Commentary (Engstrom/Langer): Management of Cancer in the Elderly

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With the aging of the Western population, cancer in the older person is becoming increasingly common. After considering the relatively brief history of geriatric oncology, this article explores the causes and clinical implications of the association between cancer and aging. Age is a risk factor for cancer due to the duration of carcinogenesis, the vulnerability of aging tissues to environmental carcinogens, and other bodily changes that favor the development and the growth of cancer. Age may also influence cancer biology: Some tumors become more aggressive (ovarian cancer) and others, more indolent (breast cancer) with aging. Aging implies a reduced life expectancy and limited tolerance to stress. A comprehensive geriatric assessment (CGA) indicates which patients are more likely to benefit from cytotoxic treatment. Some physiologic changes (including reduced glomerular filtration rate, increased susceptibility to myelotoxicity, mucositis, and cardiac and neurotoxicity) are common in persons aged 65 years and older. The administration of chemotherapy to older cancer patients involves adjustment of the dose to renal function, prophylactic use of myelopoietic growth factors, maintenance of hemoglobin levels around 12 g/dL, and proper drug selection. Age is not a contraindication to cancer treatment: With appropriate caution, older individuals may benefit from cytotoxic chemotherapy to the same extent as the youngest patients.

Dr. Balducci's review, "Management of Cancer in the Elderly" is timely and very appropriate for the journal ONCOLOGY's 20th Anniversary Series, particularly as the US population ages and the percentage of cancer patients over the age of 65 grows. As a critical spokesperson for this important issue, Dr. Balducci has, to a great extent, assumed the mantle of leadership in generating an improved clinical understanding of geriatric oncology as it applies to clinical practice. In this sense, he is standing on the shoulders of perhaps the greatest spokesperson for cancer care of the elderly, B.J. Kennedy, MD.

As a trainee in Dr. Kennedy's medical oncology program in the mid-1960s, the senior author of this editorial commentary (Paul F. Engstrom, MD) was indoctrinated not only with a passion for medical oncology as a profession (rather than a chemotherapeutic technology), but also with the need to treat each cancer patient as an individual, learning to tailor treatment to the chief complaint and the unique needs of each patient. As B.J. frequently reminded us, "we are not chemotherapists; we are oncologists." When he assumed the presidency of the American Society of Clinical Oncology, he dedicated his tenure to the research and treatment of cancer in elderly patients.

Need for Research
Two key issues that Balducci addresses—the incidence of cancer in the aging population and the biology of cancer in the older patient—raise the need to increase our research in this fascinating area. The National Cancer Institute and the National Institute for Aging recently issued P20 grants to several cancer centers to establish cancer research programs directed toward the older patient. These transdisciplinary research programs will encourage investigators to focus on the biology of cancer in the elderly, the epidemiology and distribution of elderly cancer patients, psychosocial issues as they relate to quality of life in elderly patients, the pharmacokinetics of chemotherapy agents in elderly subjects, and the effect of cancer on the surviving spouse or partner as well as the extended family.

Tailored Assessment and Management
Balducci has provided a useful summary defining the nature of older patients and elucidating their special needs. He has emphasized the need for comprehensive geriatric assessment, or some distilled version of it, and he reviews the intriguing observation that cytokines and other biomarkers such as interleukin-6 and D-dimer concentration in the circulation may be predictors of mortality and functional dependency in elderly populations. Clearly, the practicing oncologist needs a workable
definition and a user-friendly assessment tool to categorize patients in his/her practice. If relatively mundane markers can be utilized to predict the risks and benefits of treatment, this will indeed be a useful tool in geriatric oncology.

Balducci also provides a review of the management of cancer in older persons, emphasizing the need for dose reductions based on pharmacokinetics, especially volume of distribution based on glomerular filtration rates. Additionally, he discusses multidrug resistance and the heightened normal-tissue susceptibility in the elderly to the toxic effects of chemotherapy drugs.

Clinical Trials
The experience with lung cancer is emblematic of the experience in older patients. Langer et al have summarized the issues confronting elderly individuals with non-small-cell lung cancer (NSCLC). He points out that the majority of patients with NSCLC are diagnosed at age 70 or higher, although this age cohort is underrepresented in national clinical trials—a trend observed in a variety of advanced solid tumors.[1] This underrepresentation may be due to therapeutic nihilism, a lack of confidence that treatment will help, explicit exclusions in trials, misperceptions that increased age automatically equates increased vulnerability to therapy, as well as a true increase in comorbidity, frailty, and vulnerability.

While retrospective analyses have demonstrated the feasibility of standard platinum-based combinations, especially in fit individuals, toxicity—particularly myelosuppression and fatigue—tends to be worse in the elderly compared to younger patients.[2-4] To date, there are no phase III trials in this age group showing a survival advantage for platinum or non-platinum combinations vs the constituent single agents. A large body of work, however, clearly shows that single-agent therapy is superior to best supportive care, with a clear-cut improvement in time to progression, survival, and quality of life, and no clear indication that nonplatinum combinations perform better than the constituent single agents.[5,6]

In this vein, the promise of targeted agents may be especially critical. In a recent phase II trial of erlotinib (Tarceva) monotherapy in elderly patients, the clinical benefit rate was 60% and the median duration of response was 6.8 months.[7] Thus, if elderly patients are fit and able to tolerate chemotherapy the results can be comparable to those seen in younger patients with lung cancer.

Treatment Guidelines
As Balducci notes, the National Comprehensive Cancer Network (NCCN) guidelines contain a section specific to the treatment of elderly patients. They emphasize the need for geriatric assessment in all patients age 70 and older, adjustment of cytotoxic dosages for glomerular filtration rate (GFR), and prophylactic use of growth factors for anticipated neutropenia and anemia in high-risk patients receiving myelosuppressive regimens. Unfortunately, many clinicians fail to follow these directives. When outcomes of breast cancer patients treated at NCCN institutions were evaluated, one of the major reasons for lack of guideline compliance was empiric physician decision to modify treatment based on patient age or comorbid disease conditions. While this practice may potentially be appropriate, it was noted on review of many of the patient charts that they contained neither adequate documentation for dose modification nor the reasons to bypass the recommendations in the NCCN guidelines.

Finally, the application of pharmacokinetics to the clinic has helped to improve compliance and tolerability, particularly in elderly individuals. The use of the Calvert formula in carboplatin dosing is a case in point.[8] Rather than relying on height and weight alone as we typically do with body surface area (BSA)-based dosing, this formula directly considers age and renal function in dose calculation. Its routine implementation, particularly in lung or ovarian cancer patients, has helped to customize dosing for individuals and has helped to render a potentially myelosuppressive agent much safer, especially in older individuals, who might otherwise be "overdosed" using conventional BSA dosing. Nomograms of this sort are needed for other agents with which toxicity may be exacerbated by increased chronologic age.

In conclusion, the Balducci paper focuses the reader's attention on relevant issues in the treatment of elderly patients with cancer. We look forward to research that can further expedite the assessment of frailty and improve our understanding of the biology of cancer in the elderly. Ultimately, with this understanding, we will be able to enhance therapeutic outcome.

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