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Prevention and Treatment of Cancer in the Elderly

by Lodovico Balducci, M.D.

As the U. S. population becomes increasing elderly, cancer rates are expected to increase. Currently, 50 percent of all malignancies occur in the 12 percent of the population aged 65 and older.¹ While mortality from cardiovascular disease has been declining in this age group over the past two decades, cancer-related mortality has remained constant.²

Two, non-mutually exclusive hypotheses may account for higher cancer rates among the older population. First, carcinogenesis is a time-consuming process. Therefore, cancer is more likely to become detectable in older individuals.² Second, a number of molecular changes occur with aging. These changes are similar to those of carcinogenesis and prime the aging cells to the effects of late-stage carcinogens.^{3,4} Thus, older individuals are more likely to develop cancer after exposure to environmental carcinogens than younger individuals. Both experimental and epidemiological data support this hypothesis.^{3,5} The clinical consequences are important. Increased likelihood of developing cancer makes older persons ideal candidates for chemoprevention.

Several neoplasms may behave differently in the older patient. Simply put, older people may develop "different" cancers. In addition, patient age may influence tumor growth. Table 1 provides

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examples of neoplasms that may behave differently in older patients.

CANCER PREVENTION

Primary prevention of cancer. The older patient may be a candidate for all forms of primary cancer prevention, from elimination of environmental carcinogens to chemoprevention. In the case of breast cancer, chemoprevention with estrogen antagonists has entered the clinical practice.⁶ Criteria for involving older women in these programs must be established. The following criteria, based on risk/benefit calculations, are reasonable:

- life expectancy more than or equal to 10 years for women at normal risk
- life expectancy more than or equal to five years for women at increased risk (history of DCIS, family history of breast cancer)
- no risk factors for deep vein thrombosis
- no risk factors for cerebrovascular diseases.

Secondary prevention of cancer. Screening asymptomatic older people for cancer may be more productive than the screening of younger individuals. Because cancer is more prevalent among the older population, the positive predictive value of screening tests becomes more accurate.⁷ The mortality of elective surgery does not increase dramatically with age (up to age 100); therefore, screening older persons aggressively for colorectal cancer may mean a reduction in surgical mortality.

On the other hand, the value of screening of older individuals may be limited because previous screening tests have eliminated the most prevalent cases and by the shorter life expectancy of older persons. As yet, no study conclusively demon-

strates that screening mammography decreases the breast cancer-related mortality for women aged 70 and older,^{7,8} or that screening tests for colorectal cancer reduce the mortality of patients aged 80 and older.⁷ Information on other cancers, such as prostatic, cervical, and pulmonary cancers, is even less conclusive. Further, randomized study of cancer screening in older individuals is not likely at present. The elevated cost is hard to justify when a rapidly evolving technology may make such studies obsolete before they are completed.

In the absence of more evidence, it is reasonable to institute some screening plans for breast and colorectal cancer in patients with a life expectancy greater than or equal to three years, because the first benefits are seen generally after three years from the start of the screening program. In the case of breast cancer, for women at average risk, biennial mammography with yearly examination of the breast appears reasonable. In screening for cancer of the large bowel, yearly examination of the stools for fecal occult blood appears adequate.

CANCER TREATMENT

Surgery. The main differences in surgical mortality between young and older patients occur with emergency surgery, which may overtax the limited functional reserve of the older person.⁹ The mortality of elective surgery does not appear to increase dramatically with age, up to age 100.

Radiation therapy. Several large patient series document the excellent tolerance of older persons for standard radiation therapy.¹⁰⁻¹² Radiation therapy is of special value in three situations: 1) patients at high surgical risk who may still be curable, 2) symptom palliation, and 3) organ preservation, which

may obviate the need for stoma management in older persons. The safety of new radiation therapy techniques, such as hyperfractionation, remains to be established in older patients.

Cytotoxic chemotherapy. Old age brings a progressive decline in functional reserve of multiple organ systems. This decline in reserve has two major consequences for treating older persons with chemotherapy. First, it alters drug pharmacokinetics and pharmacodynamics. Second, it makes older tissue more susceptible to the toxicity of chemotherapy. While all pharmacokinetic parameters may alter with patient age, those of major concern include the volume of distribution (Vd) and the renal excretion of drugs.

The Vd is a function of body composition, and albumin and hemoglobin concentration.^{13,14} With age, the water content of the body declines, while the fat content increases. There is a consequent decline in the Vd of water-soluble agents and increase in the Vd of fat-soluble drugs. As many compounds, including the anthracyclines, the taxanes, the epipodophyllotoxins are strictly bound to red blood cells, a decline in hemoglobin may be associated with increased concentration of free drug and increased toxicity.^{15,16} Older persons may be at special risk for this complication because anemia is more likely with age.¹⁷

A progressive decline in glomerular filtration rate (GFR) occurs consistently with aging.² In older individuals, the kidneys may not excrete drugs as efficiently, consequently dose modification may be indicated.

Oral medications. How the older body absorbs oral medications has had limited impact on cancer chemotherapy up to now, because most drugs have been administered parenterally. However, the development of widely used oral fluorinated pyrimidines and other oral medications brings new interest in age-related absorption changes. Cellular aging may affect drug pharmacodynamics in normal tissues. At least two such changes have been well documented. The toxicity of fluorinated pyrimidines increases with age due to a decreased

tissue concentration of dihydropyrimidinedehydroxylase (DPD).¹⁸ And, more prolonged persistence of cisplatin-induced DNA adducts in monocytes from older individuals¹⁴ reveals increased ability of the older cell to repair DNA damage.

Chemotherapy-related toxicity. Myelodepression, mucositis, cardiomyopathy, and central and peripheral neurotoxicity appear more common and more severe the older the patient. In addition to cerebellar toxicity from cytarabine at high doses,¹⁴ older individuals may also be more subject to cognitive complications of chemotherapy, which have been recognized only recently.

MANAGING OLDER CANCER PATIENTS

Age may present special problems in cancer management. A brief look at three areas of cancer management provides examples.

Breast cancer. While the local recurrence rate of breast cancer after partial mastectomy declines with patient age,⁸ the final decision of whether postoperative irradiation can be avoided belongs to the patient. Toxicity of radiation therapy is not an issue. Radiation thera-

py to the breast is equally well tolerated in older and younger patients. For the older patient, however, radiation therapy may present special concerns. It is time-consuming, costly, and may be inconvenient for the older patient with limited access to transportation.

Avoidance of axillary lymph node dissection in the older woman has been advocated on the grounds that tamoxifen is beneficial in all postmenopausal women irrespective of hormone receptor status; that adjuvant chemotherapy is not beneficial for older women; and that axillary dissection causes additional unnecessary morbidity. None of these assumptions proved correct, however. In particular, node mapping and identification of the sentinel lymph node may prevent the need of more morbid dissection of the majority of patients.

Recent meta-analysis shows that tamoxifen decreases the mortality from breast cancer for women of all ages by approximately 30 percent. The benefits of chemotherapy, however, decline with patient age in the postmenopausal group and wane after age 70.¹⁹ The age-related decline in the benefits of chemotherapy clearly cannot be linked to

Table 1: Neoplasms whose behavior may change in the older person

| Neoplasm | Behavioral Change | Mechanism |
|-----------------------------------|---|---|
| Acute Myelogenous Leukemia (AML) | Resistance to induction treatment | <ol style="list-style-type: none"> 1. Increased prevalence of blasts expressing MDR-1 2. Increased prevalence of unfavorable cytogenic abnormalities 3. Involvement of the pluripotent stem cell by the neoplastic process |
| Large-Cell Non-Hodgkin's Lymphoma | Shorter duration of CR | Increased serum concentration of circulating II-6 |
| Celomic cancer of the ovary | Lower response rate Shorter remission duration | Unknown |
| Breast cancer | More indolent disease | <ol style="list-style-type: none"> 1. Higher prevalence of well differentiated, slow-proliferating, hormone-receptor rich tumors 2. Decreased host mononuclear cell response |
| Non-small cell lung cancer | More indolent disease | Unknown |

competitive causes of death in older women, because competitive causes of death do not affect the benefits of tamoxifen, even in the most advanced ages.

Pain management in the older cancer patient. The current guidelines of the American Geriatric Society for the management of pain in the elderly advocate a more liberal use of opioids, given the side effects of non-steroidals in older individuals. Concern that pain in older patients may—too often—go untreated triggered these guidelines. Liberal use of narcotics raises three concerns for the older cancer patient:

- Opioids may be immunosuppressive and favor the spreading of cancer.
- The side effects of narcotics, including constipation, nausea and delirium, may be unacceptable to many older patients.
- The pharmacology of narcotics becomes unpredictable in older patients. In particular, the half life of opioid glucuronides is more prolonged, and the balance of opioid receptors in CNS may change, potentiating the side effects and minimizing the benefits of the treatment.²⁰

TREATMENT OF THE FRAIL PATIENT

In frail patients functional reserves are exhausted and tolerance of stress is minimized.²¹ Although chronological age alone cannot be used to make a clinical assessment of patient age, in the majority of people, age 85 denotes the beginning of frailty.²² Currently, a conservative estimate of the frail population of this country includes 4 to 6 million people. This number is likely to climb with the increase in the aging population.⁶ The current prevalence of cancer among frail persons is about 400,000.²¹

Virtually every medical oncologist in the country is faced several times a year with the problem of managing frail patients. The problem is not moot: the life expectancy of frail patients is more than two years.²¹ These patients require continuous and effective treatment of their symptoms.

While frail patients seem candidates only for palliative measures, the management of the frail cancer patient raises several concerns.

First, is age a valid criteria to define frailty? While it is clear that dementia occurs in more than half of persons aged 85 and older, the function of the cognitively intact over 85 may be remarkably preserved. We need to examine the possibility that at least a group of people surviving beyond 85 are particularly fit and independent, and we need to examine if frailty is reversible. Second, can we grade frailty and establish hierarchies of more and less frail patients with different survival and different tolerance of treatment?

With the highest concentrations of new cancers occurring among the ever-increasing older population, practicing oncologists and the entire cancer treatment team will continue to confront these and other issues related to the geriatric cancer patient into the next century. ■

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