Cancer in the elderly: A challenge for 21st century

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For most of human history and probably to the origin of modern men, some 100,000 years ago, there was a stable pattern of birth and death, enough to produce slow population growth. Survival beyond 65 years was a rare event. During the 19th century improvements in public health and medicine began to influence forces of natural selection operating on the human species.

Since the beginning of the 20th century world population profile slowly started to change. In the West, population older than 65 years has been progressively expanding since 1950s (1). The classical pyramidal picture of population age profile has changed, and today looks more like a square because the young base has shrunk and older top has enlarged. In geriatric words, this shift is referred to as "squearing of pyramid". In some European countries such as Italy, the population older than 65 years has already exceeded the population younger than 20 years. In the USA this will happen around 2010 if the current trends in population growth persist (2).

The aging of the population has important social and medical implications. In dealing with a population of limited life expectancy, and affected by multiple conditions, the goal of treatment has shifted from cure to preservation of function and quality of life.

Cancer is an important problem in the geriatric population. The increase in cancer incidence has paralleled the aging of the population. In the aggregate, it is the second leading cause of death after heart diseases, and 50% of all documented cancers occur in 11% of the population over the age of 65 years. It is expected that as many as 60% of all neoplasms will affect older persons by the year 2010. Interestingly, incidence of many cancers levels off after age 80, suggesting the possibility of intrinsic resistance to the development of cancer in late life.

The association of cancer and aging may be explained by two nonmutually exclusive hypotheses. First, carcinogenesis is a time-consuming process and cancer may be regarded as a price one must pay for getting old. Second, older individuals may be more susceptible to the effects of late - stage carcinogens (promoters). Thus, the older persons may have a higher concentration of "initiated" cells, which are vulnerable to the action of certain promoters (3).

Neoplastic transformation at the cellular level involves many of the same genetic and molecular pathways as normal senescence. Cell immortalization and senescence reflect contrasting outcomes with similar metabolic and molecular mechanisms. For example, the cellular concentration of telomeres declines during normal aging but persists unchanged in many neoplastic systems. Most recently, the role of telomere shortening in controlling cellular senescence, and of telomerase in cellular immortalization suggest new directions of searching (4). Also, the expression of the p16 gene is enhanced during normal aging but is lacking in most cancer cells. This gene encodes the cyclin-dependent kinase 4 (cdk 4) that activates an inhibitor of cell proliferation (5).

Controversy continues over whether cancer is less aggressive in the elderly and some conflicting results have been reported. So, cancer is by large a geriatric disease but under no circumstances can be considered a consequence of normal aging.

Prevention of cancer must begin before people become old. Primary prevention is useful in older population owing to their increased susceptibility to late-stage carcinogens (6). The best evidence strongly recommends avoiding smoking, overuse of alcohol, exposure to toxic chemicals, and maintaining a low-fat, high fiber diet. Chemoprevention of cancer gains popularity today and older people seem to be ideal candidates for this technique. Indeed, many controlled studies confirmed efficacy of estrogen antagonists and SERM in breast cancer prevention. Randomized studies also showed that retinoids can prevent smoking-related neoplasms in head and neck, and nonsteroidal anti-inflammatory drugs (NSAIDs) may prevent colorectal cancer. Secondary prevention involves early detection of cancer by screening asymptomatic persons at risk. The value of these measures in older persons is not well established. However, reduced cancer related mortality can be achieved by serial mammography, annual fecal occult blood testing, serial cervical Pap smears, and possibly serial determinations of prostate-specific antigen (PSA) levels.

The management of cancer in older patients should always take into consideration probable benefits and potential risks. Proper selection of patients is the key to administering effective and safe therapy. Because aging is highly individualized, the best guide to cancer treatment may be provided by a comprehensive, multidimensional assessment of the older patients. This includes such areas of diversity as functional status, comorbidity, socioeconomic conditions, nutrition, polypharmacy and the presence of specific geriatric syndromes. All mentioned above could be estimated using appropriate scales such as: Activities of daily living (ADL); Instrumental activities of daily living (IADL); Mini mental status (MMS); Geriatric depression scale (GDS); Mini nutritional assessment (MNA); and so on. Together, they comprise so-called Comprehensive geriatric assessment (CGA) (7).

As mentioned before, age by itself is not a contraindication to cancer therapy. Two questions must be answered. First, is the patient able to tolerate life-prolonging treatment? Second, is the treatment going to improve the survival and symptoms?

Surgical treatment mortality does not appear to rise with the age (up to 80) for elective procedures. However, the incidence of postsurgical complications and hospital staying do increase with age. A number of surgical advances permit reduced extent of resection with particular benefits for the elderly. They include partial mastectomy, transanal resection for rectal cancer, intraluminal ablation in hollow organs, and stereotactic surgery in CNS.

Radiation therapy is particularly well tolerated by older patients. New forms of radiation therapy that promise to be beneficial in this group include brachytherapy for prostate cancer and radiosurgery for brain tumors. Hyperfractionated radiation appears to be more effective than standard treatment.

Chemotherapy should be strongly considered in clinical situations in which cure, prolonged survival or palliation can be achieved. Because aging is associated with important pharmacologic changes in body,antineoplastic therapy may be less well tolerated by elderly patients. The major pharmacokinetic changes include decreased renal excretion of drugs, decreased drug metabolism, and decreased volume of distribution of water - soluble drugs. Pharmacodynamic changes include decreased intracellular catabolism of
Drugs, incomplete repair of DNA damage, impaired apoptosis and increased expression of MDR-1 gene. Older patients also appear to be at special risk for severe and prolonged myelosuppression and mucositis, as well as cardiomyopathy and neuropathy. Of special interest is also chemotherapy and anemia-related fatigue in elderly.

To minimize these complications, certain measures must be taken, namely dose adjustment of drug to GFR, correction of anemia, use of antidots (G-CSF, dexrazoxane, amifostine, pyridoxine), prophylactic use antibiotics in neutropenia, fluid resuscitation in diarrhea and mucositis.

A number of new drugs allow the safe treatment in elderly because of favorable toxicity profile. These include gemcitabine, vinorelbine, and taxanes in low-weekly doses (B). A variety of older chemotherapeutic drugs remain useful. Anthracyclines should be administered by continued IV infusion on small daily doses. Mitoxantrone or liposomal form of drug may substitute doxorubicin.

Palliative therapy must be integrated into treatment plan of elderly patients, and one can always use some form of it. So, we may conclude with the following:

1. Old age carries important risk for development of cancer (but not obligatory).
2. Advanced age alone is not reason enough for withholding effective treatment that could improve survival and/or quality of life.
3. Treatment of elderly with cancer must be individualized according to CGA.
4. To define best form of treatment, old people must participate in clinical trials.
5. Geriatric oncology will be an interesting area for future research.

REFERENCES


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Do clinical trials help us to optimize chemotherapy in the elderly? The lymphoma experience

KEYWORDS: Lymphoma, Non-Hodgkin; Antineoplastic Agents; Aged

Malignant non-Hodgkin's lymphomas in the elderly are a rather common condition in medical oncology; nevertheless these conditions probably require a specific therapeutic approach. The issue is relatively controversial. Specificities of this subpopulation have been brought to attention of hematologists and medical oncologists only a decade and a half ago, when European School of Oncology Organized the first and second intercity meeting on management of non-Hodgkin's lymphoma in the elderly.

SPECIFICITIES OF PRESENTATION OF NON-HODGKIN'S LYMPHOMA IN THE ELDERLY POPULATION

The first fact that emerged by a revision of several series of non-Hodgkin's lymphoma (NHL) patients in the late eighties of the last century provided the information that at least 34%-37% of all lymphoma patients is aged over 65.

The most frequently observed histological pattern was that of a diffuse large cell lymphoma belonging to the intermediate or high-grade group according to the working formulation. In some series the diffuse large cell pattern accounted for up to 84% of all lymphomas in the elderly. Some observations claimed that the frequency of intermediate and high-grade histology among elderly patients did not significantly differ from the one observed in younger patients. However large case series confirmed that low-grade histology and follicular growth patterns are less frequently represented in the elderly group.

Another characteristic of the non-Hodgkin's lymphoma in the elderly was that initial extranodal presentation or extranodal diffusion found in 45-50% patients are the onset. The extranodal presentation or involvement might provide an additional risk or bad prognostic factor.

Another risk factor might be provided by the fact that decrease of total T cells accompanied or not by inverted helper-suppressor ratio is more marked in the elderly than in the total population of non-Hodgkin's lymphoma patients. Altered organ sensitivity to drugs, especially the age-dependent decrease in

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