PERGAMON

European Journal of Cancer 36 (2000) 1741–1754

European Journal of Cancer

www.ejconline.com

Geriatric oncology: challenges for the new century

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Received and accepted 7 April 2000

Abstract

The management of cancer in the older aged person represents one of the major immediate challenges of medicine. The response to this challenge involves answers to the following questions:

1. Who is old? Currently, 70 years of age may be considered the lower limit of senescence because the majority of age-related changes occur after this age. Individual estimates of life expectancy and functional reserve may be obtained by a comprehensive and time-consuming multidimensional geriatric assessment. The current instrument may be fine-tuned and new instruments, including laboratory tests of ageing, may be developed.
2. Why do older persons develop more cancer? It is clear that ageing tissues are more susceptible to late-stage carcinogen. Older persons may represent a natural monitor system for new environmental carcinogens, and may also represent a fruitful ground to study the late stages of carcinogenesis.
3. Is cancer different in younger and older persons? Clearly, the behaviour of some tumours, including acute myeloid leukaemia, non-Hodgkin's lymphoma and breast cancer change with the age of the patient. The mechanisms of these changes that may involve both the tumour cell and the tumour host are poorly understood.
4. Can cancer be prevented in older individuals? Chemoprevention offers a new horizon of possibilities for cancer prevention; older persons may benefit most from chemoprevention due to increased susceptibility to environmental carcinogens. Screening tests may become more accurate in older individuals due to increased prevalence of cancer, but may be less beneficial due to more limited patient life expectancy.
5. Do older persons benefit from cytotoxic treatment? The answer to this question partly stands on proper patient selection, partly on the development of safer forms of cancer treatment and prudent use of antidotes to chemotherapy toxicity.
6. What is the cost of treating older cancer patients? The treatment of older patients is generally more costly. This cost should be assessed against the cost of not treating cancer and promoting functional dependence, which by itself is extremely costly.
7. What are the endpoints of clinical trials in older cancer patients? With more limited life expectancy, the effect of treatment on quality of life is paramount. Reliable assessment of quality of life is essential for interpreting clinical trials in older individuals.

Keywords: Cancer; Elderly; Ageing; Challenges; Geriatric oncology; Life expectancy; Comprehensive geriatric assessment; Pharmacokinetics

1. Introduction

The practice of medicine is influenced by intrinsic and extrinsic forces. Intrinsic influences include new scientific discoveries, new technology, the emergence of new diseases, such as AIDS, and the disappearance of old diseases, such as smallpox. Extrinsic influences include social and demographic changes, cultural and economic pressures. The main challenge of medicine is to incorporate a rapidly evolving scene into new practice models.

The ageing of the population, a major and unexpected epidemiological event of the second half of the 20th century, represents one of the major influences on medical practice for the immediate future [1,2]. In Table 1 are summarised the consequences of ageing and the medical challenges that they involve. The examination of the table suggests major changes in traditional medical practices including:

- Accommodation of social and emotional domains in the clinical practice: older patients may not be effectively treated for their primary illness unless they have adequate transportation,

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0959-8049/00/$ - see front matter
PII: S0959-8049(00)00169-6

appropriate nutrition and exercise and in-home support [3,4].

- Shifting clinical paradigms: comorbidity and functional dependence may alter the clinical presentation of diseases and influence the management of the disease [5,6].
- Institution of multidisciplinary interventions. As ageing is multidimensional and involves different domains, the clinical intervention needs to be coupled with the intervention of other health operators, including social workers, pharmacists and nutritionists [7–10].
- Emphasis on screening and prevention. This involves prevention of diseases, such as cancer or infections [11–15], and prevention of disability and functional dependence [8,10].
- An operational concept of ageing to justify specific interventions. One such concept is illustrated in Fig. 1. Ageing is conceptualised as a progressive reduction in the functional reserve of multiple organ systems, resulting from both spontaneous exhaustion and environmental influences. Once a critical reduction in functional reserve is reached, the process becomes self-aggrandising: reduction in functional reserve leads to more diseases and disabilities that in turn hasten the depletion in functional reserve. One of the goals of geriatrics is to break this vicious circle by tackling some reversible elements of the circle. Based on this construct of ageing, a number of studies are exploring the possibility that reversal of anaemia may delay the functional dependence of older individuals [16].

Table 1
Medical challenges of ageing

Age-related clinical problem	Medical challenge
Definition of age	• Clinical evaluation • Laboratory evaluation • Comprehension of the dynamics of ageing, that may evolve over time with improved prevention of diseases and disability.
Increased incidence and prevalence of chronic diseases	• Goals of treatment: cure versus palliation • Evaluation of risk/benefits of treatment: increased risk of therapeutic complications and more limited life expectancy • Assessment and management of comorbidity • End of life management • Cost considerations
Increased incidence and prevalence of functional dependence	• Implementation of home care and home-based hospital care • Attendance of social need: institutionalisation, caregiver
Prevention	• Of disability • Of disease • Of ageing

This article reviews the medical challenges of ageing, using cancer as a reference example.

Cancer was chosen because the incidence of neoplasia increases with age [1], cancer is a major cause of morbidity and mortality for the aged [17,18], cancer is a chronic disease that stresses the limited reserves of the aged in functional, social, emotional and cognitive domains [10,11], and the outcome of cancer is influenced by comorbidity, whose prevalence increases with age [19–21].

The challenges explored include: definition of age, causal association of cancer and ageing, assessment of the biology of cancer in older persons, and prevention and treatment of cancer in the aged.

2. Definition of age

The study of cancer in the older aged person mandates a definition of the population under study. The definition of age involves two questions: when can we say that a person is old? Can we distinguish different stages of ageing and say that a person is older than another person?

Fig. 1 implies that ageing is associated with a critical restriction of the functional reserve of multiple organs systems. Table 2 offers current methods to evaluate the physiological age of a person.

The physiological age of a person is poorly reflected in chronological age, but chronological age may be used as frame of reference to institute special interventions [11]. Two chronological landmarks, the ages of 70 and 85 years seem appropriate and practical. Seventy years of age may be considered as the lower boundary of senescence, because the incidence of age-related changes start increasing sharply between the ages of 70 and 75 years [22]. Eighty-five years of age may be considered as a red flag indicating a risk of frailty, because hearing and vision deterioration cause functional dependence in

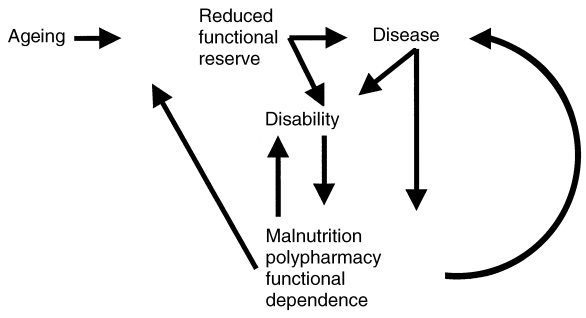

Fig. 1. Vicious circles of ageing.

Table 2
Assessment of age

Type of evaluation	Parameters	Critical considerations
Chronological age	Age 70 years	Beginning clinical senescence
	Age 85 years	Screen for frailty
Laboratory tests	Serum creatinine	Non-specific
	Serum interleukin 6 (IL-6)	Increased only in advanced ageing
	Cysteine/thiolic groups (S/d)	May be increased in presence of cancer and protein/calorie malnutrition
	D-Dimer	Non-specific
Clinical evaluation		

the majority of persons beyond this age [23] and dementia is present in more than 50% of individuals over 85 years [24].

Laboratory tests are inadequate at present to define ageing. Although the glomerular filtration rate (GFR) declines with age [25], this decline is variable from individual to individual; furthermore GFR may be affected by a host of kidney diseases, unrelated to age. Circulating interleukin-6 (IL-6) levels are increased in persons with geriatric syndromes, but this increment is not detectable at earlier stages of ageing [26]. Furthermore, the levels of IL-6 may be elevated in patients with a number of neoplasms and inflammatory conditions. The ratio between circulating cysteine and thiolic groups (S/d ratio) increases with a depletion in total body proteins, and then is expected to increase with age [27]. This ratio is very sensitive, but it may be affected also by protein calorie malnutrition and by cancer. Ongoing studies explore the possibility to tease out these different effects. The S/d ratio may prove very valuable to study the pharmacokinetics of drugs in elderly patients and to confirm the clinical impression of senescence. Given the lack of specificity, it is unlikely that this parameter may be used as the only sign of ageing. Recently it was proposed that a number of laboratory parameters including circulating D-Dimer levels and IL-6 may be used to define ageing (Harvey Cohen, AMGEN Board Of Directors, Bel Harbor FL, USA, 11 March 2000).

Clearly, the laboratory assessment of ageing is in evolution and may already provide valuable information, but can not be relied upon for the definitive determination of the physiological age of a person.

A comprehensive geriatric assessment (CGA) has been used during the past 15 years to estimate the functional reserve and the life expectancy of an older person and to detect functional, medical, social, rehabilitative and nutritional needs [19]. This assessment has proven useful in delaying the institutionalisation of older individuals by rendering home care more effective [28], in reducing the number of hospital admissions [29], in preventing delirium [30] and falls [31].

The activities of daily living (ADLs) include bathing, continence, feeding, transferring, going to the toilet, dressing [19]. Dependency in one or more of these activities classifies a person as frail [32,33], and unable to tolerate even mild stresses. The Instrumental Activities of Daily Living (IADLs) include those activities necessary for independent living, such as using transportation and telephone, managing money, the ability to shop and take medications and housekeeping [19]. Dependence in IADLs or ADLs is associated with an increased mortality rate [34,35]. In addition, dependence in some IADLs predicts development of dementia [36], and an enhanced risk of chemotherapy-related toxicity [37]. The incidence and prevalence of comorbid conditions increase with age, and comorbidity is a major cause of mortality [19–21,38]. Controversy exists about the assessment of comorbidity. Whereas the risk of death increases with the number of comorbid conditions [21,38], an assessment of the severity of comorbidity appears more meaningful than the number of comorbid conditions [19,20]. A number of comorbidity scales have been proposed to derive a comorbidity index [19,20] that quantifies the risk of death in individual cases. The Charlson's scale, of common use in geriatrics, is simple and may be applied to large-scale epidemiological studies, but may not be sensitive enough to account for all forms of significant comorbidity [11,39]. The Cumulative Illness Rating Scale-Geriatrics (CIRS-G), rates morbidity according to a scale similar to the National Cancer Institute of Canada (NCIC) scale for chemotherapy toxicity and is very comprehensive [40], but may be too sensitive to minor ailments that do not have bearing on survival. The scoring of the CIRS-G has recently been simplified by a computer program. Ongoing clinical trials compare the validity of these two scales.

A relationship exists between cognitive decline [41–43], depression [43,44], falls [45] and survival. In addition, increased mortality is predicted by malnutrition and failure to thrive [46–48], and by neglect and abuse [49].

A number of tests of physical strength have been proposed to assess the function and life expectancy of older individuals [50–54]. These tests may be helpful to identify frail persons, that is persons who have exhausted most of their functional reserve, but are not helpful in identifying earlier stages of ageing [51–54].

From this comprehensive evaluation it is possible to define patient populations of different functional reserve and life expectancy [33]. In particular, it is possible to identify the so called frail patients [32]. By general consensus, frailty implies near to exhausted functional reserve and minimal tolerance of stress. Common criteria of frailty include: dependence in one or more ADLs; presence of one or more geriatric syndromes; three or more severe comorbidities [32,55]; and inability to perform simple physical tests of strength [53,54]. The CGA also allows the practitioner to recognise individuals with well preserved functional reserve, whose life expectancy is superior to the average for their age group. More difficult is the classification of individuals 'in between' that represent the majority of persons aged 75–85 years. These individuals are not clearly frail nor clearly fit; their functional reserve allows them to tolerate some degree of stress but not all degrees of stress, and their life expectancy may be shortened to some extent. Seemingly, the recognition of these persons will not be based on a single element, but rather on a constellation of symptoms, signs and laboratory values.

Clearly, giant steps have been made to define age in physiological terms. The most immediate challenge is fine-tuning our classification of the older person and to apply this classification to the practice of oncology and of other medical specialties [56].

3. Cancer and age: causal or casual association?

The incidence of cancer increases with age [1]. At present, 50% of all malignancies occur in persons aged 65 years and older; by the year 2020 60% of all malignancies may affect the elderly, if the current demographic trends continue.

The association of cancer and ageing has at least three, non-mutually exclusive, causes (Fig. 2). First, the

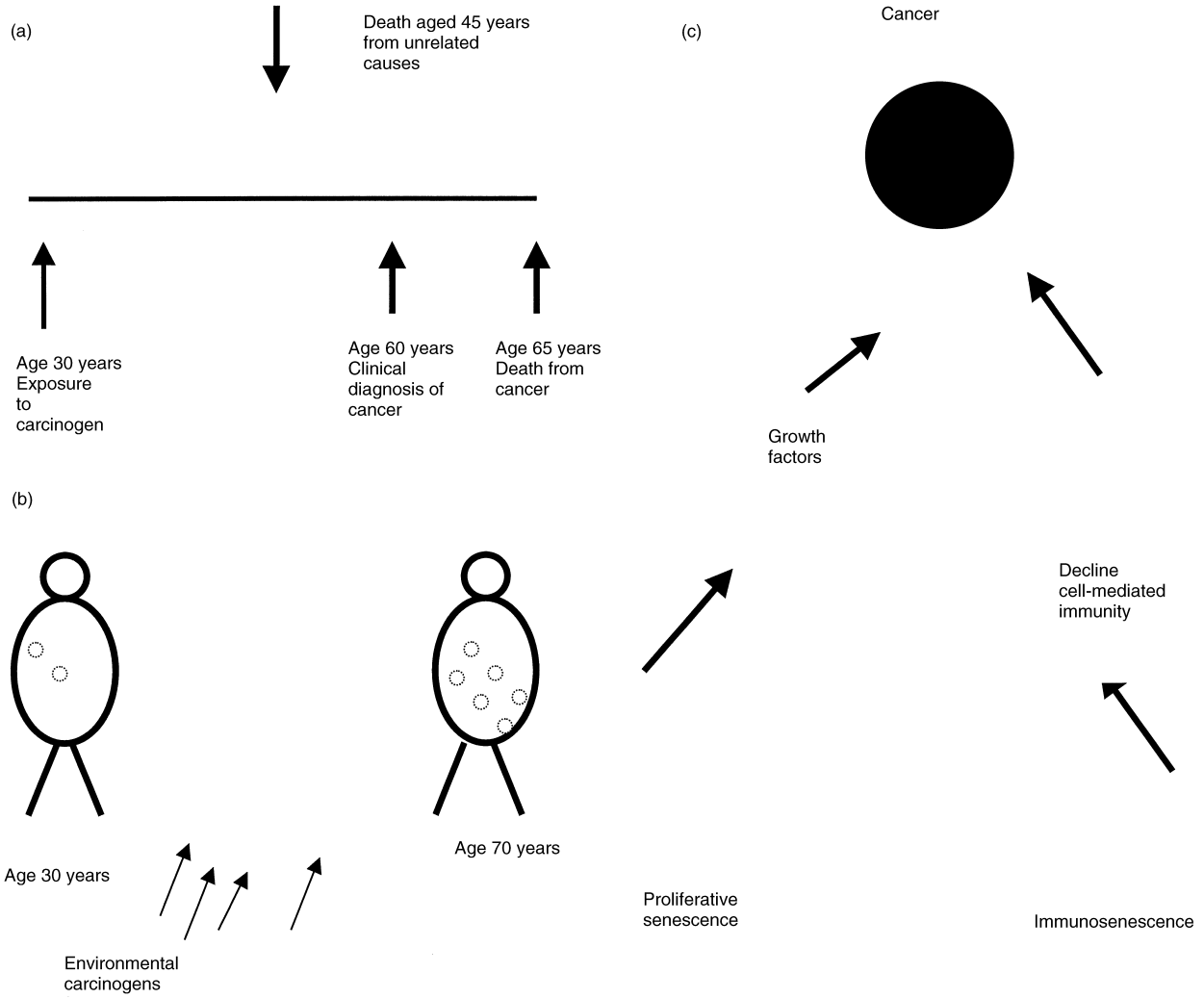

Fig. 2. Possible explanations for the association of cancer and ageing: (a) Cancer is a time-consuming process that becomes manifest preferentially in a person living to old age. (b) Older individuals present a higher concentration of cells primed to the effects of late-stage carcinogens and thus are more vulnerable to these carcinogens. (c) A number of host-related conditions favour the development of cancer in older individuals.

association may be casual (Fig. 2a). Carcinogenesis is a prolonged process that may take several years: thus persons living beyond a certain age are more likely to develop cancer. Second, older tissues are more susceptible than younger tissues to environmental carcinogens (Fig. 2b). This possibility has been clearly illustrated in experimental and epidemiological studies [57–59]:

- Some tissues of older rodents, including skin, lymphatic and nervous tissues, are more likely to develop cancer when exposed to carcinogens than tissues of younger animals [57].
- The incidence of lung cancer following exposure to dioxin, in Trieste, was higher among persons who were older at the time of exposure [58].
- The incidence of some cancers, including non-melanomatous skin cancer [59], malignant brain tumour [60], and non-Hodgkin's lymphomas [61], has increased several folds in persons aged 70 years and older during the last two decades. This increment may only be explained by an increased sensitivity of older tissues to environmental carcinogens.
- Older tissues undergo a number of molecular changes similar to those observed in the early stages of carcinogenesis, including formation of DNA adducts, DNA hypermethylation and chromosomal translocation [57,62]. Also, the so-called proliferative senescence [63] leads to resistance to apoptosis, which may predispose to the development of cancer. It should be added at this point that the molecular pathways of ageing and cancer do also diverge in some aspects. For example, the length of DNA telomeres decreases with age, but persists unchanged in cancer [63], and the expression of the *p16* gene, that regulates cell cycle, is enhanced in ageing cells and absent in various forms of cancer [64].

Third, ageing may be associated with environmental conditions that favour the development of cancer:

- Proliferative senescence [62] indicates the loss of the ability to proliferate by the ageing cell. This loss is associated with the secretion of enzymes that favour cancer metastasis and of growth factors that stimulate the proliferation of neoplastic cells.
- Immunosenescence is represented by a progressive loss in cell-mediated immunity with age. This loss may favour the development of some cancers [65].

The association of cancer and age involves both biological and clinical challenges. From the biological standpoint, it is important to identify the molecular aspects of ageing that favour cancer development and to establish whether these molecular changes may be delayed or reversed. From a clinical standpoint, the older person appears an ideal ground to study primary prevention of cancer, especially chemoprevention, that offsets the latest carcinogenetic stages [15,66].

In addition, the ongoing epidemics of skin cancer [59], brain tumours [60] and non-Hodgkin's lymphomas [61] in older individuals, suggest that older individuals may be a natural monitoring system for new environmental carcinogens. This hypothesis should be prospectively examined.

4. Cancer biology and age

The prognosis of several tumours changes with the age of the patient (Table 3). Two, non-mutually exclusive mechanisms are recognisable in age-related biological changes:

1. Older people may develop tumours that have different aggressiveness. In the case of AML, the prevalence of neoplastic cells expressing the multidrug resistance (*MDR-1*) gene increases with age [67]; in the case of breast cancer the neoplastic cells appear less malignant in older than in younger women [70,71].

Table 3
Tumour biology and patient age

Tumour	Prognosis with age	Mechanism(s)
Acute myelogenous leukaemia (AML) [67]	Worse after age 60 years	1. Increased prevalence of neoplastic cells expressing *MDR-1* 2. Involvement of the pluripotent stem cell by the neoplastic process
Non-Hodgkin's lymphoma [61,68,69]	Worse after age 60 years	Increased circulating levels of interleukin-6
Breast cancer [70,71]	More indolent with age	1. Increased prevalence of hormone-receptor rich tumours 2. Increased prevalence of well differentiated tumours 3. Increased prevalence of tumours with low proliferation rate 4. Decreased production of tumour growth factors by the older woman 5. Decreased oestrogenic production
Ovarian cancer [72]	Worse after age 65 years	Unknown

MDR, multidrug resistance gene.

2. The older tumour host may modulate differently the tumour growth. In the case of NHL, increased circulating concentrations of interleukin-6 may be responsible for the poorer prognosis in the aged [69]; in the case of breast cancer, decreased production of growth factors may render the tumour less aggressive in the older woman [70,71]. The importance of the age of the tumour host in determining tumour growth was well illustrated by Ershler in experimental systems [73]. This author demonstrated that the same load of Lewis lung carcinoma or B16 melanoma produced more metastasis and earlier death in younger than in older mice.

It is important to underline that the prognosis of cancer may either improve or worsen with the age of the patient. This finding contradicts the hypothesis of Ershler that age may be associated with more indolent tumours, as a process of natural selection [74]: as patients developing more aggressive tumours die more quickly, one may expect to find a higher prevalence of indolent neoplasms in older individuals (Fig. 3). This hypothesis is too simplistic because it does not account for the varying influence of the tumour host on tumour growth, nor does it account for the interaction between molecular changes of ageing and carcinogenesis, that may give origin to a more aggressive or treatment-fast tumour. A possible clue to this interaction may be found in myelodysplasia (MDS). MDS includes a number of conditions in which the maturation of one or more haemopoietic elements is abnormal. These conditions occur mostly in older individuals and are associated with a variable but always increased risk of AML [67]. The pathogenesis of MDS is complex and may include genetic changes as well as the production of cytokines that prevent haemopoietic maturation by the haemopoietic stroma. Another model to study the interactions of carcinogenesis and age-related molecular changes is provided by the monoclonal gammopathy that precedes multiple myeloma [75] (MGUS).

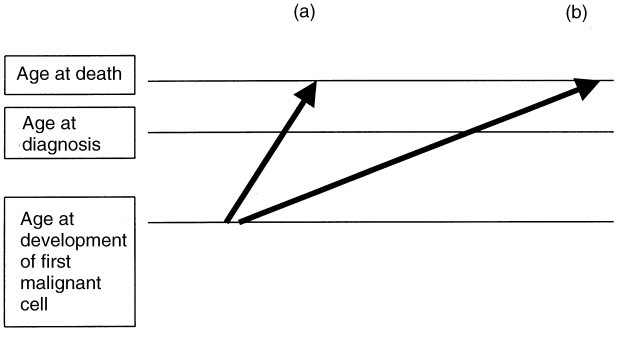

Fig. 3. Ershler hypothesis: more indolent tumours are more prevalent among older individuals because patients developing more aggressive tumours die at an earlier age.

The influence of ageing on cancer biology is an important and poorly understood issue. The main challenges include:

- To identify the main effectors of tumour–host interactions affected by age, such as the immune system, secretion of hormones, production of cytokines.
- To identify age-related conditions, such as MDS or MGUS, that may lead to neoplasia, and to use these conditions as models to study those molecular changes that link ageing to cancer.

5. Cancer prevention

Traditionally, cancer prevention has been subdivided into primary and secondary prevention [76].

Primary cancer prevention includes elimination of environmental carcinogens and administration of substances that may offset carcinogenesis (chemoprevention). Secondary prevention of cancer involves screening asymptomatic persons at risk of cancer, with the goal to detect cancer at an early and curable stage.

Due to their increased susceptibility to environmental carcinogens, older individuals are candidates for primary prevention of cancer, and in particular for chemoprevention. A number of substances including oestrogen antagonists [15], non-steroid anti-inflammatory agents, and retinoids [66] may prevent cancer of the breast, of the large bowel, and of the head and neck area, respectively. The main challenge of chemoprevention of cancer in older individuals is to establish whether the potential benefits of chemoprevention are worth the risk of complications, that may increase with age.

Secondary prevention of cancer deaths has been effective in the following conditions [77]:

- Breast cancer, for women aged 50–70 years, undergoing serial mammography every 1–2 years.
- Colorectal cancer, for persons aged 50–80 years, undergoing yearly examination of the stools for occult blood.
- Cervical cancer, for women aged 20–60 years undergoing serial cytological examination of the cervix.
- Possibly prostate cancer for men aged 50–65 years undergoing serial determinations of circulating prostate specific antigen (PSA) levels.

The benefit of screening older individuals has not been conclusively proven. Ageing may have divergent effects on screening. On the one hand, the positive predictive value of screening tests may be enhanced, given the increased prevalence of cancer among the aged. In addition, some screening tests, including physical examination of the breast may become more accurate

with ageing, due to loss of mammary fat. On the other hand, decreased life expectancy may minimise the benefits of screening. Moreover, the yield of screening tests may be reduced by previous screening that has detected all the prevalent cases [76]. Some authors have questioned whether the cost of screening older individuals for common malignancies may be more costly than commonly accepted. Karilowska calculated that screening all women over 70 years with serial mammography for breast cancer may cost more than $100 000.00 for each year of life saved and recommended that mammography after age 70 years be limited to women at highest risk of developing breast cancer [78]. In this study, women at highest risk were considered women in the upper quintile of bone density.

A recent study, based on the review of deaths from breast cancer involved in the Screening Epidemiology End Results (SEER) project indicated that women over 70 years who had not undergone mammography in the last 10 years were twice as likely to die from breast cancer than women of the same age who had undergone at least two mammograms [79]. This study strongly suggests the benefits of mammographic screening for women over 70 years.

It is unlikely that randomised controlled studies of cancer screening will be performed in the future in older individuals. Given the rapid changes in screening techniques, these studies may be obsolete by the time the final results are obtained. Given the progressive increment in life expectancy of the older population, and the development of safer and more precise screening tests, it is reasonable to assume that some form of cancer screening may be beneficial in the presence of functional independence and in the absence of life-limiting comorbidity. The main challenge related to secondary prevention of cancer involves the identification of those individuals who are more likely to benefit from screening due to prolonged life expectancy and enhanced risk of cancer.

6. Cancer treatment

Surgery [80,81] and radiation therapy [82,83] appear reasonably safe even for the most elderly. A common finding in different surgical reports is the fact that the mortality of elective surgery increases minimally with the age of the patient. The mortality from emergency surgery, in contrast, is 2–3-fold as high for persons over 70 years than it is for younger individuals. Clearly, emergency surgery overtaxes the limited functional reserve of many elderly. The high risk of mortality related to emergency surgery makes a strong case for early diagnosis of cancer for older individuals, especially for cancer of the large bowel, the major cause of emergency surgery.

The issues related to cytotoxic chemotherapy are more complex and involve age-related changes in the pharmacokinetics and pharmacodynamics of cytotoxic agents as well as the increased vulnerability of normal tissues to these drugs [84–87].

The main changes in pharmacokinetics and pharmacodynamics are illustrated in Table 4. Of the pharmacokinetic changes, restriction in the volume of distribution of water-soluble drugs and reduced renal excretion of medication are the most consequential.

Anaemia may precipitate a critical reduction in Vd, when the lean body weight is reduced: correction of anaemia with erythropoietin may ameliorate the toxicity of drugs that are highly bound to red blood cells, including taxanes, anthracyclines and epipodophyllotoxins [88–90]. Progressive reduction of glomerular filtration rate (GFR) is one of the most predictable physiological consequences of age [25]. Gellman and Taylor showed that adjusting the doses of methotrexate and cyclophosphamide to the renal function of breast cancer patients aged 65 years and older, ameliorated the toxicity of the drugs without compromising the efficacy of the treatment [91]. It is important to remember, however, that the pharmacokinetics of drugs may not be fully predictable from the GFR. Borkowski and colleagues showed that while the renal clearance of dichloromethotrexate decreased with the patient age, the total body clearance of the drug did not appreciably change, indicating that alternative mechanisms of drug elimination may become operative when the GFR declines [92].

Pharmacodynamic changes in normal tissue may enhance the exposure of these tissues to the drug and enhance the toxicity of chemotherapy [93,94]. Pharmacodynamic changes may also alter the sensitivity of neoplastic tissue to chemotherapy, as already described in the case of AML [67].

Normal tissues may become more susceptible to the toxicity of chemotherapy through at least three mechanisms:

1. Pharmacodynamic changes that may compromise the ability of the older tissues to repair DNA damage or to catabolise the drug [93,94].
2. Reduced stem cell reserve of rapidly proliferating tissues including haemopoietic tissues and mucosas [16,94]. The enhanced tissue destruction caused by chemotherapy may overwhelm the limited stem cell reserve and result in prolonged and severe neutropenia, thrombocytopenia and mucositis.
3. Reduced reserve of functional tissue, in which case additional tissue injury by chemotherapy may result in organ failure. This mechanism may be responsible for enhanced cardiotoxicity [95] and neurotoxicity [96,97] in older individuals.

Several forms of chemotherapy-related toxicity, including myelodepression, mucositis, cardiotoxicity,

Table 4
(a) Pharmacokinetic changes

Parameter	Effect of age	Mechanism	Clinical consequence
Absorption	Decreased	1. Decrease absorbing surface 2. Decreased splanchnic blood flow 3. Decreased gastric secretion and motility	May affect oral alkylating agents and new oral preparations of fluorinated pyrimidines (capecitabine, ftorafur)
Volume of distribution (vd)	Decreased, for water-soluble agents	1. Decreased total body proteins 2. Decreased haemoglobin concentration 3. Decreased serum albumin	Enhanced serum concentration and toxicity of taxanes, epipodophyllotoxins, anthracyclines, anthracendiones
Hepatic metabolism	Decreased, especially for type 1 reaction	1. Decreased hepatic blood flow 2. Decreased hepatocytic mass 3. Decreased concentration of P-450 cytochrome enzymes	Unknown; may be associated with decreased activity and increased toxicity of drugs that are heavily metabolised in the liver, such as the oxophosphorines (cyclophosphamide, ifosphamide)
Renal excretion	Decreased	Reduced glomerular filtration rate	1. Enhanced toxicity of drugs excreted from the kidneys (methotrexate, bleomycin, carboplatin) 2. Enhanced toxicity of drugs that give origin to active metabolites excreted from the kidneys (anthracyclines) 3. Enhanced toxicity of drugs that give origin to toxic metabolites excreted from the kidneys (cytarabine, high doses)
Biliary excretion	Unchanged	None	None

(b) Pharmacodynamic changes

Parameter	Effect of age	Mechanism	Clinical consequences
Repair DNA damage	Decreased	Reduced activity DNA repairing enzymes	Enhanced toxicity
Intracellular catabolism of fluorinated pyrimidines	Decreased	Deduced concentration of dihydropyrimidine dehydrogenase (DPD)	Enhanced toxicity
Drug elimination from tumour cells	Increased (AML)	Increased prevalence MDR-1 myeloblasts	Reduced activity

MDR, multidrug resistance gene.

central and peripheral neurotoxicity become more common with age [84–87]. Several retrospective studies of chemotherapy in persons aged 70 years and older failed to demonstrate an increased risk of neutropenia or thrombocytopenia among older individuals [91,98–101]. These studies are important as they show that age by itself is not a contraindication to cancer chemotherapy. However, these studies are not representative of the whole geriatric population, because they are fraught with the limitations typical of retrospective analysis:

- Older individuals were under-represented: only 10–15% of the patients included in these studies were aged 70 years and over, while 40% of cancer patients belong to this age group.
- Patients aged 85 years and older, the so-called 'oldest old' were virtually absent.
- Patients were all included in major clinical trials of cancer treatment and for this reason they were highly selected in terms of function and comorbidity.
- Many of the chemotherapy regimens used in these studies had a lower dose intensity than regimens of current use.

A number of prospective studies carried on in older individuals with lymphoma, present quite a different picture (Table 5) [102–109]. These studies showed that the risk of life-threatening neutropenia was higher than 50% in persons aged 65 years and older treated with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or a CHOP-like combination of chemotherapy, and that the risk of mortality varied between 5 and 30%. Two of these studies should be highlighted: Gomez and associates showed that the risk of myelosuppression increased especially after the age of 70 years [104]. Zinzani and colleagues proved that the risk of neutropenia and neutropenic infections could be reduced to one-quarter with haemopoietic growth factors [102]. The risk of thrombocytopenia and anaemia was also increased for older individuals. These lymphoma studies prove two important points:

Table 5
Risk of myelotoxicity, neutropenic fever and treatment-related deaths in older individuals with large-cell non-Hodgkin's lymphoma

Author [Ref.]	*n*	Chemotherapy	Age (years)	Myelotoxicity (%)	Neutropenic fever (%)	Treatment related deaths (%)
Zinzani [102]	350	VNCOP-B	60+	17	8	–
			60+	44	32	1.3
Sonneveld [103]	148	CHOP	60+	NR	NR	14
		CNOP	60+	NR	NR	13
Gomez [104]	26	CHOP	60+	24	8	0
			70+	73	42	20
Tirelli [105]	119	VMP	70+	50	21	7
		CHOP	70+	48	21	5
Bastion [106]	444	CVP	70+	9	7	12
		CTVP	70+	29	13	15
Bertini [107]	98	P-VEBEC	65+	22	4	–
			65+	46	9	2
O'Reilly [108]	63	POCE	65+	50	20	8
Armitage [109]	20	CHOP	70+	NR	NR	30

NR, not recorded; VNCOP-B, cyclophosphamide, mitoxantrone, vincristine, etoposide, bleomycin, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CNOP, cyclophosphamide, mitoxantrone, vincristine, prednisone; VMP, etoposide, mitoxantrone, prednimustine; CVP, cyclophosphamide, vincristine, prednisone; P-VEBEC, epirubicin, cyclophosphamide, etoposide, vinblastine, bleomycin, prednisone; POCE, etoposide, oncovin, cyclophosphamide.

1. The risk and severity of myelosuppression increases with age for moderately toxic chemotherapy.
2. Haemopoietic growth factors are effective in older individuals and allow administration of chemotherapy at full doses.

Based on these observations, the National Cancer Center Network (NCCN) recently proposed a number of guidelines related to the management of the older cancer patient (Table 6) [110]. The application of these guidelines is summarised in Fig. 4.

These guidelines are meant as the initial basis for future studies, not as a definitive word. A number of issues may evolve with experience. For example, it is unknown what the long-term effect of haemopoietic growth factor on the limited stem cell reserve of older individuals is going to be. Likewise, the systematic application of the geriatric assessment in older individuals may unearth unsuspected problems requiring new solutions. The guideline panel felt strongly, however, that enough data were available to lay foundations for future studies.

Table 6
Guidelines for the management of the older cancer patient proposed by the NCCN

1. Some form of geriatric assessment should be utilised in all patients aged and older for the following purposes:
2. • To identify frail individuals who are at excessive risk for any form of aggressive chemotherapy.
   • To identify older individuals who may present an increased risk of chemotherapy-related toxicity, for whom dose adjustment of chemotherapy drugs to renal function are indicated.
   • To identify problems that may prevent safe administration of chemotherapy, including comorbidity, lack of social support or transportation, malnutrition, dependence in the Instrumental Activities of Daily Living (IADL)s.
   • To assess life expectancy of older patients with cancer.
   • Use of a common language in clinical trials and in quality assurance.
3. Haemopoietic growth factors granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor (GM-CSF) should be used prophylactically in persons aged 70 years and older receiving moderately toxic chemotherapy, with dose-intensity comparable with CHOP.
4. Haemoglobin levels should be maintained at $\geqslant$120 g/l with erythropoietin.
5. The dose of drugs should be adjusted to renal function or reduced in patients with a moderate risk of toxicity, for the initial administration of treatment.
6. Mucositis should be treated aggressively, with fluid resuscitation.

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone.

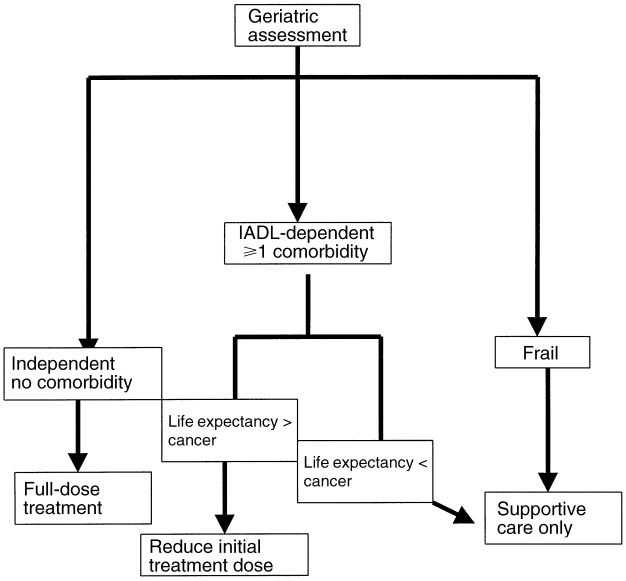

Fig. 4. Algorithm for the management of older cancer patients based on the National Cancer Center Network (NCCN) guidelines.

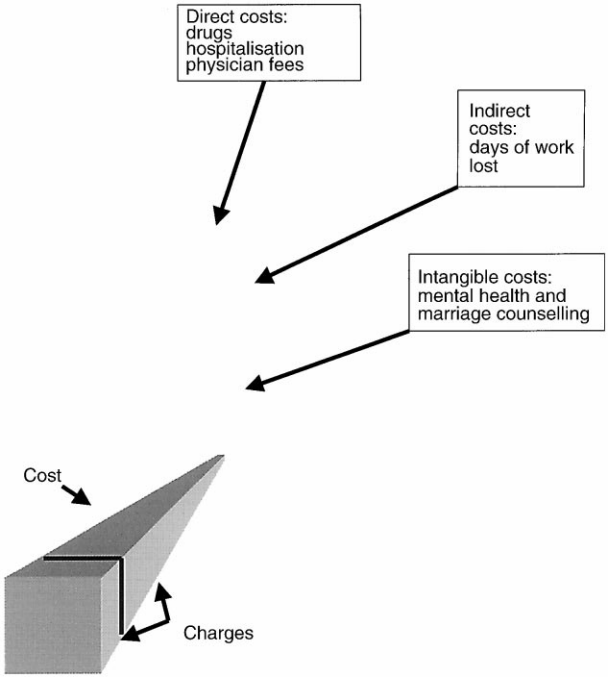

Fig. 5. Cost, charges and components of cost.

The challenges of treating older individuals with cancer chemotherapy clearly include:

- Proper patient selection to minimise toxicity and maximise benefits.
- Exploration of new drugs with improved toxicity profile.
- Understanding the most effective use of antidotes to drug toxicity.

7. The cost of cancer management in older individuals

Clearly, the treatment of older individuals with cancer is generally less cost-effective than the treatment of younger individuals, given a reduced gain in life expectancy and an increased risk of costly therapeutic complications [111]. However, this consideration should not discourage the treatment of older individuals. In Western society it is not acceptable to ration patient treatment because of cost. What appears reasonable, instead, is to explore strategies to minimise cost. To this end, it is very important to appreciate two aspects of healthcare economics:

1. Cost is a complex construct, whose component may not be easily dissected (Fig. 5). At least three elements of cost need clarification in any cost assessment:
   - Costs and charges are different entities. Cost is the amount of money necessary to obtain a certain product or a certain service. Charges are the monies that a certain product or service are priced by the seller. Charges are negotiable according to the law of offer and demand, costs are not, without an economic loss. In current studies of healthcare economics, costs and charges are often interchanged. This confusion may be legitimate in specific circumstances. For example, an insurance company may want to assess in which situations the prophylactic use of haemopoietic growth factors is less expensive than the management of neutropenic fever [112]. The costs for the insurance company are identical with the ongoing charges for drugs and hospitalisation. This confusion is not legitimate, however, when one studies broader issues of general interest, such as the management of cancer in the older person. In this situation, the identification of costs and charges may be misleading, because it would renounce a legitimate strategy of cost reduction, that is negotiating the charges.
   - Cost-reducing strategies may vary with the circumstances under which care is delivered. For example, the prophylactic use of haemopoietic growth factors for patients receiving cytotoxic chemotherapy may involve saving for a private insurance that fully pays ongoing charges of hospitalisation for neutropenic fever. The same strategy may not be cost-saving for a nationalised healthcare system, such as the Department of Veterans Affairs in which the majority of hospitalisation costs are already budgeted, irrespective of whether the patients will use the services.

- There are direct, indirect and intangible components of cost. The saving in direct cost, often advocated by healthcare operators, may involve an increase in indirect and intangible costs, that may make the total cost of the service even higher. For example, discharge from the hospital of unstable patients may improve the hospital income based on DRG, but may cause the home caregiver to lose days of work and may enhance his/her need for mental health. Failure to use erythropoietin may result in severe fatigue that may lead to functional dependence of the older cancer patient. The management of functional dependence, involving home care and institutionalisation, may increase the global cost of managing the older cancer patient well above the cost of erythropoietin, though the cost will be shifted from the healthcare industry to the patients and their families.

2. There is a cost related to not treating cancer patients. As euthanasia is not accepted in the majority of countries, cancer patients not receiving cancer chemotherapy still need symptom management that may be as expensive or more expensive than the chemotherapy. Any meaningful study of cost-effectiveness should compare the cost of treating cancer with the cost of not treating cancer.

Undoubtedly, cost management is going to be a major challenge in the treatment of older persons with cancer. A constructive way to start affording this challenge involves a honest appreciation of the issues surrounding cost by all interested parties.

8. Clinical research in the older patient with cancer

Clearly, more information related to the prevention and treatment of cancer in the older person is necessary. Perhaps the main challenge of geriatric oncology in the next decade is the planning of informative clinical trials. From the previous review, the geriatric population emerges as a highly diverse population, in terms of function, comorbidity, social support, cognitive function and emotional status. The first priority for clinical trials in older individuals appears to be the adoption of a common language, accounting for this diversity. The comprehensive geriatric assessment may provide this common ground, at least until more precise measures of ageing become available [113].

Traditionally, randomised controlled trials have provided the answer to the major questions of cancer prevention and cancer treatment. In geriatric oncology randomised controlled trials are still indispensable to answer specific questions, such as the value of adjuvant chemotherapy in breast cancer patients aged 70 years and older, or the value of shortened courses of chemotherapy in the management of large cell lymphoma. However, the value of the randomised controlled trial appears more limited in older individuals for the following reasons:

- Diversity of the population.
- Variability of endpoint. Survival, the golden standard of outcome measurement in clinical trials in younger persons, may not be always appropriate for elderly patients, with limited life expectancy. Alternative outcomes, such as freedom from progression, disease-free survival, clinical benefits, preservation of function and quality of life may be more difficult to evaluate.

Alternative forms of studies, including registry studies and community-based single-arm clinical trials should be considered in the study of the older person.

Finally, ageing may be associated with a number of barriers to the participation in these clinical trials. These barriers include:

- Inadequate information and comprehension of the consent mechanism.
- Socio-economic restrictions that prevent frequent travels to the research centre.
- Fatalistic attitudes towards ageing and diseases.
- Lack of support from family members and healthcare providers.

An intense effort of public and professional education as well as alternative forms of clinical trials, with less exacting conditions, appear necessary to bridge the current information gap related to cancer and ageing.

9. Conclusions

The management of cancer in the older aged person is becoming a progressively more common problem. The questions of this problem include:

- Is the patient going to die of cancer or with cancer?
- Is the patient able to tolerate the complications of cancer treatment?
- Is the patient likely to suffer the complications of cancer during her/his lifetime?

A reliable answer to these questions is definitely one of the main challenges of medicine during the next century. I do believe that the previous review has indicated the following research priority related to cancer and ageing:

1. A reliable assessment of ageing that allows an estimate of a person's life expectancy and functional reserve, and that allows the use of common parameters in clinical trials involving older individuals.

2. Exploration of alternative forms of clinical trials to randomised controlled trials. These trials need to accommodate alternative outcomes, meaningful for individual patients. In addition, these trials should be made user-friendly to accommodate a population with limited mobility and resources.
3. An intensive effort to improve professional and personal education appears necessary to gain public support for clinical research in the older person.
4. Better understanding of the pharmacology of antineoplastic drugs in older individuals, especially for concerns such as the volume of distribution and excretion.
5. Exploration of new and safer forms of cancer treatment in older individuals.
6. Unravelling the biological interfaces of cancer and ageing. Important translational research may emerge from these discoveries, including chemoprevention and prognosis of cancer in older individuals.

We believe that a set of prevention and treatment guidelines based on current knowledge may offer the best foundation upon which to build new research projects.

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