hypertension, and obesity. A metastatic workup was negative, and the patient underwent a total gastrectomy with a D2 lymphadenectomy with Roux-en-Y esophagojejunostomy reconstruction. He recovered well and was discharged home 1 week postoperatively. Within a month of his surgery, he started chemoradiotherapy for his Stage II (T2bN1) gastric cancer.

Gastric cancer rates have been declining over the past 75 years in the United States[51], but the prognosis has not improved, with 5-year survival being 20% to 40%.[52] Despite the fact that the incidence of the disease has fallen in the past 75 years, the number of patients diagnosed at 75 years or older is actually increasing.[52] Gastric cancer in the United States is generally seen in the elderly, with nearly 50% of cases in males and 60% of those in females being in patients older than 70 years.[53] Surgery is the only curative modality available for gastric cancer. Palliative surgery is often needed for bleeding and obstruction. An important element in deciding about gastrectomy in the elderly is the impact on the quality of life. A study that addressed this question in a small series of patients older than 70 years undergoing total gastrectomy showed that 70% of patients returned to "normal life" after 1 year.[54]

In Asia, where gastric cancer is much more common, many investigators have examined the characteristics of gastric cancer in the elderly. Symptoms at presentation and location of disease in the stomach have been found to be similar in younger and older patients.[55,56] Also, studies have shown no difference with age in the incidence of lymph node metastases and stage at diagnosis, with most patients having T3 and T4 disease at the time of exploration.[55,56]

Curative surgery for gastric cancer requires either a subtotal or a total gastrectomy depending on the location and size of the tumor. The exact extent of lymph node dissection necessary remains a controversial subject, yet most surgical oncologists perform at least a D2 resection. There have been a number of reports on the morbidity and mortality rates of gastric resections in the elderly (Table 6-2). Although preoperative risk factors, particularly cardiac and pulmonary, are increased in the elderly with gastric cancer, most complications and deaths are caused by infections, anastomotic leaks, and pulmonary problems just as in younger patients.[6,57-59] A large study from Italy reviewing gastric resections for gastric cancer over a 15-year period reported that the overall postoperative surgical complication rate was 20% in the elderly group (age 75 and older) versus 17% in the younger. The postoperative mortality rate for both groups was 3%. Multivariate analysis revealed that age was not a risk factor for either postoperative morbidity or mortality.[52]

The 5-year survival for curatively-resected patients with gastric cancer is similar for younger and older patients (Table 6-3). In a recent Japanese study, the overall survival was significantly different between the two groups ($p<0.0001$), but the cause-specific survival was not statistically different ($p=0.3447$).[60] An American study found that 5-year survival was 17% for elderly patients (older than 70 years) compared to 21% for younger patients ($p=0.45$).

In summary, there is no data to support anything less than surgical resection for gastric cancer in the elderly, and it should be offered to patients irrespective of age as the only chance for cure.

PANCREATIC CANCER

CASE 6-5

An 81-year-old man with painless jaundice presented to the emergency department. Laboratory workup revealed a bilirubin level of 18.9 mg/dL and CA 19-9 of 117 U/mL (normal <37). A CT scan showed biliary dilation but no pancreatic mass. Endoscopic retrograde cholangiopancreatography (ERCP) was unsuccessful for both diagnosis and biliary stent placement. Thus the patient was taken for surgical exploration; the pancreas was found to be hard with no discrete mass seen. Pancreatic biopsies initially revealed pancreatitis, but further biopsies confirmed adenocarcinoma. A pylorus-sparing pancreaticoduodenectomy was performed. Final pathology demonstrated a 4.5 cm high-grade adenocarcinoma with negative margins. Out of 10 lymph nodes excised none were involved by cancer.

Postoperatively the patient did well but was discharged to a nursing home for 1 month because he lived alone and needed assistance with his care. He then was discharged home and received adjuvant chemoradiotherapy. He shows no evidence of disease (NED) 1 year later.

TABLE 6-2 Gastric Resections in the Elderly

Reference (Year)	Country	Age	Number of Patients	Morbidity (%)	Mortality (%)
Wu (2000)[93]	Taiwan	≥65	433	21.7	5.1
Saidi (2004)[94]	US	≥70	24	33.3	8.33
Mochiki (2005)[95]	Japan	≥70	30*	13.3	0
		≥70	16†	25	0
Kunisaki (2006)[60]	Japan	≥75	117	29	0.85
Gretschel (2006)[96]	Germany	>75	48	48	8
Orsenigo (2007)[52]	Italy	≥75	249	29	3

*All laparoscopic-assisted gastrectomy
†All open gastrectomy

TABLE 6-3 Gastric Cancer Survival after Curative Resection: Young versus Elderly Patients (published since 2000)

Reference (Year)	Number of Patients	Age	5-Year Survival (%)	P Value
Saidi (2004)[94]	24	<70	20.8	0.45
	24	≥70	16.6	
Mochiki (2005)[95]	73	<70	98.4*	0.48
	30	≥70	95.7	
Kunisaki (2006)[60]	625	45-65	73.6	0.0001
	117	≥75	59.2	
Gretschel (2006)[96]	148	<60	59	0.05
	167	60-75	46	
	48	>75	40	
Orsenigo (2007)[52]	869	<75	54	NS
	249	≥75	47	

*Laparoscopic-assisted distal gastrectomy for early gastric cancer only

Over two thirds of patients with pancreatic cancer are older than 65 years at diagnosis.[61-63] The overall survival of all patients who present with pancreatic cancer is dismal, with 5-year survivals of 5%, up from 3% in 1986.[51] This is attributed in part to the fact that most patients with pancreatic cancer are diagnosed late in the course of the disease when surgical resection is no longer feasible. Only 9% to 15% of pancreatic carcinomas are considered resectable at presentation.[61,63]

A pancreaticoduodenectomy, with or without sparing the pylorus, is the operation of choice for the most common pancreatic lesions, which are located in the head of the pancreas. This is also the surgical procedure for periampullary, duodenal, and distal common bile duct neoplasms. Until the early 1980s, pancreatic resection was associated with an extremely high complication rate, as well as a mortality rate as high as 26% in some centers. However, in more recent years, the morbidity and mortality rates associated with pancreaticoduodenectomy have decreased significantly at specialty centers[64-66] and mortality rates of between 0 and 5% are now the standard at high-volume centers.[64,65,67] In selected elderly patients, mortality rates for surgery are acceptable and even comparable to the younger group.[13,68-70]

A review of 138 patients older than 70 who underwent pancreatic resection for malignancy reported an operative mortality rate of 6% and a morbidity rate of over 40%.[13] No significant differences were found in length of hospital stay, rate of intensive care unit admission, and morbidity or mortality rates between patients younger than 70 years and those older than 70 years. Multivariate analysis found that the only factor that was a significant predictor of complications was a blood loss of more than 2 liters. Median survival was 18 months, and 5 year survival was 21%.

A study from Johns Hopkins evaluating pancreaticoduodenectomy in octogenarians showed that they had a longer postoperative length of stay and a higher complication rate compared to younger patients. The mortality rate, however, was similar between the two groups.[71] They reported a 5-year survival rate for pancreatic cancer of 19% in patients older than 80 years and 27% in patients younger than 80, which was not a statistically significant difference.[71]

For patients with pancreatic cancer whose tumors cannot be resected, biliary obstruction can be effectively managed with stents, placed either endoscopically or percutaneously using the transhepatic approach.[72-75] Mortality rates are lower for stent placement than for surgical bypass and hospital stays are shorter. Early complication rates are lower from this procedure, but long-term complication rates such as recurrent jaundice and cholangitis are more common than with surgical bypass. These complications may be considered acceptable in view of the high surgical morbidity and mortality for biliary bypass procedures.

As with other solid tumors, if an elderly patient presents with a resectable tumor, surgery is the best therapy because it offers the best chance for cure. Another benefit of surgery is that lesions may turn out to be ampullary or biliary in origin and therefore have better survival rates, but only if resected.

MELANOMA

CASE 6-6

An 84-year-old woman presented to the office with a painful, ulcerated pigmented lesion on her left foot. She had a history of diabetes mellitus, hypertension, and obesity. Under spinal anesthesia, the patient underwent a wide local excision of the lesion from the dorsal surface of the left foot. The defect was closed with a split thickness skin graft. She also underwent a left inguinal sentinel lymph node (SLN) biopsy. The pathology showed a tumor that was level 3, 1.2 mm in depth with negative sentinel lymph nodes. She did well with no further treatment.

The overall incidence of melanoma in the United States is increasing, and surgery continues to be the mainstay of therapy. The cumulative lifetime risk of developing melanoma in the United States in 2002 was 1 in 68 compared to 1 in 250 in 1980.[76] This increased incidence of melanoma is due to an increasing incidence in the older population, as the incidence in the younger populations appears to be leveling off or even declining.[77]

The characteristics of melanoma appear to be slightly different in the elderly. Although the extremities are the most common location for melanomas in females, head and neck melanomas become more frequent with advancing age.[78,79] In men, truncal melanomas are most common, but again, head and neck melanomas become more frequent and surpass truncal melanomas after the age of 70.[78,79] Older patients have been reported to have worse prognostic indicators with increased incidence of ulceration, thicker melanomas, and deeper levels of invasion.[80-82]

A study of more than 17,000 patients showed that for each 10-year increase in age there was a decrease in both 5-year and 10-year survival rates.[83] Whether this represents a delay in the diagnosis or a worse malignant potential of these lesions in the elderly population is unknown.

The treatment for malignant melanoma is surgical excision with adequate margins and there is no evidence to suggest that the treatment for the elderly should be any different. Controversies over the width of margins and need for regional lymph node dissection have been addressed in a number of randomized trials. These studies have shown that the necessary width of margins of resection is determined by the thickness of the primary melanoma. For lesions less than 1 mm thick, a 1 cm margin is adequate.[84,85] For lesions greater than 1 mm thick, a margin of 2 cm is advised, on the basis of the results of the Intergroup Melanoma Surgery Trial.[86,87]

Although age has not been used as a criterion for determining the margins of resection, one large retrospective series did report age to be a significant independent factor in the risk for local recurrence.[89] Patients older than 60 were found to have a local recurrence rate of 7.8%, patients between the ages of 30 and 59 had a local recurrence rate of 2.5%, and patients younger than 30 had a local recurrence rate of 1.2% at a median follow-up of 8 years.

The dissection of regional lymph nodes for melanoma treatment is routine for patients with clinically positive nodes; however, the value of elective node dissection for patients with clinically negative lymph nodes has long been debated. Because regional node dissections carry significant long-term complications it would be advantageous to avoid them in patients with known negative lymph nodes. The use of SLN biopsy technique, introduced by Morton[88] in 1992, has allowed an accurate evaluation of the lymph node basin without a complete dissection. However, complete dissections are still necessary for positive sentinel nodes and for palpable nodal disease. Patients are now routinely getting SLN biopsies for any lesion greater than 1 mm in thickness. The sentinel node can now be harvested with 98% accuracy.[90]

Morton[91] reported the findings of 1,269 patients with intermediate-thickness melanomas (1.2-3.5 mm) randomly assigned to wide local excision with or without SLN biopsy. Disease-free survival was significantly higher (P=0.009) in the patients undergoing SLN biopsy compared to the observation group at 5 years because potentially positive lymph nodes were not removed from this group. The overall rate of death from melanoma and melanoma-specific survival, however, was similar for both groups; however, for patients with positive nodal metastasis, the 5-year survival rate was higher in the SLN group (72% versus 52%). Also, the number of positive lymph nodes was lower in the SLN group (1.4 versus 3.3), showing disease progression during observation. This study led to the conclusion that SLN biopsy has staging, prognostic, and survival value in patients with intermediate-thickness melanoma.

In a large retrospective analysis of the national cancer data base for melanoma (comprised of a total of 84,836 cases), factors associated with decreased survival included more advanced stage at diagnosis, nodular or acral lentiginous histology, increased age, male gender, nonwhite race, and lower income. Five-year survival was worst, stage-for-stage, in patients 60 years or older. For early disease, the 5-year survival was 81.4% for the patients older than 60 versus 90.5% for those younger than 60. For late disease, the 5-year survival was 32% for the older patients versus 40.5% for the younger ones.[92]

Because surgical treatment of melanoma can be done with low risk, in fact under local anesthesia if necessary, no one should be denied it because of age or poor performance status. Treatment of melanoma for elderly patients should be as aggressive as in younger patients.

See expertconsult.com for a complete list of references and web resources for this chapter

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CHAPTER

7

Radiation Therapy for the Older Patient

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Within 1 year of the discovery of x-rays by Wilhelm Roentgen in 1895, radiation was used for the treatment of malignancy.[1] Today, approximately 50% to 60% of cancer patients receive radiation therapy (RT) as part of their disease management.[2,3] The role of RT is particularly important for the geriatric population, given the association of aging with an increased incidence of cancer, as well as the often present comorbidities in the elderly that may preclude the delivery of more invasive or aggressive treatment alternatives.[4] Radiation therapy is an important treatment option as monotherapy or in combination with other treatment modalities for older patients with cancer.

This chapter will provide an overview of the basic mechanisms and rationale for the use of RT and discuss the process of care and toxicities associated with RT in the management of elderly patients with cancer. Radiation therapy alone is generally well tolerated in the aged, while concurrent chemoradiotherapy (CRT) requires considered patient selection due to increased treatment-related morbidity. External beam radiation delivered by linear accelerators is the treatment delivery method most often utilized by radiation oncologists for treatment of the elderly; however, other RT techniques such as brachytherapy and radiopharmaceuticals may also be useful. The increased precision of modern RT technology, which allows for significant increase in normal tissue sparing, will be discussed because of its potential import in tailoring treatment to the special needs of the aged. Radiation therapy, used in combination with other treatment modalities or as monotherapy, offers a powerful therapeutic tool for the management of the elderly patient with cancer, for both curative and palliative clinical circumstances.

MECHANISMS, RATIONALE, AND PROCESS OF CARE FOR RADIATION THERAPY

Radiation oncology deals with the therapeutic application of ionizing radiation to treat benign and malignant diseases. The most common approach used to deliver ionizing radiation is external beam radiation therapy (EBRT), which utilizes high-energy photons, or electrons produced by linear accelerators. Protons and other heavy particles, including neutrons and carbon ions, are less commonly used and continue to be studied. Radioactive isotopes generating beta particles and gamma rays are delivered by brachytherapy, the surgical implantation of radioactive sources into the body to treat cancer, and with systemic radiopharmaceutical treatments.

The benefit of radiation therapy stems from the biological fact that ionizing radiation directly and indirectly damages the genetic material of the cell, the DNA, which controls cell growth and replication. Although normal cells are also in the path of the radiation beam, they have superior DNA repair mechanisms and therefore can more readily repair damage sustained from irradiation. Cancer cells are more susceptible to this DNA damage-related disruption of cell replication and undergo cell death through necrosis or apoptosis. Laboratory studies examining the relationship of age and tumor radiosensitivity *in vitro* and within animal models are limited.[5] However, the relationship of age and radiation-induced normal tissue toxicity has been more extensively studied. From these studies, it is thought that the mechanism by which radiation affects normal tissue cells is similar in younger and older patients.[6,7]

When the cancer patient is evaluated for RT, the radiation oncologist determines whether radiation treatment is indicated in the particular clinical circumstance, establishes the specific intent of the treatment, and defines an overall treatment plan. Radiation therapy may be used alone or in combination with surgery or systemic therapies such as chemotherapy. In almost all cases, the aim of RT is to provide local control of a tumor for either a curative or palliative outcome. In the curative circumstance, a patient may accept a greater risk of toxicity associated with higher doses of RT or the addition of concurrent chemotherapy with or without surgery. In contrast, the goal of radiation therapy in the palliative setting is to ameliorate or prevent cancer-related symptoms without causing additional significant morbidity.

The decision to recommend RT and the aggressiveness of its application for elderly patients must be

individualized to the clinical circumstance, the patient's overall functional status, and his or her general medical condition. Clinical experience and the medical literature have concluded that age alone should not preclude the use of RT.[8-13] The clinical discussion to follow will illustrate that the toxicities experienced by elderly patients receiving RT are not significantly different from or more severe than those of the general cancer patient population. However, other issues beyond age may be relevant to the consideration of radiation therapy in the elderly patient. For example, the patient's general medical condition, functional status, issues of quality versus quantity of life, logistical and social obstacles to treatment, comorbidities, polypharmacy, and neurocognitive status all must be factored into the treatment decision-making process. Tools such as the Comprehensive Geriatric Assessment (CGA) allow for a broad appraisal of the physical, mental, social, and functional capabilities and limitations of elderly adults. Such formal evaluation tools may enhance the medical decision-making process regarding the appropriateness of specific treatments, including RT, and also better inform inclusion criteria for clinical trials where older patients had traditionally been excluded solely on the basis of age.[6,13]

After the radiation oncology consultation, if radiation therapy is deemed indicated and appropriate, the patient undergoes a radiation treatment planning session called a simulation. During the simulation, the patient is positioned on a simulated treatment couch in the exact position that will be used during actual daily treatment on the linear accelerator (Figure 7-1). Immobilization devices, such as a custom face mask for head immobilization or body molds or casts, are often used to help provide stable and reproducible patient positioning to enhance the accuracy of the daily treatment. Patients who are able to cooperate with the simulation and the daily treatment setup are more likely to receive accurate and precise targeting of RT throughout their treatment course. However, patients with cognitive impairment, dementia, severe anxiety, or other functional deficits that may limit compliance offer challenges to the treatment management. Such circumstances may require modifications such as alteration of treatment field size, use of anti-anxiety medications, prescribing a shortened course of therapy, or even, rarely, anesthesia.

During the simulation, imaging with x-rays, fluoroscopy, or computerized tomography (CT), sometimes combined with positron emission tomography (PET) or magnetic resonance imaging (MRI) provide visualization of the region to be treated with radiation. The images obtained are electronically transferred to a specialized dedicated treatment-planning computer, where the tumor target is defined and surrounding normal structures are contoured by the radiation oncologist. The radiation oncologist then works with a team of physicists and dosimetrists to select the appropriate radiation dose, beam energy, and beam direction(s) required to effectively treat the tumor while limiting the dose to normal tissues and critical structures. Treatment planning can take anywhere from several hours to several days depending on the complexity of the case.

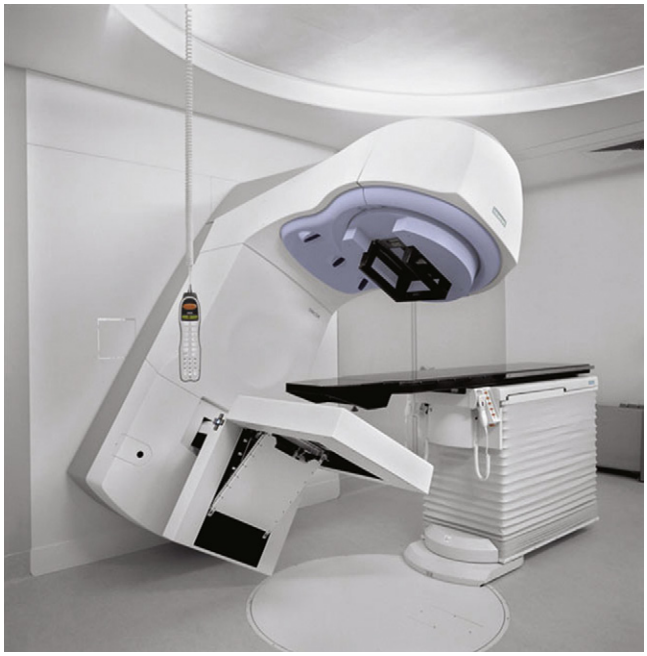

FIGURE 7-1 Linear accelerator. *(Courtesy of Siemens)*

A course of RT is typically fractionated, meaning the total dose is delivered in smaller divided doses over time, typically over several days or weeks. Conventional curative courses of RT utilize a daily dose of 180 and 200 cGy given 5 days per week and lasting between 4 and 9 weeks in duration. Palliative courses of radiation are often shorter, ranging from a single treatment to 20 treatments over 4 weeks' time. Fractionation exploits a number of radiobiological principles that increase the therapeutic benefit of radiation therapy. Fractionation allows for normal tissues to repair sublethal DNA damage between fractions, which enhances the patient's tolerance of the treatment. In addition, fractionation allows for tumor cells to undergo redistribution into more radiation-sensitive phases of the cell cycle between fractions and for reoxygenation of tumor cells between fractions, making them more sensitive to RT.

A change in fractionation scheme alters the biological effect of radiation therapy. In some cases, such as hyperfractionation (two treatments per day separated by a minimum of 4 hours), the goal is intensification of dose to improve tumor control within the limits of acute and late toxicities. By achieving a higher total dose to the tumor within the same or shorter time period without a substantial increase in acute or late toxicity, the probability of tumor control can be enhanced. Selected elderly patients with head and neck cancer have been shown to tolerate variations of such aggressive regimens.[14]

In other instances, modifications in fractionation are made to accommodate patients with mobility or

transportation issues while still providing effective tumor response, particularly in the palliative setting. An extended duration of RT can be problematic for some older patients with mobility issues, certain comorbidities, or other logistical issues hindering daily transport for treatment. In this regard, shortened treatment courses, called *hypofractionated*, made possible by advanced treatment planning methods, can enhance the applicability of RT to the unique needs of the elderly cancer patient. Hypofractionation without compromising tumor control requires an increase in the size of each fraction, and therefore will result in increased late normal tissue toxicity. However, late toxicity may not be of concern for the older patient who stands to benefit from the symptomatic relief and shortened treatment time offered by hypofractionated RT.

A review of the literature on short-course RT for aged cancer patients by Donato, et al.[15] describes various regimens used for malignancies of the brain, breast, lung, prostate, bladder, and rectum, demonstrating safe and effective palliation of symptoms in each organ system. One exception is hypofractionated palliative RT for head and neck cancers, in which the clinical benefits do not appear to outweigh toxicities. A special case of hypofractionation, called stereotactic body radiation therapy (SBRT), can be used with curative intent for a number of tumor sites and is discussed in the section on Cutting Edge RT Techniques.

BALANCING TOXICITY OF RADIATION THERAPY WITH THERAPEUTIC GOALS

The goal of radiation therapy is to maximize the probability of tumor kill while minimizing the risk of normal tissue injury. This risk-benefit analysis is influenced by the intent of treatment. For curative treatment, higher radiation doses are required to maximize tumor control. Such higher doses may be associated with increased normal tissue toxicity. For palliative cases, the aim is to deliver the minimum dose that is able to achieve durable improvement of the tumor-associated symptom while also minimizing the risks of RT-induced toxicity.

With the exception of the RT-associated symptom of treatment-induced generalized fatigue—which is not universal and most of the time does not occur—radiation toxicities and their associated side effects are local and site-specific. RT-related side effects can be categorized as acute (those symptoms occurring during the treatment course), subacute (those symptoms occurring within 3 months of treatment), and late toxicities (those occurring beyond 3 months of completion of RT).

Acute and Subacute Effects of Radiation Therapy

Acute toxicity occurs in normal epithelial tissues or other rapidly dividing cell populations within the treatment field. It demonstrates the equilibrium between cell death and stem cell proliferation in response to radiation damage. Clinically and histopathologically, the acute reaction is also characterized by inflammatory and immune responses to both radiation-induced tumor cell death and damage to normal tissue. Acute side effects are expected to occur to some degree in most curative courses of RT. Depending on the site of treatment, toxicities may include hair loss, dysphagia, odynophagia, skin erythema or desquamation, nausea, vomiting, oral mucositis, esophagitis, pneumonitis, enteritis, proctitis, and cystitis. Acute toxicities, if they are to occur, typically happen approximately 2 to 3 weeks after initiation of daily radiation therapy (Table 7-1), and are only infrequently of significant severity to warrant brief breaks in treatment or the discontinuation of therapy. The vast majority of acute side effects are managed by outpatient pharmacological interventions or nutritional modifications, are usually self-limited, and resolve within several weeks of completing the course of radiation treatment.

TABLE 7-1 Typical Acute Side Effects and Basic Management

Reaction	Management
Skin erythema/ desquamation	Aloe vera; hydrocortisone (0.5%, 1%) cream; silver sulfadiazine cream
Mucositis	Sodium bicarbonate oral gargle; diphenhydramine/viscous lidocaine/aluminum hydroxide mix; oral sucralfate suspension; amifostine
Odynophagia/ dysphagia	Hydrocodone/acetaminophen elixir, oral sucralfate suspension, nystatin suspension; preventative swallow exercises
Pneumonitis	NSAIDs, oral steroids
Nausea/vomiting	Prochlorperazine; ondansetron
Diarrhea	Loperamide; diphenoxylate/atropine
Cystitis/dysuria	Phenazopyridine; oxybutynin; tolterodine
Proctitis	Hydrocortisone (1%, 2.5%, 10%) ointment
Myelosuppression	Transfusion; brief treatment break
Fatigue	Exercise; psychosocial intervention; supportive care

Acute Effects and the Suitability of Radiation Therapy in Treatment of the Elderly

The notion that elderly patients should be offered noncurative regimens or not offered radiation as a treatment option at all because they may not be able to tolerate a curative course of radiation therapy is not supported by clinical experience or the peer-reviewed literature.[6,12,16] Indeed, aging is associated with changes in molecular and biochemical pathways at the cellular level. However, experiments have been performed on mouse[17] and pig skin,[18] mouse lip mucosa,[19] and vascular smooth muscles cells *in vitro*,[20] all of which describe similar acute normal tissue radiosensitivity across varying host ages.

One study on the acute radiation response in skin of young and old rats reported a decrease in tissue radiosensitivity correlated with age.[21] Clinically, many retrospective studies support the view that RT alone does not cause significant differences in toxicity between younger patients and older patients without other severe comorbidities and reasonable performance status. Zachariah et al. retrospectively examined the records of 203 patients aged 80 or older who received RT at facilities associated with Moffitt Cancer Center over a 7-year period and found that more than 90% were able to complete treatment without significant complications.[22] This completion rate is similar to the overall population of patients treated with RT. A similar study by Wasil et al. also concluded that older patients safely tolerate radiation therapy both for curative and palliative intent, with more than 80% of patients able to complete their planned treatment course.[23] Even CRT can be offered to provide improved outcomes in the elderly population for such diseases as locally advanced head and neck cancer, lung cancer, and esophageal cancer. Such aggressive regimens do result in an increased acute side effect profile in all age groups. Elderly patients may be more vulnerable to such stresses; thus careful patient selection and aggressive supportive management may be required.[13]

During the course of radiation therapy, patients are scheduled to see the radiation oncologist a minimum of once weekly for assessment of acute toxicities, but can and should be seen more often depending on the needs of the patient. Most common side effects are easily managed with over-the-counter medications and skin care products, though some side effects may require prescription-strength medications, and at times more aggressive interventions (see Table 7-1). All cancer patients benefit from the multidisciplinary management by social workers, dieticians, transportation aides, and other support staff. This is particularly true for many geriatric patients who battle their disease with the added burdens of social isolation, a weakened support structure, self-denial of symptom severity, and decreased patient concern regarding the critical nature of self-care and personal advocacy. Straightforward side effects may be rationalized, ignored, and exacerbated by patient ennui resulting in an increased probability of more severe treatment-related sequelae such as dehydration with electrolyte imbalance and/or dysphagia leading to malnutrition and cachexia.[12,13,16] Although the results of a study reviewing 210 patients older than 74 years treated with a variety of aggressive RT regimens for varying sites of disease concluded that curative RT is well-tolerated in older patients, the authors, for reasons similar to those mentioned earlier, also recommended more vigilant management of mucositis and diarrhea in elderly patients, who are prone to dehydration.[14]

Not uncommon in the geriatric population is the use of pacemakers and implantable defibrillator devices. There is a rare possibility of radiation-induced malfunction of these devices when they are directly in or near the treatment beam. Caution should be taken by the radiation oncologist by consulting with the patient's cardiologist and a medical physicist to ensure that the treatment will not cause untoward effects on the function of these devices.[24,25]

Subacute Effects

The most common subacute side effect of RT is radiation pneumonitis, in patients whose normal lung is necessarily within the treatment field as required in the treatment of lung cancer or breast cancer. This side effect occurs in the days and weeks following treatment and is characterized by mild symptoms of breathlessness and a dry cough. It is usually managed conservatively. In patients taking long-term steroid medication for preexisting medical problems or in those patients with severe lung disease such as chronic obstructive pulmonary disease (COPD), radiation pneumonitis may be much more severe and require management by a pulmonary specialist to prevent a more serious progression of the symptoms.

Late Effects

Late effects developing in patients who have received radiation therapy are usually associated with damage to vascular, lymphatic, nervous, and/or connective tissues or other cell populations with a low mitotic rate. These effects can occur anytime from 3 months to many years after radiation exposure. Most such problems occur between 9 and 24 months after completion of treatment; they rarely occur beyond 5 years. Most late effects caused by radiation do not rise to a level that meaningfully affects the patient's quality of life.[26] Typically, signs and symptoms such as chronic skin changes of epidermal telangiectasia and tanning, subdermal fibrosis, and mild-to-moderate soft-tissue fibrosis comprise the majority of radiation-induced late side effects. These side effects tend not to cause significant morbidity for the patient. As with acute reactions, late toxicity must be localized to the treatment field and is dependent on total dose, fractionation, and volume of the critical organs irradiated, and rare idiosyncratic patient response to radiation. In contrast to acute effects, most late-effect damage is irreversible. However, the use of tocopherol (vitamin E) and pentoxifylline has been reported to improve late-effect changes of soft tissue fibrosis in symptomatic patients.[26,27] Hyperbaric oxygen therapy has also been shown to relieve several radiation-induced late side effects.[28] Infrequently, significant permanent decrement in the patient's quality of life can result. For example myelopathy, cataracts, xerostomia, gastrointestinal stricture, pulmonary fibrosis, lymphedema, nephropathy, osteoradionecrosis. and soft tissue scarring and/or necrosis are possible rare late outcomes, even in properly administered radiation therapy.

Laboratory data do not suggest that worse late toxicities of RT are related to host age. For example, several *in vitro* studies on fibroblasts, which are thought to be the principle cells involved in late radiation response, did not demonstrate a relationship between radiosensitivity and age.[29,30] Animal studies of individual organ systems do not correlate aging with more severe late reactions, and several studies even suggest older animals show a greater resistance to the late effects of radiation. In Ruifrok et al., the latency period between spinal cord irradiation and the development of myelopathy was significantly longer in older versus younger rats.[31] Another pair of experiments from separate laboratories, examining radiation-induced nephropathy, both demonstrated decreased renal radiosensitivity in older pigs[32] and rats.[33] In one clinical circumstance, the findings are less clear-cut. For CNS malignancies, some reports suggest elderly patients receiving brain irradiation to large treatment volumes are at greater risk of cognitive decline as a result of therapy.[34,35] However, in this case, vascular comorbidities such as hypertension, diabetes, and atherosclerosis, with a higher incidence in the elderly, confound the causal analysis between age and toxicity.[36] In addition, the conventional wisdom regarding cognitive changes associated with cranial irradiation has recently been augmented by the understanding that patients with CNS primary and metastatic disease often suffer preradiation neurocognitive problems. When baseline neurocognitive measures are made before RT, the imputed effects of RT fall away.[37] Nevertheless, due care to limit the amount of brain irradiation in young and older patients remains a current tenet of good radiation oncology practice.

The concern over late toxicity may also be less relevant for some elderly patients with shorter life expectancy. In general, the risk of late complications can be reduced by decreasing the per-fraction dose. However, in such a case, the total course of radiation must be extended in order to achieve a high enough dose to control the tumor. For some patients, improving present quality of life is the higher priority over minimizing the possibility of late effects. In such cases, which are usually palliative, a shortened or hypofractionated course of RT is often effective and may provide the benefit of both symptom relief and abridged treatment days.

Comorbidities and Radiation Therapy in the Elderly

As previously described, clinical and laboratory studies do not suggest that aging alone affects the mechanisms of acute or late radiation response. However, aging is associated with comorbid illnesses, as well as with a decline in physiologic reserve.[38] It is likely that these factors play the most relevant role in the selection of elderly patients for RT as well as their tolerance of it. Common medical conditions faced by the elderly such as hypertension, atherosclerosis, heart disease, and COPD are rarely, on their own, contraindications to RT.[12] Rather, treatment and management decisions are influenced by a combination of factors including the anatomical region being irradiated, the volume of critical organs or structures in the treatment field, and the specific comorbidities and associated functional status of the patient. For example, because the older patient can be at increased risk for upper respiratory tract or urinary tract infections, special attention for the development of acute side effects in these organ systems may be warranted during their RT course. In another case, a patient with Parkinsonian tremor may pose a challenge because of his or her difficulty remaining still; however, appropriate immobilization and treatment field design usually obviates significant difficulties with delivery of RT in such patients. Finally, as elderly cancer patients already demonstrate high rates of fatigue and depression,[39] minimizing treatment-related fatigue is particularly important for such patients. Studies suggest the RT-induced fatigue is less severe and lasting than its chemotherapy[40] or combined modality counterparts,[41] and with modern RT techniques further shrinking the irradiated volume and course of therapy, even greater gains have been observed.[42] These examples highlight the heterogeneous composition of the elderly population, who despite comorbidities, with proper individualized assessment and treatment design, are still good candidates for RT. Considering the three major modalities of oncologic care, RT is often a reasonable option for the geriatric patient who may be unable to tolerate the physiologic stresses of surgery or chemotherapy.

CUTTING-EDGE TECHNIQUES IN RADIATION THERAPY

The two major factors moderating the effectiveness and toxicity of RT are dose and the volume of tissue being irradiated. The biological effect of a particular total dose of radiation is a function of the dose per fraction, the fractionation scheme, and the total time over which the dose is delivered. Refinement in dose fractionation has been studied since radiation was first applied to the treatment of cancer. In the past decade, the use of advanced imaging technologies for both tumor target delineation and intratreatment target localization, introduction of sophisticated treatment planning software, and enhanced treatment delivery instruments have vastly improved the ability to precisely irradiate tumors while sparing normal tissues. Several of these techniques are valuable for the treatment of the elderly cancer patient.

Improved Targeting

Radiation fields were once as basic as a single treatment field (port) or uncomplicated anterior/posterior opposed (AP/PA) treatment fields with or without simple blocking utilized to shape the treatment beams. These approaches may still be appropriate field designs for specific cases;

however, with the aid of improved imaging technology, especially CT, methods to deliver the dose to the target volume have dramatically improved the precision of radiation treatment. Intensity-modulated radiation therapy (IMRT), stereotactic radiosurgery (SRS), stereotactic radiotherapy (SRT), and stereotactic body radiation therapy (SBRT) are technologies used to treat tumors with the prescribed dose while at the same time dramatically minimizing irradiation of adjacent normal tissues to limit the short- and long-term side effects of treatment and maximize its therapeutic benefits.

A specific set of technologies called image-guided radiation therapy (IGRT) represents the latest advance in RT targeting. Utilizing imaging technologies of ultrasound, fluoroscopy, or CT combined with sophisticated localization techniques including stereoscopic shift technique, IGRT allows for daily localization of the treatment target, yielding increased precision of treatment and decreased normal tissue irradiation. IGRT is a critical aspect of improved targeting in RT.

IMRT

Traditionally, treatment planning decisions regarding beam angles and field shapes were made first during the isodose treatment planning process, followed by dosimetry calculations and modifications to achieve the prescribed dose to the intended target. This was called "forward" planning. Conversely, the initial step of IMRT defines the doses to the target volume and critical structures (also called organs at risk, OAR), followed by "inverse" treatment planning, which utilizes software that optimizes beam angles and shapes in order to produce the desired dose distribution. During the IMRT treatment, the patient, the treatment couch, and the beam all move, while at the same time the beam is mechanically spoiled or modulated. The result of this process is the mathematical equivalent of creating literally thousands of tiny microbeams aimed at the treatment target, producing a highly defined dose distribution irradiating the tumor while avoiding designated critical structures. (Figure 7-2)

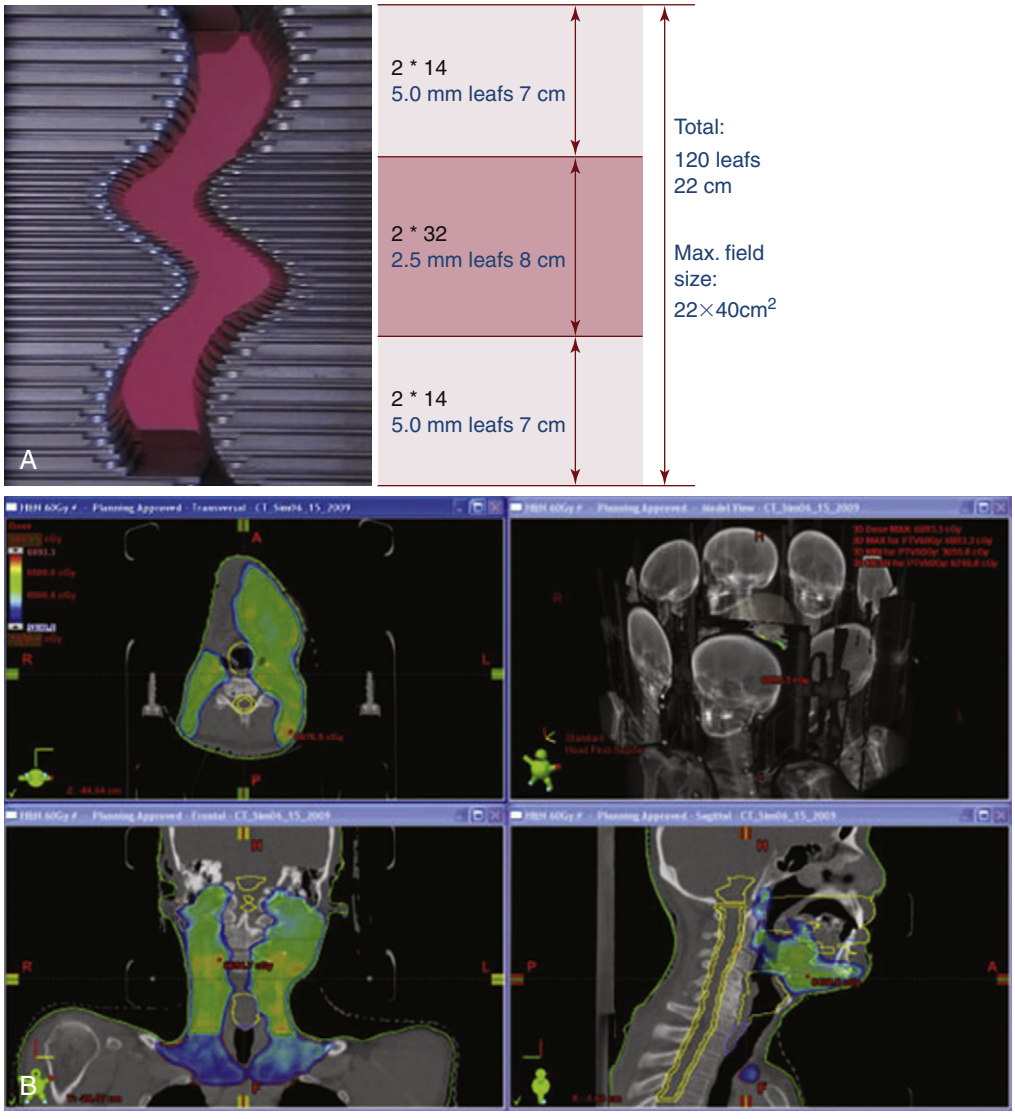

FIGURE 7-2 **A,** Multileaf collimator. **B,** IMRT plan for T2N2 oropharyngeal cancer.

In the mid-1990s, use of IMRT began experimentally at a few institutions worldwide, but the past decade has seen a rapid increase in its application. IMRT has been shown to reduce rates of xerostomia in head and neck irradiation,[43-45] permitted curative dose escalation in prostate cancer treatment while dramatically decreasing rectal and genitourinary treatment related morbidity,[46-48] and provided a retreatment option for recurrent disease in previously irradiated areas,[49-51] to name just a few examples of this technology's significant benefits to patients. IMRT has emerged as the standard of care for a number of disease sites including prostate cancer, head and neck cancer, many CNS tumors, breast cancer, anal cancer, and esophageal cancer. Many other disease sites are actively under investigation to define the potential benefits of the precision of IMRT.[52] IMRT's potential to decrease treatment-related morbidity should not be underestimated. While to our knowledge no studies have examined the application of IMRT specifically for the geriatric population, the benefit of increased normal tissue sparing in elderly patients with multiple comorbidities is intuitively apparent.

SRS

Stereotactic radiosurgery was first described by neurosurgeon Lars Leksell and radiobiologist Bjorn Larsson in 1951 as a method to treat intracranial lesions, avoiding open surgery by utilizing a machine called the Gamma Knife.[53] This technology, comprised of 201 Cobalt-60 sources focused on a single point, was developed to effectively treat a multitude of benign and malignant cranial lesions including arteriovenous malformations (AVM), acoustic neuromas, meningiomas, pituitary tumors, and primary and metastatic brain tumors. Today, a number of machines, including the Gamma Knife and modified or dedicated linear accelerators with SRS capability (e.g., Novalis TX, CyberKnife, XKnife, Trilogy, Synergy S), are able to treat cranial lesions.

The basic premises of SRS include: (1) a stereotactic frame of reference functioning to provide precise localization of an intracranial target; and (2) machinery capable of delivering one to five fractions of high dose radiation with very sharp dose fall-off gradients to minimize irradiation of surrounding tissues (Figure 7-3). A treatment course of more than five fractions to an intracranial (or extracranial) tumor in which stereotactic localization is utilized in the delivery methodology is commonly referred to as stereotactic radiotherapy (SRT).

The use of SRS has become common in the elderly patient for the treatment of primary and metastatic brain tumors, meningiomas, AVMs, trigeminal neuralgia, and primary and recurrent pituitary tumors. The procedure is minimally invasive in nature and of short duration—usually one day. Customarily, a head frame was attached to the patient's skull to ensure precision of treatment delivery, but recently technologies and techniques have been developed that allow completely noninvasive frameless treatments, which enhances patient acceptance of the procedure (see Figure 7-3). SRS is widely used for the treatment of brain metastases due to excellent local control rates and the possibility of avoiding the need for whole-brain radiation therapy (WBRT).[54-56] The potential of avoiding WBRT, typically a 2 to 3 week course of treatment, may be important for the older patient facing difficulties with daily transportation or concerns of cognitive decline from RT.[42,57]

SBRT

Treatment of extracranial tumors utilizing the precision of stereotaxis is known as stereotactic body radiotherapy (SBRT). Using only one to five fractions for the entire treatment course, it can be used to treat a number of anatomical sites effectively. Radiobiologically, the high dose and hypofractionated nature of SBRT is thought to exploit different mechanisms of cell damage than conventional RT by causing endothelial apoptosis and the upregulation of unique inflammatory cascades.[58-60] SBRT's truncated treatment course coupled with its comparable or superior tumor control as compared to standard fractionation makes it logistically beneficial for the elderly. SBRT is also a noninvasive alternative to surgery, which is of particular utility in the treatment of the older patient with significant comorbid diseases. For example, medically inoperable patients with early stage non-small cell lung cancer (with comorbidities of COPD, coronary artery disease, or cerebrovascular disease) who have historically been treated with conventional RT (with local control rates of only 30% to 50%)[61-63] are now successfully managed with three to five SBRT treatments (Figure 7-4). SBRT for early stage lung cancer has demonstrated 3-year local control and overall survival rates of 88% to 92% and 42% to 60%,[64-66] respectively, establishing a superior alternative to conventional RT and a medically equivalent option to the surgical standard-of-care, lobectomy. The use of SBRT as the primary treatment for a number of tumors including prostate cancer,[67,68] liver metastases,[69] renal primary and metastatic disease,[70] and pancreatic cancer[71] is currently under investigation. For example, SBRT for early-stage prostate cancer was first examined prospectively by King et al.[68] where five fractions of SBRT delivered every other day resulted in favorable PSA response without severe late rectal toxicities. While longer-term evaluation is necessary, this technique is a prime example of how dose and targeting modifications stemming from advancements in medical physics and discoveries in radiobiology provide a safe, effective treatment option for younger and older patients alike.

Brachytherapy

The surgical application of a radiation source placed within a body cavity (intracavitary) or implanted directly in the tissue or tumor itself (interstitial) is called

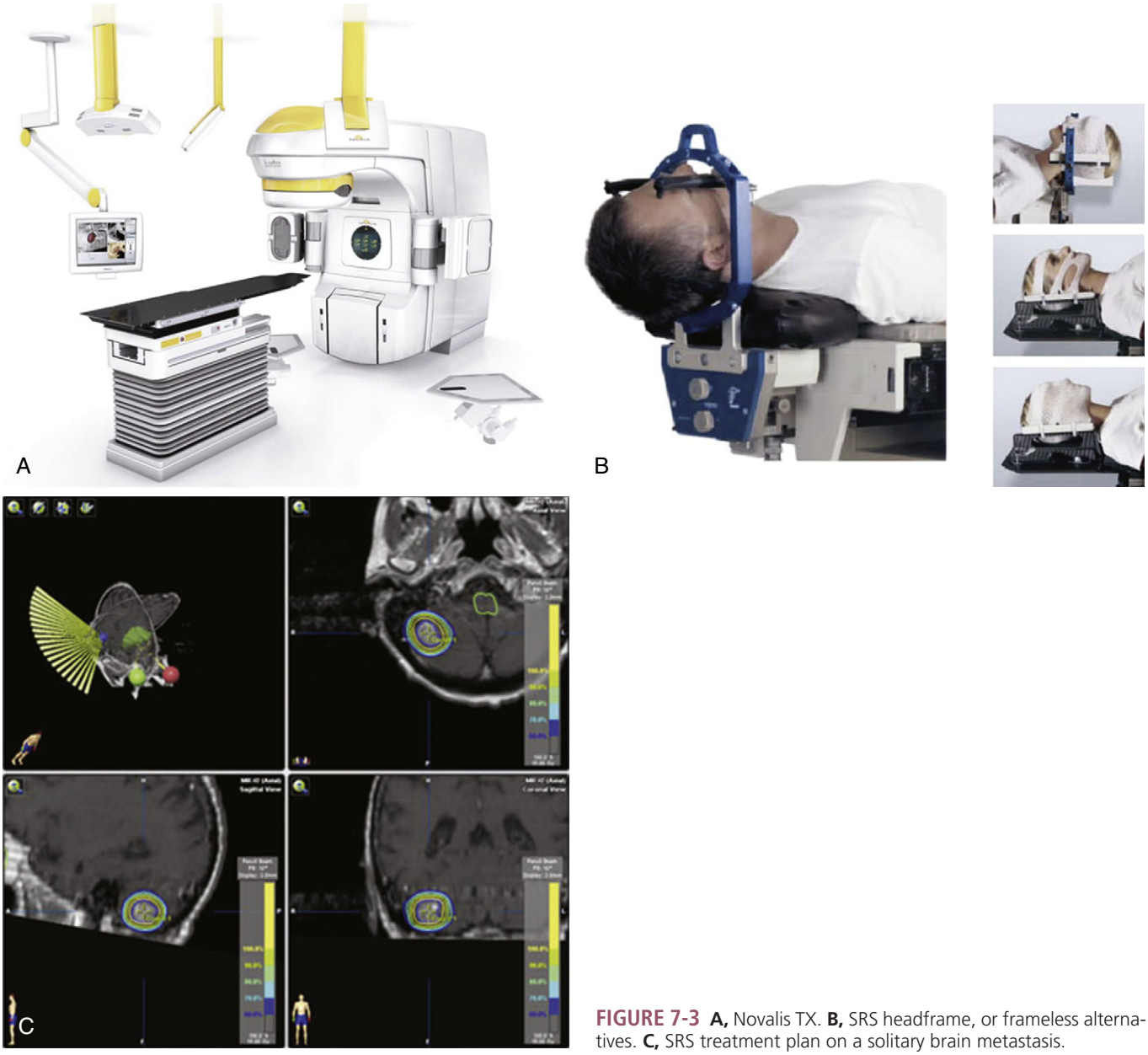

FIGURE 7-3 **A,** Novalis TX. **B,** SRS headframe, or frameless alternatives. **C,** SRS treatment plan on a solitary brain metastasis.

brachytherapy. Many of the technical advantages of SRS and SBRT including dose escalation, conformality, and short duration of treatment were first achieved by brachytherapy. Interstitial treatment is invasive and often requires local or general anesthesia or conscious sedation. It may have the concomitant risk of bleeding and infection associated with a surgical procedure. Nevertheless, in certain situations, brachytherapy allows for convenient and low morbidity treatment of tumors in the elderly.

Brachytherapy is used to treat malignant diseases throughout the body including the brain, eye, head and neck, breast, lung, esophagus, biliary tract, endometrium, cervix, prostate, and soft tissues. Two examples highlighting the usefulness of brachytherapy in the elderly are its application in the two most common malignancies in the geriatric population, breast and prostate cancer.

Postlumpectomy management of breast cancer customarily requires whole breast external beam RT over 5 to 7 weeks. Alternatively, accelerated partial breast irradiation (APBI) using brachytherapy delivers treatment in 10 fractions over the course of five days, with early clinical experience demonstrating favorable results.[72,73] ABPI is particularly applicable to the older cancer patient because of its short treatment duration. APBI compared to whole breast RT is being investigated prospectively by the large NSABP B-39 randomized trial, which is still in accrual.

Prostate "seed" interstitial brachytherapy involves the placement of radioactive isotopes directly into the prostate gland under ultrasound guidance. Due to the short half-life and lack of external penetration of the radioactive isotope, the radiation safety risks to medical personnel and the patient's family members are *de minimis*.

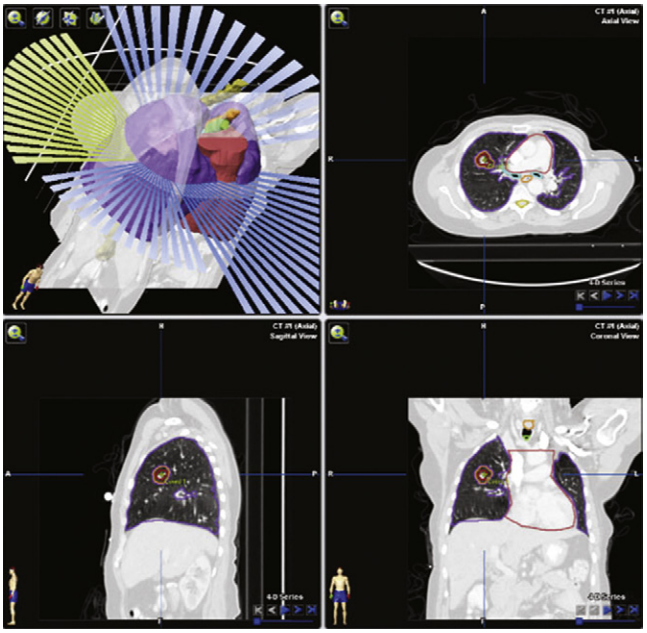

FIGURE 7-4 SBRT treatment plan of T2 non-small cell lung cancer.

It is a 1-day procedure done on an outpatient basis. It has equivalent tumor control in low-risk prostate cancer patients and low rates of toxicity similar to those associated with other RT procedures or radical prostatectomy, which is usually not offered to patients older than 70 years.[74,75]

Radiopharmaceuticals

Radiopharmaceuticals are used to treat systemic malignant disease. Given by oral, intravenous, or intraarterial routes, radioactive isotopes can be administered attached to pharmaceutical vehicles, as in radioimmunotherapy (RIT), or in an unattached soluble form, known as "unsealed source" RT.

Unsealed sources rely on the natural properties of the element to aggregate at the site of interest. For example, I-131 is absorbed and concentrated in follicular thyroid cells. As it decays, I-131 releases β particles, with a path length of 1 to 2 mm, which destroy normal thyroid and thyroid cancer cells. Other radionuclides including Sm-153 and Sr-89 are used to palliate widespread metastatic bone pain associated with metastatic breast, prostate, and lung cancer. These radioisotopes bind to hydroxyapatite, most actively at the tumor-bone interface of osteoblastic lesions, where they deliver therapeutic doses of radiation via beta decay. Myelosuppression is a possible side effect for all patients, which may be especially concerning in the aged, or when this treatment modality is used concurrently with other chemotherapeutics.[76]

Radioimmunoglobulins are monoclonal antibodies linked to a radioisotope. Y-90 and I-131 are favored because of their short half-lives, beta decay, and stability in complex with the antibody. Radioimmunotherapy is most successful in the treatment of certain lymphomas. An international phase III randomized clinical trial reported that consolidation with Y-90 ibritumomab tiuxetan compared to no additional therapy after first-line induction for follicular lymphoma improved progression-free survival from 13.3 months to 36.5 months.[77] Data from four clinical trials were pooled to examine the safety and efficacy of Y-90 ibritumomab tiuxetan in three age groups of non-Hodgkin lymphoma patients. Patients older than 70 years had similar rates of hematologic toxicity compared to the group of patients younger than 60, and rates and durations of response were similar in all age ranges.[78]

CLINICAL APPLICATIONS

Given the prevalence of cancer in the elderly, several publications have specifically examined tolerability of or alternatives to standard of care radiation regimens in the elderly. Several relevant publications by primary cancer diagnosis are discussed later in the chapter.

Glioblastoma

Glioblastoma (GB) is the most common primary central nervous system malignancy and is commonly diagnosed in the elderly. The standard of care for patients with glioblastoma is maximal surgical resection followed by fractionated external beam radiation, with concurrent and adjuvant temozolomide.[79] This regimen has been specifically studied in patients older than 65 years in two prospective single-arm trials that demonstrated a median overall survival of 11 months and acceptable toxicity.[80,81] However, a retrospective review of the same age population compared 19 patients treated with concurrent radiation and temozolomide to 20 patients treated with radiation alone and found 42% grade 3-4 toxicity among patients receiving concurrent CRT versus 0% in the patients receiving RT alone.[82] Such reports of increased toxicity in elderly patients receiving combined modality therapy have motivated the study of alternative regimens.

Radiation alone, delivered using either standard or abbreviated fractionation schemes, is associated with median survival of 4 to 8 months.[83-87] Roa et al. randomized 100 patients, age 60 or older, to postoperative standard RT (60 Gy in 30 fractions) versus abbreviated RT (40 Gy in 15 fractions) and found statistically equivalent overall survival of 5.1 versus 5.6 months.[86] Similarly, temozolomide alone has been investigated as an alternative strategy in elderly patients with glioblastoma, and median survival rates of approximately 6 months have been reported.[88-90] Minniti et al. prospectively treated 43 patients older than 70 with hypofractionated RT (six fractions of 5 Gy each delivered over 2 weeks) followed by adjuvant temozolomide, and achieved a median

overall survival of 9.3 months.[91] Of note, a recent prospective trial randomized 85 patients older than 65 with newly diagnosed high-grade glioma to best supportive care versus RT (50 Gy in 28 fractions) and found significant improvement in median survival (29.1 versus 16.9 weeks) among patients receiving RT, with no associated decrements in quality of life or cognition.[87]

Head and Neck Cancer

Curative radiation-based treatment for head and neck cancer can be associated with significant acute and chronic toxicity which often gives reason for pause when considering tolerability in an elderly patient. Concurrent chemoradiation (CRT) is standard of care for most patients with locally advanced head and neck malignancies but has been minimally studied in the elderly. Turaka et al. compared quality-of-life outcomes among patients older than 60 and younger than 50 receiving concurrent CRT and found that patients older than 60 experienced greater decrement in physical, cognitive, emotional, and functional quality-of-life endpoints.[92]

Concurrent CRT may also be associated with increased chronic toxicities. In a case-control study of patients enrolled in three RTOG randomized trials of CRT, age was found to be a significant predictor of late toxicities, with 56% of patients older than 65 experiencing late toxicity versus 31% of patients younger than 50.[93]

Prior to the era of definitive concurrent CRT, several studies examined outcomes among elderly patients receiving definitive radiation and concluded comparable cancer control outcomes and acceptable toxicity.[11,94-97] Pignon et al.[11] specifically reported toxicity endpoints among patients older than 70 receiving definitive radiation on EORTC clinical trials and noted equivalent acute mucositis and weight loss. Older patients experienced significantly greater grade 3-4 functional acute toxicity, but this did not translate to differences in overall survival, or in frequency of late radiation damage.

Among younger patients who are not chemotherapy candidates, two alternative strategies have been evaluated: altered fractionation and concurrent radiation with cetuximab, a monoclonal antibody against the epidermal growth factor receptor. Allal et al.[98] retrospectively compared outcomes of 39 patients age 70 or older and 81 patients younger than 70 treated with altered fractionation RT (specifically accelerated concomitant boost), and found equivalent acute and late toxicities. While an unplanned treatment break was observed in 8% of the elderly group and in none in the younger group, all patients completed the planned RT schedule, and there was no difference in overall survival and locoregional control between the two groups. The authors conclude that this aggressive RT-alone regimen for curative intent is feasible for appropriately selected older patients. Although the strategy of concurrent radiation and cetuximab has not been specifically studied in the elderly, the randomized trial of RT versus concurrent cetuximab and RT found a 10% improvement in 3-year overall survival with no added acute toxicities, other than acneiform rash, with the addition of cetuximab, suggesting that cetuximab may be a reasonable consideration in elderly patients able to tolerate RT.[99]

Non-Small Cell Lung Cancer

Definitive radiation is standard of care for early-stage medically inoperable non-small cell lung cancer (NSCLC), and concurrent CRT is standard of care for locally advanced NSCLC. Conventional external beam radiation has been the historical standard for patients with medically inoperable early stage NSCLC. However, rates of 5-year survival with definitive RT have ranged from 10% to 30%,[100,101] well inferior to rates of 65% to 70% achieved with surgery alone.[102] For elderly patients with early-stage medically inoperable NSCLC, recent advances in technology have allowed for alternative regimens that may be more tolerable, and potentially more effective, in the elderly. Yu et al. conducted a prospective multiinstitutional study of involved field IMRT in 80 patients with medically inoperable NSCLC and reported no grade 4 toxicity and minimal grade 3 toxicity (3.8% pneumonitis, 2.5% hematologic toxicity, and 1.3% esophagitis), with 36.7% experiencing elective nodal failure (i.e., recurrence in an initially uninvolved and untreated lymph node).[103] Stereotactic body radiation therapy, which involves the precise delivery of a limited number of high dose fractions (typically three to five fractions), has been a recent paradigm shift that has consistently achieved 3-year local control rates exceeding 85%, with minimal associated morbidity.[64-66] Delivery of fewer fractions and minimal associated morbidity may facilitate greater use of SBRT in elderly patients who have comorbidities or transportation limitations that would have precluded traditional daily fractionated RT delivery.

Movsas et al. examined the impact of age on outcome among 979 patients with locally advanced NSCLC who were enrolled on six prospective Phase II and III RTOG trials from 1983 to 1985, and found that patients younger than 70 had improved survival with more aggressive therapy (induction chemotherapy followed by standard RT, or concurrent CRT followed by hyperfractionated RT), while patients older than 70 achieved optimal quality-adjusted survival with standard RT alone.[104] Pignon et al. examined outcomes, stratified by age, among 1208 NSCLC patients who received definitive RT on one of six EORTC randomized trials and found comparable survival and acute and late toxicity, with the exception of increased weight loss in the older age groups[105]. Schild et al.[106] performed a secondary analysis of a North Central Cancer Treatment Group prospective trial of chemotherapy plus twice daily versus once daily RT to determine the impact of age on outcome. While patients

older than 70 were found to have higher grade 4+ toxicity (81% vs. 62%), grade 4+ hematologic toxicity (78% vs. 56%), and grade 4+ pneumonitis (6% vs. 1%), no differences were noted in overall survival. Rocha Lima et al. similarly conducted a secondary analysis of patients with locally advanced or metastatic NSCLC enrolled on CALGB trials 8931 and 9130 to determine the impact of age on outcome and found no differences in treatment tolerance, response, survival, or continuation of treatment between patients older and younger than 70.[107] A secondary analysis of RTOG 94-10 performed by Langer et al. found that, although patients older than 70 experienced more grade 3-4 esophagitis and grade 3 neutropenia with concurrent CRT, CRT resulted in the longest survival for patients older than 70.[108] Taken together, the data for efficacy and toxicity of radiation regimens for elderly patients with locally advanced NSCLC would suggest that fit elderly patients may benefit from aggressive combined modality therapy; however, elderly patients should be monitored closely and receive optimal supportive therapy, given expected increases in associated toxicity.

Breast Cancer

Postlumpectomy radiation is standard of care for all patients undergoing breast conservation surgery for early-stage invasive breast cancer, and is recommended for patients with high-risk features (including positive nodes, positive margins, or tumor size exceeding 5 cm) in the postmastectomy setting. Data examining outcomes among women older than 70 undergoing postlumpectomy or postmastectomy radiation suggests tolerability and efficacy. However, recent data has emerged to suggest that omission of postlumpectomy RT in select patients older than 70 may be acceptable.

The Early Breast Cancer Trialists' Collaborative Group reported a meta-analysis of 23,500 women enrolled in prospective trials of RT versus observation in the postlumpectomy setting and found that a 19% absolute reduction in 5-year local recurrence associated with the addition of RT translated into an absolute 15-year 5% reduction in breast cancer-specific mortality.[109] However, many have argued that older women with favorable-prognosis breast cancer may not significantly benefit from the addition of postlumpectomy RT. Hughes et al.[110] randomized 636 women older than 70 with pathologic T1, estrogen receptor-positive, margin-negative invasive breast cancer status post lumpectomy to adjuvant RT and tamoxifen versus tamoxifen alone. No differences were noted in rates of distant metastases or overall survival. Although local recurrences were statistically significantly fewer in the RT arm (1% versus 4% at 5 years, and 1% versus 7% at 8 years[111]), the differences were small, leading the authors to conclude that omission of RT is a reasonable choice for women older than 70 with early-stage, estrogen receptor-positive breast cancer. Because the rise in local recurrence rate in the tamoxifen-alone group (from 4% at 5 years to 7% at 8 years) would be expected to progress with longer follow-up, many practitioners maintain support for RT in the elderly patient with longer life expectancy.

When postlumpectomy radiation therapy is indicated, elderly women are acceptable candidates for hypofractionated RT, including whole- or partial-breast hypofractionated RT. Hypofractionated RT has been studied in three prospective trials that randomized patients with early-stage invasive breast cancer postlumpectomy to 50 Gy delivered in 25 daily fractions versus 41.6 Gy in 14 fractions, 39 Gy in 13 fractions, 40 Gy in 15 fractions, or 42.5 Gy in 16 fractions. The hypofractionated regimens were associated with equivalent locoregional control and survival, and equivalent or reduced morbidity.[112-114] Accelerated partial-breast RT (APBI) remains controversial, given the lack of randomized data with adequate follow-up to confirm equivalence. However, a recently released American Society for Therapeutic Radiation Oncology (ASTRO) Consensus statement concludes that women older than 60 with pathologic T1N0, estrogen receptor-positive, margin-negative, favorable-histology tumors are suitable candidates for partial breast irradiation.[115]

Randomized trials have established a survival advantage with the addition of postmastectomy radiation for younger patients with high-risk disease.[116-118] Given the exclusion of older women from these trials, Smith et al. used the SEER database to examine outcomes among women older than 70 who underwent mastectomy with or without adjuvant RT and found that postmastectomy RT was associated with a statistically significant survival advantage among patient older than 70 with high-risk disease (defined as T3/4 and/or N2/3).[119]

Gastrointestinal Malignancies

Pancreatic Cancer. The median age of diagnosis for pancreatic cancer in the United States is 72, and 42% of all patients diagnosed with pancreatic cancer are older than 75.[120] For medically operable patients with surgically resectable disease, surgery is standard of care, commonly followed by adjuvant concurrent CRT. Definitive concurrent CRT is recommended for patients with locally advanced unresectable pancreatic cancer. Miyamoto et al.[121] retrospectively examined toxicities associated with fluoropyrimidine-based concurrent CRT in 42 patients older than 75 and found that 19% required hospitalization; 17%, emergency room visits; 36%, RT treatment breaks; 7%, chemotherapy treatment breaks; and 21% failed to complete therapy. Survival outcomes were similar to those achieved in a younger patient population enrolled in prospective trials, leading the authors to conclude that the elderly may benefit equivalently from combined modality therapy, at the expense, however, of substantial treatment-related toxicity.

Rectal Cancer. Neoadjuvant or adjuvant CRT is recommended for patients with stage II or III rectal cancer. This regimen has not been prospectively evaluated in the elderly; however, the SEER database was recently examined to determine trends in utilization and completion of CRT and associated outcomes among 2886 patients older than 66 years with stage II or III rectal cancer. Completion of adjuvant CRT was associated with significant decreases in 5-year adjusted cancer mortality risk, thus highlighting the benefit of adjuvant CRT in the elderly. Only 37.5% and 54.2% of stage II and stage III patients initiated adjuvant CRT per NIH recommendations, and of those, only 47.6% and 67.5%, respectively, completed treatment. Presumably, physician expectation or patient experience of treatment-related toxicity may be significant enough to deter recommendation of and completion of therapy.[122] Existing data, however, do not demonstrate worse severity or tolerability of pelvic RT toxicities in older patients to support this line of reasoning,[10,123] and greater advocacy of CRT in fit elderly patients may be beneficial.

Although not specifically evaluated in the elderly, an alternative strategy for neoadjuvant RT delivery that has been prospectively studied and may have inherent advantages in the elderly is short-course RT, consisting of five fractions of 5 Gy each, delivered preoperatively.[124]

Esophageal Cancer. Most patients with primary esophageal malignancies will be recommended to receive CRT, either definitively or perioperatively. Mak et al.[125] retrospectively examined toxicities associated with CRT in 34 patients older than 75 and found that 50% completed CRT, 38.2% experienced grade 4 or worse acute toxicity, and 70.6% required hospitalization, emergency room visits, or RT treatment breaks. Two-year overall survival was 29.7%, leading the authors to conclude that CRT is associated with substantial morbidity in the elderly, survival is low, and future efforts should focus on improvement of treatment tolerability in the elderly. Of note, only seven patients were treated with IMRT techniques, which for esophageal cancer is becoming the treatment standard,[126,127] and which could potentially meet the needs of the geriatric patient population.

Prostate Cancer

The median age of diagnosis for prostate cancer is 68.[120] Given that elderly men with low-risk, early-stage prostate cancer will likely die with prostate cancer rather than of it, the NCCN Guidelines recommend that life expectancy be considered in management decisions and that active surveillance be discussed as a treatment option for patients with limited life expectancy. For patients who elect active treatment, external beam radiation therapy is a safe and effective option. Two retrospective series compared biochemical recurrence-free survival between patients older and younger than 75 and older and younger than 60, respectively, and found no differences in biochemical recurrence-free survival by age.[128,129] The University of Chicago examined genitourinary and gastrointestinal toxicity outcomes after prostate cancer RT among four age cohorts: younger than 60, 60 to 69, 70 to74, and 75 years and older. No significant differences were noted in acute or late GI or GU toxicity by age.[130] Brachytherapy, a procedure in which radioactive seeds are permanently implanted in the prostate gland in a single session under local or general anesthesia, is a treatment option for men with low-risk prostate cancer and has inherent logistic advantages in an elderly patient.

Radiation Therapy for Benign Conditions

Radiation therapy is an effective modality for the treatment of several benign conditions that may affect the elderly, including acoustic neuroma, pterygium, Graves disease, heterotopic ossification, meningioma, arteriovenous malformations, degenerative osteoarthritis, trigeminal neuralgia, and keloids.[131]

Palliative Radiation

Palliative radiation is effective in a variety of clinical circumstances. Symptoms that can be effectively palliated with radiation include pain from bone or visceral metastases[132,133]; cough, hemoptysis, and dyspnea from pulmonary malignancies[134]; dysphagia from head and neck cancers[135-137] or from obstructing gastrointestinal or pulmonary malignancies[138-141]; bleeding secondary to gynecologic, genitourinary, or gastrointestinal malignancies[142-144]; and neurological deficits from brain metastases or spinal cord compression.[145-148] Given that palliative radiation is commonly employed in patients with limited life expectancy, shorter course regimens have been investigated. Lutz et al.[149] recently published a comprehensive review of shorter course, or hypofractionated, palliative radiotherapy. The authors concluded that hypofractionated palliative radiation allows for "time-efficient, cost-effective, and minimally toxic" symptom palliation. This review included nine randomized trials of 8 Gy or 10 Gy delivered in a single fraction versus multiple fraction regimens for palliation of pain secondary to bone metastases and concluded equivalence. The randomized trials have repeatedly found equivalent pain relief and pain medication requirements among patients receiving a single versus multiple fraction regimen for palliation of pain from bone metastases. Higher rates of retreatment have been found among patients receiving single fraction radiotherapy, which is less of a concern among patients with limited life expectancy.

The review also examined studies of hypofractionated radiotherapy for patients with symptomatic lung cancer, pelvic malignancies, and head and neck cancer. Potential hypofractionated regimens available for patients with inoperable, advanced, symptomatic lung cancers include two- or five-fraction regimens.[150-154] For advanced symptomatic pelvic malignancies including gynecologic and

TABLE 7-2 Indications for Palliative Radiation Therapy and Rates of Improvement

Condition	Percentage of Patients Experiencing Symptom Improvement
Bone pain	73% - 93%
Brain metastases	56% - 75%
Superior vena cava syndrome	62% - 95%
Spinal cord compression	67% - 73%
Hemoptysis	48% - 88%
Dyspnea	40% - 64%
Vaginal bleeding	41% - 69%
Dysphagia	48% - 86%

Data from references 150, 156-162.

genitourinary malignancies, hypofractionated regimens have included one and three fraction regimens. Among patients with advanced head and neck cancers, quality of life improvements have been documented with a regimen known as "Quad Shot," referring to delivery of four fractions given twice daily for 2 days.[155] (Table 7.2)

CONCLUSION

Radiation therapy plays an essential role as monotherapy or in combination with other treatment modalities in the curative and palliative management of older patients with cancer. Laboratory data do not suggest that radiation-induced acute or late toxicities are age-dependent. Numerous clinical reports emphasize that age alone is not a contraindication to radiotherapy. CRT and other radical RT regimens may also be feasible in appropriately selected patients. Age-related access and medical issues such as comorbidities, logistical barriers to treatment, and waning social support can all be managed in the radiation oncology setting. In addition, modern RT technologies such as IMRT, SRS, and SBRT benefit patients of all ages, and are well-suited to address many of the management issues associated with treating the elderly cancer patient. With careful and personalized evaluation of the patient with tools such as the comprehensive geriatric assessment, elderly patients can often be offered optimal radiation therapy as part of their cancer care.

See expertconsult.com for a complete list of references and web resources for this chapter

CHAPTER

8

Adjuvant Therapy for Elderly Patients with Breast, Colon, and Lung Cancer

Daniel Becker and Dawn L. Hershman

Cancer is the second leading cause of mortality in the United States and disproportionately affects the elderly. In 2009, breast, colorectal, and lung cancer together accounted for more than one third of the 1.5 million expected diagnoses of cancer, and for about 250,000 deaths.[1] The median age of cancer diagnosis in breast, colorectal, and lung cancers was 61 years, 71 years, and 71 years, respectively.[2]

Adjuvant therapy is defined by the National Cancer Institute (NCI) as "additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back."[3] Adjuvant therapy is generally aimed at eliminating residual disease left behind at surgery. Decisions regarding the utility of adjuvant therapy weigh the likelihood of recurrence with the patient's life expectancy and susceptibility to short- and long-term toxicities. Over the past decade, increased screening with colonoscopy, mammography, and computed tomography (CT) of the chest has resulted in cancer detection at earlier stages.[4,5] Multiple different treatment modalities, including chemotherapy, radiation therapy, and biologic or targeted therapy may have a role in the treatment of early-stage cancer. Because elderly patients are often underrepresented in clinical trials, the benefits and risks in elderly populations are not well understood. However, even in settings of proven benefit, elderly patients are frequently not as likely to be offered or to receive curative therapy.[6-9]

The goals of this chapter are to introduce the major principles and fundamental practices of adjuvant therapy for breast, colon, and lung cancer in elderly patients. By the end, the reader should understand the factors that contribute to the decision to use or withhold adjuvant therapy. These factors include tumor and patient characteristics, as well as the benefits and toxicities associated with each therapy. Case presentations will highlight the challenges to providing appropriate cancer care for an individual patient. The specific cancer sections will explore prognostic factors and factors predictive of response to therapy, both of which play important roles in decisions regarding adjuvant therapy. The cancer-specific section will also offer an overview of the therapies used to treat breast, colon, and lung cancer, with a focus on how the use of those therapies may be different in older patients.

PREDICTORS OF BENEFIT FROM ADJUVANT THERAPY

Decision making about the use of adjuvant therapy is influenced by tumor and patient characteristics.

Tumor Characteristics

A prognostic factor is defined by the National Cancer Institute (NCI) as an element that can be used to define the chance of recovery from a disease or the risk or relapse.[10] A predictive factor is used to estimate the likelihood that a patient will respond to a particular therapy. Many tumor characteristics have important prognostic and predictive value. Prognostic indicators in breast cancer include tumor stage and grade, lymphovascular invasion, and hormone receptor status.[11-14] Hormone receptor status and increased HER-2/neu expression also predict response to hormonal therapy and trastuzumab, respectively.[14,15] Prognostic indicators in colon cancer include tumor stage, grade, lymphovascular invasion, and preoperative serum carcinoembryonic antigen levels.[16-18] Stage and grade are unique in their almost universal prognostic value for varied tumor types. Additional prognostic and predictive factors will be reviewed in the cancer-specific sections.

The risk of relapse after primary surgical therapy is the main contributor to any decision regarding the benefit of adjuvant therapy; often a patient whose cancer is more likely to relapse is also more likely to benefit from adjuvant therapy. Stage of disease is one of the strongest predictors of relapse risk. Staging is defined by the TNM

system, established by the American Joint Committee on Cancer (AJCC),[19] where T refers to the size of the primary tumor, N refers to the degree of lymph node involvement, and M refers to the presence or absence of distant metastases. The relationship between advancing age and stage varies by cancer. In multiple analyses, older breast cancer patients presented with more advanced-stage disease while older colon cancer patients presented at stages similar to younger patients, and older lung cancer patients presented with earlier-stage disease.[20-23] It is also noteworthy that changes in screening and medical care will influence the relationship between age and stage at diagnosis. Evidence suggests that both increased mammography and decreased use of hormone replacement therapy have contributed to the decrease in estrogen receptor-positive breast cancer in women in their 60s.[24]

The grade of the tumor is also an important determinant of relapse risk.[11,16] Although the specifics of tumor grade differ by tumor type, higher grade tumors are typically recognized by higher rates of cellular proliferation, increased invasion into surrounding tissue, and less similarity to their tissues of origin. As cancer cells acquire additional genetic changes that increase their potential to invade and metastasize, they frequently appear histologically to be less like their tissues of origin.[25] The relationship between advancing age and tumor grade is variable by tumor type.[12,26] Other tumor characteristics, including hormonal receptor status, lymphovascular space invasion, presence and absence of genetic alterations, and tumor genetic profiles influence relapse risk.[13,17]

Patient Characteristics

Patient characteristics, including life expectancy and the risk of treatment-related adverse outcomes, factor into any risk-benefit analysis about adjuvant therapy. Advanced age does not, by itself, predict toxicity from or poor response to therapy.[9,27] Advanced age is, however, associated with multiple other physiologic changes, including decreased performance status and increased numbers of comorbid conditions that may change the effects of therapy.

Pharmacokinetics. With advancing age, the body fat percentage increases, which decreases total body water and decreases the volume of distribution.[28] There is also an age-related decrease in glomerular filtration rate that prolongs the effects of medications excreted by the kidney, and which limits the use of medications with renal toxicity.[29] In addition, creatinine becomes a poor marker of glomerular filtration rate in elderly patients because of their decrease in muscle mass, which may not be recognized by the treating physician.[30,31]

Comorbidities. Coexisting renal or hepatic disease will change the half-life of administered medications, with resultant changes in the toxicity profile. Other comorbid conditions may influence the effects of therapy in ways that are less obvious. The Charlson comorbidity index was designed to predict 1-year mortality on the basis of a weighted composite score for the following categories: cardiovascular, endocrine, pulmonary, neurologic, renal, hepatic, gastrointestinal, and neoplastic disease.[32] One study of more than 1200 patients with non-small cell lung cancer noted that although a higher Charlson comorbidity score was associated with increasing age, only higher comorbidity score, and not age, was independently associated with decreased survival.[33]

Performance Status. Performance status is used to quantify the patient's functional capabilities. The two most widely used scales for performance status in oncology are the Karnofsky and Eastern Cooperative Oncology Group scales. Several studies have shown that poor performance status is associated with increased therapy-related toxicity and poor survival.[34,35] While predictive of outcome, there is evidence that these performance status scales may underestimate the degree of functional impairment in older patients, when compared with the activities of daily living (ADL) and instrumental activities of daily living (IADL) scales.[36]

Comprehensive Geriatric Assessment. The comprehensive geriatric assessment (CGA) generally includes functional status, comorbid medical conditions, cognitive status, psychological conditions, nutritional status, and medication review.[37] Functional status in a CGA may be assessed by the ADL and IADL, both of which focus on the patient's ability to complete specific daily tasks in and out of the home. The CGA predicts overall survival and toxicity of cancer treatment. It adds additional valuable information to assessments of performance status alone.[38,39]

Functional Reserve. Older patients may experience more severe toxicities than younger patients. For example, several studies have suggested significantly increased rates of neutropenia in patients older than 70 years who are receiving chemotherapy, after controlling for other risk factors.[40,41] Chemotherapeutics known to damage the heart have been shown to be more toxic in patients older than 65.[42,43] In many circumstances, the distinction between age as an independent predictor of toxicity or age as a marker for other changes that predict toxicity is unknown. Other studies have found similar rates of severe toxicity in younger and older patients treated with chemotherapy, albeit in highly selected patient populations.[7,44]

Therapy Characteristics

Each cancer-related therapy has a distinct toxicity profile, that may or may not be influenced by the patient's age, and which is weighed against the likelihood of benefit for the patient.

DISEASE-SPECIFIC ISSUES: BREAST CANCER

CASE 8-1 CASE PRESENTATION

A 74-year-old woman presents with a 4 cm mass in the left breast, discovered on her first mammogram in 5 years. Needle biopsy confirmed adenocarcinoma that expressed estrogen and progesterone receptors, but which did not overexpress the HER-2/neu protein receptor.

Pretherapy Evaluation

Comprehensive geriatric assessment reveals that the patient is completely independent by the IADL scale. Her only comorbidity is diabetes, which is controlled with oral medications; she shows no evidence of end-organ damage. She continues to work as an accountant, takes care of two grandchildren every Wednesday, and walks four mornings a week with her closest friends. The patient's cognitive function, nutritional status, and psychological state are excellent. Her medications include metformin and a daily baby aspirin.

Clinical Staging

On physical exam, the patient has a palpable 4 cm, firm, mobile nodule in the upper outer quadrant of the left breast, and a 2 cm palpable node in the left axilla.

Mastectomy versus Breast-Conserving Therapy

Total, or simple, mastectomy includes removal of the whole breast and the fascia overlying the pectoralis major. Breast-conserving surgery removes the tumor mass with specimen margins that are free of tumor. Prospective randomized trials have established the equivalence of mastectomy and the combination of breast-conserving surgery and radiation, while breast-conserving surgery without radiation results in a higher local recurrence rate and worsened survival.[45] The decision regarding appropriate breast surgery is challenging and personal. The absolute contraindications to breast-conserving surgery include multicentric disease, diffuse calcifications on mammogram, prior radiation to the chest wall, and inability to obtain clean margins.[46] Relative contraindications to breast-conserving therapy include connective tissue disease and large tumor size relative to breast size.[47] In addition, patients who are unable to receive radiation because of logistical issues may not be appropriate candidates for breast conservation surgery.

Older women are less likely to have breast-conserving surgery, and those who have it are less likely to have radiation therapy when compared to younger women.[48,49] A patient's decision as to whether to undergo a mastectomy versus breast-conserving therapy is strongly influenced by her physician's recommendation.[50]

Axillary nodal evaluation by sentinel node biopsy or nodal dissection is the standard of care for all women with invasive breast cancer.[51] Older women are significantly less likely to have axillary lymph node dissection.[52] For some, this may be appropriate, as there is evidence that women older than 70 years with estrogen receptor-expressing tumors and tumors less than 2 cm with no clinical axillary involvement may be safely treated with resection followed by tamoxifen, without axillary nodal exploration.[53] Guidelines suggest that axillary node evaluation should not be omitted in a patient who is being considered for any adjuvant therapy in addition to hormonal therapy, and specifically should be pursued in patients with higher-risk cancers.[54]

CASE 8-1 CASE CONTINUED

The patient proceeded to a lumpectomy and axillary lymph node dissection. Additional laboratory data and chest x-ray were unremarkable. The final staging is pathologic T2 (tumor >2 cm, but <5 cm), N1 (nodal involvement in 1 to 3 ipsilateral axillary nodes), M0 (no distant metastases), stage IIB. The patient had a normal echocardiogram with a left ventricular ejection fraction of 60%.

Prognostic and Predictive Factors Stage

As noted earlier, cancer stage is a universal predictor of the patient's overall prognosis. The cancer Surveillance, Epidemiology, and End Results (SEER) database tracks cancers in the US in a representative 26% of the population. In the year 2000, from the SEER database, 60% of breast cancer cases were diagnosed as localized disease with the cancer confined to the primary site; 33% were diagnosed as regional disease with spread beyond the primary site or into the local lymph nodes; and 5% were metastatic at diagnosis. The 5-year relative survival rate for localized disease was 98.3%; for regional disease, 83.5%; and for metastatic disease, 23.3%.[1] Older patients with breast cancer are more likely than younger patients to present with metastatic disease.[22]

Histology and Grade. Grade has been described earlier and represents a composite evaluation of the tumor's aggressiveness by histologic criteria. Grade is a well-established predictor of outcome.[11] Older patients tend to present with breast cancer with lower proliferative rates and lower incidence of lymphovascular invasion, both markers of less aggressive behavior.[12,55] Breast cancer may present with variable histologic patterns, and these histologic subtypes may have different clinical behavior. Approximately 75% of women with invasive breast carcinoma, a cancer of epithelial cell origin, have infiltrating ductal type carcinoma. Patients who have a component of invasive lobular carcinoma frequently present at a more advanced stage than those with purely infiltrating ductal carcinoma, and their tumors are more likely to be hormone-sensitive.[56]

Hormone Receptor Status. The expression of estrogen and progesterone receptors on the surface of breast cancer cells is both prognostic and predictive of response to hormonal therapy. Collectively, patients who are either

estrogen- and/or progesterone-receptor positive live longer than patients whose tumors are hormone receptor-negative. This association holds true after accounting for age, stage, histology, and other demographic variables. The association is also maintained in both older and younger women.[13] Tamoxifen is a selective estrogen receptor modulator (SERM) that is an estrogen receptor antagonist in breast tissue and an agonist in other tissues, including bone and uterus. Estrogen receptor (ER) status strongly predicts response to tamoxifen therapy, with a 31% reduction in the annual breast cancer death rate in ER-positive patients and no effect on patients with ER-negative disease.[14] For postmenopausal women, aromatase inhibitor therapy, either alone or given sequentially with tamoxifen, has been shown in multiple clinical trials to be superior to tamoxifen therapy alone.[57,58]

HER-2 Status. HER-2 is a transmembrane glycoprotein receptor of the epidermal growth factor receptor family. Approximately 18% to 20% of breast cancer patients overexpress the HER-2 protein. Older women are less likely to express HER-2 than younger women.[12] HER-2 expression predicted poor cause-specific survival in both older and younger women prior to the use of trastuzumab, an anti-HER-2 antibody.[59] The benefit of trastuzumab is confined to those patients with immunohistochemically confirmed overexpression of HER-2 or fluorescence in situ hybridization-confirmed elevated gene copy number of HER-2/neu.[15]

Overall Prognosis

The overall prognosis of elderly women with breast cancer is the net effect of the biology of the tumor and the efficacy and tolerability of therapy. The overall prognosis of older women has been reported in some studies to be comparable to the prognosis for younger women and in other studies to be worse than the prognosis for younger women.[23,60] Differences in receipt of adjuvant therapy likely contribute to these disparate results. In a study of 407 women aged 80 years or older who were treated during the 1990s, 12% received no therapy; 32%, tamoxifen only; 7%, breast-conserving therapy only; 33%, mastectomy; and 14%, breast-conserving therapy with adjuvant radiation therapy.[61] The 5-year breast cancer specific survival for these groups were 46%, 51%, 82%, and 90%, respectively. Age was strongly associated with less-aggressive treatment after controlling for tumor type, general health status, and comorbidities.

Adjuvant Therapies: Radiotherapy

Adjuvant radiotherapy may be used in two settings: after breast-conserving therapy and after mastectomy. A review of almost 50,000 women age 65 or older treated for breast cancer in the 1990s found that approximately 76% of the patients who had lumpectomies also had radiation therapy. Receipt of postlumpectomy radiation therapy was associated with later year of diagnosis, younger age, fewer comorbidities, nonrural residence, chemotherapy, white race, and no prior history of heart disease.[62] Older age has also been associated with longer delay between lumpectomy and radiation therapy.[63] In a randomized trial of 636 women older than 70 years with small, node-negative, ER-positive breast cancer who were assigned to either BCT with tamoxifen and radiotherapy or BCT with tamoxifen only, found that risk of local relapse was increased at 5 years, from 1% to 4% without radiation; however, survival was not significantly different between the groups.[53]

Adjuvant Therapies: Systemic

Chemotherapy. The National Comprehensive Cancer Network (NCCN) recommends adjuvant chemotherapy for all patients less than 70 years old with nodal involvement or with tumors larger than 1 cm.[51] The guidelines recommend consideration of chemotherapy for patients with tumors between 0.6 and 1 cm after evaluation of hormone receptor status, HER-2 status, and other unfavorable features including angiolymphatic invasion, high nuclear grade, or high histologic grade. Common chemotherapeutic drugs used include doxorubicin, cyclophosphamide, 5-fluorouracil, paclitaxel, and docetaxel. A meta-analysis of 194 randomized trials of adjuvant chemotherapy begun by 1990 found that anthracycline-containing compounds reduced the annual breast cancer death rate by 38% in patients younger than 50 years, and by 20% in patients aged 50 to 69.[14] Few patients older than 70 were included in these trials. Another meta-analysis established the survival benefit of adding a taxane to anthracycline chemotherapy, regardless of patient age.[64] In a dose-dependent fashion, anthracycline chemotherapy is associated with development of cardiomyopathy in elderly patients with hypertension.[43] In an effort to avoid the anthracycline toxicity, docetaxel and cyclophosphamide were compared to doxorubicin and cyclophosphamide for the treatment of early breast cancer. Sixteen percent of the trial participants were age 65 or older and, after 7 years of follow up, both disease-free survival and overall survival were better in the docetaxel/cyclophosphamide arm.[65]

In a single institution study of more than 1500 women aged 55 or older treated for breast cancer between 1997 and 2002, older age was a significant predictor of not receiving chemotherapy when indicated by guideline recommendations. This association remained after controlling for confounding factors such as stage, tumor characteristics, comorbidity score, and other demographic variables.[66] To assess the toxicity of chemotherapy for older patients in the community, one analysis of SEER-Medicare data from 1991 to 1996 found that the hospitalization rate for chemotherapy complications was 9%, which increased with increasing stage of cancer and increasing comorbidities, but did not differ by age

category.[27] An evaluation of data from four randomized trials of adjuvant therapy that compared a higher dose or more intense chemotherapy regimen with a lower dose or less intense regimen suggested that more chemotherapy was associated with longer disease-free and overall survival. There was no association between age and disease-free survival. Older patients had more non–breast cancer-related deaths.[67]

Molecularly Targeted Therapy. Trastuzumab, a monoclonal antibody against the HER-2/neu receptor, is recommended for use in patients with HER-2/neu overexpression or gene amplification and tumors larger than 2 centimeters or lymph node involvement who are receiving adjuvant chemotherapy.[51] The benefit of trastuzumab was established in a combined analysis of two randomized trials that demonstrated a 33% decreased risk of death among patients who received trastuzumab.[68] Trastuzumab is typically started either with or after chemotherapy and continued weekly to complete 1 year of therapy. Major toxicities of trastuzumab include cardiomyopathy, allergic infusion reactions, and variable pulmonary toxicities.[68] Data on the use of trastuzumab in elderly patients are limited, but suggest that efficacy and toxicity are similar in all age groups.[69,70]

Hormonal Therapy. The goal of hormonal therapy for breast cancer is to reduce estrogen stimulation of the tumor. Three major modalities are used to reduce estrogen stimulation: ovarian ablation, by oophorectomy, with radiation, or by chemical means with luteinizing hormone-releasing hormone (LHRH); estrogen receptor blockade by a partial agonist (tamoxifen); and blockade of peripheral estrogen production by an aromatase inhibitor, in women without functioning ovaries. A meta-analysis of the effects of hormonal therapy in randomized trials of more than 60,000 patients demonstrated that for estrogen receptor-positive breast cancer, tamoxifen therapy for 5 years reduced the annual breast cancer death rate by 31% over 15 years, irrespective of patient age.[14] Aromatase inhibitors (AIs) decrease conversion of androgen precursors into estrogens, and have been shown to be superior to adjuvant tamoxifen therapy in postmenopausal women in a number of large randomized trials.[57,71] AIs are less likely to cause venous thromboembolic events and endometrial cancer, but are more likely to result in arthralgias and accelerated bone loss. Aromatase inhibitors are now recommended by the NCCN as first-line hormonal therapy for postmenopausal women.[51] Subgroup analyses of the older patients in the aromatase inhibitor trials confirm that AIs have similar efficacy and toxicity in older and younger postmenopausal patients.[72] A review of more than 1500 breast cancer patients treated at MD Anderson Cancer Center between 1997 and 2002 noted that, after accounting for comorbidities and stage, among only patients with good performance status, in situations where guidelines recommended hormonal therapy, women aged 75 and older were 90% less likely to be treated with hormonal therapy than women aged 55 to 64.[66] Challenges to the effective use of adjuvant hormonal therapy include poor compliance and high cost.[73,74]

Decision Aids for Medical Therapy

Adjuvant! Online. The large amount of clinical and pathologic prognostic and predictive information is difficult to integrate into an overall assessment of prognosis for an individual patient. Adjuvant! Online is a program that synthesizes patient age, comorbidity, ER status, tumor grade, tumor size, and number of positive nodes to determine an overall risk of recurrence and death at 10 years.[75] The program has been validated in multiple cohorts.[76] The program also calculates the benefit of chemotherapy and hormonal therapy on the basis of data from large randomized trials. The results can be displayed in graphic form, printed, and given to the patient to help clarify the benefits of adjuvant therapy.

Oncotype. Traditionally, women with small, hormone-sensitive cancers have been most difficult to counsel regarding the risks and benefits of chemotherapy. Recently, a diagnostic tool has been developed, Oncotype DX, that quantifies the expression of 21 genes in a woman's tumor sample, and generates a numerical risk of distant recurrence assuming the patient were to take hormonal therapy alone.[77] The results characterize whether the patient has low, intermediate, or high risk of relapse, which corresponds to relapse rates of approximately 7%, 14%, and 31%, respectively. The results are independent of age. Retrospective studies show that tumors with high recurrence scores have a large benefit from chemotherapy and those with low recurrence scores have no benefit from chemotherapy.[78] Ongoing prospective studies are validating the predictive benefit of chemotherapy in patients with intermediate risk of metastatic recurrence

MammaPrint. The MammaPrint assay uses gene expression array technology on 70 genes to classify tumors as either good or poor prognosis. It was developed and validated on a cohort of women that included both hormone receptor negative and positive disease, as well as patients

CASE 8-1 CASE CONCLUSION

In preparation for discussion of the risks and benefits of adjuvant therapies, the patient's profile was entered into the Adjuvant! Program[75] (Fig 8-1). According to the Adjuvant! algorithm, approximately 42 patients out of one hundred patients with this profile who receive no therapy will be alive in 10 years. Twenty-nine patients are expected to die from causes other than cancer, and 29 patients are expected to die from cancer. Adding hormonal therapy would be expected to decrease the cancer related mortality by approximately 7%, and adding chemotherapy to that would be expected to decrease the cancer-related mortality by an additional 14%. The patient decided that she would pursue treatment with adjuvant chemotherapy, radiation therapy, and hormonal therapy.

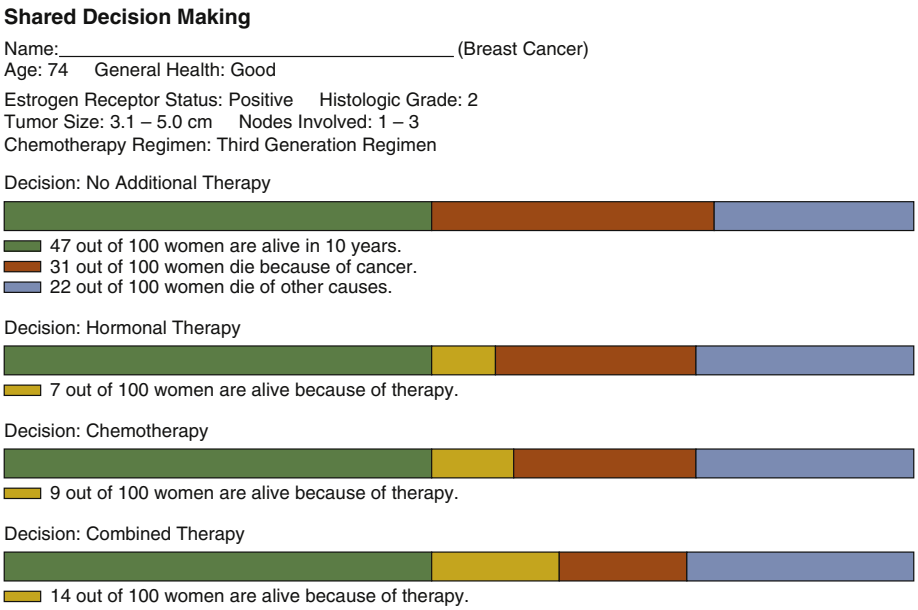

FIGURE 8-1 Breast Adjuvant Online Output. See Case 8.1.

with and without nodal involvement.[79] The MammaPrint Assay has also been validated in an older cohort (median age 62.5 years) of patients with node-negative breast cancer.[80] Prediction of response to chemotherapy is not known.

Summary

Decisions regarding adjuvant therapy for older patients with breast cancer are complex and involve consideration of all possible adjuvant options (radiation, chemotherapy, targeted therapy, and hormonal therapy). They must factor in the patient's priorities, medical conditions, functionality, and the likelihood of tumor recurrence. Therapy should not be withheld on the basis of chronological age alone.

Predictive and Prognostic Factors

Pathologic Stage. Colorectal cancers may spread by direct extension, or by hematogenous, or lymphatic routes.[81] Hematogenous dissemination from most of the colon typically follows the venous drainage to involve the liver prior to the lungs. A notable exception to this is distal rectal cancer which, because of venous drainage directly into the inferior vena cava, may metastasize to the lungs without involvement of the liver.[82] T stage in colon cancer is related to depth of invasion, without reference to the size of the mass. An evaluation of population outcomes in patients with colon cancer from the SEER database found 5-year stage-specific survival of 93.2% for stage I, 82.5% for stage II, 59.5% for stage III, and 8.1% for stage IV.[18] Number of nodes involved is an important prognostic factor.[83] Interestingly the number of nodes sampled in colon cancer surgery is also an important predictor of survival for patients with cancer in stages 1 to 3, with at least 12 nodes removed predicting a better overall survival.[84] Prognosis in colon cancer has been reported to be similar in older and younger patients.[85,86]

CASE 8-2 COLON CANCER

Case

A 76-year-old man with hyperlipidemia presents with black stool. On colonoscopy he is noted to have a 3 cm mass in the descending colon. The biopsy confirms adenocarcinoma.

Clinical Staging and Presurgical Evaluation

The patient's only comorbidities are hypercholesterolemia and hypertension. He takes atenolol and lovastatin. He lives with his wife of 18 years, retired 7 years ago from the U.S. Postal Service, and is an avid golfer. He routinely does the grocery shopping for the family. His weight is stable at 192 pounds and he is 72 inches tall. The comprehensive geriatric assessment suggests that his functional status, cognitive ability, nutritional status, and psychological profile are all adequate. The patient's laboratory analyses reveal a mild microcytic hypochromic anemia, and are otherwise normal. His CEA level is not elevated. CT scan of the chest, abdomen, and pelvis show no pathologic findings other than the mass in the descending colon.

Primary Therapy

The patient decides to proceed with hemicolectomy and lymph node dissection. Pathologic evaluation reveals an intermediate grade T3 (tumor invades through the muscularis into the subserosa), N2 (involvement of 4 or more lymph nodes) tumor, and the final stage is IIIC.

Grade and Tumor Features. Tumor grade also predicts outcome in patients with colorectal cancers.[16] Older patients present with high-grade tumors as frequently as do younger patients.[26] Additional features of the biopsy specimen, including vascular invasion,[87] lymphatic invasion,[88] and positive surgical margins are also prognostic indicators.[89,90]

Histology. More than 95% of all colon cancers are adenocarcinomas.[91] One histologic subtype, signet ring cell carcinoma, which represents only approximately 1% of all adenocarcinomas of the colon, is associated with poorer prognosis.[18,92]

Biochemical and Molecular Markers. Carcinoembryonic antigen is a glycoprotein that is overexpressed in adenocarcinoma relative to normal colon epithelial cells. Its function has not been completely elucidated, but localization on the cell surface and homology with other adhesion molecules suggests a role in cell-cell interactions.[93] DNA microsatellite instability is a marker of poor DNA mismatch repair. Microsatellite instability in tumor tissue is used to screen for the genetic defects that cause hereditary nonpolyposis colorectal cancer (HNPCC), and is also found in 10% to 15% of sporadic colon cancers. For reasons that are not entirely clear, low microsatellite instability (i.e., effective DNA mismatch repair) is associated with poor prognosis in sporadic colon cancer.[94] The relationship between microsatellite instability and age remains poorly defined.

The ras intracellular signaling molecule plays a key role in growth signaling transfer from cell surface epidermal growth factor receptors (EGFR) and nuclear DNA targets. Activating mutations of the K-ras can decrease cancer dependence on external stimuli via the EGFR.[95] Mutant K-ras has also been shown to be an important determinant of poor response to therapy with anti-EGFR antibodies in advanced colorectal cancer.[96]

Adjuvant Therapy

Chemotherapy. A benefit for chemotherapy (5-fluorouracil [5-FU] and leucovorin) over observation was first established in a pooled analysis of three randomized trials that demonstrated a 22% decrease in mortality associated with the receipt of chemotherapy in patients with stage III colon cancer.[97] Subsequently, the MOSAIC trial showed an absolute 5% disease-free survival advantage at 3 years for patients with stage III colon cancer who received adjuvant infusional 5-FU, leucovorin, and oxaliplatin (FOLFOX) relative to those who received 5-FU and leucovorin alone.[98] Patients in the FOLFOX arm experienced more neuropathy, hematologic, and gastrointestinal toxicity. Elderly patients are underrepresented in clinical trials, but both observational and subset analyses confirm the benefit of adjuvant chemotherapy in older patients.[9,99-101] Sargent and colleagues pooled elderly patient data from seven phase III trials of adjuvant 5-FU based therapy and found an overall survival benefit of 24% compared to no therapy in all age groups, including the 506 patients older than age 70.[9] A small prospective study reported increased, but tolerable, levels of neuropathy and neutropenia in patients aged 76 to 80 years old.[102] Similar benefit has been reported in multiple population-based studies.[100,103] An analysis of patients aged 65 or older in the SEER-Medicare database with stage III colon cancer reported that only 52% received adjuvant 5-FU; however, among those treated with 5-FU there was a 34% reduction in mortality.[99,104] The decision regarding the use and type of adjuvant chemotherapy is increasingly complicated with newer and often more toxic chemotherapy regimens.

Molecularly Targeted Therapy. Although bevacizumab is used in metastatic colon cancer,[105] no significant benefit for bevacizumab therapy was seen in a randomized trial of patients with early-stage colon cancer.

Decision Aids

As in breast cancer, the wealth of prognostic information from clinical, pathologic, and molecular features of each case is difficult to integrate into an adjuvant therapy benefit. The Adjuvant! program includes a prognosis and benefit estimator for colon cancer.[75] The colon cancer recurrence calculation incorporates patient age, gender, comorbidity, depth of invasion, grade, number of positive nodes, and number of examined nodes.

Recurrence Score. Early studies suggest that a recently validated 18 gene recurrence score may predict colon cancer recurrence and overall survival independent of mismatch repair, tumor grade, stage, lymphovascular invasion, and nodes examined.[106] The clinical implications of the recurrence score with regard to treatment benefits are unknown.

CASE 8-2 CASE CONTINUED

The Adjuvant! program estimates that for this patient who is in good health with a high T and N stage tumor that his likelihood of dying from cancer within the next 5 years is approximately 47% (Fig 8-2). The program estimates that using adjuvant 5-fluorouracil and oxaliplatin will reduce the likelihood of dying from the cancer by 17%. After discussion with his treating physicians and consideration of his independent performance of activities of daily living and ECOG performance status score of 0, as well as his strong desire to use all available therapy to maximize his chance of long-term survival, the patient decides that he would like to undergo treatment with adjuvant 5-FU and oxaliplatin.

Summary

Adjuvant therapy for colon cancer in the elderly should include consideration of stage, grade, CEA level, and anatomy; a geriatric assessment; and patient preference. Chemotherapy is the standard of care for patients with stage III colon cancer, but current regimens cause substantial toxicity for older and younger patients.

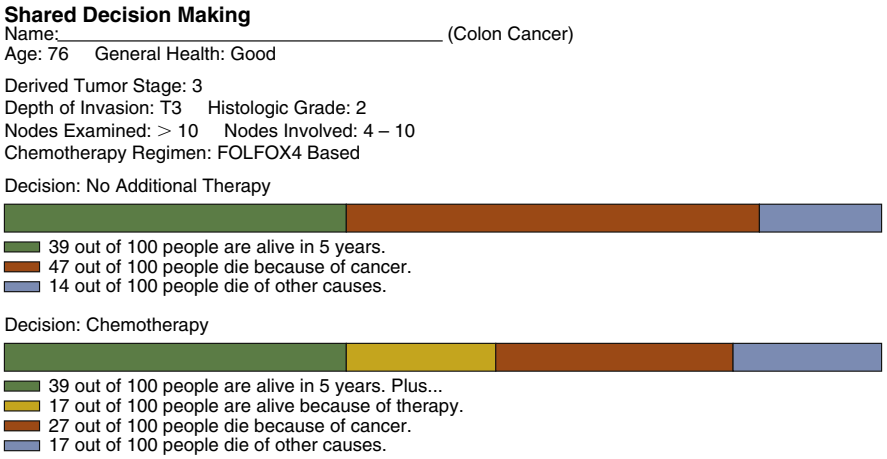

FIGURE 8-2 Colon Adjuvant Online Output. See Case 8.2.

LUNG CANCER

Lung cancer is broadly divided into small cell and non-small cell histologic types. In a recent review of the SEER database, the small cell lung cancers accounted for approximately 15% of all lung cancers, and incidence has been decreasing.[107] The histology, behavior, and therapy for these two types of lung cancer are significantly different. The section will focus on small cell type lung cancers.

CASE 8-3 CASE

A 68-year-old man with a 40 pack-year history of smoking is noted to have a 5 cm right upper lobe lung mass and enlarged right hilar nodes on a CT scan performed for evaluation of cough. Bronchoscopic biopsy reveals adenocarcinoma.

Clinical Staging and Pretherapy Evaluation

The patient reports that he has lost 10 pounds over the past 3 months. He stopped smoking 10 years ago and exercises three or four times weekly for 30 minutes to 1 hour. His medical history includes atrial fibrillation and an associated transient ischemic attack, for which he takes warfarin, and sciatic nerve pain for which he takes gabapentin. He has lived alone without assistance since his wife died of breast cancer in her 50s. He is active in the local senior center and spends about 2 hours there daily playing chess or exercising in the gym. He weighs 185 pounds, is 6 feet tall, and has a normal physical exam. The patient scores well on all components of the comprehensive geriatric assessment. Complete blood count, hepatic profile, and basic metabolic panels are within normal limits. Pulmonary function tests show no evidence of obstruction. Bronchoscopy is normal. PET/CT scan shows uptake in the mass and the right hilar nodes. Mediastinoscopy and biopsy confirms adenocarcinoma in the right hilar nodes, without evidence of mediastinal nodal involvement. MRI of the brain is normal.

Surgery

A randomized trial of lobectomy versus wedge resection reported significant increases in recurrence and death rates for patients treated with wedge resection.[108] Lobectomy or pneumonectomy are recommended by the NCCN as the standard of care for resectable non-small cell lung cancers; however, elderly patients are less likely to undergo curative surgery.[109,110] Studies on the outcomes of elderly patients after lung cancer resection have varied, with some studies reporting similar outcomes as younger patients,[111,112] and others reporting increased surgical mortality.[113]

CASE 8-3 CASE CONTINUED

The patient proceeded to right upper lobectomy and lymph node dissection. The final staging was T2 (tumor >3 cm and <7 cm), N1 (ipsilateral hilar nodes), M0, stage IIa.

Prognostic and Predictive Factors

Pathologic Stage. The AJCC staging system for lung cancer, updated in 2009, correlates well with prognosis, with 5-year overall survival ranging from 77% for small tumors without nodal spread to 2% for distantly metastatic disease.[104] Advancing age is associated with lower stage lung cancer at diagnosis.[21]

Histology. Adenocarcinoma and squamous cell carcinoma histologies comprise the majority of lung cancers, with similar histologic breakdown across age groups.[110] There is no clear consensus on the prognostic difference between the two predominant histologic subtypes.[114-116] Blood vessel invasion, however, is associated with a poor prognosis in multivariate analysis.[116]

Molecular Markers. A mutation of the epidermal growth factor receptor (EGFR) to a constitutively active form is an important predictor of response to EGFR inhibitors (i.e., gefitinib and erlotinib) in patients with metastatic cancer.[117] Studies suggested that patients older than 70 years may have similar rates of EGFR mutations to younger patients, and a similar response

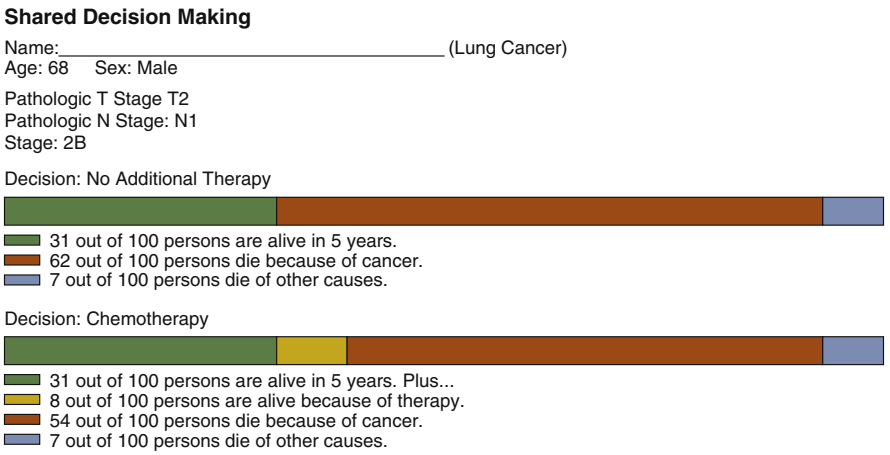

FIGURE 8-3 Lung Adjuvant Online Output. See Case 8.3.

to these therapies.[118] There is currently no proven role for molecularly targeted therapy in patients with limited-stage lung cancer. *RAS* is an oncogene whose protein serves to convey growth signals from surface receptors, including the EGFR, to the nucleus. Because the KRAS protein and EGFR are involved in the same oncogenic pathway, they are rarely mutated in the same patient's cancer. KRAS mutations predict nonresponsiveness to erlotinib.[119] Various studies have reported KRAS mutations to have either poor prognostic significance or no prognostic significance in different cohorts.[120,121] P53 is a tumor suppressor gene that is frequently mutated in lung cancer. P53 has been associated with worse prognosis and greater benefit from adjuvant therapy.[122]

Adjuvant Radiotherapy

A large French randomized trial failed to show a benefit to adjuvant radiation therapy following resection of an early-stage lung cancer.[123] A subsequent meta-analysis from 10 randomized trials confirmed this finding.[124] Survival and radiation toxicity in elderly patients were evaluated in a retrospective study of 1208 patients treated with thoracic radiation in trials of neoadjuvant, adjuvant, and definitive radiation.[125] There was no difference in survival or toxicity, including nausea, esophagitis, dyspnea, weakness, and performance status change, by age group.

Chemotherapy

A pooled analysis of five randomized trials showed that cisplatin in combination with another chemotherapy agent was associated with an 11% mortality reduction and a 5-year absolute survival benefit of 5.4%.[126] Several additional randomized trials have confirmed the benefit of adjuvant cisplatin.[127,128] Further analysis of these trials suggested that older patients received a decreased dose of chemotherapy, yet still had similar benefit relative to younger patients.[7] As mentioned previously, however, older patients are consistently underrepresented in clinical trials, and therefore the results are often not generalizable to the large population of patients diagnosed with lung cancer.[129]

Combined Therapy

There is little support for using adjuvant chemoradiotherapy in lung cancer. Two phase II trials have evaluated the potential utility of neoadjuvant radiation and chemotherapy in locally advanced disease with mediastinal nodal involvement.[130,131] Neither has shown a benefit to chemotherapy in combination with radiation therapy followed by surgery. A secondary analysis of a randomized trial of chemotherapy with either daily or twice daily radiation as definitive therapy for stage III lung cancer noted that patients older than 70 years experienced worse toxicity, including myelosuppression and pneumonitis, with combined therapy.[40]

Targeted Therapy

There is currently no role for molecularly targeted adjuvant therapy for non-small cell lung cancer

Decision Aids

Adjuvant! has a program available to calculate the benefit of chemotherapy in non-small cell lung cancer.[75] The variables used in the analysis include age, gender, number of comorbid conditions, T stage, and N stage.

CASE 8-3 CASE CONCLUSION

The patient has a discussion with his oncologist regarding the risk and benefits of adjuvant therapy (Fig 8-3). The patient understands that over 5 years he has an approximately 63% chance of dying from his cancer. He also understands that cisplatin combined with vinorelbine will likely decrease that likelihood by approximately 8%. He decides to have adjuvant cisplatin doublet chemotherapy.

Summary

Lung cancer is the number-one cause of cancer-related death. Smoking is the primary risk for lung cancer, and is also associated with comorbidities that can alter the benefits of therapy. Nonetheless, as with other cancers, elderly patients may benefit from surgery and standard adjuvant chemotherapy for lung cancer.[126] Further research is warranted to conclusively address the role of adjuvant chemotherapy in lung cancer in elderly patients.

CONCLUSION

Breast, colon, and lung cancers together will cause approximately one quarter of a million deaths in the United States in 2009. Adjuvant therapy with radiation, chemotherapy, hormonal therapy, and targeted agents offers the best chance of cure to patients diagnosed with localized disease. Elderly patients are often excluded from clinical trials, frequently have more comorbid medical illnesses, and can present with tumor characteristics that are different from those found in younger patients, all of which makes decisions regarding adjuvant therapy more challenging. Historically, older patients have been undertreated with adjuvant therapy. Prognostic and predictive features of the tumor, including stage, grade, lymphovascular invasion, and surface receptor expression should be evaluated, along with patient characteristics including a comprehensive geriatric assessment, performance status, and comorbid medical illnesses, to decide when to use adjuvant therapy for an individual patient. Validated decision aids including the Adjuvant! program and gene expression profiling can help integrate prognostic factors and stratify patients on the basis of risk of cancer recurrence.

See expertconsult.com for a complete list of references and web resources for this chapter

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CHAPTER

9

Chemotherapy

Sumanta Kumar Pal and Arti Hurria

Cancer and aging are related phenomena, as evidenced by the fact that 60% of cancer incidence and 70% of cancer-related mortality occurs in individuals older than 65.[1] Treatment of cancer in the older adult represents a multidisciplinary effort, frequently integrating medical oncologists, geriatricians, radiation oncologists, and surgeons. As chemotherapy is a commonly used anticancer strategy, collaboration between the former two groups is of critical importance. Physiologic changes that accompany aging may alter the tolerance of chemotherapy, and geriatricians, primary care providers, and medical oncologists may play a role in co-managing related side effects. There are two distinct scenarios in which chemotherapy is applied: (1) the metastatic setting, where the principal goals of treatment are maintenance of quality of life (QOL), prolongation of survival, and decreasing disease-related symptoms; and (2) the neoadjuvant and adjuvant setting, where the goals of treatment are to decrease the risk of disease relapse and disease-related mortality.

The decision to administer chemotherapy is always dependent upon the goals of treatment, as well as the potential risks and benefits to the patient. With these goals in mind, the decision is made to pursue a specific chemotherapy regimen. In the adjuvant setting, polychemotherapy regimens are delivered to eradicate residual microscopic disease through the use of multiple agents with distinct mechanisms of action. In the metastatic setting, the goal is to control disease while maintaining quality of life. The approach to metastatic disease varies on the basis of the disease one is treating. For example, in the setting of breast cancer, studies have demonstrated that combination chemotherapy in comparison to single-agent sequential therapy produces higher response rates but no difference in overall survival.[2-3] In contrast, even among adults older than 70, studies suggest that combination therapy represents a standard for metastatic lung cancer.[4] Patient-related factors, such as performance status, can also inform the decision between single-agent and combination therapy.[5] Numerous studies have also been performed across malignancies to optimize the dosing schedule of chemotherapy–notably, schedule may have a profound effect on efficacy.[6] In the older adult, where transportation and compliance are often key issues, the chemotherapy schedule is of even greater importance.

In this chapter, clinical vignettes (outlined in Table 9-1) are used to underscore general considerations for the use of chemotherapy in older adults.

CASE 9-1

G.R. is a 75-year-old man who presents to his primary care physician with persistent cough that has worsened over the course of 2 months. He is a nonsmoker, and has a past medical history notable only for mild hypertension, managed with a thiazide diuretic. A chest x-ray reveals multiple pulmonary nodules, up to 4 cm in size. He is referred to a medical oncologist, who orders further workup including imaging of the brain, chest, abdomen, and pelvis. CT of the chest reveals a 4 cm spiculated lesion in the right apex of the lung and several 1-2 cm lesions in the right lower, left lower, and left upper lobes. Other imaging studies show no evidence of distant disease. A CT-guided biopsy is performed of the 4 cm lesion in the right apex, and pathologic review of the specimen is consistent with non-small cell lung cancer, adenocarcinoma subtype. A biopsy is subsequently performed of a left lower lobe nodule, which confirms metastatic disease. The oncologist discusses with the patient the fact that the cancer is incurable and the goals of treatment are to prolong survival, minimize disease symptoms, and maintain quality of life. Ultimately, the patient elects to proceed with chemotherapy and receives a combined regimen of vinorelbine and gemcitabine. He visits his primary physician 1 week after his second cycle of therapy is completed and is neutropenic and febrile. He is admitted for IV antibiotics. Blood culture, urine culture, and chest x-ray finds no definitive source of the fever. Imaging of the chest after his second cycle suggests a response to treatment, with a decrease in size of all previously noted lesions.

DISCUSSION OF CASE 1

Older adults are largely underrepresented in oncology clinical trials, making it challenging in many scenarios to cite the benefit associated with chemotherapy within this demographic.[7] However, several datasets are emerging to allow for an evidence-based approach in this population. The benefits of chemotherapy and best supportive care in comparison to best supportive care alone were described in the Elderly Lung Cancer Vinorelbine Italian Study Group (ELVIS) trial.[8] In this study, 191 patients older than 70 with advanced non-small cell lung cancer were randomized to receive either best supportive care (BSC) or BSC along with vinorelbine chemotherapy.

TABLE 9-1 Overview of Case Discussions and Concepts

Case	Malignancy	Chemotherapy	Considerations in the Older Adult
1	Lung cancer	Vinorelbine Gemcitabine	Use of systemic therapy in advanced non-small cell lung cancer Myelosuppression related to vinorelbine and gemcitabine Use of growth factor support
2	Breast cancer	Doxorubicin Cyclophosphamide	Benefit of adjuvant breast cancer therapy Risk of congestive heart failure with doxorubicin and cyclophosphamide
3	Ovarian cancer	Cisplatin Paclitaxel	Neuropathy related to cisplatin and paclitaxel Characterization of renal function Physiologic changes with age
4	Colon cancer	5-Fluorouracil Irinotecan	Management of diarrhea related to 5-fluorouracil and irinotecan
5	Breast cancer	Capecitabine	Polypharmacy/Drug interactions Hand-foot syndrome related to capecitabine

Patients receiving vinorelbine therapy were more likely to survive to one year (32% versus 14%). Toxicities commonly seen with vinorelbine (including neutropenia, anemia, constipation, and fatigue) were more frequent in the treatment group. Nonetheless, patients receiving vinorelbine were less likely to develop symptoms related to lung cancer and had less pain.

Once a decision to receive chemotherapy is made, then the specific regimen needs to be determined, as well as the decision of whether to give monochemotherapy or polychemotherapy. Prospective randomized trials reveal conflicting data. One prospective study randomized 120 patients aged 70 or older with advanced non-small cell lung cancer to either vinorelbine alone or gemcitabine with vinorelbine.[9] Combination chemotherapy resulted in superior median survival (29 weeks versus 18 weeks, $P < 0.01$). However, these results were not replicated in a much larger study. In the Multicenter Italian Lung Cancer in the Elderly Study (MILES), the combination of gemcitabine and vinorelbine was compared to vinorelbine or gemcitabine alone in 698 patients older than 70 with non-small cell lung cancer.[10] The study results demonstrated that combination chemotherapy did not improve survival as compared to use of a single agent. Furthermore, combination therapy led to increased rates of neutropenia, thrombocytopenia, vomiting, and fatigue. Notably, the side-effect profiles of gemcitabine and vinorelbine are slightly overlapping; as with vinorelbine, gemcitabine can lead to neutropenia, anemia and fatigue.

While the MILES study heralds caution for the combination of gemcitabine and vinorelbine, recent data from French Thoracic Oncology Intergroup trial 0501 (IFCT-0501) point to the potential efficacy of a distinct doublet regimen.[4] In this phase III study, 451 patients between the ages of 70 and 89 were randomized to receive single-agent therapy (with either vinorelbine or gemcitabine), or monthly carboplatin with weekly paclitaxel. The Eastern Cooperative Oncology Group (ECOG) performance status (a clinical tool used to grade the generalized functional status of a cancer patient; Table 9-2) ranged between 0 and 2. Toxicities of both carboplatin and paclitaxel are described in detail subsequently (Case 9-3), and the doublet did elicit more hematologic toxicity than single-agent therapy. However, unlike the MILES study, significantly longer survival was observed in those patients who received doublet therapy as compared to a single agent. Thus, emerging data suggest the benefit of combination therapy among patients with good performance status.

TABLE 9-2 The Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

ECOG Performance Status	Description
0	Fully active and able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Active more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Confined to bed or chair.
5	Dead

Recognizing the toxicity profile of chemotherapeutic agents allows for preemptive strategies to mitigate adverse effects. Given that both vinorelbine and gemcitabine are known to cause myelosuppression, growth factors could be used to decrease the risk of neutropenia and associated neutropenic sepsis. Several guidelines

incorporate age-based risk stratification to aid the practitioner in appropriate use of growth factor therapy.[11] In the current scenario, given the occurrence of neutropenic fever after the first cycle of chemotherapy, growth factors are recommended with any further use of the same regimen. Neutropenic fever should be recognized by the practitioner as an oncologic emergency; prompt administration of empiric antibiotic therapy and relevant clinical examinations (including, but not limited to, blood cultures, chest x-ray, and urine culture/analysis) are essential.

CASE 9-2

A.L. is a 70-year-old woman with a history of mild hypertension and hypercholesterolemia, well-controlled with metoprolol and lovastatin, respectively. On a recent visit to her primary physician, she pointed out a lump in her right breast, which was biopsied and which revealed the presence of invasive ductal cancer. She had a lumpectomy and a sentinel node biopsy, which revealed cancerous involvement of an axillary node. An axillary dissection was performed. On pathologic analysis, the patient was found to have a 4.5 cm invasive breast cancer (hormone receptor-positive, HER-2 negative) with 5 out of 12 lymph nodes examined involving tumor. A staging work-up revealed no evidence of metastatic disease. After visiting with her oncologist, she elects to receive adjuvant chemotherapy to decrease the risk of relapse and mortality from breast cancer. She receives doxorubicin and cyclophosphamide. After two cycles of therapy, she presents to her primary physician for a routine follow-up appointment. There, she notes having increasing shortness of breath and dyspnea on exertion. On physical examination, she is noted to have increased jugular venous distension and 2+ pitting edema in her lower extremities, bilaterally. Fine crackles are auscultated on pulmonary exam.

DISCUSSION OF CASE 2

The patient described in this scenario has early stage (nonmetastatic) breast cancer; however, she has several risk factors placing her at a high risk of distant spread of the tumor, including lymph node positivity and tumor size. Adjuvant chemotherapy is given to decrease the risk of distant spread. In order to determine the magnitude of benefit from adjuvant chemotherapy, oncologists often turn to the Oxford Overview, a comprehensive meta-analysis of randomized trials of adjuvant chemotherapy in the setting of breast cancer.[12] This landmark meta-analysis includes data from 33,000 patients enrolled in 194 randomized clinical trials. Across all strata of age, there is a clinical benefit from use of multiagent adjuvant chemotherapy; however, the proportional benefit declines steadily with age. Limitations of these data include the low proportion of older adults included in randomized clinical trials (less than 7% older than 70 years); therefore, the authors acknowledge that there are too few women older than 70 to be reliably informative as to whether it confers a survival benefit. However, over the past decade two prospective trials have been reported in older adults with breast cancer that have improved our evidence base. The French Adjuvant Study Group (FASG) 08 trial suggested that the combination of epirubicin and tamoxifen (as compared to tamoxifen alone) could delay recurrence of breast cancer in women older than 65 years with operable, node-positive disease.[13] A more recent trial, Cancer and Leukemia Group B (CALGB) 49907, examined whether single-agent oral chemotherapy (capecitabine) could be used in place of standard, multiagent infusional regimens in patients older than 65 years with early-stage breast cancer.[14] A survival advantage was found with use of standard polychemotherapy infusional regimens, suggesting this remains the standard of care.

Once the decision in Case 9-2 is made to proceed with adjuvant chemotherapy, the patient embarks on a regimen of doxorubicin and cyclophosphamide and develops clinical stigmata of congestive heart failure (CHF) shortly thereafter. The association between doxorubicin and CHF is well-documented, with a higher incidence of CHF at greater cumulative doses of doxorubicin.[15] The association between increasing age and anthracycline-associated cardiac toxicity was evaluated in an analysis of 630 patients treated with doxorubicin, which demonstrated that increasing age was a risk factor for doxorubicin-associated CHF at cumulative doses greater than 400 mg/m.2[16] A SEER-Medicare analysis including patients with early breast cancer found that breast cancer survivors who had received an anthracycline-containing regimen had an increased risk of congestive heart failure in comparison to those who had not received an anthracycline or those who had not received adjuvant chemotherapy. Interestingly, this difference was most pronounced among women who were treated at ages 66 to 70, and was not observed in patients ages 71 to 90.[17] This SEER-Medicare analysis identified several other important predictors of cardiac toxicity in older women, including the presence of hypertension, diabetes, or peripheral vascular disease. In contrast, a longitudinal cardiac assessment of patients enrolled in Southwest Oncology Group (SWOG) trial 8897 (comparing adjuvant chemotherapy for breast cancer with or without doxorubicin) suggested no significant deterioration in left ventricular ejection fraction (LVEF) over time with anthracycline therapy.[18] The collective results of these studies can be incorporated into discussions with older patients considering anthracycline-based regimens. Furthermore, they may prompt a heightened awareness of potential cardiac toxicities in older adults and/or patients with specific comorbidities receiving these therapies.

Nonanthracycline alternatives to doxorubicin-cyclophosphamide adjuvant therapy are being studied. For instance, a randomized study (U.S. Oncology Trial 9735) compared doxorubicin-cyclophosphamide to docetaxel-cyclophosphamide (both regimens prescribed every 3 weeks for four cycles).[19] In this study, superior

disease-free and overall survival was observed with docetaxel-cyclophosphamide, and an update of these data suggested similar efficacy in older and younger patients. Among patients with HER-2-overexpressing breast cancer, the addition of the monoclonal antibody trastuzumab to conventional chemotherapy has shown immense clinical benefit in the metastatic and adjuvant setting.[20] In the adjuvant setting, both anthracycline and nonanthracycline-containing regimens have been explored in combination with trastuzumab. A clinical trial compared adjuvant doxorubicin-cyclophosphamide followed by paclitaxel with or without trastuzumab to docetaxel, carboplatin, and trastuzumab.[21] Notably, both trastuzumab-based regimens produced similar disease-free and overall survival, although patients receiving doxorubicin-cyclophosphamide had a numerically higher incidence of congestive heart failure. As a result of these data, there is increasing interest in studying nonanthracycline chemotherapy regimens in combination with trastuzumab, particularly for patients with cardiac comorbidity.

CASE 9-3

G.M. is an 80-year-old woman with multiple medical comorbidities (including hypertension, hypercholesterolemia, mild renal insufficiency, and diabetes) who reports several months of abdominal bloating and cramping, unrelieved with laxative use. On pelvic examination, she is noted to have some mild adnexal tenderness. Pelvic ultrasound reveals bilateral ovarian masses, both measuring 8 cm. She is subsequently taken to the operating suite for a total abdominal hysterectomy and bilateral salpingo-oophorectomy, and receives several omental biopsies and pelvic washings. On final pathologic analysis, she is found to have epithelial ovarian cancer, grade 2, and has stage II disease (i.e., confined to the bilateral ovaries). She meets with an oncologist, who recommends that she receive six cycles of intravenous carboplatin and paclitaxel chemotherapy. She begins treatment, and visits her primary physician for a routine follow-up after receiving three cycles of therapy. She notes having decreased sensation in her toes, and on pinprick examination, she appears to have decreased tactile sensation. Her neurologic exam is otherwise unremarkable. Her glycated hemoglobin level is within normal limits.

DISCUSSION OF CASE 3

In Case 9-3, it is prudent to consider the patient's comorbidities in the context of her current complaints. Given a clinical history including diabetes, ruling out any metabolic disturbances is critical. Paclitaxel and related taxane compounds are coadministered with steroids to prevent hypersensitivity reactions, and this may contribute to impaired glycemic control and worsening of diabetic neuropathy. Alternatively, the neuropathy could be a direct consequence of paclitaxel, which inhibits microtubule depolymerization and results in direct axonal injury.[22]

The patient described in this case also has mild renal impairment. While renal impairment can certainly be associated with hypertension and diabetes, there is also an anticipated decrement in renal function with increasing age. Increasing age is paralleled by a decrease in renal blood flow, and a decrease in glomerular filtration rate of 0.75 mL/min per year is observed in most individuals older than 40.[23-24] Care should be taken to use appropriate metrics to estimate renal function in the older adult. Formulas such as the Cockcroft-Gault and Jeliffe equations were validated primarily in cohorts of younger patients without renal disease.[25-26] In contrast, formulas such as the Modification of Diet in Renal Disease (MDRD) equation incorporate age, and may therefore be more accurate in estimating renal function in this population.[27-28] Precise calculation of the creatinine clearance is particularly important in the setting of carboplatin therapy, as the drug is dosed in a manner distinct from most other chemotherapeutic agents. Specifically, the dosing of carboplatin is calculated by multiplication of the creatinine clearance and the area under the concentration-time curve (AUC).

Outside of declines in renal function, multiple other physiologic changes accompany increasing age. Gastrointestinal absorption of oral agents may be compromised by decreased splanchnic blood flow, decreased secretion of digestive enzymes, and mucosal atrophy.[29-30] Furthermore, hepatic metabolism may be affected by decreased levels of cytochrome P450.[31-32] Alterations in endocrine axes, impaired cardiac function, and decreased bone marrow reserve may further affect the tolerance for chemotherapy in the older adult.[24] Physiologic changes seen with aging may lead to intrinsic differences in pharmacokinetic profiles of chemotherapeutic agents in an older population. For instance, a study assessing paclitaxel (given at a standard dose every 3 weeks) demonstrated decreasing drug clearance with increasing age, and a concomitant increase

CASE 9-4

C.H. is a 72-year-old man who visits his primary physician for follow-up of hypertension. He is otherwise healthy, is still working as a concert pianist, and his only complaint on this visit is a decrease in stool caliber and increasing constipation. Physical examination is normal, but as it has been approximately 5 years since his last colonoscopy, he is referred to a gastroenterologist for repeat examination. Colonoscopy reveals a mass in the mid-sigmoid colon, and biopsy reveals colonic adenocarcinoma. A staging evaluation includes a CT scan of the chest, abdomen and pelvis, which reveals several lesions within the liver. After a colorectal surgeon suggests that the liver lesions are not resectable, only the colonic tumor is resected. Four weeks later, he is seen by a medical oncologist who wishes to initiate chemotherapy with a combination of infusional 5-fluorouracil (5-FU) and oxaliplatin. However, given his occupation, the patient is particularly concerned about the potential for neuropathy with oxaliplatin, and ultimately elects to receive 5-FU with irinotecan. Two months later, at a routine follow-up visit for hypertension, he notes having six to eight episodes of diarrhea daily.

TABLE 9-3 Selected Studies Assessing Pharmacokinetics of Standard Chemotherapeutic Agents

Dosing Regimen	Pharmacokinetic Changes	Toxicity in Older Adults
5-Fluorouracil[38]	Clearance: ↔ with age; ↓ in female gender	Not reported
Capecitabine[49]	Clearance:↔ with age	Not reported
Docetaxel weekly[50]	Clearance: ↔ with age	Not reported
Docetaxel every 3 weeks[51]	Clearance: ↔	Severe neutropenia ↑ with age
Doxorubicin[52]	Clearance: ↓ with age	Not reported
Etoposide[53]	Clearance: ↔ with age	Moderate to severe neutropenia ↑ with age
Methotrexate[54]	Clearance: ↓ with age; ↑ with ↑ CrCl	Not reported
Oxaliplatin[55]	Clearance: ↔ with age; ↑ with ↑ GFR	Toxicity ↔ with age
Paclitaxel every 3 weeks[56]	Clearance: ↓	Moderate to severe neutropenia ↑ with age
Paclitaxel weekly[34]	Clearance: ↓ with age	Not reported
Temozolomide[57]	Clearance: ↔ with age	Neutropenia and thrombocytopenia ↑ in older women
Vinorelbine weekly[58]	Clearance: ↓ with age	Anemia and neutropenia ↑ with ↑ AUC
Vinorelbine every 3 weeks[59]	Clearance: ↔	Not reported

(Note: ↑ = increased, ↔ = unchanged, and ↓ = decreased.)
CrCl, creatinine clearance; GFR, glomerular filtration rate; AUC, area under the concentration-time curve

in the frequency of severe neutropenia.[33] Several other studies have assessed age-related changes in paclitaxel pharmacokinetics with age.[34-37] Table 9-3 summarizes these studies and others, which provide important insights into appropriate dosing of chemotherapy in older adults.

DISCUSSION OF CASE 4

Diarrhea is a side effect associated with multiple chemotherapeutic agents, including both 5-FU and irinotecan. 5-FU is an antimetabolite that can be administered in one of two schedules. When given as a bolus, the agent frequently results in myelosuppression. In contrast, when given on an infusional schedule, the dose-limiting toxicity of 5-FU is diarrhea. The pharmacokinetic properties of 5-FU have been studied extensively. In a cohort of 380 patients ranging in age from 25 to 91, it did not appear that clearance of 5-FU varied with age.[38] Separate studies have shown no difference in 5-FU toxicity or efficacy on the basis of age.[39-40]

Diarrhea is also associated with irinotecan, a topoisomerase I inhibitor, and may be either acute or delayed in onset. Acute diarrhea, caused by a cholinergic response to the drug, occurs during or within hours of treatment. In addition, a delayed-onset diarrhea often ensues 4 to 7 days after administration of irinotecan. Similar to studies of 5-FU therapy, a combined analysis of four clinical trials examined irinotecan-based chemotherapy regimens for colorectal cancer identified no difference in the risk of toxicity in comparing patients older or younger than 70.[41] In managing chemotherapy-related diarrhea, several pharmacologic strategies exist. Agents such as atropine may mitigate acute-onset diarrhea associated with irinotecan. For the later-onset diarrhea seen with infusional 5-FU, irinotecan, and various other agents, the practitioner may consider loperamide as an initial strategy. As the older adult may be more sensitive to changes in volume status, these symptoms should be followed closely with a low threshold for administration of intravenous fluids.[42]

CASE 9-5

J.R. is a 73-year-old woman who presents for follow-up evaluation of hypercholesterolemia, diabetes, and management of anticoagulation. With respect to the latter, she underwent valve replacement surgery 3 years ago for severe, symptomatic aortic stenosis, and has been maintained on warfarin since that time. Her medical history is also notable for stage II breast cancer diagnosed 6 years ago. On liver function tests, it is noted that she has a dramatically elevated alkaline phosphatase level, and transaminases are also elevated. The dose of her HMG-CoA reductase inhibitor has not been changed in several months; therefore a right-upper quadrant ultrasound is ordered for further evaluation. The study reveals multiple hypodense lesions in both lobes of the liver. Further CT evaluation of the chest, abdomen, and pelvis shows diffuse changes in the liver, suspicious for malignancy. CT-guided biopsy is performed, and pathologic analysis is consistent with metastatic breast cancer that is estrogen receptor-negative and HER-2-negative, consistent with the original tumor. The patient is referred to a medical oncologist, who initiates single-agent chemotherapy with oral capecitabine. Three weeks later, she presents for routine follow-up with a complaint of severe epistaxis, in addition to redness and burning overlying the palms of her hands and soles of her feet. A complete blood count is normal, but her INR is elevated to 5.0.

DISCUSSION OF CASE 5

Polypharmacy is a frequently encountered issue amongst older adults with cancer, increasing the risk for potential drug interactions.[43] In Case 9-5, the patient is concomitantly using warfarin and the oral prodrug capecitabine (converted systemically to the active metabolite, 5-FU). Pharmacokinetic interaction between these agents has been previously documented.[44] With cotreatment, the elimination half-life of warfarin increases by 51%, and the AUC increases by 57%. In a series of 21 patients with colorectal cancer taking this combination of medications, 30% of patients developed an INR greater than 3.0.[45] Furthermore, one third of the patients assessed experienced

TABLE 9-4 Examples of Interactions between Standard Chemotherapeutic Agents and Commonly Prescribed Drugs

Chemotherapy	Commonly Prescribed Agent	Nature of Interaction
Capecitabine	Warfarin	Use of capecitabine with warfarin can lead to a prolonged prothrombin time.[60]
Etoposide	Glucosamine	Glucosamine may induce a relative resistance to etoposide and other topoisomerase II inhibitors, such as doxorubicin.[61]
Irinotecan	Phenytoin	Doses of phenytoin may need to be increased when irinotecan is administered concomitantly.[62]
Methotrexate	Amoxicillin	Penicillins may interfere with the renal tubular secretion of methotrexate, leading to increased methotrexate levels and consequent toxicity.[63]
Vinorelbine	Clarithromycin	Coadministration may lead to increased vinorelbine exposure and myelotoxicity.[64]

a clinically significant bleeding episode. Thus, in the scenario described, more vigilant monitoring of the INR and titration of the warfarin dose accordingly may have been warranted. Numerous potential interactions exist between standard chemotherapeutic agents and commonly used drugs; although not intended to be a comprehensive list, several of these interactions are listed in Table 9-4.

In addition to the bleeding diathesis, the patient in Case 9-5 also has redness and burning overlying the palms of her hands and soles of her feet. The latter symptoms are referred to as hand-foot syndrome, or palmoplantar erythrodysesthesia. This side effect is frequently encountered with capecitabine, as well as with several new inhibitors of angiogenesis used in anticancer therapy (i.e., sorafenib). Although no uniform guidelines exist for management of this syndrome, it has been suggested that emollients may be helpful in palliating associated pain.[46] In more severe forms of hand-foot syndrome, sloughing of the skin may be observed, and secondary infection may occur. As such, progression of hand-foot syndrome should be closely monitored. Toxicities should be reported immediately to the primary oncologist, so that dose reductions can be used when appropriate. Importantly, use of a lower dose of capecitabine has been assessed prospectively in a cohort of adults older than 70 years with metastatic breast cancer.[47] This lowered dose of capecitabine may ameliorate some of the adverse effects associated with capecitabine (including hand-foot syndrome), but appears to have preserved efficacy.

CONCLUSIONS

The current chapter is intended to provide the reader with an overview of general considerations surrounding the use of chemotherapy in the older adult. As the cases suggest, the practitioner is faced with a plethora of issues, beginning with the decision of whether to administer chemotherapy. Beyond this and the initial selection of treatment, an emerging literature may aid both the geriatrician and oncologist in recognizing toxicities related to chemotherapy. These age-specific studies frequently use a cutoff in the range of 65 to 70 years to define a population of older adults. As the field of geriatric oncology moves forward, there is increasing recognition that chronologic age alone is not sufficient in characterizing older adults. Available guidelines advocate the use of clinical metrics to risk-stratify the older adult, such as the comprehensive geriatric assessment (CGA).[37] The CGA is currently being evaluated prospectively in trials conducted by the CALGB cooperative group.[48] More extensive use of these tools, which attempt to distinguish chronologic and physiologic age, may identify subpopulations of older adults who may yield particular benefit from chemotherapy.

See expertconsult.com for a complete list of references and web resources for this chapter

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CHAPTER

10

Novel and Targeted Therapies

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CASE 10-1

A highly functional 83-year-old woman with early-stage breast cancer presents for follow-up. She has a history of controlled hypertension, and had coronary artery stents placed 3 years ago after an episode of unstable angina. Three months ago, routine mammography revealed a calcified lesion in her left breast. She underwent a biopsy that revealed invasive ductal adenocarcinoma. She had a lumpectomy and sentinel lymph node dissection, which revealed adenocarcinoma in 0 of 3 sentinel lymph nodes. On review of the pathology, her tumor was 1.3 cm, estrogen receptor (ER) positive, progesterone receptor (PR) positive, HER-2 positive, high nuclear grade, and moderately well-differentiated. She has no family history of breast cancer. She received radiation therapy to her left breast and is now ready to begin adjuvant treatment with an aromatase inhibitor and possibly trastuzumab. Cardiac evaluation consisted of an electrocardiogram showing nonspecific ST-T wave changes and an echocardiogram revealing an ejection fraction of 42% with segmental left ventricular wall motion abnormalities and mild mitral regurgitation. She is given a prescription for a 30-day supply of letrozole along with calcium and vitamin D supplements. It was decided to defer trastuzumab therapy because of the cardiac abnormalities. Three weeks later, she calls stating that she is completely out of medication. The pharmacy insists that she was given the correct number of pills. The patient uses a pill box which she herself fills weekly with her seven daily medications for hypertension, hypercholesterolemia, and hypothyroidism. It is unclear where the error occurred but there is significant concern that the patient may have consumed extra doses of the letrozole.

CASE 10-2

A 78-year-old man presented to his primary care physician complaining of weakness and fatigue. His physical examination was unremarkable except for guaiac-positive stools. The patient was referred for his first colonoscopy and was found to have a cecal mass; the biopsy showed adenocarcinoma. A CT scan revealed extensive pulmonary and liver metastases. His hemoglobin level was 8.9 gm/dL, with a ferritin level of 5 ng/mL. Past medical history was significant for hypertension. The patient had been hospitalized for a transient ischemic attack 3 months ago, which caused transient dysarthria. He is currently on aspirin. Because of extensive disease, he was started on systemic chemotherapy with FOLFOX (fluorouracil, leucovorin, oxaliplatin) and supplemental iron. Bevacizumab was deferred due to his recent arterial thrombotic event and hypertension.

Cancer is a disease of older adults, with approximately 60% of cancer diagnoses and 70% of cancer mortality occurring in individuals age 65 and older. As the population ages and life expectancy increases, there are more elderly adults with cancer and several unique challenges arise in caring for them. Specifically, the physiological changes associated with aging can affect the pharmacokinetics and pharmacodynamics of cancer therapies. Because the clinical trials that set the standards for oncology care have typically underrepresented the elderly and focused on a younger patient population,[1,2] the effects of age-related changes on drug dosing and tolerance have been understudied. In this chapter, the means by which these age-related changes may affect the safety, tolerability, and efficacy of novel and targeted therapies in the elderly will be reviewed. The challenges of polypharmacy and nonadherence in this population will also be explored. Finally, existing evidence regarding the safety and efficacy of targeted agents in elderly cancer patients will be discussed.

PHYSIOLOGIC CHANGES WITH AGING

While aging is a heterogeneous process, there are some characteristic changes in physiology and organ function that can have an impact on the pharmacology and toxicity of anticancer therapy. Several reviews discuss the pharmacology of chemotherapy in older patients,[3-5] and some of the key physiologic changes that occur with aging that may affect the pharmacokinetics and pharmacodynamics of anticancer therapies will be summarized (Table 10-1).

Renal Function

With increasing age, there is a decrease in renal mass and renal blood flow. While serum creatinine is often used to approximate renal function in younger adults, it is a poor indicator of renal function in older adults because of a decrease in muscle mass with age.[6] On average, the glomerular filtration rate decreases by approximately 0.75 mL/min/year after age 40. However, this decrease is not universal and approximately one third of all patients will have no change in creatinine clearance with age.[7] There

TABLE 10-1 Physiologic Changes with Aging

Organ/System	Physiologic Change
Renal	Decreased creatinine clearance
Gastrointestinal	
• Decreased hepatic mass/ p450 system	Alterations in metabolism
• Mucosal atrophy	Decreased absorption
• Decreased secretion of digestive enzymes	Decreased absorption
• Decreased splanchnic blood flow	Decreased absorption
• Decreased gastric motility	Decreased absorption
Bone marrow	
• Anemia	Increased volume of distribution with hemoglobin-bound drugs
• Increased fat content	Decreased reserve
Body composition	
• Increased body fat	Increased volume of distribution for lipid soluble drugs
• Decreased body water	Decreased volume of distribution for water soluble drugs

are several equations that have been used to estimate glomerular filtration rate. The Cockcroft/Gault and Jeliffe formulas have primarily been validated in younger patients without renal diease.[8,9] For elderly patients with a glomerular filtration rate over 50mL/min, the Wright formula is more accurate.[10] For those with chronic renal disease, the modification of diet in renal disease (MDRD) formula is more accurate, as it takes into account age, sex, ethnicity, serum creatinine, blood urea nitrogen, and albumin.[11]

Absorption and Metabolism

As people age, they experience a decrease in splanchnic blood flow, gastrointestinal motility, and secretion of digestive enzymes, all of which, along with the mucosal atrophy that occurs with age, can alter drug absorption. In addition, hepatic mass and cytochrome P450 content decrease with increasing age. However, the consequences of these changes remain controversial.[12] As a result of changes in body composition involving an increase in body fat and decrease in total body water, the volume of distribution for drugs that are lipid-soluble increases and the volume of distribution decreases for water-soluble drugs. Many drugs are bound to albumin and, as a result, hypoalbuminemia can increase the volume of distribution of their bound drugs.

Bone Marrow

Bone marrow fat increases and bone marrow reserve decreases with increasing age. This decrease in reserve places older adults at increased risk for myelosuppressive complications from chemotherapy.[13] The American Society of Clinical Oncology (ASCO) recommends primary prophylaxis with white blood cell growth factors for the prevention of febrile neutropenia in patients older than 65.[14] ASCO had suggested use of erythropoietin-stimulating agents. However, their use will be limited because of recent data and FDA recommendations (http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm109375.htm).[15] In addition, many drugs are bound to hemoglobin; anemia can therefore increase the volume of distribution of drugs, which in turn alters their metabolism.[5,16]

POLYPHARMACY

Polypharmacy means "many drugs" and is used to describe the use of more medication than is clinically indicated or warranted. While people older than 65 years represent approximately 15% of the population, they account for more than one third of all prescription drugs taken and an even larger percentage of nonprescription drugs. This often unnecessary use of many drugs can produce noxious results such as adverse drug reactions and drug-drug interactions and can lead to increased emergency room visits, hospitalizations, and nursing home admissions.[17] A recent drug evaluation reported that three medications accounted for about one third of emergency department visits for adverse drug events in older adults: warfarin (17.3%), insulin (13.0%), and digoxin (3.2%).[18] In addition, the elderly cancer patient often needs medications prescribed to treat possible side effects of other drugs.

NONADHERENCE

Adherence is defined by the World Health Organization (WHO) as the extent to which a person's behavior corresponds with agreed-upon recommendations from a health care provider. Issues related to adherence are not well understood, and it is difficult to measure accurately. Generally, clinicians assume that patients are taking medications as prescribed and believe their patients when they say they are doing so.[19] However, many studies have shown poor adherence with medications that have proven benefit when taken appropriately. A patient's choice to follow the clinician's advice is influenced by his or her assessment of risks and benefits.[19] Some of the major risk factors for poor adherence include cognitive impairment, treatment of asymptomatic disease, inadequate follow-up, poor provider-patient relationship, adverse effects of medications, and patient's lack of belief in the benefit of treatment.[20] Poor adherence has long been acknowledged as an obstacle in improving patient care. With the recently passed health care legislation reform, there is a desire to create an infrastructure for improving health outcomes through improved adherence.[21]

As many of the new anticancer targeted therapies are administered orally, they can be taken at home, eliminating the need for intravenous access; however, this shifts

many of the responsibilities of managing the regimen from the oncologist to the patient. Even in clinical trials, a context in which the patients are highly motivated and receive extra supervision, adherence is quite variable, ranging from 20% to100%.[19] In addition, a study of anastrozole therapy adherence in early-stage breast cancer reported that approximately one in four women was not optimally adherent.[19] In 2009, at the San Antonio Breast Cancer Symposium, data from the British Columbia Cancer Agency, Vancouver, BC, Canada, were presented showing that only 40% of their population, all of whom receive medications free of charge, was compliant with hormonal therapy.

Despite the impressive efficacy of imatinib for chronic myelogenous leukemia (CML), treatment failure and suboptimal responses are seen and may be due to poor adherence.[22] From a study in Belgium evaluating imatinib adherence for CML, one third of patients were nonadherent, and those with suboptimal responses showed significantly less adherence.[23] Another prospective trial demonstrated a correlation between adherence to imatinib and major—and even complete—molecular responses.[24]

Clearly, further research focusing on strategies to improve adherence in the oncology setting is needed. One effective step to ensure appropriate prescribing and improve adherence is medication reconciliation with review of all medications at every visit. Patient and family education is another critical element in achieving medication adherence.[25] This is of particular importance in elderly patients, who often take multiple medications, and who may have difficulties managing complex regimens without assistance from caregivers.

TARGETED THERAPIES

There are three major classes of target drug therapy: endocrine therapy, monoclonal antibodies, and signal transduction inhibitor. Each class of medications and each specific drug has its own adverse reactions and safety profile. For none of these medications does enough data exist to routinely recommend dose alterations in the elderly (Table 10-2). However, many of these medications have specific side effects (Table 10-3) that are potentially more significant in an elderly population given their comorbid conditions, the prescription medications they often take, and the physiological changes associated with normal aging.

TABLE 10-2 Recommended Dose Reductions

Drug	Elderly	Hepatic	Renal
Tamoxifen	No	No	No
Aromatase inhibitor	No	No, but not studied with severe impairment	No
Bevacizumab	No	No	No
Cetuximab	No	No	No
Rituximab	No	No	No
Trastuzumab	No	No	No, unless creatinine > 2 mg/dL
Imatinib	No	Yes, severe impairment	Yes
Erlotinib	No	Yes	No
Sorafenib	No	Yes	Yes
Sunitinib	No	Not studied with severe impairment, no adjustment with mild or moderate impairment	Not studied
Temsirolimus	No	Not studied	No
Lapatinib	No	Yes, severe impairment	No
Bortezomib	No	Yes, moderate impairment	No

TABLE 10-3 Important Adverse Events

Drug	Event
Tamoxifen	Thromboembolism, ischemic cerebrovascular events, endometrial hyperplasia, endometrial cancer, and cataract development
Aromatase inhibitor	Musculoskeletal symptoms and osteoporosis
Bevacizumab	Thrombosis, bleeding, neutropenic fever, hypertension, and gastrointestinal perforation
Cetuximab	Diarrhea
Rituximab	Infusion reaction
Trastuzumab	Cardiac toxicity
Imatinib	Edema, rash, fatigue
Erlotinib	Rash, diarrhea
Sorafenib	Cardiac toxicity
Sunitinib	Cardiac toxicity
Temsirolimus	Thrombocytopenia
Lapatinib	Cardiac toxicity
Bortezomib	Thrombocytopenia

Endocrine Therapy

The oldest example of "targeted therapy" is perhaps the proposal of oophorectomy as a treatment for advanced breast cancer in 1889. Since then, drugs that inhibit estrogen signaling, whether by blocking the estrogen receptor, as with selective estrogen receptor modulators (SERM), or by inhibiting the production of estrogen, as with aromatase inhibitors, have become commonly used agents in the adjuvant and metastatic setting for older patients with hormone receptor-positive breast cancer. However, some data suggest that toxicities may vary within subgroups of older oncology patients and the impact of the different side effect profiles remains unclear.

Tamoxifen. Tamoxifen is a SERM that competes with estrogen for binding at the estrogen receptor. When used for 5 years in patients aged 70 or older with early-stage, ER-positive breast cancer, it has had a significant role in

reducing the risk of breast cancer recurrence and death.[26] However, because tamoxifen has partial estrogen-agonist effects, its use is associated with an increased risk of thromboembolism, ischemic cerebrovascular events, endometrial hyperplasia, endometrial cancer, and risk of cataract development. Notably, the increased risk of endometrial cancer is almost exclusively seen in patients older than 50 and the absolute risk remains low.[27] Clearly, these risks may influence the safety and tolerability profile of tamoxifen in older women with breast cancer, especially those with other comorbid conditions.

Aromatase Inhibitors. Aromatase inhibitors (AIs) block the enzyme aromatase that is responsible for the peripheral conversion of androgenic substrates into estrogen. Several randomized trials demonstrated superior disease-free survival with AIs compared to tamoxifen for the adjuvant treatment of postmenopausal women with early-stage, hormone receptor-positive breast cancer. While AIs have been associated with an increased incidence of musculoskeletal symptoms and osteoporosis, there has been less endometrial cancer and hypercoagulability than with tamoxifen. Notably, in a study of 1,300 women aged 70 or older, they had significantly higher incidences of fracture, new osteoporosis, and heart disease relative to younger women but there was no treatment-related association.[28] However, a meta-analysis of several randomized AI studies suggested an increased risk for grade 3 and 4 cardiovascular complications (RR 1.31, $p = 0.007$) compared to tamoxifen.[29] There remains some ambiguity regarding specific toxicities in the elderly population, but for now the evidence favors use of aromatase inhibitors for hormone receptor-positive breast cancer in postmenopausal women.

Monoclonal Antibodies

Monoclonal antibodies are the most widely-used cancer immunotherapy. The first monoclonal antibodies were made entirely from mouse cells; this posed a problem when patients developed severe allergic reactions as their immune systems mounted attacks against the mouse antibodies because they were recognized as foreign. Over time, however, techniques have been developed to replace entire or significant portions of the mouse antibodies with human parts. These part-mouse and part-human antibodies are referred to as chimeric or humanized. Monoclonal antibodies function by either activating the immune systems of patients to recognize and then destroy cancer cells or by binding to parts of cancer cells or those cells that help them grow and blocking them from working.

Bevacizumab. Bevacizumab is a humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF) from binding its receptor and thereby prevents downstream signaling events. It has been approved for use in multiple diseases. Rare but serious adverse reactions include hypertension, gastrointestinal perforation, and proteinuria. Patients also commonly experience pancytopenia, diarrhea, and fatigue. Several studies have shown improved progression-free and overall survival with the incorporation of bevacizumab into first-line therapy in advanced colorectal cancer. Relative to younger patients, grade 3 to 4 leukopenia was 5% higher in the elderly.[30] In addition, a retrospective pooled analysis of five randomized studies in 1745 patients demonstrated an increased risk of arterial thromboembolic events in those aged 65 or older who received chemotherapy and bevacizumab.[31] From a community-based registry of 1953 patients receiving bevacizumab, the safety and effectiveness of bevacizumab in patients aged 65 or older was similar to those younger than 65.[32] In this cohort, age was not a significant factor in predicting targeted bevacizumab-related safety events. Additional studies have confirmed this finding.[33] Another analysis of elderly colorectal patients at the Mayo Clinic demonstrated an increased incidence of adverse events in the population age 75 and older relative to the group 70 to 74 years of age.[34] Thus, elderly patients appear to experience more adverse events but the nature of the association between these events and the addition of bevacizumab requires further study.

The role of bevacizumab in older patients with non-small cell lung cancer (NSCLC) has been examined. A retrospective analysis of the patients aged 70 and older showed a trend towards higher response rate and progression-free survival with the use of bevacizumab, but overall survival was similar.[35] Elderly patients did have a greater incidence of grade 3 to 5 neutropenia, bleeding, and proteinuria with bevacizumab. Bevacizumab was, therefore, associated with a higher degree of toxicity but no improvement in overall survival. Bevacizumab is also approved for use in the first-line treatment of metastatic breast cancer in combination with paclitaxel. A retrospective study of patients older than 65 who received bevacizumab with chemotherapy for advanced breast cancer revealed an increased incidence of thrombosis, bleeding, neutropenic fever, and gastrointestinal perforation.

On the basis of the data, bevacizumab is beneficial as first-line treatment in elderly patients with advanced colorectal disease. However, its role in the treatment of elderly patients with NSCLC and breast cancer is less apparent, especially in patients with underlying cardiovascular disease.

Cetuximab and Panitumumab. Cetuximab is a chimeric monoclonal antibody directed to the exodomain of the epidermal growth factor receptor (EGFR), which blocks downstream signaling. Panitumumab is a fully humanized antibody also directed against EGFR. After failure of standard therapies, cetuximab and panitumumab have shown activity against metastatic colorectal cancer.[36] However, retrospective subset analyses suggest that patients with KRAS mutations do not benefit from anti-EGFR therapy.[37,38] When used in combination with irinotecan in irinotecan-resistant patients, there is also some evidence suggesting drug-resistance reversal.[36]

Cetuximab is also approved for the treatment of head and neck cancer in combination with radiotherapy.

Unfortunately, very few data are available regarding cetuximab use in elderly patients. Common side effects include fatigue, rash, abdominal pain, weakness, and diarrhea. A retrospective review of elderly patients who received cetuximab for metastatic colorectal carcinoma revealed that 75% experienced rash, 11% grade 3; and 80% experienced diarrhea, 20% grade 3-4.[39] A prospective phase II study of first-line single-agent cetuximab in elderly patient with metastatic colorectal cancer, which excluded frail patients, demonstrated 12.2% grade 3 skin toxicity.[40]

Rituximab. Rituximab is a chimeric murine and human monoclonal antibody directed against the CD20 antigen of B-lymphocytes, and is used alone and in combination with cytotoxic chemotherapeutic agents to treat lymphomas. Despite the large proportion of elderly patients in the lymphoma population, few studies have evaluated rituximab in the elderly. Most adverse reactions are infusion-related and are usually mild after the first dose. The combination of rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) appears well-tolerated and effective in those older than 60 years with aggressive non-Hodgkin lymphoma[41] and, in fact, was first studied in the elderly population.[42] In addition, the role of maintenance rituximab after CHOP chemotherapy with or without rituximab was investigated in patients aged 60 or older. Overall, nonhematological toxicity was the same in the two groups of patients.[43] It therefore seems that the incorporation of rituximab into standard chemotherapy regimens for indolent and aggressive lymphoma in the elderly does not increase overall toxicity in a significant manner.

Trastuzumab. Trastuzumab is a humanized monoclonal antibody that targets the HER-2/neu receptor. In combination with chemotherapy, overall survival is improved in women with advanced and early-stage HER-2-amplified or overexpressed breast cancer.[44] Cardiac toxicity is a significant side effect, especially in patients who received concomitant anthracycline-based chemotherapy. For those older than 60 years, the risk of cardiac toxicity is higher (21% in those older than 60 years versus 11% in those 60 years or younger), but the overall survival advantage is maintained.[45] Because of the potential for cardiac toxicity, most patients with cardiac comorbidities were excluded from the adjuvant trials of trastuzumab. However, this restriction also eliminated many older patients, and thus the available data are limited regarding the benefit of adjuvant trastuzumab for women older than 60 years; at present, they suggest that the benefits outweigh the risks.[46]

Signal Transduction Inhibitors

Signal transduction inhibitors block signals passed between molecules; these signals are often involved in many functions of the cells including death, growth, and division. Many drugs have been developed to block particular signals in the hope of precluding cancer cells from rapidly multiplying and invading other tissues.

Imatinib. Imatinib is an orally administered tyrosine kinase inhibitor metabolized by the cytochrome P450 isoenzyme 3A4. Common toxicities include edema, fatigue, rash, nausea, diarrhea, muscle cramps, and pancytopenia. Nearly all patients with CML in chronic phase treated with imatinib achieve a complete hematologic response, which is defined as normalization of the white blood cell count with no immature granulocytes and less than 5% basophils, platelet count less than 450,000/μL , and a nonpalpable spleen.[47] Complete cytogenetic response, defined as no detectable Philadelphia chromosome-positive cells, occurs in 69% of those treated with imatinib for 12 months and 87% of those treated for 60 months.[48] The use of imatinib in elderly patients with chronic phase CML or Philadelphia-positive acute lymphoblastic leukemia has been studied and has shown efficacy similar to that in younger patients.

Although gastrointestinal stromal tumors (GISTs) are resistant to conventional chemotherapy, they are extremely sensitive to therapy with imatinib. Approximately 90% of patients with GIST experience tumor control with imatinib and prolonged overall survival. In a phase III trial of imatinib in patients with advanced or metastatic GIST, only the nonhematologic toxicities of edema, rash, and fatigue correlated with advanced age.[49]

Erlotinib. Erlotinib targets the tyrosine kinase domain of the epidermal growth factor receptor (EGFR). Rare but serious events such as gastrointestinal perforation, bullous and exfoliative rash, and corneal perforation have been reported. Common side effects include fatigue, rash, and diarrhea. Extreme caution is used in patients with abnormal liver function tests. In the National Cancer Institute of Canada Clinic Trials Group (NCICCTG) BR.21 study, the use of erlotinib improved survival in patients who had experienced treatment failure with first- or second-line chemotherapy for non-small cell lung cancer. A retrospective analysis of elderly patients in this trial revealed more toxicity overall and more severe toxicity.[50] In addition, tissue samples from participants in the BR.21 study were analyzed for EGFR mutations and EGFR copy number. Mutations and high copy number were predictive of a response to erlotinib and EGFR fluorescence, while EGFR fluorescence in situ hybridization (FISH) positivity and wild type were associated with a survival benefit from the use of erlotinib.[51]

Despite the paucity of randomized prospective studies to confirm the efficacy and tolerance of erlotinib in elderly patients, it is often used as a single agent in frail patients or those with poor performance status. Notably, a phase II study of erlotinib as first-line therapy for patients aged 70 and older with advanced non-small cell lung cancer showed that 12% of patients required discontinuation of therapy compared with 5% of those in the erlotinib arm of the BR.21 trial.[52] Additional

open-label, nonrandomized studies have demonstrated tolerable toxicities with erlotinib use as first-line or subsequent therapy in elderly lung cancer patients. Erlotinib has also been studied in patients with end-organ dysfunction,[53] which may be applicable in the elderly population where end-organ dysfunction is more common.

Erlotinib, in combination with gemcitabine, for patients with unresectable pancreatic cancer has also been shown to modestly improve progression-free survival compared to gemcitabine alone.[54] Although this phase III trial did not focus specifically on elderly patients, the median age was 63.9 and ranged from 36.1-92.4. However, gemcitabine with erlotinib was associated with more toxicity including rash, death, and interstitial lung disease-like syndromes.

Sorafenib and Sunitinib. Sorafenib is an orally active multikinase inhibitor with effects on tumor cell proliferation and tumor angiogenesis. It has been shown to inhibit Raf kinase; vascular endothelial growth factor receptors 1, 2, and 3; platelet-derived growth factor receptor; FMS-like tyrosine kinase 3; c-Kit protein; and RET tyrosine kinase. It has been approved for use in renal and hepatocellular carcinoma, but seems to have activity in several other malignancies. In a subgroup analysis of a phase III trial (TARGET), adverse events were independent of age.[55] In addition, side effects caused by sorafenib were similar in both elderly and younger patients treated with the expanded access program in North America[56] and commonly included fatigue, hand-foot syndrome, diarrhea, thrombocytopenia, and neutropenia.

Sunitinib is an orally-administered, multitargeted tyrosine kinase inhibitor of VEGF receptors, platelet-derived growth factor receptors, FLT-3, c-Kit, and RET that improves progression-free survival in patients with clear cell metastatic renal cell carcinoma.[57] It is also used to treat imatinib-resistant GIST tumors.[58] Common toxicities include hypertension, decreased left ventricular ejection fraction, fatigue, diarrhea, and pancytopenia. However, there are no data regarding the toxicity in elderly cancer patients.

Most concerning in the elderly population is the potential cardiac toxicity associated with these medications.[59] Approximately one third of evaluable patients in a single observational study had a cardiac event while on these medications. All patients recovered and were able to continue treatment with a tyrosine kinase inhibitor, but almost 10% were seriously compromised and required escalation of care. The impact of this toxicity in the elderly population has not been examined.

Temsirolimus. Temsirolimus is an mTOR inhibitor that is approved for use in patients with advanced renal cell carcinoma (RCC). Because this drug is primarily metabolized in the liver, patients with moderate or severe hepatic dysfunction were excluded from clinical trials involving temsirolimus. In addition, most clinical studies of this drug have not included enough elderly patients to determine the safety and toxicity of this drug. Common toxicities include edema, rash, hyperglycemia, mucositis, nausea, anemia, neutropenia, and thrombocytopenia. Given the significantly increased amount of thrombocytopenia in a study of patients with non-Hodgkin lymphoma with a median age of 70,[60] special consideration of this toxicity may be required in elderly patients. Notably, rare and sometimes fatal cases of bowel perforation, interstitial lung disease, and acute renal failure have occurred.

Lapatinib. Lapatinib is a dual HER-1 and HER-2 tyrosine kinase inhibitor that is approved in combination with capecitabine for the treatment of advanced HER-2-positive breast cancer after progression following trastuzumab-based chemotherapy. Common toxicities include fatigue, palmoplantar erythrodysesthesias, diarrhea, nausea, anemia, and neutropenia. In addition, rare but severe hepatoxicity, left ventricular dysfunction, and pulmonary toxicity have been reported. Dose reductions are recommended with severe hepatic compromise. There are no data regarding the effects of age on the pharmacokinetics of lapatinib, but thus far no differences in safety or effectiveness have been observed between patients older than 65 years and those 65 years and younger. There is also significant concern regarding the cardiac toxicity associated with this therapy. While the absolute incidence of cardiac toxicity is low at 1.6%, predictors of this toxicity include age older than 50, baseline cardiac dysfunction, and use of antihypertensive medications.[61]

Bortezomib. Bortezomib is a proteasome inhibitor used to treat multiple myeloma, and requires dose adjustment with moderate hepatic impairment. It is also active in mantle cell lymphoma and approved for use in relapsed/refractory disease.[62] Common toxicities include edema, nausea, thrombocytopenia, sensory neuropathy, and weakness. In a study of bortezomib in combination with melphalan and prednisone in elderly patients, overall toxicity was higher in patients aged 75 or older; however, this may have been related to the physical condition of these patients.[63] In addition, it is possible that the increased incidence of hematologic toxicities was due to melphalan and not to bortezomib. When compared to elderly subgroups from previous trials, the rates of serious adverse events were similar and were generally manageable.[64]

SUMMARY

The development of novel targeted therapies has helped improve survival for patients with cancer, but the toxicities differ from those associated with traditional cytotoxic chemotherapy and include more cardiovascular and cutaneous complications. In addition, as has been reviewed, differences in physiology, organ function reserves, and resilience in elderly patients seem to affect outcomes for this special patient population. Given the current state of evidence, the benefits seem to outweigh the risks for several medications such as

aromatase inhibitors in postmenopausal women with hormone receptor-positive breast cancer, bevacizumab as first-line treatment in colorectal cancer, rituximab for indolent and aggressive lymphoma, trastuzumab for HER-2-overexpressing breast cancer, imatinib for GIST and CLL, and erlotinib to treat lung cancer. For some medications, such as sorafenib, sunitinib, and temsirolimus, there is a paucity of data. For yet other medications such as lapatinib and bortezomib, there is some evidence suggestive of increased toxicity, but its association with age as opposed to comorbid medical conditions is unclear. Clinical trials that characterize the needs and goals of therapy in elderly cancer patients are ongoing, but clearly disease-specific studies are needed to clarify the risk-benefit ratio of these newer targeted agents in the elderly population. Ultimately, the risk-benefit ratio must be considered for each individual patient to best minimize toxicity and maintain quality of life.

See expertconsult.com for a complete list of references and web resources for this chapter

CHAPTER

11

Clinical Trials in the Elderly

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CASE 11-1

A 75-year-old man with a history of diabetes and hypertension presents with newly diagnosed colon cancer. He is diagnosed with stage IIIB cancer (T3N2A), with metastases found in 6 regional lymph nodes of 20 nodes sampled. He complains of baseline neuropathy in both his feet from his diabetes. His medications include aspirin, metformin, an acetylcholinesterase inhibitor, a multivitamin, a beta-blocker, a stool softener, a 5-alpha-reductase inhibitor, and "something to help sleep." He is retired, married to a healthy spouse, and capable of full activities of daily living (ADL) and instrumental ADL (IADL). Upon checking his laboratory values, everything is within the normal range, except for an elevated creatinine of 1.2 mg/dL. He says he wants the most "aggressive care possible" and asks for "cutting edge treatment." The oncologist to whom he was referred discussed with him a current national intergroup trial comparing several potentially toxic chemotherapy regimens and offered him participation. Outside of a trial, the oncologist suggested he consider 6 months of an oxaliplatin and 5-FU regimen, but his primary physician is worried about how he will tolerate it, because of concerns about preserving his quality of life and preventing a relapse. His primary physician wonders if the clinical trial offers him more effective treatment and a chance for improved survival. What are the major issues related to the trial and this patient's participation that are likely to influence his primary care provider's recommendation?

The patient in Case 11-1 typifies the complexity of cancer management in older patients. He has several comorbidities, is highly functional, and has a cancer that has a high risk for relapse but one for which adjuvant therapy confers a major improvement in survival.[1] Although in the United States the median age at diagnosis of cancer is 67 years and the median age of cancer death is 73 years, only a few percent of all adults are recruited to National Cancer Institute sponsored clinical trials and only a fraction of these are elders.[2] Accruing patients to cancer clinical trials, especially older patients, continues to be an ever more difficult challenge. In the past, few older patients were likely to be enrolled in clinical trials,[3,4] but recent studies suggest that about 30% of accruals to all Phase II and phase III National Cancer Institute (NCI) Cancer Cooperative Group trials are patients 65 years and older.[5,6] Although older patients are less likely to be offered trial participation, when trials are offered, the rate of participation of about 50% is similar to younger patients.[7] Age bias plays a major role in whether a trial is offered, and few oncologists have been trained in the care of older patients. Options for clinical trials that focus on or include elders, overcoming barriers to accrual, and opportunities for research will be discussed in this chapter.

MAJOR ISSUES IN CLINICAL TRIAL DEVELOPMENT FOR OLDER PATIENTS

Major factors related to maximizing participation of older patients in clinical trials are listed in Table 11-1. Currently, there are at least 200 clinical trials currently enrolling patients that focus on cancer care in the elderly (www.clinicaltrials.gov). Over the past decade, there has been an increased awareness of the need for more clinical research in the older cancer patient. Clinical trials in the elderly population remain a challenge but as the general population ages, oncologists will be seeing larger numbers of elderly patients (many with poor function and substantial comorbidity) and will need data on appropriate management of these patients.

The age-related increased frequency of coexisting illnesses (comorbidities) and functional loss represents the major difference between older and younger patients with cancer. Our patient is typical of this scenario, having both diabetes and hypertension. Both comorbidity and functional loss contribute to a shorter life expectancy and may interfere with or worsen the effects of cancer treatment. Factoring the impact of comorbidities is important in both the curative and palliative setting. In the curative setting, treatments that have major negative effects on quality of life must be carefully weighed against their potential for improved survival benefit; in the palliative setting the use of surgery, irradiation, and systemic therapies should be primarily focused on preserving quality of life and improving symptoms. Clinical trials to date have not been successful in factoring comorbidity accurately into treatment decisions and have avoided dealing with these issues by excluding patients with major functional loss and comorbidities by the use of stringent eligibility criteria. Outside of a trial some internet-based programs such as Adjuvant!

TABLE 11-1 Major Issues in Clinical Trial Development to Facilitate Inclusion of Older Patients

Comprehensive Geriatric Assessment (CGA)
- Consider adding as an adjunct to eligibility; eliminate age bias
- Add as companion to trial helping to predict toxicity risk

Eligibility Criteria
- Minimize to essentials
- Organ function exclusion on the basis of metabolism of drugs used in trial

Statistical Considerations
- Consider increasing elderly cohort for positive trials with small sample of older patients.
  - Do after primary accrual goal reached (allows timely publication)
  - Use adaptive design based on elders' accrued and reported toxicity

Specific Trials for Older and/or Vulnerable and Frail Patients
- Define vulnerability and/or frailty using validated instruments.
- Aim to test effective treatments that may be less toxic.
- Use adaptive designs to minimize accrual.
- For oral agents, consider formal assessment or compliance with treatment.

Translational Research
- Consider adding biomarkers of aging or toxicity as part of trial
- Bank blood and tissue samples for future research purposes (add to consent)

(www.adjuvantonline.com) allow health care professionals to factor in the effect of comorbidity on survival for the adjuvant treatment of breast, lung, and colon cancer. Such programs, however, do not help clinicians estimate the increased risk of toxicity in sicker patients, restricting their use in treatment decisions in elders with cancer.

Comprehensive Geriatric Assessment and Clinical Trials

The key consideration in developing trials for elderly patients is the effect of treatment on the patient's overall function and well-being. Comprehensive geriatric assessment (CGA) provides as assessment of key domains related to quality of life and survival, including functional status, cognition, social support, psychological state (especially evaluation for anxiety and depression), nutritional status, and medication use.[8] The CGA is a set of validated instruments that include evaluation of the activities of daily living (ADL): eating, bathing, dressing, toileting, and getting in and out of bed; and instrumental activities of daily living (IADL): managing finances, cooking, shopping, taking medications, performing housework, traveling, and communicating with the telephone. These data can help identify vulnerable patients—those most likely to experience toxicity—and shorter versions of the assessment that can be partially self-administered are now being tested in clinical trials.[9] Preliminary data show that they are feasible in the cooperative group setting, and studies are underway to determine what components of these instruments can help predict which patients are at greatest risk for side effects. Moreover, a recent trial showed that geriatric assessment in older breast cancer survivors was not only predictive of poor tolerance of treatment as self-reported by patients, but also of mortality at 7 years.[10] Further studies of this type are needed. Studies using the CGA as a research tool in elderly cancer patients have shown that it can independently predict survival, toxicity to chemotherapy, morbidity, and mortality.[11,12] Also, incorporating quality-of-life assessment tools such as the Functional Assessment of Chronic Illness Therapy questionnaires (www.facit.org) into research trials in the elderly will help measure the impact of treatment on quality of life.

Although when one hears the term clinical trials one thinks of treatment trials, important trials now in progress are testing whether geriatric assessment can help predict treatment toxicity. Two recent trials showed that geriatric assessment when added to standard clinical variables (for example performance status and hemoglobin) can help accurately predict toxicity for older patients receiving chemotherapy both in the adjuvant and advanced setting. Extermann and colleagues assessed 518 patients 70 years and older who were initiating chemotherapy for both early and late-stage cancer.[13] A score based on clinical and geriatric assessment data clearly predicted significant differences in hematologic and nonhematologic toxicity among cancer patients. A similar study by Hurria and colleagues in 500 patients also showed the added value of geriatric assessment data in predicting moderate and severe chemotherapy-related toxicity.[14] These trials, and others in progress like these, are important. For example, several large cooperative group trials are now incorporating geriatric assessment prior to treatment and may allow for more accurate prediction of treatment-related toxicity for older patients treated with newer state-of-the-art regimens.

Eligibility Criteria

Eligibility criteria must be carefully considered when designing trials for older patients, and in most instances should be as broad as possible[6,15]; that is, "let doctors be doctors" and let doctors and patients together decide on what level of risk is appropriate. There should be no upper age restrictions. Instead, for adjuvant trials, older patients who are otherwise healthy and have life expectancies greater than 5 to 10 years should be offered participation. Using life expectancy makes much more sense and can be reasonably estimated. For trials where improving the probability of cure is not the goal, eligibility criteria should not exclude elders on the basis of arbitrary criteria such as organ dysfunction unless the

specific treatment being studied is metabolized by or has an toxic effect on the particular organ. For instance, creatinine clearance decreases linearly with increasing age; arbitrarily adding criteria with a threshold for renal function to a trial that does not include treatment that is renally excreted should be avoided. Hematologic, hepatic, and cardiac function thresholds should also be omitted when not related to the treatment being evaluated. It is estimated that by appropriately relaxing eligibility criteria, participation of the elderly in clinical trials can be increased by 60%.[6] Unless convincing data exist that support adding restrictive eligibility criteria on the basis of function, eligibility criteria should be as flexible as possible, allowing patients and their physicians flexibility in making decisions on trial participation.

Statistical Considerations

For state-of-the-art clinical trials, statistical considerations and getting an adequate sample size of older patients are also major concerns so as to make the outcome, and especially the toxicity data, generalizable to older patients. One strategy is to keep the elderly cohort open after the trial has met its major accrual goals so that one might reasonably determine that the major risks and benefits of any new treatments are similar for older and younger patients. A larger sample of older patients would be especially important in testing novel agents or procedures, as it would allow for adequate toxicity data to be gathered in this more vulnerable older population. Another strategy would be to require that a specific number of older patients be required in all phase II and III trials. This strategy, although tempting, might hamper completion of the trial, as extensive data show older patients are less likely to be offered clinical trials participation compared to younger patients. For these reasons, the strategy of leaving an elderly cohort open to evaluate a possible age-related treatment interaction appears a more practical and potentially more successful approach for future trials. Such a strategy could use an adaptive design based on the number of elders accrued to the trial and how many more elders should be accrued to better characterize any major toxicity among all the trial participants. For instance, if in a trial of 1000 patients, neutropenic fever was seen in 10% of the entire sample, and only 30 patients in the trial were 70 and older, one could leave the trial open for patients 70 and older to better determine a narrow confidence interval for this toxicity in the older age group.

Designing clinical trials specifically for the older cancer population should also be considered when there are potential differences in tumor biology with age (for example acute myelogenous leukemia, where the natural history of disease is different than in younger age groups), and where older patients—especially the frail and vulnerable—are not good candidates or are excluded from trials of regimens likely to be associated with major toxicity and loss of function. An example of a successful trial designed specifically for older patients was performed by the Cancer and Leukemia Group B and restricted entry to women 65 years and older with early-stage breast cancer.[16] The plan made certain that an adequate sample of patients 70 and older would be accrued and used a novel adaptive Bayesian design[17] to optimize the sample size. In addition, two companion trials, one assessing compliance with oral chemotherapy and another evaluating the effect of the different treatments on quality of life, were made optional but highly recommended parts of the trial; both successfully met their accrual goals. The advantage of this approach is that such trials can focus on effective but potentially less-toxic treatments, can include specific assessments such as CGA instruments for identifying patients likely to be the most vulnerable to side effects, and can include or be restricted to the frail elderly. For trials focused on vulnerable or frail populations, it is important that clear and reproducible definitions be used to define the population at risk.[18]

Translational Research

Opportunities to further understand the effects of cancer treatment in the elderly may lie in evaluating biomarkers of aging, cytokine regulation, and the molecular interactions of cancer and age.[19] For example, there is evidence that interleukin-6 (IL-6 , an inflammatory cytokine that promotes differentiation of T cells and B cells, activation of T cells and macrophages, and secretion of immunoglobulin) increases during aging.[20,21] Increased IL-6 expression has also been found in certain cancers, such as multiple myeloma, lymphoma, Hodgkin lymphoma, renal cell carcinoma, chronic lymphocytic leukemia, and breast cancer.[22,23] Older patients with cancer and high IL-6 levels might be considered for clinical trials to determine their safety and efficacy in targeting cancer. In addition, IL-6 might serve as a marker of physiologic reserve and add to information obtained by geriatric assessment in predicting toxicity. Another exciting molecular marker of aging is p16 gene expression, which increases tenfold between ages 20 and 80 years.[24] Increased p16 expression is associated with cell senescence and may possibly prove to predict organ-related toxicity from radiation and chemotherapy.

Future studies might also address host factors related to drug activation and metabolism as related to clinical outcomes. Although these issues are not specific for older patients, they are of major importance. For example, the cytochrome P450 (CYP450) metabolic enzyme CYP2D6 has a major role in tamoxifen metabolism, activating tamoxifen to endoxifen, its most active metabolite.[25] The CYP2D6 gene is polymorphic, but even the wild-type variant is affected by many antidepressants, medications that are commonly used in older patients, and which cause a decrease in the conversion of tamoxifen to endoxifen.[26] These data point out the importance of

trials that measure pharmacokinetic and pharmacogenomic parameters in older patients, especially in those taking medications that might interact with enzymes important in drug activation and metabolism.

IMPROVING ACCRUAL OF OLDER PATIENTS TO CLINICAL TRIALS

The major barriers to accrual of older patients to clinical trials are listed in Table 11-2. Identifying older patients who are eligible for trials and obtaining their consent to trials remains the major challenge in both community and academic settings and involves close collaboration with referring physicians. Oncology consultation shortly after the diagnosis of cancer allows for rapid assessment of the patient and identification of potential trials. A strong collaborative relationship with local primary care physicians who are interested in elder care will greatly facilitate this approach. Such relationships must include educating colleagues on the availability, goals, and importance of clinical trials in improving cancer care and require significant commitment by the investigator. If the focus is on accrual of vulnerable or frail patients, then close collaboration with the patient's primary care physician and establishment of relationships with geriatricians in the area will be essential for timely accrual. A strategy that includes periodic meetings to inform other health care professionals of available trials, a rapid means of seeing potential trial patients in consultation, and providing reminders of available trials, is likely to be worth the investment.

Physician-related obstacles remain a major barrier to accrual. Many physicians, even those in academic settings with strong clinical research support are unaware of trials that might be available,[7] or, more likely, are too busy to think of them in the demanding clinics of today. A checklist or computerized reminder of available trials that is attached to the paper record, or shown in a reminder window in an electronic record when the patient is seen, is likely to be helpful in facilitating accrual. In one study of barriers to trials in older patients, the three major changes physicians felt would most likely lead to higher accrual were: (1) having available personnel in clinic to explain trials to eligible patients; (2) more physician education on toxicity issues; and (3) providing transportation to older patients for trial-related visits.[7] Of note, in the same study, is the finding that when older patients were offered trials, their rate of participation was similar that of younger patients at a level of about 50%.

Nursing and staff-related obstacles are usually related to time constraints and lack of support. Depending on resources, the most effective way to increase accrual is probably to assign a nurse or other well-educated staff member to screen patients, determine their eligibility, and, most importantly and with the help of the physician, discuss trial participation with patients and obtain their consent. Too often these tasks are added to an already full range of responsibilities, with the result being no time to devote to these key tasks. An increase in reimbursement for federally sponsored trials is desperately needed to provide financial support for the trial's mission. Patient-related obstacles are present all along the trajectory of enrollment. Because older patients are generally less educated than younger patients and require more time from professionals to explain the goal of the trial, and its treatments, toxicities, and logistics, family should be included in these discussions. In addition, older patients tend to have less financial resources and frequently must rely on others for transportation. Keeping trial designs simple, using decision-making aids during discussions, and using community resources to help with transportation can all help. Focusing trials on those most likely to participate may be the best strategy when resources are limited. Clinical trial participation is more common in patients who are positive about research, hope for a cure, are altruistic, are curious and enjoy novel experiences, want to be part of something important and help with research, and who feel close with their physicians and their staff.[27]

TABLE 11-2 Major Barriers to Accruing Older Patients to Clinical Trials and Suggestions for Improvement

Identifying older patients who may be eligible for a trial
• Involves close collaboration with referring physicians and their nursing staff with focus on education about and availability of trials. Setting up an expedited consultation process is of great help.
Physician obstacles
• Educate colleagues on issues related to care of elders with cancer, including assessment of function and comorbidity, and risks of toxicity. Provide a checklist with of trials available that includes brief summary of eligibility criteria.
Nursing- and staff-related obstacles
• Identify a lead nurse or staff member to champion trials and provide funding and time for these individuals to screen and consent patients.
Patient-related obstacles
• Educate patients on rationale of trial, its goals, and its toxicity. Inform patients as to any added costs, both financial and logistic. Involve family in these discussions.

OPPORTUNITIES FOR RESEARCH

Major opportunities for research on older patients with cancer are available. Both the National Cancer Institute (http://www.cancer.gov/) and National institutes of Aging (http://www.nia.nih.gov/) have grant-funding opportunities for a broad range of interests. In addition, the American Federation for Aging Research (AFAR) has a list of useful links to companies, foundations, and organizations that support aging research, as well as its

own grant-funding opportunities (http://afar.convio.net/site/PageServer?pagename=AFAR_Links). In addition, several NCI-funded cooperative groups have supported specific committees and infrastructure to facilitate trial development and accrual of older patients.[28]

CONCLUSIONS

Cancer clinical trials in older patients remain a challenge. Age bias persists and limits offering many older patients trial participation; also, many ongoing trials still inadvertently exclude older patients by virtue of stringent but frequently inappropriate eligibility criteria. Cancer trials focused on vulnerable and frail patents are few. Nevertheless, trial participation by older patients is improving, and a small but growing number of health care professionals are aware of and interested in developing new trials for elders, overcoming barriers to participation, and improving access. Funding remains a major problem and must be increased if there is to be substantial improvement in trials research in the aging population. Education of health care professionals and the public remains a key function in increasing awareness of cancer in the elderly and the complex decisions frequently needed in caring for this growing number of patients.

SUMMARY

Older persons comprise the majority of patients with cancer but continue to be underrepresented in clinical trials. Many of the most effective cancer treatments resulting from clinical trials have been inadequately studied in older patients, limiting the generalizability of the results to elders. Thus elders, when given state-of-the-art treatments, may suffer undue toxicity that interferes with their function and quality of life. There is an increasing awareness of the lack of participation of older patients in clinical trials and many health care professionals are now interested in improving accrual of elders to trials and in developing specific trials for the elderly, especially the vulnerable and frail.

This chapter focuses on issues related to trial design that affect the accrual of older patients such as comprehensive geriatric assessment, eligibility criteria, statistical considerations, specific trials for vulnerable and frail patients, and translational research. In addition, barriers to participation in clinical trials are addressed along with strategies to overcome them, including identifying older patients for trials, physician obstacles, nursing- and staff-related obstacles, and patient-related obstacles. New trials and increased accrual of elders are greatly needed and opportunities for research are available.

See expertconsult.com for a complete list of references and web resources for this chapter

CHAPTER

12

Communication and Treatment Decision Making

Arash Naeim

CASE 12-1 CASE SCENARIO

A 75-year-old woman with newly diagnosed breast cancer, who has received primary treatment with surgery and radiation, has a consultation with an oncologist to discuss the need for adjuvant treatment. She goes to her appointment with her husband of 50 years who has early dementia and hearing loss. Although she has a college education, she finds the information the oncologist provides to be too complicated and therefore does not ask any questions, leaves somewhat unsatisfied, and is not even sure what the doctor ultimately recommended.

PHYSICIAN-PATIENT COMMUNICATION

Physician-patient communication is a process by which information is exchanged between a physician and patient through a common system of symbols, signs, and behaviors.[1] Communication is a core clinical skill in the practice of medical oncology, and health literacy has a central role in cancer patients' ability to discuss their disease and prognosis with their oncologist in a meaningful way. The average clinical career of an oncologist is approximately 40 years and can involve up to 200,000 consultations with patients and their families. As with the general population, effective communication has many positive effects on cancer patients' adjustment to the disease and its treatment, whereas poor communication has negative consequences both for health care professionals and for patients.[2,3]

Effective communication between health care professionals and patients is essential for the delivery of high-quality health care. Communication issues are often a critical factor in litigation.[4] Research has suggested that effective communication during medical encounters positively influences patient recovery, pain control, adherence to treatment, satisfaction, and psychological functioning.[5,6] Because of the threat of mortality from the diagnosis of cancer, the uncertainty of therapy efficacy, and the physical and emotional stress of undergoing chemotherapy, patients must obtain a high level of complex information during communications with their treating physician.[7,8]

Older adults diagnosed with cancer are the population group considered to be at highest risk for poor communication with health professionals. The older patient is less likely to be assertive and ask in-depth questions. Overall physician responsiveness (i.e., the quality of questions, informing, and support) is better with younger patients than with older patients, and there is less concordance on the major goals and topics of the visit between physicians and older patients than between physicians and younger patients.[9,10]

COMMUNICATION BARRIERS IN THE ELDERLY

The literature suggests that evaluating such factors as memory decline and sensory deficits are essential in geriatric patient medical visits. These common age-related communication barriers are often overlooked in the oncology consultation and frequently compromise the quality of communications. There is a broad range of cognitive loss among individuals with dementia, and unless the physician is trained to uncover this problem, it can be missed in patients with mild or even moderate loss.[11] For example, the 1999-2001 National Health Interview Surveys (NHIS) indicate that 2.3 million (7.1%) community-dwelling people aged 65 and older are limited by memory impairment or confusion, while 800,000 (2.4%) are limited by senility and dementia.[12]

In addition to cognition, hearing and vision are important components of communication. Presbycusis, or decreased hearing of higher frequency sounds, is one of the most common and significant sensory changes that affect elderly people. The incidence of sensorineural hearing loss increases each decade so that by the seventh and eighth decades, 35% to 50% of older adults have hearing impairment.[13] Vision loss also has a significant impact on physician-patient interaction, because visual cues are vital in interaction. After age 65, there is a decrease in visual acuity, contrast sensitivity, glare intolerance, and visual fields. On the basis of the 1997-2002 NHIS, 15% to 25% of older adults had visual impairment.[13] The combination of both hearing and visual

impairment among elders aged 65 to 79 was 7% and increased to 17% for individuals aged 80 and older.[13]

Physician visits for elderly patients with these functional impairments may be so difficult to coordinate that they result in frequently missed appointments. When these frail older patients finally do see the physician, the visits may be emotionally and physically stressful for them, limiting effective communication.[10,14]

HEALTH LITERACY

The Institute of Medicine defines health literacy as "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions."[13] A patient's health literacy level, which includes such skills as the ability to comprehend prescription bottle labels, follow written and oral health instructions, and understand physician dialogue, may be significantly lower than his or her general literacy level.[15] The National Adult Health Literacy Survey (NALS) published in 2003 reported that more than 50% of the United States population older than 65 was either functionally illiterate or possessed marginal literacy skills.[16] The largest study of health literacy conducted to date in the United States found that 30% of patients at two public hospitals could not read or comprehend basic health-related materials. In addition, 42% failed to understand directions for taking medications, 60% could not comprehend a routine consent form, and 26% did not understand the information written on an appointment slip.[17]

NUMERACY (QUANTITATIVE LITERACY)

It is common for oncologists and other health care providers to use information about rates, percentages, and proportions when discussing treatment and prognosis. An important component of health literacy in the context of cancer treatment is the patient's ability to understand these basic probability and numeric concepts. Health numeracy can be defined as the degree to which individuals have the capacity to access, process, interpret, communicate, and act on numeric, quantitative, graphic, biostatistical, and probabilistic health information needed to make effective health decisions.[18] Although there is a correlation between prose or print literacy and numeracy, many patients have adequate literacy but poor quantitative skills. A cross-sectional study of 200 primary care patients demonstrated that only 37% of patients could calculate the number of carbohydrates consumed from a 20-oz bottle of soda that contained 2.5 servings.[19]

Decreased numeracy competency in cancer patients may have an impact on their ability to accurately assess their own health risks. Understanding numbers is essential to comprehend risk-benefit information. Patients need to: (1) acquire information from oral discussion, text, tables, and charts; (2) make calculations and inferences; (3) remember the information (short and/or long term memory); (4) weight the factors to match their own needs and values; and (5) make trade-offs to reach a health decision.[20] Cancer communication, especially risk communication, may be hard because the patient's knowledge relevant to cancer is often fragmented and inaccurate. Moreover, the education and everyday experience of an older cancer patient may not ensure the numeracy and health literacy required to evaluate the complex and uncertain benefits from treatment.[21]

INADEQUATE HEALTH LITERACY AND OLDER CANCER PATIENTS

A limited number of studies have focused on the prevalence and impact of health literacy in geriatric cancer patients. A survey of Medicare enrollees between June and December 2007 demonstrated that 34% of English-speaking and 50% of Spanish-speaking respondents had inadequate or marginal health literacy. Reading ability declined dramatically with age, even after adjusting for years of school and cognitive impairment.[22] One study in newly diagnosed prostate cancer patients with a mean age of 67 demonstrated that low health literacy limited patient understanding of complex information regarding treatment and quality-of-life issues.[23]

PHYSICIAN COMMUNICATION

The underpinning of effective verbal communication in the medical encounter is the interaction between a patient's health literacy level and the quality of dialogue between patient and physician. "Oral literacy demand" can be defined as the aspects of dialogue that challenge patients with low literacy skills.[24] During conversations, the general language complexity increases with the greater number of sentences in the passive voice and with faster dialogue pacing, both of which have negative effects on comprehension.[24]

The use of technical terminology is an important component of oral literacy demand. Research done on adult literacy of genetic information presented during genetic counseling sessions suggests that literacy demand was proportional to the use of technical terms.[25] A doctor's choice of vocabulary can affect patient satisfaction immediately after a general practice consultation, and if the doctor uses the same vocabulary as the patient, patient outcomes improve.[26] In addition, studies have found increased "dialogue density"—or the duration of uninterrupted speech by a physician—correlates with greater oral literacy demand.[27] A review of 152 prenatal and cancer pretest genetic counseling sessions with simulated clients found that the higher the use of technical terms, and the more dense and less interactive the dialogue, the less satisfied the simulated clients were and the lower their ratings were of counselors' nonverbal effectiveness.

In addition, patients with low health literacy are less likely to ask their physician to slow down the dialogue and repeat information when their understanding is compromised.[28] Interventions to modify health care provider use of technical terms, general language complexity, and structural characteristics of dialogue can enhance overall communication by decreasing patient oral literacy demand.[24]

DECISION MAKING

Low levels of health literacy present challenges to any decision-making paradigm,[29,30] especially in the case of complex cancer treatment decisions in the elderly. Complexity in the cancer-treatment decision process originates from the fact that selection of therapy is unique to every patient. Typically, several treatment options are possible and the oncologist and patient must together carefully weigh the risk of toxicity against the potential benefit. Patient preferences, quality of life, and social responsibilities must be considered along with the stage of disease, biologic characteristics of the tumor, and comorbid illnesses.

One important factor in decision making is "self-efficacy," or confidence in one's ability to understand and communicate with physicians. Patients with high self-efficacy have been found to have fewer episodes of depression and develop more realistic goals.

An important aspect of self-efficacy is the sense of control and involvement in the treatment, which has been associated with several desirable outcomes including greater patient satisfaction, increased adherence to treatment, and positive treatment outcomes in elderly patients. Evidence suggests that cancer patients who report greater self-efficacy are better-adjusted and experience better quality of life than those with low self-efficacy.[31]

Older patients are often less assertive in communicating with physicians, less likely to ask questions, and less inclined to take a controlling role in their health care decision making.[32] Self-efficacy is a predictor of how the patient perceives and reacts to the encounter with the physician.[33] Studies in older breast cancer patients have shown that patients with higher self-efficacy are more likely to report that discussions with their physicians are helpful.[34]

CAREGIVERS/COMPANIONS AND TREATMENT DECISIONS IN OLDER CANCER PATIENTS

The effect of family caregivers and companions on cancer treatment decisions is a frequently overlooked, yet significant influence. An estimated 20% to 50% of geriatric patients are accompanied by a family caregiver or companion during their routine medical visits.[35] Most cancer patients share their diagnosis and current condition with a family member or companion. These members of the patient's "social support network" are often highly motivated to help patients manage information related to their cancer treatment.[36] They play key roles in interpretations of medical diagnosis, offering explanations, and encouraging patients to comply with their treatment plan. Their level of health literacy and actions during the medical visit are critical to defining these roles.

Patients with lower health literacy are likely to be more influenced by a caregiver or companion.[37] Specifically directed physician interactions with these individuals, including assessing their level of health literacy and providing them with appropriate written cancer information during the oncology visit, are important opportunities to optimize communication and medical decision making.[38]

The consequences of companion behavior on patient autonomy and its impact on the decision-making process during the medical visit are important areas of investigation. Several studies have found definite benefits when a family member is present, such as an increase in the amount of medical information provided.[39] Other researchers have determined a negative, intrusive effect of a third party on patient autonomy during a medical visit.[40] A study of 93 patients and companions during geriatric primary care visits found more autonomy-enhancing behaviors (facilitating patient understanding, patient involvement, and doctor understanding) than autonomy-detracting behaviors (controlling the patient and building alliances with the physician). They also found that while nonspousal companions are not as active in decision making, they are more likely to facilitate patient involvement in the visit than spouses.[35](Figure 12-1.)

DECISION MAKING IN OLDER CANCER PATIENTS

The "shared decision model" has gained consensus as the preferred method of making treatment decisions, especially in the situation where many different therapeutic strategies are equivalent. Patient autonomy is prioritized and the physician's obligation is to provide factual information and execute the patient's selected intervention.[41,42] A systematic review of studies has shown variability in older patients' desire to actively participate in their cancer treatment.[43,44] One study looking specifically at an older individual's participation in medication-related decision making identified perceived lack of knowledge, low self-efficacy, and fear as the major impediments to shared decision making.[45] Moreover, a very recent study demonstrated that statistical illiteracy (understanding the meaning of numbers) impeded both risk communication and shared decision making, and that interventions directed at changing the way information is presented could be helpful.[46]

These findings suggest that elderly patients may view their involvement in treatment decisions differently than younger patients, who are more homogeneous in their preference of the shared decision-making model. A study of hospitalized patients with advanced cancer and a palliative treatment goal demonstrated that younger age and higher Karnofsky index were significantly associated with active involvement in making treatment decisions.[47] Furthermore,

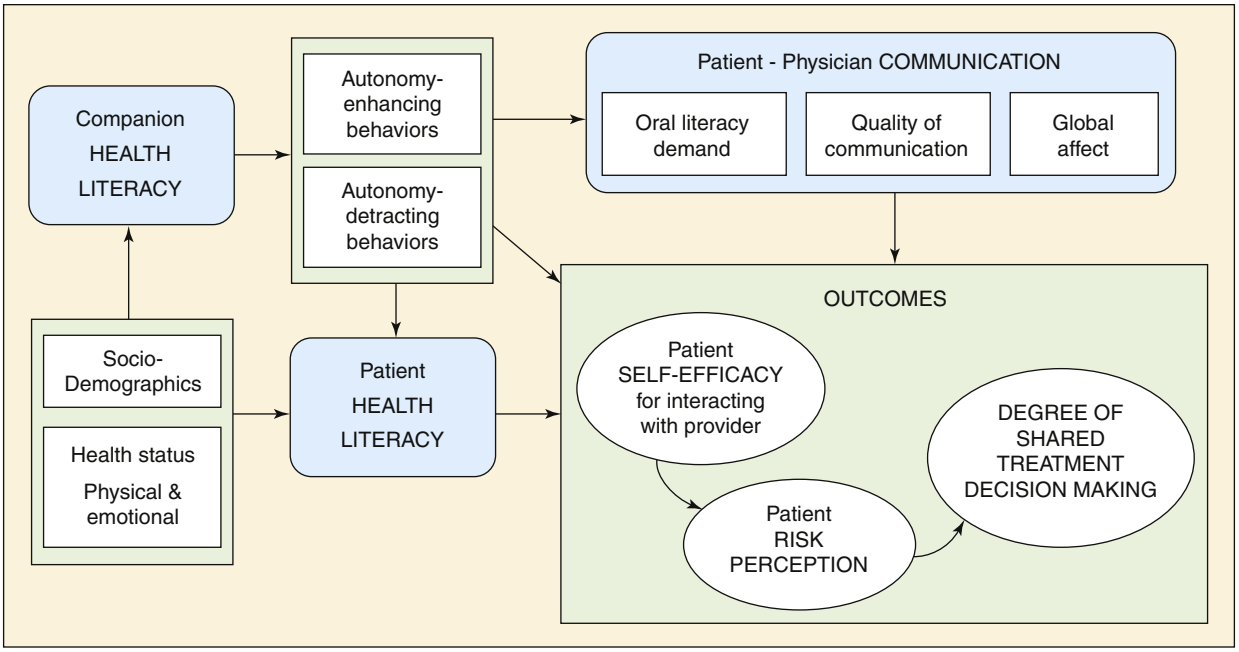

FIGURE 12-1 Impact of Three Key Variables on Outcomes The conceptual model above shows the effects of three variables (patient health literacy, patient-physician communication, and the role of the companion) on three outcomes (patient self-efficacy for decision making, risk knowledge, and satisfaction with the decision-making process). *(Reprinted with permission from Amalraj et al. Oncology 2009;23(4):369-75.)*

research in patients 70 years and older with a recent diagnosis of metastatic colorectal cancer found that relatively few (44%) wanted information about expected survival when they made a treatment decision, and 52% preferred a passive role in the treatment decision-making process.[48]

For older patients with advanced cancer, preferences for prognostic information and for an active role in treatment decision making are not easily predicted. Many factors including lower health literacy, socialized belief in the "traditional patient" role, and age bias among physicians who view older patients as passive participants can contribute to older patients assuming this passive role. Also, there may be a natural developmental tendency for older patients to want less responsibility for medical decisions and to rely on the expertise of others.[31] Explicit communication about decision-making preferences and the desire for specific facts such as prognostic information will help the oncologist distinguish which patients would benefit most from the shared decision-making model.[42, 49]

See expertconsult.com for a complete list of references and web resources for this chapter

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CHAPTER

13

Chemotherapy-Induced Myelosuppression in the Elderly

Bindu Kanapuru, Jerome W. Yates, and William B. Ershler

CASE 13-1

A 72-year-old man with a 40 pack-year smoking history is diagnosed with advanced lung cancer. His past medical history includes only hypertension. His creatinine level is 1.5 mg/dL. He lives with his daughter and is employed part-time as a volunteer in a gift shop. His daughter, a nurse, is concerned about the risks of myelosuppression with chemotherapy drugs and wonders about the benefit of chemotherapy at his age.

A 65-year-old woman with a diagnosis of node-positive breast cancer has been recommended to receive chemotherapy after surgery. She also has a history of diabetes, controlled with drugs, and she still maintains an active lifestyle. She wants to be treated with a regimen that offers her the maximum benefit, but is concerned that her age may increase the risk of infections and fatigue from the drugs.

Their primary physician decides to review the myelosuppressive toxicity of chemotherapy drugs in the elderly to help these patients make an informed decision.

PHYSIOLOGY OF AGING AS IT RELATES TO BONE MARROW FUNCTION AND RESERVE

Aging is a universal phenomenon that affects all normal cells, tissues, organ systems, and organisms. Accordingly, the bone marrow undergoes changes with age. Age-related hematologic changes are reflected by a decline in bone marrow cellularity, an increased risk of myeloproliferative diseases[1] and anemia,[2,3] and a declining adaptive immunity.[4,5]

The percentage of marrow space occupied by the hematopoietic tissue declines from 90% to 50% over the first 30 years of life and levels off thereafter, followed by a second decline to 30% at age 70, with the remaining space being taken up by fat.[6,7] A similar change occurs in the thymus, where involution begins at an earlier age and is reflected anatomically by a reduction in lymphoid mass with an increase in fat, and functionally by a steady decrease in the production of naive T cells.[8] Thus, fat infiltration into the bone marrow and thymus is associated with a reduced capacity to make new blood cells and diminished adaptive immune responses in late life.

Although age-related change in the bone marrow is well described, the exact mechanisms that regulate these changes remain speculative. For example, it remains unclear whether the age-associated expansion of marrow fat is a cause or an effect of aging and whether the changes seen in bone marrow and thymus are intrinsically related. All blood cells are derived from marrow pluripotent stem cells, which comprise 10% of the cellular fraction of cord blood but less than 1% of all adult bone marrow. Hematopoietic stem cells have a unique ability to self-renew, proliferate, and differentiate into every lineage of mature blood cells. Hematopoietic stem cells then give rise to two distinct multipotent stem cells within the bone marrow. Myeloid stem cells are precursors of granulocytes, monocytes, erythrocytes, and platelets; lymphoid stem cells are precursors of lymphocytes and plasma cells. There is always a large pool of maturing progenitors for each lineage within the bone marrow, allowing for rapid recruitment and release of cells in times of stress. The factors responsible for the constant turnover of these mature cells both inside the bone marrow and in the peripheral blood are poorly understood. However, there is evidence to support a role for both cell-intrinsic genetic programs and several hematopoietic growth factors within the bone marrow microenvironment in the regulation of hematopoiesis. Although a number of measureable changes occur in the stem cell compartment with aging, these changes do not compromise hematopoiesis in the absence of disease. Even when bone marrow is donated from a 65-year-old person to an HLA-matched younger recipient, the transferred marrow supports hematopoiesis for the life of the recipient.

Unlike the commonly held notion that stem cell compartments diminish either in number or function with age, ultimately resulting in an inability to meet homeostatic demands, age-related hematopoietic stem cell (HSC) changes appear to be an exception, at least for murine species in which this question has been most directly addressed. Early work demonstrated that marrow serially-transplanted could reconstitute hematopoietic

function for an estimated 15 to 20 life spans.[9] Furthermore, the capacity for old marrow to reconstitute proved superior to that of young marrow.[10] Subsequently, a number of investigators using a variety of techniques have concluded that HSC concentration in old mice is approximately twice that found in the young.[11-14] Some evidence suggests that the intrinsic function of HSCs changes somewhat with age, most notably with a shift in lineage potential from lymphoid to myeloid development. This may contribute to an observed relative increase in neutrophils and decrease in lymphocytes in the peripheral blood of older people.[15]Although no significant change is seen in the peripheral blood leukocyte count with aging,[16,17] several qualitative neutrophil defects have been described. For example, a decreased respiratory burst response to soluble signals,[16] defective phagocytosis,[17] and impaired neutrophil migration to sites of stress[18] have been described. Although the exact cause for these functional changes has not been clarified, it may be associated with an age-related alteration in actin cytoskeleton and receptor expression in leukocytes.[19] There is a decrease in the peripheral lymphocyte count that is first noticeable in the fourth decade, with a gradual progression thereafter throughout the remainder of the life span.[20] Studies have also demonstrated qualitative alterations in T-lymphocyte function in the elderly.[21] Although the HSC compartment is sufficient to maintain normal blood counts in older individuals who are healthy, there is now a substantial literature indicating that bone marrow reserve is diminished in the older compared to younger cancer patient, and this becomes of clinical importance for patients receiving chemotherapy or radiation.

CLINICAL OBSERVATIONS: MYELOSUPPRESSION IN OLDER CANCER PATIENTS

According to the 2002-2006 Surveillance, Epidemiology, and End Results (SEER) data from the National Cancer Institute, more than 50% of cancers are first diagnosed in patients older than 65 years. Furthermore, this group sustains approximately 70% of all cancer deaths (Figure 13-1).[22] Physicians tend to defer referring older patients for chemotherapy as compared to younger patients[23,24,25] despite evidence showing that the majority of the elderly are willing to accept cytotoxic treatment for possible benefit. Elderly patients who are referred to treatment are also likely to receive attenuated treatment when compared to younger patients. In the Annual Report to the Nation on the Status of Cancer, 1975-2002, Featuring Population-Based Trends in Cancer Treatment published in the Journal of National Cancer Institute in 2005, evaluation of cancer care delivery consistently showed that the elderly were less likely to receive standard therapy despite adjusting for comorbidities.[26] The perceived risk-benefit effect of chemotherapy, particularly concerns about increased myelosuppressive toxicity in the context of advanced age and declining health status, may influence this decision. Understanding the risk of hematological toxicity, the mechanisms related to its possible increased frequency in the elderly, and its best management may further improve treatment outcomes in the geriatric population.

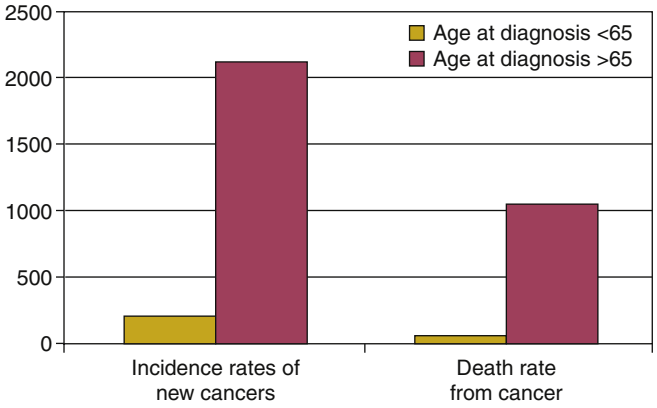

FIGURE 13-1 Age-adjusted incidence and death rates for all invasive cancers, 2002-2006. *(Adapted from SEER data.)*

BENEFIT TO OLDER PATIENTS FROM CHEMOTHERAPY

Several studies in different types of cancer including colon, lung, breast, and lymphoma have shown that older patients treated with standard intensive regimens derive similar benefit in terms of response. EORTC conducted a MEDLINE review of phase III and phase II studies of chemotherapy in the adjuvant and metastatic treatment setting of colon cancer. They recommended that cytotoxic combination chemotherapy regimens (5-FU with irinotecan or oxaliplatin) offered similar benefits in older patients and should be considered standard therapy for fit older patients.[27] In lung cancer, both the European Organisation for Research and Treatment of Cancer (EORTC) Elderly Task Force and the International Society for Geriatric Oncology found elderly patients seem to derive the same benefit from adjuvant chemotherapy as younger patients.[28] Elderly patients who receive standard-dose intensive treatments during treatment for non-Hodgkin lymphomas[29] (NHL) and breast cancer[30] also have comparable rates of response. Most of these studies also revealed that the chemotherapy tolerability is similar among the older and younger patients. In addition, despite a significant decrease in functional status during treatment, most elderly return to their pretreatment levels after completion of therapy. However, greater hematological toxicity is seen in most studies in the elderly compared to the younger patients.[30]

One of the earliest papers published evaluating the effects of chemotherapy on the elderly was a review of 19 Eastern Cooperative Oncology Group studies of advanced

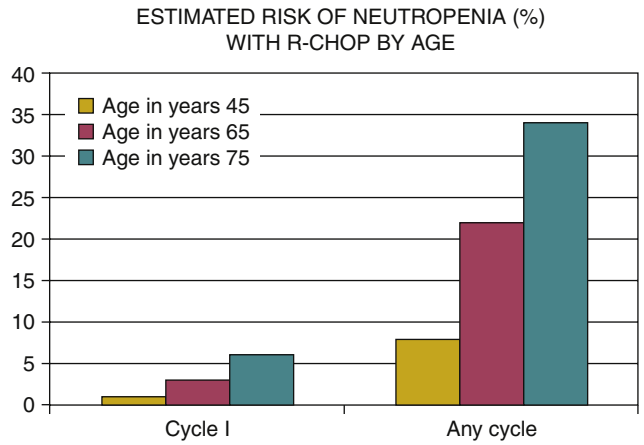

FIGURE 13-2 Estimated rates of neutropenia in an 80 kg subject with no risk factors. *(Adapted from Pettengell et al. Br J Haematol 2009;144(5):677-85.)*

cancer in eight disease sites. This study compared response rates and toxicity among 5459 patients younger than 70 to 780 patients older than 70. It reported that the elderly patients have similar response rates and survival expectancy as compared to the younger patients. Hematological toxicity was the most frequent side effect observed and was higher in those older than 70 years. Severe or worse toxicities (leukocytes less than 2000/mm^3, platelets less than 50,000/mm^3, neutrophils less than 1000/mm^3, or necessity for transfusions) was related to type of cancer, being more prevalent in patients with head and neck, ovarian, or gastric carcinomas; melanoma; and sarcoma.[31] Since then, advanced age has been consistently shown to predict an increased incidence of neutropenia, anemia, and infectious complications in multivariate regression risk models in a number of tumor types. In non-Hodgkin lymphoma patients, a risk model incorporating increasing age (10-year increments), increased dose, prior chemotherapy, recent infection, and low baseline albumin (less than 35 g/L) predicted higher risk of first-cycle febrile neutropenia with a sensitivity of 81% and a specificity of 80%.[32] Increasing age also was predictive for risk of febrile neutropenia in any cycle in this model (Figure 13-2). Pharmacokinetic studies of drugs in the elderly also demonstrate increased risk for neutropenia despite a failure to demonstrate an age-associated change in clearance.

MYELOSUPPRESSION IN ELDERLY LUNG CANCER PATIENTS

The majority (more than 50%) of non-small cell lung cancer (NSCLC) patients are older than 65 years. Chemotherapy protocols including platinum, non–platinum-based treatments like gemcitabine and vinorelbine, and taxane-based chemotherapy are widely used in treatment in either the adjuvant or advanced setting. Several retrospective analyses have found that elderly lung cancer patients benefit equally from treatment in the adjuvant setting but at the expense of increased hematological toxicity. Toxicity analysis in pooled studies of cisplatin for adjuvant treatment of lung cancer identified grade 3 neutropenia in more than 50% of patients older than 65 years.[33]

Anemia and neutropenia are the two most common short-term toxicities reported in elderly patients undergoing chemotherapy for advanced lung cancer, occurring in up to 20% of patients.[34] A recent prospective study in stage III or IV lung cancer patients also demonstrated a higher incidence (8% versus 2%) of febrile neutropenia in elderly patients older than 75 years as compared to those younger than 55 years.[35] Treatment of advanced lung cancer with combination chemotherapy regimens can also cause increased myelosuppression in the elderly. More than 80% of patients older than 65 years experienced grade 3/4 neutropenia in the TAX-326 study, which evaluated three platinum-based regimens with docetaxel/vinorelbine. In another study in which more than 15% of those enrolled were older than 70 years, cisplatin/paclitaxel or etoposide chemotherapy was associated with greater than grade 3 leukopenia in more than 70% of the elderly and anemia in more than 25%.[36] Incidence of grade 3/4 thrombocytopenia is usually low in most studies, around 10%, but this is significantly increased in regimens incorporating gemcitabine and/or carboplatin, where rates as high as 35% have been reported in the elderly population.[37] Combination regimens used in the treatment of small cell lung cancer also have a high incidence of anemia (28%), neutropenia (77%), and thrombocytopenia (26%) when evaluated in the elderly population.

MYELOSUPPRESSION IN BREAST CANCER PATIENTS

Older patients treated with chemotherapy for breast cancer have a higher risk of being hospitalized for hematological complications, including febrile neutropenia.[38] Increased hematological toxicity has been observed in the metastatic setting in elderly breast cancer patients. The Piedmont Oncology Group published their experience of hematological toxicity in the elderly in five trials conducted between 1974 and 1989 and reported twice the rates of severe neutropenia for those older than 70 who were treated with cyclophosphamide/doxorubicin regimens for advanced breast cancer. In the adjuvant setting, combination regimens of cyclophosphamide and doxorubicin, with or without paclitaxel have high rates of grade 4 neutropenia, ranging from 8% to 42% in elderly patients.[39] Fluorouracil-based combinations with methotrexate/doxorubicin and cyclophosphamide (CMF/CAF) appear to be associated with a slightly decreased risk of hematological toxicity in the elderly. For instance, in the International Breast Cancer Study Group Trial VII, which evaluated addition of CMF

to tamoxifen in the adjuvant setting, grade 3 neutropenia (neutrophil count < 750/μL) was seen in only 2.6% of patients and thrombocytopenia (< 50,000/μL) in 4.0%.[40] Very low rates of neutropenia and thrombocytopenia were also seen in the CALGB trial 8641, which tested different doses and durations of the CAF regimen.

Studies of toxicity in other solid tumors replicate findings in breast and lung cancer, with high rates of hematological toxicity in the elderly.

MYELOSUPPRESSIVE TOXICITY IN MALIGNANT LYMPHOMAS

Myelosuppressive toxicity is very common during treatment of hematological malignancies, as patients may start treatment with decreased values secondary to bone marrow invasion. In one study of 359 patients treated for malignant lymphoma ranging in age from 18 to 87 years and with 63% older than 50 years, more than 34% had hemoglobin levels less than 12 g/dL before starting chemotherapy, increasing to 49% during chemotherapy. Interestingly 53% of patients with grade 1 anemia by NCI criteria had anemia-related symptoms but were not offered any intervention.[41] Incidence of grade 4 neutropenia ranged from 4% to 91% in an analysis of 11 trials of elderly patients treated for non-Hodgkin lymphomas. The trials differed in the type of regimens used and also in the schedules administered, which most likely explains this wide range in incidence.[42] A subanalysis of a phase II trial in non-Hodgkin lymphoma in patients older than 60 years treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) therapy, reported severe neutropenia in 24% of cycles in patients aged 61 to 69 years and in 73% of cycles in patients aged 70 years or older. There was also a higher rate of neutropenic fever occurring in 8% of patients aged 61 to 69 years and in 42% of patients aged 70 years or older. Severe thrombocytopenia (<20,000/mL) was seen in 5% of patients aged 61 to 69 years and in 42% of patients aged 70 years or older.[43]

It is clear from the these data that myelosuppressive toxicity is definitely increased in the elderly as compared to the younger population. However, these retrospective analyses are hampered by limited representation of the elderly population, and the use of different definitions to evaluate the "elderly." It has been estimated that only 22% of patients in clinical trials are older than 65 years, and only about 10% are older than 70 years. Data on myelosuppressive effects of individual chemotherapy drugs in the elderly are very limited. Accordingly, we may be both overestimating efficacy and underestimating toxicity in the elderly on the basis of these trials.

Toxicities in clinical trials are generally assessed by WHO criteria, or more recently the NCI criteria, with grades from 1 through 4. However, these may be simplistic in their representation of the profound functional effects that can occur. For instance, by NCI Common Toxicity Criteria, grade 1 (mild) anemia represents a hemoglobin level of 10.0 g/dL to within normal limits; grade 2 (moderate), 8.0-10.0 g/dL; grade 3 (serious or severe), 6.5-7.9 g/dL; and grade 4 (life-threatening), less than 6.5 g/dL. Most studies report only grade 3 or 4 toxicities, as these represent the most severe toxicity. This likely underestimates the overall burden, as studies have shown that even a mild decrease in hemoglobin levels from normal in the elderly can be associated with increased morbidity and mortality.[44] Thus a true estimate of impact of anemia in the elderly is lacking.

CONSEQUENCES OF MYELOSUPPRESSIVE TOXICITY

One of the major consequences of increased hematological toxicity is that it increases the risk of suboptimal chemotherapy delivery in this group. Dose reductions are frequently employed upfront to reduce the risk of toxicity. Although this strategy has been successful in reducing myelosuppressive toxicity in the elderly population,[45] it is clearly associated with inferior outcomes and is probably one of the major factors contributing to increased mortality from cancer among the elderly.[46,47] Still, hospitalizations and mortality from febrile neutropenia are greater for elderly patients than for younger patients despite decreased dose intensity.[48] Myelosuppressive toxicity may also be persistent and decrease quality of life even long after completion of chemotherapy. Analysis of the Medicare SEER database to evaluate the incidence of chemotherapy toxicity-related conditions for 14 chemotherapy agents in elderly patients with non-small cell cancer revealed that the incidence of anemia increased from 20% to 35.9% during chemotherapy, and further increased to 30.7% to 37.6% when evaluated 3 months after chemotherapy. In a multivariate analysis, carboplatin, cisplatin, vinorelbine, paclitaxel and gemcitabine were significantly associated with development of long-term neutropenia and thrombocytopenia.

The economic burden in terms of supportive care during inpatient and outpatient hospitalization for febrile neutropenia is substantial, particularly in the management of hematological malignancies. Neutropenia has also been shown to influence the incidence and duration of nonhematological toxicities and to substantially decrease quality of life. Worsening or new-onset anemia during the course of chemotherapy significantly correlates with decreased performance status, increased fatigue, and overall decreased quality of life. Anemia also correlates with decreased survival in patients being treated for lymphomas and solid tumors. Major bleeding episodes associated with thrombocytopenia can lead to treatment delays and hospitalization, with resultant morbidity.

PREVENTING AND MANAGING MYELOSUPPRESSION IN THE OLDER CANCER PATIENT

Clearly, the hematological toxicity and adverse consequences from the same are increased in the elderly. Attempts to reduce this side effect include identifying and modifying treatment-related and patient-related factors that contribute to this increase.

MODIFICATION OF CHEMOTHERAPY TO REDUCE TOXICITY

Reduction in dose intensity has long been adopted as a way of reducing myelosuppression in the elderly population. For instance, in a retrospective nationwide survey of 567 oncology practices involving 4,522 patients with aggressive NHL treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); CHOP-rituximab (CHOP-R); or cyclophosphamide, mitoxantrone, vincristine, and prednisone (CNOP) elderly patients (older than 60 years) were more likely to receive less than 85% of the planned dose intensity, with an increased proportion of patients receiving this reduced dose for successive cycles.[49] However, as mentioned earlier, any benefit from reduced toxicity is countered by the reduced survival outcomes observed with decreased dose intensity or dose reductions.

Some chemotherapy regimens or drugs may be more myelotoxic than others in the elderly population. In a retrospective analysis of 132 patients aged 65 years or older with primary invasive breast cancer who received one of three different chemotherapy protocols: cyclophosphamide, methotrexate, fluorouracil (CMF); doxorubicin and cyclophosphamide (AC); or AC plus paclitaxel or docetaxel (AT-T); patients who received AC-based regimens were more likely to experience grade 3 or 4 hematological toxicity (32% versus 18%) and/or grade 3 neutropenic infection (29% versus 2%) as compared to those on the CMF regimen. The type of chemotherapy regimen (anthracycline compared to CMF) was a better predictor for toxicity than increased age or comorbidity score.[30] In the recent adjuvant CALGB trial (49907), breast cancer patients 65 years and older with a performance score of 0 to 2 were randomized to receive either "conventional therapy" (doxorubicin/cyclophosphamide or cyclophosphamide/methotrexate/fluorouracil [CMF]) or capecitabine. Approximately 50% of patients in the combination arm experienced severe hematological toxicity compared to less than 5% in the arm treated with capecitabine alone. However, response rates and survival were significantly better for those receiving combination therapies.

Similarly, in lung cancer patients, both docetaxel and vinorelbine demonstrated comparable efficacy in a phase III trial in older patients in terms of median survival but docetaxel was associated with more grade 3 to 4 neutropenia (82.9% vs. 69.2%).[50] Thus in a patient in whom occurrence of neutropenia will be life-threatening, vinorelbine is a reasonable option.

Incidence of specific myelosuppressive toxicities may also differ among regimens. In the elder specific subanalysis of the TAX-326 trial, patients with IIIB-IV NSCLC were randomized to docetaxel and cisplatin, docetaxel and carboplatin, or vinorelbine and cisplatin. The incidence of grade 3-4 thrombocytopenia and neutropenia was much higher in the elderly population on the docetaxel/carboplatin arm as compared to those on the other two arms. Grade 3-4 anemia was higher in the vinorelbine arm, occurring in 25% of those older than 65 years, as compared to 13.3% in the docetaxel/carboplatin arm and 5.4% in the docetaxel and cisplatin arm.[51]

Recently, a number of new drugs have been evaluated in the first-line and second-line treatment of lung cancer. Pemetrexed,[52] liposomal doxorubicin, and the newer targeted agents like erlotinib or gefitinib[53] may be less myelosuppressive and regimens incorporating these agents may be used more frequently to reduce the incidence of myelosuppression in the elderly. Interestingly, in a large analysis of advanced lung cancer patients older than 65 years, patients treated in combination with bevacizumab had a 60% rate of more than twofold increase in neutropenia within 2 months after chemotherapy. Another caveat with the use of targeted treatments in the elderly is that although hematological toxicity is reduced, nonhematological toxicity may be significantly enhanced, limiting the use of some of these drugs in this population.

Elderly patients with advanced lung and breast cancer also may be better served with a single chemotherapeutic agent than with combination regimens. A large randomized phase III trial (the Multicenter Italian Lung Cancer in the Elderly Study) of 700 elderly patients showed that the combination of vinorelbine plus gemcitabine was no more effective than single-agent vinorelbine or gemcitabine in the treatment of elderly patients with advanced NSCLC. Combination chemotherapy resulted in more thrombocytopenia (3%) than single-agent vinorelbine (<1%) and more neutropenia (13%), than single-agent gemcitabine (7%).[54]

Management of cancer in the elderly requires a careful consideration of the ultimate goal of treatment (cure versus palliation) and appropriate use of regimens to avoid further harm in this subgroup of patients.

Elder-specific trials with a gentler treatment-based approach have been proposed to improve management of older cancer patients (Table 13-1).[55,56] A pooled analysis of toxicity and outcomes in 118 elderly patients treated in two elderly-specific (inclusion criteria ≥ 65 years) and two nonspecific trials was conducted by the North Central Cancer Treatment Group. Grade 3 or worse hematological toxicity was seen in 68% of the elderly in age-unspecified trials as compared to 10% in the elderly-specific trials (neutropenia in 56% and 9% of patients, and thrombocytopenia in 14% and 1% of

TABLE 13-1 Myelosuppressive Toxicity (%) Reported in Patients in Elder-Specific Lung Cancer Trials

	Anemia		Neutropenia		Thrombocytopenia	
Regimen	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Gemcitabine/Vinorelbine	4	0	18	5	6	2
Vinorelbine [54]	1	0	14	3	4	1
Cisplatin/Gemcitabine	5		13.3	6.7	8.3	1.7
Cisplatin/Vinorelbine [55]	4.9		14.7	8.2		
Gemcitabine/Vinorelbine	2	0	16	13	3	<1
Vinorelbine	3	<1	14	11	<1	
Gemcitabine [56]	2		7	1	2	1
Docetaxel	2.3	1.1	26.1	56.8	0	0
Vinorelbine [50]	8.8	1.1	30.8	38.5	0	0

patients, respectively). There were no statistically significant differences with regard to treatment efficacy. However, conclusions from these trials are limited because of the small number of participants in the elder-specific trials.

PATIENT-SPECIFIC FACTORS AND MANAGEMENT

It remains unclear why some older individuals are predisposed to myelotoxicity and others are not. Certainly, age-related changes occur in other organs and tissues other than bone marrow that may contribute to this predisposition, particularly with regard to alterations in clearance and pharmacodynamics of potentially myelotoxic chemotherapy drugs. Awareness of these changes and appropriate adjustments for individuals with a reduced capacity to metabolize or excrete an active drug can eliminate or reduce myelosuppressive toxicity.

AGE-RELATED PHYSIOLOGICAL CHANGES

Changes in the Renal System

Age-associated changes in the kidneys including a decrease in glomerular filtration rate (GFR) and decreased concentrating ability predispose the elderly to a greater prevalence of chronic kidney disease, fluid and electrolyte imbalances, and impaired handling of drugs cleared by the kidneys with an increase in toxicity. It is estimated that GFR decreases at a rate of 1 mL/minute/year after the age of 40. Adjusting the dosage of drugs cleared by the kidneys may reduce the risk of toxicity. Assessing renal function using serum creatinine may be inaccurate as a result of decreased muscle mass in the elderly. An increased risk of hematologic toxicity was seen in older postmenopausal women with breast cancer and serum creatinine values of 1.5 mg/dL or less receiving adjuvant CMF compared to their younger counterparts. The creatinine clearance provides a more accurate estimate of renal function and can be used to predict toxicity. A retrospective study of 1,405 patients aged 65 years or older with breast cancer who were treated with CMF between 1998 and 2000 demonstrated increased hematological toxicity for those with a calculated creatinine clearance of less than 50 mL/min.[57] Increased myelosuppression associated with renal insufficiency has been observed with melphalan, fludarabine, cisplatin, etoposide and topotecan in those older than 70. Dose modifications are recommended on the basis of creatinine clearance, particularly for elderly patients being treated with these drugs. Another prospective study in older breast cancer patients showed that hematological toxicity was substantially decreased by treating with modified dosing of cyclophosphamide and methotrexate on the basis of the estimated creatinine clearance.[58] Many methods of calculating creatinine clearance are available, but the most commonly used is the Cockcroft-Gault formula, which calculates clearance on the basis of age and weight. However, this formula may also underestimate creatinine clearance in the elderly.

Changes in the Gastrointestinal System

Altered hepatic enzyme function leads to abnormalities in the metabolism of selected drugs. Decreased intracellular water, increased fat content, and low albumin in the elderly can significantly alter the volume and distribution of drugs. The pharmacokinetics and pharmacodynamics of the drugs may be influenced by their bound and unbound fractions. Both paclitaxel and docetaxel are extensively protein bound and are metabolized by the cytochrome P450 enzymes in the liver. No dose modification on the basis of age alone is recommended, but care should be exercised in elderly patients with indicators of poor nutritional status and who are on multiple drugs. Increased hematological toxicity due to altered gastrointestinal drug absorption secondary to age-associated decreased motility and decreased blood flow may be seen with oral cancer drug therapy.

TABLE 13-2 Special Considerations for Chemotherapy Drug Dosing in the Elderly

Chemotherapy	Malignancy	Effect of Age on Pharmacokinetics	Modifying factors	Side Effects
Cyclophosphamide	Lymphomas; breast cancer	No change	No dose reduction for renal or hepatic dysfunction	Increased myelosuppression in secondary to toxicity at the cellular level; hemorrhagic cystitis
Cisplatin	Head and neck, lung cancers	No change	Kidney function	Myelosuppression, renal toxicity, ototoxicity, neuropathy
Carboplatin	Head and neck, lung cancers	No change	AUC based on Calvert formula	Myelosuppression but generally well tolerated
Doxorubicin	Breast cancer; lymphomas	No change	Dose reduction in patients with hypoalbuminemia	Cardiac toxicity and myelosuppression
Vinorelbine	Lung cancer	No change	Severe liver dysfunction, highly bound to platelets	Myelosuppression
Docetaxel Paclitaxel	Lung, prostate, and breast cancers	Conflicting data on clearance in older population; no dose adjustment for age alone	Metabolized by cytochrome P450 system, highly protein-bound; high interpatient variability; caution in patients with liver dysfunction	Neutropenia, fatigue
Gemcitabine	Lung and pancreatic cancers	Small increase in mean half-life with age; no dose changes on the basis of age alone	Caution in patients with renal and hepatic impairment	Neutropenia and thrombocytopenia
Etoposide	Lung cancer, lymphomas	Increase in free etoposide levels seen with oral therapy; minor dose reductions are recommended even in elderly with normal organ function	Hypoalbuminemia, increased bilirubin, and renal dysfunction can increase toxicity	Myelosuppression
Oxaliplatin	Colon cancer	No change	Severe renal dysfunction	Neuropathy and myelosuppression
Irinotecan	Colon cancer	Reduced dose recommended in patients older than 70 years and poor performance status	Toxicity increased with severe liver dysfunction	Diarrhea and myelosuppression

PHARMACODYNAMICS OF DRUGS AND AGING

Most of the commonly used chemotherapeutic drugs do not show changes in their clearance with age (Table 13-2) in the presence of functioning renal and gastrointestinal systems. Serum concentrations from oral etoposide are known to increase with age and correlate with nadir neutrophil counts after the first cycle. The Cancer and Leukemia Group B conducted a trial (CALGB 9762) and found a significant decrease in total body clearance of paclitaxel in the cohort of patients aged 75 years or older compared with those aged 55 to 64 and 65 to 74 years, with a resultant increase in grade 3-4 neutropenia of 49%. However, other studies have failed to show any change in paclitaxel clearance with age, and dose reduction is not recommended on the basis of age. Age alone is not a basis for dose reduction for many of these drugs in an otherwise healthy elderly patient.

PHYSIOLOGICAL VERSUS CHRONOLOGICAL AGE

Although aging is associated with physiological changes that may predispose the elderly to increased toxicity, the rate of aging is not the same in all individuals. Assessments on the basis of chronological aging may not be accurate enough to determine the tolerance to chemotherapy. The number of comorbid conditions increases with age. An NIA/NCI study estimated that the mean number of comorbidities increases with age: 2.9 for those 55-64 years, 3.6 for those aged 65-74 years, and 4.2 for those 75 years or older. At least 30% of those older than 75 were estimated to have six or more comorbid conditions.[59] Increasing number and severity of comorbidities both predict for increased hospitalization from hematological toxicity during chemotherapy in elderly cancer patients and also correlate with decreased survival.[38,59,60] (Figure 13-3). Several indices of comorbidities have been developed to evaluate the risk of treatment

toxicity in elderly patients; however, they all have limitations in their application.[61] The most commonly used is the Charlson Comorbidity Index (CCI), an instrument that has been validated in cancer patients; it can predict the ability of elderly cancer patients to tolerate chemotherapy and can assist in planning treatment options.[62,63]

The general decline recognized as "frailty" is a multifactorial syndrome characterized by diminished physiological reserve and decreased ability to withstand stress. There are now objective criteria to better define this syndrome. One set of criteria, established as a component of the Cardiovascular Heart Study (CHS) included assessment of grip strength, walking speed, weight loss, exhaustion, and physical activity to define the frail phenotype. It is clear from multiple studies that frail subjects have increased comorbidities, disabilities, falls, institutionalization, and mortality. It would seem likely, but is yet unproven, that frailty would be associated with increased chemotherapy toxicity, including myelosuppression. Oncologists are familiar with functional assessment, having grown accustomed to either or both the Karnofsky or ECOG Performance Status (PS) evaluations. Nonetheless, it has been shown that nearly 40% of patients with ECOG performance status less than 2 (the level traditionally used in clinical trials) could have limitations in their activities of daily living (ADLs) and independent activities of daily living (IADLs).[64]

Because of different variables involved in predicting tolerance, the National Comprehensive Cancer Network (NCCN) has recommended a multidisciplinary approach to evaluate tolerance to chemotherapy in the elderly. A typical Comprehensive Geriatric Assessment (CGA) provides information relating to the comorbidity, functional status, cognition, mental status, social support, nutritional status, and medications of older adult patients in an effort to identify unsuspected conditions that may have an impact on the potential success of cancer therapy. This concept has been tested in older breast cancer patients in whom use of the CGA identified three or more functional deficits and poor tolerance to chemotherapy in nearly 60% of patients who had been rated by their physicians as "not ill." CGA was also used in 83 advanced ovarian carcinoma patients older than 70 years who received carboplatin AUC 5 and cyclophosphamide. Patient autonomy (functional status), comorbidities, daily medications, nutritional status, cognitive function, and the presence or absence of clinical symptoms of depression was assessed prior to starting chemotherapy. Depression symptoms and poor functional status (living at home with assistance, living with medical assistance in a specialized institution), were predictive of chemotherapy-induced severe toxicity including febrile neutropenia and early treatment withdrawal because of toxicity.[65] Despite these advances, there is no standardized method of CGA available at the present time for elderly cancer patients.

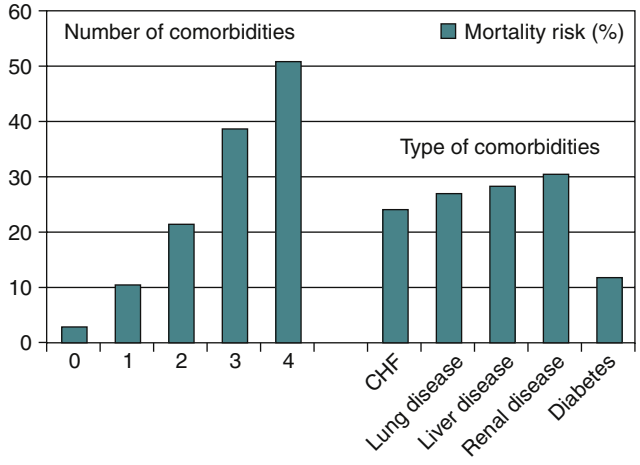

FIGURE 13-3 Mortality risk (%) from febrile neutropenia based on the number and type of comorbid illnesses. *(Adapted from Kuderer et al. Cancer 2006;106(10):2258-66.)*

MANAGEMENT OF CHEMOTHERAPY-INDUCED TOXICITY

After reviewing the available evidence and patient assessment, the 72-year-old advanced lung cancer patient is treated with single-agent gemcitabine on the basis of the results of the MILES study.

The node-positive postmenopausal breast cancer patient is treated with dose-dense adriamycin, cyclophosphamide, and sequential paclitaxel in order to maximize her treatment outcome with a curative intent.

Is there a role for prophylactic white blood cell growth factor support in these patients?

Role of Granulocyte-Stimulating Growth Factors

Retrospective review of clinical studies utilizing granulocyte colony-stimulating factor (G-CSF) and erythropoetin have shown that the elderly can respond to growth factors quickly and with a comparable increase in cell counts to younger patients. These agents are in the forefront of managing neutropenic toxicity in patients receiving chemotherapy both in primary and secondary prophylaxis and in the treatment setting. G-CSF has been shown to reduce the incidence of febrile neutropenia, hospitalization, and the need for intravenous antibiotics in metastatic breast cancer patients by more than 80%.[66] The preponderance of evidence shows that these agents are very beneficial in the elderly population as well. In elderly NHL patients, randomized trials have shown that the use of G-CSF can reduce the incidence of neutropenic infection by almost 100%. Similarly, use of G-CSF in elderly patients with acute myeloid leukemia was associated with significantly shorter duration of neutropenia and decreased use of antibiotics. Granulocyte-macrophage colony-stimulating factor (GM-CSF) also

has been shown to reduce time to neutrophil recovery as compared to placebo in elderly patients with acute myeloid leukemia (AML). Specifically, prophylactic use from the first cycle has been recommended because of the high frequency of first-cycle neutropenia seen in patients who did not receive G-CSF. In a large randomized controlled trial of elderly patients treated for solid tumors, pegfilgrastim use during the first cycle of chemotherapy decreased the incidence of grade 3 or 4 neutropenia from 68% to 26%, reduced antibiotic use and hospitalizations due to febrile neutropenia, and reduced the frequency of dose delays and dose reductions.[67] A recent systematic review and meta-analysis of randomized controlled trials comparing primary prophylactic G-CSF with placebo or untreated controls in adults with solid tumors or malignant lymphomas reported a 40% reduction in febrile neutropenia with the use of G-CSF in patients older than 65 years. Use of G-CSF in all patients regardless of age nearly halved the relative risk of infection-related and early mortality in solid tumor trials.[68] The NCCN Guidelines for Senior Adult Oncology and the American Society of Clinical Oncology (ASCO) recommend the prophylactic use of white blood cell (WBC) growth factors in clinical situations where the risk of neutropenia is greater than 20%.[69] Age older than 65 years was identified as an important patient characteristic that identified individuals for the receipt of prophylactic growth factor treatment. WBC growth factors are also recommended in older patients receiving curative therapy in the treatment of NHL or for adjuvant breast cancer treatment, where maintenance of dose intensity is essential to achieve a good outcome. Retrospective review of four randomized trials in adjuvant breast cancer reported a better overall survival in those who received more chemotherapy than in those who received less, regardless of age. The reduction in hazard of failure from more chemotherapy was 40% for those older than 65 years and 18% in those 50 years and younger.

The use of CSF therapy is also appropriate in this group when the risk of neutropenia from individual regimens is less than 20%, if other patient-related factors suggest a high risk of morbidity and mortality from neutropenia (Table 13-3). Treatment with CSF can be used to reduce the duration of neutropenia and the incidence of hospitalizations in these patients. Prophylactic antibiotic use with or without G-CSF has shown similar beneficial effect in some studies but no clear recommendation has been made about their use in elderly patients for prophylactic or secondary use for chemotherapy-induced neutropenia.

The risk of administration of growth factors is minimal, although a slight increase in thrombocytopenia has been reported with the use of GM-CSF. An increased incidence of bone and musculoskeletal pain has also been reported with use of G-CSF or GM-CSF. One note of concern, however, is that a greater number of breast cancer patients treated with white cell hematopoietic growth factors were subsequently diagnosed with myelodysplastic syndrome or acute myeloid leukemia. The exact association with this outcome is unclear as older AML patients treated with these agents did not show progression of leukemia or worse outcomes.

TABLE 13-3 Indications for Prophylactic WBC Growth Factors in the Elderly

Risk of febrile neutropenia from chemotherapy ≥ 20%
Risk of febrile neutropenia from chemotherapy 10% to 20% and presence of additional risk factors for infectious complications:
• Previous episode of febrile neutropenia
• Advanced disease
• Heavily pretreated patients
• Presence of cytopenias due to bone marrow involvement
• Malnutrition
• Current infections
• Liver or renal dysfunction
• Multiple comorbidities
• Poor performance status
To support the administration of planned doses of chemotherapy on schedule in patients undergoing treatment with curative intent (CHOP or CHOP-like regimens)

The patient with lung cancer does not receive prophylactic WBC growth factors, as the risk of febrile neutropenia with this regimen is less than 10%. He tolerates the treatment well except for increasing fatigue. Complete blood count reveals a hemoglobin level of 10 g/dL.

The 65-year-old breast cancer patient is given prophylactic filgrastim to prevent neutropenia, as the regimen is associated with a greater than 20% risk of febrile neutropenia. She also maintains dose intensity and schedule. She is noted to have a hemoglobin level of 11.5 g/dL after three cycles and reports mild fatigue.

Do they require any intervention at this time for the anemia?

Management of Chemotherapy-Induced Anemia

Anemia during cancer chemotherapy is associated with significant changes in quality of life. Recombinant erythropoietin has been used widely in the management of anemia during treatment of cancer. Although specific trials in the elderly are lacking, numerous randomized studies have shown a correlation between an increase in hemoglobin levels to 12 g/dL or more and improvement in fatigue and quality of life. Treatment with epoetin alfa and darbepoetin has also been shown to reduce the risk of blood transfusion by 18% in patients receiving chemotherapy; however, the use of these agents has come under severe scrutiny recently because of some published studies on their use with breast and head and neck cancers. In these trials of recombinant erythropoietin, an increased risk of thromboembolic events and possibly of tumor progression, with a reduction in chemotherapy response, was reported. The use of erythropoietin-stimulating agents

(ESA) is contraindicated in patients who are undergoing chemotherapy with a curative intent. Their use is also prohibited in patients with cancer-related anemia not related to chemotherapy. Although most of these trials targeted hemoglobin levels of 13 g/dL, the FDA reported that there was insufficient evidence to conclude that these agents do not decrease survival or promote tumor progression at hemoglobin (Hb) levels between 10 and 12 g/dL. The American Society of Hematology and the American Society of Clinical Oncology recommend the use of epoetin or darbepoetin for patients with chemotherapy-associated anemia and a hemoglobin concentration that is near to or less than 10 g/dL, with the primary goal of treatment being to increase hemoglobin and decrease transfusions. They recommend caution in the use of erythropoietin in patients receiving chemotherapy for hematological malignancies and those with an increased risk of thromboembolism. In patients with lymphomas, additional causes of anemia such as hemolytic anemia and bone marrow suppression should be ruled out. If patients do not respond with an increase in hemoglobin after initiating treatment, ESAs may be considered with the intent of reducing the transfusion requirement. In patients with milder degrees of anemia, the decision about the early use of erythropoietin should be made on the basis of individual circumstances and clinical situations. Priority should be given to identifying reversible causes of anemia including evaluating for deficiencies in iron, folate, or vitamin B12. Intravenous iron has been shown to increase hemoglobin response to erythropoietin, as well as to decrease the duration of treatment required to achieve the response, independent of iron stores, and may be used effectively in cancer patients.

Initial physical examination and history reveal no other cause for the anemia in these patients.

The ferritin level in the older gentleman was 250 μg/L. As he is receiving palliative chemotherapy and is symptomatic, a trial of epoietin alfa at 40,000 units weekly was started, to see if the hemoglobin levels will increase and his symptoms improve. The patient was also given intravenous iron. He responded to treatment, with an increase in his hemoglobin level to 11.5 g/dL after 8 weeks and an improvement in symptoms.

In the postmenopausal breast cancer patient, ESAs should not be used to manage anemia as her anticipated treatment outcome is cure. No specific cause was identified in this patient and there was no intervention. The patient should be followed regularly to assess her symptoms and any requirement for transfusion.

Management of Chemotherapy-Induced Thrombocytopenia

Besides treatment dose reductions or dose delays, platelet transfusions are the only effective way to manage thrombocytopenia associated with chemotherapy. The appropriate threshold for platelet transfusion during chemotherapy recommended by the ASCO is a platelet count less than 10 $\times 10^9$/L.[70] The risk of major hemorrhage is very rare above this level, and the risk of alloimmunization and platelet refractoriness can be reduced. However, these levels may have to be modified in the elderly population who may have other risk factors for bleeding including use of anticoagulant drugs and poor performance status. Interleukin-11, the only growth factor approved for management of chemotherapy-induced thrombocytopenia, is effective in reducing the requirement for platelet transfusions but is associated with fluid retention and other cardiovascular side effects that may be problematic in the elderly population.[71] The thrombopoetin receptor agonists romiplostim and eltrombopag are currently undergoing phase I and II trials for management of chemotherapy-induced thrombocytopenia.

TABLE 13-4 Recommended Domains for Research to Reduce Myelosuppressive Toxicity in Older Cancer Patients

1. Comprehensive Geriatric Assessment in elderly patients with cancer
2. Age-appropriate dose modification
3. Accurate assessment of renal and hepatic functions
4. Use of less myelosuppressive chemotherapy regimens
5. Single-agent rather than combination regimens in appropriate patients
6. Elder-specific clinical trials to assess response and tolerance to chemotherapy

CONCLUSION

Myelosuppression is an important complication of chemotherapy in elderly cancer patients and requires careful appraisal and treatment (Table 13-4). Chronological age is not the only consideration when estimating the ability of a patient to tolerate chemotherapy. The Comprehensive Geriatric Assessment evaluating multiple geriatric domains should be used when possible to help identify elderly patients likely to benefit from chemotherapy. Appropriate use of growth factors in the elderly will reduce myelosuppressive toxicity while maintaining dose intensity and can improve treatment outcomes in the elderly.

See expertconsult.com for a complete list of references and web resources for this chapter

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CHAPTER

14

Nonhematologic Complications of Systemic Treatment of Cancer in the Older-Aged Person

Lodovico Balducci

The management of cancer in the older-aged person is an increasingly common problem, because the population is aging and cancer is largely a disease of aging.[1] Aging involves a progressive loss in functional reserve of multiple organs and consequently increased susceptibility to the complications of cancer treatment. These are important for several reasons. First of all, they may cause discomfort, disease, and death. Second, they may prevent the administration of effective cancer treatment. Third, they may lead to functional dependence that is associated with poorer quality of life and higher management cost. In this chapter, the nonhematological complications of systemic cancer treatment are examined, including descriptions of both the acute and chronic complications of hormonal, cytotoxic, and targeted therapy. At the end of the chapter, the unsolved issues related to the management of cancer in the older-aged person are outlined and a research agenda to address these issues is proposed.

CASE 14-1

A 75-year-old woman is diagnosed with early-stage breast cancer. After lumpectomy and radiation, she meets with her medical oncologist who discusses adjuvant treatment; the decision is made to treat her with hormone therapy alone, and she is placed on an aromatase inhibitor. Two months later she visits her primary care provider stating that she seems to be tolerating her new medication, but asking for pain medications for her worsening arthritis. She also mentions that she had a fall about 2 weeks ago but luckily did not break any of her bones. However, the emergency department physician noted that she appeared to have some "bone weakness" on her x-ray.

HORMONAL TREATMENT

Hormonal manipulations are the mainstay treatment of prostate and breast cancer. In this section the complications of luteinizing hormone-releasing hormone (LHRH) analogs, estrogen, aromatase inhibitors, and selective estrogen receptor modulators (SERMs) are addressed.

LHRH Analogs

For more than 20 years, these agents have been used to induce chemical castration in patients with prostate cancer. The definitive benefits of this treatment have been demonstrated in only two circumstances: in the presence of metastatic disease confirmed by imaging[2] and in combination with radiation therapy for the management of locally advanced disease (stage C or III).[3] The benefits of adjuvant hormonal treatment in patients at high risk of recurrence are controversial.[4] Despite a lack of any evidence, it has become common practice to induce chemical castration in patients experiencing so-called chemical (PSA) recurrences.

In addition to loss of libido, chemical castration is complicated by hot flushes, fatigue, and possibly anemia.[5-7] It is not clear whether it may also cause cognitive decline. Fatigue is particularly ominous, as it has been associated with an increased risk of functional dependence and of death in older individuals.[8-10] Likewise, anemia has also been associated with death, functional dependence, and geriatric syndromes including falls and dementia.[11]

The best established long-term complication of castration is osteoporosis.[12-14] Treatment with LHRH analogs for longer than 1 year has been associated with increased risk of fracture that increases directly with treatment duration.[12] Other potential complications include diabetes and increased incidence of coronary events in patients with a preexisting history of coronary artery disease.[15-16]

The best management of complications from LHRH analogs is prevention, which includes avoiding the unwarranted use of these compounds. Hot flushes may respond

to progesterone, to gabapentin, and to antidepressants, but these medications carry their own set of complications. Fatigue may be ameliorated with exercise.[17] The benefit of provigil in these situations is controversial.

Bone loss may be reversed by bisphosphonates or RANK ligand inhibitors (denosumab). These compounds are recommended in patients who already have osteopenia and in those for whom treatment with LHRH analogs for longer than 1 year is planned.[13-14]

A number of alternative approaches may also obviate some of the complications of LHRH analogs. These include: intermittent castration, use of androgen antagonists in lieu of LHRH analogs, LHRH inhibitors, and novel compounds such as abiraterone and more specific androgen antagonists.

Intermittent castration has become increasingly popular,[18] though it has not been conclusively demonstrated that it is as effective as continuous castration. In one study, bicalutamide in high doses was found to be as effective as castration in patients with metastatic prostate cancer.[19] This approach may allow some patients to preserve their libido, but it is expensive and associated with painful gynecomastia (that may be prevented by prophylactic breast irradiation). It is not clear whether long-term treatment with this compound may also lead to osteoporosis, diabetes, and coronary artery disease. Direct LHRH antagonists have only recently been introduced in the management of prostate cancer.[20] Their main indication is in treatment of patients with critical metastases (such as impending spinal cord compression or urinary obstruction) for whom LHRH analogs are contraindicated. At least theoretically, the complications of these agents should be similar to those of LHRH analogs.

Two types of drugs appear particularly promising in the management of hormone-sensitive prostate cancer: abiraterone[21] and highly selective androgen antagonists.[22] Both types of compounds were found active in "hormone-refractory prostate cancer," as they antagonize the effect of dihydrotestosterone synthesized within the cancer. Abiraterone is a selective inhibitor of androgen synthesis that prevents the synthesis of dihydrotestosterone within the gonads, the adrenals, and the tumor.[21]

Estrogen

Though seldom used nowadays, estrogen may provide effective and inexpensive treatment of both prostate and breast cancers. In metastatic prostate cancer, diethylstilbestrol (DES) appears to be at least as effective as LHRH analogs.[23] Unlike LHRH, estrogen does not cause loss of libido, osteoporosis, or hot flushes. Complications include painful gynecomastia and deep vein thrombosis. A never-solved controversy is whether DES in low doses (1 mg/daily) is as effective as and less risky than the most commonly used dose of 3 mg per day. Retrospective studies suggest that this may be the case. Despite low cost and safety, the use of estrogen in metastatic prostate cancer has almost disappeared in the USA as a result of the aggressive marketing of LHRH analogs.

In metastatic breast cancer, DES at high doses (15 mg daily) is as effective as tamoxifen and may prove effective in 15% of patients whose cancer progressed while they were receiving tamoxifen.[24] The complications of this treatment include deep vein thrombosis, fluid retention, and congestive heart failure, and the risk of these increases with patient age.

Selective Estrogen Receptor Modulators (SERMs)

These include tamoxifen, toremifene, and raloxifene. Fulvestrant (Faslodex), although a pure estrogen antagonist, will also be discussed in this group.

Until recently, tamoxifen has been the mainstay treatment of hormone receptor-rich breast cancer.[25] This agent has reduced by 40% the systemic recurrence of breast cancer after surgery. Recent pharmacogenomic studies showed that tamoxifen is effective in women who are rapid metabolizers, that is, women in whom the activity of CYP2D6 is increased, because this enzyme converts the inactive parent compounds into active metabolites.[26] The concomitant prescription of tamoxifen and CYP2D6 inhibitors, such as paroxetine, should then be avoided. Toremifene has comparable activity as tamoxifen. Raloxifene is untested in the management of breast cancer. Tamoxifen and raloxifene reduce by approximately 50% the incidence of hormone receptor-rich breast cancer in women at risk.[27] Other beneficial effects of SERMs include prevention of osteopenia and osteoporosis and decreased serum cholesterol levels.[28] SERMs cause hot flushes, vaginal secretions, and deep vein thrombosis (DVT). In rare instances, tamoxifen and toremifene, but not raloxifene, cause endometrial cancer. Risk factors for DVT and endometrial cancer include age 70 or older and obesity.[29]

Hot flushes may be ameliorated by antidepressants and gabapentin.[29] The benefit of serial gynecologic exams for early diagnosis of endometrial cancer is controversial.

Being a pure antiestrogen, fulvestrant does not cause either DVT or endometrial cancer. The effect of this compound on the bone is not well understood, as it has not been studied in the adjuvant setting where long-term complications are expected.

Aromatase Inhibitors

These compounds have largely superseded SERMs in the treatment of breast cancer, in both the adjuvant and the metastatic setting.[30] Like tamoxifen, they may cause hot flushes. An especially troublesome complication is arthralgias, whose pathogenesis is poorly understood.[31] Arthralgia may represent a cause of functional

limitations in older women. Unlike the SERMs, these compounds cause osteoporosis.[30] Early treatment with bisphosphonates such as zoledronic acid did prevent bone loss in the Z-fast study[32] but it has not been proven yet that this treatment prevents bone fractures. Current recommendations for the management of osteopenia and osteoporosis include assessment of bone density at the beginning of treatment and serially thereafter and institution of bisphosphonate therapy in the presence of bone loss.[33] Prophylactic bisphosphonate treatment in all women receiving aromatase inhibitors is not recommended.

Aromatase inhibitors have also been associated with an increase in serum cholesterol, but there is no evidence that they cause increased incidence of coronary artery disease or stroke.

In conclusion, hormonal treatment is the safest form of systemic cancer therapy for older individuals. Osteoporosis and increased risk of bone fractures are common complications of chemical castration for prostate cancer and of aromatase inhibitors, but these complications may be offset by bisphosphonates or RANK ligand inhibitor. Except in its application for chemical castration in patients with a preexisting history of coronary artery disease, there is no proof that LHRH analogs may cause coronary death. Deep vein thrombosis complicates treatment with estrogen and to a lesser extent with SERMs. Age and obesity are risk factors for these complications. Aromatase inhibitor-associated arthralgia may be a cause of disability for some older women.

As is the case for any medications, hormonal treatment should not be used in conditions when the risks supersedes the benefits. That seems to be the case for chemical castration in presence of chemical recurrence of prostate cancer.

CASE 14-2

A 75-year-old woman is diagnosed with early-stage breast cancer. After lumpectomy and radiation, she meets with her medical oncologist who discusses adjuvant treatment; the decision is made to treat her with both adjuvant chemotherapy and hormone therapy. Prior to starting therapy, she visits her primary care provider with concerns about the side effects of chemotherapy, as one of her friends mentioned that it is bad for the brain and the heart. She wants to know whether she should go through with it and if there is anything that she can do to avoid these complications.

CYTOTOXIC CHEMOTHERAPY

The risk of both acute and long-term complications of cytotoxic chemotherapy increases with age. Acute complications include mucositis, cardiotoxicity, and peripheral neuropathy. Chronic complications include chronic subclinical cardiac dysfunction, peripheral neuropathy, acute leukemia, myelodysplasia, and, possibly, dementia and functional dependence.

Acute Complications

Mucositis. The risk of mucositis from fluorinated pyrimidines and anthracyclines increases with age.[34] Mucositis may lead to volume depletion because of diarrhea and dysphagia. This complication is more rapid and more severe in older than in younger individuals because the total body water decreases with age.[34] It is not clear why mucositis is more common and more severe in older individuals. A possible explanation is found in aging rodents, in whom the proliferation of cryptal cells increases with age while the reserve of mucosal stem cells is diminished.[34] This condition would predispose to mucositis by a twofold mechanism. The increased proliferation would render the cryptal cells more susceptible to destruction by cycle-active agents while the depletion of mucosal stem cells would delay the repair of the mucosal damage.

In addition to age, other risk factors for mucositis include female sex, ethnic group, and genetics, including hereditary deficiency of enzymes involved in drug metabolisms.[35] New insight in the pathogenesis of mucositis reveals that the administration of cytotoxic drugs leads to oxidative damage, activation of stress-response genes, and increased production of nuclear factor KB and inflammatory cytokines that maintain and amplify the mucosal damage.[35] In addition, chemotherapy-induced alterations in the oral and intestinal flora may also play a role in the pathogenesis of mucositis.[35]

The management of mucositis is unsatisfactory.[36-37] The only medication that was proven to reduce the incidence and severity of mucositis in randomized controlled studies has been the keratinocyte growth factor.[38] This compound has not received widespread acceptance, however, because it is expensive and requires administration over several days. Recently, oral spray of human intestinal trefoil factor has ameliorated the risk of mucositis in a double blind phase II randomized study.[39] Physiologically, trefoil factor binds to mucin and prevents mucosal damage. It is produced by goblet cells, which are destroyed by cytotoxic chemotherapy.

The substitution of intravenous fluorinated pyrimidines with capecitabine has reduced the risk of mucositis, but capecitabine in full doses is not well tolerated for other complications, especially the hand-foot syndrome. Furthermore capecitabine is contraindicated in patients with renal insufficiency, which is an almost universal condition of age and is associated with interaction with drugs metabolized through the cytochrome p450 system. The use of these drugs, such as warfarin, increases with age.

Aggressive fluid resuscitation should be initiated without delay in patients who cannot drink because of diarrhea.

Neuropathy. Peripheral neuropathy is a common complication of alkaloids, epipodophyllotoxins, taxanes, epothilones, cisplatin, and oxaliplatin.[40] The risk of this

complication increases with age. In older patients, these complications are also longer-lasting and more debilitating. Loss of sensation in the fingers may prevent the performance of basic ADLs including dressing, feeding, and toileting. Loss of sensation in the toes is associated with ambulatory difficulties and falls.

No antidote to peripheral neuropathy is available. Early discontinuance of the offending medication is the only effective prevention. In general, docetaxel appears to cause less neuropathy that other taxanes, but it is more myelotoxic.

Cardiomyopathy. The incidence of this often irreversible anthracycline complication increases with age and with medication dose.[41] The interaction of the medication with intracellular iron causes the production of free radicals that lead to a progressive damage of the cardiac sarcomeres. Cardiomyopathy may be prevented with the administration of doxorubicin by continuous intravenous infusion or with the administration of desrazoxane. This agent prevents the production of free radicals by chelating the cellular iron and preventing its interaction with the anthracyclines. Unfortunately, desrazoxane may reduce the antineoplastic effectiveness of doxorubicin[41] and is associated with increased risk of mucositis and myelotoxicity, which also become more common with age. The substitution of doxorubicin with pegylated liposomal doxorubicin (PLD) may reduce the risk of cardiomyopathy and other anthracycline complications including nausea and vomiting, alopecia, and myelotoxicity. The cancers for which the effectiveness of PLD has been proven include multiple myeloma, metastatic breast cancer, ovarian cancer, and AIDS-associated Kaposi sarcoma.[41] PLD is effective in lymphoma, although it is not clear whether it is as effective as doxorubicin. The most common strategy to prevent cardiomyopathy involves the discontinuance of doxorubicin when the patient ejection fraction decreases by at least 14% on the basis of serial measurements by MUGA or echocardiogram.

In the last few years, it has become clear that patients treated with anthracycline may experience a delayed subclinical cardiac dysfunction, whose incidence increases with age and is progressive in time. The Surveillance Epidemiology and End Result (SEER) data suggest that this complication may eventually lead to clinical cardiac insufficiency, because the diagnosis of congestive heart failure becomes more common with time among breast cancer patients who have received adjuvant chemotherapy than among those treated without chemotherapy.[42-43] It is not clear at present whether this complication may be prevented.

Dementia. An important and yet unresolved question is whether the common complication known as "chemobrain" may lead to dementia in older individuals, whose cognitive reserve is more limited than that of younger people. Reviewing the SEER data, Henke et al. reported that the diagnosis of dementia increased among older women treated with adjuvant chemotherapy for breast cancer.[44] Other authors failed to confirm these findings.[45] Perhaps the most important question is not whether the diagnosis of dementia increases after chemotherapy but whether a degree of cognitive decline occurs that leads to functional dependence, and whether it may be prevented or ameliorated. This question can only be addressed with a prospective study.

Functional Dependence. In addition to the prolongation of survival, prolongation of active life expectancy is a major goal of geriatrics. Unfortunately, at present there are few data related to the functional consequences of cancer treatment. Studies conducted at the authors' institution suggested that:

- Functional dependence was more common among older breast cancer survivors who had been treated with chemotherapy.[8,46-47]
- Fatigue, which is almost universal in older cancer patients,[48] may be an important harbinger of functional dependence.[8] The interaction of fatigue and functional dependence has been reported in the geriatric population by other authors.[9-10]

The issue is one of the most important in geriatric oncology and needs to be studied prospectively. The most urgent questions to address include:

- Does functional dependence increase with time in older individuals treated with chemotherapy?
- Is functional dependence reversible?
- Which intervention may prevent or reverse functional dependence?

Delayed Complications

Secondary Leukemia and Myelodysplastic Syndrome. Chemotherapy related acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) account for 10-20% of all cases of AML.[49,50] Based on registry data, the incidence of AML occurring as a second malignancy, among patients whom treatment is feasible, is about 5%.[51] The high incidence of AML has been attributed to the increasing use of cytotoxic drugs causing DNA damage, and to longer survival of many treated patients.

The majority of secondary leukemias resulting from the use of cytotoxic drugs can be divided into two well-defined groups depending on whether the patient has received alkylating agents (melphalan, cyclophosphamide, nitrogen mustard, etc.), or drugs binding to the enzyme DNA-topoisomerase (etoposide, doxorubicin, daunorubicin, mitoxantrone, etc.).[52-54]

AML secondary to alkylating agents are frequently associated with MDS. These typically develop 5 to 7 years after initial cancer treatment, are associated with abnormalities in chromosomes 5 or 7; and have a poor prognosis. AML secondary to a topoisomerase II reactive drug are not associated with MDS. These typically occur

within 5 years of therapy, and are frequently associated with an 11q23 cytogenetic abnormality.[55]

TARGETED THERAPY

This form of therapy was recently introduced and the complications in older individuals are poorly known. The following is a brief summary; for more detailed information, please see Chapter 10.

The incidence of *cardiomyopathy* from trastuzumab increases with age.[56] This complication, which is reversible in most cases, is caused by interference with myocardium trophism. In most cases, treatment with trastuzumab may be resumed without risk once the cardiac function is reversed.

Older individuals may be at increased incidence of *hypertension, thrombosis, and bleedin*g when treated with angiogenesis inhibitors, especially bevacizumab.[57-61] Age should not be considered a contraindication to this treatment, but may suggest closer monitoring.

The incidence and severity of *skin toxicity* from tyrosine kinase inhibitors (TKI) may also increase with age.[62] This complication may be ameliorated with early treatment with clindamycin lotion and systemic tetracyclines. If the eczema progresses in spite of these measures, the tyrosine kinase inhibitor should be discontinued to prevent severe desquamative dermatitis that may even be lethal.

It should be emphasized again that the information related to these products and aging is scarce.

A LOOK AT THE FUTURE

With the aging of the population, treatment-related decisions for the management of cancer in older individuals will become more and more common. The basic questions of these decisions involve the balance of benefit and risks. For this purpose, it is essential to know:

- what are these complications;
- how common they are;
- how preventable they are;
- which patients are at increased risk.

As most cancer patients are older than 65, it is mandatory to have an adequate representation of individuals from this age group in all clinical trials, especially in those involving new drugs. The current scarcity of information in this segment of the population is unforgivable. It means that physicians treat most older cancer patients without knowing whether the treatment is beneficial or detrimental.

In the author's opinion, these provisions would go a long way to improve our knowledge and our decision-making process:

- **Phase II studies of all new drugs in patients aged 70 and older, to study the pharmacological changes occurring with age.** It is known that after age 70, intestinal absorption, renal excretion, hepatic metabolism, and total body water all decline. In addition, the functional reserve of some systems that are targets of toxicity, such as the hemopoietic system and the mucosa may also decline. Thus it is legitimate to expect both pharmacokinetic and pharmacodynamic changes in older individuals.
- **Nationwide (or worldwide) databases of older individuals treated with systemic cancer treatment.** Given the diversity of the geriatric population, important information related to the consequences of these treatments can only be obtained with well-controlled descriptive studies. These studies may also allow the investigators to identify risk factors and to generate predictive models of benefits and risks of cancer treatment. The SEER data, coupled with the Medicare database, have been extremely helpful to identify long-term complications of cancer treatment in people aged 65 and older. These include the increased risk of bone fractures and coronary artery disease in patients treated with LHRH analogs for longer than 1 year; myelodysplasia, acute myeloid leukemia and chronic cardiomyopathy in individuals treated with anthracyclines;[12,42-44,63,64] and possibly the association of dementia and chemotherapy. Unfortunately, the SEER data do not include other variables besides chronologic age and comorbidity. Future databases should include functional dependence, degree of comorbidity, basic laboratory information (hemoglobin, albumin), and presence or absence of geriatric syndromes, and should involve periodic evaluation of function, cognition, nutrition, falls, and other problems that may compromise a person's survival and function. In this way, it may be possible to establish whether cancer treatment is a cause of accelerated aging, a key question in clinical decisions.
- **Utilization of the current predictive model of toxicity to generate new models applicable to the ever-enlarging cancer pharmacopeia.** The Chemotherapy Risk Assessment Scale in High Risk Patients (CRASH) was developed in our institution from the prospective observation of more than 500 patients aged 70 and older. This model predicts both hematological and nonhematological toxicity on the basis of the treatment regimen and individual patient characteristics, and will be presented at ASCO 2010. This model may represent a frame of reference for future study.
- Because functional dependence and cognitive impairments are likely complications of cancer chemotherapy, interventional studies aimed to prevent these complications should be performed with all determinate speed.

- The interaction of frailty and cancer treatment is poorly understood. Since frailty is a key concept in geriatrics, future studies should address the following questions: Is frailty a risk factor for treatment toxicity? Is frailty a complication of treatment? Is frailty reversible?

See expertconsult.com for a complete list of references and web resources for this chapter

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CHAPTER

15

Depression and Anxiety in the Older Patient with Cancer: A Case-based Approach

Randall Espinoza

Emotional reactions to and psychological distress from cancer illness are very common and not all are pathological. Included in these frequent responses to cancer are fear, disbelief, apprehension, and rumination, as well as other concerns about the future, disability, disfigurement, cost of care, and being a burden to others. These reactions can occur not only at the time of receiving a cancer diagnosis, but upon learning that a relapse has occurred or that treatment has failed. Distinguishing normal distress, grief, and suffering from psychiatric complications requiring systematic assessment and specific intervention is a daunting task for both the general medical physician and the specialist oncologist. Knowing when to begin a psychiatric treatment or recommend a mental health referral may not always be obvious. These challenges of assessment and treatment are, in general, even more difficult in the older patient who often contends not just with cancer alone, but concurrently with a host of other medical problems, effects of multiple treatments, and accumulating life experiences and personal losses. Among the most common psychiatric complications in cancer, depressive and anxiety disorders are also among the most difficult to manage because of the heterogeneity of presentation and presence of multiple confounds. This chapter discusses the comprehensive evaluation and management of the geriatric oncology patient with depression and anxiety and presents in a case-based approach recommendations for mental health screening and surveillance, psychotropic management, and psychological intervention.

CASE 15-1 PART 1

Judith is a 76-year-old cancer survivor. She was first diagnosed with breast cancer 8 years ago and underwent a left mastectomy followed by irradiation therapy. She did well until 3 years ago when, after a fall, she was found to have bone metastasis and was started on adjuvant chemotherapy. Her cancer was "in check" and she remained very active and socially engaged. However, over the past year she began to complain of unremitting fatigue and seemed to lose interest in many of her usual activities. Now, for the past 3 months, she is more worried about minor matters, focuses on irrelevant details, and frets over being late for appointments. Her family has noted mood changes, loss of appetite with some weight loss, and an inability to follow conversations. Judith thinks her tiredness and distractibility are the result of poor sleep as she lies awake worrying about her cancer. She adamantly denies feeling depressed or sad, saying instead, "it's my cancer again." She is angry with her oncologist for not finding another regimen to address her recurrence.

Question 1: *What is the psychological impact of cancer in the elderly?*

Question 2: *What are the mental health care needs of the older cancer patient and of the family?*

Question 3: *What is the prevalence of psychiatric disorders in late-life cancer?*

OVERVIEW

With the aging of the population and with the advent of improved cancer detection and advances in oncologic treatment leading to higher survival rates, greater numbers of older adults are at risk for developing cancer and are also living longer with cancer. Indeed, current estimates are that about 60% of all malignancies occur in persons 65 years or older and, if current population trends persist, by 2020 nearly 70% of all malignancies will occur in the older age group. Importantly, cancer is a leading cause of disability and distress worldwide, yet the psychosocial impact of cancer in the elderly is poorly understood or sufficiently recognized. Consequently, more attention must be focused on the psychological issues in cancer that affect management of the older patient.

As stated, psychological distress can present at any stage of management, and while it should not necessarily

be considered pathological, it should be assessed for and addressed proactively. Manifestations of distress are varied and individualized according to the person's unique coping style and strengths, among other factors. Symptoms of psychological distress include somatic complaints such as poor sleep, general aches and pains, stomach upset, lower gastrointestinal distress, and muscle tension, and psychological complaints like inability to focus or concentrate, distractibility, irritability, sadness or feeling blue, or worry about the future. The oncologic provider and treatment staff should be aware of these symptoms, as direct and active supportive measures are quite useful in helping patients adjust and successfully cope, and some research suggests, may prevent further behavioral complications. Helpful interventions include active listening, acknowledgment of distress, validation of concerns, explanation of symptoms or care processes, problem-solving, and reassurance. Importantly, many symptoms are time-limited and resolve spontaneously. However, it is critical that psychological distress be screened for and documented since unusually severe or prolonged distress may lead to ineffective coping and poor decision making, and may indicate that the patient is at high risk for an adverse behavioral outcome or development of a psychiatric disorder. The National Cancer Comprehensive Network (NCCN) recommends use of the "Distress Thermometer" as a simple but very effective tool for assessing patients for distress and following symptoms over time and as a way of determining when further evaluation may be needed.

At the same time that the older patient is being queried for psychological distress, it can be useful to inquire about family and social support, trying to determine if it is available and adequate. The lack of extended support has been identified as a risk factor for psychological complications and possibly poorer adherence to treatment. For example, widowhood and social isolation are established risk factors for depression and substance abuse, which then themselves may lead to missed appointments. The older patient often presents with and relies upon close family and friends and may worry that a cancer illness may place an undue burden on them. Specific needs may include transportation to appointments, in-home help or safety evaluations, assistance with simple household chores or meal preparation, or referral to social service agencies. If the older patient's spouse is also ill, the care burden may fall upon adult children who may be poorly prepared for the additional time commitment required, the financial costs incurred, and the associated schedule disruptions. In addition, for the elderly who are more frail, who are cognitively impaired, or who come from a non-Western or different cultural background, involvement of family and an extended network of friends and caregivers may be instrumental and expected. Coordination of care, identification of key family spokespersons, and family meetings are often essential in the care of the older patient in general, and with a serious illness like cancer, these communications assume greater importance. When family or caregiver dynamics are ineffectual or impaired, a distressed caregiver network or family may inadvertently contribute to the dismay and worry of the older patient. Finally, family and others may have their own concerns or misconceptions concerning cancer and may be unsure of what to expect or how to assist.

In general, depression and anxiety are not normal consequences of aging. In fact, studies of the prevalence of depression in community-dwelling healthy elderly indicate that the prevalence of major depressive disorders is lower in this age group than in the younger adult population. However, as illness burden accumulates, the prevalence of depression or anxiety in older age groups rises dramatically, whether measured by number, severity, or duration of condition(s). In the cancer population, up to 50% of patients report symptoms of psychiatric disturbance. Yet, determination of the exact prevalence of specific psychiatric disorders is difficult and prevalence estimates have varied widely because of multiple variables such as specific cancer type, study design, or demographics. Overall, prevalence of any psychological disturbance, meaning depression, anxiety, or adjustment disorder, has averaged around 30%. As no studies have focused on the epidemiology of depressive or anxiety disorders in older cancer patients, specific data for the elderly are not available. Nonetheless, a few general comments can still be made. There appears to be a strong association between depression and certain cancer types, notably head and neck, lung, and pancreatic cancers, although the exact mechanism of association is undetermined. While breast cancer in younger women may carry a higher depressive risk because of concerns about attractiveness, fertility, or general self-image, for the older female patient, especially at increasing age, the association appears to diminish. Conversely, the availability of a supportive spouse or partner diminishes the risk of developing depression or other psychological disturbances, so that widowed or single women with breast cancer may carry a higher risk of depression. However, effects of antihormone treatment with age may be another factor for which studies have not adequately controlled. Similarly, for men, prostate cancer appears to carry a higher depressive burden, with younger age at onset, degree of sexual impairment, or complications of intervention or antihormone treatment being other cofactors. As before, the availability of a supportive spouse or partner lowers the risk. In contrast, a high level of caregiver distress seems to be a risk factor for the development of psychiatric problems in older medical patients. Finally, other neurobiological factors of aging likely interact with specific cancer processes to mediate the expression and risk for development of psychiatric disturbances. In particular, acute or chronic stress, effects of tumor markers, immune responses in aging, and general systems resiliency may all play a role.

CASE 15-1 PART 1 SOLUTION

Judith's physician administers the Distress Thermometer and decides to monitor Judith's complaints. She is referred for social service assistance, because she needs transportation when her daughter is not available, and for an in-home occupational therapy safety evaluation. Since she feels alone, she is also referred to a local community breast cancer support group available through her church. Finally, to address her insomnia, she will learn yoga to try to relax before bed.

SCREENING AND DIAGNOSIS OF DEPRESSIVE DISORDERS IN GERIATRIC ONCOLOGY

CASE 15-1 PART 2

Judith comes for a routine appointment 1 month later. Despite general supportive measures, she continues to seem irritable and withdrawn. Her family reports that she no longer attends bridge games or seems to enjoy visits with her grandchildren. Judith still denies feeling depressed or sad. She says, "I'm just frustrated with life."

Question 4: *How should assessment for depression be approached?*

Question 5: *What is the differential diagnosis of depression in an older cancer patient?*

Question 6: *What tools can be used screening and diagnosis?*

While many patients may endorse some types of depressive symptoms, not all are willing to do so; thus determining who may be clinically depressed, or more precisely, who meets formal criteria for a depressive disorder is not always clear. Clinical depression affects physical, behavioral, psychological, and cognitive domains, each to a varying degree and leading to heterogeneity of presentation. Further complicating assessment are age effects and illness-related factors. However, the current diagnosis of a depressive disorder, using DSM-IV TR criteria, does not take into account this multidimensional nature of depression or recognize particular age-related or illness contributions, resulting in the overdiagnosis, underdiagnosis, and misdiagnosis of depression, especially in the elderly or medically ill populations. Criteria for Major Depressive Disorder, according to DSM-IV TR nomenclature used by psychiatrists and most mental health professionals, are listed in Table 15-1 and are outlined following a simple mnemonic "Sig E Caps." Note that symptoms must be present most days for at least 2 weeks continuously, and one symptom must include either depressed mood or anhedonia.

As indicated, when assessing an older patient with cancer, age-related factors should be taken into account; these include individual beliefs about mental illness and expectations about what life might be or mean in one's later years. Some older cohorts of patients view any expression of psychological distress as a sign of personal weakness or character flaw or with shame. Societal and cultural views often relegate older people to the background or discount their value. Sex differences in expression of psychological distress also exist. Women, because of cultural acceptance and social custom, are more open to disclosing their feelings and emotional concerns and are more accepting of psychological assistance. On the other hand, men generally tend to deny inner mental turmoil, and instead, may display distress in a culturally-sanctioned way such as with anger or aggression or may engage in risky behaviors or turn to substance abuse. Table 15-2 lists factors that confound the assessment of depression in an older person. One critical issue not to overlook is the role of therapeutic nihilism, where patient, family, and/or care provider may collude to try to "explain away" depression as a reasonable consequence of grave illness coupled with life circumstances. If this stance becomes accepted, many patients will likely suffer needlessly; depression contributes to disability and lessens quality of life, but once identified, depression is imminently treatable. Finally, patients older than 75 years who are diagnosed with a serious illness for the first time, those with preexisting cognitive impairment, those with lower levels of education, and those with a

TABLE 15-1 DSM-IV TR Criteria for Major Depression

• Diagnosis requires five of nine symptoms present for at least 2 weeks, nearly every day.	**S**: suicidal thoughts **I**: interest decrease **G**: guilt; worthlessness
• To use the mnemonic one symptom must be: – depressed mood **OR** – decrease in interest/pleasure	**E**: energy decrease **C**: cognitive problems **A**: appetite/weight change **P**: psychomotor changes **S**: sleep disturbance

TABLE 15-2 Challenges to Assessing Depression in Older Patients

- Gender differences
  - Men: anger, apathy, anhedonia but not sadness
  - Women: somatic symptoms, dysphoria
- Overexpression of somatic complaints
- Minimization of psychological problems
- Presence of medical comorbidity
  - Symptoms: fatigue, anorexia, insomnia, psychomotor slowing, pain
  - Cognitive impairment: detection and expression
  - Medication side effects
  - Competing time demands
- Presence of psychiatric comorbidity
- Rationalization: by patient, family and/or provider
  - "Reasons to be depressed . . ."
  - Nihilism

TABLE 15-3 Diagnosing Major Depression in Physically-Ill Elderly

Depression criteria should emphasize:
- change of mood or interest with at least 2 weeks duration;
- nonphysical symptoms;
- social regression or incapacity.

Anorexia, sleep disturbances, fatigue, and motor retardation:
- These should only be considered if they accompany the aforementioned depressive symptoms and cannot be explained by physical illness or its treatment.
- If present at the outset, these symptoms **get worse with mood** and are out of proportion to symptoms expected from medical illness.

past history of depression or substance abuse (usually alcohol) also appear at greater risk for developing clinical depression.

Similarly, illness-related factors can affect each domain separately or in combination, and an identified psychiatric complaint may be due to the cancer illness itself, a complication of the illness, or the effect of a cancer treatment. For example, a brain tumor may affect an area involved with drive or pleasure, pain from cancer may disrupt sleep, or use of steroids may promote irritability. Furthermore, given the prominence of certain symptoms in cancer, to wit, anorexia, fatigue, sleep disturbance, and psychomotor slowing, knowing how and when to attribute a specific symptom to depression or to cancer can be daunting. Thus when approaching any patient with cancer who presents with a psychological or behavioral concern, it is useful to try to undertake an analysis of what may be driving the complaint in order to arrive at the correct diagnosis and best solution. There are clues to help guide when a depressive symptom may be caused by a psychiatric disorder rather than to cancer or a related cancer treatment. One of the most important is the temporal relationship between the psychiatric complaint and physical illness. In most cases, a mood or behavioral change will precede a worsening of any physical component, and to add further support to a diagnosis of a depressive disorder, physical symptoms will co-vary with depressive symptoms in a proportional relationship: as depressive symptoms worsen, so will physical complaints. Table 15-3 lists additional clues to help make the diagnosis of depression when serious medical illness is present and confounds assessment. It is also worth noting that it is the degree of functional impairment resulting from illness that appears to be the greater risk factor for development of depression, especially if the older person loses a fair degree of independence or mobility and if this change occurs abruptly with little time to adjust to or accept this change. How the caregiver or spouse responds to this impairment is another critical factor. Caregivers who become anxious or distressed about the cancer diagnosis or with complications of cancer treatment can often adversely affect the mood and well-being of the patient. Having involved the caregiver at the outset of management may provide an opportunity either to assess the caregiver for treatment or to recommend a separate referral.

DIFFERENTIAL DIAGNOSIS OF DEPRESSION IN THE OLDER PATIENT WITH CANCER

While the previous discussion has focused on the diagnosis of major depression, it is important not to overlook what is involved, generally speaking, in the differential diagnosis. Included here are other medical illnesses and effects of medications or treatments, other depressive and psychiatric disorders, and life circumstances. Table 15-4 lists some considerations.

When a medical problem is found to be etiologically related or causal to the mood disorder, a diagnosis of Mood Disorder due to General Medical Condition is made. Treating the underlying medical problem may address the mood components, although frequently additional psychotropic or psychological management will be needed. However, another main point is that while major depression can present with physical complaints, many medical conditions also present with depressive symptoms, that is, depressive symptoms are not pathognomonic, and thus a careful history is critical to determining which problem is primary. For the older patient, while much of the focus will necessarily be on the management of cancer, new medical conditions can arise and exacerbations of preexisting problems may occur. Furthermore, depression can coexist with cancer, or any other medical problem, and often does. In the older patient, particular mention must be made of dementia and delirium, both of which occur more commonly with age and with increasing medical stressors or use of multiple medications. Since dementia prevalence rises with age and given that a longer life span also exposes people to a greater risk of cancer and to living with cancer, it is reasonable to expect that more patients will be afflicted with both dementia and cancer. How each condition might affect the other in terms of assessment or management is poorly understood. What is known is that the presence of dementia may influence the expression of depression, obscure its detection, or may confuse assessment. Alzheimer disease (AD), the most common type of dementia in later life, is often accompanied by a depressive complication, and indeed, up to 40% of AD patients by some estimates will experience depression over their course of illness. Importantly, studies show that depression in dementia is treatable with medications and with behavioral or psychological approaches, although the extent of improvement and durability of response varies, as would be expected in a neurodegenerative process. With regard to delirium, the main risk is in overlooking this important diagnosis. Untreated delirium carries a high mortality risk and may be a poor prognostic sign in a frail

TABLE 15-4 Differential Diagnosis of Depression in the Older Cancer Patient

Medical
- Endocrinopathies
- Metabolic derangement
- Infections
- Cardiopulmonary disease
- GI disorders
- Inflammatory processes
- Hematological conditions
- Musculoskeletal problems
- Delirium

Neurological
- Cerebrovascular disease
- Primary or metastatic tumor
- Basal ganglia disease
- Dementia

Medications
- Antihypertensives
- Analgesics (opiates)
- CNS depressants
- Chemotherapeutics

Psychiatric
- Adjustment disorder
- Anxiety disorder
- Substance-induced disorder
- Substance Abuse or Dependence disorder

Life Circumstances
- Grief and bereavement
- Social isolation/loneliness
- Poverty

GI, gastrointestinal; CNS, central nervous system.

TABLE 15-5 Common Chemotherapeutic Agents Associated with Depressive Symptoms

Corticosteroids
Vinblastine
Vincristine
Vinorelbine
Interferon
Procarbazine
Asparaginase
Tamoxifen
Cyproterone

older patient, especially if it does not clear and becomes chronic. From a psychiatric perspective, the concern for delirium is highest in medically ill patients with an abrupt onset of depressive symptoms, the presence of psychosis or acute suicidal ideation, or a history of substance abuse or polypharmacy. In addition, delirium should be considered in the differential diagnosis of patients who are hospitalized, who present to the emergency room, or whose cognitive profile appears at odds with their baseline.

When a medication or substance is thought to explain the mood disturbance, a diagnosis of Substance-Induced Mood Disorder is made, and removing the offending agent may result in improvement of the underlying behavioral problem. However, separating specific agents to see which is related to particular mood symptoms is often daunting if not impossible. With regard to the older patient, age-related changes in pharmacokinetics and pharmacodynamics are also relevant but remain understudied where cancer is concerned. The best clue again derives from history and determining whether the drug, when given, was temporally associated with induction of the observed mood or behavioral change. When a medication that seems to promote depressive feelings must be used to treat an underlying medical problem or manage a symptom, it is worth trying to find a drug with the desired effect but a different side-effect profile, from a different class or with a different mechanism of action. Similarly, other iatrogenic causes of depression cannot be overlooked; these situations usually involve polypharmacy, where drug-drug interactions are most likely a result of the sheer number of medications prescribed, and where drug monitoring is often inadequate and is more challenging the more providers are involved in a given patient's care. In management of an older patient, it may be unusually challenging to separate out the effects of narcotics on mood, cognition, and behavior, especially in the presence of pain, which, if inadequately treated, is itself a risk factor for depression. Here clinical judgment must be used and careful attention placed on the goals of pain management. Determining if and when pain control has been achieved and has led to the desired outcomes can be a helpful guide. Encouraging the use of alternative and complementary forms of pain management may be another option for the older patient with cancer. Importantly, narcotics should never be withheld for fear of promoting addiction or dependency in a patient with cancer, especially in the terminal phase of illness. Finally, it is critical not to overlook that untreated depression can amplify the perception of pain or other distressing physical symptoms, so that effectively treating any underlying depressive disorder may also result in improvement in pain.

The previous list does not include specific concerns about chemotherapeutic agents. These are listed in Table 15-5. However, much controversy surrounds this association and the causal links have yet to be definitively proven. Nonetheless, caution should be followed when a cancer patient on one of these medications develops depressive symptoms for the first time after commencement. Further study is needed.

Other depressive disorders are possible in the older cancer patient and should be considered when symptoms are either of short duration or inadequate in number to meet DSM-IV-TR criteria for major depression. Importantly, while falling short of the full syndrome, these symptoms remain clinically meaningful and can adversely affect health outcomes, increase cost of care, and lower quality of life. If unresolved, these disorders also place patients at increased risk of developing major depression over the next year. Included in this category are the DSM-IV-TR diagnoses Subsyndromal Depression, which encompasses Minor Depression, Non-Dysphoric Depression, and Brief Reactive Depression; Dysthymia, which is diagnosed when symptoms of low-grade depression last for 2 years or longer; and Adjustment Disorder with depressed, anxious, or mixed mood. With regard to the last, adjustment disorder is an abnormal excessive reaction to a life stressor such as a new serious illness like cancer, getting divorced, or death of a loved

TABLE 15-6 Screening Instruments for Depression in Older Patients

	Sensitivity	Specificity	Inpatient	Outpatient	Physically Ill	Cognitively Impaired	Responsiveness to Change
1 or 2-Question Screen	97%	67%	No	Yes	Yes	No	Limited
GDS 30, 15 item	94%	81%	Yes	Yes	Yes	Variable	Good
CSDD (19-item)	90%	75%	Yes	Yes	Unknown	Yes	Good
CES-D (20-item)	93%	73%	No	Yes	Yes	No	Good
PHQ-9	88%	88%	No	Yes	Yes	Unknown	Very Good

one, and usually begins within 3 months of onset of the stressor. Once the stressor or its consequences has terminated, symptoms resolve and should not persist beyond 6 months. Closer surveillance of these patients is suggested. Treatment of adjustment disorder is supportive and usually psychosocial and behavioral in nature rather than pharmacological.

It can be very difficult to separate out an anxiety disorder from clinical depression, given the overlap of symptoms between the two conditions. Indeed, anxiety can be a component of depression in some patients, and a certain subtype called Mixed Anxiety Depression or Anxious Depression may be more common in the elderly. Furthermore, a person can have both an anxiety disorder and a depressive disorder. Anxiety may also be a normal reaction to the diagnosis of cancer and may be part of a normal stress response. However, anxiety is not a disorder of mood, so depressed and sad feelings are absent, and anxiety does not affect interests or ability to derive pleasure. The section that follows more fully discusses assessment and management of anxiety disorders in older patients with cancer.

An often overlooked consideration in the older patient is substance abuse or dependence, either from a common substance such as alcohol or from prescription medications. When cancer enters into consideration, assessment can be confusing and management can quickly become problematic. A patient who is actively abusing cannot be reliably assessed, and every effort should be made to have the patient abstain for a sufficient period to allow for a more accurate accounting of symptoms. However, this area is controversial and not sufficiently studied in the older population or, specifically, in the situation of older cancer patients. Importantly, older patients with a past history of substance abuse or dependence appear to be at higher risk for developing depression in the context of serious illness.

Finally, life circumstances themselves may be demoralizing and discouraging, and separating out appropriate responses to these types of challenges can be daunting but should not be overlooked, minimized, or deemed pathological. Personal losses begin to accumulate and grief and bereavement, which are unavoidable, should be recognized first as normal reactions. Financial difficulties may mount, especially when faced with expensive medical treatment on a fixed income. After children and despite the availability of Medicare and Social Security, the elderly have the highest poverty rates, with older single women being most at risk for impoverishment due to a catastrophic illness. To help defray the cost of care, an older person may be forced to move from a longtime home or into a new living arrangement. With aging, a person may undertake a life review and think of past deeds, of lost opportunities, or of poor choices made and look back with regret or sadness. Finally, with age, awareness of mortality and of limited time remaining enters into consciousness, which may precipitate an existential or spiritual crisis with anxiety, panic, and despair as prominent symptoms. Thoughts of death begin to appear and enter into usual discussion, not as a symptom of suicidal ideation, but as recognition of this final stage of life. If resolved successfully, distressing symptoms subside to be replaced with peace, gratitude, and calmness.

Screening and Assessment Tools

For all the issues discussed previously, depression can be challenging to detect and diagnose in older patients with cancer. While the "Distress Thermometer" provides a simple and systematic way of identifying patients who may require heightened surveillance for psychological distress, it has yet to be effectively compared to other "gold standard" self-report or clinician-administered depression screening or diagnostic instruments that are often recommended for use in older patient samples. However, a further question is whether these latter instruments, while validated in groups of older medically ill patients, have been specifically studied in older patients with cancer. The short answer is no. Notwithstanding the lack of studies, given the importance and prevalence of depression, it remains reasonable to suggest use of screening measures and other diagnostic tools in this population until data become available. These instruments and some psychometric properties are listed in Table 15-6.

Applying the one- or two-item Patient Health Questionnaire (PHQ) screens, along with the Distress Thermometer, can be an efficient strategy to identify the patient at risk for depression. The one-item question is, "Do you often feel sad or depressed?" and can be easily asked by staff at check-in or during a routine visit. The PHQ-2 screen asks, "Over the past 2 weeks, how often have you been bothered by: (1) a lack of interest; or (2) feeling sad or depressed?" These questions are rated on a scale of 0 to 3 (range from 0 to 6) with a positive score being 3 or greater. However, if the patient screens positive on one of these questions, further assessment should follow with a diagnostic instrument such as the Center for Epidemiological Studies-Depression Scale (CES-D), Geriatric Depression Scale (GDS, various forms available), Patient Health Questionnaire-9 (PHQ-9), or, if the patient is cognitively impaired, with the Cornell Scale for Depression in Dementia (CSDD). Most of these scales can be administered in about 3 to 10 minutes. A unique feature of the CSDD is the incorporation of observer or caregiver feedback on the patient. Lastly, except for the one- or two-item screeners, most can be used both to gauge severity of depression and to follow change from treatment, so that systematic use of the tools over time, e.g., weekly or monthly, can help guide the effectiveness of interventions or the need for additional specialist mental health referral. However, it is critical to keep in mind that a number of scale attributes should be considered when using these in a geriatric cancer setting. These include the time period assessed (past week or 2 weeks, for example), completion time and item length, variable assessment of multiple mood symptoms, impact of concomitant cognitive impairment, and phrasing of individual items such as hopelessness, which may have contextual importance and differing meaning depending on the patient's age or stage of illness. Except for the PHQ-9, which queries for all depressive symptom domains according to current DSM-IV-TR criteria, the advantage of the other identified tools is the reliance primarily on the psychological symptoms of depression.

CASE 15-1 PART 2 SOLUTION

Because Judith scored positive on the PHQ-2 screen, her physician administers the full PHQ-9 to assess her depression severity and obtain a baseline score. A review of her medication list does not reveal any apparent association between her mood complaints and her current medications. In fact, it appears that as her mood has worsened, her pain and fatigue symptoms have worsened. Her chart shows that she had an episode of depression about 8 years ago when she underwent her mastectomy and worried about disfigurement; thus she is at high risk of recurrence now that she has experienced a cancer relapse. However, since she will be starting a new chemotherapy regimen, the decision is made to follow her closely and reassess whether there was any change in her mood in a couple of weeks.

TREATMENT AND MANAGEMENT OF DEPRESSION IN THE OLDER PATIENT WITH CANCER

CASE 15-1 PART 3

Judith returns to her physician's office, still feeling terrible and complaining of pain. She is not sleeping well and feels more hopeless about her condition. She asks about euthanasia and moving to a locale where physician-assisted suicide is available.

Question 7: *What are the serious consequences of depression?*

Question 8: *What treatment options are available? How are these chosen?*

Question 9: *What approach should be used for medication selection and monitoring?*

Complications of Depression

Many of the same complications that can occur in depression are also possible in an older cancer patient. Morbidity increases, as does the risk of mortality from both medical and psychiatric causes. For example, depression is associated with increased mortality from heart disease, stroke, and cancer. Management of pain, insomnia, fatigue, and anorexia, common symptoms in cancer in general, becomes more challenging in the presence of comorbid depression. Furthermore, untreated depression adds to overall health care burden, increases cost of care, and lowers quality of life, the latter being of particular concern in the oncologic population, especially when entering chronic management phases or the terminal stage of illness. Depression is also associated with increased prescription drug use and an increased risk for substance abuse, especially alcohol, which may be overlooked in the elderly population. Depression alters motivation and outlook, so that adherence to medication, treatment, or office visits may decline. Among the most serious psychiatric consequences of depression in the elderly are inanition, catatonia, psychosis, dementia of depression, and suicide. Table 15-7 lists features of these complications in the older oncologic patient and some suggested treatment options will be discussed.

While development of any of these complications will likely prompt a psychiatric referral for evaluation, the primary care or oncologic provider should be aware of their presentations since these providers, rather than mental health professionals, will be the first to encounter these patients. In a more serious or gravely ill patient, states of inanition from depression can be difficult to identify, especially in the presence of aggressive interventions or particularly toxic chemotherapy. Similarly, catatonia can occur in patients with marked metabolic derangements or other primary medical problems, so a thorough evaluation will be needed in this situation before deciding that catatonia is a complication of a serious mood disorder. Patients who are psychotic may not overtly or spontaneously endorse this material,

TABLE 15-7 Complications of Depression in the Older Oncologic Patient

		Treatment Options	
Condition	**Presentation**	**Somatic**	**Hospital**
Inanition	Marked by dehydration, weight loss, and severe functional impairment; appears delirious	Medications; ECT if no improvement	Medical or psychiatric depending on status
Catatonia	Marked by mutism, extreme withdrawal, negativism, motoric blunting or excitement, refusal of food or drink	ECT is first choice treatment	Likely psychiatric
Psychosis	Involves delusions of poverty, jealousy, nihilism, loss of body parts, fear of poisoning, paranoia, illusions, or frank hallucinations May be subtle and hard to detect if not specifically asked	Antidepressant plus antipsychotic; ECT if no improvement	Outpatient if support is available Psychiatric if refusing care or behavior is compromised
Dementia of Depression	Manifests with slowed information processing, confusion, poor attention and concentration, retrieval memory deficits, poor executive function	Medications; cognitive retraining; close surveillance	Likely outpatient unless other symptoms or caregiver stress
Suicide	Passive thoughts of death and dying, hopelessness, no future Active ideation may involve plans as well as intent	Medications; ECT if acute; requires frequent assessment	Depends on acuity and seriousness. Likely psychiatric

*ECT, electroconvulsive therapy

so specific query must be made about any unusual or uncharacteristic thoughts. Often, fear prevents patients from talking about these ideas, so that a sympathetic and trusted ear may facilitate uncovering of psychotic thinking. The older medically compromised patient is also at greater risk of developing significant cognitive impairment when seriously depressed, so that the patient may appear to be demented. This problem is worrisome for at least two reasons. First, older patients are at increased risk of developing dementia, so that a misdiagnosis or missed diagnosis of one or the other condition is possible. Second, should an older depressed patient develop this extent of cognitive impairment, the chances of converting to dementia over the next 3 to 5 years is high. However, unlike cognitive impairment due to dementia, which is rarely if ever reversible, the dementia of depression responds to appropriate depression treatment with a full recovery and ensuing improvement in cognitive deficits.

Of particular concern is the development and management of suicidal thinking. Most patients who completed suicide were never seen or treated by mental health practitioners, and some studies show that the majority of patients were in contact with their primary care physician within the last month of their life. Suicide rates are highest in the elderly population; both acute and chronic risk factors have been identified. These are listed in Table 15-8. Apart from identifying sociodemographic risk factors of suicide, which cannot be modified or easily corrected, it is critical to know those acute risk factors that are amenable to treatment and on which quick action and intervention can be lifesaving.

Sociodemographic risk factors include older age; white race followed by Native American ethnicity; and male sex, especially when single, divorced, or widowed. Other risk factors include social isolation, poor or ambivalent family relationships, and financial strain. Being aware of or asking about a precipitating event can also be helpful. Inquiring about access to lethal means, especially firearms, is a critical part of any suicide assessment.

TABLE 15-8 Acute and Chronic Risk Factors for Suicide in the Older Patient with Cancer

Acute	Chronic
Active symptoms: • Suicidal ideation • Impulsivity • Insomnia or sleep disturbance • Restlessness or agitation • Anxiety, fear or panic • Psychosis • Intoxication • Poorly controlled pain • Delirium • Hopelessness Organized or lethal plan Recent loss or widowhood Recurrence of cancer Failure of cancer treatment	Social isolation Financial strain Past psychiatric history (mood, schizophrenic, substance abuse, or personality disorder) Past history of suicide attempt Family history of suicide Past use of opioid analgesics, CNS depressants, or benzodiazepines Poorer physical functioning or impairment Chronic or multiple medical illness Chronic pain Prior brain injury Metastatic or advanced oncologic disease

However, protective factors buffer individuals from suicidal thoughts and behavior. To date, protective factors have not been studied as extensively or rigorously as risk factors in older oncologic populations. Identifying and understanding protective factors is, nonetheless, equally as important as researching risk factors. Protective

factors include effective clinical care for mental, physical, and substance abuse disorders; easy access to a variety of clinical interventions and support for help-seeking; family and community support and support from ongoing medical and mental health care relationships; skills in problem solving, conflict resolution, and nonviolent ways of handling disputes; and cultural and religious beliefs that discourage suicide and support instincts for self-preservation. Finally, patients who require immediate intervention or psychiatric assessment are those with a formed plan with a high degree of lethality and with high intent. That is, providers should take into account the chances of success of a suicide plan. The older patient with cancer may be frailer or more physically impaired, so that chances of survival from even a seemingly minor attempt may be diminished. Highly lethal means include gunshot wounds, overdose on multiple medications, hanging, and jumping.

A difficulty can arise, however, in distinguishing between the patient who is less acutely or actively suicidal with no firm plan or denial of intent from the patient in the terminal phase of illness who views life as essentially complete and desires a hastened death. Here the prior relationship with the primary care or oncologic provider can be extremely useful in determining whether the ideas: (1) relate to suicide (whether actively or passively pursuing actual death albeit with a measure of ambivalence); (2) are part of a normal developmental stage in late life; or (3) reflect a realistic assessment of terminal treatment stage. In the first situation, patients are generally distressed and ashamed of having suicidal thoughts and seek refuge and understanding from a provider who they know, and they fear rejection, abandonment, or being labeled psychologically impaired. Furthermore, in the older oncologic patient, who may have already faced many personal losses, the idea of death itself may be less sinister or tragic, but the fear of painful dying may remain quite real. The expression of suicidal thinking or of wanting to die may then be a way of communicating with the medical team and seeking reassurance that pain can and will be controlled. In this case, a measured empathetic response with more frequent monitoring and specific query about suicide is useful and usually sufficient. A patient who experiences sharing of distressful thoughts in a safe and nonjudgmental manner is more likely to call or make contact should his or her suicide plan or intent change. Thus, a relationship of trust and empathy, while no guarantee of avoidance of an adverse outcome from suicide, can be essential in a patient disclosing these suicidal ideas in the first place or in agreeing to contact the provider should the intensity or quality of ideation worsen. In the second scenario, with increasing age, awareness of mortality and death may lead to an existential or spiritual crisis that is not necessarily abnormal. An older person may have general thoughts of wanting to die or being ready to die, which are not always synonymous with suicidal thinking. Successful navigation of this psychological developmental stage results in acceptance and satisfaction with prior life choices and manifests as peace and calmness and an openness to discussion of life and its personally held meaning. Fear and distress are typically absent here and there is no devised plan of exit. Spiritual counseling, if the patient is so inclined, can be extremely comforting. In the last case, an older patient in the terminal phase of illness with thoughts of wanting to die or forgoing treatment may be expressing a wish to maintain ultimate control over intolerable pain or suffering and a desire to preserve dignity. Management includes maintaining a supportive relationship, assuring the availability of comfort care and conveying the attitude that much can be done to improve quality of life. It is critical to actively solicit and treat specific symptoms. Involvement of family or friends can make the experience less lonely and less dreadful. Open and frank discussion of poor prognosis shows patients they are valued, encourages their participation in treatment planning to the extent possible, and fosters dignity.

MANAGEMENT OF DEPRESSION

Before deciding upon an intervention, the patient should be assessed for past history of depressive episodes and substance abuse, family psychiatric history including history of depression and/or suicide, concurrent life stressors, losses due to cancer, and availability of social support. Assessment of the patient's experience with cancer deaths, of the meaning of illness, and of the patient's understanding of his or her illness and its prognosis is also important. Depression in older cancer patients can be treated with nonpharmacologic approaches such as psychotherapy or behavioral therapy, as well as with pharmacotherapy. The decision on which intervention to pursue is made on the basis of patient or family preference, severity or duration of illness, past history of response, and possibly, cancer prognosis. Usually, a combination of approaches provides the best chance for optimal improvement. However, it is important to recognize that adequate randomized controlled trials of depression treatment in the older patient across all stages of cancer illness are lacking and much of what is recommended is extrapolated from metanalyses or from studies in other medical groups or younger populations of cancer patients.

PSYCHOTHERAPY

In general, the goals of psychotherapy are to reduce emotional distress and to improve morale, coping ability, self-esteem, sense of control, and resolution of problems. Psychotherapy may be delivered on an individual basis, in group settings, or in couples or family sessions. Various forms of psychotherapy as listed in Table 15-9 have been studied in the general oncologic population; psychotherapy can be considered for use as a stand-alone treatment and not just as an adjunct to medication. Psychotherapy providers include psychiatrists, psychologists, nurses and

TABLE 15-9 Psychotherapy Treatment Models for Older Cancer Patients

Model	Goals	Sample Techniques
Psycho-education	Provide explanation of illness and treatment processes.	Describe illness stages. Discuss treatment options.
Supportive	Strengthen self-esteem and sense of control.	Allow ventilation and validation of concerns. Model active listening.
Cognitive-behavioral (CBT)	Alter maladaptive coping skills or negative thoughts.	Identify underlying emotions and triggers. Reframe negative thoughts. Correct distortions.
Problem-solving	Address specific concerns and impediments to wellness.	Define and formulate problem. Generate alternative solutions.
Insight-oriented	Understand threat to self and meaning of illness.	Explore meaning of illness. Delineate defense mechanisms.
Grief	Adapt to loss and functional decline.	Identify role changes and challenges. Attach new meaning to experiences.
Existential	Provide meaning in life.	Search for meaningful activities and endeavors. Seek context for illness.
Complementary medicine	Access all available means of support and benefit.	Try music, meditation, yoga, acupuncture, and/or massage.
Spiritual counseling	Address spiritual concerns.	Discuss religious views on suffering and death.

social workers, although there may be limitations on the availability of adequately trained geriatric therapists with experience in treating medically ill populations. However, many useful techniques, such as active listening with encouraging comments, can be done by staff in the primary care or oncologic setting. It may be helpful to set aside some time during an office visit to specifically address emotional concerns and apply these supportive measures. The decision on whether to pursue psychotherapy is made on the basis of several factors including patient preference or values, concerns about polypharmacy, and severity or type of depression. Some patients may prefer to talk about their emotional problems rather than take a mind-altering drug, which may reflect a generational attitude about psychotropic treatment. Older patients with multiple medical problems may already be on several medications so that drug-drug interactions or sensitivity to drugs may be of concern. Finally, in the older patient with milder or briefer forms of depression and with limited functional impact, response to medication may be limited or modest and response to psychotherapy superior along with producing longer sustained improvement.

BEHAVIORAL APPROACHES

Recently, interest in other nonpharmacologic treatments for depression in older patients has grown amid reports that somatic symptoms like fatigue, insomnia, and pain, in particular, may be more amenable to these treatments. These options are listed in Table 15-10. Benefits include better acceptance, improved socialization, fewer adverse effects, and avoidance of polypharmacy. Notably, these options can be combined safely with medications if needed.

TABLE 15-10 Behavioral Approaches for Management of Depression in Older Cancer Patients

Strategy	Comments
Exercise	Includes both cardiovascular fitness and strength/resistance training
CBT-I	Specific form of CBT that addresses insomnia, fatigue and pain
Meditation	Helpful for both patient and caregiver; used in different settings
Yoga	Helpful for both patient and caregiver; used in different settings
Acupuncture	Limited but promising studies in older patients

Cognitive-behavioral therapy for insomnia (CBT-I), a specific form of CBT, has recently been developed and looks to be very promising in the treatment of cancer-related fatigue and insomnia, although specific study in the older oncologic population is lacking. The benefits of exercise appear to be greater in mild to moderate forms of depression, in patients with sedentary or inactive lifestyles and significant medical comorbidity including cardiac disease and dementia, and for those residing in long-term care facilities. Caregivers who experience depression because of increased stress and care burden also appear responsive to yoga and meditation.

PHARMACOLOGIC OPTIONS

Although there are many reports on the efficacy of antidepressants in depressed patients with cancer, there are no randomized, placebo controlled trials in the older oncologic population. This observation reflects the difficulty in conducting controlled studies of drugs in

medically ill cancer patients. Nonetheless, there is much clinical experience with antidepressant drugs in this population. A specific antidepressant is often chosen on the basis of its side-effect profile, as on the whole, all medications are equally efficacious in treating depression and there is as yet no definitive evidence that newer drugs have any greater efficacy than older drugs in treatment of most forms of depression. The antidepressant agents that are better tolerated in patients with comorbid depression and medical conditions, including cancer, are the newer agents, which encompass the serotonin reuptake inhibitors (SRIs) and the novel or mixed action antidepressants. Tricyclic antidepressants (TCAs) and psychostimulants are reserved for use in selected patients. Mood stabilizers and monoamine oxidase inhibitors (MAOIs) will not be discussed here. Table 15-11 lists antidepressant drugs and some dosage recommendations, along with broad comments on their use. Note that antidepressants obtainable in the United States are only available in oral or possibly sublingual-dissolving form, so that it is not feasible to use them for patients who cannot take anything by mouth.

In general, SRIs are considered first-line treatment of depressive disorders in the older adult because of their better tolerability, ease of use, and general safety, especially in overdose. All SRIs are equally efficacious, with depressive symptoms improving after 4 to 8 weeks of a therapeutic dose. However, some studies suggest that in older populations the full effect may not be seen until after 12 or 16 weeks, so it is critical to assure patient adherence to medication. The most common class side effects are nausea, loose stool, headache, sleep disturbance (either somnolence or insomnia), sexual dysfunction, and a brief period of increased anxiety, restlessness, or even akathisia. This brief period of restlessness or increased anxiety usually occurs at the initiation of treatment, especially if the dosage is begun too high. These drugs may cause appetite suppression lasting a period of several weeks, which may be of concern in the older and frailer patient who may not have any excess weight to lose. Interestingly, after a period of weight loss or reduced appetite, some patients then experience carbohydrate craving and weight gain, but the amount is difficult to predict and is not seen uniformly in older populations. Other potential side-effects that may be more worrisome in the older patient include hyponatremia due to SIADH, sinus bradycardia, and bleeding due to an antiplatelet effect. Specific SRIs, as listed in Table 15-11, are also more prone to drug-drug interactions via cytochrome P450 mechanisms.

Although the SRIs share a similar side effect profile, there are some clinically relevant differences. Fluoxetine, for example, has the longest half-life (5 weeks) and an active metabolite norfluoxetine, which results in little, if any, risk of SRI discontinuation syndrome with abrupt cessation. Because of the relative short half-life (24 hours) of the other SRIs, patients are at risk for developing significant psychiatric, neurologic, gastrointestinal, or flu-like symptoms after abrupt withdrawal. Paroxetine causes the most anticholinergic side effects of the SRIs and causes the most weight gain. Fluvoxamine and paroxetine are more sedating, whereas fluoxetine can be activating. The former are often chosen for highly anxious patients, whereas fluoxetine is used for patients with apathy or low energy. Sertraline, citalopram, and escitalopram have fewer drug interactions, whereas fluvoxamine has the most, and this feature often limits its use.

While not specifically addressing the older oncologic patient, studies of citalopram, sertraline, fluoxetine, and mirtazapine have been shown to treat interferon-α–induced depression in clinical trials of patients with hepatitis C or cancer.

The novel and mixed-action antidepressants (venlafaxine, desvenlafaxine, duloxetine, bupropion, nefazodone, trazodone, and mirtazapine) differ from the SRIs in their mechanism of action, resulting in their different side effect profiles. Venlafaxine, desvenlafaxine, and duloxetine are serotonin/norepinephrine uptake inhibitors, with venlafaxine inhibiting serotonin reuptake at lower doses, thereby sharing some of the side effects of the SRIs while inhibiting norepinephrine reuptake at higher doses. Both duloxetine and venlafaxine have been shown to improve neuropathic pain and peripheral neuropathy in cancer patients. However, venlafaxine, desvenlafaxine, and duloxetine in a dose-dependent manner may contribute to diastolic hypertension. Bupropion is primarily a noradrenergic agent that increases dopamine reuptake at higher doses. Its stimulating effects may be beneficial to the depressed cancer patient with fatigue or excessive daytime sedation. Bupropion has fewer gastrointestinal side effects than the SRIs, but can induce diastolic hypertension in a dose-dependent manner. It increases the risk for seizures at higher doses, typically above 450 mg total, and should be avoided or used with caution in patients with seizure disorders, traumatic brain injury, or CNS pathology. Interestingly, it can assist in smoking cessation and has minimal effect on weight or sexual functioning. Although rare, it may contribute to confusion or psychotic symptoms because of its effect on dopamine. Venlafaxine, trazodone, mirtazapine, and some SRIs are useful in managing hot flashes. Trazodone may be used for its sedating properties and in low doses (50-100 mg at bedtime) is helpful in the treatment of the depressed cancer patient with insomnia. At higher doses, trazodone can cause orthostatic hypotension, thereby increasing the risk for falls. It has also been associated with priapism, and therefore should be used with caution in men. Concern about possible liver toxicity with nefazodone often limits its use, although it has mild calming effects, may promote better sleep architecture, and has less orthostatic risk compared to trazodone. Mirtazapine is a noradrenergic and specific serotonergic antidepressant. It has low affinity for muscarinic, cholinergic, and dopaminergic receptors, but a high affinity for H_1 histaminic receptors. It also antagonizes 5-HT_3 receptors. On the

TABLE 15-11 Antidepressant Medications used in Older Cancer Patients

Drug (Generic Name)	Starting Dosage mg (p.o.)	Therapeutic Range mg (p.o.), dosing*	CYP450 Effects	Comments (See Text for Details)
SRI Class				
Citalopram	5-10	10-60, qam or qhs	Not likely	Generally well-tolerated; expect fewer drug interactions
Escitalopram	2.5-5	5-20, qam or qhs	Not likely	Not yet generic; may be activating; fewer drug interactions
Fluoxetine	2.5-5	10-60, qam	2D6	Long half-life; available in elixir; moderate drug interactions
Fluvoxamine	12.5-25	50-300, bid or qhs	3A4 inhibitor	More sedating; expect more drug interactions
Paroxetine	5-10	10-60, qhs	2D6	More sedating; more anticholinergic; more weight gain?
Sertraline	12.5-25	25-200, qam or qhs	2C9, 2D6	Can be activating; possible Parkinsonism; drug interactions
Dual Action or Mixed Agents				
Bupropion extended release	75-100	100-450, qam	2D6 inhibitor	Activating; used in smoking cessation; risk for seizures
Desvenlafaxine	50	50-100, qam	3A4 substrate	Activating; not generic; may elevate diastolic BP
Duloxetine	20	40-120, qam to bid	2D6 inhibitor	Activating; not generic; may elevate diastolic BP
Mirtazapine	7.5-15	15-60, qhs	3A4 substrate	Less sedating at higher dosages; may promote weight gain
Nefazodone	25-50	150-600, bid or qhs	3A4 inhibitor	Generic only available; potent inhibitor; possible liver toxicity
Trazodone	12.5-50	25-300, qhs	3A4 substrate	Sedating; orthostasis at higher doses limits antidepressant use
Venlafaxine extended release	37.5	75-225, qam	2D6 inhibitor	Activating; IR form not well-tolerated
Tricyclic Antidepressants				
Tertiary amines				
Amitriptyline	10	25-150, qhs	2D6 substrate	Many side effects limit use in elderly
Imipramine	10	50-300, qhs	2D6 substrate	Many side effects limit use in elderly
Secondary amines				
Desipramine	10	25-200, qam	2D6 substrate	Usually activating; must follow blood levels and EKGs
Nortriptyline	10	25-150, qhs	2D6 substrate	Mildly sedating; must follow blood levels and EKGs
Psychostimulants				
Dextroamphetamine	2.5-5	5-60, bid to qid	Unknown	Best in two divided doses (AM, noon); analgesic adjuvant
Methylphenidate	2.5-5	5-60, bid to qid	None	Best in two divided doses (AM, noon); analgesic adjuvant
Modafinil	50	50-400, qam to bid	2C19 inhibitor	No generic, costly; similar side-effect profile to others
Armodafinil	50	50-250, qam	2C19 inhibitor	Isomer of modafinil; no generic, costly; similar side effects

*Dosing: Range listed is to maximum; thus divided dosing, if listed, is also to reach stated maximum.

basis of these properties, common features of mirtazapine include sedation, anxiolysis, appetite stimulation, and antiemesis. Because it can cause weight gain, it may be advantageous in the palliative care setting for anorectic-cachectic cancer patients, but it may not a good choice for those who are gaining unwanted weight from steroids or chemotherapy.

Tricyclic antidepressants (TCAs) antagonize muscarinic, cholinergic, H_1-histaminic, and α-adrenergic receptors, contributing to side effects of confusion, dry mouth, constipation, urinary retention, sedation, weight gain, and orthostatic hypotension. These side-effects are most prominent with the tertiary amines (amitriptyline and imipramine) and less so with the secondary amines (nortriptyline and desipramine). Thus, of the TCA class, the secondary amines are preferred in the older population. TCAs are still used in the oncology setting, especially when neuropathic pain is present. TCAs also exert

TABLE 15-12 Matching Antidepressant Drug to Depressive or Physical Problem

	Drug Strategy	
Symptom or Concern	**Use**	**Avoid**
Anxiety/agitation	Mirtazapine; calming SRI; or mixed agent	Activating agent especially high dose at start
Insomnia	Mirtazapine; sedating agent	Activating agent especially at night
Daytime sedation/apathy	Bupropion; psychostimulant	Sedating agent during day or a high dose
Fatigue	Bupropion; psychostimulant	Sedating agent during day or a high dose
Pain	Mixed agent; TCA; psychostimulant	High doses if using opiates concurrently
GI upset	Mirtazapine; TCA	Some SRIs empty stomach
Anorexia/weight loss	Mirtazapine; paroxetine, TCA	Some SRIs, (des)venlafaxine, bupropion
Confusion/dementia	Citalopram, mixed agent, mirtazapine	TCA, some stimulants
Hot flashes	Venlafaxine; trazodone, mirtazapine	Some SRIs
Dry mouth/stomatitis	SRIs; psychostimulant	Mirtazapine; paroxetine, TCA
Difficulty swallowing	Dissolving or elixir form	
Slow gut motility	SRI, mixed agent	TCA, agents with anticholinergic effects
Polypharmacy	Citalopram; Mirtazapine	TCA; nefazodone, some SRIs

SRI, serotonin reuptake inhibitor; TCA, tricyclic antidepressant

cardiac conduction effects, so serial EKGs should be followed when they are used. TCAs are also more lethal in overdose. Finally, it is important to follow TCA drug levels, specifically with nortriptyline which may have a therapeutic window.

In cancer patients, the psychostimulants and the newer wakefulness-promoting agents (modafinil and armodafinil) promote a sense of well-being, decrease fatigue, improve concentration and attention, and may stimulate appetite. However, anorexia may develop at higher doses. These agents are not considered antidepressants per se. An advantage of these drugs is their rapid onset and relative effectiveness, and thus they are often preferred over traditional antidepressants in the depressed patient in the terminal phase of illness or with advanced cancer. In cases where traditional antidepressants have not yet worked or achieved the desired results, psychostimulants may be used adjunctively, although data on efficacy, tolerance, and safety in the older oncologic population are largely anecdotal. Psychostimulants can potentiate the analgesic effects of opioid analgesics and are commonly used to counteract opioid-induced sedation. Also, psychostimulants can cause tremor, anxiety, agitation, delirium, nightmares, insomnia, and even psychosis, and these agents may lower seizure threshold. At higher doses, they can produce tachycardia, other arrhythmias, or hypertension. These same side effects can occur with modafinil or armodafinil but possibly less frequently. Patients can be maintained on psychostimulants for long periods, e.g., 6 months to 1 year or longer, and if tolerance develops, dose adjustments can be made accordingly.

The decision on which medication to choose hinders on several aspects. Past history of positive response to an agent or a family history of response to a particular drug may be considered. However, usually other factors to take into account include the patient's overall health, cognitive status, financial resources, other concurrent medications, and concomitant psychiatric problems such as substance abuse or psychosis. Prominent features of the depressive disorder, i.e., somatic presentation or needs, may drive drug-matching. Similarly, medication side effects may help guide selection, for example, choosing a sedating drug to address an insomnia complaint or choosing an activating drug to combat fatigue or excessive daytime sedation. Treatment of psychotic depression requires use of both an antidepressant and an antipsychotic. Possible strategies to consider in drug-matching are listed in Table 15-12 and may serve as a guide, with recognition of the need to individualize ultimate medication choice.

Should the initial drug fail after an adequate dosage and duration trial, it may be worth switching to a drug from a different class. However, if there has been a partial response to the initial drug challenge, options include: (1) increasing the dose further until the recommended maximum is reached and tolerance continues; (2) adding a second antidepressant and monitoring more closely for drug interactions; or (3) referring for psychotherapy. In any case, it is also important to assure medication adherence and to assure that the correct diagnosis has been made.

Finally, it is important for primary care and oncologic providers not to overlook the availability of and benefit derived from electroconvulsive therapy (ECT) in the older patient with severe major depression. Anecdotal reports of safety and benefit in medically ill and cancer populations do exist. Table 15-13 lists advantages and disadvantages of ECT that may help guide its implementation.

Indications for ECT include serious, life-threatening mood disorders; treatment failures; need for rapid definitive response (e.g., acute suicidality, states of inanition or catatonia); chronic depression with significant psychosocial, functional, and cognitive impairment; and psychotic depression, where ECT is probably the treatment of choice. A typical index ECT series is comprised of between 6 and 12 sessions, usually administered three times per week, although in elderly patients a frequency of twice per week is possible. Once a patient responds

TABLE 15-13 Electroconvulsive Therapy Considerations in Older Patients

Advantages	Disadvantages
• Superior efficacy (80% - 90%) in severe depression compared to antidepressant medication (when used as first-line choice) • Good efficacy (50% - 60%) in medication-resistant depression • More rapid onset of action • Good safety profile: very low mortality and low morbidity • Absence of medication side effects • Age may be a predictor of response	• Repeated general anesthesia • Cognitive and memory effects • Minor treatment side effects: headache, muscle aches, falls (especially in the elderly) • Acute relapse if a maintenance plan is not instituted • Cost of series

to ECT, it is essential that a maintenance plan to prevent relapse of depression be implemented. Maintenance plans can include combination pharmacotherapy, maintenance ECT (which occurs at decreasing frequency of weekly to monthly, for example), or a combination of medications and ECT. There presently are no data or studies of other brain stimulation therapies (vagus nerve stimulation [VNS] or transcranial magnetic stimulation [TMS]) in older cancer patients, and deep brain stimulation (DBS) remains experimental.

MONITORING PATIENTS DURING DEPRESSION MANAGEMENT

While it seems obvious, it is important to have the correct diagnosis so that the appropriate intervention, whether psychological or pharmacological, is selected. It is also recommended to have the patient and/or family share their expectations of treatment and gain a clear understanding of what the treatment is intended to do or provide. Unrealistic goals or misunderstanding of benefits can lead to poorer adherence and avoidable disappointments. Given the complexities noted, it is helpful to have a plan of care for management of depression that, besides systematic assessment of clinical symptoms with a mood scale, includes scheduled follow-up of treatment benefit and adherence. If considering a psychotherapy referral, then asking the patient or family about the outcome of the visit(s) will convey the importance of making the connection. It is also appropriate to request brief periodic reports from the therapist. Having this relationship and ease of communication allows for the provider and therapist to share useful information and identify obstacles or complications to treatment should these arise. With regard to drug management, after choosing a medication it is critical to follow through with dosage titration and to reach the recommended dosage range. Underdosing of medication is very common in primary care and among elderly depressed patients. Finally, to be effective, medication must be used for the indicated amount of time. It may take 4 to 6 weeks for maximal effect to be seen, although it may be possible to see some initial improvement after 2 weeks. However, some studies suggest that full antidepressant effects in the elderly population may take as long as 8 to 12 weeks, so it is imperative that patients remain on the medication for a sufficient duration. Additional helpful pointers for assuring an adequate medication trial are listed in Table 15-14. Repeating mood scales periodically helps to gauge the extent of response and may give direction on when a change in treatment plan or review of diagnosis is needed. Finally, it is critical that the goal of any depression treatment be full symptom remission.

TABLE 15-14 Assuring an Adequate Medication Trial in Depression

- Discuss commonly experienced side effects.
- Be sensitive to patient concerns, e.g., weight gain, constipation or loose stools, lethargy, mental dulling, sedation, or sexual dysfunction.
- Know how to intervene to address side effects:
  - Reduce medication dosage temporarily to allow for acclimation or
  - Slow titration or
  - Change timing of use.
- Ask patients to repeat back what they have heard about the selected medication.
- Bring the patient back in 1-2 weeks for a medication and symptom review.
  - Ask patients to keep a log of symptoms and side-effects.
  - Specifically query about suicidal ideation.
  - Use a mood scale, e.g., PHQ-9, to follow response.

Duration of treatment of depression depends on several factors including whether there was a past history of depression. In general, patients who have had more than three previous episodes of depression before the age of 50 may require continuous lifetime treatment. At a minimum, a patient should be treated for at least 6 months after having achieved full symptom remission. As alluded to earlier, patients who do not reach full symptom remission and who continue with residual symptoms of depression are at higher risk of relapse, experience more functional impairment, and have a lower quality of life.

CASE 15-1 PART 3 SOLUTION

Judith still scores high on the PHQ-9, sleeps poorly, and indicates that she has great difficulty completing her daily tasks because of pain. However, she specifically denies suicidal ideation. While she found support groups helpful for general discussion, she would like to see an individual therapist and also would like to review medication options. On the basis of her symptom profile, a dual-action agent is chosen, along with a benzodiazepine for about a week; she will follow up in about 2 weeks. However, she is asked to call should she have any problems with her antidepressant or should she feel worse. Her family feels secure in being with her and expresses understanding of what to do should her thinking change to suggest suicidal intent.

ANXIETY IN OLDER PATIENTS WITH CANCER

Although anxiety is experienced by most cancer patients at some point during the course of their illness and treatment, anxiety is not well-studied in the geriatric oncologic population. In general, prevalence studies of anxiety in adult cancer cohorts place the range at between 20% and 25%. Anxiety is often seen at crisis points such as the initial diagnosis or discovery of a relapse after treatment. This anxiety can be viewed as a normal reaction to a stressful and traumatic event and may even be a positive effect if anxiety motivates a patient to gather the information and support that helps inform decision making. However, it can be difficult to determine when a patient's anxiety lies out of the normal range and requires specific intervention. In general, anxiety that persists beyond the immediate period of a stressor and anxiety that causes impairment in functioning should prompt further evaluation. Anxiety may also be a component of other complications such as pain, delirium, and depression. While many patients will express anxiety symptoms, the rate of anxiety disorder and its subtypes is comparable to that in the general population. Most studies of psychiatric symptoms in cancer patients have reported a higher prevalence of mixed anxiety and depressive symptoms than anxiety alone. Correlations between measures of depression and anxiety on both clinician-rated and self-report measures are high. In all likelihood, this observation indicates that these measures tap common psychological traits such as negative affect or neuroticism. Anxiety increases with the diagnosis of cancer, peaks before surgical interventions, and frequently remains high thereafter, declining gradually during the first postoperative years. Anxiety increases as cancer progresses, and psychological health declines along with the decline in physical status. Chemotherapy administration is a source of anxiety that may develop into a conditioned anticipatory response, i.e., phobia, which may persist for years after the cessation of the chemotherapy. Radiotherapy is also associated with increased anxiety, accompanied by concerns about increased bodily vulnerability and worries about whether the radiation will cause further bodily damage. The anxiety experienced during chemotherapy and radiation therapy may paradoxically increase at the termination of treatment, as patients feel unprotected, see their physician less often, and worry about the effectiveness or durability of treatment. Patients who are participating in clinical trials and feel that they have been randomly assigned to a less-aggressive treatment modality may also experience increased anxiety.

CASE 15-2 PART 1

Thomas is an 86-year-old retired music professor with a history of prostate cancer for the last 20 years. He initially underwent a radical prostatectomy and suffered postsurgical incontinence and sexual dysfunction, which has been distressing. He had been maintained on antihormonal therapy and was doing well until recently when repeat PSAs began to elevate. He presented twice to the emergency department with panic attacks and his wife is concerned about his behavior.

Question 10: *How does anxiety manifest in a patient with cancer?*

Question 11: *How is anxiety diagnosed and what anxiety scales can be used to aid in diagnosis?*

Question 12: *What is the differential diagnosis?*

DIAGNOSIS OF ANXIETY

In the older cancer patient, the diagnosis should be approached comprehensively, but judiciously. Systematic assessment is paramount and includes a careful history, review of medications or treatments, review of past psychiatric and family psychiatric history, assessment of current family or social support, and review of basic laboratory results. In some cases, older patients may have a pre-existing anxiety disorder and, in fact, anxiety disorders are generally more prevalent than depressive disorders in older population cohort studies. In addition, older patients with anxiety may be at higher risk of current or past abuse of alcohol, benzodiazepines or other CNS depressants. Symptoms of anxiety may be grouped, as are depressive symptoms, into both cognitive and somatic domains. The cognitive or psychological symptoms can encompass fear of death, loss of control, thoughts of impending doom, hypervigilance, overgeneralizing, and catastrophizing. The somatic symptoms are often found in panic attacks and can include hyperarousal, tachycardia, shortness of breath, sweating, nausea, abdominal upset or distress, loose stools, trembling, and dizziness. Screening tools such as the single Anxiety Question, Beck Anxiety Inventory, Hospital Anxiety and Depression Scale and the Memorial Anxiety Scale for Prostate Cancer are examples of measures that might be routinely given to older patients and applied in office or hospital practice. The single anxiety question "Are you anxious?" while simple to use, nonetheless in a palliative care sample showed insufficient specificity to exclude patients who were not anxious.

DIFFERENTIAL DIAGNOSIS OF ANXIETY

The differential diagnosis of anxiety in an older patient with cancer can be challenging, as several factors may interact to contribute to anxiety. As shown in Table 15-15, medical conditions, medication or treatment effects, psychiatric disorders, and life circumstances must be considered.

Patients who are delirious may appear anxious, restless, and agitated and may exhibit marked impulsivity. Severe pain can make patients appear anxious, and when

TABLE 15-15 Differential Diagnosis of Anxiety in the Older Cancer Patient

Medical
- Delirium
- Endocrinopathies
- Pulmonary disease (COPD, emboli)
- Cardiac disease (Arrhythmia, MI, CAD)
- Gastrointestinal disorder (IBS)
- Metabolic derangement
- Pheochromocytoma

Neurological
- Seizure disorder
- Brain tumor
- Paraneoplastic syndrome

Cancer-related
- Type
- Initial diagnosis
- Recurrence
- Treatment failure
- Pain

Medications
- Asthma agents
- Steroids
- Chemotherapeutics

Psychiatric
- Generalized Anxiety Disorder
- Panic Disorder
- Phobias
- Posttraumatic Stress Disorder
- Substance-Induced Anxiety Disorder
- Adjustment Disorder with anxiety
- Mood Disorder

Life Circumstances
- Financial strain
- Disruptive family or social relationships
- Housing problems or changes

COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; CAD, coronary artery disease; IBS, irritable bowel syndrome.

the pain is adequately treated, patients usually experience a marked reduction in anxiety symptoms. Patients with diseases of the respiratory system, such as lung cancer, or patients in respiratory distress can present with anxiety and restlessness. This anxiety can set off a cycle of worsening shortness of breath followed by more anxiety. An acute event such as a pulmonary embolus may also initially present with a patient appearing quite anxious. The symptoms of anxiety in these cases may respond initially to an anxiolytic medication, but the patient's anxiety will ultimately better respond to the proper medical intervention. Sepsis, endocrine abnormalities, hypoglycemia, hypercalcemia, and hormone-secreting tumors may all be associated with anxiety symptoms. There is some evidence that depression, anxiety, and panic attacks can occur in patients with pancreatic cancer, although the mechanism is not entirely clear. Several medications or treatments are associated with anxiety. Examples include medications used for their antiemetic properties. Steroids and other antiemetics can cause anxiety or akathisia, which is a motor restlessness accompanied by subjective feelings of distress and hyperactivity. In addition, withdrawal from alcohol, benzodiazepines, or other CNS depressants is associated with rebound anxiety.

From a psychiatric perspective, DSM-IV-TR describes a variety of anxiety disorders. A patient may have a preexisting anxiety disorder or may develop an anxiety disorder after a cancer diagnosis. The spectrum of anxiety disorders includes diagnoses such as generalized anxiety disorder, panic disorder, and posttraumatic stress disorder. It also includes phobias, such as a fear of needles or claustrophobia. These may have great impact on cancer patients who must undergo multiple tests and procedures such as magnetic resonance imaging, injections, and intravenous treatments. An anxiety response may also be conditioned. Patients may have anxiety symptoms emerge as an anticipatory response to a repeated aversive treatment such as chemotherapy, to difficult procedures, or to places associated with painful experiences. When associated with an acute stressor such as news of illness or treatment failure, an adjustment disorder with anxiety can be diagnosed, especially if the symptoms are time-limited. As previously noted, depressive disorders are often accompanied by anxiety symptoms and deciding which is primary can be very complicated. The importance of diagnosing an anxiety disorder accurately is that evidence suggests greater and more sustained benefit from particular psychotherapies like CBT or problem-solving therapy (PST) over medications, which take a longer time to work and to which some anxious patients appear more sensitive. Finally, as in mood disorders, general life circumstances can be associated with anxiety or stress, and anxious reactions to these situations should not necessarily be deemed pathological, especially if anxiety helps to motivate a person to adopt more effective coping strategies, to make needed changes, or to seek appropriate help.

CASE 15-2 PART 1 SOLUTION

Further workup is ordered which reveals that he now has bone metastases. However, a brain MRI is negative for masses or worrisome lesions. While he has a history of depression, he denies any mood-related or other symptoms and instead reports that he primarily feels nervous, ruminates about his relationship with his wife, and worries about how he might respond to new treatments, given the bad outcomes previously experienced. Given the apparent association with news about recurrence, his physician diagnoses an adjustment disorder with anxious mood and will reassess periodically.

TREATMENT OF ANXIETY IN THE OLDER CANCER PATIENT

The most effective management of anxiety in cancer patients incorporates all modalities, that is, psychotherapy, behavioral therapy, and pharmacologic management. During the initial evaluation of the patient's symptoms, both emotional support and information are given to the patient. Exploration of the patient's fears and apprehensions about disease progression, upcoming procedures, or psychosocial concerns often alleviates a substantial degree of anxiety. Patient concerns usually include death, physical suffering, increased

CASE 15-2 PART 2

On follow-up, it is learned that he again presented to the emergency department with another panic attack but fortunately, workup for acute medical problems was negative. Despite explanation of his condition and the available treatment options, he remains worried and feels overwhelmed; however, he again denies symptoms of depression and is not hopeless or suicidal.

Question 13: *What treatment options are available for anxiety disorders?*

Question 14: *When and how should medications for anxiety be used?*

dependence, loss of dignity, changes in social role functioning, spiritual matters, and worry about finances or employment.

PSYCHOLOGICAL TREATMENTS

The same types of psychological interventions previously mentioned in management of depression can be useful in addressing most anxiety situations or disorders. These have been shown earlier in Table 15-9. General measures involve showing support, acceptance and positive regard toward the patient; placing an emphasis on working together to achieve desired results; communicating a hopeful attitude that the goals of care will be achieved; showing respect for how the patient adapts to or handles difficulty; and focusing on the patient's strengths and acknowledging how successful the patient has been on his or her own, thereby promoting a sense of mastery and control. Each of these measures communicates to the patient one's active concern and continued involvement in his or her care. Patients with anxiety may benefit from specific cognitive-behavioral interventions including reframing negative, irrational thought processes; progressive relaxation; distraction; guided imagery; meditation; biofeedback; and hypnosis. These techniques are also used to treat the anxiety symptoms associated with painful procedures, pain syndromes, office visits, waiting for results, and anticipatory fears of chemotherapy and radiation therapy. Other psychotherapeutic techniques such as supportive and insight-oriented therapy may be helpful to reduce anxiety symptoms and allow for better coping with the cancer.

PHARMACOLOGICAL MANAGEMENT

The decision to use medication to manage anxiety is typically guided by the degree and pervasiveness of symptoms and the associated functional impairment. In mild cases of anxiety, supportive or behavioral measures should be pursued first, although formal psychotherapy referral may also be considered. In more severe cases of anxiety, while medications can be very useful, it is important to understand which symptoms will respond best and over what time frame, and to explain to the patient what to expect from a drug intervention and what the treatment plan for medication management will include. Somatic symptoms of anxiety are especially amenable to treatment and respond quickly. However, judicious use is necessary, particularly in the older patient for whom concerns about side effects or drug-drug interactions are high. Commonly used medications for anxiety are listed in Table 15-16.

For patients who experience persistent apprehension and anxiety, the first-line drugs are the benzodiazepines. Lorazepam and alprazolam are useful for anxiety, nausea, and panic. Both lorazepam and alprazolam have been shown in controlled trials to reduce postchemotherapy nausea and vomiting, as well as anticipatory nausea and vomiting. Benzodiazepines have amnestic properties; when given before chemotherapy or a procedure, this effect may reduce the likelihood that a conditioned aversion will develop. A longer-acting benzodiazepine, such as clonazepam, may provide more consistent relief of anxiety symptoms and have mood-stabilizing effects as well. The short-acting to medium-acting benzodiazepines, as well as the nonbenzodiazepine hypnotics (zolpidem, zaleplon, eszopiclone or ramelteon) may be effective for insomnia. Low-dose antipsychotics, such as haloperidol, olanzapine, and risperidone, may be more effective for the patient who is both anxious and confused. For patients with compromised hepatic function, the use of intermediate-acting benzodiazepines, such as lorazepam, oxazepam, and temazepam, is preferred. These drugs are metabolized by conjugation with glucuronic acid and have no active metabolites, and thus may be considered for use in patients with liver disease. Drowsiness and somnolence are the most common adverse effects of benzodiazepines. Reductions in dose and the passage of time eliminate these effects. Mental status changes may result from benzodiazepine use and are more common in elderly patients and in those with advanced disease, comorbid cognitive impairment, and impaired hepatic function. For the treatment of panic disorder and agoraphobia, the benzodiazepines and antidepressant medications (TCAs and SRIs) have demonstrated effectiveness. Although alprazolam rapidly blocks panic attacks, withdrawal can be difficult after prolonged use. In anxious patients with severely compromised pulmonary function, the use of benzodiazepines that suppress central respiratory mechanisms may be unsafe. A low dose of an antihistamine, nonbenzodiazepine or antipsychotic medication can be useful for these individuals.

Note that antidepressant medications have also been used in the management of anxiety disorders although, as stated before, no randomized controlled trials exist in the older cancer patient population. The same concerns regarding antidepressants pertain when used for treatment of anxiety instead of depression, but a few features are different. First, the lowest dose possible should be used when initiating an antidepressant drug, especially if it has

TABLE 15-16 Antianxiety and Sedative-Hypnotic Medications Used in Older Cancer Patients

Drug	Starting Daily Dose, Oral	Comments
Benzodiazepines		*Higher risk of falls, confusion*
Alprazolam	0.125 to 0.5 mg tid to qid	Short acting, helps nausea
Lorazepam	0.25 to 0.5 mg bid to tid	Intermediate, no active metabolites
Oxazepam	10 mg bid to tid	Intermediate, no active metabolites
Temazepam	15 mg qhs	Intermediate, no active metabolites
Diazepam	2-5 mg bid to tid	Long acting, has metabolites
Clonazepam	0.25-0.5 mg bid to tid	Long acting
Nonbenzodiazepines		*Minimal cognitive problems*
Buspirone	5-10 mg bid to tid	May take 4-8 weeks for effect
Hypnotics		*May cause confusion, falls*
Zolpidem	5-10 mg qhs	
Zaleplon	5-20 mg qhs	
Eszopiclone	1-2 mg qhs	
Ramelteon	8 mg qhs	Possible P450 effects
Antihistamines		*May cause confusion, sedation*
Hydroxyzine	10-25 mg bid to tid	
Diphenhydramine	25-50 mg bid to tid	Do not use in dementia
Neuroleptics		*Possible cardiac risk? Monitor QTc*
Aripiprazole	2-5 mg qam or qhs	Not sedating, less EPS
Haloperidol	0.25-0.5 mg bid to qhs	Not sedating, more EPS
Risperidone	0.25-0.5 mg bid to qhs	More EPS, mild sedation
Olanzapine	2.5-5 mg bid to qhs	Metabolic changes, sedation
Quetiapine	12.5-25 mg bid, tid or qhs	Orthostasis, sedation
Others		
Trazodone	12.5-50 mg bid to qhs	Orthostasis, sedation

EPS, extrapyramidal symptoms

CASE 15-2 PART 2 SOLUTION

Because this patient has now presented to the emergency department on several occasions, it is necessary to offer treatment. It is learned that he previously saw a therapist, and that he is interested in revisiting issues related to his marriage and to his concerns about aging and mortality; thus he agrees to undergo psychotherapy. In addition, because his anxiety symptoms are now more frequent, he is offered low-dose lorazepam to use as needed when he has a panic attack; it is also suggested that he begin an antidepressant for more sustained benefit and to avoid cognitive side effects from lorazepam, a concern of his. As he expresses psychological distress with gastrointestinal disturbances, a medication is chosen that has fewer GI side effects. A follow-up appointment is scheduled in 2 weeks, and he is instructed to call his physician should he worsen or have any medication difficulties or exacerbation of his anxiety.

"activating" properties, in an anxious patient, or when the patient expresses many somatic complaints. These patients tend to fixate on and misinterpret body sensations, so that any possible side effect quickly becomes worrisome. Second, the dose should be increased gradually at modest increments of a quarter or half pill. Third, the medication should be adjusted slowly, every 1 to 2 weeks, or when the patient has acclimated. Fourth, the dosage needed to treat an anxiety disorder may ultimately be higher than what is needed to manage depression; this may present a problem, as some side effects occur in a dose-dependent manner. Lastly, given the slow titration, immediate effects may not be available, so it is important not to let the patient get discouraged. To help during this slow initiation and gradual titration phase, temporary use of a benzodiazepine may be considered. Also, while waiting for anxiolytic medication to take effect, other supportive or behavioral measures can be used concomitantly.

SUMMARY

With the aging of the population and the success of cancer treatments, there are increasingly more elderly patients diagnosed with, being treated for, and likely living with cancer. Comprehensive oncologic management must recognize and address the psychological distress and possible psychiatric sequelae experienced at each stage of illness or associated with treatment. Mental distress and psychiatric complications should not be seen as unavoidable consequences of cancer in later life. Management should also take into account the distinctive challenges and needs of the older-age patient. Discussed in this chapter are the diagnosis and management of depression and anxiety in the older cancer patient. Issues to consider in the geriatric population include presence of comorbid medical or psychiatric conditions, effects of concurrent treatments, probable polypharmacy, consequences of aging on drug metabolism, and unique

later-life psychosocial and developmental perspectives. Each of these, singly or in combination, can influence the presentation and management of psychiatric disorders. Successful treatments for depression and anxiety in the older cancer patient encompass psychological, behavioral, and pharmacological interventions, and optimal outcomes often require a combination of approaches. Primary care and oncologic providers should be aware of the criteria for diagnosis, availability of and indications for treatment, options for drug management, commonly experienced drug side effects, and strategies to assure adherence and the best outcomes. Despite a large body of experience, however, more specific research on older cancer patient populations is needed to better assess the efficacy, safety, and effectiveness of these interventions.

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CHAPTER

16

Cancer Pain in Elderly Patients

Bruce Ferrell

Pain is the most feared aspect of cancer for most patients and families. For cancer patients, pain often means the cancer is getting worse and death may be imminent. Pain is the most common source of both physical and existential suffering and often leads patients to functional decline, anxiety, depression, and social isolation. These facts are ironic, given the current availability of highly effective drugs and other interventions for pain relief. Ample evidence exists to indicate that cancer pain can be controlled and suffering effectively reduced for almost all cancer patients.

The approach to cancer pain assessment and management is different in elderly versus younger persons. Older persons may underreport pain for a variety of reasons, despite functional impairment, psychological distress, and needless suffering related to pain. They often present with concurrent illnesses and multiple problems making pain evaluation and treatment more difficult. Elderly persons have a higher incidence of side effects to pain medications and a higher potential for complications and adverse events related to many cancer and pain treatment procedures. Despite these challenges, pain can be effectively managed in most elderly patients. Moreover, clinicians have an ethical and moral obligation to prevent needless suffering and provide effective pain relief, especially for those near the end of life.

PHYSIOLOGY OF CANCER PAIN

Cancer may be nociceptive or neuropathic. Identification of the physiologic process by which pain is perceived may help guide clinicians' choice of pain management strategies. Treatment aimed at specific pathophysiologic pain mechanisms may be more effective. Nociceptive pain is largely the result of stimulation of somatic or visceral pain receptors. Nociceptive pain may arise from tissue injury, inflammation, or mechanical deformation. Examples include tissue injury by tumor enlargement, organ obstruction, ischemia, inflammation, or injury related to diagnostic or treatment procedures such as surgery. Pain from nociception usually responds well to common analgesic medications, relief of the underlying cause, and tissue healing. Neuropathic pain results from pathophysiologic processes that arise in the peripheral or central nervous system. Examples include tumor pressure or infiltration of nerves, neurotoxicity due to chemotherapy, and posttraumatic neuralgia (after amputation or mechanical nerve injury). Neuropathic pain mechanisms may be identified by association with known disease processes (e.g., postherpetic neuralgia or chemotherapy neurotoxicity), by neuroanatomical location (e.g., a dermatomal pattern), or specific descriptions of the character of the pain. Neuropathic pain may cause a radiculopathy, a pain sensation that travels along a nerve pathway. Common characteristics may include allodynia (a light touch elicits a painful sensation) or hypersensitivity (a painful sensation or pinprick elicits a hyperactive response), as well as descriptions of anesthesia, "pins and needles," or "like electricity." In contrast to nociceptive pain, neuropathic pain syndromes have been found to respond frequently to nonconventional analgesic medications such as anticonvulsant and antidepressant drugs. Some pain syndromes are thought to have multiple or unknown pathophysiologic mechanisms for which treatment is more problematic and unpredictable. Examples include fibromyalgia, recurrent headaches, and some vasculitic syndromes.

It is important to remember that all pain perception is modified by individual memory, expectations and emotions. These psychological mechanisms may enhance or diminish pain perception at the cortical level. Pain perception related to a purely psychological mechanism appears to be extremely rare in older people. These disorders akin to conversion reactions are more often related to somatoform disorders where nociceptive or neuropathic pain mechanisms become deeply entwined in psychological and behavioral pathology. Thus the assessment and treatment of pain should always take into consideration the psychological aspects of pain perception, and professional psychological and psychiatric interventions should be included in the multidimensional approach to pain management when appropriate.

Age-related changes in pain perception have been a topic of interest for many years. Elderly persons have been observed to present with painless myocardial infarction and painless intraabdominal catastrophes. The extent to which these observations are attributable to age-related changes in pain perception remains uncertain. Studies of pain sensitivity across the life span have shown mixed results. Decreased pain sensitivity

(increased threshold) with aging can be supported by evidence of decreased numbers of receptors and changes in nerve conduction. Increased pain sensitivity (decreased threshold) with aging can also be supported by evidence of alterations in spinal cord and central nervous system processing (poorer endogenous analgesia). If these observations are correct, overall pain perception may not change much with aging. Clearly, additional studies are needed to define age-related changes specific to nervous system function and pain perception.

ASSESSMENT AND MEASUREMENT OF PAIN IN OLDER PATIENTS

Accurate pain assessment includes an estimate of pain intensity. Pain intensity can be estimated using a valid and reliable pain scale. Pain scales can be grouped into multidimensional and unidimensional scales. In general, multidimensional scales with multiple items often provide more stable measurement and evaluation of pain in several domains. For example, the McGill Pain Questionnaire has been shown to capture pain in terms of intensity, affect, sensation, location, and several other domains that are not possible to evaluate with a single question. The Brief Pain Inventory is a two-dimensional scale that includes intensity and interference with activities. This instrument, originally established for evaluation of cancer pain, has recently been validated in elderly patients, as well as in those with other causes of pain, and has been translated into several foreign languages (Figure 16-1).

Unidimensional scales consist of a single item that usually relates to pain intensity alone. These scales are usually easy to administer and require little time or training to produce reasonably valid and reliable results. Examples include the verbally administered 0 to 10 scale, a single-item visual analog scale, or one of several word descriptor scales that are available. These scales have found widespread use in many clinical settings to monitor treatment effects and for quality assurance indicators. It is important to remember that unidimensional pain scales often require framing the pain question appropriately for maximum reliability. Subjects should be asked about pain in the present tense (here and now). For example the interviewer should frame the question "How much pain are you having right now?" Alternatively the interviewer can ask, "How much pain have you had over the last week?" or "On average, how much pain have you had in the last month?" The latter questions require accurate memory and integration of pain experiences over time that may be more difficult for patients. Recent studies in those with cognitive impairment have shown that pain reports requiring recall are influenced by pain at the moment. Thus it may be more useful to use unidimensional scales to assess pain frequently at the moment while evaluating pain reports over time, much the way vital signs are used. This is especially true for those with some cognitive impairment.

Pain Assessment in Those with Cognitive Impairment

Cognitive impairment, Alzheimer disease, stroke, or dementia can present substantial challenges to pain assessment. Fortunately, it has been shown that pain reports from those with mild to moderate cognitive impairment are no less valid than other patients with normal cognitive function. Weiner and associates have shown that these reports are usually reliable (stable over time) as well. Experience has shown that commonly available instruments are feasible for use in most patients with cognitive impairment. Thus most elderly patients with mild to moderate cognitive impairment appear to have the capacity to report pain accurately and reliably using commonly available methods.

Patients with severe cognitive impairment may represent substantial challenges for which no generalizable methods for pain assessment have been identified. Although it has been assumed that those in deep coma do not experience pain, it is not clear that such brain damage necessarily results in complete anesthesia. Patients with "locked-in syndrome" (having intact perception and cognitive function but no purposeful motor function and no means of communication) may suffer severely. Unfortunately no reliable methods exist to assess pain in these individuals. Health care providers must be aware of these situations and provide analgesia empirically, especially during procedures or for conditions known to be uncomfortable or painful. More often, most of those with severe cognitive impairment can and do make their needs known in simple yes or no answers communicated in various ways. For example, those with profound aphasia can often provide accurate and reliable answers to yes and no questions when confronted by a sensitive and skilled interviewer. For these patients it is important to be creative in establishing communication methods for the purpose of pain assessment.

Although pain is an individual experience, the use of family and caregivers in the assessment of pain can sometimes be helpful. Among patients with cognitive impairment, the history is often only obtainable from family or close caregivers. Family and caregivers are an excellent source of qualitative information about general behavior, medication usage, actions that seem to reduce pain, and actions that seem to aggravate pain. It is important to remember, however, that family and caregivers are limited in their interpretation of events and behaviors. In fact, evidence has suggested that when it comes to estimating pain intensity, proxies are not always very accurate or reliable. Our studies of elderly cancer patients suggest that caregivers may overestimate pain intensity and distress. It is often distressing to family and other

caregivers who feel helpless in managing severe pain. Both physicians and nurses have been found to underestimate pain and to provide inadequate pain medication. In the final analysis, family and close caregivers can be valuable sources of qualitative information, but they probably should not be relied on entirely for quantitative assessment of pain intensity or distress, especially among those patients able to communicate their pain experiences.

MANAGEMENT OF CANCER PAIN

A variety of both drug and nondrug methods are available and effective in cancer pain management. Data clearly shows that patients benefit most from a multimodal approach incorporating both drug and nondrug strategies along with requisite patient and caregiver education, follow-up, and support. Patients should be given an expectation of pain relief, but it may be unrealistic

STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: _____/_____/_____ Time: _____

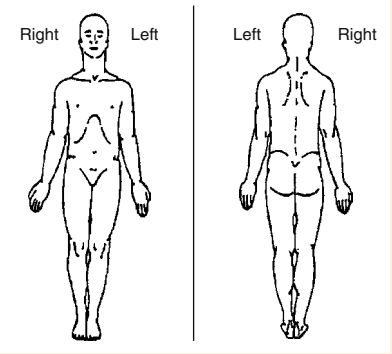
Name: _____ _____ _____

Last First Middle initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

FIGURE 16-1 Brief Pain Inventory (Short Form).

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% No Relief	10%	20%	30%	40%	50%	60%	70%	80%	90%	100% Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

B. Mood

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

C. Walking Ability

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

E. Relations with other people

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

F. Sleep

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

G. Enjoyment of life

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

FIGURE 16-1, cont'd

to suggest or sustain an expectation of complete relief for some patients with persistent pain. The goals and trade-offs of possible therapies need to be discussed openly. Sometimes a period of trial and error should be anticipated when new medications are initiated and titration occurs. Review of medications, doses, use patterns, efficacy, and adverse effects should be a regular process of care. Ineffective drugs should be tapered and discontinued. Patients and caregivers benefit from the empowerment often associated with "patient-controlled analgesia;" encouragement in the use of physical methods such as heat, cold, massage, and distraction; and the use of other cognitive behavioral techniques. Patient and caregiver education and instruction for these "self-help" interventions should be a part of the pain management plan for every patient with serious pain.

ANALGESIC DRUGS FOR CANCER PAIN

Any patient who has pain that impairs functional status or quality of life is a candidate for analgesic drug therapy. Analgesic medications are safe and effective in elderly people. All analgesic interventions carry a balance of benefits and burdens. For some classes of pain-relieving medications (opioids, for example) elderly patients have been shown to have increased analgesic sensitivity.

However, elderly people are a heterogeneous population, thus optimum dosage and known side effects are difficult to predict. Recommendations for age-adjusted dosing are not available for most analgesics. In reality, dosing for most patients requires beginning with low doses with careful upward titration, including frequent reassessment for dosage adjustments and optimum pain relief.

The use of placebos is unethical in clinical practice and there is no place for their use in the management of acute or chronic pain. Placebos, in the form of inert oral medications, sham injections, or other fraudulent procedures are only justified in certain research designs where patients have given informed consent and understand that they may be receiving a placebo as a part of the research design. In research, placebos help identify and measure random or uncontrollable events that may confound results of some research designs. In clinical settings, placebo effects are common, but they are neither diagnostic of pain nor indicative of a therapeutic response. The effects of placebos are short-lived and most patients eventually learn the truth, resulting in loss of patient trust and more needless suffering.

Acetaminophen

Acetaminophen is the drug of choice for elderly persons with mild to moderate pain, especially that of osteoarthritis and other musculoskeletal problems. As an analgesic and antipyretic, acetaminophen acts in the central nervous system to reduce pain perception. Despite the lack of anti-inflammatory activity, studies have shown that acetaminophen is as effective as most nonsteroidal anti-inflammatory drugs (NSAIDs). Given in a dose of 650 mg to 1000 mg four times a day, it remains the safest analgesic medication for most patients compared to traditional NSAIDs and other analgesic drugs. Unfortunately, acetaminophen overdose can result in irreversible hepatic necrosis. Therefore, the maximum daily dose should never exceed 4,000 mg per day. Some authors have suggested that the maximum dose of acetaminophen should be reduced in hepatic insufficiency. Unfortunately, evidence to identify a level of hepatic impairment justifying a dose adjustment has not been validated.

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) have analgesic activity both peripherally and centrally. They are potent inhibitors of cyclooxygenase and prostaglandin synthesis that have effects on inflammation, pain receptors, and nerve conduction and may have central effects as well. Clinical trials have found no advantage of COX-2–specific inhibitors compared to traditional nonspecific COX-inhibiting NSAIDs in terms of peak pain relief, total pain relief, and in indices of joint inflammation in patients with arthritis. Safety profiles of these agents have been impressive in reduction of gastrointestinal injury, renal toxicity, and bleeding diathesis, but concerns about a higher risk of cardiovascular events have reduced their overall appeal. Moreover, COX-2–specific inhibitor NSAIDs appear to have similar problems compared with traditional NSAIDs with respect to the incidence of both drug-drug and drug-disease interactions.

NSAIDs are appropriate for short-term use in inflammatory conditions such as gout, calcium pyrophosphate arthropathy, acute flare-ups of rheumatoid arthritis, and other inflammatory rheumatic conditions. They have also been reported to relieve the pain of headache, menstrual cramps, and other mild to moderate pain syndromes. Individual drugs in this class vary widely with respect to anti-inflammatory activity, potency, analgesic properties, metabolism, excretion, and side-effect profiles. Moreover, it has been observed that failure of response to one NSAID may not predict the response to another. A disadvantage of NSAIDs is that they all demonstrate a ceiling effect, that is, a level at which increased dose results in no further increase in analgesia. A large number of NSAIDs are now available; however, there is no evidence to support a particular compound as the NSAID of choice. Several are available over-the-counter without a prescription.

Use of high-dose NSAIDs for long periods of time should be avoided in elderly patients. The concomitant use of misoprostol, histamine-2 receptor antagonists, proton pump inhibitors, and antacids is only partially successful at reducing the risk of significant gastrointestinal bleeding associated with NSAID use. Also, the side-effect profiles of gastroprotective drugs in this population must be weighed against their limited benefits. For those with multiple medical problems, NSAIDs are associated with an increased risk of drug-drug and drug-disease interactions. NSAIDs may interact with antihypertensive therapy. Thus, the relative risks and benefits of NSAIDs must be weighed carefully against other available treatments for older patients with chronic pain problems. For some patients, chronic opioid therapy, low-dose or intermittent corticosteroid therapy, or many other nonopioid analgesic drug strategies may have fewer life-threatening risks compared to long-term, high-dose NSAID use.

Opioid Analgesic Medications

Opioid analgesic medications act by blocking receptors in the central nervous system (brain and spinal cord) resulting in a decreased perception of pain. Selected opioid analgesic medications are listed in Table 16-1. Opioid drugs have no ceiling to their analgesic effects and have been shown to relieve all types of pain. Short-term studies have suggested that elderly people, compared to younger people, may be more sensitive to the pain-relieving properties of these drugs. This has been shown for acute postoperative pain and chronic cancer pain. Advanced age is associated with a prolonged half-life and prolonged pharmacokinetics of opioid drugs. Thus,

TABLE 16-1 Selected Opioid Analgesic Medications for Pain*

Drug	Starting Dose (Oral)	Description	Comments
Morphine (Roxanol, MSIR)	30 mg (q4h dosing)	Short-intermediate half-life; older people are more sensitive than younger people to side effects	Titrate to comfort; continuous use for continuous pain; intermittent use for episodic pain; anticipate and prevent side effects
Sustained-release morphine (MS Contin, Oramorph, Avinza)	MS Contin - 30-60 mg (q 12 h dosing) Oramorph - 30-60 mg (q 12 h dosing) Avinza - 30-60 mg (q 24 h dosing)	Morphine sulfate in a wax matrix tablet or sprinkles; MS Contin and Oramorph should not be broken or crushed; Avinza capsules can be opened and sprinkled on food, but should not be crushed	Titrate dose slowly because of drug accumulation; rarely requires more frequent dosing than recommended on package insert; immediate release opioid analgesic often necessary for breakthrough pain
Codeine (plain codeine, Tylenol #3, other combinations with acetaminophen or NSAIDs)	30-60 mg (q 4-6 h dosing)	Acetaminophen or NSAIDs limit dose; constipation is a major issue	Begin bowel program early; do not exceed maximum dose for acetaminophen or NSAIDs
Hydrocodone (Vicodin, Lortab, others)	5-10 mg (q 3-4 h dosing)	Toxicity similar to morphine; acetaminophen or NSAID combinations limit maximum dose	Same as codeine
Oxycodone (Roxicodone, OxyIR; or in combinations with acetaminophen or NSAIDs such as Percocet, Tylox, Percodan, others)	20-30 mg (q 3-4 h dosing)	Toxicity similar to morphine; acetaminophen or NSAID combinations limit maximum dose; oxycodone is available generically as a single agent	Same as morphine
Sustained-release oxycodone (OxyContin)	15-30 mg (q 12 h dosing)	Similar to sustained-release morphine	Similar to sustained-release morphine
Hydromorphone (Dilaudid)	4 mg (q 3-4 h dosing)	Half-life may be shorter than morphine; toxicity similar to morphine	Similar to morphine
Methadone (Dolophine)	Equal analgesic potency is dose-dependent and difficult to predict; significant overdose risk when switching from other opioids	Serum half-life 18 hr; analgesic half-life 8-12 hr. Highly lipid soluble; metabolism by oxidation and dependent on liver cytochrome enzyme activity.	Black box warning: Significant risk of drug accumulation.
Oxymorphone IR (Opana) Oxymorphone ER (Opana ER)	10-20 mg (q 4 h) 5 mg (q 12 h) in opioid naive	Slightly more potent than morphine, not as potent as hydromorphone	Same as morphine
Transdermal fentanyl (Duragesic)	25 μg patch (q 72 h dosing)	Reservoir for drug is in the skin, not in the patch; equivalent dose compared to other opioids is not very predictable (see package insert); effective activity may exceed 72 hrs in older patients	Drug reservoir is in skin, not patch. Titrate slowly using immediate release analgesics for breakthrough pain; peak effect of first dose may take 18-24 h; not recommended for opioid-naive patients
Fentanyl lozenge on an applicator stick	Rub on buccal mucosa until analgesia occurs, then discard	Short half-life; useful for acute and breakthrough pain when oral route is not possible	Absorbed via buccal mucosa, not effective orally

*A limited number of examples is provided. For comprehensive lists of other available opioids, clinicians should consult other sources.

elderly people may achieve pain relief from smaller doses of opiate drugs than younger people.

Opioid drugs have the potential to cause cognitive disturbances, respiratory depression, constipation, and habituation in older people. Drowsiness, performance-based measures of cognitive impairment, and respiratory depression associated with opioids should be anticipated when opioids are initiated and doses are escalated rapidly. Drowsiness, cognitive impairment, and respiratory depression occur in a dose-dependent fashion and can be used to judge dose escalations. If patients have unrelieved pain with little drowsiness or cognitive impairment, doses may be escalated. Tolerance usually develops in a few days to these side effects, at which time, patients usually return to a fully alert status and baseline cognitive function. Until tolerance develops, patients should be instructed not to drive and to take precautions against falls or other accidents. But once tolerance to these effects

has developed, patients can return to normal activities including driving and other demanding tasks despite high doses of opioid drugs. In fact, cancer patients are often observed to improve physical function once pain is adequately relieved on opioid analgesics.

Constipation is a side effect of opioid drugs to which older patients do not develop tolerance. The management of constipation usually includes increasing fluid intake, maintaining mobility, and use of cathartic medications. Some patients find relief with remedies like prune juice or other natural laxatives. Other patients may require more potent osmotic laxatives such as milk of magnesia, lactulose, or sorbitol. But for many patients opioid-induced constipation may require potent stimulant laxatives such as senna or biscodyl. It should be remembered that stimulants should not be used until impactions have been removed and obstruction has been ruled out. Finally, some patients require regular enemas to ensure bowel evacuation during high-dose opioid administration for severe pain.

Nausea also occasionally complicates opioid therapy. Nausea from opioid medications may result from several mechanisms and may wane as tolerance develops. Traditionally, antiemetics such as prochlorperazine, chlorpromazine, and antihistamines have been the mainstay of treatment for nausea in younger patients. Recently low-dose haloperidol has been used, with anecdotally noting of a lower side effect profile compared to other neuroleptic drugs. It should be remembered that all of these agents have high side-effect profiles in elderly patients including movement disorders, delirium, and anticholinergic effects. Thus clinicians should choose antiemetic medications with the lowest side effects, and continue to monitor patients frequently.

It is important for clinicians who prescribe opioid analgesics to understand issues of tolerance, dependency, and addiction. Tolerance is a pharmacologic phenomenon that occurs with many drugs. Tolerance is defined by diminished effect of a drug associated with constant exposure to the drug over time. For opioid drugs, tolerance is difficult to predict. In general, tolerance to drowsiness and respiratory depression occur much faster than tolerance to analgesic properties of the drug. Previous reports that described tolerance among cancer patients resulting in the need for massive doses of morphine to achieve adequate analgesia were probably misinterpreted because those patients also had rapidly advancing cancer. More recent studies of opioid-managed arthritis pain have noted that tolerance was not often significant. In fact some patients have been noted to remain on stable doses of opioids for many years without demonstrating significant tolerance to the analgesic effects.

Dependency is also a pharmacologic phenomenon associated with many drugs including, for example, corticosteroids and beta-blockers. Dependency is present when patients experience uncomfortable side effects when the drug is withheld abruptly. Fortunately, these symptoms can be ameliorated easily by tapering opioids over a few days. It is important to remember that physiologic effects of opioid withdrawal are usually not life-threatening compared to the serious syndromes common with alcohol, benzodiazepine, or barbiturate withdrawal.

Addiction is a behavioral problem and is defined in such terms. Addictive behavior is defined by compulsive drug use despite negative physical and social consequences and the craving for effects other than pain relief. Addicted patients often have erratic behavior that can be observed in a clinical setting in the form of selling, buying, and procuring drugs on the street, and the use of medication by bizarre means such as dissolving tablets for intravenous self-administration. It is now clear that drug use alone is not the major factor in the development of addiction. Other medical, social, and economic factors play immense roles in addictive behavior. It is also important to not construe certain behaviors as necessarily addictive behaviors. Hoarding of medications, persistent or worsening pain complaints, frequent office visits, requests for dose escalations, and other behaviors associated with unrelieved pain have coined the term "pseudoaddiction". Laws, regulations, and unintentional behavior by prescribing clinicians may require patients to hoard medication and seek other physicians for additional help. In fact, true addiction is rare among patients taking opioid analgesic medications for medical reasons. This is not meant to imply that opioid drugs can be used indiscriminately, only that fear of addiction and side effects do not justify failure to treat pain in elderly patients, especially those near the end of life.

Other Nonopioid Medications for Pain

A variety of other medications not formally classified as analgesics have been found to be helpful in certain specific pain problems. The term "adjuvant analgesic drugs," although frequently used, is a misnomer in that some of these nonopioid drugs may, in certain cases, be the primary pain-relieving pharmacologic intervention. Table 16-2 provides some examples of nonopioid drugs that may help certain kinds of pain. The largest body of evidence available relates to the use of these drugs for neuropathic pain, such as diabetic neuropathies, postherpetic neuralgia, and trigeminal neuralgia. Tricyclic antidepressants, anticonvulsants, and local anesthetics are the most frequently used nonopioid analgesics for neuropathic conditions. In general, these drugs have had limited success in pain syndromes that are not associated with neuropathic mechanisms. Typically about 50% to 70% of patients have a measurable response and of those most only experience partial relief. Thus these drugs are not often panaceas and are rarely totally successful as single agents. Usually these agents work better in combination with other traditional drug and nondrug strategies in an effort to improve pain and keep other drug doses to a minimum. Failure of response to one

TABLE 16-2 Selected Nonopioid Medications for Pain*

Drug	Description	Comments
Acetaminophen (paracetamol)	Mechanism of action not known (probably central-acting)	Drug of choice for mild to moderate musculoskeletal pain; maximum dose = 4 gm/24 hrs; reduce dose by half in patients with severe hepatic insufficency
Nonsteroidal anti-inflammatory drugs (NSAIDs) Nonspecific COX inhibitors: Ibuprofen, naproxen, diclofenac	Effective for mild to moderate pain and inflammatory conditions; high side-effect profile in older persons including gastrointestinal bleeding, drug-drug and drug-disease interactions	Should not be used at high dose for long periods of time; proton pump inhibitors or misoprostol may reduce GI toxicity by 50%
Nonsteroidal anti-inflammatory drugs (NSAIDs) Specific COX-2 inhibitors Celecoxib (Celebrex), valdecoxib (Bextra)	No advantage over other NSAIDs in terms of pain efficacy or anti-inflammatory activity; GI toxicity compared to other NSAIDs is 50% less	Use has been controversial because of increased risk of myocardial infarction; one product (rofecoxib [Vioxx]) removed from the market in U.S.; continue aspirin in those with cardiovascular risk
Tricyclic antidepressants: (Amitriptyline, desipramine, nortriptyline, others)	Older people are more sensitive to side effects, especially anticholinergic effects; desipramine or nortriptyline is better choice than amitriptyline	Complete relief unusual; used best as adjunct to other strategies; start low and increase slowly every 3-5 days; not recommended for first-line therapy because of anticholinergic side effects
Norepinephrine modulating antidepressants: Duloxetine (Cymbalta), venlafaxine (Effexor)	Efficacy has been established, but studies are small and generally weak	Best in combination with other management strategies
Serotonin reuptake inhibitors (SSRI) Sertraline (Zoloft), paroxetine (Paxil)	Little or no effect on pain	Not recommended for pain
Anticonvulsants Clonazepam, carbamazepine	Carbamazepine may cause leukopenia, thrombocytopenia, and rarely aplastic anemia; clonazepine side effects may be similar to other benzodiazepines in the elderly	Start low and increase slowly; check blood counts on carbamazepine
Gabapentin (also an anticonvulsant) (Neurontin)	Less serious side effects than other anticonvulsants	Start with 100 mg and titrate up slowly; TID dosing; monitor for idiosyncratic side effects such as ankle swelling, ataxia, etc.; effective dose reported 100-800 mg q 8 h
Pregabalin (Lyrica)	Essentially identical to gabapentin	Start low and go slowly
Antiarrhythmics mexiletine (Mexitil)	Common side effects include tremor, dizziness, paresthesias; rarely may cause blood dyscrasias and hepatic damage	Avoid use in patients with preexisting heart disease; start low and titrate slowly; monitor EKGs; q 6-8 h dosing
Local anesthetics Lidocaine (intravenous) Lidocaine transdermal patch (Lidoderm) Capsaicin	IV lidocaine associated with delirium Transdermal patch has minimal systemic absorption. Capsaicin depletes nerve endings of Substance P.	IV lidocaine may predict response to anticonvulsants and antiarrhythmics May apply up to 3 patches alternating 12 h intervals to improve pain, reduce denervation hypersensitivity, and decrease systemic absorption May take 2 weeks to peak effect
Tramadol (Ultram)	Partial opioid and serotonin agonist; more of a norepinephrine antagonist; may cause drowsiness, nausea, vomiting, and constipation	Has ceiling effect; dose > 300 mg/24 h usually not tolerated because of nausea; q 4-6 h dosing
Muscle relaxants (baclofen, chlorzoxazone [Paraflex], cyclobenzaprine [Flexeril])	Sedation; anticholinergic effects; abrupt withdrawal of baclofen may cause CNS irritability	Mechanism of action not precisely known; monitor for sedation and anticholinergic effects; taper baclofen on discontinuation
Substance P inhibitors (capsaicin) Available OTC; for topical use only	Burning pain during depletion of substance P may be intolerable by as many as 30% of patients; may take 14 days for maximum response; avoid eye contamination	Start with small doses; can be partially removed with vegetable oil
NMDA Inhibitors Ketamine Dextromethorphan	N-Methyl-D-aspartate antagonists (NMDA) Ketamine: potent anesthetic Dextromethorphan: common cough suppressant	Ketamine only available IV Both may cause delirium

*A limited number of examples is provided. For comprehensive lists of other available pain medications, clinicians should consult other sources.

TABLE 16-2 Selected Nonopioid Medications for Pain—cont'd

Drug	Description	Comments
Drugs for osteoporosis Calcitonin Bisphosphonates	Pain-relief mechanisms unknown	Not effective on pain other than osteoporosis
Corticosteroids Prednisone Dexamethasone	Decrease inflammation in many tissues.	Classic corticosteroid side effects limit overall usefulness in chronic pain.

particular class of drugs does not necessarily predict failure of another class of agents. In general, nonopioid medications for neuropathic pain should be chosen according to lowest side effects. Treatment should usually start with lower doses than recommended for younger patients and doses should be escalated slowly on the basis of known pharmacokinetics of individual drugs and appropriate knowledge of disease-specific treatment strategies. Unfortunately, most of the nonopioid medications for pain management have high side-effect profiles in elderly people. Thus these medications often have to be monitored carefully.

Tricyclic antidepressants have been the most widely studied class of nonopioid medications for pain. The mechanism of action for these drugs is not entirely known, but probably has to do with interruption of norepinephrine- and serotonin-mediated mechanisms in the brain. Because of the high level of anticholinergic side effects, most tricyclic antidepressants are no longer considered first-line therapy for neuopathic pain. Other studies of the serotonin reuptake inhibitors, which may have lower side-effect profiles for elderly people, have had mixed reviews and most have not been shown effective for pain management. Newer norepinephrine-modulating drugs such as duloxetine (Cymbalta) and venlafaxine (Effexor) may be more effective.

It has been known for many years that some medications with antiepileptic activity may relieve the pain of trigeminal neuralgia (tic douloureux). Among these drugs, gabapentin and pregabalin have become the drugs of choice for most neuropathic pain. Clinical observations suggest that these agents have a significant analgesic effect on many neuropathic pains with a much lower side-effect profile compared to other antiepileptic drugs and most antidepressants as well.

Muscle relaxant drugs include cyclobenzaprine, carisoprodol, chlorzoxazone, methocarbamol and others. It is important to know that cyclobenzaprine is essentially identical to amitriptyline with similar side effects, and carisoprodol has been removed from the European market because of concerns about drug abuse. Although these drugs may relieve skeletal muscle pain, their effects are nonspecific and not related to muscle relaxation. Therefore they should not be prescribed with the mistaken belief that they relieve muscle spasm. If muscle spasm is suspected to be at the root of the patient's pain, it is probably justified to consider another drug with known effects on muscle spasm (e.g., benzodiazepines, baclofen). Baclofen is an agonist of gamma butyric acid. It has been used as a second-line drug for severe spasticity related to central nervous system injury, demyelinating conditions, and other neuromuscular disorders. Discontinuation after prolonged use requires slow tapering because of potential for delirium and seizure.

Current information does not support a direct analgesic effect of benzodiazepines. Although they may be justified for management of anxiety or in a trial for the relief of muscle spasm, the high risk-profile of these drugs in elderly persons usually obviates the potential benefit as an analgesic.

Calcitonin may be helpful in various cases of bone pain and as a second-line treatment for some neuropathic conditions, particularly postosteoporotic vertebral fractures, pelvic fractures, and bony metastasis. The mechanism by which calcitonin relieves pain is unknown. Apart from hypersensitivity reactions, the main side effects include nausea and altered serum levels of calcium and phosphorus. Bisphosphonates may also provide analgesia in patients with cancer metastasis, particularly of breast, prostate, and multiple myeloma. Data are more promising for pamidronate and clodronate.

Topical analgesics may be helpful for certain regional pain syndromes. Placebo-controlled trials of lidocaine 5% patch have been largely limited to neuropathic pain. It has been shown to be helpful in cases of postherpetic neuralgia, but the benefit does not usually compare to that of systemic gabapentin or tricyclic antidepressants. Nonetheless, the patch has found widespread "off-label" use for a variety of conditions such as osteoarthritis and wound care. The patch is contraindicated in advanced liver failure because of decreased lidocaine clearance; however, among other patients, pharmacokinetic studies have suggested safe systemic lidocaine levels even with doses as high as four patches in 24 hrs. Adverse reactions are rare, mild, and mostly related to skin rash.

Eutectic mixture of lidocaine and prilocaine (EMLA) is a local anesthetic capable of penetrating the skin to produce cutaneous anesthesia. However, there is significant risk of systemic toxicity if used repeatedly or near mucous membranes or open wounds.

Topical capsaicin cream has been shown to provide some benefit in the reduction of both neuropathic and nonneuropathic pain, although as many as 30% of subjects may not be able to tolerate the burning sensation associated with treatment initiation. Depletion of substance P with resulting anesthesia may require several days or weeks of exposure. Newer formulations with NSAIDs, local anesthetics, or tricyclic antidepressants may help ameliorate the burning sensation and reduce premature treatment cessation.

Topical NSAIDs have shown some efficacy in a few studies of neuropathic and nonneuropathic pain. Studies of topical aspirin, indomethacin, diclofenac, piroxicam, and ketoprofen have been reported. The biology of these agents is not fully understood, although the reported toxicity seems to be low.

Antinociceptive effects have been observed with the use of cannabinoids in animal models and a few controlled human trials. In older patients, the therapeutic window for cannabinoids appears to be narrow because of the dysphoric response that older patients and those using higher doses may experience.

ANESTHETIC AND NEUROSURGICAL APPROACHES TO PAIN MANAGEMENT

A wide variety of anesthetic and neurosurgical approaches to pain are available and some require highly specialized skills. Although it is beyond the scope of this chapter to review details of all of these techniques, a few deserve mention.

Trigger-point injections have been used extensively for the treatment of myofascial pain syndromes. Myofascial pain with trigger points was first recognized more than 50 years ago. In a relatively high percentage of cases, trigger points may initiate a reflex mechanism that produces referred pain, tenderness, and muscle spasm. With local injection of the trigger point followed by stretching and reconditioning of the muscles, the myofascial pain syndrome usually subsides. More recently, similar results have been obtained using ice massage or vapocoolant spray applied topically, followed by specific muscle stretching and physical therapy techniques. Nonetheless, trigger-point injection with dilute local anesthetics may be highly effective when combined with specific physical therapy for many myofascial pain syndromes.

Continuous drug infusions are highly effective for providing steady-state analgesic drug levels. Continuous infusions can be maintained by implantable pumps or external devices to deliver intravenous, subcutaneous, intrathecal, or epidural medications. Continuous infusions of opioid drugs have found widespread use in severe chronic cancer pain, especially among those near the end of life. Other uses have included continuous infusion of muscle relaxants for patients with severe muscle spasm from spinal injury, multiple sclerosis, or end-stage Parkinson disease. Whether these invasive high-tech strategies are appropriate for patients with all kinds of chronic pain remains controversial. These techniques are very expensive, but they are often reimbursed by third-party payers. These issues have raised ethical issues about the application of high-tech strategies for patients who might be equally well managed using oral medications that are not reimbursable. In general, these methods should be used only when oral medications become ineffective or the oral route of administration is no longer viable. More work needs to be done to justify these risky and expensive techniques that need to be carefully monitored in nursing homes, home care, and other low-tech long-term care settings.

NONDRUG STRATEGIES FOR PAIN MANAGEMENT

Nondrug strategies, used alone or in combination with appropriate analgesic medications, should be an integral part of the care plan for most elderly patients with cancer pain. Nondrug strategies for pain management encompass a broad range of treatments and physical modalities, many of which carry low risks for adverse effects. Used in combination with appropriate drug regimens, these interventions often enhance therapeutic effects while allowing medication doses to be kept low to prevent adverse drug effects.

Physical exercise is important for most patients with pain. A program of exercise can be tailored to most patients' needs and is extremely important for rehabilitation and the maintenance of strength and endurance. There is no evidence that one form of exercise is better than another, so programs can be tailored for the individual's needs, lifestyle, and preference. The intensity of exercise along with frequency and duration must be adjusted to avoid exacerbation of the underlying condition while gradually increasing and later maintaining overall conditioning. It is important to remember that feeling better often gives rise to a false impression that the discipline of regular exercise is not necessary. Continued encouragement and reinforcement is often required. Unless complications arise, the program of exercise should be maintained indefinitely to prevent deconditioning and deterioration.

Psychological strategies have also been shown to be helpful for some with significant pain. Cognitive therapies are strategies aimed at altering belief systems and attitudes about pain and suffering. Cognitive therapies include various forms of distraction, relaxation, biofeedback, and hypnosis. Behavioral therapies are strategies aimed at enhancing healthy behaviors and discouraging abnormal behavior that is unpredictable and self-defeating. Cognitive therapy can be combined with behavioral approaches, and together they are known as cognitive-behavioral therapy. Cognitive-behavioral therapy in its purest form includes a structured approach to teaching coping skills that might be used alone or in combination

with analgesic medications and other nondrug strategies for pain control. Effective programs can be conducted by trained professionals with individual patients or in groups and there is some evidence that the effect is enhanced with caregiver involvement. Although it may not be appropriate for those with significant cognitive impairment, there is evidence from randomized trials to support the use of cognitive-behavioral therapy for many patients with significant chronic pain.

Finally, a variety of alternative therapies are also used by many patients. Many patients seek alternative medicine approaches with and without the knowledge or recommendation of their physician or other primary care provider. Alternative medicine approaches to chronic pain may include homeopathy, spiritual healing, or the growing market of vitamin, herbal, and natural remedies. Although there is little scientific evidence to support these strategies for pain control, it is important that health care providers not abandon patients or leave them with a sense of hopelessness.

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CHAPTER

17

Cancer-Related Fatigue in the Older Patient

Betty Ferrell and Virginia Sun

CASE 17-1 CASE STUDY

Mr. D is an 80-year-old man who has been diagnosed with stage IV prostate cancer, with metastatic disease to the bones. He has a history of chronic arthritis and diabetes. His blood sugar is not optimally controlled, and he has had two recent visits to the emergency department for uncontrolled blood glucose. Over the years, as a result of his uncontrolled diabetes, Mr. D gradually developed diabetic peripheral neuropathy, and he uses a walker to help with ambulation. The neuropathy has interfered significantly with his functional status, and he relies on a niece who lives close by to shop for food and everyday essentials. His wife died six months ago, and he admits that he is still mourning his loss. He also reports that he is "exhausted," "tired to the bone," and is just "worn out." Mr. D has agreed to participate in a clinical trial testing a new chemotherapy to treat his prostate cancer.

This case study illustrates the multiple factors influencing cancer fatigue in the elderly. Cancer is a disease affecting predominantly older persons, with incidence and prevalence increasing with age.[1-4] In addition to cancer, many older persons have comorbid medical conditions (e.g., cardiomyopathies, diabetes, depression) rendering them more susceptible to illness and treatment and limiting their functional capacities.[5] Fatigue from cancer and/or its treatment is the most commonly reported symptom by older cancer patients and affects 70% to 100% of those receiving treatment for cancer.[3,6,7] The National Comprehensive Cancer Network (NCCN) defines cancer-related fatigue (CRF) as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.[8] This chapter discusses the current evidence regarding cancer-related fatigue in the elderly and provides recommendations for the assessment and management of this distressing symptom in the elderly cancer population.

ETIOLOGY OF CANCER-RELATED FATIGUE

To date, the mechanisms and pathophysiology of CRF are largely unknown, although many studies have attempted to describe possible etiology and mechanisms related to its manifestation in cancer patients. Possible CRF mechanisms include cytokine production (i.e., IL-6), abnormal serotonin regulation, neuromuscular dysfunction, and abnormal levels of muscle metabolites.[9-12] CRF may also be caused by treatments such as chemotherapy, radiation therapy, bone marrow transplantation, biological response modifiers, or contributing factors such as pain, emotional distress, anemia, altered nutritional status, sleep disturbance, decreased activity, and comorbidities.[8] CRF is thought to have peripheral as well as central components as its biologic basis. Peripheral components are those factors that cause negative energy balance that result in fatigue. Factors that contribute to this negative energy balance include cancer, cancer treatments, systemic infections, hypothyroidism, anemia, malnutrition, metabolic abnormalities, sleep disorders, and psychological factors (depression, anxiety).[12,13] Central components include hypothalamic-pituitary-adrenal (HPA) axis hyperactivity, and increases in immunologic factors and cytokines (T lymphocytes, IL-1 antagonists, tumor necrosis factor receptor II).[12,14-18] All of these potential components of CRF are important in elderly cancer patients, and may contribute to the etiology of CRF in this older population.

CANCER-RELATED FATIGUE ACROSS THE DOMAINS OF QUALITY OF LIFE

CRF affects all aspects of the patient's quality of life (QOL) and can persist 5 to 10 years after completion of treatment.[19,20] The impact on the patient's physical functioning is exceptionally distressing and has been reported as being more distressing than pain or nausea.[21-23]

CRF affects physical functioning and can be very debilitating.[24-26] For the general geriatric population,

the need for assistance with activities of daily living (ADLs) and instrumental activities of daily living (IADLs) is an independent predictor of morbidity and mortality. The older cancer patient is more likely to have functional limitations in ADLs than the general elderly population.[27] For many patients, physical activity levels decrease during and after treatment, with some patients not returning to prior treatment levels. This can lead to a cycle of declining physical activity leading to increased fatigue, which leads to further decreased conditioning, and increased weakness and fatigue during any physical activity.[4]

Luciani and colleagues conducted a retrospective cross-sectional study of 214 patients aged 70 or older, seen over the course of 3 months in their Senior Adult Oncology Program.[28] Patients were screened with a questionnaire assessing ADLs, IADLs, performance status (PS), cognitive impairment, depression, and malnutrition. In addition, each patient was assessed for fatigue using the Fatigue Symptom Inventory that measures four aspects of fatigue: severity, frequency, daily patterns of fatigue, and interference with daily activities; complete blood counts and chemical panels were also obtained. Eighty-one percent of the patients reported fatigue and the interference score of fatigue was a probable mediator for dependencies in ADLs ($p < 0.001$) and IADLs ($p < 0.001$), and poorer PS ($p < 0.001$). Data revealed a correlation between severity, interference, and frequency of fatigue and depression, but only hemoglobin level partially correlated with fatigue. Anemia correlated with decreased functional status. All fatigue dimensions were significantly associated with ADL and IADL dependencies and with the Geriatric Depression Scale. The authors concluded that fatigue in the elderly could represent a long-term complication of cancer and cancer treatment that may accelerate functional decline.[28]

Comorbid conditions in the older cancer patient are also causes of morbidity and mortality, affecting life expectancy, tolerance to treatment, and quality of life.[29,30] Those older than 65 years have an average of three comorbidities, with the most common being cardiovascular disease, hypertension, COPD, arthritis, and depression.[31] Comorbidities were found to be a prevailing issue among 867 elderly patients with newly diagnosed breast, prostate, lung, or colorectal cancer. Kozachik and Bandeen-Roche conducted a secondary analysis on this population and followed the patients at four points in time (6 to 8 weeks, 12 to 16 weeks, 24 weeks, and 52 weeks) during the year after their diagnosis.[2] The patients also completed a demographic questionnaire, the Comorbidity Index, and the Patient Symptom Experience. The researchers sought to determine whether the patient's sex, age, comorbidity status, cancer site, stage of disease, or treatment regimen predicted patterns of pain, fatigue, and insomnia over time. The mean patient age was 72.6 years, 54% were men, and reported a mean of more than two comorbidities. Twenty-seven percent reported four or more comorbidities. The top four comorbid conditions reported were heart problems (31%), arthritis (20%), high blood pressure (50%), and chronic lung disease (16%). Results revealed that advanced age was not significantly associated with increased patterns of pain, fatigue, and insomnia. Comorbidities were correlated with pain, fatigue, and insomnia only at wave 1 and 4 observation times. Sex was associated with significant risks of reporting fatigue and insomnia or fatigue and pain, with women reporting the most fatigue and sleep disturbance. Treatment modality was associated with significantly increased risks of pain, fatigue, and insomnia. Having late-stage lung cancer and reporting pain, fatigue, and insomnia at wave 2, 3, and 4 observation times were significantly associated with death.[2]

The psychological impact of CRF in older cancer patients can greatly diminish their quality of life. CRF affects the patient's social activities, leisure time, and responsibilities.[32] There is debate as to whether a correlation exists between fatigue and depression. However, depression occurs in approximately 20% to 50% of patients with cancer.[33-41] It is the most common psychiatric disorder among cancer patients and yet is frequently undiagnosed because of the oftentimes coexistent symptoms from cancer and/or cancer treatment, such as fatigue, pain, and appetite loss.[42-44] As in the aforementioned case study, depression and grief for this elderly patient are important considerations in a plan of care.

Hwang, Chang, Rue, and Kasimis assessed multidimensional independent predictors of cancer-related fatigue and found that dyspnea, pain, lack of appetite, feeling drowsy, feeling sad, and feeling irritable predicted fatigue independently.[45] Physical and psychological symptoms predict fatigue independently in the multidimensional model and superseded laboratory data.[45] Liao and Ferrell assessed fatigue in the elderly and found a significant relationship between fatigue and depression, pain, number of medications, and physical function.[46] Respini and colleagues found that fatigue correlated with depression in older cancer patients to a degree comparable to that in younger patients.[7] This study assessed the prevalence and correlates of fatigue in 77 cancer patients aged 60 or older during outpatient treatment with chemotherapy or pamidronate. An older study conducted by Hickie and colleagues examined the prevalence and sociodemographic and psychiatric correlates of prolonged fatigue syndromes of 1593 patients attending four general primary care practice settings.[47] Twenty-five percent reported prolonged fatigue and 37% had a psychological disorder. Of the 25% with fatigue, 70% had both fatigue and psychological disorder, while 30% had fatigue only. Data revealed that patients with fatigue were more likely to also have a depressive disorder.[47] The literature clearly shows the

interrelationship between fatigue and psychological disorders.

FATIGUE ASSESSMENT

CASE 17-1 CASE UPDATE

Mr. D comes to the clinic today for his third course of treatment and reports that he has been "very tired" for the past week, and that he is unable to perform some activities of daily living, such as buying groceries and cooking. When asked to rate his fatigue intensity over the past 7 days, he reports that it is a 6 out of 10. According to Mr. D's subjective rating, he is currently suffering from moderate fatigue. His oncologist initiated a more focused fatigue history and examination in addition to a comprehensive geriatric assessment. Mr. D was queried about the onset, pattern, and duration of his fatigue over the past 7 days. While conducting a thorough assessment of treatable contributing factors, his oncologist focused on Mr. D's two comorbidities: chronic arthritis and diabetes, as well as bereavement from his wife's recent death. On the basis of this medical history, the oncologist focused his queries around factors related to the comorbidities that may be contributing or exacerbating Mr. D's CRF: uncontrolled pain from his chronic arthritis and neuropathy, his activity level, his nutritional status, possible depression secondary to complicated bereavement, and possible anemia secondary to three courses of clinical trial treatment. Mr. D admits that the pain related to his chronic arthritis has been flaring recently, and that his activity level has been low. He also reports that he has been unable to sleep at night because of the arthritis flare-ups.

An essential component of managing CRF in the elderly is a thorough assessment. First, comorbidities need to be assessed and addressed to determine other factors that may be contributing to fatigue related to cancer treatments. Elderly patients with a history of diabetes or other comorbidities may be at higher risk for experiencing debilitating fatigue if treatment is planned. After assessing for comorbidities, patients should be asked to rate their fatigue level on a numerical analog scale (0-10). The NCCN guidelines recommend the following cut-offs for fatigue severity: 0 to 3 for "none to mild," 4 to 6 for "moderate," and 7 to 10 for "severe."[8] The guidelines recommend that all patients with a reported fatigue severity of moderate to severe intensity should be assessed using a focused history and examination to pinpoint treatable causes. Treatable causes include anemia, pain, insomnia, malnutrition, and emotional distress.[8] Finally, any referrals made to supportive care experts such as a dietician, rehabilitation, social work, psychology/psychiatry, or support groups should be documented. The NCCN guidelines recommend using an interdisciplinary model for managing CRF.[8]

FATIGUE MANAGEMENT

CASE 17-1 CASE UPDATE

On the basis of Mr. D's CRF assessment, referrals to supportive care experts such as a dietician, physical therapist, psychologist, social worker, and pain specialist were considered in order to manage the treatable causes. An endocrinologist was also consulted to assess whether Mr. D's diabetes continues to be poorly controlled. Mr. D was given patient education materials that included information about CRF and its management. His nurse discussed the education material, including strategies of fatigue management such as energy conservation and physical activity. His oncologist also discussed the use of medications such as Ritalin to manage his CRF, but Mr. D declines because he doesn't want to have to take another "pill."

Pharmacologic

A number of pharmacologic agents have been evaluated for the treatment of cancer-related fatigue. The class of pharmacologic agents that shows the most promise in managing cancer-related fatigue is psychostimulants, which are known to increase level of alertness and motivation. Methylphenidate has been evaluated in HIV patients and advanced cancer patients.[48,49] In a pilot study by Bruera and colleagues, an improvement was shown in general well-being and depression, as well as in fatigue scores as measured by the FACIT-F.[50] Because of the rapid onset of action and short half-life of methylphenidate, a subsequent double-blind, randomized, placebo-controlled trial by Bruera and colleagues tested a patient-controlled methylphenidate protocol for patients with a self-reported fatigue intensity of 4 or more as measured by the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F).[51] The dosage tested in this study was methylphenidate 5 mg or placebo every 2 hours as needed, up to four tablets per day, with fatigue assessment at day 8, 15, and 36. Fatigue intensity decreased significantly at day 8 in both groups, but there was no significant difference in fatigue improvement.[51] However, in the open-label phase, a significant improvement in fatigue was found between groups, and was sustained through days 15 and 36.[51] It was unclear whether the extended improvement during the open-label phase was an independent result or due to placebo effect. Although there is evidence on a preliminary level to support the effectiveness of psychostimulants for the treatment of cancer-related fatigue, some caution needs to be taken, particularly for geriatric oncology patients. Because of the rapid onset of these agents, as well as their behavioral effects and tolerance issues, there is an increased risk for side effects. The most common side effects of psychostimulants include agitation and insomnia, which may cause more harm than benefit for elderly cancer patients.[48] Cardiovascular side effects such as hypertension,

palpitations, arrhythmias, as well as confusion, psychosis, and tremors are rare side effects, but again may be potentially dangerous for elderly cancer patients. These common and potential side effects limit the use of this class of agents for elderly cancer patients because of contraindications for cardiovascular and other comorbid conditions.

Modafinil has been tested as a fatigue treatment option. In a study of breast cancer survivors, Morrow and colleagues reported an 86% reduction of fatigue intensity with a modafinil dosage of 200 mg per day.[52] Donepezil, an agent used in the treatment of Alzheimer dementia, was evaluated by Bruera and colleagues in a double-blind placebo-controlled trial of donepezil 5 mg per day compared to placebo.[53] The study results were negative, with no statistically significant difference shown between groups. Toxicities are also a problem for this drug including nausea, vomiting, diarrhea, muscle and abdominal cramps, and anorexia, which may limit its use in the geriatric oncology setting.[48,54] Studies exploring the use of antidepressants as a possible mechanism for managing fatigue demonstrated no differences in fatigue scores.[12]

Nonpharmacologic

A number of systematic reviews and one Cochrane review have been undertaken to examine the efficacy of nonpharmacologic strategies, such as exercise, in fatigue management.[55-57] A detailed assessment by a rehabilitation expert such as a physical therapist should be accessed, if available, in order to prescribe a comprehensive and safe exercise regimen. The prescribed exercise regimen should be initiated gradually and at a pace based on the individual's capabilities. Table 17-1 provides an outline of key concepts to be included in patient education for CRF. The outline includes education points on what fatigue is, common causes of fatigue, common words used to describe fatigue, what patients should tell their clinicians about fatigue, energy conservation principles, and the principles of exercise.

TABLE 17-1 Key Concepts for Patient Education on CRF

1. Definition of cancer-related fatigue (CRF)
2. Common causes of CRF
3. Common words used to describe cancer-related fatigue (i.e., feeling tired, weak, worn out, not being able to concentrate)
4. What to tell your clinician
5. Energy conservation principles (prioritize activities, ask for help, establish structured routine, balance rest and activities, establish regular bedtime)
6. Other management strategies (physical activity, sleep hygiene, maintaining adequate nutrition)

Adapted from Borneman T, Piper BF, Sun VC, et al: Implementing the Fatigue Guidelines at one NCCN member institution: process and outcomes. J Natl Compr Canc Netw 2007;5:1092-101.

There are several treatable causes that have an impact on CRF. Nutrition is one that is of particular importance for the elderly cancer patient. Geriatric patients in general may also be at higher risk for malnutrition. Potential reasons include more difficulty accessing healthy food items, poorly fitted dentures, or inability to prepare healthy meals secondary to functional limits. Geriatric oncology patients may be particularly at risk because of gastrointestinal side effects (nausea, diarrhea) and poor appetite secondary to cancer treatment.[58] It is important in oncology to stress the importance of optimizing nutrition, particularly in relation to fatigue management. Patients should be provided with adequate information on potential side effects so they are aware of what to expect during treatment. If unable to eat regularly, patients can be advised to switch their eating habits from three large meals per day to six smaller meals spread throughout the day. The importance of maintaining adequate fluid intake should be emphasized, unless contraindicated. Finally, if available, referrals to nutrition experts such as dieticians should be initiated to aid elderly patients with optimizing their nutrition as a strategy for fatigue management.

Another treatable cause that may aggravate CRF is sleep deprivation. As a result of the natural course of aging, the length and quality of REM sleep decreases as the aging process continues.[5] Elderly cancer patients may be at higher risk for greater sleep disturbance. Patients can be instructed on the principles of sleep hygiene. These principles include the avoidance of caffeinated drinks or intense exercises before going to bed. Maintaining a dark, cool, and quiet sleep environment may help with inducing and enhancing sleep.[59] If possible, patients should be strongly encouraged to limit their daily nap times to no more than two 60-minute naps per day. This strategy will help in maintaining the quality of nighttime sleep. Relaxation or sleep-inducing strategies, such as warm baths, milk, or soothing music, can be used.

Stress-management strategies, such as meditation, massage, or muscle relaxation, may also be used to manage cancer-related fatigue. [60-62] Any contributing factors, such as anxiety, should be addressed by supportive care experts and assessed as a possible contributor to sleep disturbance. Patients should be assessed for any other symptoms, such as uncontrolled pain, that may be interfering with the quality of sleep. Maintaining physical activity during the day may help with promoting sleep at night, and patients should be encouraged to remain as active as possible. Finally, if pharmacologic intervention is warranted, clinicians can discuss the various options available either over the counter or prescribed and, together with the patient, a pharmacologic agent should be chosen that will provide the greatest benefit without debilitating side effects.

THE NCCN CLINICAL PRACTICE GUIDELINES FOR CRF

The NCCN guidelines include several standards of care for the assessment and management of CRF. First, the NCCN recognizes that fatigue is a subjective experience that should be assessed using patient-reported outcomes.[8] Second, fatigue should be screened, assessed, and managed for all patients. Patients and families should be informed that fatigue management is an integral part of comprehensive oncology care.[8] Finally, fatigue should be included as an important component of all clinical outcomes research, and should be routinely assessed in all oncology research settings.[8]

Fatigue management within the NCCN guidelines is categorized on the basis of the subjective rating of the symptom on a 0 to 10 scale. It is recommended that all patients be screened for the presence or absence of fatigue. Management for patients who report absent or mild levels of fatigue (0 to 3) includes the provision of education about fatigue and common strategies for managing the symptom.[8] Periodic rescreening is recommended, daily for inpatient settings and during subsequent follow-up visits for outpatient settings.[8] It is also helpful for clinicians to understand the common barriers to optimal fatigue assessment and management. Table 17-2 provides a list of common patient- and professional-related barriers to fatigue management. Understanding and recognizing these potential barriers will aid the clinician in devising individualized fatigue management plan for elderly cancer patients.

As discussed previously in the case study, patients who report moderate to severe fatigue (4 to 10) should undergo a focused history and physical examination to determine the potential causes of fatigue. Table 17-3 provides a list of the essential components of this thorough evaluation. The NCCN guidelines identify seven treatable contributing factors of fatigue. These factors include pain, emotional distress, sleep disturbance, anemia, nutrition, activity level, medication side effects, and other comorbidities.[8] For elderly cancer patients, emphasis should be placed on potential medication side effects due to polypharmacy and comorbidities. Finally, because fatigue may be a problem at several different points throughout the disease trajectory, ongoing reassessment should be continued at all follow-up visits.

TABLE 17-2 Barriers to Effective Fatigue Management

Patient-Related Barriers	Professional-Related Barriers
1. Don't want to bother clinicians	1. Failure to initiate discussion regarding CRF
2. Concern that treatment may be altered	2. Assume that fatigue is related to the normal process of aging
3. Don't want to be perceived as complaining	3. Failure to recognize that fatigue is a problem
4. Assume that they just have to live with it	4. Not aware that there are effective treatments for fatigue
5. Belief that there are no treatments for CRF	5. Lack of knowledge in principles of fatigue assessment and management

See references 8, 65.

RESEARCH IN CRF MANAGEMENT

There are several important areas of research that are needed to further understand fatigue in elderly cancer patients and to further enhance assessment and management. First, CRF research should be designed specifically to target the elderly population. By doing so, the specific needs of elderly cancer patients can be better elucidated. Armed with more descriptive studies to explore the needs, attitudes, knowledge, and experience of CRF in the elderly, tailored patient education for the assessment and management of fatigue can be developed. Patient education for elderly cancer patients must acknowledge the fact that fatigue is common in cancer, and that elderly patients should be encouraged to discuss the symptom with their clinicians. Functional status should be assessed in detail for the elderly cancer patient, since a limitation in function may lead to inactivity or malnutrition, which can aggravate fatigue. Loss of functional independence has been associated with reduced survival, diminished quality of life, depression, and financial burden for patients, and fatigue is a primary cause of functional dependence for elderly cancer patients.[28] It has been reported that fatigue may accelerate the functional decline of elderly cancer patients.[28] Although evidence-based clinical guidelines are available for managing CRF, it is unclear whether these guidelines are generalizable to elderly cancer patients, because most of the evidence has not been tested specifically in an elderly sample population. While most recommendations can be applied to the elderly population, there may be issues that are specific

TABLE 17-3 Components of a Comprehensive Fatigue Assessment[8]

1. Current disease status
2. Type and length of treatment
3. Fatigue onset, pattern, duration, change over time
4. Associated or alleviating factors
5. Interference with function
6. Patient's perception of the causes of fatigue
7. Assessment of treatable contributing factors
   - Pain
   - Emotional distress
   - Sleep disturbance
   - Anemia
   - Nutrition
   - Activity level
   - Medication side effects (polypharmacy)
   - Comorbidities

to the elderly that are not thoroughly addressed in the guidelines.

Over the last decade, exercise and physical activity has emerged as a potentially effective strategy for managing CRF. The abundance of evidence can be recognized by the publication of numerous systematic reviews and a Cochrane review to determine the scientific evidence behind the efficacy of exercise. However, many limitations still exist in the current evidence on exercise. The quality of studies published thus far is widely variable.[55] There are issues with statistical power because many studies were limited by a small sample size.[55,63] In randomized controlled trials conducted on activity-based interventions, a variety of regimens were used. This variation makes it difficult to determine the most effective type of exercise for fatigue management. Future research is necessary to determine which parameters of exercise are most effective in managing fatigue. These parameters include type of exercise (aerobic or resistance), mode of exercise, length and frequency of sessions, and the amount of intensity that is required..[23,55,64] These parameters should also apply for developing activity-based interventions for the elderly cancer patient. Because comorbidities and functional dependence are common in the elderly population, it is crucial to develop modes of activities that are realistically feasible for this understudied population. Although experts are calling for research that produces more long-term follow-up outcomes of activity-based interventions, it may be equally important to focus on short-term outcomes in the elderly population. Finally, outcome measures used to assess fatigue in research should be psychometrically tested in elderly populations to establish reliability and validity, as perceptions of fatigue may be different.

Chapter Summary

Cancer is primarily a disease of the older population. As the geriatric population of the United States increases, it is expected that more elderly individuals will be treated with cancer. Fatigue continues to be recognized as the most common and distressing chronic complication of cancer and its treatments. Fatigue affects all aspects of quality of life, and can lead to reduced social interactions and functional independence for the elderly. Clinicians should be aware of evidence-based strategies to assess and manage cancer-related fatigue. An interdisciplinary, comprehensive model of fatigue management incorporating focused assessment and patient education can be helpful in supporting elderly patients and families who are experiencing fatigue. Future research in fatigue should focus on describing the unique aspect of fatigue in the elderly cancer population and develop tailored interventions that are specific and realistic for this understudied population.

See expertconsult.com for a complete list of references and web resources for this chapter

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CHAPTER

18

Nausea and Vomiting

Roxana S. Dronca and Charles Loprinzi

CASE 18-1 CASE PRESENTATION

J.J., a 69-year-old woman, is a former smoker of 60 pack-years who presents with a stage IIIA (T2N2M0) primary lung adenocarcinoma. She was not considered a surgical candidate. The final treatment recommendation was definitive chemoradiation therapy, with plans for two cycles of neoadjuvant chemotherapy prior to the start of radiation because of the large lung mass and inability to deliver safe radiation doses. The initial chemotherapy plan included a combination of cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2) every 21 days.

On further discussion of potential chemotherapy side effects, Mrs. J. expresses concern regarding the potential for severe nausea and vomiting associated with the treatment, as she suffers from severe motion sickness and remembers having had significant nausea with her two pregnancies. She asks whether anything can be done to prevent and treat chemotherapy-associated nausea and vomiting.

Nausea and vomiting are two of the most feared and most commonly reported symptoms[1] in patients with cancer, and can occur either as a result of the malignancy itself or from antineoplastic treatment. Over the last few decades, significant progress has been made in the development of more potent and effective chemotherapeutic agents. However, there is a significant cost in term of toxicity and the side effects of treatment, which often limit management options. Among the cancer treatment-related side effects, chemotherapy-induced nausea and vomiting (CINV) are, historically, two of the most common[2-4]; they can significantly affect patients' quality of life, functional ability, and adherence to potentially useful and curative anticancer therapy.[5,6]

PATHOPHYSIOLOGY OF NAUSEA AND VOMITING

The vomiting reflex is triggered by afferent impulses to the vomiting center from vagus nerve terminals in the wall of the small bowel, the chemoreceptor trigger zone, or the cerebral cortex; the act of vomiting occurs when efferent impulses are sent to a number of organs and tissues such as the abdominal muscles, salivary glands, cranial nerves, and respiratory center. It is now thought that the central site of the emetic reflex, previously referred to as the "vomiting center"[7] and most recently named the "central pattern generator,"[8] is not an isolated area within the central nervous system but rather a group of loosely organized neurons throughout the medulla that interact through various pathways to coordinate the sequence of behaviors during vomiting.[9,10] The primary sources of afferent input to the central pattern generator include the area postrema (commonly referred to as the "chemoreceptor trigger zone")[11] and the gastrointestinal tract through vagal and splanchnic afferents,[12] which terminate primarily in the nucleus tractus solitarius [9] and, to a lesser extent, the area postrema. These two central nervous system centers are collectively referred to as the dorsal vagal complex.[11,13] The area postrema is located at the caudal end of the fourth ventricle, on the dorsal surface of the medulla oblongata where the blood-brain barrier is relatively permeable, and is therefore positioned to detect emetic stimuli in either the blood or the cerebrospinal fluid.[11]

The main neurotransmitters implicated in the pathogenesis of acute and delayed CINV include serotonin (5-HT), substance P, and dopamine, which bind to 5-HT$_3$, neurokinin-1 (NK1), and dopamine D$_2$ receptors, respectively.

- The 5-HT$_3$ receptors are found on the terminal ends of the vagal afferent nerves,[14] as well as in key areas of the human brain stem, including the area postrema and the nucleus tractus solitarius.[15] Preliminary evidence suggests that the selective 5-HT$_3$ receptor antagonists exert their action mainly by antagonizing the action of serotonin at the 5-HT$_3$ receptors on the peripheral vagal afferent terminals.[16,17]
- The tachykinin NK1 receptors are widely distributed throughout the central and peripheral nervous system, as well as the respiratory, cardiovascular, genitourinary, and gastrointestinal tracts.[18] It is currently thought that the NK1 receptor antagonists exert their action at a central level and that penetration of the blood-brain barrier is essential for their ability to prevent cisplatin-induced emesis.[19]

TYPES OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING SYNDROMES

Three distinct chemotherapy-induced nausea and/or vomiting syndromes have been described: acute, delayed, and anticipatory. Although the exact mechanism behind each syndrome is unclear, this classification has important implications for both prevention and management of CINV. Acute CINV occurs within 24 hours of chemotherapy administration; it may occur within 1 to 2 hours, with a peak incidence at 4 to 6 hours.

Delayed CINV is arbitrarily defined as occurring more than 24 hours after chemotherapy. Although it is most common after high-dose cisplatin, it has been associated with other agents as well, such as carboplatin, oxaliplatin, or the combination of cyclophosphamide with an anthracycline. For cisplatin, nausea and vomiting typically reach maximal intensity at 48 to 72 hours, and can last up to 5 or more days.[20]

Anticipatory CINV is a conditioned response that tends to occur when nausea and vomiting have been poorly controlled with previous cycles of chemotherapy.[21,22] Previous neutral stimuli become conditioned stimuli that elicit anticipatory nausea and/or vomiting, which can then be brought on by the smell of the hospital, the sight of the clinic, the treating physician, or the chemotherapy suite. Although usually associated with negative past experiences, anticipatory nausea and/or vomiting has also been described in patients who have a high expectancy of developing nausea despite never having received any cancer treatment.[23] The incidence of anticipatory CINV can be as high as 57%,[24] with nausea occurring more commonly than vomiting. Risk factors associated with the development of anticipatory nausea and/or vomiting include previous history of motion sickness,[22] age younger than 50 years,[25] past history of anxiety or depression,[24] uncontrolled acute or delayed CINV with previous cycles,[22] or chemotherapy extended over a prolonged period of time.

EMETOGENICITY OF CHEMOTHERAPEUTIC AGENTS

The most important factor in predicting CINV is the emetogenicity of the chemotherapeutic agent(s) used. Several classification schemes have been proposed[26-29] that reflect the likelihood of emesis with both single agents and combination chemotherapy. The development of such algorithms has been of great value in providing a framework for the management of CINV and for the development of antiemetic treatment guidelines. In 2004, the Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC) held a consensus conference whereby a modification of the original schema of Hesketh et al.[26] was proposed.[29] This classification, utilized by both MASCC and the American Society of Clinical Oncology updated guidelines,[30] divides intravenous chemotherapeutic agents into four categories on the basis of risk (incidence) of emesis in the absence of prophylaxis (Table 18-1):

- High: greater than 90% emetic risk
- Moderate: 30% to 90% emetic risk
- Low: 10% to 30% emetic risk
- Minimal: less than 10% emetic risk

A new problem with utilizing this classification system is the growing use of oral chemotherapeutic

TABLE 18-1 Emetic Risk of Intravenously Administered Antineoplastic Agents

Emetic Risk (incidence of emesis without antiemetics)	Agent
High (> 90%)	Cisplatin
	Mechlorethamine
	Streptozotocin
	Cyclophosphamide ≥ 1,500 mg/m^2
	Carmustine
	Dacarbazine
	Dactinomycin
Moderate (30% to 90%)	Oxaliplatin
	Cytarabine > 1 g/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide < 1,500 mg/m^2
	Doxorubicin
	Daunorubicin
	Epirubicin
	Idarubicin
	Irinotecan
Low (10% to 30%)	Paclitaxel
	Docetaxel
	Mitoxantrone
	Topotecan
	Etoposide
	Pemetrexed
	Methotrexate
	Mitomycin
	Gemcitabine
	Cytarabine ≤ 1 g/m^2
	Fluorouracil
	Bortezomib
	Cetuximab
	Trastuzumab
Minimal (< 10%)	Bevacizumab
	Bleomycin
	Busulfan
	2-Chlorodeoxyadenosine
	Fludarabine
	Rituximab
	Vinblastine
	Vincristine
	Vinorelbine

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agents, which tend to be prescribed over a period of several days to weeks. This makes it difficult to assess the contribution of acute versus delayed CINV and, as a result, antiemetic regimes recommended for single-dose intravenous agents may not apply to oral cytotoxic or targeted agents. The 2004 MASCC updated guidelines include[29] a separate listing of the estimated emetic risk of the most commonly used oral antineoplastic agents.

IDENTIFYING PATIENTS AT INCREASED RISK FOR DEVELOPMENT OF CINV

In addition to the emetogenic potential of chemotherapy drugs, there are also well-described patient factors predisposing for more or less emetic trouble with specific regimes, which have been supported in multiple studies. The patient characteristics predicting development of more severe CINV include:

- Poor emetic control with prior chemotherapy[31]
- Younger age (less than 65 years)[32,33]; increasing evidence indicates that older patients tend to tolerate chemotherapy better than younger patients
- Female gender[32]; in addition, emesis during pregnancy seems to be associated with an increased risk of developing CINV[34]
- Low alcohol intake (10 or less alcoholic drinks per week in one study)[32,35]
- Low social functioning or high fatigue scores[32]
- Tumor burden[36] – in one ovarian cancer study, patients 55 years or older with large (greater than 2 cm) tumors had more acute and delayed CINV
- Poor control of acute CINV increases the risk of delayed nausea and vomiting
- Presence of other causes of nausea and vomiting including constipation, which may be more frequent in elderly patients

Increased use of medications (polypharmacy) resulting from the presence of various comorbid conditions in older individuals may result in an increased risk of side effects and nausea.[37]

DIFFERENTIAL DIAGNOSIS OF NAUSEA AND VOMITING IN PATIENTS WITH CANCER

In addition to chemotherapy and radiation therapy, many other factors can contribute to the development of nausea and vomiting in patients with advanced cancer. While it may be difficult to distinguish among the various causes, most patients will have additional signs, symptoms, or test abnormalities that can be helpful in pointing to the correct etiology. A thorough history and physical examination, as well as guided laboratory and imaging evaluation, may be critical steps in the assessment of nausea and vomiting in this patient population. The list is comprehensive, but most patients will have one or more of the contributing factors:

- Medications (most importantly narcotics, nonsteroidal anti-inflammatory drugs, antibiotics); a careful medication history, including nonprescription drugs is essential
- Postoperative nausea and vomiting following general anesthesia
- Gastroesophageal reflux disease (GERD) or peptic ulcer disease; absence of typical reflux symptoms does not rule out GERD
- Gastric outlet obstruction from malignancy or peptic ulcer disease
- Gastroparesis resulting from tumor involvement of the vagus nerve or lower thoracic spinal sympathetic plexus, paraneoplastic gastrointestinal dysmotility (described with small cell lung cancer and rarely other malignancies, and associated with antineuronal nuclear [ANNA-1, anti-Hu] or other antibodies[38,39]), and medications (i.e., anticholinergic drugs); patients usually complain of vomiting food eaten several hours earlier, and a succussion splash may be detected on physical examination
- Pancreatitis
- Cholecystitis
- Constipation
- Bowel obstruction; feculent vomiting suggests advanced obstruction or a gastrocolic fistula
- Peritoneal metastases and malignant ascites
- Mesenteric ischemia
- Increased intracranial pressure; vomiting may be projectile, and is usually associated with other focal neurologic signs or symptoms
- Metabolic causes (hyponatremia or hypernatremia, hyperglycemia, renal or hepatic insufficiency)

TYPES OF ANTIEMETIC AGENTS

Serotonin (5-HT$_3$) Receptor Antagonists

The successful development of 5-HT$_3$-receptor antagonists, a drug class that has a high therapeutic index for prevention of CINV, was a major breakthrough in the management of this clinical problem. A large number of clinical trials have since been conducted, proving their efficacy and safety. As of this date, five such 5-HT$_3$-receptor–selective antagonists have found their way in clinical practice: four first-generation agents (granisetron, ondansetron, dolasetron, and tropisetron) and one second-generation agent (palonosetron).

First-Generation 5-HT$_3$ Receptor Antagonists

- Numerous clinical trials using various doses, routes, and schedules of administration have demonstrated that first-generation 5-HT$_3$ antagonists are equally effective in preventing acute CINV.[40-43] This was further supported by the results of two large meta-analyses.[44,45]

- 5-HT_3 first-generation agents share similar low side-effect profiles, which most often include headache, constipation, transient asymptomatic elevation in liver transaminases, and reversible clinically insignificant ECG changes (including prolongation of the QTc-interval).[43] ECG changes are most prominent 1 to 2 hours after the drug administration and return to baseline within 24 hours. Although clinically important adverse cardiovascular events associated with these changes are excitingly rare,[46] particular care should be taken in elderly patients who are more likely to use other cardiovascular medications, therefore increasing the risk of drug-drug interactions and side-effects.
- A single daily dose of a 5-HT_3 receptor antagonist prechemotherapy seems to be as effective as multiple daily doses or a continuous intravenous infusion, offering both convenience and potential cost savings.[47] In addition, each drug has a plateau in therapeutic efficacy at a definable dose level, above which further dose escalation does not improve symptom control.[47]
- Oral administration is equally efficacious as the intravenous route, even with highly emetogenic therapy.[47] An orally disintegrating ondansetron tablet is also available for patients with dysphagia or anorexia and provides equivalent treatment to the oral swallowed formulation.[48] In addition, a granisetron transdermal patch was recently approved by the Food and Drug Administration (FDA)[49] and has been proven to be no less effective than oral granisetron when applied 24 to 48 hours prior to the first dose of chemotherapy [50]
- Combining 5-HT_3 antagonists with dexamethasone further improves their efficacy.[51]
- The role of first-generation 5-HT_3 receptor antagonists in preventing delayed CINV is less clear. A meta-analysis found that adding a 5-HT_3 antagonist to dexamethasone does not improve its effectiveness in preventing delayed emesis.[52] Similarly, a recent randomized study found that first-generation agents were not better than prochlorperazine in controlling delayed doxorubicin-induced nausea and that the proportion of patients reporting delayed nausea exceeded 70% in both groups.[53]

A Second-Generation 5-HT_3 Receptor Antagonist (Palonosetron)

- Palonosetron has a significantly higher binding affinity for the 5-HT_3 receptor and a longer half-life (approximately 40 hours) compared to first-generation agents.[54]
- A single intravenous dose of palonosetron was shown to be as effective as a comparable dose of dolasetron in preventing acute CINV and superior in preventing delayed emesis.[55]
- The safety profile of palonosetron is similar to first-generation 5-HT_3 antagonists.[55]
- No dose adjustments or special monitoring are required for geriatric patients.[56]
- Intravenous palonosetron is FDA-approved[56] for prevention of acute and delayed nausea and vomiting associated with moderately and highly emetogenic cancer chemotherapy as a single dose on day 1; repeat dosing in the days after chemotherapy or in the setting of multiday regimens has not been well studied.

Neurokinin-1-Receptor Antagonists (Aprepitant)

The implication of substance P in the pathogenesis of acute and delayed CINV has led to the development of aprepitant, a novel neurokinin-1 antagonist; preliminary trials conducted in late 1990s demonstrated the high clinical efficacy of neurokinin receptor blockage for the prophylaxis of acute and delayed emesis associated with highly emetogenic chemotherapy.[57] Subsequently, the approval of aprepitant for general use significantly improved the ability to prevent CINV in patients receiving moderately and highly emetogenic chemotherapy.

- Two phase III clinical trials, including a total of 1,043 patients receiving chemotherapy of high emetic risk (cisplatin), demonstrated a significantly improved control of acute and delayed CINV with the three-drug regimen of oral aprepitant (125 mg on day 1; 80 mg on days 2 and 3), ondansetron (32 mg intravenously on day 1), and dexamethasone (12 mg orally on day 1; 8 mg/d on days 2-4) over the standard combination of ondansetron (32 mg intravenously on day 1) and dexamethasone (20 mg orally on day 1; 8 mg twice daily on days 2-4).[58]
- Similarly, aprepitant was shown to be more effective in preventing emesis when added to a standard regimen of ondansetron and dexamethasone versus the standard regimen of ondansetron and dexamethasone in 866 patients with breast cancer undergoing moderately emetogenic chemotherapy (cyclophosphamide alone or in combination with doxorubicin or epirubicin).[59]
- Aprepitant plus dexamethasone alone does not seem to be as effective as the three-drug combination regimen including a 5-HT_3 receptor antagonist.[60]
- Aprepitant is FDA-approved for use, in combination with other antiemetic agents, for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly and moderately emetogenic cancer chemotherapy.[61]
- Chronic continuous use of aprepitant for prevention of nausea and vomiting has not been studied and is not recommended.[61]
- An intravenous version of aprepitant (fosaprepitant dimeglumine) has been recently approved for use in the United States as a 115 mg infusion 30 minutes

prior to chemotherapy on day 1, followed by standard dose oral aprepitant (80 mg) on days 2 and 3.[62] Efficacy is thought to be similar to the oral regimen, although data are limited.[62]

- Aprepitant is both a moderate inducer and moderate inhibitor of cytochrome P450 enzyme 3A4 (CYP3A4) and a moderate inducer of CYP2C9[63] and therefore can alter the metabolism of certain drugs. Aprepitant should be used with caution in patients receiving concomitant medications that are metabolized through CYP3A4, as it could result in elevated plasma levels of these medications. Induction of warfarin metabolism may lead to clinically significant decrease in the International Normalized Ratio (INR) of prothrombin time and therefore increased monitoring may be required in the 2-week period following administration of aprepitant with each chemotherapy cycle.[61]
- The oral dose of dexamethasone (a CYP3A4 substrate) should be reduced by approximately 50% when coadministered with aprepitant, in order to achieve exposures of dexamethasone similar to those obtained when it is used without aprepitant.[61] Nonetheless, these recommendations do not apply when corticosteroids are used as anticancer therapy (i.e., part of a combination chemotherapy regimen).[30]

Dopamine Receptor Antagonists

Benzamides. Metoclopramide is the most commonly used drug in this class. It blocks type 2 dopamine receptors and 5-HT_3 serotonin receptors (when used in higher doses used to prevent CINV) in the chemoreceptor trigger zone, increases lower esophageal sphincter tone, and enhances bowel and gastric motility. The usual recommended doses are 20 to 40 mg orally every 4 to 6 hours (conventional dose) or 2 to 3 mg/kg (high dose).[64] Metoclopramide crosses the blood-brain barrier, and side effects include extrapyramidal reactions such as acute dystonia, akathisia, and possible irreversible tardive dyskinesia, especially with prolonged use of high doses and in the elderly. Diphenhydramine or hydroxyzine can be used to antagonize the dopaminergic toxicity of metoclopramide. In addition, metoclopramide can lower the seizure threshold and increase the risk of convulsions in patients with epilepsy.[37] In the past, metoclopramide combined with dexamethasone was the antiemetic regimen of choice for preventing delayed CINV,[65,66] but it has largely been replaced by the use of 5-HT^3 antagonists and aprepitant.

Phenothiazines. Phenothiazines, such as prochlorperazine (Compazine), thiethylperazine (Torecan), promethazine (Phenergan), and chlorpromazine (Thorazine) act predominantly as dopamine receptor antagonists, but they also have anticholinergic and antihistaminic blocking effects. Phenothiazines are useful in the treatment of nausea and vomiting caused by various gastrointestinal disorders, but their role in prevention of highly-emetogenic CINV is limited.[64] However, they still play a role in the treatment of mild CINV, as well as breakthrough nausea and vomiting.[29,67] Phenothiazines can be given intravenously, intramuscularly, orally, or rectally, making them very useful in patients who have difficulties with intravenous access or are unable to tolerate oral intake. Side effects include extrapyramidal symptoms (acute dystonia, akathisia, tardive dyskinesia), anticholinergic effects (dry mouth, urinary retention, tachycardia, drowsiness), and sedation. Acute dystonia is more common in younger, than in older, patients and, as with metoclopramide, diphenhydramine or hydroxyzine can be used to antagonize extrapyramidal system receptors. Intravenous administration of prochlorperazine can cause marked hypotension, especially in the elderly and especially if administered too rapidly.

Butyrophenones. The two drugs in this class, droperidol (Inapsine) and haloperidol (Haldol) are type 2 dopamine receptor antagonists. Although they have stronger antiemetic effects than phenothiazines, the incidence of extrapyramidal side effects is higher. Other side effects include sedation, hypotension, and clinically significant QTc prolongation associated with an increased risk of sudden death. Droperidol is currently rarely, if ever, used for the prevention of CINV. Haloperidol can be administered intramuscularly, intravenously, or orally; however, its prolonged half-life (18 hours) often limits its use. Before the introduction of 5-HT_3 receptor antagonists, butyrophenones were used as an alternative to high-dose metoclopramide[68]; however, their utilization has markedly decreased in recent years.

Atypical Antipsychotics. Olanzapine is a new atypical antipsychotic drug which blocks dopaminergic, serotoninergic, antihistaminic, muscarinic, and dopaminergic receptors. Olanzapine was initially found to be effective in patients with advanced cancer who required opioid analgesics for pain.[69] In a recently published small phase I study, Passik and colleagues used olanzapine for prevention of moderate and highly-emetogenic CINV in a dose of 5 mg daily for 2 days prior to chemotherapy and 10 mg daily for the subsequent 8 days (days 0-7).[70] Four of six patients receiving highly emetogenic chemotherapy and nine of nine patients receiving moderately emetogenic regimens achieved complete control of delayed nausea, with the main side effect being grade 3 depressed level of consciousness in 3 of 15 patients treated. A similarly high complete response rate and an acceptable toxicity profile were achieved in two subsequent phase II trials when olanzapine and dexamethasone were combined with granisetron and palonosetron, respectively.[71,72] Olanzapine is available in oral and injectable (intramuscular) formulations. The main side effects are extrapyramidal and anticholinergic reactions, sedation, as well as weight gain and an associated risk of diabetes when used for a prolonged period of time.[73,74]

Corticosteroids

Corticosteroids are among the most commonly used antiemetics because of their low cost, efficacy, and wide availability. At equivalent doses, all corticosteroids appear to have comparable efficacy and can be used interchangeably.[30] Dexamethasone and methylprednisolone are the most thoroughly studied; dexamethasone is used most often because of its availability in generic forms and the variety of dosage formulations. The efficacy of oral and intravenous formulations appears to be equivalent; therefore oral formulations are usually recommended because of ease of administration and low cost. The mechanism of action has not been fully elucidated and there is no clear evidence to support central neurotransmitter blockade with corticosteroid use. The main side effects include insomnia, agitation, mood changes, indigestion/epigastric discomfort, increased appetite, weight gain, and hyperglycemia.[75] Therefore, patients with a prior history of diabetes or those receiving NSAIDs should be closely monitored when corticosteroids are administered. Adrenal insufficiency has not been described with the short courses of corticosteroids (2 to 4 days) used in the prevention or treatment of CINV.

Single-agent corticosteroid treatment, such as dexamethasone (8 mg), is currently recommended for the prophylaxis of acute emesis with low-emetogenic chemotherapy.[29] Corticosteroids are most useful, however, when used in combination with aprepitant and 5-HT_3 serotonin receptor antagonists in patients receiving chemotherapy of moderate or high emetogenic potential.[30] For prevention of acute CINV induced by highly emetogenic chemotherapy, a dose of 20 mg of dexamethasone is recommended before chemotherapy, when given in combination with a 5-HT_3 serotonin antagonist,[76] but the dose should be decreased to 12 mg when aprepitant is added to the regimen.[29,30,77] For patients receiving moderately emetogenic chemotherapy, a single dose of 8 mg of dexamethasone is currently recommended before chemotherapy.[29,30,78]The recommended dexamethasone dose for prevention of delayed nausea is 8 mg daily for 2 to 3 days following chemotherapy.

Other Agents

Benzodiazepines. Benzodiazepines are weak antiemetic agents and their use as single agents to prevent CINV is not recommended. Benzodiazepines are mainly used as adjunctive agents to reduce anxiety, anticipatory nausea and vomiting,[79,80] and refractory emesis occurring despite adequate prophylaxis regimens.[30] Lorazepam (Ativan) and alprazolam (Xanax) are the most commonly used drugs in this class. The main side effect of benzodiazepines is sedation; therefore elderly patients and patients receiving medications with additional central nervous system depressant activity (e.g., phenothiazines, opioids) should be carefully monitored.

Antihistamines. Antihistamines do not have significant antiemetic activity and should not be used as single agents in the prevention or treatment of CINV. Antihistamines are mainly used as adjunctive agents to prevent dystonic reactions with dopamine receptor blockers, or for treatment of nausea in patients with advanced cancer when the nausea is thought to be mediated by the vestibular system.[81]

Cannabinoids. Despite the controversy that surrounds the use of cannabinoids for CINV, several studies using delta-9-tetrahydrocannabinol (THC) have shown this agent to be an effective antiemetic, compared to placebo and even prochlorperazine.[82,83] Drugs in this class are available as plant extracts (dronabinol or tetrahydrocannabinol) and semisynthetic substances (nabilone, levonantradol). The most frequently used doses are 5 to 10 mg orally every 6 to 8 hours for dronabinol and 1 to 2 mg orally every 12 hours for nabilone. In a systematic review[84] of efficacy and adverse effects of cannabinoids in the prevention of CINV, it was found that they were more effective antiemetics than prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone, or alizapride. However, cannabinoids have not been proven to be more effective in patients receiving mildly or very highly emetogenic chemotherapy. Side effects occurred more frequently with cannabinoids and included dizziness, dysphoria, depression, hallucinations, paranoia, and hypotension. Some potentially "beneficial" side effects include euphoria and sedation. As with other agents having a lower therapeutic index, cannabinoids should be reserved for patients who are intolerant of or refractory to 5-HT_3 serotonin receptor antagonists, aprepitant, or dexamethasone.[30]

Treatment Recommendations General Principles Regarding Emesis Control in Patients Receiving Chemotherapy

- The main goal of antiemetic therapy in patients with cancer undergoing chemotherapy is prevention of nausea and/or vomiting. Patients who experience acute nausea or emesis are also much more likely to develop these complications 24 hours or more after treatment.[20]
- Therapy should start before the administration of chemotherapy and cover at least the first 3 days for agents with high emetic risk.[20 29]
- Oral administration of antiemetic agents is equally efficacious as the intravenous route, even with highly emetogenic therapy, and therefore the oral route is preferred unless the patient is unable to tolerate or swallow oral medications.
- The choice of the antiemetic regimen should be based upon the emetogenic potential of the chemotherapeutic agent(s) used, side-effect profiles, and patient-specific factors including previous experience with antiemetics.

- For multidrug chemotherapeutic regimens, the choice of antiemetics should be on the basis of the drug with the highest emetogenic potential, although adding low- or moderate-risk agents usually increases emetogenicity by one level.[26]
- For multiday chemotherapy regimens, it has been recommended that antiemetics appropriate for the emetogenic risk of chemotherapy should be administered during each day of treatment. Nonetheless, there is a lack of formal guidelines for this situation.
- The best management of anticipatory nausea and/or vomiting is adequate control of acute and delayed CINV,[29] use of anxiolytics (although the response is usually not maintained as chemotherapy treatment continues),[29,85] and use of behavioral therapies involving desensitization.[29,86]
- Other potential causes of nausea and vomiting should be excluded and treated, if possible.

PREVENTION OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING (CINV)

High-Emetic-Risk Chemotherapy

Acute CINV

- A three-drug antiemetic regimen is currently recommended to prevent acute nausea and vomiting in patients who receive highly emetogenic chemotherapy. The regimen includes a single dose of a 5-HT_3 receptor antagonist on day 1, along with aprepitant and dexamethasone.[29,30,87] (Table 18-2.)
- Other antiemetic agents, such as metoclopramide, butyrophenones, phenothiazines, or cannabinoids, are not appropriate first-choice agents in this patient population, unless they are intolerant or refractory to 5-HT_3 antagonists, NK1 receptor antagonists, and dexamethasone.[30,87]

TABLE 18-2 Dose and Schedule of Antiemetics to Prevent Emesis Induced by Antineoplastic Therapy, by Emetic Category Risk

Emetic risk category	Antiemetic regimen	Dose	Schedule
High (>90%)	**5-HT_3 serotonin receptor antagonist**		
	• Ondansetron (Zofran)	Oral: 24 mg IV: 8 mg or 0.15 mg/kg	Day 1 prechemotherapy
	• Granisetron (Kytril)	Oral: 2 mg IV: 1 mg or 0.01 mg/kg	
	• Dolasetron (Anzemet)	Oral: 100 mg IV: 100 mg or 1.8 mg/kg	
	• Palonosetron (Aloxi)	IV: 0.25 mg	
	• Tropisetron (Navoban)	Oral or IV: 5 mg	
	Dexamethasone	Oral: 12 mg Oral: 8 mg	Day 1 prechemotherapy Days 2-4
	NK1 receptor antagonist		
	• Aprepitant (Emend)	Oral: 125 mg Oral: 80 mg	Day 1 prechemotherapy Days 2,3
	• Fosaprepitant	IV: 115 mg	Day 1 prechemotherapy
Moderate (30% -90%)	**5-HT_3 serotonin receptor antagonist**		
	• Ondansetron (Zofran)	Oral: 16 mg IV: 8 mg or 0.15 mg/kg	Day 1 prechemotherapy
	• Granisetron (Kytril)	Oral: 2 mg IV: 1 mg or 0.01 mg/kg	
	• Dolasetron (Anzemet)	Oral: 100 mg IV: 100 mg or 1.8 mg/kg	
	• Palonosetron (Aloxi)	IV: 0.25 mg	
	• Tropisetron (Navoban)	Oral or IV: 5 mg	
	Dexamethasone*		Day 1 prechemotherapy
	• without aprepitant	IV: 20 mg Oral: 12 mg	Days 2,3†
	• with aprepitant	Oral: 8 mg	
Low (10%-30%)	Dexamethasone	Oral: 8 mg	Day 1 prechemotherapy
Minimal (< 10%)	Routine prophylaxis not recommended		

*The use of the three-drug antiemetic regimen is recommended for chemotherapeutic regimens incorporating a combination of anthracycline and cyclophosphamide.

†The value of administering dexamethasone beyond day 1 in patient receiving the three-drug antiemetic regimen has not been studied; in patients who do not receive aprepitant, oral dexamethasone on days 2 and 3 is recommended for prevention of delayed CINV induced by chemotherapy of moderate emetogenic risk.

- Lorazepam, diphenhydramine, H_2 blockers, or proton pump inhibitors may be useful adjuncts to antiemetic drugs, but they should not be used as single agents.[87]

Delayed CINV

- In all patients receiving cisplatin and all other chemotherapeutic agents of high emetic risk, the combination of aprepitant and dexamethasone is recommended to prevent delayed nausea and vomiting, on the basis of its superiority to dexamethasone alone (See Table 18-2).[29,30]
- The combination of dexamethasone and a 5-HT_3 antagonist to prevent delayed emesis is no longer recommended, as data have failed to demonstrate that the combination is superior to dexamethasone alone in this setting.[88,89] In addition, a recent trial has found that the combination of aprepitant and dexamethasone is superior to ondansetron and dexamethasone in the prevention of cisplatin-induced delayed emesis.[90]

Moderate-Emetic-Risk Chemotherapy

Acute CINV

- The standard antiemetic regimen to prevent acute nausea and vomiting in patients who receive moderately emetogenic chemotherapy is a combination of 5-HT_3 antagonist plus dexamethasone (See Table 18-2).[29,30] No clinically significant differences have been sufficiently clarified between the five different 5-HT_3 receptor antagonists for prevention of acute nausea in this setting and there is no difference in efficacy between oral versus intravenous administration.
- The MASCC and ASCO guidelines currently recommend the use of an aprepitant-based antiemetic regimen for any chemotherapeutic regimen that includes the combination of cyclophosphamide and anthracycline (which is technically classified as a moderately emetogenic regimen, but actually treated as a highly emetogenic regimen), on the basis of a recent trial in breast cancer patients.[59] This antiemetic regimen has not yet been tested specifically in patients receiving the CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) regimen.
- NCCN guidelines suggest that aprepitant be added for patients undergoing treatment with selected agents, such as carboplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, and methotrexate, as these agents seem to be more emetogenic than the other moderate-risk agents.[87] However, no studies so far have investigated the use of the three-drug antiemetic regimen in patients receiving moderately emetogenic chemotherapeutic agents other than the combination of cyclophosphamide and an anthracycline.
- The recommended dose of dexamethasone for prevention of acute CINV is 8 mg on day 1 when used in combination with a 5-HT_3 antagonist.[29,30]

Delayed CINV

- In patients receiving a doxorubicin and cyclophosphamide (AC) regimen, aprepitant and dexamethasone is recommended for prevention of delayed nausea and vomiting.[30,91]
- Patients who receive chemotherapies of moderately emetogenic risk other than AC should receive antiemetic prophylaxis with oral dexamethasone (preferred) 8 mg daily on days 2 and 3[30] or a 5-HT_3 receptor antagonist (See Table 18-2).[29]
- Palonosetron is FDA-approved for the prevention of delayed nausea and vomiting with moderately emetogenic chemotherapies. In some randomized trials, palonosetron appears to be superior to other short-acting 5-HT_3 antagonists, particularly regarding delayed CINV. In these trials, about 5% to 10% of fewer patients vomited with palonosetron than with shorter-acting 5-HT_3 antagonists. The 2006 ASCO guidelines do not endorse the use of this drug over other 5-HT_3 antagonists, as the trials comparing this agent with other drugs in this class were designed as equivalency trials and did not include dexamethasone; also influencing this is the availability of aprepitant. Of note, the cost for palonosetron is significantly higher than for other oral 5HT_3 antagonists.

Low- or Minimal-Emetic-Risk Chemotherapy

- For patients administered low or minimal emetogenic risk chemotherapy there is little evidence from clinical trials to identify patients at risk for developing CINV.[29]

Acute CINV

- Single-agent dexamethasone (8 mg) is recommended for prophylaxis of acute emesis when low (10% to 30%) emetogenic risk chemotherapy agents are administered (See Table 18-2).[29,30]
- No routine prophylaxis is recommended for patients receiving minimal (<10%) emetogenic risk chemotherapy.[29,30]

CASE 18-1 CASE UPDATE

Mrs. J. has completed two cycles of neoadjuvant chemotherapy with a good response in the size of the lung mass. Her nausea and vomiting have been well controlled with the combination of granisetron, aprepitant, and dexamethasone, and she only required infrequent use of rescue prochlorperazine between treatments. She is now scheduled to start concurrent chemoradiation therapy with a planned radiation dose of 6000 cGy in 30 fractions along with cisplatin (50 mg/m^2) days 1 and 8, and etoposide (50 mg/m^2) days 1 through 5, both at a 15% dose reduction, administered every 4 weeks. She is asking about the side effects of daily radiation therapy and whether anything can be done to prevent nausea and vomiting related to this therapy.

Delayed CINV

- No routine prophylaxis is needed for prevention of delayed CINV in patients receiving low or minimal emetogenic risk chemotherapy.[29,30]

RADIATION-INDUCED NAUSEA AND VOMITING

The exact mechanism of radiation-induced nausea and vomiting has not been fully elucidated, but it is thought to result from the combination of direct mucosal injury and serotonin release.[92] In patients receiving radiation therapy (RT), nausea and vomiting is in general less problematic, but also less predictable than with CINV. It is therefore important to identify the populations at risk in whom antiemetic therapy should be administered routinely on a preventive basis, versus those in whom it may be administered as needed. The major risk factors associated with an increased risk of emetogenicity in context of RT include irradiated site and radiation field size (> 400 cm^2).[93] Other important considerations include dose of radiotherapy administered per fraction, total dose, and pattern of fractionation,[94] as well as patient-related factors, such as previous chemotherapy.[93]

The new MASCC guidelines[95] define four risk level categories on the basis of irradiated site:

- High risk (> 90% risk): total body irradiation
- Moderate (60% to 90% risk): upper abdomen irradiation
- Low (30% to 59% risk): thorax and pelvis irradiation
- Minimal (< 30% risk): head and neck/extremities/cranium/breast irradiation

PREVENTION OF RADIATION-INDUCED NAUSEA AND VOMITING

High Emetic Risk: Total Body Irradiation

- Recommended prophylaxis is with a 5-HT_3 receptor antagonist with or without a corticosteroid before each fraction and for at least 24 hours after.[30,95]
- Complete control of nausea and vomiting with 5-HT_3 receptor antagonists varies between 50% and 90%.[96-98]
- No randomized trial has evaluated the addition of dexamethasone, but the recommendation is made on the basis of the additive effect found in CINV control.

Moderate Emetic Risk: Upper Abdomen

- Recommended prophylaxis is with a 5-HT_3 receptor antagonist before each fraction for the entire duration of the cycle.[30,95]
- Published trials have demonstrated that 5-HT_3 receptor antagonists are more effective than phenothiazines, metoclopramide, or placebo in this patient population.[99-101]

Low Emetic Risk: Thorax, Pelvis, Craniospinal, and Cranial Radiosurgery

- Recommended prophylaxis is with a 5-HT_3 receptor antagonist before each fraction for the entire duration of the cycle.[30,95]
- No randomized trials have evaluated the effectiveness of different antiemetics in this patient population, but one trial suggested superiority of a 5-HT_3 receptor antagonist to placebo.[102]
- The incidence of emesis in patients undergoing craniospinal irradiation and cranial radiosurgery is not entirely known; therefore these patients are empirically judged as low risk and similar prophylaxis with a 5-HT_3 receptor antagonist is recommended.

Minimal Emetic Risk[30,95]

- Treatment should be administered on an as-needed basis for patients experiencing radiation-induced nausea and/or vomiting.[30,95]
- Recommended rescue treatment is with a 5-HT_3 or dopamine receptor antagonist.
- For patients experiencing nausea and/or vomiting, prophylactic treatment should then be continued for each remaining radiation day.

MANAGEMENT OF BREAKTHROUGH EMESIS

Breakthrough emesis is defined as vomiting that occurs on any day of treatment despite administration of optimal antiemetic prophylaxis.[29] Breakthrough emesis represents a challenging situation for the practicing physician, as it is difficult to reverse CINV when it has occurred despite round-the-clock administration of prophylactic medications. There are no randomized trials investigating the use of rescue antiemetics for breakthrough emesis and no clear guidelines for treatment of patients with breakthrough nausea and/or vomiting. General principles of therapy include:

- Rescue antiemetics should be administered on demand when breakthrough emesis occurs during chemotherapy.
- Rectal or intravenous administration may be necessary in patients unable to take oral medications.
- An additional antiemetic from a different drug class should be considered, although switching to a different 5-HT_3 receptor antagonist has also been proposed.[103]

- It is not known whether substituting to a second generation 5-HT_3 receptor antagonist (i.e., palonosetron) would be more beneficial in controlling breakthrough nausea occurring despite prophylactic use of first-generation agents.[29]
- Multiple concurrent agents in alternating schedules may be necessary,[87] such as adding dopamine receptor antagonists (e.g., phenothiazines, or high-dose metoclopramide[30]), neuroleptic agents (haloperidol, olanzapine), benzodiazepine (lorazepam), or cannabinoids (dronabinol, nabilone).
- Patients should be carefully evaluated for chemotherapy risk and prophylactic antiemetic regimen used, concurrent comorbidities (such as electrolyte abnormalities, presence of brain metastases, bowel obstruction, or other gastrointestinal abnormalities), and tumor burden/progression.
- Antacid therapy should be considered for patients with GERD or dyspepsia.[87]

CASE 18-1 CASE UPDATE

Mrs. J. has completed her therapy and did well for 12 months. Unfortunately, she suffered a relapse, with prominent liver metastases. She made an informed decision not to undergo any additional chemotherapy. She has, rather, opted for hospice care. Currently, her biggest symptoms are anorexia, nausea, and vomiting.

MANAGEMENT OF NAUSEA AND VOMITING IN PATIENTS WITH ADVANCED CANCER

Nausea and vomiting are common and distressing symptoms in patients with advanced incurable cancer and often pose significant challenges to treating medical oncologists and primary care physicians. Nevertheless, in the palliative care setting, there is a paucity of data regarding effective treatments for nausea and vomiting that occur independently of chemotherapy or radiation therapy. The following points are worth considering when treating nausea and vomiting in advanced cancer:

- The main goal is to treat and correct reversible underlying causes, if possible, such as treatment of brain metastases, metabolic abnormalities, constipation, or bowel obstruction. Nonetheless, in terminally ill patients, the etiology is frequently multifactorial and reversal of the underlying cause is oftentimes not very feasible.
- Dietary suggestions can be provided, such as intake of frequent small meals, or avoidance of food odors, although these have not been properly studied and likely have limited efficacy overall.
- Pharmacological therapies are the mainstay of treatment in most patients, although a recent systematic review of antiemetics in patients with advanced cancer[104] found that the available evidence is sparse and only a limited number of randomized controlled trials have been conducted. On the basis of the available data, the following conclusions can be made:
  - Metoclopramide seemed to be more effective than placebo for the treatment of cancer-associated dyspepsia[105]; dexamethasone may potentiate its antiemetic effect in patients in whom nausea persists.[106]
  - Data regarding the efficacy of 5-HT_3 receptor antagonists in this setting are conflicting,[104] although they probably do provide some benefit.
  - The evidence for other commonly used antiemetics in patients with terminal cancer (prochlorperazine, haloperidol, cyclizine, olanzapine) is weak or nonexistent.[104,107]
  - Megestrol acetate is helpful for appetite enhancement and control of nausea and vomiting in this patient population; the main adverse effects include venous thromboembolism[108] and edema.[109]
  - It is sometimes necessary to use a combination of drugs (added sequentially) that attack different receptors associated with nausea and vomiting:
    - Antidopaminergic (e.g., metoclopramide, prochlorperazine, or haloperidol)
    - Hormonal (e.g., dexamethasone or megestrol acetate)
    - Antihistaminic (e.g., diphenhydramine)
    - 5HT_3 receptor antagonist (e.g., ondansetron or granisetron)

The treatment of inoperable bowel obstruction in patients with terminal cancer is aimed mainly at symptom control. The goal of pharmacologic approaches is to preserve the patients' quality of life and to enable them to die comfortably "without tubes."[107] Clinical-practice recommendations for the management of bowel obstruction in patients with advanced cancer exist and have been published in 2001 by the European Association for Palliative Care (EAPC).[110]

- Dexamethasone is a standard recommendation for treatment of malignant bowel obstruction [104] given its anti-inflammatory effects and reduction of fluid influx into the bowel lumen, which could result in temporary reversal of the obstruction.[111]
- The prokinetic agents metoclopramide and domperidone are contraindicated in patients with complete obstruction, although they can sometimes still be considered for those with partial obstructions or ileus.[107]

- Antisecretory drugs such as anticholinergics, antihistaminics, proton-pump inhibitors, or octreotide may also help to control nausea and vomiting; a recent systematic review found octreotide to be superior to hyoscine butylbromide in the medical management of inoperable malignant bowel obstruction.[112]

Summary

In closing, the management of chemotherapy-induced nausea and vomiting (CINV) is a prominent clinical problem. Inadequately controlled nausea and vomiting can significantly affect patients' quality of life and functional ability and is a source of severe emotional distress for both patients and their families. While major advances have been made in recent years, nausea and vomiting in cancer patients remain problematic issues and continue to pose significant challenges to practicing oncologists and primary care providers. Over the past two decades, multiple treatment options have become available for treating nausea and vomiting in patients with cancer. However, the vast number of ways to intervene upon this problem may seem overwhelming to the busy practitioner whose patient is in the examination room waiting for a solution. Clinical guidelines are systematically being developed to assist physicians in delivering evidence-based care[30,113-115]; however, for numerous clinical situations there is no high-level clinical evidence or complete consensus among the experts. This chapter presents options for the prevention and treatment of CNIV on the basis of data and clinical experience gathered over the past several decades.

See expertconsult.com for a complete list of references and web resources for this chapter

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CHAPTER

19

Insomnia in Aging

Octavio Choi and Michael R. Irwin

This chapter will provide a broad overview of insomnia in aging, divided into three sections. The first section will review the epidemiologic literature as it relates to insomnia and aging. As will be discussed, older people suffer from higher rates of insomnia, and much of this increase appears to be related to the development of medical comorbidities, including cancer diagnosis and treatment, that interfere with sleep. The second section will provide a conceptual approach to the diagnostic assessment of insomnia in the elderly. Many of the most common insomnia-related conditions in the aged population will be reviewed. As most cases of insomnia in this population are associated with comorbid psychiatric and medical illness, a thorough evaluation of insomnia in older adults requires a systematic consideration of related comorbidities. Finally, the third and last section will discuss the health and quality-of-life consequences of insomnia in the older adult. The presence of insomnia is thought to exacerbate numerous health conditions including psychiatric illness, obesity, and pain syndromes, which together emphasize the clinical importance of diagnostic ascertainment and treatment of insomnia in older adults.

EPIDEMIOLOGY AND CLASSIFICATION

CASE 19-1

Ms. S is a 70-year-old woman with breast cancer, recently started on adjuvant hormone therapy, who is being seen by her physician for a routine examination. During the examination, she says she is tired and not sleeping well. What questions should her doctor ask to determine whether she might have insomnia?

Insomnia Prevalence in the General Population

In epidemiologic studies, the prevalence of insomnia in the general population is reported to vary widely, with estimates ranging from 6% to 48%,[1] with variation due in part to differing definitions of insomnia. More recent studies have increasingly used more precise and stringent definitions of insomnia, which has resulted in lower calculated prevalence rates. Epidemiologic studies of insomnia can be conceptualized as belonging to one of four different categories, in a sense reflecting the evolution of insomnia definitions over time[1]:

1. Insomnia defined by the presence of insomnia symptoms, such as difficulty initiating or maintaining sleep, results in prevalence rates at 30% to 48% in the general population;
2. Insomnia defined by the presence of insomnia symptoms and daytime consequences, results in prevalence rates of 9% to15%;
3. Insomnia defined by subjective dissatisfaction with sleep quality, results in prevalence rates of 8% to 18%;
4. Insomnia defined by diagnosis using a formal classification system such as the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-V), results in prevalence rates of 4.4% to 6.4%.

The first group primarily includes older epidemiologic studies that detected insomnia simply by the presence of various symptoms, such as difficulty initiating sleep (DIS), difficulty in maintaining sleep (DMS), or early morning awakening (EMA). A representative study of this era is a 1979 study of 1006 adults, which reported an insomnia prevalence rate of 32.2% in the general Los Angeles population.[2] Subjects were simply asked whether they had trouble falling asleep, woke up during the night, or woke up too early in the morning; endorsement of any these insomnia symptoms was used to indicate insomnia. However, such a broad approach leads to an overestimation of the prevalence of clinically significant insomnia, as it includes people who may suffer from insomnia symptoms only occasionally, or experience only mild symptoms. To address this limitation, subsequent studies have refined the diagnosis of insomnia to include frequency and severity criteria. For example, when frequency criteria of insomnia symptoms of 3 or more times per week are included, prevalence rates drop to 16% to 21%. Similarly, if insomnia is defined as "great or very great difficulty" in initiating or maintaining sleep, prevalence rates drop to 10% to 28%.[1]

The second diagnostic approach restricts the definition of insomnia to require the presence of insomnia symptoms (such as DIS, DMS, or EMA), as well as daytime functional impairment, such as daytime sleepiness, irritability, and trouble concentrating. Using this more

refined definition, prevalence rates range from 9% to 15% and average around 10% in the general population.[1] As will be discussed later in more detail, the presence of clinically-significant daytime impairment is a key criterion in establishing a diagnosis of insomnia in all modern sleep disorders classification systems.

The third diagnostic approach focuses on an alternative definition of insomnia, requiring only the report of a subjective sense of dissatisfaction with sleep quality, with the consequence of feeling unrested upon awakening. This definition yields prevalence rates similar to the second group, 8% to 18%. Importantly, this approach is a relatively recent definition, and there is still some controversy amongst sleep experts over whether individuals with this complaint share similar pathophysiologic mechanisms with insomniacs as defined in the first two groups.[3] For example, patients with obstructive sleep apnea may have severely disrupted sleep as a result of multiple apneic episodes throughout the night; however, they are often unaware of this and thus tend to answer "no" when asked whether they have difficulty falling or staying asleep at night. These subjects would thus not be categorized as insomniacs in the first two groups. However, they would tend to be included in the third group, as most patients suffering from this condition report waking up feeling unrested.[4] Despite this controversy, however, there is a general consensus that a subjective sense of sleep dissatisfaction is a useful marker of insomnia, and it is included in the diagnostic criteria for insomnia under the DSM-IV classification system as the criterion of "nonrestorative sleep."

The fourth approach ascertains insomnia using formal diagnostic classification systems, which together reflect the evolving understanding that insomnia is a constellation of symptoms that may be part of a larger disease process or a diagnosis in its own right, according to specific inclusion and exclusion criteria. Increasingly, insomnia is recognized to occur within the context of comorbid mental and physical illnesses, a point that will be discussed in more detail later in this chapter.

CASE 19-1 CONTINUED

After hearing that Ms. S has been having trouble sleeping, the physician should inquire about the severity and frequency of the sleep problems by asking whether she has been having trouble going to sleep, waking up in the middle of night, or waking up too early and having difficulty going back to sleep—or all three symptoms. Ms. S reports that she only occasionally has difficulty going to sleep, but often wakes up and cannot resume her rest, reporting episodes of lying in bed where she is not sure whether she is sleeping or not for "hours on end" and "sometimes she gets up and begins her day even though she has not slept." Upon further questioning, it appears that these episodes of waking occur nearly every night during the week, and that she feels "exhausted" during the day and sometimes sad and depressed. She dismisses the notion that she snores, and says that her husband never complains of her snoring either at night or during her naps during the day.

Risk Factors for Insomnia

There are numerous risk factors for insomnia, including female gender, advancing age, social isolation (divorced/widowed/separated), low socioeconomic status, unemployment, drug use (alcohol or illicit substances), medication use, and medical and psychiatric comorbidities. Whereas many of these risk factors have been extensively reviewed elsewhere,[1] several of these risk factors deserve further discussion in this chapter. As most cases of insomnia in older adults occur within the context of comorbid illnesses, it is essential for the clinician concerned with insomnia to be aware of these comorbidities so they can be diagnosed and treated, with consequent impact on insomnia symptoms. Associated physical illness is especially prevalent in the elderly, and is a major contributing factor to insomnia in this age group; this will also be discussed later in this chapter.

Insomnia Comorbidities

Most of those with insomnia suffer from comorbid physical and mental illnesses, which are presumed to contribute to the onset and perpetuation of insomnia symptoms.[1,3,5] Indeed, one study showed that 53% of respondents with insomnia symptoms reported suffering from a "recurring health problem," and 33% reported "needing help for emotional problems" in the previous year, both significantly higher than noninsomniacs.[2] Subsequent studies have consistently reported that insomniacs suffer from rates of physical and mental illnesses that are higher than for persons without insomnia.[6-8]

However, when discussing medical and psychiatric conditions contributing to insomnia, sleep specialists are increasingly moving away from the term "secondary," preferring instead the term "comorbid." This change reflects an appreciation for the fact that with most diseases associated with sleep disorders, especially mental illness, causality is unclear and complex. For example, insomnia may be an antecedent of major depressive disorder, or may develop after depressive symptoms.[9,10] In addition, insomnia may persist after all other depressive symptoms remit, suggesting that once established, other factors, such as psychological conditioning, may perpetuate it. In such cases, it would be inaccurate to label the insomnia as "secondary" to the major depression, and treatment of major depression alone (for example with an antidepressant) would not be adequate for alleviation of insomnia. This is an important clinical issue, for the presence of insomnia alone is a major risk factor for future depressive relapse especially in older adults or older cancer patients. Hence, amongst clinicians, the term "insomnia secondary to" may focus treatment efforts on the comorbid illness, with a resulting potential to lead ultimately to undertreatment of the insomnia itself.

Insomnia and Psychiatric Illnesses

Cross-sectional surveys of insomnia and mental health symptoms have reported that 30% to 60% of those with insomnia symptoms have an associated mental disorder, compared with approximately 15% for persons without insomnia.[7,10] Major depressive disorder is most frequently associated with insomnia, followed by generalized anxiety disorder. Alternatively, over 80% of those with major depression, and over 90% of those with anxiety disorders, suffer from insomnia.[1] Indeed, the single most common comorbid disorders related to chronic insomnia are major depression and anxiety disorders,[11] with multivariate logistical regression models indicating that the presence of depression is the strongest single factor predicting insomnia.[6] Insomnia is more strongly associated with major depression than with any other medical disorder, with relative risk two to three times greater than all other medical conditions surveyed.

Longitudinal studies have established that insomnia in the absence of psychiatric symptoms is a risk factor for the later development of major depression, in both young[12] and aged populations[9,13,14] with odds ratios ranging from 3 to 4. Furthermore, when insomnia is chronic, the risk for developing major depression is significantly higher; one study reported that when insomnia was present for over 1 year, there was a four-fold increased risk for developing a major depressive episode in that year.[10] Interestingly, time sequence analyses have shown that insomnia symptoms precede the onset of depressive symptoms in most cases.[7]

Taken as a whole, it is of critical clinical importance to evaluate the presence of psychiatric comorbidity in patients presenting with insomnia. Clinicians should be especially vigilant for depression, as older persons are subject to psychosocial factors that increase the risk for depression, including retirement, social isolation, bereavement, and widowhood.[8] Furthermore, these data also suggest the potential for targeted treatment of insomnia, even in the absence of psychiatric symptoms, to reduce the risk of developing future depressive episodes.[15]

CASE 19-1 CONTINUED

Because Ms. S reports sleep problems and feeling depressed, her physician follows up and asks whether her sadness lasts all day long. She says that some days when she has not slept that she feels depressed all day, but then remembers that whenever she can get a nap or has a good night that she is her usual self, enjoying gardening and cooking for her family. However, further questioning reveals that there was a time after the death of her sister, who also had breast cancer, that she felt very sad and depressed, and that these feelings lasted nearly every day for nearly 6 months before she saw her previous physician who gave her an antidepressant medication. In fact, in recounting this episode, she notes that it was during the time that she was caring for her sister in the terminal stages of breast cancer that she became anxious about her own health and first began having trouble sleeping. Even after her mood returned to normal, she continued to have more nights than not in which she had problems sleeping. However, whenever she goes on a vacation or sleeps somewhere other than her bedroom, that her sleep is restful. She feels like her "bed is filled with worry."

Insomnia and Cancer Survivorship

Poor sleep is one of the most common complaints in cancer patients. In breast cancer survivors, chronic diagnostic insomnia shows a prevalence of 19%, which is three to five times higher than rates of diagnostic insomnia diagnosis found in the general population.[16,17] Insomnia symptoms are also elevated in breast cancer survivors, with a prevalence of 51%, two to five times higher than the general population.[16,17] Finally, in heterogeneous samples of cancer survivors, a two-to-threefold increase in the prevalence of insomnia symptoms is found as compared to rates in healthy adults.[18,19]

In survivors of breast cancer, impairments of sleep are primarily characterized as problems falling asleep,[20] with difficulties of sleep maintenance[21] and duration also reported. Indeed, in women who have received a diagnosis of breast cancer and undergone treatments, over 45% continue to complain of sleep problems, with 25% of all breast survivors reporting use of sleep medications on a routine basis.[16] As noted earlier, 19% fulfill diagnostic criteria for chronic insomnia including prolonged (>30 minutes) difficulty initiating sleep or returning to sleep after nighttime awakening, which together are associated with distress and clinical impairments in daytime functioning. Moreover, high rates of sleep complaints are found several years after initiation of adjuvant therapy for cancer, suggesting that insomnia develops a chronic course in a substantial proportion,[16,22] contributing to continued impairment in quality of life.

Less is known about the clinical factors that precipitate and/or perpetuate insomnia in breast cancer survivors. While it is generally assumed that insomnia is secondary to psychological distress and anxiety of cancer diagnosis and treatment, sleep problems are frequent even in those patients who report low levels of anxiety.[23] Likewise in cancer survivors with insomnia, less than 20% are comorbid for depression and/or anxiety disorders,[24] consistent with comorbidity rates in the general population.[1,25] Nocturnal awakenings are also often attributed to symptoms of pain in cancer patients,[26] although pain is less likely to be a factor in breast cancer survivors who show no indication of residual or recurrent disease.[27,28] In contrast, among breast cancer survivors, social factors may be relevant; highly educated and single women have a fourfold increased risk of insomnia.[16] Moreover, older age also increases the vulnerability for insomnia in cancer survivors.

Other clinical factors, such as treatment variables, should also be considered. For example, women undergoing chemotherapy showed a progressive increase

in the number of awakenings, in which the number of awakenings increased with the number of treatment cycles, which was in turn related to increases in numbers of menopausal symptoms.[29] However, other studies report that the prevalence of insomnia was not related to time since diagnosis nor to treatment type,[16,30] and that the incidence of insomnia is similar across groups who receive different treatment (e.g., surgery, chemotherapy, radiation).[31] Among breast cancer survivors, hormone therapy (i.e., tamoxifen) is often used as an adjunct to radiation or chemotherapy, induces estrogen insufficiency, and is implicated in the onset of trouble sleeping because of menopausal symptom side effects. Although several studies have not consistently related tamoxifen treatment to either the onset or maintenance of insomnia symptoms,[32,33] nocturnal vasomotor symptoms are associated with less efficient and more disrupted sleep in healthy menopausal women.[34-37]

CASE 19-1 CONTINUED

After the diagnosis and treatment of her breast cancer, Ms. S further reported that her worrying about her health seemed to be about the same as it had been since her sister's death. However, now not only was she having trouble getting to sleep, but the problems waking up were more problematic. Sometimes, after the tamoxifen treatment, she had severe night sweats that woke her, but then again the main problem was getting back to sleep after she had woken. To help her with her sleep, she had started taking a sleeping pill to get through the night. Although she was able to sleep, she awoke feeling "fuzzy" in her thinking and had trouble even reading the newspaper. Finally, she stopped taking the sleeping pill after she had woken in the middle of the night and fallen as she was walking to the bathroom. Her physician completed her assessment, and found no other medical issues. On the basis of the severity and chronicity of her sleep complaints, the diagnosis of chronic insomnia was made and she was referred to a clinical psychologist for treatment with cognitive behavioral therapy for insomnia.

Insomnia and Aging

Numerous studies have documented a positive correlation between insomnia symptoms and advancing age, with prevalence rates reaching close to 50% in elderly individuals (defined as older than 65 years), depending on the definition of insomnia used. In one representative study, the incidence of insomnia symptoms (difficulty falling asleep, staying asleep, or early morning awakening) increased with age: 23% for 18 to 30 year-olds, 37% for 31 to 50 year-olds, and 40% for those older than 51 years,[2] with a composite rate for all age groups at 32.2%. Women had higher prevalence rates of insomnia at all age points studied, with an average ratio of 1.4:1.

Although the prevalence of insomnia *symptoms* increases with advancing age, the relationship between age and insomnia *diagnoses* is less clear, with some studies reporting a stable prevalence with age and others reporting an increasing prevalence with age.[1] Taken as a whole, the rate of insomnia diagnoses appear to be stable between ages 15 and 45, increases from age 45 to 65, and remains stable after age 65. Interestingly, this correlates well with polysomnography studies, which indicate that sleep architecture in healthy subjects begins to change starting in early adulthood and become relatively constant after the age of 60. Age-related changes include decreases in sleep efficiency, decreases in percentage of slow-wave and rapid eye movement (REM) sleep, decreases in REM latency, and increases in percentage of stage 1 and 2 sleep.[38]

There are several factors that might account for the discrepancy between insomnia symptoms and insomnia diagnoses in terms of prevalence rates with age. For example, older people often report more sleep complaints, such as nighttime awakenings, but these complaints are often not associated with daytime functional impairment, a necessary criterion for an insomnia diagnosis. Hence many of these older adults receive a diagnosis of "dyssomnia not otherwise specified" rather than insomnia. In addition, older adults often suffer from a higher prevalence of nocturia, which may result in multiple nighttime awakenings. However, without difficulty falling back asleep, daytime functional consequences are minimal.[39] Finally, many elderly suffer from insomnia symptoms resulting from so called "primary sleep disorders" that are conceptualized as noninsomnia diagnoses within the DSM-IV classification system, such as circadian rhythm shift disorder, breathing-related sleep disorder, and limb movement disorders, and the prevalence rates of all these conditions increases sharply with age.[40]

Whereas it is not fully known what accounts for the rise in insomnia symptoms with age, the increasing prevalence of medical comorbidities is likely to play a key role. In 2004, a survey was conducted of 1506 older adults (aged 55 to 84 years) in the general United States population as part of the National Sleep Foundation's 2003 "Sleep in America" poll.[39] When comparing the 55- through 64-year-old to the 65 years and older groups, the older group reported significantly more heart disease, hypertension, arthritis, cancer, stroke, and enlarged prostates. Whereas 25% of the 55 to 64 year olds reported no medical conditions, only 12.8% of those older than 65 years reported no medical conditions, a statistically significant difference between the two age groups. In addition, this study demonstrated a significant inverse relationship between the number of medical conditions and self-perceived quality of sleep. Amongst subjects with no medical conditions, 54% reported an "excellent" quality of sleep, and only 10% reported a "fair/poor" quality of sleep. For those with one to three medical conditions, 42% reported excellent sleep, and 22% fair/poor sleep. For those with four or more medical conditions, only 32% reported excellent sleep and 41% fair/poor sleep. Interestingly in another study,[41] insomnia rates were not correlated with age amongst the elderly (those

older than 65 years), after controlling for health status. In other words, age was not a significant independent variable in predicting sleep complaints in the elderly; rather, declines in physical and mental health predicted insomnia.

Taken as a whole, the data indicate that the elderly suffer from higher rates of insomnia symptoms compared with younger subjects, and much of this appears to be due to increasing medical comorbidities with age. Indeed, despite the normal age-related changes in sleep architecture mentioned earlier, healthy elderly appear to sleep as well as young adults. The prevalence of primary insomnia diagnoses (that is, insomnia without medical, psychiatric, or neurological comorbidities) is the same in elderly and young adults. Thus, when insomnia is detected in the elderly, it is incumbent upon the clinician to diagnose thoroughly and treat medical, psychiatric, and neurological comorbidities that may be interfering with sleep.

DIAGNOSIS AND EVALUATION

In this section, a systematic approach to the diagnosis and evaluation of insomnia in the elderly will be presented, taking into account the fact that most insomnia symptoms in the elderly occur in the context of comorbid health conditions. Often it will be important to interview not only the patient, but his or her caregiver, who may be more aware than the patient of sleep disturbances during the night, as well as symptoms such as snoring of which the patient may be unaware.

The clinician must ascertain if the patient has a complaint of difficulty initiating or maintaining sleep, or has a complaint of nonrestorative sleep, lasting for at least 1 month (the **First Criterion**). Moreover, the sleep disturbance must cause "clinically significant distress or impairment" during the day (the **Second Criterion**).

Useful screening questions are:

- Do you have trouble falling asleep or staying asleep at night?
- Does this cause problems for you during the day?
- Do you feel extremely sleepy during the day or have trouble staying awake?

The **Third Criterion** requires the clinician to rule out primary sleep disorders (which include narcolepsy, breathing-related sleep disorders, and circadian rhythm sleep disorders) and parasomnias. If there is a strong suspicion of a primary sleep disorder, a referral to a sleep specialist may be appropriate; additional testing including polysomnographic studies (Table 19-1) can be useful in establishing a definitive diagnosis.

The **Fourth Criterion** requires ruling out psychiatric comorbidities, especially major depression, which is the most common single diagnosis in individuals with insomnia. Clinicians should inquire whether their patients have been feeling sad or anxious, and whether they have risk factors for depression such as retirement, social isolation and bereavement. As mentioned earlier, because of the complex causal relationship between insomnia and mood disorders, treatment often involves treating both the mood disorder (i.e., with antidepressants) and insomnia symptoms (i.e., with hypnotics). Insomnia that persists after remission of depression substantially increases the risk of depressive relapse.[9]

The **Fifth Criterion** requires that the clinician rule out general medical conditions (Table 19-2), medications, and drugs of abuse (Table 19-3) as contributing factors to insomnia. As discussed earlier, medical conditions are frequently associated with insomnia symptoms

TABLE 19-1

Disorder	Description	Helpful Diagnostics	Treatment
Narcolepsy	Excessive sleepiness associated with sleep paralysis and hypnogogic hallucinations	Polysomnographic studies; caregiver interview	Sleep hygiene; lifestyle changes; medication
Obstructive sleep apnea	Distinctive snoring pattern (loud snores and brief gasps lasting 20-30 seconds)	Polysomnographic studies; caregiver interview	Treat underlying breathing disorder
Advanced sleep phase syndrome	Advancement of sleep/wake cycle such that they tend to fall asleep earlier and wake earlier	Sleep diary; caregiver interview	If needed, exposure to bright light later in the day to shift circadian rhythms
Restless leg syndrome	Disagreeable leg sensations ("tingling," "crawling," or "aching") that occur at bedtime and interfere with onset of sleep and are temporarily relieved by moving the legs	Caregiver interview	Sleep hygiene; lifestyle changes; medication
Periodic limb movement disorder	Clusters of repeated limb jerks that lead to brief awakenings	Polysomnographic studies; caregiver interview	Sleep hygiene; lifestyle changes; medication
Parasomnias	Behavioral or physiologic events during sleep-wake transitions (i.e., sleep terror, sleep walking, or REM behavior sleep disorder, which is an intermittent failure of sleep paralysis)	Polysomnographic studies	Psychiatric evaluation; neurologic evaluation; medication

TABLE 19-2 Common Drugs That Cause Insomnia

- Alcohol
- Caffeine
- Marijuana
- Chocolate
- Nicotine (including nicotine patch)
- Oral contraceptives
- Decongestants/cold medicines
- Antidepressants (e.g., SSRIs)
- Dopamine agonists
- Thyroid hormones
- Bronchodilators
- Anticonvulsants
- Antineoplastic agents
- Corticosteroids
- Beta-agonists
- Theophylline
- Antihypertensive agents
- Antilipid agents
- Diuretics
- Appetite suppressants
- Psychostimulants and amphetamines

TABLE 19-3 Common Conditions That Can Cause Insomnia

- Hyperthyroidism
- Arthritis or other painful condition, such as bone metastasis
- Chronic kidney disease
- Cardiovascular disease
- Chronic obstructive pulmonary disease
- Gastroesophageal reflux disease
- Brain tumors or metastasis
- Stroke
- Headaches
- Alzheimer disease
- Seizures
- Parkinson disease
- Diabetes
- Menopause

and in many cases are thought to play a role in causing or aggravating insomnia. Thus, it is imperative that the clinician first identify and treat medical comorbidities. Conceptually, they may be categorized as illnesses that give rise to respiratory distress (asthma, chronic obstructive pulmonary disease, pulmonary edema secondary to heart failure), pain (malignancy, arthritis, rheumatic disease, musculoskeletal pain, chronic pain, heart disease, GERD, diabetes), and neurodegenerative conditions (dementia, Parkinson disease, stroke). Hypertension has also been linked to insomnia in the elderly, perhaps as a marker for autonomic hyperarousal, or as a consequence of activating antihypertensive medications. In older men especially, nocturia secondary to prostate conditions may be a prominent cause of difficulty maintaining sleep; reduced fluid intake before sleep may be helpful in these cases. Older women may be prone to postmenopausal hot flashes that may interfere with sleep. Despite optimal management of medical conditions, separate treatment for insomnia symptoms may also be necessary, a topic that is discussed in detail elsewhere in this book.

Medications and Sleep

Numerous medications are thought to interfere with sleep (see Table 19-3). Activating medications include central nervous system stimulants, beta-blockers, bronchodilators, calcium-channel blockers, corticosteroids, decongestants, diuretics, stimulating antidepressants, and thyroid hormones.[40] Changing the timing of administration of stimulating medications to earlier in the day will often improve sleep at night. The clinician should also assess for substance use. Caffeine and cigarette use both interfere with sleep and their use should be minimized. As caffeine has a half-life that ranges from 3 to 10 hours (averaging 5 hours), caffeine intake should be restricted to earlier in the day. It may be important to remind patients that caffeine is found not only in coffee, but in decaffeinated coffee, teas, and sodas.

The clinician should be aware that many people suffering from insomnia will use alcohol at night to help them sleep. Alcohol is a central nervous system depressant that does accelerate sleep onset. However, because of its short half-life, blood levels rapidly drop, causing awakening from sleep later in the night. In addition, there is rapid tolerance, such that prolonged use of alcohol at bedtime loses its effects on sleep onset, but sleep disruption remains. Patients should be counseled that the use of alcohol at night is counterproductive to good sleep and should be given other, more effective, treatment options.

TREATMENT

For patients suspected of having poor sleep hygiene and/or psychophysiologic insomnia, cognitive behavioral therapy (CBT) for insomnia may be especially helpful. CBT for insomnia, which combines stimulus control, sleep restriction, sleep hygiene (Table 19-4), and cognitive restructuring, has been found to be at least as effective as prescription medications for the treatment of chronic insomnia, with an efficacy in older adults comparable to the benefits reported in middle-aged adults.[42] For example, when temazepam was compared with CBT for the management of chronic primary insomnia in the elderly, both treatments were found effective when measured at 8 weeks. However, only the CBT groups (CBT alone, or CBT in combination with temazepam) maintained their clinical gains at 3, 12, and 24-month follow-ups.[43] The NIH noted in its "state of the science" consensus statement that while prescription hypnotics were found to be efficacious in the short-term management of insomnia, little data existed supporting long-term benefits.[3]

TABLE 19-4 Sleep Hygiene

Avoid alcohol, nicotine, caffeine, and chocolate several hours prior to bedtime.
Reduce nonsleeping time in bed.
Avoid a visible bedroom clock.
Avoid trying to make yourself sleep.
Establish a regular sleep schedule.
Exercise every day.
Deal with worries before bedtime.
Adjust your environment.
Make sure room is not too warm.
Minimize light.
Minimize sound.
Make sure bed and pillow are comfortable.

In addition, prescription hypnotics are associated with numerous side effects, including residual daytime sedation, cognitive impairment, and motor incoordination. As CBT does not appear to produce adverse effects, clinicians may wish to consider this as a more effective and potentially less harmful intervention for primary insomnia.

HEALTH AND QUALITY-OF-LIFE CONSEQUENCES OF INSOMNIA IN THE OLDER CANCER PATIENT

One of the challenges in determining the contribution of insomnia to health conditions is disentangling the role of insomnia per se from the comorbidities that usually accompany it. As reviewed earlier, chronic insomniacs as a population are sicker than noninsomniacs, because insomnia usually occurs in the context of medical or psychiatric illness. Most of the studies that will be discussed here are cross-sectional epidemiologic studies that are subject to this potential underestimation bias. In addition, these studies are not specifically focused on the older cancer patient. As a field, there is a strong need for more long-term prospective studies in older cancer patients, which would be less susceptible to this bias, as well as for interventional laboratory studies, which can more directly support causality.

Public Health Burden

Numerous studies have established that insomniacs utilize the health care system at higher rates than noninsomniacs. In a survey of 1,100 managed care enrollees in the United States, individuals reporting insomnia had significantly more emergency room visits, more calls to the doctor, and more use of over-the-counter drugs than those without insomnia.[44] Another survey of primary care clinic patients demonstrated that insomniacs had greater health care utilization, more days of disability due to health problems, and greater functional impairment as measured by self-reported physical and social disability.[45] In both of these studies, the associations persisted after controlling for medical and psychiatric comorbidities.

A 1995 study estimated the annual direct costs for insomnia in 1995 to be $13.93 billion.[46] This included costs for medications ($1.97 billion) and health care services related to insomnia ($11.96 billion). Somewhat surprisingly, the biggest expense in this analysis was nursing home costs, which totaled $10.9 billion, or 78% of total insomnia-related direct costs. Although this figure is seemingly high, 70% of caregivers cite sleep disturbances in their decision to institutionalize, often because their own sleep was affected, with 20% specifying sleep disturbance as their primary reason.[47] Estimates of total (direct and indirect) insomnia-related costs in the US alone range from $30 billion[48] to $107.5 billion annually.[49]

DAYTIME FUNCTIONAL IMPAIRMENT IN INSOMNIA

One of the most robust findings in the literature is that people with insomnia feel that their insomnia impairs their ability to function in a variety of domains. Compared with noninsomniacs, they report feeling more fatigued during the day,[50] and feel sleepier when driving a car.[51] Interestingly, one finding[49] was that in the 2-year period studied, insomniacs were involved in twice as many serious car accidents as noninsomniacs, although this result did not quite reach statistical significance. Amongst elderly insomniacs, sleeping difficulties contribute to slowed reaction times[52] and impaired balance leading to a greater risk of falls in this population.[53]

Insomniacs also complain that they have trouble remembering things,[51] have trouble concentrating, and more often feel confused than noninsomniacs, which may be why they report significantly lower levels of self-esteem, job satisfaction, and efficiency at work. A study in the elderly population[1] reported that the presence of excessive daytime sleepiness was a significant risk factor for cognitive impairment including attentional deficits, delayed recall, difficulties in orientation, and memory. These symptoms are of particular concern in older people, because they may be misinterpreted as symptoms of dementia or mild cognitive impairment.

INSOMNIA AND MORTALITY

If insomnia worsens medical and psychiatric conditions and increases the chances of falls and accidents, one may expect that insomniacs would be at higher risk for premature death. What is the evidence for this? A prospective study[54] of over one million people in the general population concluded that sleep durations of less than 6 hours and more than 8 hours were associated with a significantly increased risk of all-cause mortality over a 6-year period. The best survival was found among those who slept 7 hours a night, resulting in a U-shaped

survival curve that has been replicated in other studies in the United States[55] and Japan.[56] This study also reported that severity of insomnia was associated with shorter survival in a dose-dependent fashion, although this effect went away after controlling for comorbidities. This result suggests that insomnia per se does not affect mortality; rather, it affects mortality exclusively by worsening other health conditions. However, a significant limitation of this study was that insomnia was not well-defined (participants were simply asked, "How many times a month do you have insomnia?" without providing criteria for what constituted insomnia), limiting the conclusions that may be drawn about insomnia in this study.

A more recent prospective study amongst healthy community-dwelling elderly provides strong evidence that insomnia is associated with increased mortality, by providing an objective assessment of sleep disturbance using polysomnography.[57] After controlling for age, gender, and medical burden, individuals with baseline sleep latencies of greater than 30 minutes were found to have 2.14 times greater risk of death over a mean follow-up of 12.8 years. Poor sleep efficiency and disturbed REM sleep were also found to be significantly correlated with greater risk of death. This study is remarkable in part due to the fact that sleep parameters were objectively measured with polysomnography for all 185 subjects, differentiating it from earlier studies that used subjective self-reports to measure sleep disturbance, with similar results.

Taken as a whole, the epidemiologic data support the hypothesis that insomniacs are at greater risk for premature death than noninsomniacs, even after controlling for medical and psychiatric morbidity, and that this is in part due to increased incidence of cardiovascular disease. Associational studies do not prove causality, however. Insomnia could either be a sensitive early marker of physical decline due to other causes, or it could play a more active role in contributing to a dysregulation of physiology that ultimately leads to disease.

Summary

Insomnia is a complex phenomenon. It is a sensitive marker for both medical and psychiatric illness, and also appears to be an active participant in causing disease. Insomnia sits at the crossroads of multiple fundamental biologic mechanisms, through which it affects a dauntingly large array of illnesses including some of the most urgent health epidemics of our time such as cancer, cardiovascular disease, obesity, and diabetes. A note of hope for the clinician is that because insomnia is tied to so many fundamental disease processes, the application of effective treatments for insomnia may serve to have salutary effects on many of the conditions that are affected by it. The restoration of good sleep may prove to be a keystone in improving the health of older adults in general, older cancer patients undergoing treatment, and older cancer survivors.

See expertconsult.com for a complete list of references and web resources for this chapter

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CHAPTER

20

Nutritional Support for the Older Cancer Patient

David B. Reuben

CASE 20-1 CASE DESCRIPTION

An 80-year-old man has had a several-year history of low-grade B-cell non-Hodgkin lymphoma with a presacral mass and systemic light chain amyloidosis involving the heart, the gastrointestinal tract, and probably his kidneys. His chief complaints have been loss of appetite and nausea. The patient also has a longstanding history of monoclonal gammopathy with an IgM level rising to 1400 mg/dL. In response to bortezomib and dexamethasone, his IgM paraprotein almost normalized and his light chains were reduced by half. The patient was not able to tolerate any further bortezomib treatment because of side effects of nausea and diarrhea, resulting in dehydration and prerenal kidney failure. His nausea improved with low-dose prednisone. Despite his poor appetite, the patient's weight has remained stable over 2 years. However, he has had intermittent edema and persistent pleural effusions.

Nutritional support for the older cancer patient varies at different points during the course of a malignancy (Table 20-1). At the earliest stage, nutritional support (e.g., supplementation with vitamin D) may be used to attempt to prevent cancer. A recent meta-analysis of cohort and case-control studies on the effects of vitamin D supplementation and blood-circulating 25-hydroxy vitamin D levels suggests a protective effective effect on the risk of developing breast cancer.[1] However, these observational data findings await confirmation in clinical trains and this approach is too preliminary to be recommended.

The second stage is at the time of diagnosis. If a tumor has been detected by screening, older cancer patients may have no symptoms; the main concern is whether they have any nutritional deficiencies that would interfere with primary treatment of the malignancy. In contrast, weight loss may be a presenting symptom for many malignancies, especially colorectal cancer and lymphomas.

During the course of cancer treatment, weight loss and nutritional complications may be the result of tumor progression causing anorexia, structural or functional disturbances of dentition or the gastrointestinal tract, depression that commonly accompanies cancer, or due to side effects of treatment (e.g., mucositis).

The cancer-related anorexia/cachexia syndrome is a hypercatabolic state (increased resting energy expenditure) with high levels of tumor-activated or host-produced immune responses (e.g., proinflammatory cytokines) to the tumor. Clinical manifestations include loss of appetite and weight, especially lean body mass; tissue wasting; metabolic alterations; fatigue; and reduced functional status.

Nutritional supplementation may be needed to allow the patient to continue to receive treatment or to maintain functional status. Sometimes older cancer patients may become so sick that they cannot tolerate oral feeding and more aggressive enteral or parenteral nutritional support may be considered. An emerging concept is the use of nutritional therapy (e.g., dietary modifications to reduce energy from fat and increased intake of vegetables, fruits, and fiber) to prevent recurrence of malignancies, especially breast cancer.

Finally, there is a stage of advanced cancer when nutritional support may be palliative (e.g., feeding the patient for comfort or pleasure in spite of risks of aspiration).

The knowledge base for nutritional support of the older cancer patient is limited, in part because of the difficulty in studying this population. The sickest, most malnourished patients are often excluded from clinical trials of nutritional support.[2] Even when eligible for clinical trials, sick older cancer patients may be reluctant to participate. Moreover, the published trials on nutritional support focus on older populations or cancer populations rather than older patients who have cancer. Hence, much of what can be gathered from the literature are extrapolations from studies conducted on one population or the other. Most of the clinical trials have focused on survival and cancer recurrence rather than functional status or quality of life. Many more published studies have relied on retrospective analysis of patients who did or did not receive a treatment. Because these patients were not randomly assigned to treatment, no conclusions can be reached about the effectiveness of these interventions; these studies are not considered in this chapter.

The approach to nutritional support of the older cancer patient is further complicated by general approaches and

TABLE 20-1 Nutritional Support by Stage of Cancer in Older Persons

Stage	Nutritional Support	Evidence
Primary prevention	• Vitamin D	• Observational (cohort and case-control)
Early after detection	• Nutritional counseling	• Small clinical trials
	• VNS if malnourished	• Meta-analysis but not confined to cancer patients
	• PN if malnourished pre-operatively for head and neck cancer	• Small clinical trial
	• Treat depression	• Clinical trials but not confined to cancer patients
Tumor progression/ treatment side effects	• Disease treatment to relieve structural abnormalities • Treat mucositis	Anecdotal
Cancer-related anorexia/ cachexia	• Megestrol acetate • Corticosteroids	• Clinical trials • Small clinical trial
Prevention of recurrence	• Reduce energy from fat and increased intake of vegetables, fruits, and fiber	• Clinical trials (inconclusive)
Advanced cancer	• Palliative care	• Anecdotal

VNS, volitional nutritional support; PN, parenteral nutrition

some tumor-specific approaches. In particular, the role of nutritional support has been the focus of considerable research on head and neck and gastrointestinal malignancies. The findings of these studies may or may not be applicable to older persons with other malignancies.

In this chapter, approaches to nutritional assessment and monitoring, general approaches to nutritional support, pharmacologic appetite stimulants, and nutritional support of the patient with advanced cancer will be described, concluding with a summary of recommended care.

NUTRITIONAL ASSESSMENT AND MONITORING

Weight and Body Mass Index

Weighing the patient is easy and provides a general indication of whether the patient is getting adequate nutritional intake. Weight loss and low body mass index (BMI) have been associated with adverse outcomes in older persons. In a 4-year cohort study, the annual incidence of involuntary weight loss (defined as loss of more than 4% of body weight) among community-dwelling veterans was 13.1%. Over a 2-year follow-up period, involuntary weight losers had an increased risk of mortality (RR = 2.4, 95% CI = 1.3 to 4.4) that was 28% among weight losers and 11% among those who did not lose weight. Voluntary weight losers had a 36% mortality rate during this time.[3] Weight loss also has prognostic value among cancer patients independent of disease stage, tumor histology, and patient performance status.[4] Among community-dwelling old persons, body mass index (BMI) demonstrates a "U" shaped relation with functional impairment, with increased risk among those at the lowest and highest BMIs.[5]

In older persons, involuntary weight loss may be the presenting symptom of cancer. A case series of 306 patients with unexplained weight loss who were followed for at least 1 year reported that 38% had cancer; it also reported on blood tests (complete blood count, erythrocyte sedimentation rate, and biochemical profile) that were useful, particularly in excluding patients who had cancer. If none of these were abnormal, the likelihood ratio for a diagnosis of cancer was 0.2 (95% confidence interval 0.1-0.4).[6]

Nevertheless, the interpretation of weight as a nutritional indicator is complicated. Weight may remain stable or even increase among those who are progressively malnourished, because of other factors contributing to weight such as edema, ascites, and pleural effusions.

Depression Screening

Depression in cancer patients is a cause of anorexia and weight loss that may respond to antidepressant treatment or psychotherapy. A simple screen such as the Patient Health Questionnaire-9 (PHQ-9) (or its shorter version, the PHQ-2[7]) can be used to detect depressive symptoms.

Biochemical Measures

Serum albumin is the best-studied serum protein and has prognostic value for subsequent mortality and morbidity in community-dwelling older persons.[8,9,10,11] Because serum albumin does not fall quickly (half-life 18-21 days) in protein deprivation, it may be quite a useful indicator for chronic moderate to severe undernutrition. In contrast, proteins with shorter half-lives such as prealbumin (half-life 2-3 days) and transferrin (half-life 8-9 days) may respond to nutritional interventions more quickly and may be better for monitoring treatment.

Other Measures

Anthropometric measures such as midarm muscle circumference and skin-fold thickness tend to be less reliable in older persons.[12] Lymphocyte count, which is low (<1500 cells/mm^3) in protein-energy malnutrition, is also sometimes used as a measure but may not have independent prognostic value beyond albumin.[13]

GENERAL APPROACHES TO NUTRITIONAL SUPPORT

Nutrition Counseling

Nutrition counseling (NC) on the use of regular foods has resulted in less anorexia and better quality of life compared to nutritional supplements or ad libitum feeding in patients with colorectal cancer[14] or head and neck malignancies[15] receiving radiotherapy.

Volitional Nutritional Support

Volitional nutritional support (VNS) is defined as a "liquid formulation containing at least a nonprotein source of calories and nitrogen that is taken orally by the patient with specific instructions regarding its consumption on a scheduled basis."[2] These formulations are often used as supplements to oral diets and differ from supplements or snacks containing real food. A review of data from meta-analyses of 16 randomized clinical trials of mostly malnourished older persons (most of whom did not have cancer) indicated better survival among those receiving VNS.[2] The effects on functional status were more variable. In contrast, VNS has not been shown to have beneficial effects on mortality among patients undergoing chemotherapy or radiation therapy.

Enteral Nutrition

Enteral nutrition (EN) is defined as "the infusion of a putative complete nutrient formulation through a tube placed in the upper gastrointestinal tract."[2] In studies of patients receiving chemotherapy, surgical treatment, or radiation therapy, EN has not been beneficial. Gastrostomy tubes are associated with complications such as dislodgement, leakage with peritonitis, and aspiration.

Parenteral Nutrition

Parenteral nutrition (PN) is defined as "the intravenous provision of nitrogen and 10 kcal/kg/day of nonnitrogenous calories via either a central or peripheral venous catheter."[2] An American Gastroenterological Association technical review concluded that among cancer patients undergoing chemotherapy or radiation therapy, PN causes net harm.[16] In part, this poor risk-benefit ratio is because of parenteral nutrition's common complications of sepsis and catheter occlusions. Nevertheless, in both the United States and Europe, cancer is the most common diagnosis for which home parenteral nutrition is prescribed.

One situation in which parenteral nutrition may be beneficial is in malnourished (weight loss ≥ 10% of usual body weight) gastrointestinal cancer patients who are undergoing surgery. A randomized clinical trial indicated fewer overall complications rates among a group receiving preoperative PN for 10 days and 9 days postoperatively compared to a control group (37% versus 57%, p=0.03). Among the 40 patients aged 65 to 80 years, the trend was similar except there was no benefit on the rate of infectious complications, which occurred in 45% of treated elderly patients.[17]

When replenishing older cancer patients by means of any route, clinicians need to be alert to the possibility of precipitating the refeeding syndrome. This typically occurs in malnourished cancer patients who have had poor oral intake and then receive intravenous glucose-containing fluids, or enteral or parenteral nutrition. Symptoms occur most commonly within 2 to 4 days of refeeding and are caused by the glucose-induced acute transcellular shift of phosphate resulting in hypophosphatemia, hyperglycemia and hyperinsulinemia, which may be accompanied by hypokalemia, hypomagnesemia, and fluid retention. When serum phosphate levels drop below 0.5 mm/L, patients are at higher risk for cardiac arrhythmias, heart failure, respiratory failure, and neurologic complications such as paresthesias, delirium, muscle weakness, paralysis, and seizures. Supplementing intravenous fluids with potassium phosphate or oral phosphate and potassium may help prevent this syndrome.[18]

Pharmacologic Appetite Stimulants

Megestrol Acetate. Megestrol acetate is the most commonly used and best-studied appetite stimulant in cancer patients. A 2008 meta-analysis of patients with the cancer anorexia-cachexia syndrome concluded that megestrol acetate resulted in appetite improvement (RR 3.0, 95% CI 1.86-4.84) and weight gain (RR=1.71, 95% CI 1.24-2.36). Higher doses, 400 mg to 800 mg, were more effective than lower dosages. Slightly more than half of treated patients responded with increased appetite. However, less than one-third of patients responded with weight gain, and the effect was not statistically significant when outcomes of weight gain of at least 5% or 10% were considered.[19] The drug had no effect on survival or functional status. Megestrol (or medroxyprogesterone acetate) has also been combined with other agents including EPA, L-carnitine, and thalidomide. In a preliminary analysis of a five-arm trial treating the cancer-related anorexia/cachexia syndrome,[20] megestrol or medroxyprogesterone acetate was demonstrated to be superior to pharmacological support including eicosapentaenoic acid on outcomes of appetite, fatigue as measured by the Multidimensional Fatigue Symptom Inventory-Short Form, and quality of life as measured by the EuroQol (EQ-5D). Any potential benefit of megestrol must be weighed against potential adverse effects including thromboembolic events (e.g., deep venous thrombosis and pulmonary emboli) and adrenal suppression, which is of unknown clinical significance.

Cannabinoids. Cannabinoids have been reported to stimulate appetite. There are a variety of cannabinoids (single-extract and whole or partially purified extracts of

Cannibis sativa L.), as well as routes of their administration (oral and inhaled). In the United States, dronabinol, a synthetic delta-9-tetrahydrocannabinol (THC), and nabilone, a dronabinol analogue, are available by prescription. In a trial comparing oral THC, whole-plant cannabis extract, and placebo in treating the cancer-related anorexia/cachexia syndrome, there were no differences in appetite or quality of life among the three groups.[21] In a head-to-head comparison, megestrol was superior to dronabinol in improving appetite (75% versus 49%, p=.0001) and producing weight gain of at least 10% (11% versus 3%, p=.02); the combination of the two dugs provided no additional benefit.[22]

Corticosteroids. Corticosteroids are effective in reducing nausea and increasing appetite for a short time. However, these agents have not been demonstrated to increase weight.

Other approaches to treating cancer-related anorexia/cachexia include eicosapentaenoic acid (EPA), which is an omega-3 fatty acid that reduces lipolysis by attenuation of the stimulation of adenylate cyclase, and tumor necrosis factor-α (TNF-α) inhibitors. Neither approach has been demonstrated to improve appetite, weight, or clinical outcomes.

NUTRITIONAL SUPPORT OF ADVANCED CANCER

There is little evidence that nutritional support affects survival or quality of life in patients with advanced cancer. Nevertheless, two professional organizations have recommended nutritional support in certain circumstances. The French National Federation of Cancer Centers states that enteral or parenteral nutrition may be beneficial for patients with bowel obstruction or other sources of food intolerance but are not recommended in patients with a prognosis of less than 3 months or with a Karnofsky score of less than 50%. The Capital Health Home Parenteral Nutrition Program, in Edmonton, Canada, has established the following criteria for home parenteral nutrition: for a potential survival benefit, the duration of treatment is expected to be longer than 6 weeks, the Karnofsky score should be over 50%, and there must be a supportive home environment. In the United States, patients with advanced or terminal cancer are rarely given enteral or parenteral therapy and such treatment would not be covered under the Medicare hospice benefit.[23] Rather, management focuses on palliating symptoms in advanced cancer patients. For those who have dysphagia, approaches include:

- feedings that rely on small, frequent amounts of pureed or soft foods;
- avoiding spicy, salty, acidic, sticky, and extremely hot or cold foods;
- keeping the head of the bed elevated for 30 minutes after eating;
- treating painful mucositis, when present, with a 1:2:8 mixture of diphenhydramine elixir: 2%-4% lidocaine: magnesium-aluminum hydroxide as a swish-and-swallow suspension before meals. If the cause is candidiasis, then clotrimazole troches or oral fluconazole would be appropriate.

For advanced-cancer patients who have anorexia, patient and family education on the effects of disease progression that result in lack of appetite and weight loss may be the most important intervention. Liberalizing the patient's diet to include calorically dense foods (e.g., sweets, ice cream, alcoholic beverages) may be helpful. Symptoms of dry mouth can sometimes be alleviated by ice chips, popsicles, moist compresses, or artificial saliva.

Summary

In summary, despite the importance of nutritional status in the older cancer patient, there is scant research that nutritional support is of value, except in certain instances. The best evidence supports the following:

- Patient weights are probably the most valuable method of detecting and monitoring nutritional status in older cancer patients.
- Nutrition counseling during treatment may be valuable in patients with gastrointestinal or head and neck cancers.
- Depression is a treatable cause of weight loss in cancer patients.
- Parenteral nutrition may be beneficial in malnourished (weight loss ≥ 10% of usual body weight) gastrointestinal cancer patients who are undergoing surgery.
- In higher doses, megestrol acetate provides a modest amount of benefit toward reducing weight loss in a minority of patients with the cancer anorexia-cachexia syndrome.
- Corticosteroids may reduce nausea and provide short-term appetite stimulation but have no benefit on weight.
- Use of volitional nutritional support (oral supplements), enteral nutrition, and parenteral nutrition is not supported by current scientific data.
- For older patients with advanced cancer, the care should focus on palliating symptoms and educating the patient and family about the disease progression and prognosis.

Further research will be necessary to identify optimal nutritional support for older cancer patients and for those with specific tumors (e.g., head and neck, gastrointestinal) that particularly affect nutritional status. Nutritional approaches to prevent cancer and its recurrence are exciting but unproven strategies. For those with more advanced cancer, providing adequate nutrition in the face of tumor-related effects on appetite and loss of lean body mass remains a challenge.

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CHAPTER

21

Complementary and Alternative Medicine in the Older Cancer Patient

Lisa M. Schwartz

CASE 21-1 CASE HISTORY

J.D. is a 76-year-old woman with a history of breast cancer. She was diagnosed a little over 3 years ago with a 2.3 cm poorly differentiated infiltrating ductal carcinoma of the upper outer quadrant of the right breast. She elected to undergo a lumpectomy and sentinel lymph node biopsy. The tumor was estrogen and progesterone receptor-negative (ER/PR–) and HER-2/neu negative, the sentinel lymph node was negative, and there was some lymphovascular space invasion. She met with a medical oncologist who strongly recommended that she receive chemotherapy. The potential side effects of chemotherapy frightened her, and several months of chemotherapy would definitely interfere with her plans to cruise the Mediterranean with her newly retired husband. Her husband had worked very hard running the family business all the years that they had been married, and had promised to hand the business over to their children when he turned 75. The cruise was a fortieth wedding anniversary trip, and she was looking forward to finally spending some quality time with her husband. She declined any adjuvant therapy other than radiation and even compromised with her radiation oncologist to receive a shortened course of therapy with slightly larger doses of radiation each day, which was still an accepted course of treatment. She took a variety of "natural" remedies recommended by friends and family, which she used to maintain her general good health and boost her immune system. On her 3-year follow-up visit, her radiation oncologist appreciated a mass in the right axilla. A biopsy confirmed the presence of an ER/PR– infiltrating ductal carcinoma in an axillary lymph node. J.D. was told she needed surgery and chemotherapy or she would soon die of her breast cancer. Her feeling about the matter was that the recommended therapies would incapacitate her and she would much rather spend the time that she had left enjoying her 6-month-old and 2-year-old grandchildren. She presented to an integrative physician requesting alternative therapies for her recurrent breast cancer.

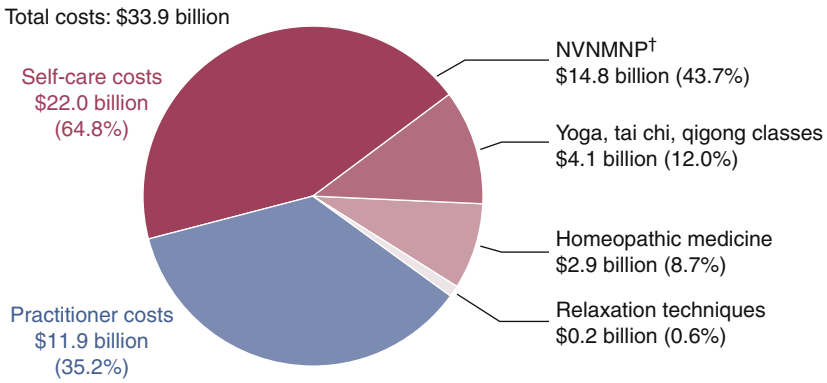
The use of complementary and alternative medicine (CAM) among the general population has grown tremendously in the last couple of decades. Eisenberg's initial report in 1993 and follow-up survey in 1997 shed light upon the number of American patients who sought out "unconventional care" (defined as therapies neither taught widely in medical schools nor generally available in most hospitals).[1-2] Those survey results revealed that in 1990, one in three patients (34%) reported using an unconventional therapy in the previous year, and by 1997, that number had increased to 42%, resulting in an estimated 629 million visits to CAM providers, which exceeded the number of visits to all U.S. primary care physicians during the same time period. According to the National Center for Health Statistics, Americans spent a staggering $33.9 billion out of pocket on CAM visits and products in 2007.[3] (Figure 21-1.)

This chapter reviews the incidence of CAM use among cancer patients, the pitfalls that may be associated with its use, and the evidence to support certain therapies during cancer treatment.

WHY DOCTORS NEED TO ASK

Primary care physicians and oncologists are very likely to have cancer patients using complementary therapies either during their active treatment or as survivors. A survey of 453 outpatients seen in the MD Anderson Cancer Center clinics between December 1997 and June 1998 showed that 83.3% had used some form of CAM.[4] A recent review of the literature revealed that between 64% and 81% of cancer survivors use vitamin or mineral supplements.[5] Gansler et al. examined the use of "complementary methods" in survivors of ten different cancer types using data from the American Cancer Society's Study of Cancer Survivors-I (SCS-I).[6] Among these 4139 cancer survivors the most commonly used therapies were as follows: prayer/spiritual practice (61%), relaxation (44%), faith/spiritual healing (42%), nutritional supplements/vitamins (40%), meditation (15%), religious counseling (11%), massage (11%), and support groups (10%).

Because women are more likely to use CAM,[7-8] it is not surprising that among cancer patients, breast or ovarian



†Nonvitamin, nonmineral, natural products.
NOTES: Percentage refer to the total out-of-pocket costs in 2007. Totaling individual self-care cost percentages is affected by rounding. Estimates are based on household interviews of a sample of the civilian, noninstitutionalized population. DATA SOURCE: CDC/NCHS, National Health Interview Survey, 2007.

FIGURE 21-1 Out-of-pocket costs for complementary and alternative medicine. Americans spent a total of $33.9 billion out-of-pocket for complementary and alternative medicine in 2007. There were also more visits to complementary medicine providers than there were to primary care physiscians.[3] *(Adapted from Nahin, RL, Barnes PM, Stussman BJ, Bloom B. Costs of Complementary and Alternative Medicine (CAM) and Frequency of Visits to CAM Practitioners: United States, 2007.* National health statistics reports; no 18. *Hyattsville, MD: National Center for Health Statistics. 2009.)*

TABLE 21-1 Reasons Patients Use CAM

Richardson[4] (cancer patients)	• A desire to feel hopeful • A belief that the therapies were nontoxic • A desire for more control in medical decision making
Barnes[7] (all patients)	• Conventional medical treatments would not help (67%) • Conventional medical treatments were too expensive (46%) • Therapy combined with conventional medical treatment would help (78%) • Suggested by a conventional medical professional (66%)
Astin[10] (all patients)	• More congruent with their own values, beliefs and philosophical orientations toward health and life
Verhoef[11] (cancer patients)	• Belief that it would work • Desire to gain some control over medical decision making • A feeling of hope in a last resort effort

cancer survivors are the most likely to use complementary therapies.[6] Between 63% and 83% of breast cancer patients use some form of complementary therapy.[9] The reasons patients give for trying CAM therapies are listed in Table 21-1.

In spite of the high proportion of patients using CAM, only a minority of them discuss it with their physicians. According to the Eisenberg surveys, 72% of patients who were using CAM did not discuss it with their physicians. A review of the literature revealed that between 31% and 68% of cancer patients do not discuss their supplement use with their physicians.[5] There are clearly barriers to communication between patients and their physicians regarding CAM therapies. Interviews with cancer patients have revealed three common themes describing these barriers: physicians' indifference or opposition to CAM use, physicians' emphasis on scientific evidence, and patients' anticipation of a negative response from their physician.[12]

COMPLEMENTARY, ALTERNATIVE, AND INTEGRATIVE: WHAT'S IN A NAME?

There is an important distinction to make between "complementary" and "alternative" medicine. The National Center for Complementary and Alternative Medicine (NCCAM) defines "complementary" therapies as those that are used in addition to conventional therapies and "alternative" therapies as those that are used instead of conventional therapies. The major categories of CAM therapies as defined by NCCAM are given in Table 21-2.

The term "integrative medicine" applies to a practice that incorporates evidence-based complementary therapies with conventional care; considers patients' beliefs about health, illness, and treatment when making recommendations; and empowers patients to participate in their health care decision-making process.[13]

One of the reasons physicians give for being reticent to use or recommend CAM is the paucity of well-conducted clinical trials involving CAM therapies. NCCAM is the branch of the National Institutes of Health (NIH) responsible for conducting research into CAM therapies and disseminating reliable information on CAM to the public. NCCAM started out in 1991 as the Office of Alternative Medicine (OAM) and its budget has grown from an initial $2 million to $128.8 million in 2010. Over $295 million was spent on CAM research at the NIH in 2009. This,

TABLE 21-2 The Major Categories of CAM as Defined by NCCAM

Whole Medical Systems	Whole medical systems are built upon complete systems of theory and practice. Often, these systems have evolved apart from and earlier than the conventional medical approach used in the United States. Examples of whole medical systems that have developed in Western cultures include homeopathic medicine and naturopathic medicine. Examples of systems that have developed in non-Western cultures include traditional Chinese medicine and Ayurveda.
Mind-Body Medicine	Mind-body medicine uses a variety of techniques designed to enhance the mind's capacity to affect bodily function and symptoms. Some techniques that were considered CAM in the past have become mainstream (for example, patient support groups and cognitive-behavioral therapy). Other mind-body techniques are still considered CAM, including meditation, prayer, mental healing, and therapies that use creative outlets such as art, music, or dance.
Biologically Based Practices	Biologically based practices in CAM use substances found in nature, such as herbs, foods, and vitamins. Some examples include dietary supplements, herbal products, and the use of other so-called natural but as yet scientifically unproven therapies (for example, using shark cartilage to treat cancer).
Manipulative and Body-Based Practices	Manipulative and body-based practices in CAM are based on manipulation and/or movement of one or more parts of the body. Some examples include chiropractic or osteopathic manipulation and massage.
Energy Medicine	Energy therapies involve the use of energy fields. They are of two types: *Biofield therapies* are intended to affect energy fields that purportedly surround and penetrate the human body. The existence of such fields has not yet been scientifically proven. Some forms of energy therapy manipulate biofields by applying pressure and/or manipulating the body by placing the hands in, or through, these fields. Examples include Qi Gong, Reiki, and Therapeutic Touch. *Bioelectromagnetic-based therapies* involve the unconventional use of electromagnetic fields, such as pulsed fields, magnetic fields, or alternating-current or direct-current fields.

From the National Center for Complementary and Alternative Medicine (http://nccam.nih.gov/health/whatiscam/overview.htm)

CASE 21-1 CASE HISTORY CONTINUED

J.D. met with an integrative physician and explained her reservations about receiving conventional care for the axillary recurrence of her breast cancer. She felt guilty about not taking the medical oncologist's advice but did not feel that he had listened to her concerns about therapy. She was anxious, depressed, and not sleeping. She was looking for a natural way to treat her cancer that she could control and which wouldn't have side effects that could interrupt her time with her grandchildren. After all, if she got chemotherapy now, she wouldn't be allowed to be around her grandchildren. Her niece had already recommended several supplements and dietary changes that she read about online and, although J.D. was heeding her niece's advice, she had doubts about the effectiveness of these interventions and her ability to continue to afford them. She also had noticed that the mass under her arm had gotten a little larger and was beginning to hurt. The integrative physician reviewed J.D.'s regimen with her including the evidence (or lack of evidence) to support each supplement's use. Ultimately, they decided that she would incorporate more soy, fruits, and vegetables in her diet; go for a 30 minute walk with her husband every day; and attend yoga and guided imagery classes at the cancer center. Her concerns and misconceptions about surgery and chemotherapy were addressed, as well as the impact these treatments would have on the time she spends with her family. She agreed to the surgery, and was encouraged to use acupuncture to manage the postoperative nausea that had been so debilitating after her first surgery.

however, pales in comparison to the amount spent on biomedical research, which, in 2003, was an estimated $94.3 billion.[14] Determining research methodologies pertinent to CAM therapies presents some obstacles as well. The challenges in conducting research on CAM therapies range from finding appropriate placebos for nonpharmacologic interventions to dismantling a whole systems practice like traditional Chinese medicine down to one well-defined intervention. The reductionist method is the standard in conventional medical research but may not be applicable to practices combining many treatment modalities as components of a comprehensive therapy. Nonetheless, there is a growing body of literature on the usefulness of some CAM therapies in the treatment of cancer patients, especially with regard to symptom management.

BOTANICALS AND NUTRITIONAL SUPPLEMENTS

Cancer patients commonly use dietary supplements, most often without the guidance or expertise of a knowledgeable practitioner. Well-intended oncologists sometimes resort to asking patients to discontinue all supplements during treatment, further diminishing a patient's sense of control over his or her own health care and promoting an attitude of nondisclosure. This lack of discourse can lead to harmful drug interactions, potentially decreasing the efficacy of some chemotherapeutic agents and radiation therapy. Opening a dialogue with patients about their supplement use helps to protect them, allows them to participate in their care, and promotes a sense of mutual respect between patient and physician. This section includes some general precautions about the use of dietary supplements; the remainder of the chapter will address some supplements and other interventions that are effective in treating common symptoms and side effects related to therapy.

COMMON ANTIOXIDANTS

- Vitamins A, C, and E
- Coenzyme Q10 (ubiquinone)
- Melatonin
- Carotenoids (alpha and beta carotene, astaxanthin, zeaxanthin, lutein, lycopene)
- Flavonoids
- Isoflavones
- Resveratrol
- Curcumin
- N-acetylcysteine
- Alpha lipoic acid
- Selenium
- Zinc

FIGURE 21-2 List of Common Antioxidants. These are some of the more common antioxidants that patients receiving chemotherapy and radiation should probably avoid.

One of the more hotly debated issues regarding the use of supplements during conventional cancer care is whether antioxidants interfere with or reduce the side effects of therapy.[15-19] Patients commonly start taking antioxidants when they are diagnosed with cancer because of the misperception that antioxidants prevent cancer and the assumption that what prevents cancer must also be good for treating cancer (Figure 21-2). In fact, there have been no large randomized controlled trials showing that antioxidants prevent cancer or reduce overall mortality.[20-21] In addition, the process of oxidation that results in the creation of free radicals is critical to the antineoplastic effects of radiation and many chemotherapeutic agents. Proponents of the use of antioxidants typically cite experimental and clinical data on tumoricidal effects, induction of apoptosis, and reduction in side effects from chemotherapy or radiation.[15] The obvious concern is that the administration of antioxidants leads to the protection of tumor cells, as well as normal cells, from oxidative damage. To illustrate this point, consider the largest randomized placebo-controlled clinical trial done examining the use of antioxidants during radiation in a group of head and neck cancer patients. In this study 540 patients were randomly assigned to receive α-tocopherol (a component of vitamin E) and β-carotene (a component of vitamin A) or placebo during radiation therapy. The patients in the α-tocopherol and β-carotene group had fewer adverse acute reactions (although no difference in quality-of-life measures), but local recurrence was 37% more likely in this group.[22] While future research may reveal antioxidants that help to mitigate treatment side effects without decreasing the efficacy of chemotherapy and radiation, the safest recommendation at present is to avoid antioxidants during treatment.[19]

Interactions with chemotherapy drugs and radiation are not the only concern in this population. The most common dietary supplement-drug interactions are with anticoagulants, cardiovascular drugs, oral hypoglycemics, and antiretrovirals.[23] These are all frequently used drugs in an aging population. Some of the more common dietary supplement-drug interactions are listed in Table 21-3, and resources for evaluating a potential interaction are given at the end of this chapter.

Another area of concern is the adulteration of botanicals and dietary supplements. One of the more egregious abuses of the public trust with regard to the safety and integrity of herbal products was the contamination of a product known as PC-SPES and its removal from the market by the Food and Drug Administration (FDA). PC-SPES was an herbal combination that was sold as a supplement to promote prostate health and was used by patients to treat prostate cancer. Preliminary trials demonstrated a decrease in PSA and testosterone with the administration of this supplement. Publicly funded, larger clinical trials were planned for PC-SPES until independent laboratories reported the presence of diethylstilbestrol (DES) in several batches of the product. Further evaluation revealed that the product was adulterated with other prescription drugs (warfarin, alprazolam, and indomethacin).[26]

This is just one example of the quality and safety issues surrounding the use of dietary supplements. The Dietary Supplement Health and Education Act of 1994 (DHSEA) required the FDA to regulate dietary supplements as foods rather than as drugs, which means that supplements do not need approval from the FDA prior to entering the market. While this ensures the availability of these products to consumers, it comes with the consequence of a lack of regulatory oversight. The FDA does have the responsibility of regulating the manufacture of dietary supplements, and as of June, 2010, all manufacturers must be in compliance with current good manufacturing practices (cGMP). Given the large number of dietary supplement manufacturers, enforcement of these regulations may be difficult.

The industry is not completely without quality control, however. Many companies undergo voluntary independent testing of their products by the United States Pharmacopeia (USP) and ConsumerLab.com. Products displaying the USP verified seal or the ConsumerLab.com mark have completed this testing and been found to be of good quality.

While many physicians may not agree with the notions of patient self-diagnosis and self-treatment that are facilitated by the availability of dietary supplements, the fact remains that the practice exists. Hence the onus is on physicians to learn at least the basic essentials of indications, side effects, and potential drug interactions of dietary supplements.

CANCER-RELATED PROBLEMS AND CAM INTERVENTIONS

The remainder of this chapter provides recommendations that any physician can utilize to help cancer patients navigate the maze of treatment, side effects, and survivorship. The recommendations that follow are evidence-based. The evidence is not always from randomized,

TABLE 21-3 Common Herb-Drug Interactions and Precautions in Oncology[24-25]

Botanical Product	Common Uses	Potential Drug Interactions and Precautions
Ginseng, American or Asian	To improve cognition, immune function, and energy; promotes blood sugar metabolism	None known but diabetics may need to monitor blood sugars due to a potential hypoglycemic effect
Black Cohosh	Menopausal symptoms	None known
Echinacea	Prevention of colds; used for immune support in cancer patients	None known; no documented interactions with immunosuppressive drugs
Garlic	Hyperlipidemia and atherosclerosis Prevention of colds	May enhance the effect of antiplatelet therapy and warfarin
Ginkgo	To improve cognition; to improve blood flow to the brain and extremities	Contraindicated in bleeding disorders; may enhance the effect of antiplatelet therapy and warfarin
Green tea	Reduce risk of cardiovascular disease and cancer	Can diminish the effect of dipyridamole; possible synergistic effects with sulindac and tamoxifen Large amounts of caffeine may increase the side effects of theophylline Antagonizes the tumorcidal effect of bortezomib (Golden 2009)
Ginger	Nausea	None known; anecdotal reports of interaction with warfarin but not proven
Kava	Anxiety and sleep	Should not be taken with alcohol, barbiturates, and other drugs with significant CNS effects Large doses may cause scaly ichthyosis
Milk thistle	Liver diseases and "cleansing"	An antioxidant; no known drug interactions
St. John's Wort	Depression	Should not be taken with prescription antidepressants; may interact with oral contraceptives, warfarin, theophylline, Indinavir, cyclosporine, digoxin Avoid alcohol Induces CYP3A4
Saw Palmetto	Prostate health, urinary outlet obstructive symptoms	None known; may cause mild nausea when taken without food

controlled trials, but it is enough to open doors to further exploration.

Nausea and Cachexia

Even with significant advances in pharmaceutical options for the treatment of chemotherapy-induced nausea, over 70% of cancer patients still report it as a problem.[27] Postoperative nausea may also be an unpleasant part of many cancer patients' experiences. Acupuncture (or a similar variation) has been shown in several studies to be useful for chemotherapy-induced and postoperative nausea. In fact, the 1997 NIH Consensus Conference on Acupuncture found that there was ample scientific evidence to support a recommendation of acupuncture for the treatment of postoperative and chemotherapy-induced nausea and vomiting.[28]

A more recent review of the literature examining trials of acupuncture point stimulation in preventing chemotherapy-induced nausea and vomiting found that acupuncture and electroacupuncture (applying an electrical current to the acupuncture needle while inserted) were significantly more effective than placebo or noninvasive forms of acupuncture point stimulation.[29]

Investigators at Duke University Medical Center examined the use of electroacupoint stimulation (slight electrical current applied through an electrode placed on an acupuncture point) in the treatment of postoperative nausea and vomiting.[30] The participants were selected from a group of patients undergoing major breast surgery and were randomized to electroacupoint stimulation, ondansetron, or sham control (electrodes placed but without stimulation). Both treatment interventions were more effective at controlling nausea and emesis than the sham control. In addition, patients in the electroacupoint stimulation group had lower pain scores. A meta-analysis of nonpharmacologic methods of treating postoperative nausea and vomiting (acupuncture, electroacupuncture, transcutaneous electrical nerve stimulation, acupoint stimulation, and acupressure) showed that these methods were as effective as antiemetics in preventing early and late vomiting.[31]

Ginger (*Zingiber officinale*) is commonly used as a home remedy for an upset stomach. Traditional Chinese medicine uses ginger to treat nausea; it has also been useful in treating pregnancy-associated nausea.[32] In a randomized controlled trial of 644 cancer patients receiving chemotherapy, ginger capsules were found to be effective at significantly reducing nausea, even in the setting of standard 5-HT_3 receptor antagonist antiemetics.[27]

Another nutritional problem commonly encountered in oncology practices is cancer cachexia. Cancer cachexia is a condition involving complex metabolic processes, as well as reduced nutritional intake. It leads to a significant reduction in lean body mass, extreme fatigue, and ultimately immobility. In part, the metabolic hyperactivity in this condition is attributed to the production of

proinflammatory cytokines. For this reason, omega-3 fatty acids as inflammatory mediators have been explored for supportive care in this condition. Several studies in pancreatic cancer patients have shown positive effects of omega-3 supplementation (especially eicosapentaenoic acid or EPA) in terms of weight gain, performance status, and quality-of-life measures.[33] A recent review of the literature on omega-3 fatty acids in the treatment of cachexia in patients with advanced cancer of the pancreas and upper digestive tract showed that supplementation with 1.5 to 2.0 grams per day of EPA and docosahexaenoic acid (DHA) resulted in improvements in multiple measures; one study actually showed a significant improvement in survival.[34-35]

Diarrhea and Mucositis

The gastrointestinal tract is often an innocent victim when it comes to the efficacy of therapeutic agents in destroying rapidly dividing cells. The loss of cells in the GI tract and bone marrow is sometimes the dose-limiting factor in administering chemotherapy or abdominal/pelvic radiation. In addition to routine supportive measures for diarrhea (hydration, small meals, avoiding fiber, and antidiarrheal drugs), patients may benefit from taking glutamine. Glutamine helps to maintain the mucosal integrity of the gut epithelium. In a randomized controlled trial of 70 patients who were receiving 5-fluorouracil (5-FU) chemotherapy for treatment of advanced colon cancer, oral glutamine at a dose of 6 grams three times a day significantly improved intestinal absorption and permeability compared to placebo.[36] Another placebo-controlled trial was done in breast cancer patients receiving cyclophosphamide, epirubicin, and 5-FU chemotherapy, with 30 grams of glutamine per day.[37] These investigators showed that glutamine lessened intestinal permeability and did not interfere with chemotherapy; however, no clinical difference was seen in diarrhea and stomatitis scores. There are also case reports that glutamine has been effective in preventing late diarrhea associated with irinotecan.[38]

Mucositis can affect up to 40% of patients receiving chemotherapy at standard doses and as many as 75% of patients receiving high-dose chemotherapy.[39] Also, despite advances in radiation therapy, mucositis is an almost universal side effect of head and neck irradiation. Ulceration of the oropharyngeal mucosa is painful, creates difficulty swallowing and speaking, inhibits adequate nutritional intake, and can lead to delays in treatment that potentially affect tumor control. Glutamine is useful in this group of patients as well. A randomized controlled trial of 326 breast cancer patients receiving anthracycline-based chemotherapy showed that glutamine in a proprietary drug delivery system (Saforis) significantly reduced the incidence of oral mucositis.[39] A pilot study in 17 head and neck cancer patients receiving radiation showed a reduction in oral mucositis with administration of a glutamine solution as an oral rinse four times a day.[40]

Xerostomia

Xerostomia, or dry mouth, is primarily caused by radiation to the head and neck region. With the development of more precise radiation treatment planning systems, better patient immobilization, and real-time imaging techniques, the incidence of permanent xerostomia has been significantly reduced, but it remains a significant quality of life issue for many patients. Acupuncture has proven to be very useful in improving salivary flow rates in patients who have received radiation to the head and neck. In one retrospective review of 70 patients with xerostomia from radiation, Sjögren syndrome, or other causes, patients received 24 acupuncture treatments; statistically significant differences were found in stimulated and unstimulated salivary flow rates compared to baseline.[41] These results were independent of the etiology of the xerostomia. At 3 years follow-up, those who had continued to receive some acupuncture treatments had significantly more salivary flow than those who did not receive additional treatment. Johnstone et al. developed a xerostomia inventory (XI) as a validated tool to help objectively measure the effects of acupuncture, as subjective measures of xerostomia are not always consistent with objective salivary flow rates. In a report on 50 patients who had received 318 treatments, 70% of patients had a response to acupuncture as indicated by improvements in the XI. Most patients required treatment every 1 to 2 months for a lasting effect; however, in 26% of the patients, the effect lasted for 3 months or more.[42-43]

Fatigue

The National Comprehensive Cancer Network (NCCN) defines cancer-related fatigue as "a distressing persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning."[44] Fatigue can be the result of treatment (surgery, chemotherapy, or radiation) or an effect of the disease itself. It is the most prevalent symptom reported by cancer patients,[45] and they often need reassurance that this is a common and expected part of their cancer journey. Patients should be screened for fatigue and referred to medical professionals experienced in dealing with cancer-related fatigue. The exact etiology is not clearly understood, and there are many related conditions including anemia, nutritional deficiencies, sleep disturbances, and emotional distress that contribute to the sensation of fatigue (Figure 21-3).

Nonpharmacologic evidence-based recommendations for dealing with fatigue include exercise and other activity enhancement (preferably under the direction of physical and occupational therapists), massage, yoga, meditation, and psychoeducational therapies aimed at stress reduction (Figure 21-4).[46-47] A recent phase II

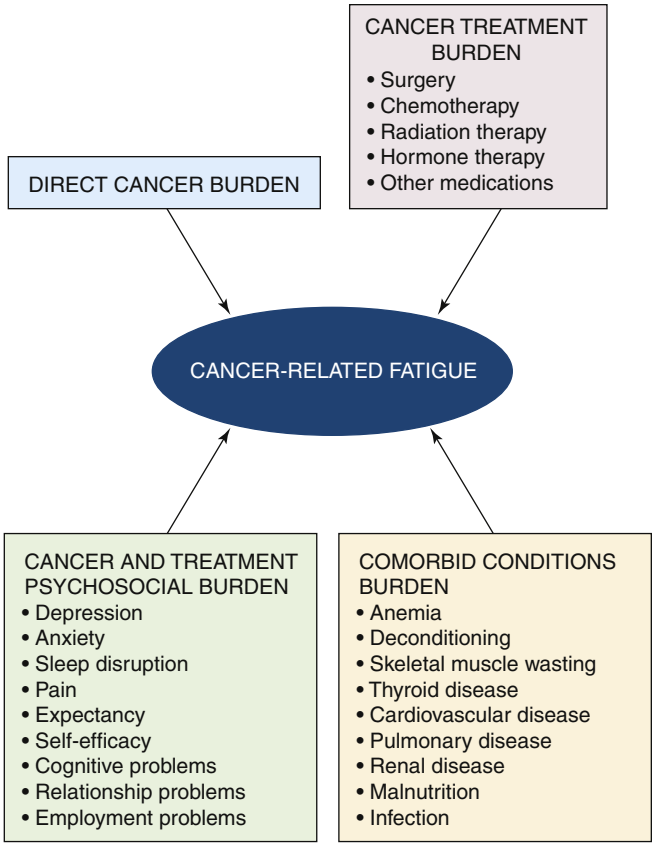


FIGURE 21-3 Related factors contributing to fatigue in the cancer patient. *(Reprinted with permission from Mustian KM, Morrow GR, Carroll JK, et al: Integrative nonpharmacologic behavioral interventions for the management of cancer-related fatigue. The Oncologist 12(suppl 1):52-67, 2007.)*

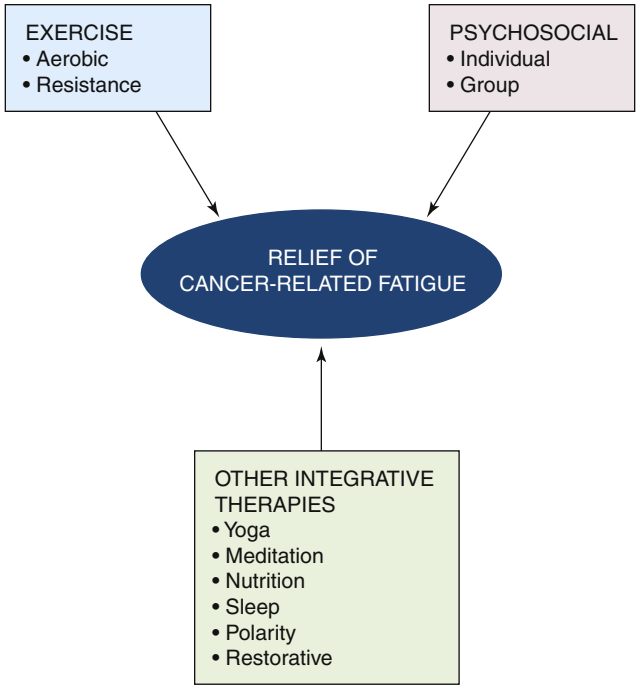


FIGURE 21-4 Nonpharmacologic interventions for cancer-related fatigue. *(Reprinted with permission from Mustian KM, Morrow GR, Carroll JK, et al: Integrative nonpharmacologic behavioral interventions for the management of cancer-related fatigue. The Oncologist 12(suppl 1):52-67, 2007.)*

study in cancer patients with persistent fatigue after chemotherapy showed that a short course (4 to 6 weeks) of acupuncture resulted in a mean improvement of 31% in the Brief Fatigue Inventory, a finding that met predefined criteria meriting it for further study. Perhaps what is most impressive about this finding is that the group of patients studied had completed their cytotoxic therapy an average of more than 2 years earlier and the fatigue had become chronic and persistent.[48]

Hot Flashes

Coping with menopausal symptoms is a fact of life for more than 50% of women and can interfere with quality of life for years after menopause.[49-50] Breast cancer patients are often faced with the symptoms of menopause around the time of their diagnosis and treatment either as a natural course of life or induced by chemotherapy and/or antiestrogen therapy. The difference in management for those who have or who are at risk for breast cancer is that hormone replacement therapy is an even less palatable treatment option than for the general population. An integrative approach to the management of menopausal symptoms in this group of patients involves advising patients about appropriate dietary, exercise, and relaxation practices first, followed by advice about nutritional supplements and botanicals. Numerous studies have shown that a healthy diet is one that is largely plant based and includes lots of fresh fruits and vegetables, lean meats, whole grains, and olive oil.[51] There is evidence that lifestyle and dietary changes can positively influence hot flashes and mood changes.[52-53] Aerobic exercise has been shown to decrease hot flashes, improve sleep, elevate mood, and generally enhance quality of life in menopausal women.[54-55] Relaxation techniques may also be helpful in alleviating some of the symptoms of menopause. These include paced respiration (controlled diaphragmatic breathing), progressive muscle relaxation, and behavioral relaxation.[56] Anecdotally, relaxation practices such as meditation, yoga, or massage have been helpful.

Soy has long been of interest to women because of the association of a lower incidence of breast cancer in populations that tend to include more soy in their traditional diets. The evidence for the effectiveness of soy in the treatment of vasomotor symptoms of menopause is inconclusive.[57-59] There are some positive trials supporting the use of soy for the treatment of hot flashes.[59-61] Its effectiveness is presumably due to the fact that the isoflavones in soy have weak estrogenic activity. Because of this estrogenic activity, there is concern about the use of soy in breast cancer survivors or women at high risk for breast cancer. The soy isoflavone genistein can stimulate the growth of breast cancer cells,[62] interfere with the inhibitory effect of tamoxifen on breast cancer cells, and

increase the expression of estrogen-responsive genes in mice.[63] These experimental findings, along with theoretical concerns, have resulted in anxiety among physicians and patients alike about the safety of soy consumption in breast cancer patients. Here it is important to make the distinction between soy consumption in food products versus concentrated soy isoflavones in nutritional supplements. In the Shanghai Breast Cancer Survival Study, 5042 female breast cancer survivors in China were followed for a median of 3.9 years, and information on various lifestyle exposures after cancer diagnosis was collected. Soy food intake was inversely associated with total mortality and breast cancer recurrence.[64] This effect was still evident regardless of estrogen receptor status or whether or not the patient was taking tamoxifen. In another study, blood levels of tamoxifen, its metabolites, and soy isoflavones were examined in an Asian-American population of breast cancer patients. Soy food intake was determined with a food frequency questionnaire. There was no evidence that soy food intake adversely affected levels of tamoxifen or its metabolites.[65] In summary, soy foods may be beneficial in breast cancer survivors with regard to total mortality and breast cancer recurrence; however, the data on the usefulness of soy foods in the treatment of hot flashes are inconclusive and further studies are warranted. Furthermore, concentrated soy isoflavones in the form of nutritional supplements should be avoided in breast cancer survivors given the potential for stimulation of breast cancer cell growth.

Black cohosh (*Actaea racemosa*, *Cimicifuga racemosa*) was once thought to have estrogenic properties but more recent evidence shows that it is actually not a phytoestrogen.[66] Numerous clinical trials have been conducted on the efficacy of black cohosh in the treatment of menopausal symptoms, with mixed results. Although these trials have varied significantly in methodologic quality, design, and type of herbal extract used, the preponderance of the evidence supports the use of black cohosh for the treatment of hot flashes,[56-57,66-67] with a recent meta-analysis showing a reduction in vasomotor symptoms by 26% with the use of black cohosh.[68]

Antiestrogen therapy is sometimes the cause of hot flashes and can lead to treatment compliance issues unless the symptoms are dealt with effectively. Although venlafaxine has been extensively used in this group of patients, it is not without its own side effects and antidepressant stigma. A recent randomized trial compared venlafaxine to acupuncture for control of vasomotor symptoms due to antiestrogen therapy. Both groups responded to treatment with a decrease in the number of hot flashes, fewer depressive symptoms, and general improvements in quality of life, with acupuncture being equivalent to venlafaxine. While the acupuncture group did not experience any adverse effects, the venlafaxine group reported 18 adverse events including nausea, dizziness, anxiety, and dry mouth. In addition, the acupuncture group reported improvement in energy, clarity of thought, and sense of well-being.[69]

Pain

Pain can be an issue at any point in the process of cancer management. It can be transient, as a result of procedures, or more chronic, because of progression of disease or complications of treatment. In older patients, who may be more sensitive to the side effects of opioids, it can be an especially difficult symptom to manage. In this population, it would be wise to optimize nonpharmacologic methods of pain control. Some of these interventions are massage, mind-body therapies, and acupuncture.

In one randomized study of women undergoing breast cancer treatment, massage significantly reduced physical discomfort compared to controls, an effect that persisted even 11 weeks after the intervention ended.[70] A systematic review of massage for palliation of cancer-related symptoms showed that pain, nausea, anxiety, depression, anger, stress and fatigue were all alleviated with massage, although the quality of the studies in general was poor.[71]

Mind-body therapies can reduce anxiety and distress, thereby reducing the perception of pain. Support groups, self-hypnosis, imagery, and relaxation techniques have been shown in smaller randomized trials to reduce cancer pain but larger, higher-quality studies are needed before definitive conclusions can be drawn.[72]

Acupuncture is widely used to control pain of various etiologies. The World Health Organization considers it effective for the treatment of cancer pain[73] and it is part of the National Comprehensive Cancer Network (NCCN) pain management guidelines as a recommended nonpharmacologic intervention.[74] A randomized controlled trial of auricular acupuncture for cancer pain was performed at a pain management clinic in a large comprehensive cancer center in France.[75] Ninety patients with chronic pain related to cancer were randomized to auricular acupuncture, placebo auricular acupuncture, or placebo auricular seeds. Auricular acupuncture resulted in a statistically significant decrease in pain compared to the two placebo groups (36% versus 2%). Acupuncture has also been examined in a randomized controlled fashion in patients who have pain and dysfunction after a neck dissection.[76] In this study, patients were randomized to acupuncture or usual care (physical therapy, analgesics, and/or anti-inflammatory drugs). Patients who received acupuncture rather than usual care had significantly better outcomes as measured by a composite score assessing pain, function, and activities of daily living. Acupuncture patients also fared significantly better with xerostomia, which was a secondary outcome measure.

In conjunction with the widespread use of aromatase inhibitors (AIs) in breast cancer, another painful scenario has emerged. A significant proportion of women taking AIs experience arthralgias that are serious enough to interfere with quality of life and medication compliance. A randomized, controlled, blinded study of true versus sham acupuncture was conducted in this group

of patients. There was significant improvement in joint pain, stiffness, physical function, and physical well-being in women who received true acupuncture.[77]

Peripheral Neuropathy

The true incidence of chemotherapy-induced peripheral neuropathy (CIPN) is undetermined because of a lack of standards regarding symptom classification, measurement, and clinical evaluation.[78-80] For neurotoxic agents, CIPN is often the dose-limiting factor in administering the drug and can result in a dose reduction or a switch to a potentially less effective regimen. The most common offending agents are listed in Table 21-4. Standard pharmacologic interventions for symptom management are generally the same as those used for peripheral neuropathy due to other causes and include various antidepressants and anticonvulsants.

Several complementary therapies aimed at prevention of CIPN have been evaluated. A recent randomized, double-blinded, placebo-controlled trial examined the use of vitamin E in CIPN prevention and found that there was no effect of the vitamin E with regard to incidence of CIPN, time to onset of symptoms, or dose reductions in chemotherapy.[81] Glutamine has been effective in reducing the incidence of CIPN in breast cancer patients receiving paclitaxel.[82] In this nonrandomized trial, patients who received glutamine 10 mg tid for four days beginning 24 hours after the paclitaxel infusion had fewer symptoms and signs of CIPN, as well as less interference with activities of daily living. The authors of this study report that they did not find any alteration in the pharmacokinetics of paclitaxel with the administration of glutamine. Further study of this intervention in a larger, randomized controlled trial is warranted.

A meta-analysis of alpha lipoic acid in the treatment of diabetic polyneuropathy showed a 24% improvement in total symptom score with the administration of 600 mg of intravenous alpha lipoic acid each weekday for three weeks.[83] Unfortunately, as alpha lipoic acid is a potent antioxidant, it should probably not be administered concurrently with chemotherapy until there is evidence that it will not interfere with the chemotherapy's effectiveness. It may, however, be useful for patients with CIPN after therapy has been completed.

TABLE 21-4 Chemotherapies That Can Cause Peripheral Neuropathy

Drugs	Malignancies for Which They Are Commonly Used
Vincristine and vinblastine	Lymphoma and leukemia
Bortezomib and thalidomide	Multiple myeloma
Cisplatin, oxaliplatin, carboplatin	Ovarian, lung, colorectal, bladder, head and neck, cervical cancers
Paclitaxel and docetaxel	Ovarian, breast, lung cancers

Although acupuncture for treatment of CIPN has only been reported in one small case series of five patients, these patients had significant relief of pain with treatment.[84] Acupuncture has been useful in the treatment of neuropathy related to diabetes and HIV.[85-88] One study also showed improvements in nerve conduction studies with acupuncture.[89]

LIFESTYLE CHANGES AND CANCER SURVIVAL

Many patients express an interest in adopting a healthier lifestyle after surviving cancer treatment.[90] Older cancer survivors are at increased risk for second malignancies, cardiovascular disease, obesity, and other comorbidities.[91] There is ample evidence that being physically active and eating a healthy diet are associated with an improved quality of life and lower risk of cancer recurrence. In a study of older long-term cancer survivors, greater amounts of exercise and better diet quality were associated with better physical quality of life outcomes and, in contrast, a greater body mass index was associated with reduced physical quality of life.[92] Breast cancer survivors with a high vegetable and fruit intake (≥5 servings per day) combined with a high physical activity level (≥9 MET-hrs/week or the equivalent of walking 30 minutes/day, 6 days/week) had a reduction in mortality of approximately 50% compared to survivors in the lowest quartiles for fruit and vegetable consumption and physical activity.[93] Holmes et al. found that the relative risk of death from breast cancer in women with hormone-sensitive breast cancer who exercised for 9 or more MET-hrs/week was half that of women who were less physically active.[94] Two separate prospective observational studies have also shown a decrease in risk of death in colon cancer survivors who exercise. The first involved 832 patients who were enrolled in a randomized adjuvant chemotherapy trial for stage III colon cancer.[95] The 3-year disease-free survival was 75% in patients who exercised for fewer than 18 MET-hrs/week compared to 84% in patients who exercised for more than 18 MET-hrs/week. The other observational group came from the Nurses' Health Study and involved 573 women with stage I-III colorectal cancer.[96] Cancer-specific and overall mortality were inversely related to physical activity levels.

In spite of this evidence, very few survivors actually meet the recommendations from the American Cancer Society regarding diet, exercise, and smoking cessation. A survey of over 9,000 survivors revealed that only 15% to 19% of patients meet dietary recommendations, 30% to 47% meet physical activity recommendations, and only 5% meet dietary, exercise, and smoking-cessation recommendations.[97] Clearly there is room for improvement in educating patients about the importance of lifestyle changes in cancer survivorship.

Summary

The management of cancer patients is complex and that complexity only increases with age. A patient's utilization of therapies that are not a part of a physician's standard knowledge base presents additional challenges. The first step in addressing those challenges is to ask about the use of dietary supplements and complementary therapies. This chapter has reviewed some of the safety issues surrounding the use of CAM, as well as the evidence to support certain therapies. Equipped with even a modest understanding of these therapies, a physician should be able to engage his patients in a dialogue about CAM use, empower them to participate in their care, and guide their choices to keep them from potential harm.

See expertconsult.com for a complete list of references and web resources for this chapter

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CHAPTER

22

The Role of Rehabilitation in the Older Patient with Cancer

Lucia Loredana Dattoma and Patricia A. Ganz

CASE 22-1

B.S. is a 77-year-old woman with a history of breast cancer, diagnosed at age 56 when she was found to have a right upper quadrant breast mass on screening mammogram, along with axillary lymphadenopathy on physical examination. She underwent right modified radical mastectomy and complete right axillary lymph node dissection. Pathologic examination confirmed right invasive cancer with lobular tubular features, well-differentiated, with six positive lymph nodes. The tumor was estrogen receptor and progesterone receptor-positive (ER/PR+). Imaging studies revealed no metastatic disease so the patient began radiation therapy and was placed on tamoxifen. She also developed right upper extremity lymphedema and arm dysfunction as a result of the surgery.

After remaining cancer-free for nearly 16 years, she presented to her physician complaining of radiating back pain, frequent falls, and increasing debilitation in the past 6 months from persistent right arm lymphedema and dysfunction. She was noted to have an elevated alkaline phosphatase and was found to have lumbar metastasis. Imaging studies revealed no further metastatic disease except for a new lesion in the left breast measuring 13 mm. She was treated with radiation to the lower back. While undergoing radiation she was offered subacute rehabilitation but refused it at first. Once she was educated on the benefits of "short-term" rehabilitation she agreed and was admitted to a skilled nursing facility (SNF), where she received physical and occupational therapy, pain management, and psychosocial therapy. Because B.S. was depressed and lacked adequate social support, she was adamant about not wanting to undergo another operation that would further debilitate her by also reducing her left arm function. After receiving radiation therapy, psychotherapy, and rehabilitation she agreed to undergo left modified radical mastectomy and modified lymph node dissection. Following her second operation, she returned to the SNF and received an additional 2 weeks of rehabilitation before she went home.

Rehabilitation services provide a multidisciplinary approach to preventive interventions that can enhance physical and psychosocial functioning; these interventions can be directed at limitations that may result from the diagnosis or treatment of cancer. The rehabilitation team begins by assessing and treating the whole patient and gaining an understanding of the individual's limitations and his or her disease process, along with an awareness of his or her leisure and vocational activities and desire to maintain a healthy and productive lifestyle, regardless of age or disease severity.

Rehabilitation plays an important role for the older adult patient with cancer. With the aging of the population, there will be an expansion of the number of older adults with cancer, as nearly 60% of all cancer diagnoses are made in patients 65 years old and older. As a result of older age, many of these patients already have multiple coexisting chronic conditions and functional limitations. Therefore it may be important to maximize overall quality of life and emphasize both mental and physical preparation prior to cancer treatment in the older adult. Anticipation of patient needs prior to treatment, as well as intervention with rehabilitation services during and after cancer treatment, may be particularly important in maintaining function and stable health when cancer co-occurs with other chronic health conditions.

As in the aforementioned case, patients who receive rehabilitation before and during aggressive cancer treatments have a higher likelihood of regaining premorbid functional status. Therefore rehabilitation promotes long-term health and wellness, whether as part of curative or palliative care.

REHABILITATION NEEDS OF THE OLDER PATIENT WITH CANCER

Treatment and technological advancements in medicine have led to prolonged survival rates in patients diagnosed with cancer. In fact, it is estimated that nearly two thirds of patients treated for a cancer will survive the initial phase. However, the sequelae of cancer treatment, whether it be surgery, hormones, chemotherapy or radiation, may lead to significant distress and hence make cancer a chronic disease. For example, B.S. developed right

upper extremity lymphedema and arm dysfunction from her initial surgery nearly 20 years ago. This impairment was physically and emotionally debilitating, leading her initially to decline additional surgical intervention for her recurring cancer in the left breast.

Rehabilitation needs of the older adult with cancer vary according to the phase of the disease, with physical needs being greatest in advanced cancer. Cancer in all age groups, but particularly in older patients, is very heterogeneous in its manifestations, biology, responses to treatment, and time course. Being aware of the rehabilitation needs of the older adult with cancer as associated with disease phase, site-specific cancer, and treatment options and/or toxicities will empower the oncologic team and patient to initiate preventive interventions in a timely fashion.

Common Related Rehabilitation Issues The most common rehabilitative problem faced by an older patient with cancer is physical. The extent of dysfunction ranges from none to severe depending on the disease, time of diagnosis, and cancer severity. Ideally, all patients who receive a cancer diagnosis should have some degree of rehabilitation at some point during the course of the disease and its treatment. The key is to identify the problem and intervene early. In many cases, being proactive and getting a physical therapy consultation before the symptoms present may improve the long-term functional outcome. The goal in obtaining physical therapy is to maximize quality of life by maintaining mobility and stamina and retaining the ability to perform basic activities of daily living. Consultation with the hospital rehabilitation service before a patient's discharge from the hospital is invaluable, and maximizes the patient's chance of maintaining physical function and independence while at home.

The next most common rehabilitative problem in cancer patients is psychosocial issues including depression, anxiety, fear, sexual difficulties, and social and interpersonal problems. Psychosocial concerns are usually not acknowledged or understood by the older adult and are frequently missed by the treating physician. Hence they are often overlooked and may remain untreated until the later part of the disease course. A needs assessment should be done at the time of diagnosis, at the time of any recurrence, or whenever the prognosis has changed or is poor, as these are the periods when patients are most likely to develop psychosocial problems and may need professional intervention. Some patients may benefit from early consultation with a psychologist or psychiatrist. Psychosocial issues will be discussed further in a later chapter. (See Table 22-1.)Sexual difficulties are another area of rehabilitative need in some older patients with cancer. Depression, fatigue, distorted body image, hair loss, surgical scars, and weight loss can lead to decreased sexual desire and feelings of unattractiveness. Some surgical interventions and radiation therapies may lead to impairment in sexual function. Sexual problems

TABLE 22-1 Common Rehabilitative Issues

- Physical dysfunction – impaired mobility, stamina, and ADL
- Psychosocial problems – depression, anxiety and fear of recurrence
- Sexual difficulties – decreased sexual desire, sexual dysfunction
- Diet and nutrition – anorexia and malnutrition, obesity and decreased physical activity

are commonly overlooked by physicians and are frequently not discussed by the patient because of fears and embarrassment. It may help the patient and partner cope with posttreatment difficulties with sex and intimacy if the physician inquires about and discusses these issues with them. This may be particularly important for cancers that involve the pelvic organs, such as prostate cancer, rectal cancer, bladder cancer, and cervical cancer, especially when both surgery and radiation are used, and when stomas may be required. Sex therapy is warranted for some patients to help them recover.

A fourth area of rehabilitative need is diet and nutrition. Older adults with cancer are at very high risk for developing malnutrition, often because many of them also have comorbidities in addition to their cancer. Patients who have excessive weight loss due to early satiety and anorexia may derive benefit from a nutrition consultation to identify problems with the current dietary pattern and aid with a supplemental plan. A speech therapy consultation may be beneficial for patients with dysphagia or difficulties swallowing. Some patients may need an appetite stimulant such as megestrol acetate, which has been shown to have some benefit in preventing cachexia. However, megestrol acetate also has many adverse effects and is contraindicated in many older patients. Mirtazepine is an antidepressant that has been used successfully as an appetite stimulant and which has a lower side effect profile. This drug may benefit a depressed patient with anorexia who is also struggling with insomnia. Patients who become very malnourished, especially those requiring prolonged periods of radiation and/or chemotherapy, may benefit from a short period of intravenous hyperalimentation or gastrostomy tube placement for supplemental nutrition.

Obesity and lack of physical activity may be a problem for some cancer patients. Weight gain after cancer and/or obesity puts patients at higher risk for recurrence of breast, colon, and prostate cancers. Maintaining physical activity and a prudent diet can be an important focus for rehabilitation.

Cancer-Specific Rehabilitation Issues

Breast CancerAs with the patient described at the beginning of the chapter, many women suffer both physically and emotionally from the diagnosis and treatment of breast cancer. Breast cancer is the most common cancer

in women in the United States. Surgical treatments for breast cancer have evolved over the past 30 years, so that modified radical mastectomies are done less frequently (about 35% of cases), and most women receive a segmental mastectomy with whole breast irradiation. Removal of the axillary lymph nodes and radiation to the axilla can lead to complications of arm swelling and difficulties with range of motion. Fortunately, these procedures are being done less frequently; the current strategy is biopsy of a "sentinel node" to determine whether the breast tumor has spread outside the breast. When this does not show spread, surgery to the axilla can be avoided. Nevertheless, there are many older women who have had mastectomies at an earlier time and who may experience problems with arm swelling and function. The most common problems that occur with the surgical treatment of breast cancer are upper extremity edema, limited mobility, pain, tingling, numbness and weakness, fatigue, difficulty lifting, and trouble following through with housework. For B.S., this significantly affected her quality of life and she nearly refused surgical intervention when her breast cancer recurred in the other breast. She underwent occupational therapy including an exercise program, elevation, and a supportive sleeve, which collectively improved her right arm function and decreased the edematous swelling. During this period, she also received psychotherapy, was started on an antidepressant, learned about the new conservative surgical options and therefore agreed to have surgery to remove the left breast cancer.

Surgical reconstruction of the breast should be offered to all women who undergo mastectomy. However, surgical reconstruction poses its own risks for the older adult and many patients either choose not to undergo this intervention or are not considered candidates for surgical reconstruction.

Other rehabilitative problems that occur with breast cancer are, as mentioned earlier, sexual and body image problems. This may be worse in patients who undergo concomitant radiation and chemotherapy, as these treatments may lead to decreased sexual desire and impaired vaginal lubrication. Sexual problems that continue or become psychologically debilitating should be addressed in sexual therapy with a qualified psychotherapist, to include the patient and her partner.

Prostate Cancer

Prostate cancer treatment can range from radical prostatectomy to pelvic irradiation or watchful waiting. Any or all of these can lead to sexual, urinary, and/or bowel dysfunction. Focus on quality of life during rehabilitation is important because patients with this disease may survive many years after their diagnosis.Sexual impairment such as erectile dysfunction or impotence occurs in the early stages of prostate cancer and is frequently caused by surgery such as radical prostatectomy or from body image distortion due to castration and/or pelvic irradiation. It remains controversial whether nerve-sparing surgeries result in a lower incidence of sexual dysfunction. As in the patient discussed here, sexual therapy may be necessary for some patients, and should include both the patient and his partner.

CASE 22-2

C.W. is a 76-year old man with a 10-year history of prostate cancer. At the time of diagnosis, his serum prostate-specific antigen level was 4.9 ng/mL and the tumor's Gleason score was 4+3. He was treated with external beam radiation therapy. He tolerated this therapy reasonably well except for some prominent urinary frequency and sexual dysfunction. This was emotionally distressing and he and his wife sought sexual therapy. His quality of life improved as a result and his PSA level dropped to 2.0 ng/mL (this suggests that the treatment did not eradicate his disease). However, his PSA level began to rise again, reaching 8.8 ng/mL about 3 years after treatment. A bone scan showed evidence of metastasis to a right seventh rib. He was placed on androgen deprivation therapy with a gonadotropin-releasing hormone analog and his PSA rapidly dropped to 3.0. He complained of worsening fatigue, urinary retention, and mid-to-lower back and right hip pain.

About 2 years later he had a third recurrence and received a series of endocrine therapies that eventually stabilized his PSA in the range of 3 ng/mL. However, he suffered a stroke with a left-sided hemiparesis about 2 years after the third recurrence and was hospitalized. As he recovered, he complained of fatigue, weakness, and depression. He was transferred to a skilled nursing facility where he underwent physical and occupational therapy and psychiatric evaluation and treatment. His prostate cancer symptoms of back and hip pain, urinary retention, and fatigue continued and his PSA rose to 9.1 ng/mL, so he was started on chemotherapy. However, after the first cycle of docetaxel chemotherapy he suffered considerable toxicity including diarrhea, stomatitis, and severe fatigue. It was at this time that he advised his oncologist that he did not wish to continue chemotherapy as it was impairing his quality of life. He agreed to undergo another course of rehabilitation before returning home to his family.

The patient in Case 22-2 suffered from urinary incontinence; however, bowel incontinence is also a very common problem following radical prostatectomies or pelvic irradiation, while urinary retention is common when watchful waiting is practiced. Bladder and bowel training programs can be helpful in coping with these impairments. Pain control, through use of sustained-release narcotic analgesics, nonsteroidal anti-inflammatory agents, and palliative radiation therapy, should be a focus in patients with advanced disease. Maintaining physical function through pain control can prolong independence and improve quality of life.

Colorectal Cancer

The rehabilitative needs of patients who undergo treatment for colon cancer often relate to bowel changes and, in the case of advanced disease, obstructing lesions. For patients with a stoma, consultation with an enterostomal therapist is critical for education and for the management of the ostomy. Unfortunately, because of the urgency of this patient's need for surgery, he did not

CASE 22-3

F. H. is a 74-year-old man with end-stage colorectal cancer who was admitted to the hospital for nausea, vomiting, and abdominal pain. He was found to have colonic obstruction from a 5 cm cecal mass and two other lesions in the distal transverse and sigmoid colon. Review of systems revealed poorly controlled low back pain that began 3 months ago; poor sleep, which he attributed to pain; and several months of impaired concentration and anorexia, with a 40-pound weight loss.

F.H. underwent complete cecal excision and colectomy with subsequent right-sided colostomy. His hospitalization was complicated by prolonged intubation because of respiratory failure and hospital-acquired pneumonia, *Clostridium difficile colitis,* and deep vein thrombosis in the left leg. Anticoagulation had to be discontinued because of retroperitoneal bleeding; an inferior vena cava filter was placed. He was eventually extubated, but required placement of a gastrostomy tube because of severe dysphagia. Because of his debilitated state, he was deemed a poor candidate for chemotherapy; he was thus transferred to a skilled nursing facility for occupational and physical therapy.

The patient's SNF course was marked by frustration that resulted from persistent pain and alternating constipation and diarrhea. Both palliative care and psychiatric services were consulted to help manage his pain and to evaluate his cognitive difficulties. His back pain was caused by a metastatic lesion at L3 and was treated with escalating doses of controlled-release oxycodone and as-needed doses of short-acting oxycodone. His psychiatric history was unremarkable. On mental status examination, F.H. was awake and amiable, but uncomfortable. He denied feeling depressed or guilty. However, he said that he was embarrassed by having colostomy and would no longer enjoy his hobbies or spending time with family or friends.

As his SNF stay progressed, he appeared more withdrawn, had no interest in learning ostomy care, refused therapy, and became less hopeful that his pain, his difficulty maintaining attention, and his bowel problems would resolve. He was started on an antidepressant and psychotherapy and eventually began cooperating with physical and occupational therapy, became receptive to ostomy education, and experienced a reduction in pain to a tolerable level.

receive ostomy information preoperatively; as a result, he suffered significant distress in the following months. His emotional difficulties adjusting to the stoma impaired his ability to learn ostomy care. It is important to encourage a patient who has an ostomy to view and touch it, so as to give him enough self-confidence and independence to provide ostomy care for himself.

Some patients also experience sexual dysfunction due to bodily distortion and function of elimination; erectile dysfunction is not uncommon in men who undergo invasive abdominorectal surgery. A patient's partner may have some difficulties adjusting to the bodily changes; this may lead to discord, feelings of lack of support, and sexual impairment. Some patients and their partners may benefit from sexual therapy.

Rectal dysfunction including constipation, diarrhea, and incontinence frequently occurs in patients who undergo excision of localized bowel tumors, hemicolectomies, or irradiation therapy. These may be improved by bowel training programs and, in seriously debilitating cases, a referral to a proctologist or gastroenterologist may be warranted.

Lung Cancer

Lung cancer is the single most common cause of cancer mortality in the United States today. This is especially true in the older adult population. The lung cancer survival rate is low, perhaps because the disease is usually at an advanced stage when diagnosed, as was true for the aforementioned patient. The significant toxicities of both chemotherapy and radiation therapy may also contribute to morbidity and mortality.

CASE 22-4

L.D. is a 71-year-old woman, formerly a heavy smoker, who was hospitalized after a 2-month history of worsening dyspnea, anorexia, and an unintended weight loss of 40 pounds. A chest x-ray revealed a left hilar mass, and ultrasound of the abdomen showed liver lesions indicating metastatic disease. Bronchoscopy was diagnostic for small cell lung cancer. She received a protocol of combination chemotherapy on a 4-week schedule. Subsequently, she suffered significant side effects of worsening anorexia, nausea, vomiting, and extreme fatigue. She spent all of her waking time in bed. She was thus referred for outpatient rehabilitation and received 1 hour of physical therapy three times per week.

At 3-month follow-up, she was found to be in complete remission. However, she presented 5 months later with worsening low back pain, dyspnea, and new-onset seizure disorder. Second-line chemotherapy and steroid therapy were initiated. She suffered significant toxicities from the chemotherapy without much clinical improvement. She became severely debilitated and developed cognitive impairment as a result of the brain metastasis. According to the patient's wishes, terminal supportive care was provided under the direction of her son who represented her interests with a durable power of attorney for health care.

Older adults with lung cancer commonly have serious pulmonary symptoms such as cough, dyspnea, fatigue and poor endurance. Addressing the issue of smoking cessation in these patients is often complex; cessation of smoking is advised to improve symptoms, but if the patient has advanced disease it may be psychologically challenging to address a lifelong addiction. In addition, chemotherapy and radiation treatments may compromise lung and cardiac function, leading to further exacerbation of symptoms. There may also be underlying coronary artery disease that preexisted the cancer diagnosis and which may be exacerbated by cancer therapy. Some patients will require supplemental oxygen for poor oxygenation and/or anxiety-related disorders. As described in Case 22-4, quality of life is often compromised by rapidly worsening disease and from the toxicities of chemotherapy.Patients with lung cancer experience greater severity of symptoms, physical distress, and emotional

TABLE 22-2 Cancer-Specific Rehabilitation Issues

- Breast cancer – Lymphedema, arm dysfunction, fatigue, therapy toxicities, sexual difficulties, body image problems, psychosocial
- Prostate cancer – Sexual, urinary, and bowel dysfunction; therapy toxicities;compromised quality of life; psychosocial.
- Colorectal cancer – Ostomy care, body image problems, sexual dysfunction, therapy toxicities, psychosocial
- Lung cancer – respiratory dysfunction, cardiovascular compromise, fatigue, therapy toxicities, psychosocial

distress than other cancer types. Low physical reserve prior to treatment is common. Often these patients are of lower socioeconomic status and may not have the supportive resources of more affluent patients. Subacute and outpatient physical and occupational therapy may be necessary in these patients and, for better results, should be initiated prior to the first cycle of chemotherapy and continued throughout the treatment course. It is advisable that psychotherapy and pharmacotherapy be initiated early in the diagnosis and treatment process given the aggressive nature and course of lung cancer. It is also wise to get pulmonary and cardiology consultants to work with the patient and his or her physicians; they can aid with the cardiopulmonary deterioration that accompanies lung cancer and its treatment course. (See Table 22-2.)

LATE EFFECTS AND REHABILITATION

The older adult with cancer is less likely to survive cancer than the younger adult. This is perhaps due to age and comorbidities. However, the few older adults that can be considered cancer survivors are at risk for suffering many different late effects. The late effects are usually a result of cancer treatments such as surgery, chemotherapy, and irradiation therapy.

To provide some examples: surgery for abdominal or pelvic cancers may lead to small bowel obstruction years later from surgical adhesions; chemotherapy agents such as doxorubicin can lead to cardiac problems; irradiation can lead to injury of soft tissue organs such as the bladder, causing a secondary cancer or bladder dysfunction.

Medical problems that develop secondary to a primary therapy can be treated with rehabilitation. Older patients with a history of cancer who develop cardiopulmonary dysfunction caused by chemotherapeutic agents benefit from physical therapy either in an outpatient or subacute setting, depending on the severity of the disease and its acute exacerbations. In addition, bladder dysfunction can be treated with a bladder training program and pelvic exercises.

Rehabilitation can play an important role in preventing and treating most late effects caused by cancer treatment. Rehabilitation for secondary cancers for older patients should be treated in the same way as rehabilitations for primary cancers, as discussed in this chapter.

BARRIERS AND POTENTIAL INTERVENTIONS FOR SUCCESSFUL REHABILITATION

Like all treatments, rehabilitation also faces its own barriers. Like the patient described in Case 22-1, if an older patient receives a new diagnosis of cancer during a hospitalization, when she is offered subacute rehabilitation while undergoing treatment such as irradiation therapy, she refuses because of the new found fears that surround her diagnosis and its current treatment. She is unaware of the debilitating effects of radiation and chemotheraphy and therefore is unable to foresee her immediate need for physical and psychological rehabilitation. Her rehabilitation treatment leads to a stay in a skilled nursing facility, heightening her anxiety. When patients learn that SNF is a glorified name for a nursing home, they may adamantly refuse to go, because of the notion that nursing homes are for old, demented, and neglected patients. In addition, many perceive nursing homes as providing poor care. It may be beneficial to let patients know that nursing homes have two kinds of patients: the rehabilitation patient and the long-term care patient. The focus for the rehabilitation patient is short-term physical and occupational therapy, while the focus for the long-term care patient is making the SNF a safe home. It can also be helpful and empowering to encourage a patient to do his or her own research on local nursing homes and to check their rates. Lastly, encourage patients and families to tour potential SNFs so as to find the place where they will feel most at home.

Other barriers to rehabilitation options are adjustment and depression. Adjusting to the diagnosis of cancer at an advanced age leads to feelings of denial. Denial is one of the stages of grief and, if rehabilitation is offered during this stage, the patient is likely to decline. Low motivation and depression leads to poor participation with any type of rehabilitation; this can prove detrimental and lead to a downward spiral.

WHERE REHABILITATION CAN OCCUR

While many people think of substance abuse when they hear the word "rehab," rehabilitation therapy can take many forms. Rehabilitation can occur in several different settings depending on disease severity, duration of necessary therapy, insurance benefits, and patient preference. However, what is common among all forms of rehabilitation is that they include a multidisciplinary team consisting of a doctor, a nurse, and a therapist. There may be multiple therapists involved in the care of a single patient as the patient may require occupational, physical, speech, and/or psychosocial therapy.

Outpatient rehabilitation is less structured than inpatient or residential facilities. It indicates that a patient is

well enough to leave the hospital and offers more continuity with daily living. The patient's physician is also confident that the patient is likely to complete a rehabilitation program on an outpatient basis. The number of sessions depends on the situation. Some patients attend rehabilitation once a day or multiple times per day, while others may attend outpatient rehabilitation once to three times per week. Outpatient rehabilitation is effective for cancer patients who would like to maintain their premorbid function while undergoing cancer therapy.

Inpatient rehabilitation takes two forms: subacute and acute rehabilitation. The difference between the two is the ability of the patient to participate in intensive physical or occupational therapy. Acute rehabilitation requires a patient to work 3 hours per day, 7 days a week. Usually these patients are medically stable, for example a premorbidly high-functioning stroke patient with minimal residual weakness. Generally, acute rehabilitation is not effective for cancer patients as they can be significantly debilitated and many are unable to sustain an intensive therapy program.

Subacute rehabilitation requires inpatient care for 1 to 2 hours of physical and/or occupational therapy per day 5 to 6 days a week. These therapy sessions may be divided for improved patient participation. Subacute rehabilitation is generally offered by skilled nursing facilities, better known as nursing homes. Patients in this setting may also benefit from speech and psychosocial therapy, and may be able to obtain additional treatments such as dental, optometric, and podiatric care.

Patients who qualify for subacute rehabilitation are those who need short-term rehabilitation, are motivated, and have a reasonable potential to meet their rehabilitative goals. The older adult cancer patient is at very high risk of developing debility during the course and treatment of the disease. Therefore, this patient would benefit from subacute rehabilitation either before initiating aggressive cancer therapy or throughout the treatment course to prevent a severe debilitating event. In addition, older cancer patients who become severely debilitated and deconditioned from a prolonged hospital course or surgical intervention are also good candidates for subacute rehabilitation.

Summary

Rehabilitation plays an important role in the care of the older adult with cancer. Rehabilitation needs of the older adult with cancer vary according to the phase of the disease. These needs vary from physical dysfunction to malnutrition to sexual impairment to psychosocial issues. Ultimately, the importance of rehabilitation of an older patient with cancer is its potential to minimize treatment exacerbations, improve overall quality of life, and maintain physical function. Hence, whatever a patient's diagnosis or course of treatment, it is important for his or her physician to consider rehabilitation as a preventive and/or concomitant treatment to maximize the patient's quality of life.

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CHAPTER

23

Surveillance

Janet Pregler

As defined by the Institute of Medicine, surveillance in the context of the treatment of cancer survivors encompasses three elements: surveillance for cancer recurrence, surveillance for second cancers, and surveillance for medical and psychosocial late effects of cancer treatment.[1] In the care of the elderly, the approach to surveillance should be considered in the overall context of the health of the patient. As an example, active surveillance for cancer recurrence and second cancers may not be appropriate in patients whose comorbidities (e.g., moderate to severe dementia, end-stage chronic obstructive pulmonary disease) make further cancer treatment impossible or inadvisable. For these patients, the emphasis should be on initiating timely and appropriate palliative treatment if symptoms of cancer recurrence develop.

This chapter will discuss surveillance in the context of the treatment of cancer survivors who are considered to be in remission or cured, with an emphasis on cancers commonly encountered among the elderly. The strategies discussed presume that the overall health of the patient is such that active surveillance for cancer recurrence and second cancers is of potential benefit. Specific strategies and guidelines are reviewed for survivors of common cancers among the elderly, including breast, prostate, and colon cancer.

CASE 23-1

A 66-year-old woman presents for preventive care. Her past medical history is significant for stage 1 breast cancer diagnosed by mammography 2 years previously. The tumor was estrogen and progesterone receptor-positive and HER-2/Neu negative. She was treated with lumpectomy with sentinel node evaluation and radiation therapy. Her current medications include an aromatase inhibitor. She asks the following questions: (1) What follow-up tests do I need? (2) Should I have an annual breast MRI? (3) Should I be tested for the BRCA gene?

CASE 23-2

A 72-year-old man presents for preventive care. He underwent radical prostatectomy at age 60 for prostate cancer. His PSA is now undetectable. He asks: (1) How often do I need PSA testing? (2) Do I need to see a urologist on a regular basis?

GENERAL PRINCIPLES OF SURVEILLANCE

Surveillance strategies should be guided by available evidence, when possible. Although randomized trials have addressed many important surveillance issues for common cancers, published surveillance strategies are based partly on expert opinion.[2,3,4] An important element of performing surveillance in cancer patients who are free of disease is ensuring that other, unrelated medical issues or problems, as well as non–cancer-related preventive measures, are not overlooked. This is particularly relevant in the elderly, who frequently suffer from comorbidities that are unrelated to cancer.

Asymptomatic cancer survivors are often followed clinically on a regular basis for indefinite periods by medical, surgical, and/or radiation oncologists In recent years, there has been recognition that a "one size fits all" approach to selecting the appropriate clinician to perform follow-up of cancer survivors is not appropriate. Important issues to consider in determining which clinicians should provide surveillance for disease-free survivors include balancing access to appropriate expertise with overall accessibility, affordability, and coordination of care. Although more research is needed, available evidence suggests that well-trained generalists are as capable as oncologists of performing surveillance, and that nurses working with oncologists also provide high quality surveillance care.[3,4]

Because all elderly patients have significant preventive health needs, elderly cancer patients who are cancer-free should have a primary care clinician as part of their health care team. For many patients, once treatment is completed, surveillance may be effectively performed by the primary care clinician, with consultation with the oncologist on an as-needed basis. Elderly patients at high risk of recurrence may be best served by co-management by an oncologist and a generalist or geriatrician. Co–management may also be indicated for elderly patients who have a high likelihood of complications from therapy, particularly early in their posttreatment course. Co–management should also be available should the patient, the generalist or geriatrician, or the oncologist feel it is in the patient's best interest. Specialized survivorship clinics may be appropriate for some patients. Guidelines tools

(described later) exist to assist physicians in performing evidence-based surveillance for patients who have been treated for common cancers.

Testing for recurrent disease should be performed proactively if recurrence can be treated for cure. Examples include serial PSA testing in prostate cancer patients, examination and mammography of preserved breasts in breast cancer patients, and computed tomography (CT) scanning to detect liver metastases in high-risk colon cancer patients. Randomized trials have not shown either survival or quality-of-life benefit for strategies that test for incurable disease before patients are symptomatic, even though such strategies may identify disease before it is clinically apparent.[2,4] For this reason, performing laboratory or radiological tests to detect asymptomatic metastatic disease that is incurable is not recommended. As an example, performing "routine" bone scans and liver-associated enzyme tests in asymptomatic breast and prostate cancer survivors is not recommended.[3,4]

Surveillance for second primary cancers is performed when such cancers are frequent. As an example, the absolute incidence of contralateral breast cancer in breast cancer survivors is 0.5% to 1% per year. Annual screening mammography is therefore recommended.[5] Appropriate genetic testing is indicated to identify cancer syndromes where enhanced screening and/or other preventive measures to prevent second cancers are available. Research suggests that screening and interventions are beneficial for such patients.[2,3] Because genetic testing has only recently been widely performed, it is important to ascertain the family history of all cancer survivors, including those whose treatment was remote, to identify those who may benefit from genetic testing.

Surveillance for medical and psychosocial aftereffects of treatment is often overlooked after the initial treatment is completed. All cancer survivors should have regular contact with a physician who accepts responsibility for this aspect of care. Long-term medical effects are treatment-specific; the physician responsible for identifying complications of treatment must therefore be informed of the treatment the patient received.

Patient education is an important element of surveillance. Patients should be informed of current recommendations for surveillance, as well as signs and symptoms of recurrence and late treatment effects. Physicians performing surveillance of medical and psychosocial effects should be aware of community and peer resources for their patients.

Recently, the Institute of Medicine has promoted the concept of a "survivorship care plan." A survivorship care plan provides a comprehensive summary of care and recommended follow-up in written (and, ideally, electronic) form, is clearly and effectively explained to the patient at the completion of active therapy, and is communicated to all members of the patient's health care team.[1]

SURVEILLANCE ISSUES FOR CANCERS WHERE SURVIVORS ARE COMMON AMONG THE ELDERLY

Breast Cancer

There are over two million breast cancer survivors in the United States.[6] Most of these women will die of causes unrelated to their breast cancer diagnosis. The risk of breast cancer increases with age, making breast cancer a common diagnosis among elderly women. Treatment usually consists of surgical resection of the cancer by lumpectomy or mastectomy and sentinal lymph node biopsy. Patients with positive lymph node biopsy may undergo lymph node dissection. Adjuvant therapy includes radiation therapy of the affected breast for patients treated with lumpectomy, and chemotherapy and/or hormonal therapy depending on the characteristics of the tumor. Commonly used chemotherapeutic agents include cyclophosphamide, methotrexate, fluorouracil, doxorubicin, and paclitaxel in various combinations, and trastuzumab. Hormonal agents include aromatase inhibitors (anastrozole, letrozole, and exemestane), and selective estrogen receptor modulators (tamoxifen).[7]

Surveillance for Cancer Recurrence. Recommendations for surveillance for recurrence among breast cancer survivors are mainly based on the results of large clinical trials performed in the late 1980s and early 1990s that randomized women to either intensive or conservative follow-up strategies. Both groups underwent periodic history and physical examination and mammography. The intensive follow-up groups in addition underwent periodic laboratory testing including both blood and radiological tests. Although women followed with batteries of tests had recurrences detected, on average, 3 months earlier, there was no difference in survival between groups after 10 years of follow-up, and satisfaction with care was identical in the two groups.[8,9,10] Although additional methods of early detection of distant recurrence, such as positron emission tomography/computed tomography (PET/CT) scanning and serological tumor marker testing, have become more widely used since the 1990s, the availability of these tests has not changed expert opinion that such testing is not beneficial.[3]

Surveillance for breast cancer recurrence focuses on the use of physical examination and mammography in preserved breasts to detect local recurrences, which are potentially curable, at an early stage. Surveillance for distant recurrence, which is incurable, is accomplished by history and physical examination, with additional testing as indicated. It is important that women be informed of the signs and symptoms of recurrence, because palliative treatment may be delayed if symptoms such as musculoskeletal pain or cough are not recognized as cancer-related. American Society of Clinical Oncology guidelines for surveillance in breast cancer are summarized in Table 23-1.

TABLE 23-1 Summary of Frequently Cited Recommendations for Follow-up for Common Cancers *(Assumes Patient is a Candidate for Further Therapy)*

Type of Cancer	Organization	Summary Recommendations
Breast	ASCO	History and physical examination every 3-6 months for 3 years, every 6-12 months for 2 years, then annually*
		Mammography 6 months after radiation therapy (if breast preserved), then annually
		Genetic (BRCA) testing when indicated (Table 23-2)
		Specifically NOT recommended in asymptomatic patients who lack other indications: CBC, chemistry panels, tumor markers (CEA, CA 15-3, CA 27.29), bone scans, liver ultrasounds, CXR, CT scans with or without PET, breast MRIs
Colon	ASCO	Colonoscopy 3 years after operative treatment, and then every 5 years if normal; flexible proctosigmoidoscopy every 6 months for 5 years for rectal cancer patients who have not been treated with pelvic radiation
		History and physical examination every 3-6 months for 3 years, every 6-12 months for 2 years, then at discretion of the physician for patients diagnosed with stage II or III colorectal cancer
		CEA measurement every 3 months for 3 years for patients diagnosed with stage II or III colorectal cancer
		CT of the chest and abdomen annually for 3 years for patients at high risk of recurrence†
		Specifically NOT recommended in asymptomatic patients who lack other indications: CXR, CBC, liver function tests
Prostate	National Comprehensive Care Network	PSA measurement every 6-12 months for 5 years, then annually
		Digital rectal exam annually‡

See references 2, 3, 23.
ASCO, American Society of Clinical Oncology; CBC, complete blood count; CXR, chest x-ray; CEA, carcinoembryonic antigen; PSA, prostate-specific antigen
*Includes patient education regarding symptoms of recurrence and "regular gynecological follow-up"
†Not rigorously defined. Includes stage III patients, some stage II patients with adverse risk factors
‡History and physical examination is recommended for patients at high risk of recurrence

Surveillance for Second Cancers. Compared to women who have not had breast cancer, breast cancer survivors have a two to six times greater risk of developing breast cancer in the contralateral breast. Physical examination and mammography are recommended to detect second cancers at an early stage. Unfortunately, studies have shown that many elderly breast cancer survivors do not receive appropriate mammographic screening. In one recent national study, over 30% of elderly breast cancer survivors did not receive recommended screening, despite being enrolled in integrated health care systems.[11]

Magnetic resonance imaging (MRI) with gadolinium has been shown to have increased sensitivity compared to mammography in women at highest risk for breast cancer, including women with BRCA mutation or equivalent risk. However, screening MRI is not currently recommended for women who, like most breast cancer survivors, do not have a lifetime risk of primary or recurrent cancer of 20% or greater[12] Lack of specificity of screening MRI continues to be a problem, with 25% or more of subjects in studies of screening MRI requiring additional imaging to further define abnormalities, the vast majority of which are benign.[13] The role of screening MRI continues to be studied.

Recently, increasing emphasis has been placed on identifying breast cancer survivors whose family history identifies them as being at high risk for carrying a BRCA gene. American Society of Clinical Oncology recommendations for selecting breast cancer survivors for BRCA testing are summarized in Table 23-2. Breast cancer survivors with the BRCA gene have a risk of developing ovarian cancer of 1.4% per year, which is ten times the rate observed in breast cancer survivors without the BRCA mutation. They also have a risk of developing contralateral breast cancer of over 5% per year.[14] These risks accrue over the patient's entire life, so otherwise healthy elderly women should be considered for testing as part of a strategy to prevent future cancers. For elderly women for whom genetic testing might not be indicated because of comorbidities, testing may still be indicated if the patient wishes to obtain genetic information to inform family members of the potential for genetic risk. In case-control cohort studies, prophylactic salpingo-oophorectomy reduces subsequent ovarian cancer risk by 90%.[15] Many women also choose prophylactic mastectomy. For BRCA-positive women who do not elect prophylactic mastectomy, annual screening MRI of the breasts with gadolinium is recommended.[12] The costs of genetic testing, prophylactic surgery, and screening MRI are generally included in insurance coverage for patients who meet published indications.

Late Medical and Psychosocial Effects in the Elderly. Fortunately, advances in surgical treatment have reduced the number of breast cancer survivors with severe lymphedema. However, a significant number of

TABLE 23-2 Criteria for Referral of Breast Cancer Survivors for Genetic Counseling for BRCA Gene Testing

Ashkenazi Jewish heritage
Personal history of bilateral breast cancer
Personal history of ovarian cancer
First- or second-degree relative with ovarian cancer at any age
First-degree relative with a history of breast cancer diagnosed before age 50
Two or more first- or second-degree relatives with breast cancer diagnosed at any age
Relative diagnosed with bilateral breast cancer
Male relative diagnosed with breast cancer

Adapted from Khatcheressian JL, Wolff AC, Smith TJ, et al. American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol. 2006 Nov 1;24(31):5091-7. Epub 2006 Oct 10.

women still undergo lymph node dissection, and late presentation of lymphedema continues to occur. Patients are generally advised to avoid compression, venipuncture, and trauma to the arm ipsilateral to lymph node dissection. All patients who have undergone axillary lymph node dissection should be aware that they should report swelling to their clinician. Elevation and the use of a lymphedema sleeve are the usual treatments. Although patients have often been counseled to avoid weight lifting with the affected arm, a recent study suggests that exercise, including moderate weight lifting, may be beneficial in preventing or ameliorating lymphedema.[7,16]

Elderly women who were taking estrogen prior to their breast cancer diagnosis may develop hot flashes when estrogen is stopped. Treatment with aromatase inhibitors and tamoxifen are also associated with hot flashes. Selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine reuptake inhibitors (SNRIs), and gabapentin are effective interventions to treat vasomotor symptoms. SSRIs are generally avoided in patients taking tamoxifen because SSRIs may alter tamoxifen metabolism in some women, rendering it less effective. Vaginal dryness and dyspareunia may be treated with nonhormonal vaginal moisturizers or low-dose intravaginal estradiol (some experts recommend using intravaginal estradiol with caution).[5,7]

Women treated with aromatase inhibitors are at risk for treatment-associated arthralgias and musculoskeletal pain. Musculoskeletal symptoms also occur with tamoxifen treatment but less frequently. Imaging should be considered to evaluate for possible metastatic disease. Medical management with acetaminophen or other pain medications may be considered. Nonsteroidal anti-inflammatory drugs are avoided in the elderly, when possible, because of an enhanced risk of bleeding complications. Consideration of change or cessation of adjuvant treatment is sometimes unavoidable.[5]

Breast cancer survivors are at high risk of osteoporotic fracture. All breast cancer survivors should have adequate intake of calcium (1200-1500 mg daily) and Vitamin D (1000-2000 IU daily), and have bone densitometry performed at age 65 and each 5 years thereafter, or more frequently if indicated by low bone mineral density or other risk factors. Adjuvant treatment with aromatase inhibitors places patients at very high risk of fracture. For this reason, patients treated with aromatase inhibitors should have bone densitometry performed at initiation of therapy, and annually while receiving therapy. Bisphosphonate therapy is the preferred treatment of osteoporosis in breast cancer survivors.[17]

Patients who undergo radiation of the left chest wall are at increased risk of cardiovascular disease. The usual strategies to reduce cardiovascular risk, including screening and treatment of hypertension, diabetes, and hypercholesterolemia, as well as promotion of a healthy lifestyle including exercise, weight maintenance, and healthy diet, are recommended. Patients who receive treatment with anthracyclines or trastuzumab are at risk of congestive heart failure. No effective prophylaxis is known. Patients should be monitored and, if congestive heart failure develops, they should be treated according to the standard medical protocols.[7]

Patients treated with tamoxifen are at increased risk of uterine cancer, venous thrombosis, and cerebrovascular disease. Vaginal bleeding should be promptly evaluated by endometrial biopsy.

Cognitive dysfunction, depression, fatigue, and weight gain are all commonly reported in breast cancer survivors and they should be diagnosed and treated as per the usual strategies. Symptoms of cognitive dysfunction and fatigue should be fully evaluated in the elderly to ensure that they do not represent unrelated comorbid processes (such as Alzheimer disease, hypothyroidism, or other systemic disease).[5]

Prostate Cancer

Prostate cancer is the most common cancer in American men. Of the 10 million cancer survivors in the United States, 18% are survivors of prostate cancer. Treatment modalities include radical prostatectomy, external beam radiotherapy, and permanent (low-dose) brachytherapy. Active surveillance (close monitoring of men with prostate cancer with curative treatment offered only to those who fit certain criteria) and watchful waiting (management of men medically unsuitable for curative treatment consisting of initiation of palliative treatment for symptoms) are also strategies for management of prostate cancer. Patients with disease that is at very high risk of recurrence may be treated with androgen-deprivation therapy in addition to other modalities. These strategies will not be discussed further in this chapter. Recurrence (defined by elevated serum prostate-specific antigen [PSA] after initial treatment) is relatively common, ranging from 10% in those with low-risk cancers to over 60% in high-risk patients. Within 10 years of initial treatment,

10% to 20% of men with high-risk clinically localized prostate cancer die of the disease.[18]

Surveillance for Cancer Recurrence. The cornerstone of monitoring for cancer recurrence is serial PSA measurement. There is marked variation among various guidelines groups as to the recommended frequency of PSA measurement, which reflects the lack of randomized, controlled trial data on this topic. In general, testing is advised no more frequently than every 3 months, with many groups endorsing longer intervals after patients have been disease-free for a specified length of time. The role of digital rectal examination (DRE) is controversial. Some groups recommend it only if the PSA is judged to be abnormal. Others recommend annual examination. Guidelines from the National Comprehensive Cancer Network are summarized in Table 23-1.

Late Medical and Psychosocial Effects in the Elderly. Erectile dysfunction is reported by up to 80% of prostate cancer survivors. Erectile function may improve with time after prostate cancer surgery, but generally declines with time after radiation treatment. Phosphodiesterase inhibitors are effective in improving erectile dysfunction in up to 75% of men who have undergone nerve-sparing radical prostatectomy, as well as men who have undergone radiation therapy. Elderly men are less responsive to phosphodiesterase inhibitor treatment compared to younger men. Intraurethral and intracorporeal alpostadil is offered to men who do not respond to phosphodiesterase inhibitors, and is useful for men who have received all types of treatment, including those who had non–nerve-sparing treatment. In studies, about half of men show benefit.[19,20]

Urinary incontinence is reported by 10% to 20% of prostate cancer survivors. Urinary continence improves for up to a year after surgery. Urinary incontinence is treated with pelvic floor exercises, behavioral modification, and weight loss. Electrical stimulation for bladder retraining, periurethral collagen injection, and surgery to place an artificial sphincter or bulbourethral sling are sometimes recommended.[20]

Additional side effects in men treated with radiation therapy and brachytherapy include hematuria, cystitis, bladder contracture, urethral stricture, rectal bleeding, rectal ulceration, rectal/anal stricture, and chronic diarrhea. All are uncommon. Patients should be specifically asked about these complications, and treated or referred to specialists for treatment. Because these side effects are often associated with psychosocial distress, screening for depression is recommended by some experts.[4,20]

Colon Cancer

Colorectal cancer is a disease of the elderly. Two thirds of invasive colorectal cancers are diagnosed in persons older than 65 years. In persons older than 75 years, colorectal cancer is the most common cancer diagnosis. There are over 1 million survivors of colorectal cancer in the United States.[1] Treatment generally consists of surgical resection, followed by adjuvant 5-fluorouracil, leucovorin, capecitabine, oxaliplatin, or irinotecan in various combinations for patients with high-risk stage II or stage III disease.[21]

Surveillance for Cancer Recurrence. According to current guidelines from the American Society for Clinical Oncology (Table 23-1), surveillance should include a history and physical examination, serial colonoscopy, and, for patients with rectal cancer who have not been treated with pelvic radiation, flexible proctosigmoidoscopy at frequent intervals. Serial carcinoembryonic antigen (CEA) testing is recommended for patients who are candidates for surgery or chemotherapy. Because several studies have shown survival advantage for colorectal cancer survivors with resectable metastases in the liver and lung, computed tomography of the chest and abdomen is recommended annually for three years for patients at high risk of recurrence, usually defined as those with node-positive malignancies, if the patient would otherwise be a candidate for resection. Chest x-rays, complete blood counts, liver-associated enzyme tests, and other molecular or cellular marker tests are not recommended at present.[2]

Surveillance for Second Cancers. In addition to serial colonoscopy as recommended for surveillance for cancer recurrence, colon cancer survivors should be assessed to determine whether testing for Lynch Syndrome (hereditary nonpolyposis colon cancer) is indicated. Experts recommend patients with Lynch Syndrome undergo colonoscopy every 1 to 2 years.

Patients with Lynch syndrome are also at risk for uterine, urological, and additional gastrointestinal malignancies. For women, prophylactic total abdominal hysterectomy and bilateral salpingo-oophorectomy may be of benefit. Enhanced surveillance for urological and upper gastrointestinal malignancies is also recommended by some experts.[22] Criteria for Lynch Syndrome testing in patients with colon cancer are listed in Table 23-3.

Late Medical and Psychosocial Effects in the Elderly. Long-term colorectal cancer survivors do not differ from healthy controls in terms of physical functioning. Advanced age and lower income are associated with lower levels of function. Long-term effects include fatigue, pain, and diarrhea. Bowel symptoms are more frequent among rectal cancer survivors. Although negative body image is more common among survivors with ostomies, as are symptoms of diarrhea and cramping, overall quality of life, social functioning, and activities of daily living do not appear to be permanently affected. Depression, however, is relatively frequently reported. Some experts recommend screening for depression in colon cancer survivors.[21]

Over 90% of patients treated with adjuvant oxaliplatin develop peripheral neuropathy during active therapy. However, only about one in 10 patients reports persistent symptoms after completion of treatment. Such

TABLE 23-3 Recommendations for Testing to Identify Patients Who May Have Lynch Syndrome (Hereditary Nonpolyposis Colon Cancer)

1. Patients should be offered genetic counseling and tumors should be tested for microsatellite instability when one or more of the following exist:
   - Colorectal cancer in patients younger than 50 years.
   - Colorectal cancer with suggestive histology including tumor-infiltrating lymphocytes, Crohn-disease–like lymphocytic reaction, mucinous or signet-ring differentiation, or medullary growth pattern in patients younger than 60 years.
   - Multiple colorectal cancer tumors, or colorectal cancer diagnosed in patients with a history of another tumor associated with Lynch syndrome (endometrial, stomach, ovarian, pancreatic, uterine, renal pelvic, biliary tract, brain, or small bowel cancer, or sebaceous adenomas or keratoacanthomas) in patients of any age.
   - Colorectal cancer or tumor associated with Lynch syndrome (endometrial, stomach, ovarian, pancreatic, uterine, renal pelvic, biliary tract, brain, or small bowel cancer, or sebaceous adenomas or keratoacanthomas) diagnosed before age 50 years in at least one first-degree relative.
   - Colorectal cancer or tumor associated with Lynch syndrome (endometrial, stomach, ovarian, pancreatic, uterine, renal pelvic, biliary tract, brain, or small bowel cancer, or sebaceous adenomas or keratoacanthomas) diagnosed at any age in two first- or second degree relatives.
2. Patients who fulfill above criteria and have high microsatellite inability and/or loss of DNA mismatch repair gene expression should be offered germline testing for Lynch syndrome genes.
3. When tumor testing is not feasible, testing for germline mutations may be considered for patients with a family history suggestive of Lynch syndrome.

Adapted from Lindor NM, Peterson GM, Hadley DW, et al. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome. JAMA 2006; 296:1507-17.

patients may benefit from pharmacological treatments for neuropathy, as well as specialty referral for pain management. Chronic diarrhea is generally managed with antidiarrheal regimens and the use of incontinence garments. Patients may not volunteer symptoms, so physicians should actively ask about bowel problems during follow-up. Patients who have undergone pelvic radiation for rectal cancer are at increased risk for pelvic fracture; thus all survivors with a history of pelvic radiation should undergo bone-mineral density testing, and medical treatment of osteopenia and osteoporosis should be considered. Survivors of pelvic radiation also commonly suffer from urinary and sexual dysfunction including urinary incontinence, erectile dysfunction in men, and vaginal dryness in women. Phosphodiesterase inhibitors have shown benefit for erectile dysfunction in men after pelvic radiation. Vaginal dilators may be of benefit for women with vaginal stenosis after pelvic radiation.[21]

REVIEW OF INTRODUCTORY CASES

CASE 23-1 CASE CONTINUED

A 66-year-old woman presents for preventive care. Her past medical history is significant for stage 1 breast cancer diagnosed by mammography 2 years previously. The tumor was estrogen and progesterone receptor-positive and HER-2/Neu negative. She was treated with lumpectomy with sentinel node evaluation and radiation therapy. Her current medications include an aromatase inhibitor. She asks the following questions: (1) What follow-up tests do I need? (2) Should I have an annual breast MRI? (3) Should I be tested for the BRCA gene?

ASCO guidelines recommend this patient be followed by serial history and physical examination and annual mammography, with further testing only for symptoms or physical findings. Because the patient is on an aromatase inhibitor, annual bone densitometry is recommended, with bisphosphonate treatment if osteoporosis is diagnosed. Annual breast MRI is recommended for patients with a lifetime risk of primary or recurrent breast cancer of 20% or greater. Women who carry the BRCA gene or who underwent chest wall radiation for Hodgkin disease between the ages of 10 and 30 years fit these criteria regardless of other factors. For other women, to determine whether MRI is indicated, one of several validated models that take into account family and personal historical factors to determine lifetime risk of breast cancer can be used (e.g., Gail, Claus, and Tyrer-Cusik models). These can be accessed electronically.[12] If the patient is of Ashkenazi Jewish descent, or fits family history criteria documented in Table 23-2, testing for the BRCA gene should be considered.

CASE 23-2 CASE CONTINUED

A 72-year-old man presents for preventive care. He underwent radical prostatectomy at age 60 for prostate cancer. His PSA is now undetectable. He asks: (1) How often do I need PSA testing? (2) Do I need to see a urologist on a regular basis?

Annual PSA testing is recommended for men who are disease-free 5 or more years after treatment for prostate cancer. Whether or not the patient sees a urologist should be determined by patient and physician preferences. However, if the patient elects not to be seen by a urologist, the primary physician should specifically inquire about erectile dysfunction and urinary incontinence and treat and/or refer if appropriate.

Chapter Summary

Surveillance in disease-free cancer survivors includes three elements: surveillance for cancer recurrence, surveillance for second cancers (including genetic testing to guide preventive and surveillance strategies, when appropriate), and surveillance for late medical and psychosocial effects. Surveillance strategies should take into account the patient's overall health status and treatment preferences. Although active surveillance for cancer recurrence and second cancers is appropriate for many elderly patients, some patients with significant comorbidities are not candidates for further curative treatment. For all patients,

there should be strong emphasis on initiating timely and appropriate palliative treatment if symptoms of incurable cancer recurrence develop. Available evidence suggests that well-trained generalists can provide surveillance care equivalent to specialists for some common cancers. Co-management or specialized survivorship clinics with or without the involvement of specifically trained nurses may be indicated for some patients.

Guidelines are available to help determine surveillance strategies for survivors of common cancers. These are summarized in Table 23-1. Surveillance is an area of active research. More and better evidence-based information on how to best provide surveillance will likely be available in the near future.

See expertconsult.com for a complete list of references and web resources for this chapter

CHAPTER

24

Long Term Effects and Cancer Survivorship in the Older Patient

Mary E. Sehl, Erin E. Hahn, Amy A. Edgington, and Patricia A. Ganz

CASE 24-1 CASE 1: OLDER BREAST CANCER SURVIVOR PRESENTATION

M.H. is an 87-year-old woman who has been a breast cancer survivor for several years. She had been diagnosed 6 years earlier with a 2.3 cm, node-positive, estrogen receptor-positive, infiltrating ductal carcinoma. She was originally treated with lumpectomy, followed by chemotherapy and radiation therapy, which she tolerated well. She has since completed almost 5 years of endocrine therapy with an aromatase inhibitor. Her coexisting illnesses include osteopenia, gastroesophageal reflux disease, and glaucoma. The patient is a retired pianist who continues to perform as an entertainer locally. She has a very supportive social network of friends in the area and two sons who live out-of-state. She is also active with swimming and bridge.

CASE 24-2 CASE 2: OLDER PROSTATE CANCER SURVIVOR PRESENTATION

S.W. is a 79-year-old prostate cancer survivor. Eight years prior, he was referred for a prostate biopsy after his prostate specific antigen (PSA) level had risen to 5.4 ng/mL. The pathology revealed a Gleason 3+4=7 prostate cancer involving both the right and left lobes of the prostate with no capsular extension of disease. He underwent radical prostatectomy at that time and was followed with PSA measurements. Because of a rise in PSA level 3 years later, he was treated with external beam radiation. He is currently followed with yearly PSA measurements, which have been undetectable. The patient also has hypercholesterolemia, hypertension, aortic stenosis, congestive heart failure, multinodular goiter, osteoarthritis, and memory loss. The patient ambulates with a cane. He lives in an assisted living facility and has a caregiver during the day. He has a supportive family and they live close by.

With long-term survival from cancer rising, the number of cancer survivors is growing, and the majority (61%) of cancer survivors are aged 65 and older. According to a 2003 report of the National Cancer Institute (NCI) Office of Cancer Survivorship, there are over 10 million cancer survivors in the United States, representing 3.6% of the population. These numbers are expected to rise, given the increasing incidence of cancer and the aging of the population. Currently, an estimated one in every six people older than 65 years is a cancer survivor, highlighting the need to increase awareness and emphasize how to best care for this growing population in the oncology and geriatrics communities.

Because of improvements in cancer therapies, the 5-year and extended disease-free survival rates for early-stage breast, colorectal, and prostate cancer are over 90%. Likewise, early-stage melanoma, Hodgkin lymphoma, and cancers of the bladder, uterine cervix, and testes are associated with excellent survival outcomes. As a result, for most cancer survivors, death is more likely to occur from competing illnesses. However, cancer treatment modalities including surgery, radiotherapy, node evaluation, chemotherapy, and endocrine therapy have been shown to be associated with late effects that may persist for up to 20 years after initial treatment, including cognitive effects, physical effects, psychosocial adjustments, and functional decline. Many of these late effects overlap with physiological changes that occur with advancing age and with medical conditions associated with advancing age, making them an important focus in the care of the older cancer patient.

DEFINITION OF CANCER SURVIVOR

According to a broad definition developed in 1986 by the National Coalition for Cancer Survivorship, any cancer patient or close family member of a cancer patient, from the time of diagnosis until death, may be considered a cancer survivor. More recently, the term survivor has been used to denote a more focused period of time beginning after the completion of initial treatment with curative intent, when the patient is being seen posttreatment

and in follow-up (Ganz 2005). It is this period of time that will be the focus of this chapter. Important issues that arise in this period of time with respect to managing symptoms and late effects, as well as health care maintenance and screening in this population, will be addressed.

HETEROGENEITY OF AGING CANCER SURVIVORS

Cancer in patients older than 65 years is a heterogeneous process in a heterogeneous population. Heterogeneity arises in the number and severity of coexisting illnesses, cognitive function, physical activity and performance status, and social connectedness. (Balducci 2008) While one patient aged 95 may be skiing, another aged 67 may be bed-bound. Surviving and thriving while experiencing the impacts of cancer and its therapy is a personal and individualized process, especially in the older patient. The two cases described earlier highlight the dramatic individual differences that can be seen in the older population.

PALLIATION, PREVENTION AND HEALTH PROMOTION

The goals of care for survivors have been well summarized as the 3 Ps of survivorship: palliation, prevention, and health promotion. (Ganz) With palliation, the intention is to improve quality of life. This goal is especially important in older people with complex and chronic illness. Concentration is placed on reducing the severity of prolonged disease symptoms where there is no curative medical treatment. These symptoms include pain, fatigue, depression, physical limitations, cognitive changes, lymphedema, sexual dysfunction, and menopause-related symptoms.

The main focus of the second P, prevention, is providing systematic follow-up required to screen for late-onset complications of cancer and its treatment. Complications that can arise as a result of treatment, such as osteoporosis, heart disease, and cataracts, are often conditions that are also associated with aging. The goal of this screening is early detection and early intervention for these complications. Another goal of prevention is to screen for second malignancies, and to counsel patients on chemoprevention and lifestyle modification that may decrease risk of a second malignancy.

Finally, the goal of health promotion is to endorse risk reduction for common health problems. In the older patient, these problems include other chronic diseases, such as diabetes and heart disease, as well as functional decline. Therefore, the focus of this third P is on educating patients about the importance of increasing physical activity, avoiding weight gain, and avoiding exposures that are harmful. For example, one harmful exposure, alcohol consumption, in older adults is associated not only with risk of malignancy, but also with increased risk of falls, medication interaction, and depression.

COMPREHENSIVE CARE FOR SURVIVORS

A clinical program designed to meet the special health needs of cancer survivors should be multidisciplinary in nature. Under this concerted approach, the patient undergoes a nutritional evaluation, psychological evaluation, social work assessment, and evaluation by physical therapy and occupational therapy. Recommendations are discussed as a team and an integrated care plan is formulated together with the primary care physician. This comprehensive model has already been proven to be effective in geriatric medicine and is likely to be of great benefit for older cancer survivors. The shared care model that has been recently developed for survivor care will be discussed later in the chapter.

LATE EFFECTS OF CANCER TREATMENT

Late effects have been attributed to chemotherapy, surgery, radiotherapy, and endocrine therapy; these effects can persist for decades. There is a great deal of overlap between late effects of cancer therapy and the physiological changes that occur with advancing age. Table 24-1 highlights this overlap and lists by system the late effects of therapy that commonly occur in cancer survivors alongside the potentially interacting age-related changes in that physiological system.

Functional decline is another important late effect that can occur in cancer survivors, and is a significant concern in the older patient. Cancer survivors are twice as likely as persons without a history of cancer to report limitation in an activity of daily living. Disability is an important concern in the older patient, highlighting the need for functional assessment in older cancer survivors.

CASE 24-1 CASE CONTINUED CONCERNS RAISED

M.H. describes feelings of anxiety regarding cancer recurrence. She also has been concerned about making commitments to piano performances that she may not be able to keep. Lately she has been suffering nocturnal leg cramps from her aromatase inhibitor therapy and, as a result, has been experiencing insomnia. She also notes a decline in how many laps she can swim at the pool, sometimes with difficulty catching her breath, although she does not have any shortness of breath at rest.

CASE 24-2 CASE CONTINUED CONCERNS RAISED

S.W. presents with symptoms of fatigue, memory changes, shortness of breath, and depressed mood. He sometimes feels sad and isolated, and describes worries about cancer recurrence, as his brother recently passed away from oral cancer.

TABLE 24-1 Late Effects of Cancer Therapy and Age-Related Physiologic Changes

System	Chemotherapy	Radiotherapy	Surgery	Endocrine Therapy	Age-Associated Physiologic Changes
Cardiovascular	Cardiomyopathy, congestive heart failure	Scarring, inflammation, pericardial effusion, pericarditis, coronary artery disease	—	Venous thrombotic events	Decreased cardiac output, decreased maximum oxygen consumption, increased inflammatory cytokines
Pulmonary	Pulmonary fibrosis, inflammation interstitial pneumonitis	Pulmonary fibrosis, decreased lung function	Shortness of breath	—	Decreased FEV1, decreased D_LCO, decreased total lung capacity
Gastrointestinal	CASH, hepatic fibrosis, cirrhosis	Malabsorption, biliary stricture, liver failure	Intestinal obstruction, hernia, altered bowel function, nausea, vomiting	—	Impaired peristalsis, delayed gastric emptying time, impaired absorption, decreased liver blood flow
Genitourinary	Hemorrhagic cystitis	Bladder fibrosis, small bladder capacity	Incontinence	Vaginitis	Diminished bladder capacity, enlarged prostate
Renal	Decreased creatinine clearance, delayed-onset renal failure	Decreased creatinine clearance, hypertension	—	—	Increased blood pressure, decreased creatinine clearance
Hematologic	Myelodysplasia, acute leukemia	Myelodysplasia, cytopenias, acute leukemia	—	Anemia	Anemia
Musculoskeletal	Avascular necrosis	Osteonecrosis, fibrosis, atrophy, deformity	Accelerated arthritis	Osteopenia	Decreased bone density, decreased muscle strength and muscle volume
CNS	Problems with thinking, learning, memory; structural brain changes; paralysis, seizure; fatigue	Problems with thinking, learning, memory; structural brain changes; hemorrhage; fatigue	Impaired cognitive function, motor sensory function, vision, swallowing, language, bowel and bladder control, phantom pain (amputation), fatigue	Mood changes, fatigue, generalized weakness, hot flashes	Decreased brain weight, increased reaction times, diminished smell, decreased digit span and block span, impaired circadian rhythm and sleep
Peripheral nervous system	Peripheral neuropathy, hearing loss	—	Neuropathic pain	—	—
Pituitary	Diabetes	Growth hormone deficiency, other hormone deficiencies	—	—	Decreased growth hormone and DHEA, impaired insulin sensitivity
Thyroid	—	Hypothyroidism, thyroid nodules	—	—	Decreased thyroxine secretion
Gonadal	Sterility, early menopause	Sterility, ovarian failure, early menopause, Leydig cell dysfunction	Retrograde ejaculation, sexual dysfunction, testosterone deficiency	—	Decreased testosterone, decreased LH and FSH, decreased estradiol
Oral health	Tooth decay	Dry mouth, poor enamel, dental carries	—	—	Decrease in salivary flow rate

Continued

TABLE 24-1 Late Effects of Cancer Therapy and Age-Related Physiologic Changes—cont'd

System	Chemotherapy	Radiotherapy	Surgery	Endocrine Therapy	Age-Associated Physiologic Changes
Ophthalmologic	Cataracts	Cataracts, dry eyes, visual impairment, retinopathy	—	Cataracts	Reduction in pupil size, loss of accommodation, impaired night vision
Skin	Rashes	Burn	Impaired wound healing, cosmetic effects	—	Epidermal atrophy, increased stiffness in dermal collagen, slower wound healing
Lymphatic	—	Lymphedema	Lymphedema	—	—
Immune	Impaired immune function, immune suppression	Impaired immune function, immune suppression	Impaired immunity and risk of sepsis (splenectomy)	—	Impaired cell-mediated immunity
All tissues	Second cancer	Second cancer	—	Endometrial cancer	Increased risk of cancer

FEV1, forced expiratory volume in 1 sec; D_LCO, lung diffusing capacity for carbon monoxide; CASH, chemotherapy-associated steatohepatitis; DHEA, dehydroepiandrosterone; LH, luteinizing hormone; FSH, follicle-stimulating hormone

NEED FOR SURVIVORSHIP CARE PLAN

On the basis of reviews of SEER Medicare claims data (Earle 2003, Earle 2006, Earle 2007, Snyder 2008), it has become apparent that a shared survivorship care plan is needed to ensure better preventive care for cancer survivors. In addition to the standard follow-up in oncology practice that focuses on surveillance for cancer recurrence and management of the adverse effects of treatment, the survivorship care plan needs to address the long-term effects of cancer and its treatment. (Earle 2006, Ganz 2008) The care plan should address the potential for late sequelae of treatment (Ganz 2006, Ganz 2008), particularly in an older population, who are at higher risk for organ dysfunction and second malignancies. In addition, there should be a focus on the ongoing psychosocial burden of a cancer diagnosis (Ganz 2008), which is an especially important concern in an older population that is at higher risk for depression and social isolation.

HOW TO FACILITATE SHARED CARE?

A very important component of the survivorship care plan is to facilitate the coordination of care with other physicians. (Ganz 2008) There has historically been some ambiguity about the responsibility for providing ongoing medical care for cancer survivors (Ganz 2005, Nekhlyudov 2009). According to a survey conducted by the ASCO Cancer Prevention Committee, when oncologists were asked the question, "To what extent do you provide ongoing medical care, including health maintenance, screening, and preventive services," 31% responded always, 48% sometimes, 15% rarely, and 5% not at all. (Ganz 2005) The majority (74%) felt that it was the role of the oncology specialist to provide this type of continuing care to cancer survivors and 66% felt comfortable providing it. A recent study examining the attitudes of patients, oncologists, and primary care providers revealed that while patients expect their oncologists to be primarily responsible for cancer recurrence, they expected both their oncologists and primary care providers to be involved in surveillance for cancer recurrence and other cancer screening, and they preferred their primary care physicians to be solely involved in general preventive care and treatment of other coexisting illnesses. (Cheung 2009, Nekhlyudov 2009) Generally, primary providers and oncologists agreed with their patients. Although primary care providers expected most of the responsibility for preventive care, oncologists expressed interest in shared care for prevention. (Cheung 2009, Nekhlyudov 2009)

Under the shared care model, it will be important for both oncologists and primary care providers to take responsibility for incorporating interventions into routine care for cancer survivors. For example, at the beginning of adjuvant therapy for breast cancer, strategies of prevention for weight gain should be discussed. While many patients spontaneously initiate positive behaviors, such as diet and physical activity, many older patients do not. (Demark-Wahnefried 2005, Ganz 2005) It will be important to encourage modification of behaviors and initiate preventive exercise programs in this population at risk for decline in strength, functional activity, and independence.

CONTENTS OF TREATMENT SUMMARY AND SURVIVORSHIP CARE PLAN

Table 24-2 describes the contents of the treatment summary and survivorship care plan. In addition to a complete medical history, family history, and social history, the treatment summary should include both the history

TABLE 24-2 Treatment Summary and Survivorship Care Plan Contents

Treatment Summary
Provider contact information
Medical oncologist
Radiation oncologist
Surgical oncologist
Primary geriatrician
Surgical history
Procedures and dates
Complications
Pathology and stage
Histopathology, TNM stage, biologic marker data
Chemotherapy history
Treatments and dates
List all agents and number of cycles received
Total dose (e.g., anthracycline)
Growth factors received, blood transfusions
Complications
Endocrine therapy history
Dates
Side effects
Other therapies (e.g., biologically targeted therapy)
Dates
Side effects, adverse reaction
Radiation history
Date started, date finished
Fields radiated
Total dose (Gy)
Survivorship Care Plan
Pertinent medical conditions
List of current medications, allergies
Family history, social history
Current symptom review
Current psychosocial assessment
Recent screening and diagnostic tests
Recommendations
Cancer management and surveillance
Late effects monitoring
Psychosocial concerns
Symptom management
Health Promotion
Prevention
Bone health
Weight management and physical activity
ASCO guidelines for follow-up care for specific cancer

of cancer diagnosis, including detection, pathological findings, and staging; and a complete cancer treatment summary, including chemotherapy treatment summary, surgical history, and summary of radiation therapy and other oncologic medical therapies. The chemotherapy treatment summary should include the names and cumulative doses of each agent, and the radiation therapy summary should include the fields radiated as well as the total dose received.

The survivorship care plan should be comprehensive, should include psychosocial and supportive care needs, and should identify which providers will be responsible for specific aspects of continuing care. It should reflect the past and current toxicities experienced by the patient, and project long-term late effects that may potentially arise as a result of the treatment received. A current symptom review should be performed and included, as well as a current psychosocial assessment. The care plan should also contain pertinent recent screening and diagnostic tests for cancer recurrence and other medical conditions, such as mammography, bone density, lipid measurements, and other blood work (e.g., vitamin D level). The care plan should also include a complete list of providers, including primary geriatrician, surgeon, medical oncologist, radiation oncologist, and other specialists, such as pain specialist or pulmonologist, involved in the oncological care of the patient. Specific recommendations should be in the care plan, including cancer management and surveillance, late-effects monitoring, psychosocial concerns, symptom management, health promotion and prevention, and weight management and physical activity. Finally follow-up care and test recommendations regarding radiologic tests, self-examination, coordination of care, and genetic counseling referral should be included.

TIMING OF THE CARE PLAN

The treatment summary and survivorship care plan should first be delivered at the completion of surgery and adjuvant radiation and/or chemotherapy. Additional times to update the care plan include at the end of a course of adjuvant endocrine therapy, or after additional treatment decisions are made, such as after genetic testing that necessitates preventive surgery and other interventions.

WHO PREPARES THE CARE PLAN?

There is a great deal of variation in clinical settings and organization of care during the initial phase of cancer treatment. In some cases, the cancer patient is seen by several different cancer care providers, including a radiation oncologist, a medical oncologist, and a surgical oncologist. The medical oncologist will need to develop strategies to integrate survivorship care planning in the office practice. When patients receive surgery alone, the surgeon can serve as the designated clinician providing survivorship care planning. It is best to summarize the care plan in a report for the patient to keep. The report should also be placed in the chart, so that it can be accessed and updated by the primary care geriatrician and other specialists involved in the care of the patient.

Many times the physician is the sole practitioner in the office qualified to provide education and counseling regarding past cancer treatment and potential long-term and late effects of treatment, as well as advising the frequency and type of follow-up visits needed

CASE 24-1: CONTINUED RECOMMENDATIONS

Because this patient still has both breasts, her cancer surveillance recommendation included maintenance of regular breast exams and mammography. In addition, she was recommended to have cardiovascular surveillance with an echocardiogram, given her exposure to left-sided chest radiation and history of anthracycline. For her psychosocial concerns, she underwent a depression screen and discussion, which indicated that depression and anxiety may be contributing to her insomnia. It was recommended that she discuss pharmacological options with her primary care physician or be referred to a psychiatrist. For her insomnia, she was recommended to consider participating in a study on T'ai Chi and sleep seminars as nonpharmacologic treatment options for insomnia in breast cancer survivors.

CASE 24-2: CONTINUED RECOMMENDATIONS

Cancer surveillance was addressed for this patient with the recommendation to continue PSA monitoring with his primary care physician, with referral to a urologist if changes or symptoms were noted. For his fatigue and shortness of breath, he was referred to cardiology for complete evaluation of his cardiovascular health. For his cognitive changes, he was referred for cognitive rehabilitation services. A comprehensive geriatric assessment was recommended to evaluate both physical and emotional health and to discuss maintenance of a healthy nutritional status, increasing physical activity, and reducing the risk of falls. Finally, for his depressed mood, he was referred for individualized, short-term counseling.

to monitor for cancer recurrence. In larger practices, where oncology nurse specialists or advanced practice nurses participate in patient care, components of the survivorship care planning visit can be delegated to the nurse. Primary care physicians can also be involved in ensuring that components of the survivorship care plan are complete, and that comprehensive care has been addressed.

ACCESS AND IMPLEMENTATION OF CARE PLAN

Recommendations for monitoring for cancer recurrence and recommended strategies for health promotion and disease prevention are summarized in the treatment summary and survivorship care plan, which can be given to the patient and placed in the patient's chart so that it can be conveyed to the primary geriatrician. Ideally, enough time should be set aside at key transition points where care planning is indicated. Screening for depression and anxiety is vital at these times, with referral to a mental health specialist if there are any signs or symptoms of depression, along with referral to appropriate support groups and community resources. Concerns regarding sexuality, intimacy, and vocation should also be addressed at the end of acute treatment, with resource referral when needed.

Establishing practice models in the community setting to improve the coordination of care for cancer patients in the posttreatment phase of the illness trajectory is vital to successful shared-care specialist/primary care collaboration. ASCO has developed templates for treatment summaries and care plans for breast and colon cancer. These and other resources on preparing a survivorship care plan are listed in Table 24-3. It is important for the oncologist and geriatrician to try to coordinate care with the patient's other physicians and to identify, with the patient, who will take care of ongoing health needs. Care of cancer patients is often subsumed by oncologists during the acute phase of their disease because of the complexity of the cancer and its treatment. However, especially in the older patient, it is important to attend

TABLE 24-3 Important Web Links/ Resources

Resources for Survivors:
American Cancer Society Survivors Network: Available at www.cancer.org; csn.cancer.org
CancerCare: Available at www.cancercare.org
IOM report "From Cancer Patient to Cancer Survivor: Lost in Transition": Available at www.iom.edu/CMS/28312/4931/30869.aspx
Susan G. Komen for the Cure: Available at www.komen.org
Lance Armstrong Foundation: Available at www.livestrong.org
Living Beyond Breast Cancer: Available at www.lbbc.org
NCI Office of Cancer Survivorship: Available at http://cancercontrol.cancer.gov/ocs/
The Wellness Community: Available at www.thewellnesscommunity.org
The National Coalition for Cancer Survivors: Available at www.canceradvocacynow.org/
Cancer.Net: Available at www.cancer.net
People Living With Cancer: Available at www.cancer.net
Vita – Restoring Life after Cancer: Available at www.vita.mednet.ucla.edu
Resources on Preparing a Survivorship Care Plan:
ASCO treatment summary and care plan templates for breast and colon cancer: Available at www.asco.org/treatmentsummary
Haylock PJ, Mitchell SA, Cox T, et al: The cancer survivor's prescription for living, *Am J Nurs* 107:58-70, 2007.
Livestrong Care Plan from the OncoLink website: Available at http://www.livestrongcareplan.org/
Resources on Preparing a Survivorship Care Plan:
ASCO treatment summary and care plan templates, both generic and specific for breast, lung and colon cancer: Available at www.asco.org/treatmentsummary
Haylock PJ, Mitchell SA, Cox T, et al: The cancer survivor's prescription for living, *Am J Nurs* 107:58-70, 2007.
Livestrong Care Plan from the OncoLink website: Available at http://www.livestrongcareplan.org/
Journey Forward survivorship care plan builder: Available at http://www.journeyforward.org

to chronic care needs and health promotion during this time, as well as in follow-up; this is best done in the primary care setting. A clear and concise treatment summary and survivorship care plan can empower the older cancer survivor and the primary care physician to take charge of future care, with consultation of the medical oncologist and other specialists as necessary.

RESOURCES AVAILABLE TO CANCER SURVIVORS

The treatment summary and survivorship care plan can serve as both a communication vehicle and an educational resource for the cancer survivor. Table 24-3 lists additional resources available to cancer survivors. In the older patient, focus should be placed on establishing a social network for education and resources on wellness, and promotion of preventive strategies such as nutrition and physical activity. Patient empowerment is critical to ensuring successful implementation of the care plan.

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CHAPTER

25

Managing the Older Cancer Patient at Home

Pattie Jakel and Joseph Albert Melocoton

It is estimated that by the year 2050, about 79 million individuals in the United States will be older than 65 years.[1] Older adults are the fastest growing segment in the U.S. population. Cancer incidence is projected to rise as the general population ages, and is a leading cause of mortality in the elderly.[2] Because of advances in modern medicine, life expectancy has increased significantly and cancer has become a chronic disease. Cancer is a major health concern in the United States, yet information about the services and programs for older adults with cancer are still limited.[3] The current health care system has undergone major changes regarding reimbursement. Inpatient lengths of stay have been significantly reduced under curtailed reimbursement, and the burden of care has shifted to outpatient and home care. The older adult population has unique needs that pose a tremendous challenge to health care professionals. Designing a comprehensive plan of care after hospital discharge should address the behavioral and functional issues prevalent among elderly patients with cancer, such as medication adherence and home safety. Furthermore, an understanding of specialized programs or geriatric resources (involving a multidisciplinary approach) is essential to optimizing health outcomes for this important patient population.

MEDICATION ADHERENCE AMONG ELDERLY CANCER PATIENTS

CASE 25-1

H.T. is a 65-year-old woman who has been newly diagnosed with chronic myelocytic leukemia (CML) in its chronic phase. Her medical history is significant for hypertension, diet-controlled diabetes, and depression. She received patient education on her diagnosis and the intended therapies. She does not yet fully comprehend her diagnosis and is overwhelmed at the prospect of cancer treatments. She lives alone in an apartment with no immediate family. She drives a long way to her medical appointments.

She started treatment with an oral antineoplastic agent, and experienced nausea with the medication despite antiemetic therapy. She returned to the clinic a week later complaining of nausea and vomiting; her serum potassium level was 3.

Scope of Problem

As the nature of cancer therapy shifts from acute to chronic care, medication adherence or compliance has become an increasingly important concern. Compliance or adherence refers to the ability to maintain health-promoting regimens, whether it involves taking a medication, performing an exercise program, or carrying out lifestyle changes.[4] Some experts assign a subtle difference to the meaning of compliance and adherence but they will be used interchangeably for the purpose of this chapter.

Because the elderly often have multiple comorbidities, an older adult takes, on average, three to twelve prescription drugs and one to four nonprescription drugs per year. However, it is estimated that only about 60% take their prescribed medications properly. There are currently more than 20 oral agents in the cancer armamentarium and dozens more in the pipeline. With the significant increase in the use of oral agents for treating cancer or otherwise, there is also a concurrent potential increase in the risk of nonadherence among the elderly. Nonadherence to oral medications is a barrier to optimal therapy and can impair health through delayed healing, promote disease recurrence, or even hasten death. Nonadherence is not only an impediment to the full therapeutic benefit of the regimen but is also associated with increased health care costs due to frequent physician visits and hospitalizations.[5, 6]

Factors Involved in Nonadherence

The financial impact of medication nonadherence to the U.S. health care industry is estimated to be $100 billion per year.[7] To ensure safety, quality of care, and improved treatment outcomes, it is imperative that patients adhere to a medication regimen. Nonadherence can have crucial implications to oncology. Nonadherence to a drug regimen is a multifaceted issue and involves three major variables: *patient, physician, and treatment*.[8]

Patient variables relate to individual factors that are associated with medication adherence such as physical

and cognitive decline, intentional nonadherence, inadequate support system, lack of belief about treatment, and psychological illnesses, particularly depression. Memory deficits, poor visual acuity, and diminished manual dexterity can also contribute to medication nonadherence. The elderly may have challenges understanding complex regimens and therefore may have difficulty complying with the directions as instructed. Furthermore, nonadherence can be intentional; the reasons for this are complex. A study on chronically ill patients who were starting a new medication found that a third did not comply with the prescribed regimen; for 50% of these, the nonadherence was intentional because of medication side effects.[9] Knowledge and beliefs about health can also influence medication-taking behavior, although these variables have yet to be validated in research studies. Patients may adhere to the medication regimen if they believe that the medication will help and that the potential benefit outweighs the risk. In addition, mood disorders such as depression can also influence medication adherence. Depression is a common comorbid chronic illness in older adults that is underdiagnosed and undertreated. Compared to patients who are mentally stable, the medication nonadherence rate is 27% higher among depressed patients.[10] Physician factors refer to the patient-physician interaction. The relationship between the doctor and the patient, the communication skills involved, and the physician's cultural competence, as well as his or her comfort in dealing with older patients, all contribute to adherence to therapy. Poor patient-provider communication, inadequate discussion of side effects, and lack of patient understanding about the effectiveness of treatment may foster dissatisfaction and mistrust that can hamper effective medication adherence.[5] Another problem is the lack of awareness and recognition by health care providers of the existing problem of medication nonadherence.

Treatment variables refer to the medical and economic considerations that can affect medication adherence such as side effects, duration of treatment, medication costs, polypharmacy, and complexity of drug regimen. Because of chronic conditions, the elderly tend to be on multiple medications. Medication side effects are a major reason that older adults skip doses or stop taking their medications. A study on adjuvant therapy with tamoxifen revealed that women were four times more likely to be nonadherent to the regimen if they experienced side effects.[11] Thirty-five percent of older adults who took five or more medications were prone to adverse reactions.[12] Likewise, patients who are on therapy for an extended period have a high rate of discontinuation. The higher the number of medications, the less likely the elderly will adhere to therapy. The elderly take, on average, four to seven prescription medications, three over-the-counter medications and one herbal supplement.[13, 14] Polypharmacy and multiple medication doses required per day create a complex of medication regimen and increase the risk of drug reactions among the elderly.

Solutions to the Problem

Patient education is important to promoting medication adherence in the elderly. A specific set of educational methods should be tailored to their learning needs, and assessment should focus on their memory, attention, and executive functioning. There are several aids to medication planning and organization. Methods that were found to be beneficial in promoting medication adherence include utilization of a timed pill box, placing containers in a familiar location, taking medications in synchrony with meals/bedtime, getting reminders from others, and using a check-off list or written instructions.[15] Written instructions in large letters or bullet and list format seem beneficial. When discussing medications, it is likewise helpful to provide general information first, followed by how to take the medicine, the outcomes or side effects to watch for, and signs or symptoms of when to call the doctor. Memory-enhancing methods such as medication schedules, refrigerator medication charts, electronic reminders or alarms, or an electronic medication-dispensing device can also enhance patient medication adherence. Medication cards that list current medications can heighten drug compliance; this list can be shared with other prescribing providers who can update and review drug regimens at each clinic visits.

Refilling prescriptions can also be challenging for the older adults. A system to assist in procuring or refilling prescriptions such as a mail-order pharmacy, pharmacy automatic-refill service, or telephone reminder calls can be very beneficial. Modified medication containers or blister packs may make it easier for those who are physically challenged to open medication containers. The pharmacy can be a good resource when choosing alternatives for preparing medications for administration, such as utilizing tablets that are easier to break or providing correct medication dosages that don't require breaking. A comprehensive pharmacy medication adherence program or system that includes patient education, pharmacy consultation, and follow-up can enable elderly patients to adhere more closely to their medication regimens.[16] Pharmacy reviews to decrease polypharmacy, such as the Beers criteria[17] for potentially inappropriate medication use, can be a helpful guide when considering medications that should be avoided in patients age 65 and older and can identify adverse drug interactions.

The importance of engaging the help of family members or supportive caregivers can never be overemphasized. Family members and caregivers provide emotional and regimen-specific support. They provide important clues and information that are valuable when considering the functional status, cognitive capacity, health maintenance, and medication habits of the aging population.

Overall, there is no single best method to promote medication adherence in the older adult population. A multifaceted approach is warranted (Table 25-1 for a summary of practical recommendations to improve medication adherence in the elderly).

TABLE 25-1 Practical Strategies to Improve Medication Management for the Elderly

Factors associated with nonadherence to oral medications	Helpful recommendations for increasing adherence
Patient-related variables	
Cognitive deficits	*Use of memory cues* (taking medications based on routine or synchrony with meals/bedtime); *Memory-enhancing methods or devices* (pre-poured or timed pill box; utilizing a medication dispensing service; automatic dispensers with voice-activated message; telephone call reminders; placing containers in a familiar location; medication calendar or charts; wristwatch with alarms; medication diary; dose-reminder cards)
Physical deficits	Use of blister packs, or easy-open containers/non-childproof containers; consult with pharmacy regarding medication modification (correct dose of medications, easy-to-break tablets)
Other: depression, intentional nonadherence, lack of belief about treatment, inadequate support system.	Assess and treat depression; explore health concerns for noncompliance; reinforce benefits of therapy; discuss the danger of missed medications; refer to social worker or discharge planner on community resources; enlist help of family members/caregivers; annual physical exams
Physician-related variables	
Poor patient-provider relationship or communication	Regular contact and consistent patient support (nonjudgmental attitude, active listening, reinforce adherent behaviors, cultural sensitivity, convenient follow-up schedules) Provide patient education and periodic drug review (medication side effects, benefits of therapy, asking for feedback, keeping messages simple, providing informational resources)
Treatment-related variables	
- Side effects	- Modify regimen to reduce adverse effects
- Complexity of regimen	- Simplify the regimen and dosing schedule: Review prescribed and nonprescribed medications; Enlist the help of other physicians involved.
- Medication costs	-Seek assistance with procuring medications; learn about insurance coverage; consult with other physicians about availability of drug samples; use of generic drugs; participate in drug company programs; refer to social worker regarding Medicare prescription coverage (www.medicare.gov/MedicareReform). Review if drug regimen is efficacious and economical.
- Polypharmacy	- Medication review semi-annually; check duplicate drug therapies; use combination drugs or alternative routes; screen for drug interactions; create an updated medication list to share to providers; apply Beers criteria on medication review.[17]

Health Care Providers' Role

The physician's role is central and key to successful medication adherence in the elderly. The physician should constantly assess personal characteristics (physical/cognitive/emotional skills), relationship orientation, and the way a patient absorbs and process information (self-efficacy), because all patients are unique. Listening to the patient is very important. It helps to have comfort in dealing with older patients. Enhanced patient-provider communication fosters adherence by creating trust and improves patient satisfaction with care.[5] It is essential to have regular contact and consistent patient support at all levels of care. During a patient clinic visit, it is important for providers to screen for potential adverse drug interactions and identify any medications of concern. It is necessary to have an updated list of all medications including dose frequency and to have the patient provide this list to other prescribing providers when necessary.[18]

Elderly patients require a substantial need for more information when starting a new medication. It is necessary keep the information simple and clear, both in verbal and written form. Start with what the patient already knows and discuss the names of the drugs being ordered and its effect. Always provide time for questions. Physicians should carefully explain information regarding treatments and should reinforce disease characteristics, risks and benefits of treatments, and the proper use of medication.[7] It is important to discuss medication side effects from the start of treatment so that patients may know what to expect and be better able to deal with adverse reactions to therapy. An understanding of how some medications might have different effects on people of various ethnicities, as well as a knowledge of age-related changes in metabolism and drug interactions are essential.

Also, it is imperative to identify barriers to adherence; questioning techniques about medication-taking behaviors should be nonjudgmental and may include statements such as "How do you take your medications?" "Do you stop taking medication when you feel better/when you feel worse?" and "Are you having difficulty taking your medications daily?" It is also helpful to inquire about situations that may have an impact on medication adherence such as missed doses and what the patient should do in the situation of a missed dose. Caregivers should be involved in the plan of care. They can reinforce adherent

behaviors. Getting feedback at each clinic discussion can help to uncover and address issues that can have important implications to medication adherence and overall health. If the patient has difficulty understanding a particular medication at a previous clinic encounter, then reviewing the drug again at the next visit would be very helpful to encouraging adherence. It is also beneficial to discuss special instructions such as taking medication with food or the proper way to use an inhaler, as well as side effects to monitor or report.

Assistance Programs

It is a known fact that the more costly the medication, the less likely that older adults will procure the medication or adhere to a regimen that includes it. Lack of funds, especially at the end of the month, is a major factor in why older adults have difficulty filling their prescriptions.[19] The out-of-pocket costs, high copayment, or a lack of prescription drug coverage can create a tremendous financial burden for chronically ill adults and can be a major barrier to medication adherence.

Helpful suggestions to ease medication procurement for the elderly include the use of drug samples from prescribing physicians, participation in copayment assistance programs from pharmaceutical corporations, and pharmacy consultation on utilizing generic instead of brand name drugs. Patients can be referred to a social worker to navigate the system or to help them obtain Medicare or other insurance coverage.[20, 21] Several states have pharmacy assistance programs that help eligible persons pay for their prescription drugs.

CASE 25-1 CONTINUED

H.T. had been unable to fill her antiemetic prescription because of a high copayment for drug regimens. She had thought of stopping therapy entirely, because of her limited income, but had reluctantly refilled only her oral antineoplastic agent and not the antiemetic medication. At this clinic visit, an antiemetic and replacement with intravenous potassium were ordered. The oncologist explored her economic challenges to filling her prescriptions, assessed her self-care skills and her current stressors or depression, and offered encouragement and support to maintain a proactive stance in her medical oncology care. During this clinic visit, the physician modified her antiemetic regimen; a cheaper alternative prescription to manage delayed nausea was ordered, and a drug sample was given. She was also referred to the nurse navigator and social worker regarding local/national cancer support groups or other resources that she might find helpful. She was also informed about psychosocial assistance when necessary. A copay assistance program was also explored and a pharmaceutical drug representative was contacted.

Specific information regarding expected side effects, adverse reactions of the medication regimen, and commonly encountered drug-drug interactions were reiterated. Her questions were answered and she feels satisfied to continue with her cancer therapy. The oncologist also collaborated with the patient's primary care doctor and discussed what they would do to comanage this patient's care effectively.

HOME SAFETY

Homecare Services

The older adult population's cancer illness experience and needs differ substantially from those of younger age groups because of multiple chronic medical conditions that often compound the oncologic diagnosis. The current health care system, typified by shorter hospital stays and an increased shift of cancer treatments from hospital to ambulatory settings, has concomitantly caused a great challenge for older adults by making it necessary for them to cope in the home setting with the physical and psychosocial difficulties associated with cancer. Homecare for older adults with cancer may necessitate a multidisciplinary approach, requiring integration, continuity of care, and coordination of a number of service disciplines such as social workers, pharmacists, physical therapy (PT), speech therapy (ST), or occupational therapy (OT). A description of these skilled and ancillary services can be found in Table 25-2. Several patient-safety issues that

TABLE 25-2 Skilled Home Care Services

Services	Indications	Example
Physical Therapy	Functional limitations in mobility, strength, range of motion; wound debridement	Gait training and strengthening exercises
Speech-Language Pathology Services	Language, speech, and swallowing disorders	Assessment, evaluation, and therapy to regain or strengthen speaking and swallowing skills (also listening, reading, and memory skills)
Occupational Therapy	To improve activities of daily living and achieve independence through therapy; occupational therapists can also perform environmental assessments	Therapeutic activities, energy conservation methods, task simplification, use of adaptive equipment
Ancillary Services		
Social services	Psychosocial assessment and evaluation of patient and caregiver that affect treatment or recovery	Counseling, resource finding, referrals
Home health care aide	Support services for skilled nursing therapy (not covered by Medicare unless patient is receiving skilled nursing care).	Custodial care or assistance with activities of daily living (bathing, grooming, transportation, meal preparation, and light housekeeping tasks)

can affect health outcomes upon discharge relate to issues including but not limited to medication adherence, living situation, and physical and cognitive functioning. Much of the decision is left to clinicians' individual assessment and clinical judgment when it comes to identifying characteristics of patients needing homecare referral, as Medicare regulations only dictate that patients be homebound and have a need for skilled assistance.[22] In addition, situational variables that present special challenges to recovery, health maintenance, and safety for this high-risk population include transportation, social support, maintaining independence, and financial resources. To be eligible for Medicare reimbursement, home health services should be deemed medically necessary by a physician and should be provided on an intermittent or part-time basis. Medicare law prohibits reimbursement for ancillary services unless a skilled service is initially ordered and provided. Physicians can refer to home health services or services may be requested by a family member or patients themselves.

Homecare is significantly different compared to the hospital setting and, thus far, there is limited data and research on patient safety problems encountered at home.[23] Issues for patients who are receiving care at home may be its unregulated setting compared to the hospital setting, greater autonomy exercised at home, and the complex physical, social, emotional and functional dimensions involved. Quality care for the elderly should consider safety risks during discharge planning. Doran et al. in a 2009 study[24] identified the most prevalent safety risks in the older adult population; they were polypharmacy, physical decline, cognitive decline, living alone, and a history of two or more falls. For the elderly with cancer, impaired functional status is the most frequent predictor of the need for homecare referral, although cancer stage and plans for adjuvant therapy are important when making informed referral decisions.[25]

Discharge planning should take into account the identification of patients likely to suffer adverse health consequences. It should consider the patient's care needs, preferences, caregiver support, and financial responsibilities so as to promote safe transition across care settings. The discharge plan focuses on the medical and social resources of the patient and should address his or her physical and cognitive function, postacute living arrangements, and functional status in areas such as eating, dressing, toileting, and ambulation. Factors to include in determining discharge needs include goals of care (rehabilitation, palliation, hospice), skilled nursing needs (PT, OT, ST), functional capacity (before and during hospitalization), equipment and supportive needs, social support, medication lists, insurance, and prognosis.

Home Safety Evaluation

Problems with an older adult's environment can interfere with optimizing his or her health and with achieving goals of care; thus an environmental or home assessment is warranted. Furthermore, unintentional falls are a growing public health concern and a common cause of nonfatal injuries for people older than 65 years.[26] The goal of a home safety evaluation is to develop and implement strategies to preserve a person's ability to function safely and independently at home and may include an assessment of the environment, residential observation of the elderly, and determination of the older adult's fall risk and health status.[27]

A home safety evaluation can be performed to assess for actual and potential safety problems in a patient's home environment. When doing a home safety evaluation, the physical infrastructure, bathroom facilities, storage layout, room features, accessibility, and even medical waste disposal and availability of resources or support persons are considered.

Some home safety assessment recommendations are covered by Medicare/Medicaid. Services can be paid out-of-pocket or by insurance. Home safety evaluation is necessary to identify factors that affect home safety (lighting, overall aesthetics, furnishings, clothing, rooms, electronic appliances, rooms, bathroom equipment, doors, handles, locks, stairs, light switches, remote controls, handrails, tub or faucet handles). Extrinsic factors are also considered (entryway, driveway, walkway). Safety hazards can be identified (clutter, electronic equipments, extension cords, pool, hot tubs, water temperature) and steps can be ensured to promote a safe environment for the elderly patient. Home hazard modifications can thus be recommended, which may include setting goals, enlisting social support, coordinating care, providing referrals, and planning with the patient, family, and health care professionals. A home safety evaluation can be performed by a registered nurse (RN), physical therapist, or occupational therapist. Performance of a safety evaluation involves a team approach. The physician, nurse practitioner, or physician assistant may order a home safety evaluation. Home safety evaluations are also available through community service programs, and a number of private agencies can do home safety evaluation.

If the individual has a history of safety "red flags" (history of falls, mobility/balance difficulties, cognitive impairments), a home safety evaluation by a trained health professional such as a nurse, physical therapist, or occupational therapist can be initiated for further assessment and a house visit can then be made (Table 25-3 for sample checklist). The need for assistive devices is also part of the assessment and a prescription can be obtained as indicated.

A typical scenario in a home safety evaluation consists of the physician recognizing a homebound patient needing skilled services. In conjunction with hospital discharge planners, a referral for home health care services will be made. A home hazard and safety assessment will be performed prior to patient discharge or can also be initiated upon discharge. If a home safety evaluation is performed during discharge, a physical therapist or occupational

TABLE 25-3 Sample Home Safety Evaluation Checklist

Floors	Clear pathway (no objects or clutter on the floor); no throw rugs or use of double-sided tape to prevent slipping; no exposed or frayed cords or electrical wires
Stairs and steps	No uneven or broken steps; adequate lighting; accessible light switches; no torn or loose carpets; available handrails (loose handrails are fixed and available on both sides of the stairs); marked steps for easy identification
Kitchen	Things are accessible or at waist level; steady step stool
Living room	Removing unsafe chairs (too low or no arms)
Bathrooms	Nonslip rubber mat; available grab bars or support inside tub or next to toilet; water temperature at 120° F
Bedroom	Easy-to-reach lamp; adequate distance of the side of the bed to the wall
Others	No toxic substances (should be properly stored if present); appropriate medication storage; first-aid kit availability; telephone access; waste disposal

therapist will transition the client from wheelchair to car. The therapists will follow the older adult at home, and the physical therapist can start a safety evaluation by, for example, measuring the height of the bed or the width of the door, while the occupational therapist assesses safety barriers as well. Safety deficits are identified after the evaluation and then modifications, adaptive techniques, and recommended safety devices are discussed with the patient, family, or caregivers, on the basis of the assessment. Environmental safety recommendations are advocated and family members or caregivers can be trained on other accommodations or adaptations to ensure an optimal level of daily performance and improve patient outcomes overall.

Other Homecare Issues

Other practical issues pertinent to a patient's plan of care relate to resources. Many community agencies offer senior programs and services. Several local cancer support groups, faith-based groups, and agencies on aging in the community can provide resources for transportation, chore services, adult day care, and a variety of senior activities. Local and national cancer agencies provide assistance with transportation, such as the Road to Recovery program of the American Cancer Society, and other public or private sector programs. Some transportation services are provided in the community on the basis of age and health insurance.

Preserving independence while maintaining safety should always be the goal, and physicians should always be alert and assess the cause when a deficit is noted. Long-term treatment and medical care for the older adult with cancer often involves periodic medical visits, lifestyle modifications, and prolonged medication or equipment use to manage symptoms or side effects of cancer treatments. Unmanaged symptoms from cancer and its treatments expose the elderly patient to depression or psychological disabilities. Alternative living arrangements such as nursing home placement may be necessary when it is no longer safe or possible to keep the elderly patient functioning adequately at home. The home environment may not be the best place for maintaining health when someone has vision, hearing, or mobility deficits. Factors to consider when recommending long-term care placement include medical stability, orientation, activities of daily living (ADL), skilled therapy requirement, living condition, and resources. Potential issues of guilt or role-restructuring within a family or caregiver network should be addressed and caregiver support should be considered when long-term care placement is the best course of action for the patient.

A doctor's order for homecare should include and specify the type of skilled care and unskilled services required as well as the frequency of the services ordered. It should clearly explain to the payer why rendering the service is reasonable and necessary. If orders have to be amended, it should clearly specify and indicate what is to be changed and the reason for the changes. The frequency of the service incorporated in the care plan should be justified by the changes in the patient's medical condition.

LONG-TERM CARE OPTIONS FOR THE OLDER ADULT

The aging population in the United States has resulted in a large number of people with chronic illness and a declining ability to care for themselves in their homes. Many older patients do not suffer from a single life-threatening illness but rather a slow progression of illnesses with physical and psychosocial burdens that can elicit caregiver burnout. Studies have shown that elderly patients with comprehensive discharge plans by skilled professionals such as advanced practice nurses have much lower risk for discharge failures.[28-29] If these patients are followed up in their homes, they have decreased readmission rates and a longer time at home between hospitalizations. Comprehensive plans need to be prepared with the family to allow for successful transitions between hospital, home, and skilled nursing facility (SNF).

Locating services for the elderly can be a daunting task for the patient, the family, and the health care provider. It is critical to understand the Medicare system and what is covered for the patient older than 65 years. It is important to note that some patients may have Medicare supplement insurance plans, either from the American Association of Retired Persons (AARP) or as part of their retirement package.[30] These policies are usually purchased by a Medicare patient. This insurance usually covers only 20% copayment for Medicare benefits and does not cover long-term custodial care (Table 25-4).

TABLE 25-4 Medicare

Medicare Basics

- People age 65 or older
- People under 65 with certain disabilities
- People of any age with end-stage renal disease

The Different Parts of Medicare

Medicare Part A (Hospital Insurance)

- Helps cover inpatient care in hospitals
- Helps cover skilled nursing facility, hospice, and home health care

Medicare Part B (Medical Insurance)

- Helps cover physician services, outpatient care, and home health care
- Helps cover some preventive services

Medicare Part C (Medicare Advantage Plans – like HMO or PPO)

- A health coverage option run by private insurance companies approved by and under a contract with Medicare

Medicare Part D (Medicare Prescription Drug Coverage)

- Prescription drug option run by private insurance companies approved by and under contract with Medicare

Medicare Coverage Choices

Original Medicare

- Fee-for-service coverage
- Federal government management
- Provides Part A and B coverage
- Patient can see any doctor or hospital that accepts Medicare
- Patient can join a Prescription Drug Plan
- Patient can buy a Medigap (Medicare Supplement Insurance) policy sold by private insurance companies to fill the gaps in Part A and Part B

Medicare Advantage Plans (HMO or PPO)

- Run by private insurance approved by and under contract to Medicare
- Provides Part A and Part b coverage but can charge various amounts for certain services

TRICARE Coverage

- Coverage for active-duty military or retirees and their families.
- Retired military must enroll in Part B to keep TRICARE coverage

Other Medicare Health Plans

- Part of Medicare but not a Medicare advantage plan
- Most plans provide Part A and Part B coverage, and some also provide prescription drug coverage
- Include Medicare Cost Plans, Demonstration/Pilot Programs and Programs of All-Inclusive Care for the Elderly (PACE)*.
- Patients may choose a Homecare Agency from the participating Medicare-Certified Home Health Agencies in their area. Medicare Advantage Plan (HMO or PPO) or other Medicare Health Plans may require the patient to use a contracted agency. Medicare has a "Home Health Compare" tool on the web that compares agencies by location. Check www.medicare.gov- click "Resources" and then "Home Health Agencies." Please see Table 4 on options for elderly patients covered by Medicare.

Medicaid

- Joint Federal and state program that helps pay medical costs for those with low-income; programs vary from state to state
- Possible coverage for services that Medicare does not cover (nursing home, home health)

Note: Based on information from the U.S. Department of Health and Human Services- Centers for Medicare and Medicaid services.[30]
*PACE is a Medicare and Medicaid program that allows patients who would need a nursing home to remain at home. PACE provides all the care and services covered by Medicare and Medicaid as well as additional medically-necessary care and services not covered. There are limited service areas that provide PACE services. Check this website for covered areas: www.medicare.gov/Publications/Pubs/pfd/11341.pdf

CASE 25-2 CASE STUDY

DL is a 69-year-old widowed man with stage III colon cancer who completed 6 months of chemotherapy. Various family members stayed and offered assistance to the patient. The patient presented for follow-up with his primary physician approximately 6 months after chemotherapy, appearing unkempt. His son reported that the patient has not been eating, has not been taking his medications correctly, and has not been participating in activities at the senior center.

Possible warning signs that elderly patients are failing to care for themselves at home:

- *Personal hygiene changes, i.e., failure to bathe, wearing the same clothes all the time, or sleeping in the same clothes*
- *Responses such as, "Why should I bathe or change my clothes? I do not go out anymore."*
- *A dusty/dirty residence that was formerly neat*
- *A lack of food in the refrigerator or placing to-go orders on a regular basis may signal difficulty driving, or a physical problem with lifting groceries*
- *Tiredness and constant complaints may be a sign of depression*
- *Forgetting to pay bills, turn off stove, leaving water running, not taking medications, or leaving the phone off the hook*

The physician ordered a home safety evaluation and the physical therapist reported that the patient was struggling at home. Meals-on-wheels were provided for the patient and it was arranged that the senior access shuttle would provide transportation to the senior center once a week.

One month later, the patient was admitted for 3 days with urosepsis, and was confused and weak. To qualify for Medicare SNF coverage, the patient must be hospitalized for at least 3 days. The patient was sent to a subacute rehabilitation facility (acute rehabilitation requires performance of physical/occupational therapy for 3 hours per day) with a skilled need of IV antibiotics and daily physical therapy. He stayed 30 days, with Medicare paying 80% of the cost and the other 20% paid for by the patient's retirement health insurance plan with Blue Cross. His family arranged for the patient to sell his home and the patient was moved to an assisted living complex. The patient will receive services: shower help, daily dressing help, three meals per day, shuttle rides for appointments and shopping, and twice-daily medication administration. The cost for this patient is between $1,800-2,500 per month. If the patient's physical needs increase, assisted living will be able to care for the patient until he requires total care. If an elderly patient requires 24-hour care and does not have a skilled need, the patient must pay for custodial care (Medicare does not cover this type of care). If the patient qualifies for Medicaid, there are a limited number of beds in a SNF that can care for these patients.

Summary and Conclusions

Aging has become a worldwide phenomenon and United States demographics indicate an unprecedented growth of the older adult population. Geriatric care poses a unique challenge to health care providers and the health care system in general. Managing older adults with cancer and associated chronic conditions can be complex, as cancer management extends well beyond the initial diagnosis and treatment. This chapter has reviewed factors, such as medication adherence, that can have an impact on effective disease management for the older adult population. The elderly are the largest users of prescription medications and are at risk for problems in medication management. Since a drug's effectiveness is dependent on its therapeutic concentration, medication adherence has critical implications for older adults with cancer. Practical recommendations for increasing adherence were outlined. This chapter also discussed safety considerations for an older adult transitioning care from hospital to a home setting.

More people are surviving cancer as a result of breakthroughs in cancer screening, diagnosis, and treatment. The period following hospitalization may be one of the most challenging times for cancer symptom management. Discharge planning should consider a comprehensive geriatric assessment to guide individualized client service planning for a variety of home health and home care services. Also, home safety evaluation to identify safety risks (modifiable and amenable to interventions), should be considered when setting priorities for service provision upon discharge. Lastly, uncoordinated health care services can adversely affect health outcomes for the elderly. Health care providers are encouraged to keep abreast of state and federal regulations concerning health care. Use of community resources is highly advocated. Useful links and resources for supportive geriatric care are also provided.

In summary, interdisciplinary management is crucial to ensure a positive effect on the health outcomes of older adult patients with cancer. Systematic approaches are needed to determine resources available, to identify the type of health care assistance needed, and to refer to appropriate services as required. Comprehensive geriatric care is best provided by a team of health care professionals with the goal of preserving the elderly person's social, cognitive, and physical function, thereby reducing health care costs and maintaining quality of life.

TABLE 25-5 Long-term Care Options and Medicare Coverage

Types of Long-Term Care	Services
A. Home Health Care	
• **Medicare may pay if patient is elderly or disabled living in their own home.** • **Patient must be home bound** • **Covered under Part A & B** • **Plan of care must be signed by MD and services provided by a Medicare certified agency** • **Medicaid programs may pay for home health aides depending on the state**	• Skilled nursing care- services and care that can only be performed safely and correctly by a licensed registered nurse, e.g., IV medications, pain pumps, wound care, TPN, and tube feedings • Homemaker/Health Aides- 2-3x/week - House Cleaning; laundry; bathe and dress - Plan and shop for meals - Move patient from bed - Physical Therapy- 2x/week • Speech Language pathology • Occupational Therapy
	Durable Medical Equipment (DME)
	Patient pays 20% of Medicare- approved amount in Parts A & B • Oxygen Equipment • Wheelchairs (non-electric) • Walkers • Hospital Beds. Medicare Does Not Cover DME services such as: • 24 hour care at home • Meal delivery • Homemaker care (bathing, shopping, cleaning laundry, and mobility help) when there is no skilled nursing need. • Shower chairs and commodes
B. Hospice Care	
Medicare will cover hospice care if the physician certifies that the patient has less than 6 months to live.	• Hospice staff on call 24/7 • Manages patient's pain • Assists family to care for patient • Assist patient and family with emotional, psychosocial and spiritual aspects of dying • Provides medications supplies and all equipment
Four Levels of Medicare Coverage for Hospice • **Routine Home- Nursing Care and Home Health Aide, Social Work and Chaplain** • **Continuous Home Care- allowed only in periods of crisis; can be at home or inpatient hospice.** • **Respite Care- 5 days of consecutive care. Inpatient Hospice, hospital of SNF.** • **General Inpatient Care- only for pain control and symptom management. Medicare does not cover the room and board in a SNF under hospice for reasons other than those listed here.**	
Some states have "homes for the dying" in the community. These homes can be at no charge or just cost between 6,000-8,000 thousand dollars per month. The home usually is staffed by an RN, care partner and volunteers. Patients can also be seen by a hospice nursing agency with nursing support, chaplain, and aide visits.	
Check this informative website: **www.compassionandsupport.org**	

Continued

TABLE 25-5 Long-term Care Options and Medicare Coverage—cont'd

Types of Long-Term Care	Services
C. Skilled Nursing Facility/Nursing Home	
Patient responsibility with Medicare: • **$0 for the 1st 20 days each benefit period** • **$137.50 per day for days 21-100 each benefit period** • **All cost for each day after day 100 in a benefit period.** **Admissions allowed only after a 3-day inpatient hospital stay for a related illness or injury or within 30 days of hospitalization.**	• Semi-Private Room • Meals • Skilled Nursing Care (intravenous medications, wound care) • Rehabilitative Services including physical therapy, occupational therapy and speech therapy • To qualify the patient must have a skilled nursing need such as. • SNF may specialize in short term or acute care nursing care, intermediate care or long-term care. **Medicare does not cover long-term or custodial care in this setting.** Web Links for Choosing SNF: - www.medicare.gov/nhcompare - www.aarp.org_promtions/text/life.nursinghomechecklist.pdf - www.aarpmagazine.org - www.nccnhr.org/public/50_156_455.cfm.
D. Assisted Living for Seniors	
• **Non-medical aspects of daily living** • **Medicare covers none of the cost** **Cost Range from $800-$ 4,000 or more per month depending on location**	• Help with aspects of daily living- bathing, dressing, mobility, and eating • Separate private living areas with a common dining room and social room • Social activities • Transportation • Physical activities • Some have specialized care for: cognitive disabilities, respite care, short term care, and hospice. • Some states allow for medication distribution by a non-license medical assistant under the direction of an RN
E. Board and Care	
• **Not covered by Medicare** • **Can be senior subsidized housing, Housing and Urban Development (HUD), or Section 8 Housing** • **Rent based on ability to pay** • **Long waiting lists for limited income patients**	• Apartment setting for 100 residents • Home setting for 6 residents or less • Activities of daily living (ADL) assistance • Communal meals • Daily staff contact • Usually with 24-hour non-medical supervision Useful links: www.helpguide.org/elderly/board_care_homes_seniors_residential.htm
F. Adult Day Care	
• **No Medicare coverage** • **Medicaid may pay for services provided in a state licensed facilities** • **Some private long-term insurance may pay**	• Health monitoring • Social activities • Meals • Safety and security • Alzheimer's/dementia care • Assistance with ADLs • Exercise • Mental stimulation • Transportation

Note: Based on information from the U.S. Department of Health and Human Services- Centers for Medicare and Medicaid services.[30]
SNF, skilled nursing facility

See expertconsult.com for a complete list of references and web resources for this chapter

CHAPTER

26

Caregiver Burden

Barbara A. Given, Charles W. Given, and Paula Sherwood

A cancer diagnosis is often acute in onset and sparks an abrupt need for diagnostic and treatment decisions for the patient and family. Family members find that the patient's cancer treatment trajectory poses physical, psychological, and social challenges, particularly for older patients. Shortened inpatient care and more complex outpatient treatment regimens require family members to become active partners in cancer care. This complex and changing care by family members challenges their knowledge and skills, as they do not know how to provide "cancer care."

Family members often take primary responsibility for symptom management, wound care, pumps and equipment, transportation, mental health, support, and medication administration, while maintaining their own daily responsibilities, as well as those of the person with cancer, and coping with their emotional responses to the patient's diagnosis and the uncertainty of the future.[1] Uncertainty is intensified by the disease, treatment responses or failures, the patient's emotional and physical responses, and how these demands and pressures bear upon family caregivers. In addition, cancer and cancer-related treatment may alter family functioning and communication patterns, family member occupational roles, and social roles.[2] Increasingly, the health care system demands that informal caregivers behave more like formal care providers to achieve optimal patient clinical outcomes. In turn, caregivers require support and training, as well as coordination and communication with health care providers, to carry out the tasks of care. Patients' outcomes depend on the partnerships among the patient and his or her family caregiver and oncology providers. Providers need to recognize that patients and family members react as a unit and thus both members of the dyad have a legitimate need for assistance and care.

The purpose of this chapter is to review caregiver burden: the needs, roles, and concerns of family caregivers (typically spouses or adult children) providing care to older cancer patients undergoing cancer treatment. Spouses of older patients will be the primary focus because they comprise the largest group of caregivers for the older adult. Implications and recommendations for improving practice suggest how providers can engage family caregivers to participate more effectively in patient care.

DEFINITION OF BURDEN

Family caregiving is defined as the provision of unpaid aid or assistance and care by one or more family members (defined broadly) to another family member with cancer. This care extends beyond the usual family activities, such as cooking or household chores that are a part of normal daily life; it also includes critical components of health care. Among them are symptom management, nutrition support, response to illness behaviors (e.g., anger), modification of usual roles, interpersonal care (e.g., communication), implementation of prescription regimens, acute episode management, use of community resources, and navigation of the health care system.[3-5] Caregivers make major decisions, adjust to change and challenges, access resources for care, provide direct care, and coordinate patient visits with the health care system. Coordinating care (such as scheduling appointments, requesting medical records, and arranging transportation) can add substantially to caregivers' responsibilities and may increase burden.[6,7]

Burden, a negative reaction, is a multidimensional concept that stems from the imbalance between the social, psychological, and economic consequences permeating a care situation and the caregivers' coping strategies to meet the demands of patient care.[4,5,8-12] Caregivers who are unable to apply effective coping strategies to care demands may develop burden, which, if sustained, may lead to depression (see Assessment).[13-19]

Caregiver depression is considered to be a secondary or long-term mood disturbance that may develop as a result of unrelieved stress or burden.[20-24] Depression may emerge as a consequence of sustained caregiver burden and may be manifested by feelings of loneliness, sadness, isolation, fearfulness, and irritability.[25] Caregiver depression may be less dependent on recent changes in the patient's status and more dependent on whether the caregiver is able to employ coping mechanisms to alleviate burden before it progresses to depression.[2,19,23-27] In order to stop the progression of caregiver burden into more serious psychological responses, it is imperative that health care providers communicate with patients and their families to define and prioritize appropriate care demands and care tasks. Defining expectations for family caregivers can be beneficial for patients and

families, as well as for oncology providers. The establishment of clear instructions, along with education on what to expect in the way of possible side effects or complications and what can be done to manage care at home will engage family members in assisting the patient and will reduce their uncertainty. For providers, patients and families become allies in patient care management, as well as sentinels to detect and report problems and clinical complications. If these problems are identified early, they can help prevent interruptions or delays in treatment.[23,25,28] While providing care may result in negative emotional and physical consequences for caregivers, it is important to remember that care provision can also engender satisfaction and meaning. Positive consequences, such as rewards, self-esteem, support, uplifts, and satisfaction, may provide a buffer to the negative effects of caregiving.[29-31] More research is warranted to identify ways of expanding positive aspects of care in the face of increased and recurring care demands.

CASE 26-1

The patient is a 68-year-old woman who presented for evaluation of unusual behavior: she kept asking her 72-year-old husband whether he could smell the oranges. Computed tomography (CT) of the brain did not show a bleed, but magnetic resonance imaging (MRI) demonstrated a mass. Surgery and a biopsy were scheduled for the next day to have the tumor removed; the diagnosis confirmed glioblastoma multiforme.

The patient was experiencing left-sided weakness and extreme fatigue. She was unable to properly bathe and feed herself or use the bathroom unaided. Her husband had to quickly figure out the proper ways to take care of her. He set up a bed for her on the first floor of their house.

Every morning, the patient's husband had to take her to the hospital for treatment. After treatment, she usually experienced nausea, loss of appetite, and increased fatigue. Her husband also had to learn to take notes at all of her doctor's appointments so that he could effectively manage her care and help with symptom management.

As the patient's condition began to deteriorate, her personality changed and she became very demanding and irritable. Her husband began to feel alone and distressed and didn't know how to do deal with his situation. He appreciated the help that he received, but he began to lose sleep and felt physically and mentally exhausted. He wanted to take care of his wife, but he was having trouble coping and felt burdened with the required care.

CAREGIVER CARE DEMANDS

Care demands include dealing with patients' physical care, nutrition, spiritual support, symptom management, housekeeping, transportation, and financial needs. Regardless of the level or intensity of involvement, disruption of daily activities, competing demands, and unfamiliar physical care demands, those that produce anxiety or uncertainty have been shown to result in caregiver burden.[31-33] Each type of caregiver task involvement demands different skills and knowledge, organizational capacities, and social and psychological strengths.[5,11] Unmet demands for care are a large source of burden for family caregivers and have been associated with poorer caregiver health, higher costs of care, and higher incidence of psychiatric diagnosis.[34,35] Caregivers also need information about their own self-care, the importance of networking with other caregivers, the importance of maintaining social support and contacts, and warning signs about their own levels of stress.[2,36]

Care demands stemming from the presence of neuropsychiatric and cognitive dysfunction (e.g., agitation, inappropriate behavior, and apathy) are particularly stressful for caregivers.[37-39] Management of cognitive and neuropsychiatric sequelae may produce higher levels of caregiver distress than assisting with impaired physical functioning.[31,39-41]

Moreover, as the caregiving situation evolves, there are additional opportunities for role ambiguity, role confusion, and role overload. Negative consequences for the caregiver, such as increased burden, can arise as caregivers seek to balance caregiving with work, family, and leisure activities.[42-45] The key to overcoming role ambiguity is to understand when new changes are likely to occur or when expectations shift as patient status changes.[46]

CASE 26-2

J., 64, taught children with learning disabilities, while her husband B., also 64, worked from home as a consultant.

When B. was diagnosed with a brain tumor, words that J. could not understand swirled through her mind: grade III, astrocytoma, malignant neoplasm, radical resection, biopsy, parietal, craniotomy.

She read journals, blogs, and Web sites and was overwhelmed with the diversity of the information she was reading. The thought of potential care demands competing with her work hours caused considerable stress.

Direct-Care Tasks

For caregivers of older cancer patients, direct-care activities occur at end of life or among patients who are disabled. These direct-care tasks include dressing changes, catheter care, wound care, and equipment and medication management. Medication management may be particularly burdensome for family caregivers. Older patients often have numerous comorbid conditions in addition to cancer. For the caregiver, the severity of patients' functional impairment and disability has been consistently shown to increase care demands on the caregiver and restrict other caregiver roles, thereby increasing caregiver distress.[40,47,48] Caregivers should be encouraged to facilitate the patients' return to normal physical functioning; however, this assistance may be problematic for older caregivers who have their own functional limitations. Providers can offer guidance and

direction so caregivers can receive the assistance they need to provide care.

Cancer treatment can complicate preexisting medication regimens for other comorbidities, which means that caregivers must receive training, guidance, and access to comprehensive information to help them perform safe and effective medication administration. For example, oral-targeted therapies are especially complex; with oral agents, caregivers must rely on different sources for refilling prescriptions (specialty pharmacies, mail-order plans) and may rely on other mechanisms for reimbursement (e.g., private insurance and Veterans Administration benefits). Caregivers require education not only on how to administer medication but also on how to monitor for side effects and make critical decisions (e.g., dosing, withholding, and discontinuation).[49,50]

Symptom management often becomes a primary role for caregivers as a result of patient treatment, and successful management of symptoms is associated with lower caregiver burden. Patients experience multiple and severe symptoms from treatment, including pain, nausea, fatigue, shortness of breath, and anorexia.[15,29,51-57] Several researchers have demonstrated that patient depression is closely linked to caregivers' mental health.[58,59] This shared level of distress demonstrates that both the patient and caregiver need care consideration.[58] Patients and their family caregivers should be screened for depression throughout the care trajectory and receive treatment if they are clinically depressed.

Increased symptoms can occur in elderly patients with multiple comorbid conditions and may also accompany different cycles of treatment or certain protocols. Interventions designed to help the caregiver with patient symptom management may lower the negative reaction and burden. [60] Unfortunately, symptom resolution does not eliminate the caregiver role; caregivers report that they continue to provide assistance and are often on call for months after active treatment is over.[2,47]

Employment

Caregivers must adapt their employment obligations so as to manage and meet care demands,[8,61-63] which may result in missed days, work interruptions, leaves of absence, and reduced productivity. While vacation and personal time are always options, caregivers may also use the Family Medical Leave Act, which provides family members time to provide care. Generally, studies on employed caregivers report that 20% to 30% experience work-related challenges and distress.[64,65] When faced with employment demands, women appear particularly at risk for emotional distress and greater perceived care demands.[66] For some caregivers, however, employment provides respite and serves as a buffer to distress.[27,66-68]

CAREGIVER-RELATED ISSUES

Multiple caregiver characteristics have been linked with the degree to which a family member will perceive burden associated with providing care. Understanding these groups of caregivers is vital for identifying those at risk for burden. Gender, for example, has been established to be differentially related to caregiver distress. Overall, caregiving is reported to be more stressful for women (wives and daughters) than for men (husbands and sons), yet women have been shown to be more responsive to caregiver interventions.[2,47,69]

Older age presents challenges, especially for caregiver spouses who may be on fixed incomes, and who may be in poor physical health themselves. Low personal and household incomes, loss of income, out-of-pocket expenses, and limited financial resources all contribute to caregiver stress for these older caregivers.[45,47,68,70] However, studies have consistently revealed that adult children, especially daughters, exhibit higher levels of burden and lower well-being than older caregivers. This may be related to an increase in competing demands of family, work, leisure, and social obligations for younger caregivers.

CAREGIVER HEALTH CONDITIONS

Caregivers who are burdened consistently report lower levels of physical health. Although the sources of caregivers' lower levels of physical health are multifaceted and to some extent unexplored, caregivers report higher levels of chronic conditions, pain, sleep disturbance, fatigue, headaches, lower immune functioning, altered response to influenza immunizations, slower wound healing, higher blood pressure, and altered lipid profiles.[19,29,71-79] Caregivers have been shown to have marked changes in a broad array of neurohormonal and inflammatory parameters in the year after patient diagnosis. The most striking changes were in systemic inflammation and increased risk for coronary heart disease. Data suggest that caring for a family member with brain cancer may heighten vulnerability to coronary disease, as well as other metabolic, autoimmune, and psychiatric conditions sensitive to inflammation.[25] Older caregivers with higher levels of depression, fatigue, and pain reported lower physical functioning.[80]

In addition to burden, depression, and demands of the tasks of care, older caregivers may themselves have chronic diseases, which are often left unattended as a result of care demands. Caregivers may forgo personal health maintenance due to the pressures of providing care for others.[13,81] Primary care providers need to encourage caregivers to manage their own health problems to continue providing quality care. Studies have shown negative caregiver outcomes when spouses are hospitalized.[82,83] Providers must remain vigilant of caregivers' health and the potential impact this may have on their ability to provide patient care.

CASE 26-3

L.'s husband has colorectal cancer and is unable to provide basic self-care as a result of disease progression. An aide comes in daily for an hour to bathe him. He has a colostomy that needs vigilant attention. The skin surrounding his stoma looks normal and the stoma is pink and appears healthy. The room is filled with medical supplies.

L. confided that her symptoms of congestive heart failure have gotten worse in the past couple of weeks. She states that she gets winded very easily and she has occasional chest pain. She also has a history of atrial fibrillation and she can feel her heart fluttering. She does not want her health to keep her from caring for her husband. She is intentionally keeping her health problems from her husband's medical team. She states her diabetes is well controlled with insulin injections. She takes alprazolam for anxiety, which has gotten much worse since her husband's diagnosis.

Social Support

The availability and use of social networks and social interaction have been shown to alleviate and prevent caregiver burden.[84] Feelings of emotional connectedness and cohesion with one's social network protects caregivers from burden and distress. Support such as understanding, counseling, and acting as a confidant may help moderate their burden.[74,85,86] It is important for providers to communicate with caregivers on how to effectively monitor and manage their patients.

Relationship to the Patient

Wives, husbands, daughters, and sons approach the practice of caregiving in different ways.[31] Spousal caregivers of older cancer patients have been shown to be at high risk for caregiver burden because they live with the patient, provide the most extensive and comprehensive care, maintain their role longer, often assume other household tasks, and tolerate greater levels of patient disability.[29,87] Alternatively, spouses may have stronger established patterns of decision making with the patient, which can facilitate treatment and symptom management decisions. Other researchers report that adult children are at high risk for burden because of a larger disruption in lifestyle from competing demands (careers, children, their own spouse).[88] Providers should assess the patient/caregiver relationship from the beginning and observe changes over time to understand when mounting strain, tensions, and burden may occur.

Preexisting discord in family relationships may be aggravated by the care process, by decision making, and by how different family members respond to the challenges of cancer care.[89-91] Perceived family conflict, withdrawal, changes in family dynamics, and loss of intimate exchange with the cancer patient may be associated with a range of negative psychosocial patient outcomes, as well as with caregiver burden. Among caregivers in relationships that are less mutually satisfying, patient needs may restrict caregivers' usual activities, which in turn may increase caregiver resentment and burden.[15,47,90,92]

Socioeconomic Status and Insurance

Socioeconomic status poses unique challenges for caregivers of cancer patients. For most caregivers of spouses, Medicare provides basic coverage of health benefits, yet there are limits to coverage for ambulatory care services, some home care services, and limitations in payment for some drug protocols, particularly those that are newly approved by the FDA. The challenges for older cancer patients and their caregivers include copays and supplemental insurance for new expensive treatments. Medicare coverage is limited in what is covered and the amount covered. Out-of-pocket costs are often high. Concerns about financial status are pervasive; for example, oral agents may cost thousands of dollars per month, often with a copay.[63,70]

CASE 26-4

A. is a 68-year-old woman whose husband was recently diagnosed with lung cancer. A. reports a very weak family support system. She has two daughters who are married and live out-of-state.

A. has a great deal of concern about her finances; her husband was laid off around the same time as the diagnosis and is having trouble finding new employment because of his physical limitations. She has extremely large copayments for the medical care. She would like more financial assistance but there seems to be none available and she feels the pressure of financial costs. Above all, A. wants to take care of her husband, and feels burdened by the financial uncertainty and by her husband's future.

CAREGIVER TRAITS

Providers should assess caregiver traits and personal resources to help them alleviate distress. Dispositional optimism is a stable personality trait that can be thought of as a generalized expectancy of good outcomes, even in the face of adversity. Those with a sense of optimism feel they can better endure the negative effects of caregiving. Caregiver optimism has been associated with better quality of life, lower depression, less delay and anxiety in seeking care, and higher expectation of a positive outcome of medical care, making optimism a protective mechanism against burden. Optimists may be using different coping strategies than pessimists when confronted with stressful events.[93,94] Pessimism has been found to be a warning sign for compromised health in the caregiver. Caregiver optimism, for example, is directly related to how family members perceive the care situation and, in turn, relates to the degree of burden caregivers will perceive.[85,90,95,96] Another caregiver trait similar to optimism is mastery, which is the perception of their sense of

worth as a caregiver and how they perceive their ability to meet the demands of providing care.[66,85,97] Interventions are recommended to strengthen optimistic attitudes and weaken the pessimistic view, without giving a false sense of optimism when a cure is not possible. Mastery has been shown to positively influence caregivers' level of burden, their depressive symptoms, and their response to care.[98,99] Caregivers with a high sense of mastery have reported using more problem-focused coping strategies to meet care demands[100-102] and ultimately have indicated a lower level of caregiver burden.[30,103,104] Health care practitioners can strive to improve caregivers' sense of mastery by enhancing their knowledge and skills and reducing their feelings of uncertainty, thus lowering the risk for emotional distress. Caregiver mastery can also be improved by implementing educational and cognitive behavioral interventions for meeting caregiver needs to provide care.[97]

RISK ASSESSMENT FOR CAREGIVER BURDEN

Risk assessments for caregivers are vital to identify individuals at risk for negative outcomes and to provide information on resources for patient and caregiver care, such as cancer-related community resources (e.g., major cancer support organizations), as well as sources of additional information (e.g., Internet Web sites). The assessment should address major areas of functioning including role, social, and family functioning and should identify any practical problems stemming from care demands, such as managing equipment, finances, household tasks, arranging appointments, and transportation).

A risk appraisal measure (RAM), a brief screen for caregivers, has been used for dementia. It assesses multiple dimensions of risk and adverse outcomes in six areas: depression, burden, self-care and health behaviors, social support, safety, and patient problem behaviors. The RAM (Table 26-1) appears to be an efficient and easily administered tool that could provide a "road map" of interventions for providers. Such a tool would increase the likelihood for a caregiver to receive assistance in the areas needed to prevent or relieve burden.[105] (See Table 26-1).

Another caregiver assessment form has been developed by the American Medical Association.[106] This assessment focuses on caregiver stress, depression, need for support, and need for decision making. Both assessment forms are brief and may be useful for screening caregivers for emotional and physical distress. A more in-depth multidimensional caregiver burden tool, such as the Caregiver Reaction Assessment,[9] is suggested for long-term monitoring and planning interventions.

Overall areas to be included in a comprehensive assessment include: relationships between members of the dyad; necessary role changes; patient care requirements (symptoms, ADL, IADL); information needs about diagnosing treatment and expectations; care coordination; hours of care; capacity of caregiver; caregiver's own health status and expected role in care and support; and resources available for care. (Table 26-2).

TABLE 26-1 Risk Appraisal Measure (RAM)

Domain	RAM Items
Self-care and healthy behaviors	Sleep Rating of physical health
Patient problem behaviors	Information symptoms Feels stress with trying to help patient with ADL
Burden	Stress trying to meet responsibilities Strain around patient Feels good as a result of caregiving
Depression	Felt depressed last week
Social support	Satisfaction with help from friends Satisfaction with support from others
Safety	Felt like yelling Felt like hitting Able to leave patient alone

ADL, activities of daily living.

ASSESSMENT OF FAMILY CAREGIVER TO PLAN CARE

Cancer caregiver needs vary across experiences and thus providers must identify those needs and know they may change at key transition points, such as when the patient's care level goes from active treatment to palliative care. Reassessment is necessary and should be conducted regularly. Health care providers need to recognize that caregivers have varying levels of knowledge and skills and shoulder different levels of burden as they deal with constantly changing stages of patient demands. Providers must consider their approach on the basis of a given caregiver's skills and level of knowledge, and tailor their interventions to those needs. Personal and community resource referrals also depend on family caregiver needs.

CAREGIVER CHARACTERISTICS

Caregiver Self-Care

Caregivers involved with older cancer patients need to ensure that they consider their own self-care. Studies have shown that they discontinue vital health screenings and self-care such as exercise. Some studies have shown that increased health care use, increased total costs of care, and increased rates of psychiatric diagnosis may occur up to 2 years after caring for an older patient with cancer.[35]

Role of Primary Care Provider. With appropriate information and support in place, primary care physicians[107] appear willing to assist cancer patients and their family caregivers during treatment. Primary care physicians

TABLE 26-2 Assessment of Family Caregiver to Plan Care

Type and Quality of Prior Family Relationship (Prior to incident of care)
1. What was the quality of the relationship between the patient and family?
2. What is the usual decision-making and communication pattern about health care within the family?
Initiation and Maintenance of the Family Role
1. What is the duration of the "care" relationship expected to be with the formal system?
2. What are the expectations for patient and family involvement in care?
Patient Characteristics:
1. What are the care requirements?
2. What are the signs and symptoms of disease or treatment that require family assistance?
3. What are the emotional and supportive needs?
Care System and Involvement Required:
1. What are the care requirements?
2. What is the patient's functional level and what family involvement is needed?
3. What are the hours of care per week? Per day?
4. What components of home care cause the *family* difficulty or distress?
5. What are the skills and assistance needed from the formal system?
Factors Related to Diagnosis and Treatment:
1. What are the patient and family expectations and knowledge about the course of the disease and its treatment?
2. What is the expected length of the overall treatment?
3. What is the likely treatment outcome? (Is recovery expected?)
Family Member Characteristics:
1. What is the relationship of the patient to the family members assisting with care?
2. What other family, work, or social roles exist for those helping with care?
3. What roles have been given up by the family to maintain the care (work, family, social)?
4. What are family member/formal system interactions around care?
5. What emotional support do family members need, are they burdened? Do they express burden?
Patient's and Family's Role in Care:
1. What is the availability of family members to assist with care?
2. Do the family members feel they have adequate knowledge/skills needed to provide care?
3. Does the family feel "prepared" and competent to care?
4. In what areas do family members need assistance? Which treatments?
5. What skills do family members need?
Support and Resources for Care
1. What "other" family resources are available to assist with care?
2. Is there adequate perceived support available?
3. What other resources should be mobilized to assist the family?
Care Outcomes and Status:
1. What negative reactions or burdens from home care are evident from the family member?
2. What is the perceived impact of care on the family member's physical and mental health?
3. How does the family perceive that care affects their daily activities and role responsibilities? Do they express burden?

can regularly monitor caregivers for distress, particularly at critical time points in the patient's disease trajectory. Referrals for psychological counseling and support, caregiver education, and assistance toward improving communication are vital.

INTERVENTIONS TO SUPPORT CAREGIVERS

Family caregivers need to feel better prepared to handle care demands including decision making, symptom control, and medication administration. When caregiver needs are not addressed, their physical and mental health is at risk, which may threaten the level of care the cancer patient receives. To ensure the appropriate and effective delivery of services, providers need to: (1) link patients and families to needed community and health care services; (2) coordinate care; (3) ensure that patients and families receive follow-up care; and (4) monitor the effectiveness of services upon patient referral. Often, family members do not take advantage of the available services. The capacity and ability of the caregiver also determines what resources are needed.

Caregivers develop a pattern of care, such as shared involvement, often within the first 6 to 8 weeks of care. They often describe their approach as trial and error.

Caregivers share care activities and respond together along with the patients to the demands of the illness and the patient's plan of care. Patients' preferences and abilities are the driving force in determining what the pattern of care is. Caregivers faced with unclear, incomplete, unknown, and changing role expectations may experience more role strain and burden and may not perform their duties as effectively as possible. Caregivers should be a major part of the plan of care developed for the older cancer patient. Providers need to assist caregivers to perform care tasks, coordinate resources, or find the support they need.

Interventions to help the patient with cancer require the caregiver to build skills, solve problems, and set priorities specific to the needs of the older patient. Interventions must help to alleviate caregiver distress, improve patient outcomes, and reduce health service utilization. Interventions should also be directed toward caregivers' emotional needs including assistance with stress reduction, time management, burden reduction, depression and anxiety management, and consideration of the caregiver's own health maintenance and self-care.[108] From the interventions used to help caregivers, only small to moderate effects have been found, but caregivers' burden can be reduced, their ability to cope can be improved, and their confidence in their ability to provide care can be increased. More-prepared, less-distressed caregivers will be better equipped to provide positive care for patients.

Educational and Informational Interventions

It is important that caregivers get education to help with problem solving and decisions, as well as information about the disease, its treatment, management of signs and symptoms, and prevention of adverse events. However, caregivers often become saturated and overwhelmed with too much information, which may not be tailored to their needs and which may be contradictory and irrelevant. Caregivers should be receiving information as they need it and when they can use it. A coach, mentor, or guide is found helpful by caregivers as they try to apply their new knowledge and skills.[4] In turn, caregivers can use that information to learn how to make care decisions.[109] When information alone is provided, it should give caregivers an opportunity to translate their new knowledge into action for patient care. There are numerous modes for information delivery, such as voice response systems, Web-based sites, and printed toolkits; all are readily available to aid patients and caregivers. Cancer centers can then provide recommendations about these informational resources to caregivers so that they will be directed to appropriate and credible sites. Caregivers need information in order to know and understand the patient's illness, his or her care needs, and their own role in that care. Information can improve caregivers' self-efficacy and may increase their accuracy in determining which symptoms patients are experiencing.[110]

Social Support Interventions

Caregivers need support from their families, from their coworkers, and from health care providers,[2] and should identify a key support person in each of these areas. Social support may come in various forms; several Web-based social networks have shown promise in reducing burden. There is preliminary evidence that telephone counseling may also increase social problem-solving skills and provide social support.[111] Good relationships, contact with friends, and social support from family and friends contribute to positive caregiver responses.[112] Social networks have proven vital in determining caregivers' responses to providing care: Those with strong social networks can receive much-needed guidance and support.[95] Supportive interventions focus on building rapport and creating an opportunity and forum to discuss difficulties, successes, and feelings about caregiving. Social support interventions[113] allowed participants in group settings to provide mutual support to one another, provided opportunities to share methods of dealing with caregiving difficulties, and identified strategies to incorporate these ideas into care.

Problem-Solving Skills and Psychoeducational Interventions

Psychoeducational interventions that concomitantly focus on providing information, teaching problem-solving skills, and utilizing psychological support and counseling approaches to decrease caregiver distress have lent tremendous support to caregivers. Psychoeducational interventions often involve multiple components that address areas such as symptom management, monitoring of problems, coordination of resources, health care communication, cognitive reframing, and emotional support,[16,114,115] and have produced improvements in caregiver levels of emotional tension and confidence, as well as in positive problem-solving skills for the management of care demands.[59,116-121]

Providers can assist caregivers by encouraging them to challenge negative thoughts, engage in positive activities, and develop problem-solving abilities that focus on time management, emotional control, and incorporating these skills into day-to-day care demands.[122,123]

Home Health Care Interventions and Care Coordination

Few intervention studies have focused on how home care support for family caregivers enhances coordination of care, improves support, and benefits caregiver outcomes.[124] Unfortunately, home health care interventions are unlikely to be reimbursed unless skilled care is required. Although community services may provide

assistance to family members, particularly older spouses, the need to arrange community resources contributes to the complexity of the care family members must provide. In addition, they may be reluctant to accept help for a variety of reasons. They often need help in finding the resources that are available in the community. Interventions that help family members mobilize resources such as chore services, homemaker services, or transportation should be considered. Assessing need and the care trajectory over time is crucial.

Summary

The duration and depth of care provided by family members and its impact on patient outcomes is underrecognized and often underappreciated. Concern for caregivers as partners in patient care and caregiver outcomes deserves careful attention by providers. A family plan of care should also be considered when an older person has a cancer diagnosis. Providers are challenged to recognize the value of the early and continued involvement of family members as care partners. Once this occurs, practitioners can more accurately identify situations that place caregivers at risk for burden and distress, which ultimately will decrease untoward hospitalizations and emergency department visits and improve patients' quality of life. Balancing the achievement of patient outcomes against the impact that providing this care has upon family members is the ultimate goal for family cancer care.

See expertconsult.com for a complete list of references and web resources for this chapter

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CHAPTER

27

Communication and Coordination

Peter Ward and James W. Davis Jr.

Coordination of care between oncologists and geriatricians is essential in the care of patients with cancer. Geriatric patients with cancer often have multiple complex comorbidities, making their oncology care more complex as well. Studies have shown that shared care models, where primary care physicians (PCPs) and geriatricians have an active role in the management of geriatric oncology, may improve patient satisfaction. Good communication between geriatricians and oncologists is the key part of this shared care model, but many other disciplines may be involved as well. In this chapter, a case study is presented that illustrates potential pitfalls in communication between the oncologist and the geriatrician during the different stages of cancer care. The chapter will also demonstrate how a shared care model works, the preferred methods of communication in certain circumstances, and how good communication may improve outcomes.

CASE 27-1

A.G. is an 81-year-old woman with a history of hypertension; a widow, she lived alone and was independent in her daily activities. She had complained about declining memory and family members had become concerned about her ability to continue to live alone and drive a car. She was forgetful about taking medications but her score on the Folstein mini-mental state examination (MMSE) was 28/30 (within normal limits). She declined to have help at home and was considering a move to assisted living. Several months prior to diagnosis she began to lose weight. She later complained of a dry cough. Chest x-ray showed a large (9.5 cm) mass in the right upper lobe of the lung.

WORKUP

The geriatrician or PCP usually initiates the workup of most cancers. There can be many potential ways to conduct the workup and preliminary consultation with an oncologist at this time can be helpful. For example in the case described above, the PCP may not know whether the patient needs to see a pulmonologist to attempt a diagnosis via bronchoscopy or if it would be more expedient to have an interventional radiologist perform a computed tomography (CT)-guided biopsy. It is preferable that these tests and procedures be ordered prior to the first consultation with the oncologist. There is often an urgency to make a diagnosis, especially if the patient is at a potentially curable stage. The fastest and most efficient way to communicate during this stage of cancer care is directly by phone or via email. Not only can this expedite the workup, but the PCP can also try to set up the initial consultation for the patient with the oncologist, assuming the workup will be completed in 1 to 2 weeks. This can be a critical time for the development of shared care, where the PCP and the oncologist begin to define their respective roles in communicating diagnosis, prognosis, and plans for future care. It is essential to give the patient and family clear information and to establish lines of communication so the family will know how to access care and address problems as they arise.

Often, these impromptu consults are termed "curbside" consults. Studies of "curbside" consultations have shown that advice by means of email, fax, and telephone has been shown to be very useful.[1] They can often be used to determine the need for a more formal consultation. This may be especially true in geriatric oncology. The geriatrician who has a high suspicion of cancer in a patient may be unsure whether to pursue a time-consuming, expensive, and potentially distressing workup for a patient with multiple comorbidities. A "curbside" consultation may help clarify whether or not the patient would be fit enough to tolerate treatment before embarking on the workup. "Curbside" consultations have also been shown to improve or maintain good relationships with other physicians. Interestingly, more subspecialists than primary care physicians felt that "curbside" consultations were important for maintaining good relationships among physicians.[2] However, these types of informal consultations have potential pitfalls. Studies have shown that the information conveyed may be incomplete or inaccurate. Also many physicians, especially subspecialists, may dislike "curbside" consultations because of the potential legal ramifications of giving such informal

advice; also, there may be no reimbursement for time spent answering these types of consults.

Another barrier to communication is the preference of the oncologist to have a tissue diagnosis before getting involved in a case. This is more often a problem in the academic setting where physicians tend to be salaried than in community cancer centers where oncologists see patients on a fee-for-service basis and are competing for referrals. However, if the referring physician knows the oncologist and maintains open lines of communication, especially in the academic setting, there is usually more willingness to assist in the workup before the first formal consultation.

DIAGNOSIS AND REFERRAL

CASE 27-1 CONTINUED

A.G. failed to keep several appointments for interventional radiology and diagnostic studies. Social services were contacted and the family became more involved. She appeared weaker and more confused. She was brought to appointments by family members but did not always recall the purpose of the visits. With the help and encouragement of her family, she moved into an assisted-living facility. Her lung biopsy revealed well-differentiated squamous cell carcinoma. She and family members met with a geriatric oncologist.

The time between the diagnosis and referral can be crucial. Good communication between the oncologist and the PCP can reduce delays between diagnosis and treatment. The uncertainties of treating geriatric patients with cancer can sometimes exacerbate these delays. In a study of breast cancer patients, the main factors that were independently related to delays in care were older age, lack of Social Security, and advanced stage.[3] Other barriers that may prevent older patients from being referred to an oncologist have been identified. The most common issues cited by PCPs are long waiting lists, mandatory tissue diagnosis before referral, and the belief that oncologists seldom relate to PCPs. In this same study, 86% of PCPs said they would refer an older patient with early-stage, potentially curable cancers, but only 65% would refer those with advanced-stage, potentially incurable cancers. Factors that influence the PCP's decision to refer were a patient's desire to be referred, the type of cancer, the stage of the cancer, and the severity of the cancer symptoms. According to this study, age was not a factor in the primary's decision of whether or not to refer the patient.[4]

When the decision to refer the patient is made, what is the best way to refer? This depends on the urgency of the referral. Someone with life-threatening disease is usually hospitalized where multiple subspecialists can be consulted simultaneously and a treatment plan can be made together. In patients who have rapidly progressive disease but are medically stable, coordination of care usually occurs in the outpatient setting. These urgent consults are best communicated by phone. As electronic medical records and resources become more frequently used, email may also be an effective way of communicating an urgent consult. A study of an email consultation service at the Walter Reed Army Medical Center showed that this could be a viable option. In a 20-month period, 3121 consultations were logged. The average time to response was approximately 12 hours. The implementation of the system required little extra training on the part of the users. In general, the use of this system mirrored the usual clinical practice of consultation and response. However, the study did identify potential barriers, such as a lack of secure communication and difficulty assigning workload credit for the participants, which may limit the use of this system in a broader setting.[5] Other reasons to refer by phone or email, as opposed to sending a letter, are to convey sensitive information, to relate any psychosocial problems that may affect treatment, or to convey information that may be too complex to communicate through a letter (Table 27-1).

TABLE 27-1 When Should a Referral Be Communicated By Phone?

- When the consult is urgent
- When there is sensitive information to convey (i.e., patient dissatisfaction with previous consultants)
- If there are any psychosocial problems that may affect treatment
- If the case is too complex to convey in a written form

Although telephone consultations seem to be the quickest and most direct way to initiate a consultation, some potential pitfalls of using this method of communication have been studied. A qualitative study of telephone consults between physicians identified five sources of tension: presentation, context, fragmented clinical process, reason for call, and responsibility. Consultants complained that the pace of conversation was too fast or too slow. Sometimes information was not conveyed because of the accent of the caller or because the caller was disorganized when describing the case. A case that may be extremely urgent from the perspective of the caller, may be just one of 10 phone consults that an oncologist receives during a day in which he is seeing 20 other patients in the office. The clinical process in phone consultations is fragmented and information passed from caller to consultant can be inaccurate or incomplete. A PCP may call a consultant for reassurance about a case; the consultant may view this as inappropriate, especially if his or her opinion is different from the caller's. Responsibility for a case may cause tensions in both directions. A caller may be trying to pass the responsibility of a complex case on to a consultant; alternatively, a consultant may find it easier to have a patient transferred to his or her hospital so as to see the patient in person, while the caller is reluctant to release the patient from his or her own care. All of these tensions tend to undermine the quality of care. (Table 27-2.)

TABLE 27-2 Five Sources of Tension during Telephone Consultations

Tension	Examples
Presentation	The pace, accent, organization, and tone of the caller or consultant may make it difficult for the other to understand or may create emotional tension.
Context	An urgent and important case to the caller may be just one of 10 telephone calls the consultant receives while rounding on other patients.
Fragmented Information	The consultant has to rely on observations and knowledge of the caller and information may be inaccurate or incomplete.
Responsibility	It may be easier for the consultant to take over the care of the patient, while the caller is only asking for advice and is not willing to give up the responsibility of the patient's care.
Reason for Call	The consultant may be asked to provide information that the caller could find in the medical literature, but may not have time to search for.

In the same study, the caller's and consultant's strategies for averting these tensions were reported. In some instances, the strategies used by the consultant to abate tension were seen by the caller as exacerbating tension. An example that was cited was a case where a consultant asked for the patient's laboratory results and the caller reported them as "all normal." The consultant then asked for the specific values of certain tests and the caller felt he was "being talked down to." Although they didn't offer specific strategies to avoid these circumstances, the authors of this study felt that it was important for both callers and consultants to recognize these tensions. They concluded that many physicians are poorly trained in professional communication skills and recommend that this be given greater importance in medical school curricula.[6]

In some circumstances, consults are made by means of a referral letter. A study of referral letters from PCPs to oncologists showed that the amount of information contained in the letters was quite variable. The key pieces of information for the PCP to convey to the oncologist are outlined in Table 27-3. As illustrated in the case above, the patient's "back story" can often be as important as the diagnosis and comorbidities. As pertains specifically to geriatric patients, a knowledge of geriatric syndromes such as cognitive impairment, history of falls, or other signs of frailty can strongly impact the oncologist's treatment plan. If this information has not been passed on from a physician who knows the patient well, it can sometimes be missed in an initial visit with the oncologist, who usually does not have the time to do a complete geriatric assessment.

In the initial consult note from the oncologist to the PCP, there are certain pieces of information that the PCP regards as essential, as listed in Table 27-4. When patients first consult with an oncologist, they often find the amount of information they are given to be overwhelming. They then see their PCP and ask for information on things such as prognosis and potential toxicities. They may even ask the PCP whether or not to pursue treatment. If this information is conveyed in the oncologist's consult note, it can keep everyone "on the same page."[7]

TABLE 27-3 Essential Information on Referral From PCP to the Oncologist

- Reason for consult
- Past medical history/chronic medical conditions that may affect oncology treatment
- Current medications
- Pertinent information on tests performed and the results
- Contact information of other consultants involved
- What the patient has been told about his or her diagnosis
- Concerns about any psychosocial problems that may affect treatment
- If there is a need for an interpreter and whether the patient is competent to make decisions

TABLE 27-4 Essential Information in the Consultation Reply Letter

- Restatement of the reason for consult
- Diagnosis and prognosis
- Details of the treatment plan
- Treatment goals and patient wishes/expectations
- Potential toxicities of the treatment and suggestions for management of these toxicities
- Concerns about psychosocial problems that may affect treatment
- What the patient has been told
- How to contact the oncologist

TREATMENT

CASE 27-1 CONTINUED

After A.G.'s consultation with the geriatric oncologist, plans were made for her to begin chemotherapy treatment for her lung cancer. Before treatment began, the patient was seen in the emergency room for a fall and a lumbar spine compression fracture was found. She became less mobile and required increased assistance in her assisted-living facility.

Good communication leading up to the point when the patient starts treatment can make the comanagement easier. Many questions arise at this point, such as how care will be coordinated and how complications will be monitored and treated. If the patient is hospitalized, who will assume responsibility during hospitalization? The answers to these questions may depend on the setting.

In a small community hospital, patients may be under the care of a hospitalist or the primary physician, with oncology consulting, whereas most academic centers have oncology wards where patients are primarily cared for by oncologists. One may assume in most settings that the oncologist would make most treatment decisions at this point, but a recent study of patient preferences showed that greater involvement by the PCP was associated with better patient satisfaction. Patients often prefer having treatment options described by the oncologist, but they depend on their PCP to discuss goals of care. Oncologists also prefer the PCP's involvement in discussions regarding goals of care.[8]

Patients often turn to their PCP when they are faced with difficult medical decisions after visits to specialists. This can be very evident when a geriatric patient is offered enrollment in a clinical trial. Most frequently, the invitation to participate in a clinical trial is introduced by the oncologist. Patients may feel pressured and suspect that the oncologist may be biased towards having the patient participate in the trial. Before enrolling in the trial, the patient may consult with his or her PCP. This is the time when the communication between the PCP and the oncologist will be crucial in order to do what is best for the patient. During this interaction, the oncologist can stress that there is a lack of level I evidence for optimal treatment of geriatric oncology patients. If there is good trust between the patient and the PCP, the importance of clinical trials can be presented in an unbiased way.

During the patient's cancer treatment, there are many aspects of care that the PCP may have more experience with, such as diabetes, COPD, or other chronic conditions. In many circumstances, the PCP may be the first to recognize signs of depression in a patient during treatment. In the same regard, the PCP may have more experience with treatment of depression. Close collaboration with the oncologist can minimize potential drug interactions between chemotherapy and any new medications added to the patient's regimen during this phase. Other issues that may fall under the expertise of the PCP during treatment include sexual concerns, fertility, contraception, and general health and nutrition.[14] In the case described above, a geriatrician would likely have more experience and knowledge about what additional services the patient may need in the assisted-living facility to improve her performance status before she begins chemotherapy.

Many of the common cancers in geriatric patients have a prolonged course of treatment. Breast cancer and prostate cancer patients often survive for many years. What prevents good communication during the treatment phase? A survey of PCPs comanaging patients undergoing chemotherapy showed that one of the most valued aspects of communication is the accessibility of the oncologist.[9] Both the oncologist and the PCP are extremely busy, and trying to reach one another by phone can often interrupt other patients' visits. A solution to this problem is for the oncologist to provide an email address in the consult reply letter. The PCP often serves as the first contact for health concerns that arise either as a consequence of the cancer or for unrelated problems such as in the aforementioned case. The PCP can alert the oncologist of such events before the patient's next visit and adjustments can be made in the treatment plan, so that unnecessary visits may be avoided. In the case above, the PCP alerted the oncologist to the patient's change in performance status and her treatment was delayed.

TOXICITIES

CASE 27-1 CONTINUED

After physical therapy and increased support from her family, A.G. was able to improve her functional status and began treatment for her lung cancer. She received her first cycle of gemcitabine, which she tolerated without any immediate side effects. About 12 days later, she began to have nosebleeds and presented to her geriatrician's office. A complete blood count was checked and she was found to be thrombocytopenic.

Managing toxicities of chemotherapy can be challenging for PCPs. As the armamentarium of chemotherapy continues to expand, it is increasingly difficult for PCPs to keep up with potential side effects of newer agents. In the case above, the primary care physician may or may not recognize thrombocytopenia as a common side effect of gemcitabine. Even if the PCP does recognize it, he or she would most likely call the oncologist to discuss how to manage this toxicity. As mentioned before, it is important to explain potential toxicities and strategies for management of these side effects in the initial consult note sent from the oncologist to the PCP. A simple and effective way of doing this is to include in the reply letter a standard information sheet with data regarding the cancer type, potential side effects, and recommendations for their management. Less than 20% of oncologists' consult letters contain this information. A group of general practitioners (GPs) in Australia were randomized to receive either a fax of an information sheet regarding a patient's chemotherapy regimen in addition to a consult reply letter or to receive just the reply letter alone. The intervention group showed a significant increase in their confidence in being able to manage the side effects of chemotherapy. They also showed increased satisfaction with communication. When compared to the reply letter alone, the information sheet was shown to be significantly more instructive. In addition to these findings, it is notable that the study had a response rate of 84%, which speaks to the utility of this intervention. Interventions such as these not only help to inform the primary care physician, but they can potentially also help oncologists

by decreasing the number of patients that are seen in their treatment centers for care of chemotherapy toxicities. This is a win-win situation, and one which can help maintain good lines of communication between oncologists and PCPs.[10]

FOLLOW-UP/SURVEILLANCE

CASE 27-1 CONTINUED

A.G. appeared to have a partial response after four cycles of therapy. She returned to her geriatrician with the understanding that her chemotherapy was finished and she did not require any further treatment. Her geriatrician and her oncologist had not spoken since the treatment had completed. The geriatrician was unsure of the follow-up plan and of whether she was in fact done with her treatment.

In the same way that it is important for the oncologist to inform the PCP about potential toxicities during the treatment phase, it is equally important for information on survivorship care to be communicated. As the number of long-term cancer survivors continues to grow and oncologists are forced to give preference to patients who are being actively treated, some of the burden of providing survivorship care will be carried by PCPs. During the surveillance period the PCP may not know how often the patient will need follow-up labs, CT scans, or other screening measures. In the case above, the PCP isn't sure if and when the patient may require more treatment. In addition, many chemotherapeutics may have long-term toxicities, such as heart failure with anthracyclines, which PCPs will need to follow as well. A study of PCPs who provide survivorship care showed that many of them feel undertrained to take on this burden. The study also showed that 82% of those surveyed believed that primary care guidelines for adult cancer survivors were not well defined.[11] Another study of breast cancer survivors looked at the patients' confidence in their PCP's ability to provide survivorship care. These women rated their PCP-related survivorship care at a level of 65 out of 100. They felt confident in the PCP's ability to provide general care, psychosocial support, and general health promotion, but expressed doubt about the PCP's knowledge of follow-up care, long-term toxicities of chemotherapy, or treatment of cancer-related symptoms. Unfortunately, only 28% of these patients felt that their PCPs and oncologists communicated well.[12]

In the geriatric population of cancer survivors, the issue of frailty is especially important. PCPs play an important role not only in screening and assessing for frailty in cancer survivors, but in managing frailty and keeping it from progressing. Cancer treatment can push a patient who is close to becoming frail past the threshold and into frailty. In these situations, it is best that the PCP take the lead in managing the patient, while the oncologist plays the role of advisor.

A study of collaboration between oncologists and PCPs in Canada showed that oncologists desire more involvement from PCPs in taking care of patients in remission. Both oncologists and PCPs expressed frustrations when trying to collaborate. The PCPs cited difficulty accessing oncologists and reluctance to contact oncologists because they were embarrassed by their own lack of knowledge. Oncologists surveyed in this study cited inadequate time, difficulty contacting, and unfamiliarity with most of the family physicians because there were so many of them. They noted that these PCPs varied in their interest in providing survivorship care. The oncologists also felt that PCPs sometimes gave patients preconceived ideas that exaggerated the toxicities of chemotherapy prior to the first consultations, thereby creating mistrust. Oncologists stressed the importance of passing information both ways between them and the PCPs. As much as they want to educate PCPs about potential toxicities, they also want to receive information from PCPs about when patients are admitted to the hospital, their tests, their surgery reports, and their incidental illnesses.

The oncologists expressed that they believed their role in survivorship care should be providing reassurance, managing toxicities, detecting recurrences, and gathering data for clinical trials. The authors noted that although oncologists treat patients with a multidisciplinary approach, they rarely include family physicians in these teams. They point out that there can often be an exclusive nature to cancer centers and they can be thought of by PCPs as a "black box." In the conclusion of the study, the authors identify several solutions to these problems. One proposal is for oncologists to identify a core group of PCPs who have a special interest in providing survivorship care. In order to provide survivorship care, it is important that the oncologist and the PCP discuss the patient at the beginning and the end of the cancer treatment. The authors also point out the importance of establishing follow-up guidelines that delineate who will be responsible for the patient in which circumstances. As a way of helping PCPs and oncologists get to know each other, the oncologists suggested holding informal seminars with case presentations to provide continuing medical education. They also suggested having an open house as a way of dispelling the idea of the cancer center as a black box.[13] (Table 27-5).

Although the roles of the PCP and the oncologist may be well defined during the surveillance period, it is less clear who is responsible for the patient at the end of life. At the end of life, whose responsibility is it to arrange for hospice care? This will to a great extent depend on patient preference. There may be other factors that influence this such as the stage at presentation to the oncologist, the length of treatment time, and the frequency of visits to the PCP during treatment. This is one of the most critical times for good communication between the

TABLE 27-5 System-Based Strategies for Improving Communication between Oncologists and PCPs

- Using templates when composing consult letters
- Including standardized educational materials with consult reply letters
- Including back-office phone numbers with consultation letters
- Giving patients discharge summaries to hand-deliver to the next provider after hospitalization
- Holding an open house at the cancer center
- Maintain a two-way flow of information

oncologist and the PCP. In cases where the PCP knows the patient well and has maintained contact during the treatment, it may be important to have a sense of closure with the patient and their family. In cases where the patient has progressed through multiple lines of therapy and it is unclear whether he or she would benefit from more treatment, the responsibility of introducing the concept of hospice clearly falls on the oncologist.

Summary

Good communication between primary care physicians and oncologists from the workup to end-of-life care has been shown to improve patient satisfaction. This can be accomplished by the transfer of key pieces of information at the time of referral, after the initial consultation, and at times of transfers of care. The development of shared-care models during oncology treatment is increasingly important as patients navigate systems with multiple different specialties involved. PCPs often feel inadequately trained in their ability to comanage patients with cancer and they appreciate when oncologists share educational materials about treatment, toxicities, and surveillance. Most oncologists are not trained to recognize and manage geriatric syndromes and they rely on the referring geriatricians to point out signs and symptoms of frailty that may complicate cancer treatment. Methods to improve communication start with availability, outreach, and recognition of tensions during transmission of information. In the future, it will be important to study whether shared-care models have any impact on outcomes such as morbidity and mortality.

See expertconsult.com for a complete list of references and web resources for this chapter

CHAPTER

28

Palliative Care, Hospice and End of Life

Susan Charette and Elizabeth Whiteman

Cancer is a feared diagnosis at any age and, for the older patient, it can present a greater challenge and options for cure may be more limited. Traditional cancer care is typically focused on the disease process: reducing tumor burden and achieving remission. However, when patients are asked what kind of care they want if serious and life-threatening disease occurs, their preferences include pain and symptom control, avoidance of prolongation of the dying process, a sense of control, concern for the burden they may place on family, and an opportunity to strengthen relationships with loved ones.[1]

Palliative care addresses these issues and is an invaluable asset in the management of the older cancer patient. Much like the discipline of geriatric medicine, the palliative approach is interdisciplinary and addresses issues that arise in physical, psychological, social and spiritual domains. Unfortunately, many health care providers believe that palliative care and hospice are only indicated when the patient is in the final stage of their illness and near death. This limited view of palliative care and hospice is commonplace and does not address their potential usefulness and benefit in the care of the older cancer patient.

This chapter will provide an introduction to palliative care and hospice for the older cancer patient. Special attention will be paid to common issues that arise for these patients including pain and nonpain symptom management, as well as the Medicare Hospice Benefit, determining prognosis, and advance directives.

CASE 28-1

Mrs. T. is an 85-year-old woman with a history of rheumatoid arthritis and mild cognitive impairment. She is a widow who lives in her own apartment two blocks away from her only child, a daughter. She is independent in her activities of daily living and her instrumental activities of daily living. At a routine doctor's appointment, Mrs. T reports a persistent cough and mild dyspnea on exertion for the past 2 months. A chest x-ray demonstrates a mass with an associated postobstructive pneumonia. Further studies are obtained and Mrs. T. is diagnosed with stage 4 non-small cell carcinoma of the lung. Both the patient and her daughter are shocked by the diagnosis. Upon meeting the oncologist for the first time, the daughter asks, "What are my mother's options?"

PALLIATIVE CARE AND HOSPICE

The terms palliative care and hospice are not synonymous but complementary. Palliative care is centered on the relief of suffering for patients with life-threatening or debilitating illness and the improvement of quality of life for patients and their families.[2] Palliative care focuses on the needs and goals of the patient and his or her family, in addition to the tumor and its treatment. Pain control, symptom management, psychosocial needs, goals of care, and quality of life are primary endpoints. Palliative care is interdisciplinary and incorporates medicine, nursing, social work, psychology, nutrition, and rehabilitation.[3] Treatments and interventions are used to control symptoms but not to advance or accelerate the death process.[4]

Mrs. T. has stage 4 non-small cell lung cancer and she will not be cured. She and her daughter need to be informed that while curative treatment is not available, there may be treatments that may decrease her tumor burden, reduce her symptoms, maintain her function, and improve her quality of life. By choosing a palliative chemotherapy or referring a patient for palliative radiation, the oncologist is doing palliative care. If the oncologist or primary medical doctor needs help controlling symptoms or discussing goals of care, an inpatient or outpatient palliative medicine consultation may be available to help address these issues. For older patients with cancer, especially those with advanced disease at the time of diagnosis, palliative care should start early in the course of care.

"Hospice" can represent a philosophy of practice as well as an agency or facility that provides care for patients with end-stage disease. Hospice utilizes a comprehensive, palliative approach to care that is interdisciplinary and symptom-focused. Most older patients in the

United States with advanced cancer will be eligible for the Medicare Hospice Benefit under Medicare Part A. Eligibility for Medicare Hospice benefit is determined by four criteria. First, the patient must be eligible for Medicare A. Next the patient must have a terminal condition and two physicians must certify that life expectancy is 6 months or less, given his or her prognosis. The patient must choose hospice care and the patient or agent must give informed consent. Finally, comprehensive care has to be provided by a Medicare-certified hospice. If these criteria are satisfied, all medicines, durable medical equipment, and care related to the terminal diagnosis are covered. Medicare Part B will still pay for covered benefits for any health problems that are not related to the terminal diagnosis.[5] Patients who meet criteria for hospice benefit have to be reviewed by the interdisciplinary team and certified by the medical director or hospice physician. Benefit periods consist of two 90-day periods, followed by an unlimited number of 60-day periods if life expectancy remains at 6 months or less.

Under the Medicare Hospice Benefit, the hospice team must include a physician, nurse, bath aide, social worker, chaplain, volunteers, and possibly therapists when appropriate.[6] Bereavement support for 1 year after a patient's death is also included in this benefit. All medical supplies and durable medical equipment and any medication related to the terminal diagnosis and for symptom control are covered by the benefit. Most patients receive hospice services in their private home or in the nursing home setting. Although not commonplace, freestanding hospice facilities provide room and board along with care by the hospice team when the patient qualifies under "Inpatient Status," which is typically for symptoms out of control. Most private insurance companies will also use Medicare-certified hospice criteria to enroll patients in hospice. Hospice care must provide comprehensive palliative care for terminally ill patients with a usual estimated life expectancy of 6 months or less. The care must include treatment of physical symptoms, social support, spiritual and emotional care, and bereavement care. Hospice benefits can play an important role when the patient and the physician agree that inpatient or other aggressive treatments are not in the patient's best interest. The patient care will focus on symptom management with a switch to full palliation of symptoms and care, usually outside the inpatient hospital setting.

Hospice care can take place in different settings and the Medicare benefit provides four levels of care: routine home care, continuous home care, general inpatient care, and respite care.[7] Routine home care is the most common level of care. Most patients receiving this level of care are in the home or nursing home setting. Patients have to be able to care for themselves at home or have appropriate caregiver support. The Medicare Hospice Benefit does not cover the cost of caregivers or nursing home room and board. All other services mentioned above are covered and the hospice must provide 24-hour on-call services. Continuous home care is for crises and for management of acute symptoms. This care can be provided in the home or in a long-term nursing home setting as well. Nursing care from 8 to 24 hours is arranged to provide intensive palliation of symptoms; such care may include titration of pain medications and the use of intravenous medications to gain control of symptoms. General inpatient care is for control of acute pain or symptoms that cannot be managed in the home or nursing home. This level of care can be provided in an inpatient hospital or freestanding hospice. Respite care is provided for caregivers that need relief or a break and is offered for up to 5 days at a time. Care can be provided 24 hours per day and includes custodial care at a hospice facility, intermediate care facility, or a hospital that contracts with the hospice.

EPIDEMIOLOGY

The need for palliative care among our older cancer patients will continue to grow in the coming years. There were nearly 1.5 million new cancer cases in the United States projected for 2009.[1] One in four Americans die from cancer, and 70% of these cancer-related deaths occur in persons older than 65 years.[1,8] These numbers are expected to increase dramatically with the aging of our population; also, older patients are more likely to have advanced or incurable disease at diagnosis and therefore are in greatest need of palliative care.[8]

An ongoing challenge will be how to meet the palliative care needs of these patients. While the number of hospitals with palliative care programs has doubled over the last 10 years, the 2008 American Hospital Association Annual Survey of U.S. Hospitals reported that only 31% of hospitals have such programs.[9] These hospitals tend to be the larger hospitals, often those affiliated with academic medical centers; large segments of the population are therefore left underserved.

Hospice agencies are more commonplace, yet referrals are often made late and their services are underutilized. Patients are dying in the hospital when they want to die at home. The median length of stay in a hospice during 2005 was 26 days; one third of patients enrolled during the last week of life and 10% on the last day of life.[10] Hospice admissions happen late for a wide range of reasons. Most notably, it is often difficult for patients, families, and the health care team to switch out of treatment mode, give up the hope for a cure, and discuss worsening prognosis and death.[3] In states where there is more access to palliative care services, patients are less likely to die in a hospital and are less likely to spend time in an intensive care unit or critical care unit during their last 6 months of life.[3]

CASE 28-1 CONTINUED

Mrs. T. is found to be a poor candidate for surgical resection due to the extent of her disease. However, she is offered radiation treatment which she accepts. She and her daughter were informed of the risks of radiation, which may include fatigue in older patients. They also were told the radiation was palliative and would not cure the cancer at this stage. Now Mrs. T. spends most of her days in bed. She has little energy and needs help with dressing and bathing. She ambulates with a walker.

DETERMINING PROGNOSIS

(For a more comprehensive discussion on functional assessment, see Chapter 4 on "Functional Assessment.") Determining prognosis is a challenge for most physicians. Not only must a difficult prediction be made but also, the physician must often break bad news to the patient and his or her loved ones. Almost universally, patients and their families want to maintain hope for a cure, and if that is not possible, the hope that the cancer will not progress. Elderly cancer patients may have multiple medical problems, cognitive impairment, and functional limitations at baseline. These deficits may reduce their ability to tolerate cancer treatments, increase their risk of side effects, and adversely impact their prognosis. For older patients in whom cure is not possible, the goals of care should focus on controlling symptoms and maximizing function.

The best predictor of prognosis among cancer patients is performance or functional status. Functional status refers to one's ability to carry out his or her activities of daily living and instrumental activities of daily living. For older patients, functional status is often impaired at baseline and may decline following interventions such as surgery, chemotherapy, and radiation; it may not recover. This impaired functional status may limit cancer treatment options and contribute to physical and psychological distress. Cognitive impairment is more common in older patients and, depending on the degree of the deficit, may not only reduce available treatment options but also increase the risk of delirium and worsened cognitive impairment during the course of treatment.

There are a number of different tools that have been developed to assess function. Two well-known scales are the Karnofsky Performance Status Scale and the Eastern Cooperative Oncology Group (ECOG) scale. The Karnofsky Performance Status Scale rates function from 100% (normal) to 0 (dead). The ECOG rates function from 0 (normal) to 5 (dead). A median survival of 3 months roughly correlates with a Karnofsky score less than 40% or ECOG greater than 3.[11] Typically, if a patient spends more than 50% of his or her time in bed, with progressively worsening function and an increase in other symptoms, then a prognosis of less than 3 months is likely.[11] Newer tools are available and incorporate function, signs, and symptoms: the Palliative Prognostic Score (PaP) and the Palliative Performance Scale.[12,13] These scales utilize more patient information and the added detail may help provide a more comprehensive and reliable assessment.

Discussing prognosis early in the course of care is ideal. It gives patients and their families the opportunity to consider their options and understand what to expect. Discussions should address how the patient's concomitant medical conditions may affect the cancer course, the treatment choices, and the overall prognosis. For older patients with multiple comorbidities, poor functional status, and moderate to advanced cognitive impairment, a palliative approach may be appropriate earlier in the course of care and, for some patients, it may be indicated at the time of diagnosis. These recommendations should be shared with patients and their families, and will likely evolve over the course of care.

CASE 28-1 CONTINUED

Mrs. T. has been undergoing radiation therapy. She arrives in your office in a wheelchair, as her shortness of breath with exertion has worsened. She also states her appetite is low and that she is constipated. She feels anxious about what is going to happen next.

Laboratory studies reveal that she is hypercalcemic; an x-ray shows progressive growth of the tumor mass.

Her hypercalcemia is treated with IV fluids and she is placed on routine medication to prevent her constipation. Discussions about future goals of care reveal she would like to continue further palliative radiation if possible, but wishes to be more comfortable.

In a discussion about advance directives, Mrs. T. states that, if she had a reversible condition, she would want it to be treated with antibiotics or other short-term treatments. If she was not going to recover, or if the risk of treatment outweighed the benefit, she would not want her life to be prolonged on machines. She fills out an advance directive stating her wishes and lists her daughter as her power of attorney in the event she cannot make decisions on her own.

ADVANCE DIRECTIVES

An advance directive is a legal document by which patients specify their treatment preferences, goals of care, and an alternate decision maker or agent if they are unable to make their own decisions. A living will is a legal, written document that outlines a patient's treatment preferences if and when there is a time that he or she is unable to communicate them. A durable power of attorney (DPOA) is a commonly used document by which patients appoint an agent to be their decision maker or healthcare proxy if they lose the capacity to make decisions. A DPOA is useful in that it ensures a flexible form of decision making, since the agent can respond to unanticipated problems that a written document may not predict. Advance directives are state-specific and patients must complete the form from their own state to ensure that their wishes will be carried out. It is very important that an advance

directive is completed for the older cancer patient. If a patient chooses to list a DPOA, it should be a person who will respect and follow the patient's wishes.

The Physician Orders for Life-Sustaining Treatment (POLST) Paradigm program is designed to improve the quality of care people receive at the end of life.[14] The POLST is a new form that has been implemented in some states, including California and Oregon (Figure 28-1). The POLST outlines the patient's treatment preferences and underlying medical condition and must be completed and signed by the patient or health care proxy and by his or her physician. The POLST specifically documents

HIPAA PERMITS DISCLOSURE OF POLST TO OTHER HEALTH CARE PROFESSIONALS AS NECESSARY

Physician Orders for Life-Sustaining Treatment (POLST)

EMSA #111 B
(Effective 1/1/2009)

First follow these orders, then contact physician. This is a Physician Order Sheet based on the person's current medical condition and wishes. Any section not completed implies full treatment for that section. Everyone shall be treated with dignity and respect.

Last Name
First/Middle Name
Date of Birth Date Form Prepared

A *Check One*

CARDIOPULMONARY RESUSCITATION (CPR): ***Person has no pulse and is not breathing.***

☐ **Attempt Resuscitation/CPR** ☐ **Do Not Attempt Resuscitation/DNR** (**A**llow **N**atural **D**eath)
(Section B: Full Treatment required)

When not in cardiopulmonary arrest, follow orders in **B** and **C**.

B *Check One*

MEDICAL INTERVENTIONS: ***Person has pulse and/or is breathing.***

☐ **Comfort Measures Only** Use medication by any route, positioning, wound care and other measures to relieve pain and suffering. Use oxygen, suction and manual treatment of airway obstruction as needed for comfort. Antibiotics only to promote comfort. ***Transfer*** *if comfort needs cannot be met in current location.*

☐ **Limited Additional Interventions** Includes care described above. Use medical treatment, antibiotics, and IV fluids as indicated. Do not intubate. May use non-invasive positive airway pressure. Generally avoid intensive care.

☐ ***Do Not Transfer to hospital for medical interventions. Transfer*** if comfort needs cannot be met in current location.

☐ **Full Treatment** Includes care described above. Use intubation, advanced airway interventions, mechanical ventilation, and defibrillation/cardioversion as indicated. ***Transfer*** *to hospital if indicated. Includes intensive care.*

Additional Orders: _____

_____

C *Check One*

ARTIFICIALLY ADMINISTERED NUTRITION: ***Offer food by mouth if feasible and desired.***

☐ No artificial nutrition by tube. ☐ Defined trial period of artificial nutrition by tube.

☐ Long-term artificial nutrition by tube.

Additional Orders: _____

D

SIGNATURES AND SUMMARY OF MEDICAL CONDITION:

Discussed with:

☐ Patient ☐ Health Care Decisionmaker ☐ Parent of Minor ☐ Court Appointed Conservator ☐ Other:

Signature of Physician

My signature below indicates to the best of my knowledge that these orders are consistent with the person's medical condition and preferences.

Print Physician Name	Physician Phone Number	Date
Physician Signature (required)	Physician License #	

Signature of Patient, Decisionmaker, Parent of Minor or Conservator

By signing this form, the legally recognized decisionmaker acknowledges that this request regarding resuscitative measures is consistent with the known desires of, and with the best interest of, the individual who is the subject of the form.

Signature (required)	Name (print)	Relationship (write self if patient)

Summary of Medical Condition	Office Use Only

SEND FORM WITH PERSON WHENEVER TRANSFERRED OR DISCHARGED

FIGURE 28-1 Example of the California POLST Form.

HIPAA PERMITS DISCLOSURE OF POLST TO OTHER HEALTH CARE PROFESSIONALS AS NECESSARY			
Patient Name (last, first, middle)		Date of birth	Gender: M F
Patient Address			
Contact Information			
Health Care Decisionmaker	Address		Phone Number
Health Care Professional Preparing Form	Preparer Title	Phone Number	Date Prepared

Directions for Health Care Professional

Completing POLST

- Must be completed by health care professional based on patient preferences and medical indications.
- POLST must be signed by a physician and the patient/decisionmaker to be valid. Verbal orders are acceptable with follow-up signature by physician in accordance with facility/community policy.
- Certain medical conditions or medical treatments may prohibit a person from residing in a residential care facility for the elderly.
- Use of original form is strongly encouraged. Photocopies and FAXes of signed POLST forms are legal and valid.

Using POLST

- Any incomplete section of POLST implies full treatment for that section.

Section A:

- No defibrillator (including automated external defibrillators) should be used on a person who has chosen "Do Not Attempt Resuscitation."

Section B:

- When comfort cannot be achieved in the current setting, the person, including someone with "Comfort Measures Only," should be transferred to a setting able to provide comfort (e.g., treatment of a hip fracture).
- IV medication to enhance comfort may be appropriate for a person who has chosen "Comfort Measures Only."
- Non-invasive positive airway pressure includes continuous positive airway pressure (CPAP), bi-level positive airway pressure (BiPAP), and bag valve mask (BVM) assisted respirations.
- Treatment of dehydration prolongs life. A person who desires IV fluids should indicate "Limited Interventions" or "Full Treatment."

Reviewing POLST

It is recommended that POLST be reviewed periodically. Review is recommended when:

- The person is transferred from one care setting or care level to another, or
- There is a substantial change in the person's health status, or
- The person's treatment preferences change.

Modifying and Voiding POLST

- A person with capacity can, at any time, void the POLST form of change his/her mind about his/her treatment preferences by executing a verbal or written advance directive or a new POLST form.
- To void POLST, draw a line through Sections A through D and write "VOID" in large letters. Sign and date this line.
- A health care decisionmaker may request to modify the orders based on the known desires of the individual or, if unknown, the individual's best interests.

This form is approved by the California Emergency Medical Services Authority in cooperation with the statewide POLST Task Force.

For more information or a copy of the form, visit **www.capolst.org**.

SEND FORM WITH PERSON WHENEVER TRANSFERRED OR DISCHARGED

FIGURE 28-1, cont'd

preferences regarding cardiopulmonary resuscitation, medical interventions, and artificial nutrition. The premise for the POLST is effective communication of patient wishes, documentation of medical orders on a brightly colored form, and a promise by health care professionals, including emergency medical personnel, to honor these wishes.[15]

SYMPTOM MANAGEMENT

Pain

(For a more detailed discussion of the evaluation and management of pain, see Chapter 17 entitled, "Pain.")

Pain is prevalent among older cancer patients, yet it often goes undiagnosed and undertreated. Research has

shown that as many as 80% of older persons diagnosed with cancer experience pain during the course of their illness.[16] Pain control is critical, as uncontrolled pain may affect quality of life, diminish hope, increase depression, and contribute to disordered sleep, appetite disturbances, and cognitive dysfunction.[17,18]

There are numerous challenges to optimal pain evaluation and management in older cancer patients. Persistent pain is epidemic among older adults and is most commonly associated with musculoskeletal disorders such as degenerative spine conditions and arthritis.[19] Other prevalent pain conditions include peripheral neuropathy, postherpetic neuralgia, nighttime leg cramps, and claudication.[19] These conditions may cloud the picture of new or worsening cancer-related pain and impede its treatment. Patients and their families are often hesitant to use opioids due to the potential for adverse drug reactions and addiction.[20] Physicians and other health care practitioners have similar concerns and, typically, receive minimal training in pain management. These factors contribute to the reluctance among physicians to prescribe opioid medications to older patients.[18] These concerns have been augmented by increased attention in the media on the potential for abuse and overdose. While barriers exist, pain management is essential for optimizing function and improving quality of life.

The first step in pain management is assessment. Unfortunately, many older patients and health care professionals expect pain to be a normal part of aging. Patients do not think to report their pain, or they try to bear it and accept it. Other patients may think that their physician is too busy and do not want to be viewed as a "bad patient" with another complaint. Physicians may be focused on the management of the cancer and complaints of pain and other symptoms may get deferred. The best place to begin a pain assessment is to ask, "Are you in pain?" This question has been validated in patients who are cognitively intact as well as those with mild to moderate cognitive impairment. A variety of assessment tools are available including pain scales, the pain thermometer and the faces scale as well as more comprehensive tools.

Pain management is an integral part of palliative care. A wide range of pharmacologic agents are available to manage pain. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be effective for bony pain from bone cancer and metastases; however, they must be used with discretion in older patients because of their potential side effects including elevated blood pressure, renal insufficiency, dyspepsia, and upper gastrointestinal bleeding. NSAIDs are best used for short periods of time, and the concomitant use of an antacid agent or proton pump inhibitor may reduce their risk for GI side effects. For mild pain in a patient with multiple comorbidities and no contraindications, acetaminophen may be useful, especially if dosed around the clock. For older patients with moderate to severe pain, stronger agents such as tramadol and opioid agents such as morphine, oxycodone, or hydromorphone will be required, and dosing will likely need to be around the clock with as-needed dosing for breakthrough pain. Adjuvant agents offer synergy in pain control and address specific types of pain. Antidepressants and antiepileptics for neuropathic pain, corticosteroids for inflammation, and bisphosphonates for bone pain have been shown to be effective. Additionally nonpharmacologic approaches such as radiation treatment, acupuncture, massage, TENS units, and other types of therapy may be useful additions to a pain management plan. For pain that is difficult to control, a palliative medicine consult or pain management consult may be needed.

CASE 28-1 CONTINUED

Mrs. T. is continuing with her radiation. She was placed on low-dose morphine for her shortness of breath and is using oxygen as needed. She feels she is able to be more active and get out of the house with assistance in her wheelchair. Her constipation is controlled with around-the-clock anticonstipation medication and her appetite is stable. Despite feeling better, her weight continues to drop and her CT scans show the cancer is progressing.

Constipation

Constipation is a common problem in the elderly and may be more severe near the end of life. Multiple factors contribute to this, such as opioid use, immobility, and dehydration due to poor oral intake. Patients need to be evaluated for treatable causes such as medications or electrolyte abnormalities. Associated abdominal pain may contribute to other problems such as anorexia, nausea, or vomiting. Constipation can be controlled and the goal is to keep stool moving and avoid impaction.

Table 28-1 lists some common laxatives that can be useful in treating constipation. Docusate sodium and other stool softeners often are not strong enough alone to treat cases of severe constipation. They need to be used in combination with stimulant laxatives. Fiber products may have to be discontinued, especially if a patient's fluid intake is poor, as these products may contribute to more impaction. When opioids are started, a laxative should always be given routinely to prevent constipation.[21] The patient needs to be monitored for worsening symptoms. Stimulant laxatives such as senna, cascara, and bisacodyl can be used on a routine basis to keep bowel movements regular and patients comfortable. Side effects, however, may be abdominal cramping, and bloating. Saline laxatives such as magnesium hydroxide and magnesium citrate often work faster; however, caution should be taken in patients at risk for electrolyte depletion and dehydration. These can be harsher on the gastrointestinal tract. Osmotic laxatives may be easier to tolerate but side effects can include pain and bloating. Polyethylene glycol can be used for constipation, mixed in water or juice. Methylnaltrexone is a newer agent approved for

TABLE 28-1 Treatment for Constipation

Drug	Mechanism	Dose	Comment
Docusate sodium	Softener	100-250 mg bid	Often minimally effective used alone
Senna	Stimulants	187-1496 mg bid	Can cause cramps
Cascara		325 mg qd	
Bisacodyl		5-20 mg po or pr qd	
Magnesium hydroxide	Saline laxative	15-40 mL po qd-bid	Diarrhea, electrolyte abnormalities
Magnesium citrate		120-240 mg qd	
Sodium phosphate		20-30 mL po or pr	
Lactulose	Osmotic	5-40 mL po qd-bid	Pain and bloating, diarrhea, dehydration
Sorbitol		15-30 mL po qd-bid	
Polyethylene glycol		17-36 mg po qd-bid	
Psyllium	Bulk-forming	1-2 tablespoons qd	Need adequate fluid intake
Methylcellulose		1-2 mg qd	Need adequate fluid intake
Methylnaltrexone bromide	Selective mu-receptor blocker	8-12 mg SQ QOD	NOT for bowel obstruction

subcutaneous injection for opioid-induced constipation. It has been used in patients receiving palliative care who have been unresponsive to laxatives. It is a selective mu-receptor blocker.[22] It will not reverse the pain control of opioids and does not cross the blood-brain barrier. It is, however, contraindicated for patients in whom there is suspicion of gastrointestinal obstruction.[23] Also, it has only been tested for short-term use. Patients should always be assessed for fecal impaction. Suppositories or enemas must be used in patients who have poor rectal tone or who are too weak to assist in defecation. Also, in cases of severe fecal impaction, trained staff must manually disimpact the rectum prior to starting any laxative treatment. Patients should be routinely monitored and reassessed for symptoms, as adjustments in medication may need to be made.

Nausea and Vomiting

Nausea and vomiting is a common problem. Multiple etiologies such as underlying diseases other than cancer, the cancer itself, medications, or severe constipation can all add to the symptoms. First, the underlying cause must be determined so that the appropriate treatment can be provided. Causes of nausea can be broken down into four categories: central nervous system (CNS), gastric obstruction or ileus, medication side effect, or metabolic abnormalities. Patients may also have other contributing factors. Once the main cause is determined, appropriate treatment can begin. The oral route is preferred; however for those with intractable symptoms, rectal or parenteral routes are an option (Table 28-2). Dopaminergic agents such as prochlorperazine and promethazine can be used orally, rectally, or intramuscularly. These agents are often useful for treating drug-induced nausea and vomiting. The side effects of these antiemetics include drowsiness and extrapyramidal symptoms. Despite these potential side effects in the elderly, these medications can be very helpful and short-term use may benefit patients by controlling symptoms and improving quality of life. For CNS causes of nausea and vomiting, haloperidol or droperidol can be helpful. Patients who are at risk for increased intracranial pressure may be started on corticosteroids and these may concomitantly improve their symptoms of nausea and vomiting. For patients with significant bowel disease, corticosteroids can relieve bowel edema and improve nausea. High doses of corticosteroids should be used with caution in the elderly as they can lead to gastric irritation, delirium, and fluid retention. Serotonin-receptor blockers are often helpful in cases of chemotherapy-induced nausea and vomiting. Anticholinergics and antihistamines can be useful, especially in cases of vestibular nausea and central nervous system disease. However, care should be taken with these agents, as anticholinergic side effects such as dry mouth, drowsiness, dizziness, blurry vision, and confusion can be difficult for elderly patients to tolerate. Benzodiazepines are often helpful and may help relieve nausea, especially if the nausea is related to anxiety. Patients must be continually reassessed for the underlying cause of nausea and vomiting; they should use these medications on an as-needed basis.

Dyspnea

Dyspnea can be a debilitating symptom for many patients. Causes may include the underlying cancer or progression of illness and terminal condition. Patients may have an uncomfortable awareness of breathing, rapid breathing, or air hunger.[24] Dyspnea can be significantly uncomfortable for patients, and their families may be distressed by the patient's fluctuating respiratory rate, by hearing increased secretions, and by the gurgling sound or "death rattle" that often is heard when a patient is nearing death. It is important to assure patients that the relief of these symptoms and overall comfort is the goal of care (Table 28-3). Often, other treatments must be reassessed for appropriateness; these should be discussed with the

TABLE 28-2 Treatment for Nausea and Vomiting

Drug	Mechanism	Dose	Comment
Prochlorperazine	Dopamine antagonist	5-20 mg PO/IM/IV q4-6h, 25 mg PR q 8-12h	EPS side effects
Promethazine	Dopamine antagonist	25 mg PO/PR q4-6h	EPS side effects
Droperidol	Dopamine antagonist	2.5-5 mg IM/IV q4-6h	EPS side effects
Haloperidol	Dopamine antagonist	0.5-5 mg PO/IV/IM/SC q4-6h	EPS side effects
Metoclopramide	Dopamine antagonist	5-20 mg PO/IM/IV/SC q6h	EPS side effects
Ondansetron	Serotonin receptor blocker	8 mg PO/IV/SC q8h	Chemotherapy-induced nausea
Granisetron	Serotonin receptor blocker	0.5-1 mg PO/IV/SC q12h	Chemotherapy-induced nausea
Diphenhydramine	Antihistamines	25 mg PO/IV/IM q4h	For vestibular symptoms
Meclizine	Antihistamines	25-50 mg PO q4-6h	For vestibular symptoms
Dexamethasone	Corticosteroid	1-4 mg PO/IV q6h	For chemotherapy induced nausea, or increased intracranial pressure
Prednisone	Corticosteroid	5-20 PO q4h	For chemotherapy induced nausea, or increased intracranial pressure
Scopolamine	Anticholinergic	1.5 mg patch q72h	Delirium risk
Hyoscyamine	Anticholinergic	0.125 mg tid	Delirium risk
Dronabinol	Cannabinoid	2.5-7.5 mg PO bid-tid	Chemotherapy-induced nausea
Lorazepam	Benzodiazepine	0.5-2 mg PO/SC/IM q4h	For reducing anxiety, nausea
Diazepam	Benzodiazepine	5-10 mg q4h	For reducing anxiety, nausea

TABLE 28-3 Treatment for Shortness of Breath and Increased Secretions

Class of Drug	Examples	Dose	Comment
Shortness of Breath			
Oxygen		2-10 L/min by nasal cannula	Use for patient comfort, shortness of breath
Opioids	Morphine	5-15 mL PO/SL/PR	Decrease patient perception of breathlessness; titrate up to patient comfort
	Methadone		
	Oxycodone		
Benzodiazepines	Lorazepam	1-2 mg PO/SL	Can help with anxiety and breathlessness
	Diazepam	2.5-10 mg PO/SL	
Secretions			
Scopolamine patch		1-3 patches q1-2 days	In alert patient, may cause dizziness and dry mouth
Hyoscyamine		0.125 mg PO q4-6h	Less sedation than scopolamine
Glycopyrrolate		0.2-1 mg PO q4-6h	Least sedation and fewer CNS side effects
Atropine drops		2-4 drops PO/SL q2-4h	Can be used when patient is unable to swallow and as needed

patient, the family and the physician. Interventions such as antibiotics for acute infection and diuretics for fluid overload can be considered based on the patient's preference and the stage of the disease process.[25]

As the body starts to shut down, renal function decreases, the circulatory system slows, and patients are at higher risk for fluid overload. Treatment with intravenous fluids may make symptoms of shortness of breath worse. Also, tube feedings may have to be slowed or discontinued, as the patient may be at higher risk of fluid overload and aspiration. Patients should be allowed to eat as they can tolerate; however, food consistency may have to be changed if they are having more difficulty chewing or swallowing. Patients who are too lethargic to eat should not be forced, as aspiration is a high risk and can make the breathing even more labored.

Oxygen is used to improve patient's symptoms and can be used easily. Patient's life expectancy will not be prolonged by the use of oxygen; however, the patient may have less air hunger and may have the sensation of breathing easier.[26] Opioids are the main pharmacologic agents for treating dyspnea. Morphine sulfate can be used orally, sublingually, intravenously or rectally. Doses can begin very low, starting at 5 to 10 mg every 2 to 4 hours. However, it should be titrated up at least by 30% to 50% until symptoms are controlled. Patients can be placed on continuous long-acting doses of the opioid preparation, but short-acting opioid formula should still be available for severe symptom control as needed. Titration should be based on the patient's symptoms, not on his or her respiratory rate. Studies on nebulized morphine and hydromorphone have shown variable results. The benefit over enteral narcotics is still unclear and more research is needed.[27,28]

Benzodiazepines can also be effective in treatment of dyspnea. Patient may feel symptomatic relief as well as

less anxiety and air hunger when symptoms are more severe. Benzodiazepines may need to be used around the clock and may need to be titrated based on the patients symptoms. Nonpharmacologic methods to help reduce shortness of breath include placing the patient in a more open room, using air from a fan, keeping the patient in an upright position, relaxation techniques, and support for the patients spiritual or psychological needs.

Dyspnea at the end of life is often caused by secretions and difficulty with swallowing. Many patients have recurrent aspiration. If a patient is still eating, the benefit of quality of life versus the risk of aspiration must be considered. Many patients are willing to take some risk for the benefit of being able to enjoy food. Many patients may be more uncomfortable due to increased secretions from fluid overload, aspiration, infections, and inability to control secretions. Often medication to help dry secretions can be beneficial. Scopolamine patches can be used and are helpful in drying secretions. Side effects include dizziness, blurred vision, and oral dryness. Hyoscyamine is less sedating than scopolamine and can be used orally when the patient can still swallow. Glycopyrrolate has fewer CNS side effects and can be used orally and intravenously. It does not cause as much drowsiness compared to the others and the risk for delirium is low. This is often a safer alternative in the elderly patient who still is awake and at high risk for delirium. In patients who cannot swallow and who are mostly unconscious, atropine drops can be used orally or sublingually. These can be used to dry oral secretions and help reduce the gurgling from the throat often heard when a patient is nearing death and has no control over secretions, sometimes referred to as the "death rattle." Medications to help control secretions are listed in Table 28-3. Often, patients' caregivers can be trained to help clear secretions by using swabs to clear out the oropharynx, suctioning gently with a bulb syringe, and making postural changes to clear the airway.

Depression

(For more comprehensive discussion and treatments, see Chapter 16 on "Depression.")

Depression is a common problem among elderly cancer patients. A recent systematic review found that approximately 15% of palliative care inpatients suffer from major depression and that the prevalence of all depressive disorders including minor depression, dysthymia, and depressive adjustment disorders is likely to be twice this value.[29] Unfortunately, depression is often overshadowed by other physical complaints. Depression is reported less often than pain and fatigue when patients are asked about common symptoms.[29] It can be especially confusing with cancer patients, because many of the biological symptoms of depression are expected consequences of cancer and its treatment such as fatigue, sleeplessness, change in weight, and loss of appetite.[29] Other indicators of depression in the terminally ill are suicidal ideation and feelings of hopelessness, helplessness, worthlessness, and guilt.[30] Anxiety often coexists with depression and may be an associated symptom. Older cancer patients facing death may experience a depressed mood; it can be difficult to differentiate when depressed mood or normal grief becomes clinical depression.[29] These distinctions are important, as depression significantly impacts functional status and quality of life.[29,30]

Given these complexities, what is the best way to identify depression in elderly cancer patients? The short answer is to ask the patient. Research has shown that patient interviews are superior to self-report and visual analogue scales for the identification of depression, and a diagnostic interview is the gold standard.[29,31] Certainly, the ideal tool in the clinical setting would be one that is quick, easy, and reliable. Chochinov et al. demonstrated that incorporating a single-item interview for depressed mood and asking "Are you depressed?" reliably and accurately diagnosed the presence of depressed mood.[31] The authors also suggested that inquiry regarding loss of interest and pleasure in activities may be additive.[31] Once identified, further questioning is required through thorough history taking and possibly the implementation of additional questionnaires such as the Geriatric Depression Scale (GDS) or the Patient Health Questionnaire-9 (PHQ-9). Other questionnaires ask more questions and have been found to be reliable; examples include the Hospital Anxiety and Depression Scale and the Beck Depression Inventory.[32,33] These may be useful and offer a more definitive diagnosis of depression rather than just the identification of depressed symptoms; however, their length and requirement for prolonged attention may make them hard to complete with frail elderly patients.[29] While self-report and visual analog scale measures are not reliable in making the diagnosis of depression, they may be useful to quantify the severity of a depressive syndrome, once it is identified, and in monitoring change over time.[31] Once depression is suspected in a patient, further history should be obtained and further information gathered to assess for a history of depression, its prior treatments, successes and failures; medical etiologies; or contributors such as thyroid disease, anemia, and electrolyte disturbances.

Treating depression may lead not only to an improvement in physical symptoms but also have a major impact on quality of life and, possibly, survival.[34] Treatment may be effective even in those who are terminally ill and it carries minimal risk. A consensus panel by the American College of Physicians/American Society of Internal Medicine reported that psychotherapeutic interventions have been shown to be effective in relieving depressive symptoms, improving quality of life, and prolonging life, while psychopharmacologic treatments may relieve depressive symptoms and alleviate psychological distress in a majority of patients.[30] Simultaneous symptom management,

especially pain control, is essential, as poorly controlled pain is a risk factor for depression.[30] Additional nonpharmacologic interventions are also important including psychological support, spiritual support, and symptom management. Talking through concerns, answering questions, and reassuring the patient that his or her pain will be relieved are all important. This type of support can be provided in the context of an office visit or visit to the infusion center by staff and by the interdisciplinary team if hospice is involved. A palliative care approach will help ensure that comprehensive care is provided.

There are many available antidepressants; it may seem difficult to choose the right one for an older patient with advanced cancer. The risk/benefit ratio is low with treatment and there is little reason not to consider a trial of intervention. Important considerations include: good side effect profile, little or no interaction with other drugs used in palliative care, additional benefits (e.g., helpful with neuropathic pain or somnolence), quick onset of action, and safe in liver or renal failure.[34] Citalopram and sertraline are selective serotonin reuptake inhibitors that have been shown to be effective and well tolerated in palliative care patients.[34] These agents are preferred, as they have few active metabolites to accumulate and cause toxicity when compared with fluoxetine.[30] Mirtazepine, a noradrenaline and specific serotonin antagonist (NaSSA), is particularly useful in patients with insomnia, poor appetite, nausea, and anxiety.[34] Duloxetine may be a good choice in patients with concomitant neuropathic pain. Venlafaxine may be useful for patients not responsive to the SSRIs. Antidepressants typically require a 4-week trial period to determine effectiveness. If one agent has not been effective, then try switching to a different agent. If there is still no improvement, or if additional symptoms such as paranoia, delusions or active suicidal ideation are present, then the involvement of a psychiatrist is recommended.

Depression routinely goes unaddressed in the older cancer patient. Physicians may not recognize depression in their patients and often lack the knowledge and skills to identify depression.[29,30] Patients, their families, and health care providers believe that psychological distress is a normal feature of the dying process and fail to differentiate natural, existential distress from clinical depression.[30] Other barriers exist including the stigma of depression, a lack of time to address the issue during clinical encounters, the concern that talking about depression will cause further distress, and physician reluctance to prescribe psychotropic agents.[30] Optimal care for the older cancer patient requires that depression be looked for and treated.

Anxiety and Agitation

Anxiety and agitation are common near the end of life and may be more difficult to control than other symptoms. Terminal restlessness can be assessed and treated to improve the patient's life. Patients may have multiple factors adding to agitation such as disease process, electrolyte abnormalities, shortness of breath, uncontrolled pain, medication side effects, or psychological fear and depression. Intervention goals are to provide patients with comfort and the best-possible quality of life. Patients with advanced cancer who have anxiety are more likely to have difficulties in the physician-patient relationship.[35] In the elderly, depression, delirium and the possibility of cognitive dysfunction can make evaluation and treatment more complex.

As for depression, anxiety can present in many ways. Poor symptom management can add to more anxiety. Patients should be assessed for uncontrolled pain, shortness of breath, constipation, and nausea at every encounter. Poor sleep can also lead to anxiety. Patients may have depression with an anxiety component and appropriate medication should be started. Patients who are debilitated or who require more care may often feel anxious about becoming a burden on family or caregivers. Appropriate and early intervention to discuss care needs and possibilities for care facilities should come earlier in the course of illness. Social, spiritual, and cultural aspects also must be addressed. A patient whose death is impending may wish to reconcile with loved ones with whom he or she lost contact. Some patients may need religious or spiritual support. All these disciplines should be offered and considered in a patient who seems to be more anxious. Medication can often help in patients who are still undergoing active care and even for those on hospice care. SSRIs are common antidepressants that can help with anxiety, as well as with depression. Anxiolytics, such as benzodiazepines, can often be used in acute anxiety. Caution should be taken in the elderly, as the side effects of benzodiazepines can include confusion and agitation. They are not recommended for long-term use for chronic anxiety in the elderly.[36] For those who are near the end of life, they can be used more acutely. During the dying process, when some patients may suffer from terminal delirium and agitation, around-the-clock benzodiazepines and, often, antiseizure medications can be used for sedation. Antipsychotics, especially atypical antipsychotics, are often used and can be helpful in acute anxiety or agitated state, particularly in patients with underlying cognitive impairment. Mood disorders and underlying psychiatric disorders should be assessed and treated. Patients may also benefit from psychological support, spiritual support, and social support. Anxiety often stems from patient's fears of pain and suffering. There is a high association of depression and anxiety in patients with chronic medical problems, as is the case for many elderly. The addition of a cancer diagnosis will often exacerbate the condition. Use of interdisciplinary team members, spiritual support, family involvement, and psychiatric and psychological support should be instituted early.

Delirium

Delirium is also highly prevalent at the end of life and in acute illness. Delirium is defined as an acute state of disturbed consciousness. Usually, it is abrupt in onset and associated with fluctuating symptoms. Patients may be lucid at intervals then decline again. These symptoms can be treated and it is often reversible. Patients who are over 65 years old are at the highest risk for delirium. Delirium can increase length of hospital stay in older patients and can increase mortality.[37] Delirium in cancer can be a challenging diagnosis. It can represent a reversible condition, new disease in the brain, or an irreversible part of the evolution of the terminal disease.[38] Distinguishing delirium from dementia can often be difficult, especially in patients with a history of dementia. In delirium, confusion occurs acutely and is associated with altered consciousness. Dementia is usually a slow and progressive cognitive loss. When delirium is superimposed on a patient with dementia, diagnosis can be difficult.[39]

As delirium can be a reversible condition, it is important to evaluate the cause and to treat it if possible (Table 28-4). One of the main causes of delirium is drug toxicity. Medications to treat acute illness such as antibiotics, centrally acting antihypertensives, and steroids are common in the acute-care setting. In addition, medications used for palliation of symptoms including opioids, benzodiazepines, antipsychotics, anticholinergics, and antiseizure drugs can all cause delirium, especially in older patients. Metabolic abnormalities and endocrine disorders as well as acute fever, hypotension, and infection are all risks for confusion. Patients with cancer are highly susceptible to delirium from the disease itself or due to consequences of the cancer treatment. Hematologic abnormalities and neurologic causes including new cerebral vascular event, infection, head trauma, seizures, or bleeding should be considered. Toxic effects of antineoplastic treatments and new CNS tumor to the brain and meninges can cause acute changes in consciousness.[40] In elderly patients, underlying psychiatric disorders such as dementia can make delirium more pronounced and difficult to diagnose. Patients with depression, anxiety, or agitation can present with confusion as the main symptoms.[41] Alcohol, drug, or medication withdrawal can add to delirium. In an elderly patient, environmental changes such as sleep deprivation, inability to communicate because of hearing loss, vision loss, and change in environment can increase the confusional state.

After addressing the reversible causes, delirium is usually treated with antipsychotic agents. In an elderly patient, care must be used in dosing and the potential for oversedation is high. Often, older patients will better tolerate atypical antipsychotics. Side effects can be detrimental to patients; they should be monitored for extrapyramidal symptoms manifested by stiffness, tremor, and confusion. Benzodiazepines are also often used but should be used with caution as they can cause more

TABLE 28-4 Causes of Delirium

Drug toxicity
- Steroids, antibiotics, narcotics, benzodiazepines, antipsychotics, antihypertensives, anticholinergics, antiseizure drugs

Metabolic
- Electrolyte abnormalities: sodium, calcium
- Renal or liver failure
- Paraneoplastic syndrome

Endocrine abnormalities
- Glucose
- Thyroid disorder

Infections and fever

Hematologic abnormalities

Neurologic
- New CVA, infection, head trauma, seizures, bleed

Nutritional deficiencies: B12, thiamine, folic acid

Toxic effects of antineoplastic treatments
- Chemotherapy
- Radiation therapy

CNS tumor: brain metastasis, meningeal metastasis

Hypoxia
- Respiratory failure
- Cardiac failure
- Metabolic

Alcohol or drug withdrawal
- Chronic or acute alcohol
- Benzodiazepines
- Antipsychotics
- Antidepressants

Psychiatric illness
- Depression, psychosis
- Underlying dementia (higher risk)

Environmental
- Sleep deprivation, pain, unfamiliar surroundings
- Poor vision, hearing loss, immobility

CASE 28-1 CONTINUED

Mrs. T. is admitted to the hospital with increased confusion. A CT scan of the brain reveals a new brain lesion with edema. She is started on IV steroids; her oncology team requests a Palliative Care consult as she is not a candidate for any further radiation due to her severe decline and progression of the disease. At this time, Mrs. T. is unable to comprehend the medical situation and lacks the capacity to make decisions. Her daughter wants to know what her options are for care. She believes her mother would like to be at home.

Mrs. T. becomes hypotensive and is in respiratory distress. Her daughter understands that her mother's current condition is irreversible and that, if she is intubated, it is unlikely that she would return to her prior level of function. Based on previous discussion and her mother's advance directives, she decides to make her mother's status "Do not resuscitate" (DNR) and to make comfort the goal. Mrs. T. is placed on IV morphine and all blood draws are stopped. Her breathing becomes more comfortable and she dies in the hospital with her daughter and friends at her bedside.

confusion, especially in the elderly.[42] Patients may have a paradoxical reaction and become more acutely hyperactive and more confused.

The Last Hours

The end of life is never easy. It can be difficult for patients and families, as well as for the health care team. As a patient enters the last few days to hours of death, physical capabilities diminish and need for care increases. The goals of care need to be readdressed and treatments often must shift to assure patients comfort. Normal physiologic changes usually include weakness, decreased appetite, neurologic dysfunction, and decreased blood perfusion. Families and health care team should focus on a treatment plan with comfort as the goal. Routine use of artificial nutrition and IV fluids is not recommended during terminal care. Too much fluid can cause more discomfort and can add to breathlessness, cough, and secretions. Edema and skin breakdown can be more painful and intravenous lines can cause more discomfort.[43] As death approaches, there may be changes in respirations including Cheyne-Stokes breathing, accessory muscle use, and death rattle. Appropriate medication for comfort should be instituted. Patients are at risk for terminal delirium; medications for pain, agitation and confusion can be given routinely. Decreased perfusion will present as mottling of the skin; tachycardia and hypotension are part of the natural dying process. It is important to attend to skin care, repositioning of the patient, and control of increased secretions, as these will provide more comfort for the patient. Invasive and potentially uncomfortable treatments, such as suctioning, should be avoided. Swabbing the oral cavity, as well as applying moisture to the lips and moisture drops to the eyes can reduce discomfort.[44] During this time, any spiritual and cultural support should continue and family should be allowed to be with the patient and trained to assist in care if they wish.

IMPROVING END OF LIFE CARE FOR OLDER CANCER PATIENTS

Palliative medicine is gaining recognition as a valid and important field in medicine. Over the last 10 years, significant advances have been implemented to improve the palliative care that patients receive, including national guidelines for quality of care, multidisciplinary educational offerings, research opportunities, and resources for clinicians.[3] Through these efforts, palliative care knowledge and expertise is increasing among health care providers.[3]

"Hospice and Palliative Medicine" became a recognized subspecialty within the American Board of Medical Specialties (ABMS) in 2008. "Hospice and Palliative Medicine" is a subspecialty of ten participating boards including the American Boards of Internal Medicine, Anesthesiology, Family Medicine, Physical Medicine and Rehabilitation, Psychiatry and Neurology, Surgery, Pediatrics, Emergency Medicine, Radiology, and Obstetrics and Gynecology. The American Board of Internal Medicine (ABIM) is responsible for administering the certification examination on behalf of all 10 cosponsoring boards. Physicians who demonstrate the requisite experience in hospice and palliative care may sit for the examination during the grandfathering period from 2008 to 2012. After 2012, physicians will be required to complete a minimum of a 12-month or ACGME-accredited fellowship in Hospice and Palliative Medicine.

Multiple educational opportunities have been developed to improve the knowledge and skills in palliative care among health care practitioners. The End-of-Life Nursing Education Consortium (ELNEC) is a train-the-trainer model for nurses of all levels including faculty, ward nurses, and advanced care specialists in palliative and end-of-life care.[45] Over 5000 nurses in 50 states have received ELNEC training through these national courses and are sharing their new expertise in educational and clinical settings.[3] While this is a significant effort, this number reflects less than 0.2% of practicing nurses.[3] Utilizing a similar model, the Education for Physicians on End-of-Life Care (EPEC) is also a train-the-trainer program created to introduce physicians to the core competencies of palliative care.[46] The curriculum components include a comprehensive syllabus, trainer notes, recommended teaching approaches, slides, video trigger tapes, and an annotated reference list.[3] EPEC-Oncology (EPEC-O) was designed for practicing oncologists and the interdisciplinary team caring for persons and families with cancer and offers the same EPEC curriculum with a focus on patients with cancer.[3] These three curricula can be accessed at national courses and through Web-based learning. The End-Of-Life/Palliative Education Resource Center (EPERC) is an online resource for palliative care educational material supported by the Medical College of Wisconsin.[47] EPERC offers "Fast Facts," a collection of over 200 peer-reviewed and evidence-based summaries on key topics including pain, nonpain symptoms, communications skills, ethics, terminal care, and clinical interventions used near the end-of-life.[47] These "Fast Facts" are useful for self-learning as well as teaching students and trainees. Other EPERC offerings include suggested articles and links to other Web-based resources.

Additional resources offer guidance in the development and implementation of a palliative care program. The Center to Advance Palliative Care (CAPC) is a national organization whose mission is to provide "health care professionals with the tools, training, and technical assistance necessary to start and sustain successful palliative care programs in hospitals and other health care settings."[48] CAPC provides a large number of services including a comprehensive Web site, training and mentoring programs through their Palliative Care Leadership Centers™ (PCLC), online courses, discussion boards, and publications.[3,48]

Over the last 10 years, there have been increased research efforts in palliative medicine. Areas that continue to lack adequate data and need rigorous research include treatment decisions, family care, and advance directives.[3] Funding is becoming increasingly available for research in palliative care; two current options are include the National Palliative Care Research Center and the American Cancer Society (ACS) Initiatives for Palliative Care Research.[3] The doors are wide open for research pursuits in palliative medicine. Further high-quality research in hospice and palliative medicine is essential to develop a foundation for evidence-based practice.

CASE 28-1 CASE REVIEW

In the case of Mrs. T., there are several important considerations that might have improved her end-of-life care. As an elderly patient with other comorbidities, with functional limitations, and who was diagnosed with an incurable cancer, she was at high risk for side effects and decline. Discussions on goals of care could have been held earlier with the patient and primary medical doctor. The patient would have preferred to be at home at the end of her life. But once her condition took an acute turn, she was too unstable to be moved. Initiating hospice earlier in the course of her care could have allowed her to complete palliative radiation, as well as allowing for improved symptom management and quality-of-life focus. The hospice would probably have provided more social support for the patient and her daughter and she might have been able to stay in her home, if that was her wish. In a case such as this, palliative care can be initiated at the time of diagnosis and follow-up can be in a palliative clinic, which can work in conjunction with the oncologist and primary physician.

CONCLUSION

Palliative care and hospice are invaluable resources in the care of the older cancer patient. In the United States, medical care for patients with advanced illness has been characterized by untreated physical symptoms, poor communication between providers and patients, and treatment decisions in conflict with patient and family preferences.[3,49] With the aging of our population there will be more and more older patients diagnosed with cancer, many of whom may have advanced disease at the time of diagnosis, and the need for knowledge and clinical skills in palliative care by the oncologists and interdisciplinary team that care for them will only grow. National experts recommend a change in health care to include palliative care early in the course of cancer, in order to familiarize patients and their families with palliative care and hospice services, start communication about death earlier in the course of cancer treatment, and provide an opportunity for a discussion of goals of care among the physician, patient, and family.[3]

Palliative medicine offers health care professionals a holistic model of care and an approach to older cancer patients that addresses their physical and psychosocial needs. Essential components include a discussion of prognosis, as well as discussion of expected symptoms and how they will be managed. Such discussions should also clarify expectations, address fears, review goals of care, and determine treatment preferences, including intensity of care and code status. Improving the care of older cancer patients requires that the medical community have greater awareness of the importance of these issues and how they affect disease course, functional status, and quality of life. Physicians and other health professionals who care for older patients with advanced cancer need to be competent in the management of pain and nonpain symptoms and know when to ask for help. Educational, clinical, and research opportunities in palliative medicine are available; however, they must continue to be expanded and, most importantly, health care providers must access and utilize them. Palliative care consultation and referrals to hospice should be implemented earlier and ultimately should become standard-of-care in the management of the older cancer patient.

See expertconsult.com for a complete list of references and web resources for this chapter

CHAPTER

29

Ethical Issues Related to Assessing Decision Making Capacity

Anne Walling and Neil S. Wenger

CASE 29-1 CASE DESCRIPTION

Ms. S. is a 74-year-old woman with colorectal cancer metastatic to liver and brain. Although she has told friends that she no longer wants aggressive therapy and would not want to be intubated or spend time in intensive care and would like to die at home "when it is my time," she has been hesitant to bring this up with her doctor as she knows that he was considering recommending her for a new clinical trial. She was an only child, her husband died 10 years ago, and she never had children. She does not have an advance directive and has not specified a durable power of attorney agent to make health care decisions. Her next door neighbor brings her to the emergency department one night for progressive confusion and fever. At presentation, her blood pressure is low and her cognitive status fluctuates. The emergency physician explains to the patient that she requires treatment in the intensive care unit (ICU). The patient states that she wants to go home. What should the emergency physician do?

Great importance is placed on the ethical principle of autonomy in medicine, as practiced in the United States today, and ensuring that a patient's medical care is guided by his or her preferences is central to upholding this ethical principle.[1] Ideally, patients would always actively participate in decisions about their own medical care. Unfortunately, the brain commonly becomes dysfunctional in the setting of organ failure and severe illness, and this is particularly true in the cancer patient. Patients with cancer can lose the ability to direct their care because of malignancy directly affecting the brain, as an effect of severe illness elsewhere in the body, and as a result of medication effects. Delirium is common in elderly patients and in patients with advanced cancer.[2,3,4] Delirium often presents just as patients are becoming more seriously ill (and often will need decisions to be made regarding aggressiveness of care) and right before death. For example, in the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT), 28% of patients with lung or colon cancer suffered from confusion in their last 3 days of life.[5,6] However, such cognitive changes can be reversible and, in one study, 50% of episodes (often those precipitated by a change in opioid dose or by dehydration) in patients with advanced cancer were reversible.[2] In addition, elderly patients have increasing rates of impaired cognition as they age. Patients with cognitive impairment who retain the ability to make decisions at baseline are at greater risk of developing delirium under the stress of illness.[7]

Cognitive dysfunction has many implications for the elderly cancer patient. In general, cognitive dysfunction is a poor prognostic sign in older patients.[8] Patients with cognitive dysfunction are also particularly challenging to care for and require special attention to care planning above and beyond the average patient. For example, patients with cognitive dysfunction may have problems with adherence to treatments and may require the assistance of a caregiver. In addition, these patients may lack the capacity to make decisions about their own health care. Because of the prevalence of delirium and cognitive impairment among elderly patients with cancer, assessment of decision-making capacity will almost always be necessary in the trajectory of disease of an older cancer patient; for this reason, it is essential to understand what decision-making capacity is. Decision-making capacity is defined as the ability to participate in making medical decisions. To have this capacity, a patient must: (1) understand the relevant information needed to make an informed decision; (2) have the ability to appreciate the clinical situation and its consequences; (3) reason about treatment options; and, ultimately, (4) communicate a choice.[9,10]

For example, a man with myeloma who sustained a pathologic femur fracture and is refusing pinning of the fracture but cannot understand that surgery is needed or is unable to conceive of the risks and benefits of surgery lacks decision-making capacity because he does not understand the relevant information. If the man refused surgery but did not understand that without the

procedure he will be unable to walk for months, if ever again, and that he would be likely to die if left to lie in bed for this time does not exhibit decision-making capacity because he cannot appreciate the clinical situation and its consequences. If the man refused surgery because "all operations are scary" and cannot even consider the option of surgery or the risks and benefits of surgery versus alternative treatments, then the case would be an example of a patient who lacks decision-making capacity because he cannot reason about treatment options. Lastly, a man who cannot or will not communicate a decision does not exhibit decision-making capacity. In nearly all cases, more than one aspect of capacity is compromised in a patient lacking decision-making capacity. Yet, teasing out the aspect of capacity that is lacking when a patient is deemed incapable can be a valuable exercise to ensure that a patient lacks capacity and also as a focus to attempt to enhance capacity.

Capacity is evaluated by a physician asking a series of questions. Table 29-1 shows specific questions and comments that can aid a physician in assessing capacity. For example, a physician can assess a patient's understanding by asking, "Please tell me in your own words the problem with your health now." "What is the recommended treatment?" A physician could then assess a patient's ability to appreciate the situation and its consequences by asking, "What is treatment likely to do for you?" or "What do you think will happen if you choose not to proceed with the treatment?" A patient's ability to reason through treatment options might be determined by asking, "Why do you prefer (or why do you not want) the treatment?" Lastly, asking, "Can you tell me your decision?" helps assess the patient's ability to communicate his or her decision. If a patient is able to answer these questions in a coherent fashion (that is the patient displays decision-making capacity), then he should be

TABLE 29-1 Legally Relevant Criteria for Decision-Making Capacity and Approaches to Assessment of the Patient

Criterion	Patient's Task	Physician's Assessment Approach	Questions for Clinical Assessment	Comments
Communicate a choice.	Clearly indicate preferred treatment option.	Ask patient to indicate a treatment choice.	Have you decided whether to follow your doctor's [*or my*] recommendation for treatment? Can you tell me what that decision is? *If no decision*: What is making it hard for you to decide?	Frequent reversals of choice because of psychiatric or neurologic conditions may indicate lack of capacity.
Understand the relevant information.	Grasp the fundamental meaning of information communicated by physician.	Encourage patient to paraphrase disclosed information regarding medical condition and treatment.	Please tell me in your own words what your doctor [*or I*] told you about: the problem with your health now; the recommended treatment; the possible benefits and risks (or discomforts) of the treatment; any alternative treatments and their risks and benefits; the risks and benefits of no treatment.	Information to be understood includes nature of patient's condition, nature and purpose of proposed treatment, possible benefits and risks of that treatment, and alternative approaches (including no treatment) and their benefits and risks.
Appreciate the situation and its consequences.	Acknowledge medical condition and likely consequences of treatment options.	Ask patient to describe views of medical condition, proposed treatment, and likely outcomes.	What do you believe is wrong with your health now? Do you believe that you need some kind of treatment? What is treatment likely to do for you? What makes you believe it will have that effect? What do you believe will happen if you are not treated? Why do you think your doctor has [*or I have*] recommended this treatment?	Courts have recognized that patients who do not acknowledge their illnesses (often referred to as "lack of insight") cannot make valid decisions about treatment. Delusions or pathologic levels of distortion or denial are the most common causes of impairment.
Reason about treatment options.	Engage in a rational process of manipulating the relevant information.	Ask patient to compare treatment options and consequences and to offer reasons for selection of option.	How did you decide to accept or reject the recommended treatment? What makes [*chosen option*] better than [*alternative option*]?	This criterion focuses on the process by which a decision is reached, not the outcome of the patient's choice, since patients have the right to make "unreasonable" choices.

From Applebaum, PS. Assessment of Patients' Competence to Consent to Treatment. N Engl J Med 2007;357:1834-40.

able to accept or reject medical care, even if the physician disagrees with the patient's decision.[9]

It is important to note that decisions about a patient's capacity have to be made on an individual basis. It is often possible for patients with psychiatric disorders or dementia to make at least some decisions, if not all of them. Although a patient's past history can inform a capacity assessment, prior capacity determinations or prevalent diagnoses should not be assumed to deem a patient incapable of making future decisions. For example, a patient with a history of schizophrenia and a history of lacking decision-making capacity who is now receiving treatment that controls psychosis may be able to participate in his health care treatment decisions. In addition, a patient with a history of dementia, who had been actively participating in decision-making concerning breast cancer treatment, may suffer a decline in her cognitive abilities so that she is no longer able to meaningfully choose between treatment options.

When should a physician complete a capacity assessment of a patient? A good rule of thumb is that any time informed consent or refusal is required in medical care, it should be clear that a patient has decision-making capacity. In the above case, Ms. S. is refusing admission to the ICU and demanding to go home. However, she shows signs of a serious infection and is, at times, lethargic. In order to accept Ms. S.'s refusal of ICU admission, the emergency physician must assess her capacity to make that decision.

CASE 29-1 CONTINUED

After explaining to the patient her current situation, the recommended treatment and why it is needed, the emergency physician asks Ms. S. to tell him in her own words what her health problem is and the recommended treatment. Ms. S. is unable to answer this question. She also does not respond meaningfully when the doctor asks her additional questions about what is happening to her. Although lethargic, she continues to demand that she go home. The emergency physician decides that Ms. S. does not have the capacity to make decisions, admits her to the intensive care unit (using implied consent), and attempts to identify a potential surrogate decision maker for the patient.

Although Ms. S. is able to communicate that she wants to go home, she is unable to articulate why and how she came to this decision. Therefore she does not have decision-making capacity to make the venue-of-care decision. Since Ms. S. does not have an advance directive or any prior medical record note regarding preferences for care, the emergency physician decides that the appropriate course of action is to treat the patient in the intensive care unit.

In practice, a formal evaluation of capacity is not completed for every patient who expresses preferences regarding the acceptance or refusal of a medical intervention. However, some degree of judgment about the patient's ability to form and express preferences must occur every time a patient makes a decision.[11] For selected patients, it is important that a formal capacity assessment be performed and documented in the medical record. If a patient has an underlying cognitive impairment, if a patient is at high risk of delirium due to an underlying medical condition, or if a patient's expressed preferences fall outside of a range generally comprehensible to others, a more rigorous evaluation of capacity that covers all four of these elements is required, especially if the proposed procedure or clinical condition has serious clinical consequences to the patient.[1] It is important to recognize that some patients, especially those with slowly emerging dementia, are able to mask their cognitive impairment. Mini-mental status exams (MMSE) and other objective tests should be considered in all vulnerable elders to assess cognitive status when important decisions are being made.[12]

Ms. S., in the case above, is an elderly woman with metastatic brain disease and signs of acute infection, all of which put her at high risk of delirium; thus she deserves a formal evaluation of capacity. Documentation about decision-making capacity for a patient should cover all four areas that are assessed: understanding of relevant information, ability to appreciate the clinical situation and its consequences, ability to reason about treatment options, and ability to communicate a choice. In this case, a physician might document, "Ms. S. is expressing the desire to go home. Although comfort-oriented care at home may be a reasonable option given her metastatic disease, we have no evidence that she previously desired this course of treatment. Ms. S. is unable to describe or understand her current clinical situation, does not understand the implications of her situation, and cannot engage in reasoning about her treatment options. Therefore, despite the fact that Ms. S. is asking to go home, this cannot be considered a reasoned decision. Ms. S. lacks decision-making capacity at this time. Because she has a potentially life-threatening condition that needs emergent care, we will treat her using implied consent and search for an appropriate surrogate decision maker until she regains the ability to make decisions for herself." On the other hand, if Ms. S. had been able to express that she knew she had cancer and had decided that she never wanted to go to an ICU, was ready to die, and did not want to die in a hospital, she would have displayed that she had capacity to make this decision (even though she has risk factors for incapacity).

There are methods or tools available to assist in the assessment of decision-making capacity. Many of the tools available for clinical research are not adequate for assessing all four domains of decision-making capacity.[13] Some tools for clinical practice have been developed; however, these are often time-consuming. For example, the MacArthur Competence Assessment Tool (MacCAT-T) assesses the domains of decision-making

capacity using a structured interview format. The Capacity to Consent to Treatment Instrument varies from the MacCAT-T in that it uses clinical vignettes to test a patient's understanding rather than using a structured interview format. The Hopemon Capacity Assessment Interview (HCAI) is also similar to the MacCAT-T but uses semistructured interviews and was initially designed to specifically assess medical and financial decision making in nursing home patients.[14]

THE PATIENT DOES NOT HAVE CAPACITY. WHAT NEXT?

Once a patient is deemed to lack capacity, a physician must decide how to proceed. Regarding Ms. S., the physician should make sure that there is not an advance directive or POLST (Physician Orders for Life Sustaining Treatments) form that states the patient would not want ICU care. If no such documentation exists, in an emergency situation the physician often must act without explicit informed consent from the patient. In a less emergent situation, the physician would look for an appropriate decision maker and ask the surrogate decision maker how to proceed. A surrogate decision maker should always be advised to make decisions based on a patient's previously expressed wishes and, if there had been no wishes expressed, to make a "substituted judgment" that considers a patient's values and prior behaviors to figure out what the patient would want.[15]

CASE 29-1 CONTINUED

Ms. S. is transferred to the ICU where she receives antibiotics and fluids. Mechanical ventilation is not required overnight. Upon examination in the morning by the ICU team, although Ms. S. is still somewhat lethargic, she seems less confused. Her capacity is reassessed. Although she still is unable to answer all questions about her treatment options and reason through a decision, she identifies her neighbor (at her bedside) by name as her dearest friend. She also says that her neighbor is like her sister and knows what she wants. Although the doctors don't think she has the capacity to make a treatment decision, they believe that she is capable of identifying a surrogate decision maker. Later, the physicians return to assess the consistency of her wishes and the patient is able to clearly confirm that she wants her neighbor to make medical decisions for her.

One must also take into account the practical aspects of care in designing treatment options for a patient. Issues of "practical" versus "best" treatment often arise in considering treatment options for a patient incapable of making a treatment decision. For example, if an incapable patient is refusing to ingest a particular medication, it may be impossible to force him or her to take the medication. Despite the fact that this medication might be the preferred treatment, it might not be a reasonable option for this patient; a different set of potential treatments must be considered. The long-term consequences of a therapy also should be considered. For example, for a patient with severe chronic psychosis who develops leukemia, it may be feasible to sedate the patient to receive outpatient chemotherapy as an inpatient, but it may be infeasible to keep that patient hospitalized for the following weeks to monitor for fevers and neutropenia, especially if he or she is not cooperative with hospital staff. Treatments must be practical in order to be implemented.

There are two points about decision-making capacity raised in this part of the case. One is that decisional incapacity is not necessarily a permanent condition.[16] In fact, decision-making capacity often fluctuates. In this case, the patient initially presented with delirium and did not have the ability to make decisions. However, after receiving fluids and antibiotics, her delirium diminished and her ability to make decisions increased. As delirium can wax and wane, so can a patient's ability to make decisions. Patients who are found to lack capacity for a decision at one point should be continually assessed and, in particular, should be reassessed during treatment of the underlying condition. Patients who lack capacity due to psychotic and mood disorders may regain capacity with treatment. There are situations in which patients lack capacity because they lack trust in the information provided or the providers. In such circumstances, decision-making capacity may, at times, be enhanced by improved communication or even by changing providers.

As noted in the case continuation above, even if a patient lacks capacity to make one medical decision, this does not necessarily mean that she lacks capacity to make all decisions.[17,18,19] Drane suggests that a "sliding scale" exists in which increasingly more stringent standards of capacity are required as the consequences of the patient's decision embody more risk.[20] For example, it is generally accepted that the capacity requirements for a patient to name a surrogate decision maker are less stringent than for more complex medical decisions. Some suggest that even patients with severe dementia may be able to identify a surrogate decision maker if they can pass a careful screening process. A set of criteria that could be used to judge whether a nursing home resident has the ability to name a health care proxy showed reasonable reliability and validity when tested among 200 nursing home residents. Even among patients who had a MMSE score of less than 10, 50% were able to name a health care proxy.[17]

Who can assess decision-making capacity in a patient? Any able treating physician can evaluate decision-making capacity, and it is the responsibility of a physician proposing a treatment that requires consent or refusal to ensure that the patient making the choice has the capacity to do so. This responsibility can be fulfilled by the physician carrying out the capacity evaluation or by consulting another physician to perform the assessment. A common misunderstanding is that a psychiatric consult is necessary to perform a formal capacity evaluation.

Although a psychiatric consult can be useful in cases in which a patient is thought to lack decision-making capacity due to a psychiatric disorder, for most medical cases (where incapacity is due to dementia or delirium) any medical doctor with experience in capacity assessment can become qualified to carry out a formal capacity assessment.

How does one deal with uncertainty when assessing decision-making capacity? Test, retest, and retest. When possible, the best way to deal with uncertainty is reassessment. Usually, over time, a patient's mental capabilities will improve or worsen, making the decision less uncertain. Information garnered early in the effort often can inform later retesting and provide insight into a patient's beliefs and capabilities so as to solidify the assessment of each of the aspects of capacity. When prior information about values and behaviors is available, this can inform the capacity assessment as well. When practical aspects of a case make it impossible to take this approach, consider consulting a specialist with expertise in capacity assessment, such as a psychiatrist. An ethics consultation might also be considered. Refusal to participate in a psychiatric assessment—such as refusal to participate in decision making— can constitute incapacity if a patient's capability cannot otherwise be known.[21] The courts are another approach to capacity assessment; however, they are not usually available in a timely fashion and should be reserved for situations in which a decision maker will have to be appointed or for the rare circumstance in which there is uncertainty that requires a legal solution.

CASE 29-1 CONTINUED

In a bedside discussion with the physicians and nurses, Ms. S.'s neighbor and surrogate decision maker is asked about her friend's overall goals for care. She is able to recall multiple conversations that she has had with Ms. S. in which Ms. S. indicated that when it was her time, she wanted to avoid aggressive measures such as mechanical ventilation, and that she wished to die peacefully at home. The neighbor also explained that Ms. S. had felt in recent weeks that her "time" was here. Ms. S.'s neighbor also said that she was willing to care for her friend at home. Based on these preferences, the physicians recommend transferring Ms. S. home with hospice care. Ms. S.'s neighbor strongly believes this is what Ms. S. would want and Ms. S. nods in agreement.

Although not legally appointed, Ms. S.'s neighbor is an acceptable surrogate decision maker. The goal of a surrogate decision maker is to make a decision that is consistent with what the patient would want. Ms. S.'s neighbor did not have difficulty with this because the patient and her neighbor had had clear, frequent, and recent discussions about the patient's preferences for care. In turn, Ms. S.'s neighbor was clear, consistent, and reasoned in her decision making.

Surrogate decision making is not always this easy. One challenge is that the identified surrogate decision maker must demonstrate decision-making capacity. If a surrogate decision maker is deemed incapable (applying the criteria discussed above) to make decisions, an alternate decision maker must be found. Most advance directives designate an alternate. Most states have laws that designate the closest available relative as an appropriate surrogate decision maker. As a last resort, a court-appointed decision maker may be necessary.

Another common challenge to surrogate decision making comes when the surrogate does not have a clear idea of what choices the patient would make. If the surrogate cannot explain the patient's previously stated wishes and a substituted judgment (based on the values and prior behaviors of the patient) is impossible, then the surrogate decision maker should be guided to make a "best interest" decision *from the patient's perspective*. A common pitfall is a surrogate deciding to pursue a plan that fits what he or she would personally want for the patient rather than placing himself in the patient's shoes. While some surrogate decision makers get this concept implicitly, with others considerable effort is needed to help them overcome the strong desire to make a self-serving choice.

A physician may be able to help guide decision making by stimulating conversation about the patient's personality, passions, and attitudes toward their disease and medical care. For the surrogate who is unable to relate the patient's preferences or to make a substituted judgment, we have found it valuable to have the surrogate recount "who this person is." What was this patient like? What were her goals and aspirations? What made him tick? If it cannot be known what this patient would want right now, what sorts of decisions would be most consistent with the essence of her being?

AVOIDING A COMMON MISTAKE

A common mistake made by physicians who care for elderly patients with complex medical issues is to not assess capacity until the patient disagrees with the physician's recommendations (Table 29-2). Patients with various levels of cognitive impairment may not have the capacity to make decisions, for example, about whether to initiate chemotherapy. This might not be obvious, especially if a patient is agreeing to recommended therapies. Testing for and documentation of decision-making capacity in older patients who are making important medical decisions should be routine.[16]

PLANNING FOR INCAPACITY

Even among critically ill cancer patients,[22] only a small proportion of individuals have completed an advance directive. In addition, studies suggest that patients with terminal illness often do not communicate their preferences for care either to their surrogate decision makers or their physicians.[23,24] Thus the high rate of incapacity anticipated among elderly cancer patients means

TABLE 29-2

Ten Myths About Decision-Making Capacity

1. Decision-making capacity and competency are the same.
2. Lack of decision-making capacity can be presumed when patients go against medical advice.
3. There is no need to assess decision-making capacity unless patients go against medical advice.
4. Decision-making capacity is an "all or nothing" phenomenon.
5. Cognitive impairment equals lack of decision-making capacity.
6. Lack of decision-making capacity is a permanent condition.
7. Patients who have not been given relevant and consistent information about their treatment lack decision-making capacity.
8. All patients with certain psychiatric disorders lack decision-making capacity.
9. Patients who have been involuntarily committed lack decision-making capacity.
10. Only mental health experts can assess decision-making capacity.

From Ganzini L, Volicer L, Nelson WA, Fox E, Derse AR. Ten myths about decision-making capacity. J Am Med Dir Assoc 2005;6(3 Suppl):S100-4.

that preserving autonomy in this vulnerable population requires primary care physicians, oncologists, and other clinicians caring for these patients to discuss the importance of surrogate decision makers and advance care planning early in the trajectory of illness, as well as at sentinel events, such as onset of metastatic brain disease, beginning of a palliative chemotherapeutic regimen, and admission to an ICU.[25] Discussing patient preferences for care and documenting a surrogate decision maker for cancer patients can improve the match of treatment with prognosis and preferences. If Ms. S. had been unable to name her neighbor as her surrogate decision maker, there would have been no way to ensure that medical decisions reflected what she would have wanted. Discussing these topics in advance, while sometimes difficult, will ultimately increase patient autonomy and make it more likely that the care patients receive is consistent with their goals.

INFORMED CONSENT AND CANCER CLINICAL TRIALS

This chapter uses a clinical case to display the importance of decision-making capacity in informed decision-making. It is important to note that assessment of and attention to decision-making capacity is also critical in research. Providing informed consent for participation in a cancer clinical trial requires a high level of understanding and the capacity to reason through complex trade-offs. For the older cancer patient, assessment of decision-making capacity prior to obtaining informed consent for research should be routine.[26]

FUTURE RESEARCH

Evidence suggests that physicians, even including psychiatrists, may inconsistently apply the standards for decision-making capacity.[27] There is still a great deal to learn about decision-making capacity and the best ways to care for patients who lack decision-making capacity. It is important to study how capacity is tested in practice, what errors are common, and the clinical implications of such errors. In addition, better standardized methods of measuring decisional capacity that are practical for the clinical setting are needed. Such tools should account for the magnitude of the decision and should have the capability to be used in a serial fashion to assess change over time. Moreover, we need to know more about how to enhance capacity among patients who are marginally capable of making decisions or whose capacity waxes and wanes. The better the set of tools available to assess and maximize decision-making capacity, the greater the likelihood that decision-making capacity will be appropriately used in clinical care.

Chapter Summary

Ideally, a patient would always actively participate in decisions about his or her own medical care. Unfortunately, delirium and cognitive impairment are common among elderly patients with cancer and therefore capacity assessment will almost always be necessary in the trajectory of disease of an older cancer patient. In most situations, capacity assessment can be performed by the physician obtaining consent from a patient for treatment; however, psychiatric or ethics consultation may be helpful in some cases. A strategy for assessing decision-making capacity has been suggested.

When a patient lacks decision-making capacity, an appropriate surrogate decision maker should be identified and counseled about making a substituted judgment on behalf of the patient. Advance care planning is recommended in the elderly cancer patient to ensure that treatment decisions are made in accordance with a patient's goals, even after the patient loses the capacity to actively participate in decision making.

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See expertconsult.com for a complete list of references and web resources for this chapter

SUGGESTED READINGS

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CHAPTER

30

Economic Burdens and Access to Care Barriers for the Older Cancer Patient

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CASE 30-1 CASE DESCRIPTION

A 75-year-old man with type 2 diabetes and hypertension presented to his physician with fatigue and constipation. His complete blood count showed a low hemoglobin level and evidence of iron deficiency; colonoscopy revealed a sigmoid colon mass. He had missed a routine screening colonoscopy appointment 3 years ago, but a prior colonoscopy approximately 15 years ago had been unremarkable. He subsequently underwent surgical resection of the mass, which was found to be a T3N1M0 adenocarcinoma of the sigmoid colon. His surgical course was complicated by a wound infection but he has been continuing to recover slowly from his hospitalization. His daughter has been helping with his wound care and dressing changes. His oncologist recommends adjuvant chemotherapy with a 6-month course of oral capecitabine, and he leaves the clinic with a prescription, along with instructions for proper use of the medication.

Up until now, he has been purchasing his antihypertensives and diabetes medications online from a Canadian pharmacy and has therefore not enrolled in a Medicare Part D prescription plan. His wife died 3 years ago from breast cancer, and he lives with his daughter and son-in-law. He does receive monthly Social Security checks. Alhough he has a small amount of savings left, much of it was depleted by expenses related to his wife's cancer.

After checking online, he discovers that a 1-month supply of capecitabine will cost approximately $2,000, which he knows he cannot afford. He decides not to mention this to his daughter, since she has been so worried after her husband lost his job a month ago. He calls the nurse at the oncologist's office to tell her that he is not interested in adjuvant chemotherapy, but that he will come back for routine checkups. A follow-up appointment is scheduled in 3 months.

About a year later, he develops pain on the right side of his abdomen. A computed tomography (CT) scan shows extensive metastases to the liver. Systemic chemotherapy is recommended, and he is now going to the oncologist's office every 2 weeks to receive FOLFOX + bevacizumab. He develops significant neuropathy and nausea from chemotherapy. He has been taking his nausea medications only when the nausea is severe, because the medication is quite expensive. Because his neuropathy has worsened, his daughter now has to drive him to all of his clinic appointments and chemotherapy appointments. Because of side effects from chemotherapy, he does not have the energy to play with his grandkids. He feels nauseated, tired, and sad most of the time. He feels guilty and wishes he could just "slip away."

Old age is typically a period of declining income and increasing health care expenditures. For example, Americans older than 85 who do not have cancer have household incomes 47% lower and out-of-pocket health expenditures 77% higher than those between 55 and 65 years of age. Between these two age groups, out-of-pocket health expenditures increase from 3% to 9% of household income (Table 30-1).[1]

The economic realities can be even harsher for those older Americans who suffer from cancer. Out-of-pocket health expenditures are 32% higher for cancer patients over age 65 than for people in this age group without cancer.[2] The Consumer Bankruptcy Project (CBP) found that 10% of families of all ages that filed for bankruptcy due to medical reasons cited cancer as their main illness.[3] These higher economic burdens borne by elderly cancer patients persist in spite of a high percentage of health insurance coverage for this age group relative to younger people (99.6% vs. 86.4%).[4]

To understand the special economic problems encountered by older cancer patients, an examination of the patchwork system of insurance coverage in the United States is necessary. In addition, any discussion of the economic burdens of older cancer patients should include the costs incurred by relatives and other uncompensated caregivers. This chapter describes the coverage system under Medicare and Medicaid for the majority of older adults in the United States, focusing on potential sources

TABLE 30-1 Income, Out-of-Pocket, and Total Health Expenditures by Age Group and Cancer Diagnosis (1996-2006)

	Income		Total Expenditures		Out-of-pocket	
Age	Not Cancer	Cancer	Not Cancer	Cancer	Not Cancer	Cancer
55 - 65	$33,065	$33,122	$4,264	$15,705	$894	$1,762
65 - 75	$24,045	$25,359	$5,396	$13,585	$1,037	$1,408
75 - 85	$19,551	$20,408	$7,047	$12,773	$1,296	$1,656
≥ 85	$17,522	$18,817	$7,741	$12,172	$1,586	$1,945

of high out-of-pocket expenses for patients with cancer. Average out-of-pocket expenditures for older patients with and without a cancer diagnosis are described using data from the Medical Expenditures Panel Survey (MEPS). MEPS is a nationally representative survey of medical expenditures by households and individuals that has been conducted by the Agency for Healthcare Research and Quality (AHRQ) every year since 1996.[5] Finally, the costs and burdens borne by family members of elderly patients with cancer are explored.

HEALTH INSURANCE BENEFITS AND COSTS

Medicare

Medicare covers 98.9% of all Americans age 65 and older. It is available to all those who qualify for Social Security benefits and is by far the largest health insurer in the U.S. There are four major parts of Medicare coverage. Part A covers hospitalization (excluding physician fees), home health, hospice, and a limited number of days of nursing home care. Part B covers physician fees and outpatient care. Part C is a managed care option operated by private companies and covers the same expenses (and sometimes more) that Parts A and B cover. Part D covers prescription drugs.[6]

Most Medicare enrollees do not pay any premiums for Part A coverage, but do pay a deductible ($1,068 in 2009) and coinsurance (from $0 to $534 per day in 2009, depending on the length of stay) for each hospital stay. The few who do pay premiums (i.e., people who do not qualify for Social Security, also known as *voluntary* Part A beneficiaries) are charged $443 per month for basic coverage.[7] Medicare also pays for part or all, up to the first 100 days (in a lifetime), of long-term hospitalization or nursing home care. Specifically, Medicare pays for all of the first 20 days and the enrollee must pay $133.5 per day for stays between 21 and 100 days.

Because of the limits to Part A coverage, the greatest exposure to high out-of-pocket expenses for Part A enrollees comes from hospital stays that last for more than 60 days and nursing home stays that last for more than 20 days. For example, a 120-day hospital stay would generate $25,000 of expenses not covered by Medicare and a 100-day nursing home stay will generate $10,000 in noncovered expenses. Long nursing home stays are quite common. 8.5% of all nursing home residents over the age of 65 have a diagnosis of cancer and 72.6% of those cancer patients have stays that last longer than 100 days. With an average monthly charge of $4,290 in 2004, the out-of-pocket cost of a long nursing home stay can be financially devastating.[8]

Part B beneficiaries pay a monthly premium of $96.40—more if their individual income is over $85,000 per year. In addition to the monthly premium, Part B beneficiaries pay an annual deductible of $135 plus 20% of all Part B payments to providers. Medicare Part B facility payments are determined by prospective payment systems that dictate the payment for each type of patient visit. Physician fees paid by Medicare are determined by the resource-based relative value scale (RBRVS).

Part C (Medicare Advantage) is an optional type of insurance coverage that Medicare beneficiaries can substitute for Part A, Part B and Part D coverage. These plans are administered by private insurance companies, mainly health maintenance organizations (HMOs) and preferred provider organizations (PPOs). As of 2009, 23% of Medicare enrollees are covered by Medicare Advantage plans.[9] Medicare pays the plan administrators approximately 15% more per enrollee than it pays for fee-for-service enrollees. This relatively generous payment system is responsible for the increased participation in Medicare Advantage plans by private insurers in 2003. This increased competition has attracted many enrollees to Medicare Advantage plans, but is a source of controversy.

Part D, implemented in 2006, provides coverage for prescription drug costs. Enrollees pay a minimum monthly premium of $24.80, a $180 to $265 annual deductible and 25% of full drug costs up to $2,400. Once out-of-pocket expenses reach $3,850, the enrollee pays only 5% of additional drug costs.[10] The range of uncovered drug costs is known as the "donut hole", a gap in coverage. In 2008, the coverage gap was $3,216 for plans offering the standard Medicare Part D benefit; by 2019, it is projected to be nearly $6,000.[11]

Medicaid

Medicaid covers 8.7% of all Americans age 65 and older who are actively treated for cancer.[12] Each state determines its own terms of eligibility for Medicaid coverage

TABLE 30-2 Out-of-Pocket and Total Health Expenditures by Cancer Diagnosis and Expenditure Category, Age 65 and Older (1996-2006)

	Expenditures					
	Without Cancer		With Cancer		Difference	
Category	Out-of-pocket	Total	Out-of-pocket	Total	Out-of-pocket	Total
Drugs	$738	$1,437	$895	$1,771	$157	$334
Office visits	$138	$1,247	$247	$3,232	$110	$1,985
Home health	$90	$569	$133	$867	$43	$298
Hospitalization	$33	$2,321	$67	$5,371	$34	$3,050
Outpatient	$20	$427	$41	$1,816	$21	$1,389
Other	$316	$1,002	$388	$1,755	$73	$753
Total	$1,335	$7,003	$1,772	$14,812	$437	$7,809

but, in general, Medicaid is intended to cover the indigent population. Consequently, Medicaid coverage does not normally require premiums, deductibles, or coinsurance payments. Indeed, Medicaid often pays the Medicare premiums, deductibles, and coinsurance payments for people who are enrolled in both Medicare and Medicaid.

In 2008, Medicaid physician fees were 72% of Medicare physician fees.[13] Consequently, Medicaid's fee payments are so low that some physicians claim to not accept new Medicaid patients. This could result in less access to health care for Medicaid patients; however, this access problem for Medicaid enrollees may be less acute for cancer patients than for other types of patients. In a 2006 survey of physicians who accepted new patients, only 4% of oncologists responded that they did not accept new Medicaid patients, while none responded that they did not accept new Medicare patients. Primary care physicians and other specialists responded that 18% did not accept new Medicaid patients and 12% did not accept new Medicare patients.[14]

Importantly, Medicaid covers nursing home expenses. Since Medicare coverage ends after 100 days, many long-term nursing home residents must deplete their life savings before becoming eligible for Medicaid. For nursing home residents over the age of 65 with a diagnosis of cancer, 34% are covered by Medicaid at the start of a stay that lasts for more than 100 days; however, the percentage jumps to 65% by the end of the stay.[1]

TOTAL AND OUT-OF-POCKET HEALTH EXPENDITURES

The costs of cancer care to Medicare are substantial and vary by tumor site, phase of care, stage at diagnosis, and survival. Costs are greatest in the initial year of treatment and in the final year of treatment and also increase with stage.[16,17,18] Older patients being treated for cancer—regardless of their insurance status—face significantly higher out-of-pocket and total health expenditures than patients without cancer.[19] From 1996 to 2006, annual total health expenditures for members of this age group being treated for cancer were more than double those for members not being treated for cancer ($14,812 vs. $7,003). Out-of-pocket expenditures for these two groups averaged $1,772 and $1,335, respectively—a 33% increase from the noncancer group.[20] Although the difference in total health expenditures is due mainly to expenditures for office visits, hospitalization, and outpatient visits, the single largest component of the difference in out-of-pocket expenditures is for prescription drugs, $896 vs. $738. Over this time period, half of total drug expenditures for older cancer patients were paid out-of-pocket. Only 7% of other types of health expenditures are paid out-of-pocket.[20] Table 30-2 provides complete figures.

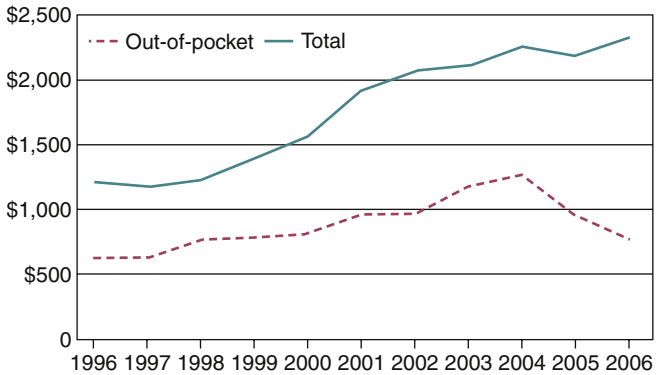

FIGURE 30-1 Annual per Capita Drug Expenditures by Cancer Patients Age 65 and Older, 1996-2006 (2006 dollars)

It was because of high out-of-pocket expenditures for prescription drugs that the Medicare Prescription Drug, Improvement, and Modernization Act (i.e., Medicare Part D and Medicare Advantage Plans) was enacted in 2003. Figure 30-1 shows the annual per capita drug expenditures for cancer patients age 65 and older from 1996 to 2006. Although total drug expenditures continued their upward trend over this time span, out-of-pocket drug expenditures have decreased from $1,269 to $777 (39%) since 2004.[20] This sizable decrease in out-of-pocket drug expenditures for the elderly cancer patient is likely due in part to Medicare Part D; however, since Part D did not become operational until 2006, it is also likely that some of the decrease, especially in 2005,

was due to the enhancement of Medicare Advantage plans that began earlier than 2006. The decrease in some of these out-of-pocket prescription costs might have been offset by premiums and deductibles related to Medicare Part D and Medicare Advantage plans.

Despite the variable total expenditures by cancer type, cancer patients uniformly experience significant out-of-pocket costs (range $257-$1,620). Table 30-3 shows the geometric mean values for annual total and out-of-pocket expenditures by type of cancer.[20]

Patient time during treatment is a nonpecuniary cost that is usually not included in out-of-pocket costs. One 2007 study concluded that the value of patient time totaled $2.3 billion in 2005 and varied substantially by tumor site.[21]

ACCESS TO CARE AND QUALITY OF CARE

Some studies have concluded that access to care and quality of care for the older cancer patient are not all that they could be. Many clinicians may be influenced by ageist beliefs that are not supported by scientific evidence. For example, one study concluded that oncology health care professionals had negative attitudes towards elderly people with regards to their residential patterns, cognitive style, personal appearance, and personalities.[22] Another published report noted that mastectomy has been used as a standard treatment for older women, because it was believed that changes in body image would not bother them, although evidence shows that older women also suffer problems with body image after mastectomy.[23] Inadequate local therapy is associated with reduced survival in elderly women treated with breast-conserving therapy.[24] Older adults being treated for cancer may not be provided appropriate palliative care[25] and may often experience diminished quality of life.[26] Some limits to care could be self-imposed. In a survey of elderly adults, respondents were more likely to recommend end-of-life treatment for a spouse when it was financed by Medicare than by the patient's own savings.[27]

Despite the near universality of health insurance coverage of the elderly, many cancer patients perceive problems in the quality of their care. Even when restricting the sample to those who have health insurance, cancer patients aged 65 and older are less likely than younger cancer patients to report that their doctors listen to them (odds ratio [OR] = 0.76, $p < 0.01$), explain their treatment to them so that they will understand (OR = 0.78, $p < 0.01$), and show them respect (OR = 0.74, $p < 0.01$). Also, older cancer patients are less likely to report that their doctors spend enough time with them (OR = 0.82, $p = 0.04$). Overall, older cancer patients are less likely than younger cancer patients to give their doctor a high overall ranking (OR = 0.79, $p = 0.01$).[28]

Older cancer patients' perceptions of their access to care are generally more favorable than their perceptions of their quality of care. Older cancer patients were nearly half as likely as younger cancer patients with health insurance to report any difficulties or delays in getting needed care (OR = 0.55, $p < 0.01$) and there was no statistically significant difference between older and younger patients in the percentage reporting that they were able to obtain health care when needed (OR = 0.92, $p = 0.54$).[31]

TABLE 30-3 Annual Total and Out-of-Pocket Expenditures by Type of Cancer, 1996-2006 (2006 Dollars)

		Total Expenditures			Out-of-Pocket Expenditures		
			95% Conf. Int.			95% Conf. Int.	
Type of Cancer	n	Mean	LB	UB	Mean	LB	UB
Pancreas	14	$30,594	$13,635	$68,647	$928	$336	$2,559
Multiple Myeloma	15	$16,658	$8,208	$33,807	$1,620	$944	$2,779
Liver	33	$16,116	$8,941	$29,047	$1,246	$594	$2,612
Lung	140	$16,054	$13,411	$19,220	$1,023	$763	$1,371
Ovary	15	$15,936	$3,530	$71,948	$765	$307	$1,910
Thyroid	20	$15,627	$7,246	$33,699	$1,337	$854	$2,092
Colorectal	184	$11,707	$9,594	$14,286	$873	$775	$984
Cervix	10	$11,380	$6,597	$19,629	$588	$218	$1,586
Kidney	25	$10,595	$5,659	$19,834	$683	$166	$2,816
Bone	44	$10,523	$8,141	$13,602	$1,119	$887	$1,412
Non-Hodgkin	69	$9,375	$7,138	$12,314	$966	$684	$1,365
Bladder	85	$8,443	$7,182	$9,927	$1,098	$816	$1,476
Leukemia	90	$8,125	$6,229	$10,599	$937	$825	$1,065
Uterus	30	$7,511	$4,708	$11,981	$1,563	$924	$2,646
Breast	431	$6,723	$6,214	$7,275	$1,299	$1,177	$1,433
Prostate	562	$6,354	$5,935	$6,802	$826	$776	$879
Melanomas	63	$6,090	$4,706	$7,880	$890	$777	$1,020
Head and Neck	78	$5,687	$3,362	$9,621	$805	$600	$1,079
Stomach	24	$5,187	$1,650	$16,305	$257	$165	$401

CAREGIVER COSTS

Many costs of caring for older cancer patients are borne by their friends and relatives. These costs include financial and productivity losses and psychological and physical stressors. For all types of illnesses, one study in 1997 concluded that the cost of informal caregiving was more than six times as great as formal home health care.[29] Another study found that caregivers of elderly cancer patients sacrifice more than 3 hours per week more than caregivers for noncancer patients.[30] This loss in productivity surpassed a billion dollars for the United States in 2001. Yet another study found that when family labor is included in the cost calculations, average cancer home care costs for a 3-month period are not much lower than the costs of nursing home care.[31] Out-of-pocket and labor costs for family caregivers of breast cancer patients have been found to be equal to approximately half of the amount of costs borne directly by the patient.[32]

Several studies have found that caregivers of elderly cancer patients have higher depression scores or worse health than control subjects.[33-36] The mental health effects on the spouse of the elderly cancer patient can continue well beyond the death of the patient.[37] Providing care for older cancer patients can be especially stressful because such patients often have premorbid or comorbid conditions, such as dementia.[38] Caring for an elderly cancer patient can also have its rewards, since some caregivers report feelings of satisfaction and a greater sense of self-worth.[39]

CONCLUSION

The older cancer patient encounters many serious economic consequences. At a time in their lives when incomes are fixed and declining with every additional year of age, out-of-pocket costs are increasing. Time costs for older cancer patients and their informal caregivers are also quite burdensome. The physical and emotional effects on the friends and relatives are difficult to measure monetarily, but are very substantial nonetheless.

Although the out-of-pocket costs are significant, they are quite small in comparison with total monetary costs of care, because of the near universality of health insurance coverage for the elderly in the United States. In recent years, out-of-pocket prescription drug costs have declined significantly as a result of changes in Medicare coverage. Despite these changes, cancer patients, as compared with patients with other diseases, may be more vulnerable to high out-of-pocket costs related to the "donut-hole," nursing homes, and other types of medical expenditures.

Chapter Summary

Old age is a period of declining incomes and increasing medical costs for everyone; however, these economic constraints are even worse for the older cancer patient. Almost every older cancer patient is covered by Medicare and nearly 9% are covered by Medicaid. Medicare covers most hospitalization, outpatient, and physician services, but is less generous with prescription drugs and nursing home expenses. Changes in Medicare coverage for prescription drugs enacted in 2004 led to a 39% reduction in out-of-pocket expenditures by older cancer patients in 2006.

There is published evidence that many oncology healthcare professionals hold negative attitudes towards elderly people. Older cancer patients are more likely than younger cancer patients to believe that their physicians do not listen to them or show them the proper amount of respect. The economic and psychological costs of cancer care for the elderly are not restricted to the patients. Many informal caregivers suffer from depression and physical illnesses that are associated with their burdens.

See expertconsult.com for a complete list of references and web resources for this chapter

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