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Position Paper

EORTC elderly task force position paper: Approach to the older cancer patient

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ABSTRACT

As a result of an increasing life expectancy, the incidence of cancer cases diagnosed in the older population is rising. Indeed, cancer incidence is 11-fold higher in persons over the age of 65 than in younger ones. Despite this high incidence of cancer in older patients, solid data regarding the most appropriate approach and best treatment for older cancer patients are still lacking, mostly due to under-representation of these patients in prospective clinical trials.

The clinical behaviour of common malignant diseases, e.g. breast, ovarian and lung cancers, lymphomas and acute leukaemias, may be different in older patients because of intrinsic variation of the neoplastic cells and the ability of the tumour host to support neoplastic growth.

The decision to treat or not these patients should be based on patients' functional age rather than the chronological age. Assessment of patients' functional age includes the evaluation of health, functional status, nutrition, cognition and the psychosocial and economic context.

The purpose of this paper is to focus on the influence of age on cancer presentation and cancer management in older cancer patients and to provide suggestions on clinical trial development and methodology in this population.

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0. Introduction

As a result of an increasing life expectancy, the incidence of cancer cases diagnosed in the older population is rising. Indeed, cancer incidence is 11-fold higher in persons over the age of 65 than in younger ones.[1] Approximately 60% of all cancers and 70% of cancer mortality occur in people older than 65 years.[1] Despite this rapid increase in cancer incidence and cancer-related mortality with age, our knowledge about ageing and cancer and about optimal treatment for older cancer patients is still far from adequate.

The purpose of this paper is to focus on the influence of age on cancer presentation and cancer management in elderly cancer patients and to provide suggestions on clinical trial development and methodology in this population.

1. Definition of 'old'

The cut-off point at which an adult is considered 'old' has not been well defined. Ageing is a highly individualised process and all the changes involved in this process cannot be predicted solely on the basis of chronological age. Thus, it is clear that there is an emerging need for developing tools to better evaluate a patient's 'functional age' rather than chronological age.

An important question is why we have to define the term 'older'. In the oncology field where anti-cancer treatments are toxic and have substantial side-effects, it is crucial to define patient's risk-benefit profile. Specific aspects of the disease, patient and treatment considerations all affect the profile. Older patients may have an increased toxicity risk when treated with chemotherapy and to a lesser degree with radiotherapy and a decreased life expectancy. Both these parameters might change the risk-benefit profile.

From a practical point of view, a chronological landmark is the age of 70. After this age, there is an increased incidence of age-related physiological changes, which is a risk factor for altered pharmacokinetics and pharmacodynamics, potentially leading to increased treatment-related toxicity. Furthermore, differences in efficacy of treatment are observed mainly in older patients with haematological malignancies.[2] Hence age 70 is a reference point commonly used in clinical trials in oncology.[3] Obviously this cut-off is arbitrary. From a regulatory point of view, the European Medicines Agency (EMEA) considers 65 years of age as a cut-off for the definition of 'old' patients.[4,5]

2. Biological markers of ageing

A possible approach is to try to assess homeostatic reserve through biochemical markers.[6] Inflammation markers are considered as a predictive tool for frailty and mortality in the elderly.[7] Some studies found that the 'frailty' phenotype in aged individuals is associated with pathologic laboratory markers, such as interleukin-6 (IL-6).[8] However, IL-6 may be elevated in several inflammatory conditions and is non-specific. In addition, other studies have demonstrated that with increasing patient frailty, albumin levels fall significantly and C-reactive protein levels increase markedly. A study in healthy, community-dwelling older individuals over 70 years of age combined several laboratory measures of inflammation: albumin, CRP and IL-6.[9] A combination of these markers predicted 3- and 7-year mortality.

Furthermore, growing evidence points to the crucial role of telomeres in cellular ageing.[10–12] Telomeres are DNA–protein complexes that cap chromosomal ends and thereby promote chromosomal stability. When cells divide, the telomere is not fully replicated, leading to telomere shortening with every replication. *In vitro*, when telomeres shorten sufficiently, the cell is arrested into senescence. *In vivo*, it has been observed that telomeres also shorten with age in all replicating somatic cells that have been examined, including fibroblasts and leucocytes. Therefore, telomere length can serve as a biomarker of a cell's biological and chronological 'age'. There is also a growing body of evidence suggesting that short telomeres are a significant risk factor for age-related diseases, in particular hypertension, insulin resistance, atherosclerosis, myocardial infarction, stroke and dementia.[13,14] Intriguingly, telomere shortening has also been implicated in cancer; telomere dysfunction has emerged as an early event associated to genetic instability leading to tumours. Moreover, it has been hypothesised that chemotherapy accelerates ageing through telomere shortening.[15]

3. Under-representation of older patients in cancer clinical trials

Despite the high frequency of cancer in the elderly population, elderly patients are frequently under-represented in clinical trials evaluating new cancer treatments.[16–18] Indeed, statistically significant under-representation of the elderly was noted in registration trials for all cancer treatments except for breast cancer hormonal therapies, and this under-representation was more pronounced for patients 70 years or older.[19] A Southwest Oncology Group (SWOG) analysis reported that the proportion of older cancer patients ($\geqslant$65 years of age) enrolled in their clinical trials was significantly less compared with the percentage of older patients in the United States (US) population of patients with cancer (25% versus 63%, respectively; p-value < 0.001). When the age cut-off was set at 70 years, the proportions of patients enrolled in SWOG trials and those in the US population of patients with cancer were 13% and 47%, respectively (p-value < 0.001).[17] Furthermore it should be underlined that these studies are highly likely to suffer from selection bias in favour of treatment, since only older patients considered 'healthy enough' would have entered those studies.

As a result it is difficult to reach evidence-based clinical recommendations. Consequently the elderly are often undertreated or receive therapies which have not been tested in relevant clinical trials. Potential explanations for this situation are the belief that elderly patients are in general incapable of tolerating the treatment toxicities and also the limited expectations for long-term benefits on the part of physicians, patients or their families. A systematic review of the barriers to the recruitment of older patients to cancer clinical trials revealed the barriers related to cancer trial design (e.g. the majority of cancer trials in the past prohibited participation

of elderly patients on the basis of restrictions on comorbid conditions or organ function requirements to optimise treatment tolerability) and the barriers related to physicians (e.g. the perception that the patient would not be able to tolerate the treatment due to comorbidities and advanced age).[20] Furthermore, patient-related barriers have been reported, such as difficulty accessing university hospitals, lack of adequate information about the availability of clinical trials and the need to obtain their treating physician's endorsement to participate in a clinical trial.[21,22]

Another reason why elderly patients have been excluded from clinical trials is the higher intercurrent death rate that decreases the statistical power to discriminate between the standard and the experimental arm. A high rate of intercurrent events requires a proportional increase in the number of inclusions. Given the difficulty to motivate the patients in Europe and elsewhere to join in clinical trials, any attempt to optimise inclusion 'return' by excluding some patient categories have been the rule rather than the exception.

4. Is cancer prognosis different in the older

The physical history and prognosis of some neoplasms may change with patient's age. Acute myeloid leukaemia[23] and non-Hodgkin's lymphoma[24] are associated with poor prognosis in elderly patients. In the case of breast cancer advancing age is associated with more favourable tumour biology (the prevalence of well-differentiated, hormone-receptor positive, HER-2 negative tumours is higher in the older).[25,26] On the other hand the incidence of positive lymph nodes is higher in older breast cancer patients[27] but there is no significant difference in outcome compared with young ones.[26] Axillary lymph node involvement seems to vary with age at diagnosis; its probability decreases with increasing age up to the age of about 70 years, but increases again thereafter.[28] However, this increase is mainly seen in smaller tumours and suggests a different behaviour of small breast cancers in elderly patients. It was hypothesised that decreased immune defence mechanisms, related with ageing, may play a role in earlier invasion into lymph nodes. In the future gene expression analyses may yield more information as to the differences in tumour biology between older and younger patients.

A number of studies have not been able to demonstrate that age is a poor prognostic factor for survival in Non-Small Cell Lung Cancer (NSCLC).[29–31] The largest study, which included 5000 patients and evaluated the prognostic impact of 77 variables in NSCLC, could not show a relevant impact of age on survival.[31] Interestingly, Albain et al.[29] performed a retrospective analysis of the SWOG database with 2531 NSCLC patients and reported that older patients ($\geqslant$70 years of age) had longer overall survival (p-value: 0.02). In a similar way no significant difference has been reported between elderly and young colorectal cancer patients in terms of survival.[32,33] Overall, these data suggest that there are some differences in biology and prognosis in older individuals, but in general prognosis and behaviour are much more influenced by classical tumour characteristics (tumour grade, extension) than by age itself. However, when considering overall survival, one also has to take into account that older patients are at increased risk of dying from other causes (independent of their cancer) than their younger counterparts.

5. How to effectively select elderly cancer patients suitable for treatment; the role of geriatric assessment

In routine clinical practice, the major issue of the older population is heterogeneity. Some older patients will tolerate chemotherapy as well as their younger counterparts, while others will experience severe toxicity, requiring treatment reduction, treatment delay or permanent discontinuation. Thus, a major issue confronted by oncologists treating older cancer patients is how to effectively select patients suitable for standard or attenuated therapy. This is mainly relevant for treatments such as classical chemotherapy and high risk surgery, which can have severe potential impact on functionality, quality of life (morbidity) and even potentially life-threatening toxicity (iatrogenic mortality). Predicting chemotherapy toxicity is particularly critical in the treatment of advanced cancer, where the principal goal is palliation. Identifying the patients who have increased risk of toxicities will allow oncologists to better select patients, to propose treatment modifications, make rational dose reductions, implement supportive measures and develop interventions to decrease the risk of toxicity and in general better tailor the treatment plan on an individual level. The use of such a clinical instrument will help avoiding subjective decisions on patient selection and will allow better comparison of oncological results among homogeneous patient populations.

Comprehensive Geriatric Assessment (CGA) is an approach developed and used by the geriatricians to set up an individualised and proactive care plan. It evaluates the patients' global and functional status, in order to improve treatment decisions and outcomes (Table 1). The CGA estimates a patient's functional status, the presence of comorbidities, mental status and emotional conditions, social support, the nutritional status of the elderly patient, polypharmacy and the presence or absence of geriatric syndromes.[34,35]

The role of CGA in the care of the older patients in general was evaluated by a meta-analysis of 28 controlled trials which demonstrated that CGA if linked to geriatric interventions reduced early re-hospitalisation and mortality in older patients through early identification and treatment of problems.[36] Data concerning CGA and its ability to detect unknown health problems in elderly cancer population are consistent and promote its use in everyday clinical practice. Furthermore, CGA is also promising in enlightening health parameters linked to severe treatment-related toxicity when treatment is applied in oncologic patients.[37] It provides more relevant information than chronological age and Performance Status (PS).[38] In connection with survival, CGA also reveals relevant items which have an impact on survival, such as dependency and depression symptoms at baseline. The identification of clinical problems allows the planning of interventions and thereby improves patients' fitness and quality of life. Two randomised trials evaluated the impact of implementing interventions in the outpatient care of elderly cancer patients on the basis of CGA results,

Table 1 – Comprehensive geriatric assessment measures and instruments used.

Assessments	Instrument	Administration
Dependency	Activities of Daily Living (ADL)	Self-administered
Dependency	Instrumental Activities of Daily Living (IADL)	Self-administered
Depression	Geriatric Depression Scale (GDS)	Self-administered
Cognition	Mini-Mental State Examination (MMSE)	Interviewer-administered
Comorbidity	Charlson Comorbidity Index (CCI)	Self- or interviewer-administered or chart-based
	Cumulative Illness Rating Scale-Geriatric (CIRS-G)	
Nutrition	Mini Nutritional Assessment (MNA)	Interviewer-administered
	Body mass index	
Polypharmacy		
Geriatric syndromes		
Mobility/falls	Timed-up-and-go-test	Performance-test
	Tinetti	Performance-test

and demonstrated a statistically significant benefit in survival[39] and functional status.[40]

The CGA approach allows the discrimination of patients into three broad categories: (a) fit elderly patients who do not have any serious comorbidity and no dependence (fit patients); (b) frail patients with significant dependency and comorbidities and finally (c) patients with some IADL dependency with or without severe comorbidity (vulnerable patients). Patients in the first group are good candidates for almost every form of cancer treatment as they tolerate anti-cancer treatment as well as their younger counterparts with similar outcomes in terms of survival.[41–43] Patients of the second group are usually offered only best supportive care or only single-agent palliative chemotherapy, while for the third category of patients, which is the biggest, individualised approaches and specific clinical trials are recommended.[44] Also for surgery, instruments for geriatric assessment have been studied and have been shown to be independent risk factors for postoperative morbidity.[45] CGA is used in geriatric medicine to initiate special interventions to improve or at least stabilise functional status and general health. To that end geriatricians work with an interdisciplinary team including physiotherapists, occupational therapists, psychologists, dieticians and social workers.

However, although CGA clearly reveals extra information and the International Society of Geriatric Oncology (SIOG) recommends a CGA-based approach to elderly cancer patients, the best form of CGA for cancer patients remains to be defined.[46] Another important issue of CGA is the feasibility of implementing it in every day clinical practice. Administering all questionnaires included in CGA to all elderly cancer patients is a time and man-power-consuming procedure, not always reimbursed by health systems, explaining why, outside geriatric medicine, it is often not used in routine clinical practice. Because of these difficulties in the use of CGA in every day practice, several shorter screening tools have been developed in cancer patients, such as Vulnerable Elders Survey (VES-13),[47] the Groningen Frailty Indicator (GFI)[48] and the G8 instrument.[49] These screening tools are used to select patients with impairment who need further multidisciplinary evaluation. However, none of these screening tools has been prospectively validated (using full-CGA as gold-standard) and tested in oncology patients. The VES-13 is a self-administered questionnaire that consists of 12 items for functional capacity, physical status and patient's perception of his health and one question for age.[47] In a pilot study VES-13 accurately identified elderly prostate cancer patients who were defined as having impairment by CGA.[50] The GFI questionnaire is a screening tool, which includes 15 items in physical, cognitive and psychosocial functioning domains, to determine a person's level of frailty.[51] In a study with 83 patients, 65 years of age or older who had solid malignant tumours, GFI was able to predict most of the EORTC QLQC-30 scales significantly.[48] The G8 questionnaire is a very simple screening tool, which includes seven Mini Nutritional Assessment items and age (<80, 80–85, >85), for a total score ranging from 0 (poor score) to 17 (good score).[49] In an exploratory study in 364 cancer patients, 70 years of age or older, the cut-off score was set at 14, and with that threshold G8 had 90% sensitivity and 60% specificity.[49] This cut-off is now prospectively being validated in a large Nation-wide French study (Oncodage). An abbreviated form of CGA was developed by Overcash et al.[52] This evaluation includes 15 items and shows good correlation with the full-CGA evaluation.

If CGA is to be of value for older cancer patients, the problems it uncovers have to be solved or if this is not feasible, they have to be taken into account when determining cancer treatment. A close collaboration with specialists in geriatric medicine is highly recommended whenever possible.

Of course, it needs to be acknowledged that CGA is not the only predictive factor for chemotherapy toxicity, which can also be related to important differences in pharmacogenetics and chemotherapy pharmacokinetics. Moreover, a CGA is a momentary evaluation that can change in time and can be influenced by treatment (e.g. before or after surgery) and disease (e.g. inflammatory cancer syndrome, cancer fatigue). Optimally, CGA should be performed before any treatment has been done, but even then it can be important to ask if there have been recent changes that might be related to disease, and that might be reversible if the tumour is treated.

6. Cytotoxic chemotherapy and toxicity in older cancer patients

Ageing is associated with several physiologic changes in organ function that could alter drug pharmacokinetics and have

an impact on cytotoxic chemotherapy tolerability and toxicity.[53] Renal function, as indicated by the glomerular filtration rate, is reduced with age.[54] The decline in renal function affects the excretion of drugs whose main route of elimination is the kidney, such as platinum derivatives and methotrexate. Serum creatinine alone is insufficient as a method of renal function evaluation and creatinine clearance should be evaluated in every elderly cancer patient. After evaluating creatinine clearance, dose adjustment should be made, in order to reduce the incidence of toxicity.[55]

Bone marrow reserves also diminish with increasing age, and myelotoxicity can be substantially increased.[56] Several studies demonstrated that the risk of neutropaenia increases with age. Adjuvant treatment for breast cancer is associated with a lower neutrophil nadir in older patients.[57–59] Similarly, a higher risk of neutropaenia is reported after treatment for elderly lung cancer patients.[60,61] Furthermore, several prospective studies in elderly patients with lymphoma have demonstrated an age-related increase in neutropaenia and neutropaenic infections in patients treated with CHOP-like regimens.[62–64] A recent meta-analysis demonstrated that the use of recombinant colony-stimulating factors was associated with a reduced risk of febrile neutropaenia, documented infection and infection-related mortality.[65] Given the higher risk of neutropaenia and neutropaenic infections in older patients, the European Organization for Research and Treatment of Cancer (EORTC)[66] and the International Society for Geriatric Oncology (SIOG)[67] recommend the prophylactic use of haematopoietic factors in elderly cancer patients treated with chemotherapy of dose-intensity analogous to CHOP regimen. Similar recommendations have been issued by the National Comprehensive Cancer Network (NCCN)[68] and American Society of Clinical Oncology (ASCO).[69]

Another important issue in elderly cancer patients is anaemia. Anaemia increases with age and in combination with reduction in total body water, which is frequently observed in the elderly, can result in a reduced volume of distribution and higher peak concentration of hydrophilic drugs.[70,71] Furthermore, anaemia is also associated with cardiovascular disease, congestive heart failure and coronary death.[72] Chemotherapy-induced anaemia can be prevented by maintaining Hgb levels at 12 g/dl with the use of transfusion or epoetin. This approach is recommended by NCCN[68] and ASCO[73] and EORTC.[74] However, the safety of epoetin in cancer patients is a matter of debate, certainly if used outside the approved indications.[75,76]

Similarly, changes with age within the gastrointestinal system can result in decreased gastrointestinal motility, reduced splanchnic blood flow and secretion of digestive enzymes and mucosal atrophy and can result in a higher incidence of mucositis and diarrhoea that has been reported in older individuals.[77]

On the other hand it should be noted that a potential consequence of adapted chemotherapy is the danger of decreased efficacy. Dose de-escalation or the choice of less toxic, perhaps less active drugs, all concur to decrease the treatment efficacy. Therefore, dose or drug adaptation should include a discussion on the trade-offs between toxicity and efficacy.

7. Comorbidities

Multiple comorbid diseases are common in elderly cancer patients. A thorough assessment of comorbidities in cancer patients is required because it will determine the patients' life expectancy (i.e. more immediate medical problem could end the patient's life before the cancer itself becomes life-threatening). The overall burden of comorbidity has a negative impact on patient's survival[78,79] and on the patient's ability to tolerate treatment or may be a contraindication for cancer treatment (e.g. trastuzumab in patients with congestive heart failure). The number and severity of comorbid conditions can be assessed with the questionnaires such as the Charlson Comorbidity Index (CCI)[80] and the Cumulative Illness Rating Scale-Geriatric (CIRS-G).[81,82] Furthermore co-existing medical problems also lead to significant use of medication and polypharmacy has been reported as a significant factor which contributes to increased chemotherapy toxicity.[83,84] The contribution of the clinical pharmacist is of great value in these complex situations.

8. Geriatric syndromes

Additional important issues regarding the treatment of elderly cancer patients are the presence of geriatric syndromes (dementia, delirium, depression, falls, neglect and abuse, spontaneous bone fractures and failure to thrive), the level of social support provided and the nutritional status of the elderly patient. Presence of dementia has been reported as a negative prognostic factor for survival[85,86] and absence of adequate social support has been reported as a predictor of mortality in the elderly population.[87] Poor nutritional status results in decreased 1-year survival among the elderly people.[88]

9. Outcome measures for clinical trials

Overall Survival (OS): The 'gold standard' of outcome measurement in cancer clinical trials is overall survival. However, this may not be the most appropriate outcome for elderly patients treated for cancer, especially for cancers with an indolent course[89] or in cases of patients with significant comorbidities which have been associated with decreased life expectancy and negative impact on cancer treatment outcome.[90,91] As older patients are likely to die from other causes than cancer,[92] the potential gain from a new therapy in terms of overall survival is likely to be small and can possibly be best evaluated when considering disease- or treatment-specific events only.

Progression-Free Survival (PFS): PFS is defined as the time elapsed between randomisation in the clinical trial and documented tumour progression or death from any cause. PFS requires shorter follow-up than overall survival but it suffers from the same shortcoming than overall survival in that non-disease-related deaths tend to dilute the treatment effect and thus may not be a suitable end-point in the elderly population.

Disease-Specific Survival (DSS): DSS is defined as the time elapsed between randomisation and death due to the

malignant disease. Disease-specific survival differs from overall survival in that the event of interest is disease-related death only. In DSS, deaths not related to the malignant disease are censored. As a consequence, this end-point will better reflect the treatment benefit. An explicit clinical classification of deaths as disease related or non-disease related is required for the definition of this end-point.

Time to Progression (TTP): TTP is defined as the time elapsed between randomisation and tumour progression. It differs from PFS in that the event of interest is only disease progression and patients who die prior to progression are censored. This outcome shares the same advantages that DSS in that non-treatment-related effects are filtered out, but on the other hand lethal toxicity will be missed by using TTP. In that sense, PFS is more sensitive than TTP for evaluating severe toxicity leading to treatment-related deaths.[93]

Time to Treatment Failure (TTF): TTF is defined as the time elapsed between randomisation until treatment discontinuation due to disease progression, unacceptable toxicity, death or any other event of interest. A major issue in elderly cancer patients, especially in advanced disease stages where treatment aims at palliation and not cure, is treatment-related toxicity. Toxicity of an anti-cancer treatment is age dependent. Although older patients are willing to receive chemotherapy in the same way as younger patients, they are less willing to continue treatments with severe toxicities.[94] This end-point gives the opportunity to take into account the issue of toxicity and not only efficacy. The limits of TTF are however that it does not take into account rare situations where significant toxicity occurs, but patients have very good disease outcome thereafter. However, in most cases where palliative chemotherapy is given, TTF is probably a relevant outcome.

Therapeutic success: An interesting outcome for phase II trials in older individuals was reported by Ardizzoni et al.[95] This end-point, which was named 'therapeutic success', combined efficacy, toxicity and patient's compliance with treatment. A 'therapeutic success' was defined as a patient receiving at least three cycles of chemotherapy, at the planned dose (without dose reduction), and schedule (no treatment delay beyond two weeks) and having a response (either complete or partial) without experiencing grade III/IV toxicity. Variations of this design are possible, such as defining therapeutic success as being progression free at a fixed time point without having grade III/IV non-haematological or grade IV haematological toxicity. This seems to be an attractive and relevant end-point for specific situations in geriatric oncology and requires further exploration. However, there is no consensus about the most appropriate outcome to be used in older-specific trials, and the most appropriate end-point can be different in various clinical settings.

The considerations above explain that the magnitude of the observed treatment benefit will differ depending on the events that have been included, ignored or censored in the definition of the outcome.[96] This is especially relevant in the elderly population where patients experience competing events which interfere with the disease-specific outcome of interest.

The main goal of cancer treatment should be to avoid discomfort related to/caused by cancer progression and its related consequences (loss of functionality, inability to stay at home, deterioration of quality of life). Thus, the following outcomes for older-specific trials should also be considered:

Health-Related Quality of Life (HRQoL): HRQoL is a major concern for cancer patients, and it can be affected by symptoms caused by cancer, as well as by treatment-induced toxicity.[97] For elderly patients especially, anti-cancer treatment is not just how much additional time they can gain, but how valuable is that time. Elderly patients are less willing to compromise their HRQoL for the potential for increased survival.[98] Thus, HRQoL maybe an appropriate outcome for elderly-specific trials, but it remains to be defined how to measure/quantify HRQoL optimally, and which cut-offs are relevant as end-point for clinical trials.

Quality-Adjusted Survival: Q-TWIST approach. This methodology partitions the survival time of the patient into three consecutive health states (time with toxicity resulting from treatment; time without symptoms of disease or toxicity; time from progression/relapse to death) and assigns utility weights to each state.[99] The Q-TWIST value is the sum of the weighted health state durations and is used for the treatment comparisons. This approach quantitatively adjusts periods in which treatment toxicities or symptoms of disease progression are present to reflect the potentially reduced value for the patient. In principle this is a very nice approach, but the great difficulty is to determine/quantify the weight factor for quality of life during the different periods.

Preservation of functional capacity/independence: In a similar way, maintenance of function and independence should be one of the major principles of cancer management in the elderly since a negative impact on patient's functional capacity will have a negative impact on survival as well.[100] The prolongation of 'active' life expectancy seems much more important than the prolongation of life expectancy as such. But also here, there are important methodological concerns such as definition of functional dependence, optimal cut-off, and the fact that other handicaps can interfere with functionality (e.g. leg amputation 40 years ago after car accident) while it might not have real impact on quality of life in that individual.

10. EORTC elderly task force suggestions/considerations for cancer clinical trials in older patients

Heterogeneity in elderly patients is a major issue in clinical research. In past clinical trials, data collected on elderly patients were quite sparse as age above 70 years old was often an exclusion criterion. Therefore extrapolation of results of many clinical trials to the older population is questionable.

10.1. Trial design

An important issue is whether specific trials for older patients should be designed or whether clinical trials with no upper age limit are adequate for drawing conclusions for the general elderly cancer population. Indeed, several retrospective age-specific subgroup analyses of randomised trials without upper age limit demonstrated similar results between younger and older patients.[41,42,101–104] However, a major limitation of generalising this conclusion is that these retrospective analyses are highly likely to suffer from selection bias since only the 'fittest' elderly patients would have been enrolled in these trials. Moreover, not all elderly patients are suitable for standard treatments administered to younger patients, but should be treated according to their frailty status (vulnerable or frail patients). Therefore, specific trials need to be designed for vulnerable or frail older patients as well. In cases where specific trials for older individuals are not possible, the inclusion of patients above 70 years old in clinical trials should certainly be encouraged.[5] These patients should be reasonably representative of the general older population. According to European Medicines Agency (EMEA) guideline an adequate number (usually more than 100 patients) are needed in order to detect clinically meaningful differences between younger and elderly patients.[5] EMEA should force pharmaceutical companies to provide data on elderly patients. The companies are quite reluctant to test their new compounds in this population, since unexpected or even unrelated (side) effects might 'kill the drug'. Pharmaceutical companies are obliged to follow the Paediatric Investigation Plan (PIP) guideline of the EMEA[105] when conducting clinical trials to provide evidence when they want to have a paediatric claim for children for their products. A similar approach is needed for older patients.

Clinical trials in the older population are difficult to design due to several reasons such as the fact that elderly patients display much greater heterogeneity (compared to younger patients). Another important issue is that elderly patients in clinical practice are treated in many different ways, which makes comparison on outcome difficult. One of the major advantages of studies within EORTC or other large cooperative groups is that large cohorts of patients are treated in an identical way which allows interpreting more adequately differences in toxicity and outcome in elderly patients.

It is probably relevant to design separate specific trials for frail, vulnerable and fit elderly patients. Fit patients can probably be included in general population studies. Frail patients would probably require soft therapy approaches versus pure palliative care. Vulnerable patients are the most difficult group; standard versus 'softer' versus no therapy could be studied, depending on the setting.

Another approach of novel drug early phase studies is to progressively increase the inclusion criteria.[106] Instead of progressively increasing the dose of a drug, the level of comorbidity or functional limitations of the patients are increased. If dose-limiting toxicities are encountered at the first cycle of chemotherapy, then the starting dose of chemotherapy is reduced (or all less-toxic regimen is used) in the next cohort of patients. Instead of 3 patients per cohort, 6 could be used as older patients present multiple sources of heterogeneity.

10.2. Include some form of geriatric assessment

All older patients participating in a cancer clinical trial should have some kind of geriatric assessment. A two-step approach has been suggested: a short simple screening tool could be used to identify the fit patients that do not need a full geriatric assessment. For the others, a more formal Comprehensive Geriatric Assessment (CGA) is required (in collaboration with the geriatricians) since it will provide a more complete view of the patient's status and will allow the identification of patients who have increased risk of toxicities. Predicting chemotherapy toxicity is particularly critical in the treatment of advanced cancer disease, where the principal goal is palliation. On the other hand, it is unlikely that CGA will be the only predictor of benefit of therapy, since this is also affected by disease characteristics and pharmacogenomic differences between patients. The use of such a clinical instrument will help avoiding subjective decisions on patient selection and will allow better comparison of oncological results among clinical studies. Unfortunately, insufficient data are available at present.[34,107] Cut-off levels to identify the three different groups of patients have not yet been defined. They might differ according to the type of treatment tested in the trial and might also be different for more toxic than less-toxic regimes. There is thus a great need to address geriatric assessment prospectively in well designed and sufficiently powered clinical trials looking at the predictive value of CGA. EORTC Elderly Task Force will integrate the G8 screening tool in future trials including older patients.

Besides the use of CGA for better global view on the patient, it can also be used as a tool for stratifying/randomising patients in clinical studies.

In addition, an (preferably uniform) evaluation of comorbidity is important, e.g. with CCI or CIRS-G score, since comorbidity can have a major impact on outcome independent from therapy.

It is to be remembered that findings of CGA have to be acted upon. If, for example, malnutrition is detected, measures have to be taken to improve the nutritional status prior to or, at least during treatment.

Evaluation should be repeated during treatment to measure its impact on other dimensions than tumour response alone.

10.3. Define appropriate outcome measure

One of the key elements of the design of a clinical trial is the selection of the outcome measures and primary end-point. Several outcome measures are possible, and the choice probably depends on the specific situation and goals of the study. An elderly-specific outcome should be evaluated in addition to traditional outcomes.

Although the ultimate goal of anti-cancer treatment is to increase the overall survival, in the case of elderly patients other outcomes, such as time to progression or disease-specific survival, functional independency, time to treatment failure and a combination of efficacy and toxicity, may be more appropriate. It is important to measure and document changes in social situation, functionality and quality of life, and we would recommend an assessment of the treatment benefit by the patient himself/herself.

10.4. Other considerations

Many cytotoxic drugs are excreted renally or pharmacokinetics are altered in case of renal dysfunction. Before treatment administration, an optimal assessment of renal function is mandatory for any treatment that can be influenced in case of renal dysfunction. Serum creatinine alone is insufficient as a mean for renal function evaluation and more reliable approaches such as creatinine clearance should be used. Additionally, dose modifications should be done, according to creatinine clearance, in order to minimise the toxic effects.[108]

Since pharmacokinetics can clearly change in older individuals,[109] it is important to investigate this in older individuals, also in the more frail population. The problem is often to find funding for this kind of studies, and probably the only solution is to make it obligatory for drug registration.

Because older patients are more susceptible to treatment-related toxicities, special precautions should be taken:

- Due to higher risk of myelotoxicity, prophylactic use of G-CSF in elderly cancer patients treated with chemotherapy of dose-intensity analogous to CHOP regimen is recommended.[66,67,69]
- Hgb levels should be maintained where possible at 12 g/dl for prevention of anaemia. This will improve patients' feeling of fatigue and decrease the incidence of cardiovascular events.[73] Erythropoietin should be used within the approved indication since off-label use has been correlated with inferior outcome.[75,76]
- Elderly patients are more likely to develop mucositis, diarrhoea and dehydration[56] All measures should be taken to reduce their occurrence. General practitioners and relatives should be informed as to when readmission to the hospital is indicated since older individuals are less tolerant of these side-effects than younger patients. Elderly patients developing mucositis and diarrhoea should be treated with caution and immediately offered all supportive care needed.

Translational research in general, and also more specifically focussing on biomarkers of senescence, is also of utmost importance, and should be integrated wherever possible.

11. Suggestions to improve the organisation of the clinical and research activity of geriatric oncology

The indications and suggestions of this EORTC Task Force could be better implemented and applied if a specific activity for neoplasia in the elderly could be organised in the main hospitals and oncological institutions.

Specific activities for cancer in the elderly worldwide (mainly in USA and Europe) are currently carried out in some medical oncology departments of general hospitals but also in some cancer institutes, as well as, but to a minor extent, in geriatric departments.[110]

A document to encourage better organisation of the clinical practice in managing cancer in the older through the availability of an efficient network allowing optimal clinical activity and research has been produced by a specific SIOG Task Force.[111] This activity, with minor differences among the various places, is taking place through a Geriatric Oncology Programme (GOP). Such a clinical activity can be defined as a coordinated effort of medical oncologists, geriatricians, physiotherapists, nurses and social workers to generate treatment plans for older cancer patients. The GOP should address the following goals: (1) to provide comprehensive care through a multidisciplinary approach that considers age-associated conditions which influence cancer management; (2) to conduct clinical trials in representative older patients; (3) to reduce adverse outcomes such as nursing home placement and hospitalisations; (4) to allow patients to continue to live in their primary area of life either at home, hospice, or in nursing home and (5) to educate health professionals, the public, older patients and their families about cancer therapy and research.

Expected benefits from a structured Geriatric Oncology Programme are: to identify centres of excellence in order to enhance referrals, to develop and disseminate expertise on the provision of specific cancer care, to motivate and support clinical and translational research, to enhance social support and quality of life and to provide expert management in continuous care for follow-up care.

12. Conclusion

As world population ages, cancer in the older individuals becomes a significant health problem because the incidence of most cancer types increases with age. Despite this high incidence, there is a lack of elderly-specific clinical trials. These trials are necessary in order to develop evidence-based clinical recommendations for this specific population.

A number of important questions regarding elderly cancer patients remain to be answered and should be the areas of future research.

- Development of more precise (clinical and laboratory) methods for assessment of ageing.
- Validation of geriatric assessment tools in oncological setting.
- Definition of cut-off levels of CGA to define the three groups of patients according to the type of disease and treatment regarded as standard.
- Implementation of a uniform evaluation of older patient that will allow the comparison of results among different studies.
- Development of coordinating networks of medical oncologists, geriatricians, physiotherapists, nurses and social workers and Geriatric Oncology Programmes.
- Selection of more appropriate outcomes for trials in older individual.

The ultimate objective should be to develop evidence-based treatment recommendations for older patients that will take into account not only the chronological age, but

also the 'biological age' of the patient, and the delicate balance between life expectancy, benefits and risks of treatment.

Conflict of interest statement

None declared.

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