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Geriatric oncology

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Contents

Abstract

The discussion of breast cancer in the older woman implies an outline of unique aspects of cancer and aging. In this analysis, five aspects are highlighted because they pertain to breast cancer control: the diversity of the older population; the age-related increase in cancer susceptibility; the changes in tumor biology that occur with aging; and the implication of these factors for the prevention and treatment of cancer. The comprehensive geriatric assessment accounts for the diversity of the older population in terms of functional reserve and life expectancy and allows an individualized approach to the elderly. The increased susceptibility of the aged to environmental carcinogens has multiple causes and provides theoretical support to cancer prevention to the older individuals. The natural behavior of cancer may change with age due to intrinsic changes in the tumor cells as well as in the tumor host and may lead to both increased and decreased aggressiveness of the neoplasm. In the case of breast cancer, age seems associated with a more indolent tumor. Cancer screening seems effective in older patients with a life-expectancy of 5 or more years. Treatment of cancer with chemotherapy may be associated with increased risk of complications, especially mucositis and neutropenia. The latter may be ameliorated by prophylactic use of growth factors and correction of anemia.

Keywords: Cancer, elderly; Oncology; Geriatric oncology, neutropenia; Mucositis; Geriatric assessment

1. Introduction

To introduce the issues of breast cancer in the older woman, this article highlights unique aspects of cancer in the aged that support the need of a special expertise in geriatric oncology. The clinical and biologic interactions

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Table 1
Comprehensive geriatric assessment (CGA) and its implications

Functional status	
Activities of daily (ADL) and instrumental activities of daily living (IADL)	Relation to life-expectancy, functional dependence and tolerance of stress
Comorbidity	
Number of comorbid conditions and comorbidity indices	Relation to life-expectancy and tolerance of stress
Mental status	
Folstein Minimental status	Relation to life-expectancy and dependence
Emotional conditions	
Geriatric Depression Scale (GDS)	Relation to survival; may indicate motivation to receive treatment
Nutritional status	
Mininutritional assessment (MNA)	Reversible condition; possible relationship to survival
Polypharmacy	Risk of drug interactions
Geriatric syndromes	
Delirium, dementia, depression, falls, incontinence, spontaneous bone fractures. Neglect and abuse, failure to thrive	Relationship to survival. Functional dependence

of aging and cancer are explored and related to the discussion of breast cancer.

2. Clinical definition of age

Aging may be conceived as a progressive decline of stress tolerance due to a restriction in the functional reserve of multiple organ systems as well as in personal and social resources [1]. Aging is highly individualized and poorly reflected in chronology. Clinical evaluation of age should account for the diversity of the older population in terms of life-expectancy, incidence and prevalence of disease, degree of functional dependence, cognition, emotions and socio-economic resources [1,2].

Table 2
Taxonomy of aging according to Hamerman [10]

Group	Characteristics
Primary	No functional dependence; negligible comorbidity
Intermediate	Dependence in one or more IADLs; stable comorbidity (e.g. stable angina, chronic renal insufficiency, etc.)
Secondary or frailty	One of the following criteria: (i) dependence in one or more ADLs; (ii) three or more comorbid conditions or one poorly controlled comorbid conditions; (iii) one or more geriatric syndrome
Near death	

Currently the evaluation of the older person is based on a comprehensive geriatric assessment outlined in Table 1. The CGA has proven effective in preventing admissions of older individuals to the hospital and long term care facilities, in preserving functional independence and preventing some geriatric syndromes, such as falls and in-hospital delirium [3–9]. Though it has not been conclusively established whether the CGA has an effect on the survival of older individuals, consensus exists on the fact that the CGA is important for the preservation of health, independence and quality of life [8].

Based on the results of the CGA, four taxonomic groups of older individuals may be defined [10] with different rehabilitative potential, life-expectancy [11] and presumably tolerance of stress [10] (Table 2). Of these groups, the secondary or frail is the best defined. Frailty is a condition in which minimal stress may precipitate severe and even lethal complications, due to negligible functional reserve [12]. Clearly, the frail person is not a good candidate for aggressive cytotoxic chemotherapy nor for preventative intervention whose benefits may appear only years later. It is important to remember however that the median survival of frail persons is in excess of 2 years [13]: many older women with breast cancer metastatic to the bones are frail and necessitate effective palliation capable to preserve quality of life. Low dose chemotherapy including oral capecitabine [14], weekly gemcitabine, vinorelbine and taxanes, may best achieve this goal. Two complementary definitions of frailty are in use. The classical definition includes at least one of the following: dependence in one or more ADLs; presence of three or more serious

Table 3
The VES questionnaire for the definition of vulnerability

Element of assessment	Score
Age	
75–84	1
≥ 85	3
Self-reported health	
Good or excellent	0
Fair or poor	1
ADL/IADL—needs helps in:	
Shopping	1
Money management	1
Light housework	1
Transferring	1
Bathing	1
Activities—needs help in	
Stooping, crouching or kneeling	1
Lifting or carrying 10 lbs	1
Writing or handling small objects	1
Reaching or extending arm above shoulder	1
Walking 1/4 mile	1
Heavy housework	1

comorbid conditions; presence of one or more geriatric syndromes [12,13]. A new and more comprehensive definition includes at least three of the following parameters: involuntary weight loss $\geq 10\%$ of the original body weight over 1 year; slow movements, fatigue, difficulty in initiating movements and decreased grip strength [15]. The diagnosis of frailty may be supported by the laboratory: Cohen et al. found that the concentrations of interleukin 6 and D-dimer in the serum were consistently increased in frail persons [16].

Clearly, the intermediate group, to whom the majority of the older cancer patients belong, is the less well defined. In a daring comparison, these patients are to geriatrics what adolescents used to be to pediatrics: a highly diverse population for whom it is difficult to recognize defining hallmarks. These persons have residual functional reserve and may gain back some degree of functional independence. To the majority of them, the appellation of vulnerable may be attributed. Vulnerability is defined by a score of 4 or more in a 13 item tests (Table 3) [17] and is associated with decreased survival and enhanced risk of functional decline over 2 years. Seemingly, vulnerability represents the initial step toward frailty and is reversible to some extent.

In the guidelines for the management of the older cancer patient, the National Cancer Center Network (NCCN) recommended that some form of geriatric assessment be used because the CGA may provide [18]:

- Gross estimate of life-expectancy on the basis of functional status, comorbidity, presence of geriatric syndromes [19–30].
- Gross estimate of tolerance of chemotherapy. Both comorbidity and functional status may predict the risk of chemotherapy-related toxicity [31–33].
- Recognition of reversible comorbid conditions that may interfere with cancer treatment.
- Recognition of special social economic needs that may interfere with cancer treatment, including the presence and effectiveness of the care-giver that is responsible for managing the daily life of the dependent elderly [34].
- Management of nutrition and medications. Older individuals are prone to under-nourishment and polypharmacy [35,36] that may lessen both effectiveness and safety of cancer treatment.
- Adoption of a common language essential both for retrospective evaluation of quality of care and for prospective assessment of outcome in clinical trials.

A common application of the CGA to clinical practice, for patients whose cancer may shorten their life-expectancy is illustrated in Fig. 1. With proper adjustments, this algorithm may also be applied to the prevention of cancer.

Other forms of age assessment include laboratory and physical performance tests. As aging may be associated with a progressive accumulation of cytokines and other markers of inflammation in the circulation [37], several studies have focused on the determination of these substances. The discovery that frailty is associated with increased concentrations of Il6 and D-Dimer is encouraging because if may provide a confirmation of the diagnosis of frailty by laboratory data [16]. Another condition that may be defined in the laboratory is somatopause [38], a catabolic condition that may overlap frailty and involves reduced production of growth hormone in addition to increased concentration of cytokines in the circulation.

A number of physical performance tests including 'grip strength' and 'rising and going from an arm-chair' predict the development of disability and functional dependence [39–41]. These tests have the potential to complement the CGA and also to screen patients who may most benefit from the CGA.

3. Age and tolerance of chemotherapy

Age may influence effectiveness and safety of cytotoxic chemotherapy at three levels: pharmacokinetics, pharmacodynamics and tolerance of normal tissues.

The pharmacokinetic changes include reduction in the glomerular filtration rate (GFR) [42] and in the volume of distribution of water-soluble agents [42]. The excretion of parent compounds and cytotoxic metabolites whose main venue of elimination is the kidney may decrease with age.

The volume of distribution of water-soluble drugs is a function of the body composition, the albumin levels and the hemoglobin concentration because many of these drugs are bound to red blood cells and a drop in red blood cell mass is associated with increased concentration of free drug in the circulation [42]. At least five studies showed that hemoglobin is an independent risk factor for myelotoxicity from a number of agents, including anthracyclines, epipodophyllotoxins, and camptothecins [33,43–46]. In older individuals, the decline in total body proteins and total body water may eliminate compensatory mechanisms capable to buffer the increase concentration of free drugs [47].

Drug absorption has become of concern since the introduction of new oral agents [14]. These include oral fluorinated pyrimidines (capecitabine and UFT), temozolamide and tyrosine phosphokinase inhibitors. Oral formulations of taxanes, topoisomerase I inhibitors, platinum derivatives and navelbine are undergoing clinical trials [14]. The bioavailability of drugs does not seem affected at least up to age 80 [14].

Pharmacodynamic changes may both influence the effectiveness and the tolerance of chemotherapy. Age-

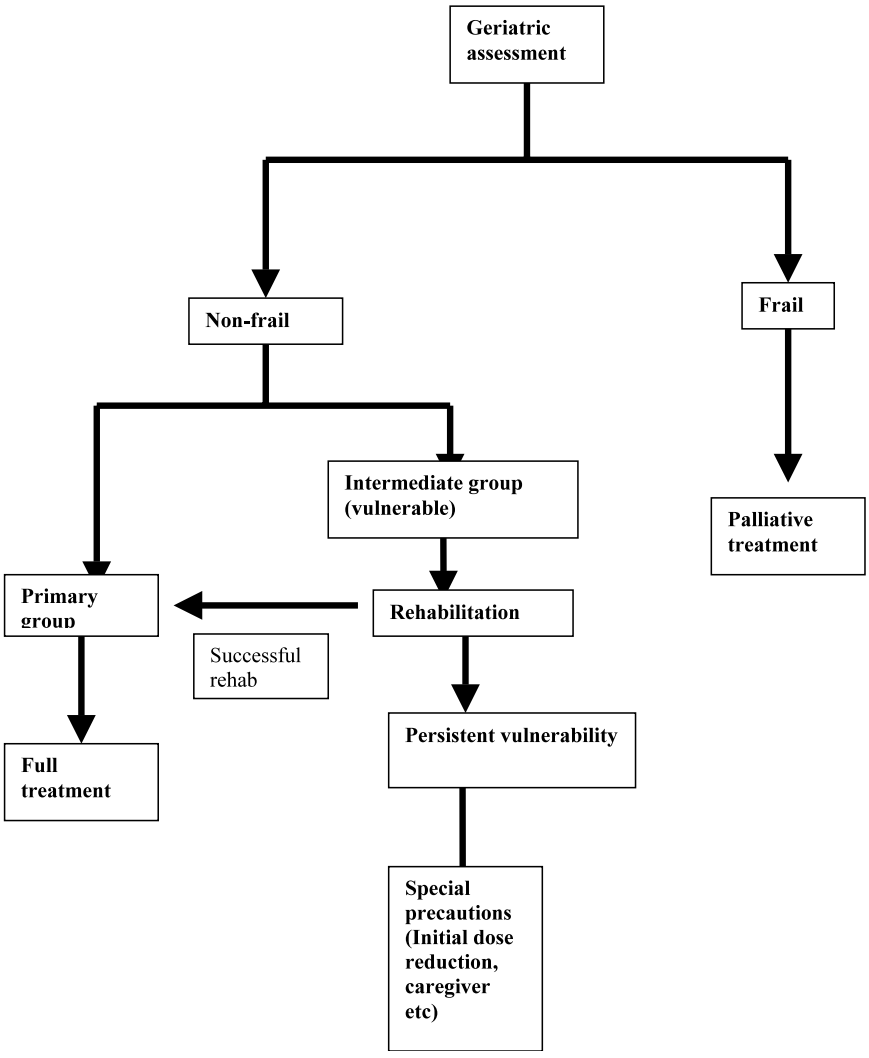

Fig. 1.

related changes include the increased prevalence of MDR-1 in AML [48] and the decreased ability of normal monocytes to clear cisplatin-induced DNA adducts in persons >70 [49]. Other changes that may reduce the effectiveness of chemotherapy include hypoxia of tumor tissue and decreased proliferation of neoplastic cells in the elderly [42].

The normal tissues whose susceptibility to chemotherapy increases with age include the mucosas, the hemopoietic system, the heart and the peripheral and central nervous systems [42].

A recent review of the experience of the North Central Cancer Treatment Group (NCCTP), involving more than 1400 patients with cancer of the large bowel revealed that age 65 and older was an independent risk factor for mucositis induced by fluorinated pyrimidines [50]. Previous studies have shown that the mortality related to these agents was almost exclusively due to mucositis and involved mostly patients >65 [51]. Mucositis should be always treated aggressively in older individuals. The substitution of capecitabine for intravenous flurinated pyrimidines may lessen the risk of mucositis because capecitabine is activated by thymidylate synthetase, present almost exclusively in neoplastic cells and the exposure of normal tissues to the active principle is minimized [14]. Two forms of keratinocyte growth factors are undergoing clinical trials and appear very promising because they have reduced the incidence and severity of mucositis by almost 40% in randomized-controlled studies [52]. Specific studies of these factors in elderly individuals are wanted.

Age is a definite risk factor for neutropenia. Dees et al. demonstrated that the neutrophil nadir after treatment with doxorubicin and cyclophosphamide decreased with the age of the patients [53] and myelotoxicity was cumulative for those >65, but not for younger patients. Kim et al. reported that the risk of myelotoxicity in patients with solid tumors increased with age [54]. Likewise, Crivellari et al. showed that the risk of neutropenia increased with age in women treated

adjuvantly with CMF [55]. Eight studies of patients age 60 and older with large cell lymphoma, treated with CHOP or a CHOP-like combination of chemotherapy showed a risk of grade 4 neutropenia in excess of 50%, a risk of neutropenic infections as high as 47% and a mortality risk varying between 5 and 30% [56–63]. Furthermore, the duration of hospitalization for neutropenic infections appears increased in older individuals [64].

Prevention of neutropenic complication may involve reduction of the doses of chemotherapy, prophylactic use of hemopoietic growth factors and prophylactic use of antibiotics. Dose reduction appears ill-advised, at least in the case of lymphoma [65,66] and breast cancer [67] because it compromises the tumor control. At least four randomized controlled studies demonstrated that filgrastim reduces by 50–75% both the risk of neutropenia and neutropenic infection in older individuals [56–58,68] and this appears as the safest preventative strategy. Prophylactic oral antibiotics are complementary to the use of growth factors, but their effectiveness has not been studied in older patients and compared with colony-stimulating factors. Based on these considerations, the National Cancer Center Network (NCCN) recommended in its guidelines that prophylactic growth factors be used in patients aged 70 and older receiving moderately toxic chemotherapy of dose/intensity comparable to CHOP [18].

Though the risk of anthracycline-related cardiac toxicity increases with age, this complication is uncommon until a dose of doxorubicin of 300 mg/m^2 has been administered (or equivalent doses of other compounds). Routine use of antidotes to cardiac toxicity in older individuals currently is not recommended.

4. Association of cancer and aging

The incidence of most malignancies increases with age [69–71], at least up to age 85 and may decline after age 95 [72]. More than 50% of all neoplasms occur in persons aged 65 and older in the US [70,71].

The association of cancer and age may be accounted for by three, non-mutually exclusive mechanisms (Table 4). The most obvious explanation is the time length of carcinogenesis. Molecular aging is associated with changes that favor and other changes that may oppose carcinogenesis [73]. Pro-carcinogenetic changes include DNA adducts, DNA hypomethylation and genetic instability [74,75] while shortening of telomeres, reduced telomerase activity and activation of the P16 antioncogene may oppose carcinogenesis [76,77]. In experimental rodents certain tissues, including the cutaneous, the lymphatic, the hepatic and the nervous tissues become more susceptible to environmental carcinogens with age [78,79].

Table 4
Mechanisms accounting for the association of cancer and aging

Timelength of carcinogenesis
Increased susceptibility of aging tissues to environmental carcinogens:
Molecular changes of aging
Experimental data
Epidemiological data
Environmental conditions that favor the growth and the spread of cancer:
Proliferative senescence
Immunesenescence

Paradoxically proliferative senescence, that is the lost of self-replicative ability by a cell, may predispose to cancer. Senescent cells lose the ability to undergo apoptosis and thus may live indefinitely, like cancer cells. In addition, senescent cells release both tumor growth factors (heregulin) that stimulate tumor growth and metalloproteinases that favor metastatic spreading [80,81]. The role of immune senescence in cancer development is inconclusive; in some cases, such as lymphomas and other highly immunogenic tumors, immune senescence may favor the development of cancer, but in other cases, including breast cancer, it may delay neoplastic growth [82].

5. Age and tumor biology

The behavior of some neoplasms varies with age (Table 5). The prognosis may both improve, as is the case of breast cancer [83], or worsen with the age of the patient, as is the case of acute mylogenous leukemia and large cell lymphoma [84,85]. At least two biological mechanisms may account for changes in prognosis. Thinking of cancer as of a plant, the growth of the plant may be influenced by the nature of the seed (the tumor cell) or the nature of the soil (the older tumor host).

The influence of the age of the tumor host on cancer growth was shown by a pivotal experiment of Ershler et al. [86]. These authors injected the same load of B16 melanoma and Lewis lung carcinoma in younger and older mice and found that the survival was shorter and the number of metastases higher in the younger animals.

In humans, clinical evidence suggests both a ‘seed’ and a ‘soil’ effect. The worst prognosis of AML is accounted for by a higher prevalence of MultiDrug resistance 1 and that of NHL may be due increase concentrations of Interleukin 6 in the circulation [85,87]. In the case of breast cancer, it is reasonable to entertain both a ‘seed’ and a ‘soil’ effect. The prevalence of well-differentiated, hormone-receptor rich tumors increases with age, whereas both ovarian failure and immunesenescence may contrast the growth of breast cancer [83].

Table 5
Age and changes in cancer prognosis

Neoplasm	Age-related changes in prognosis	Mechanism(s)
Acute myelogenous leukemia	Worse: Increased resistance to chemotherapy Increased mortality during induction	Seed effect: Increased prevalence of MDR1 expressing cells Increased prevalence of stem-cell leukemia
Non-Hodgkin's lymphoma	Worse: Decreased duration of complete remission	Soil effect: Increased circulating concentration of interleukin 6
Breast cancer	More indolent disease	Seed effect: Increased prevalence of hormone-receptor rich well differentiated tumors Soil effect: Decreased production of sexual hormones Immunosenescence
Celomic ovarian cancer	Worse: Decreased remission duration Decreased survival	Unknown

Table 6
Influence of age on prevention and treatment of breast cancer

Prevention
Chemoprevention
Secondary prevention (screening)
Treatment
Postoperative radiation therapy following partial mastectomy
Axillary lymph node dissection
Primary medical treatment of operable breast cancer
Choice of adjuvant hormonal therapy
Choice of adjuvant chemotherapy
Treatment of metastatic disease in the frail woman

6. Breast cancer and age

The changes in life expectancy, treatment tolerance and cancer risk and cancer behavior may influence both the prevention and the treatment of breast cancer (Table 6).

6.1. Cancer prevention

Age-related factors may both favor and disfavor cancer prevention. In favor are:

- Increased risk of breast cancer which suggests the appropriateness of chemoprevention;
- Increased prevalence of breast cancer, that improves the positive predictive value of screening tests;
- The good general condition of the majority of elderly women developing breast cancer [88].

Factors that mitigate against prevention include:

- Age-related decreased life-expectancy;
- Age-related risk of complications from preventative interventions, especially chemoprevention;
- More indolent tumor growth;
- Influence of previous screening tests on the detection of new cancers.
- Cost.

Chemoprevention of breast cancer with SERMs results in reduced incidence of hormone-receptor risk breast cancer by 50–70% over 5 years [89,90]. Tamoxifen and raloxifen may also reduce the risk of osteoporotic fractures, but the risk thrombo-embolic complications from these drugs increases with age. In view of the fact that no survival benefits has emerged so far from chemoprevention of breast cancer, the adoption of this strategy in clinical practice appears premature. Gail et al. calculated that chemoprevention with tamoxifen may be beneficial for a woman aged 70 only if her risk of developing breast cancer is higher than 7% in 5 years [91]. The introduction of the aromatase inhibitors may offer new and safer opportunities for chemoprevention. These drugs appear both safer and more effective than the SERM. Exemestane has the additional advantage that may prevent osteoporosis and reduce the incidence and severity of hot flashes.

The use of serial mammograms in women aged 50–70 is supported by randomized controlled trials showing that screening reduced by 20–30% the cancer-related mortality [92]. After age 70, the value of screening mammography is supported by two case-control studies. Dutch investigators showed that continuing mammography up to age 75 is associated with a decreased risk of breast cancer related mortality [93]. Reviewing the data of Surveillance, Epidemiology and End Results (SEER), McCarthy et al. found that women aged 70–79 who did not undergo any mammography after age 70 were twice as likely to die of breast cancer as women who had undergone at least two screening mammography [94]. It is reasonable to conclude that some form of screening is beneficial after age 70 for all women with a

life expectancy of 5 years or longer. Open questions include:

- What is the value of the physical examination of the breast (PEB) in older women? Presumably the detection of breast cancer by palpation may become more productive with age-related atrophy of the mammary fat. Two studies suggest that PBE was as effective as mammography in the detection of invasive cancer [95,96]. The PBE may be preformed during any office visit, preventing the cost and the inconvenience of mammography.
- What is the ideal interval between mammograms? Virtually all studies used an interval longer than 12 months; in view of the fact that breast cancer is generally more indolent, a 2- or even 3-year interval appears reasonable [92].
- Can we target a population at particular risk for prevention, so sparing the rest of the older women the cost and the inconvenience of screening? This possibility was studied in a decision analysis by Kerlikowske, who demonstrated that one may half the cost of screening asymptomatic women for breast cancer over age 70, without compromising the benefits, by limiting the screening to women in the upper quintile of bone density [97]. This approach deserves particular attention as the growing of the older population may render general screening unaffordable.

6.2. Cancer treatment

Several studies have concluded that the risk of local recurrence of breast cancer after partial mastectomy declines with the age of the patient [83]. Although postoperative radiation therapy appears to reduce the risk of recurrence for patients of all ages and tumors of all sizes, the benefits of radiation decline with age and may become negligible after age 65, especially for tumors ≤ 1 cm as largest diameter [98].

The benefits of lymph node dissection in older persons has been debated, but probably this has become a non-issue since the introduction of lymph node mapping, which allows to select for axillary dissection women at high risk of involvement [99].

The primary medical treatment of operable breast cancer with tamoxifen has produced inferior results than surgery in terms of local control and survival. In view of the safety of partial and even total mastectomy, this approach should probably be abandoned [100]. This issue may be revisited with the aromatase inhibitors that may be both more effective and less toxic than the SERMs [101].

The aromatase inhibitor anastrozole proved superior to tamoxifen as adjuvant hormonal treatment of breast cancer, in terms of recurrences and new contra lateral cancer over 5 years [101]. A number of issues still need to be addressed before advocating the frontline use of aromatase inhibitors in the adjuvant setting:

- What is the effect of these drugs on bone mineral density and cognition? It is reasonable to expect that the aromatase inhibitors may favor osteoporosis and cognitive decline by preventing the synthesis of estrogen.
- Are all aromatase inhibitors the same? In vitro exemestane seems to prevent osteoporosis, probably due to the steroidal formulation of this compound. Furthermore, anostrozole, letrozole and exemestane show different potency in the inhibition of aromatase.
- While it is clear that simultaneous administration of tamoxifen and anastrozole is not superior to tamoxifen alone and may be inferior to anastrozole alone, it is legitimate to ask whether SERMs and aromatase inhibitors in sequence are more effective than either group of compounds.
- Are aromatase and Cox-2 inhibitors synergistic? This possibility is suggested by the fact that Cox2 inhibitors seem to down regulate the concentration of aromatase in tissue culture.

The Oxford meta-analysis shows that the benefits of adjuvant chemotherapy decline with the age of the patient suggesting one of three possibilities [102]:

- Increased chemotherapy related mortality, which has not been reported;
- Inadequate chemotherapy dose, which is possible;
- Decreased effectiveness of the chemotherapy, that is also possible.

Two types of study appear necessary in this population: one involves the selection of the patients who may benefit most from adjuvant chemotherapy, the other administration of chemotherapy in full doses with the support of colony stimulating factors. For the patient selection, one may use the decision analysis proposed by Extermann et al. who demonstrated that the threshold for risk of recurrence and breast-cancer related death above which adjuvant chemotherapy is beneficial to older women, increases with age [103].

The management of the frail patients involves mainly palliative measures. It is important to realize that frail individuals are very susceptible to the complications of opioids and low dose chemotherapy may represent the most effective form of palliation for these individuals.

7. Conclusions

This review demonstrates that:

- The older population is diverse in terms of life expectancy and tolerance of stress; this diversity should be accounted for at times of preventative and therapeutic intervention;
- The risk of common complications of chemotherapy increases this age. After age 70, the risk of mielodepression is so predictable as to justify prophylactic use of growth factors for moderately toxic chemotherapy;
- Age is associated with both increased risk of cancer and changes in the biology of cancer, which may affect both prevention and treatment of cancer in older individuals.

On the basis of these facts, we conclude that the management of cancer in older individuals requires knowledge of and expertise in evaluating biological and clinical changes of aging and justify a special training in geriatric oncology.

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Biography

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