CLINICAL INVESTIGATION

Considerations in the design and conduct of clinical drug trials in older cancer patients

The incidence of cancer cases diagnosed in the older population is rising. However, despite this high incidence, several important issues regarding the optimal approach to older cancer patients remains to be elucidated, mostly due to underrepresentation of these patients in clinical trials. The first important issue is associated with the fact that older patients display much greater heterogeneity compared with younger patients. Thus, we need to find reliable tools to discriminate patients who will tolerate treatment and benefit from a standard approach, from others who will experience significant toxicity and will require a more attenuated approach. Another important question is whether clinical trials should have an age-specific design with certain end points or an age-unspecified design. Should we have age-specific trials in all disease settings and for all older patients? In the case of age-specific trials, which is the most appropriate methodology and the most appropriate end point? The purpose of the current article is to discuss the abovementioned issues.

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It is well known that cancer is a disease of the elderly. Although older patients (≥65 years of age) represent approximately 15–20% of the total population, cancer incidence is 11-fold higher in this demographic than in younger groups and approximately 60% of all cancers occur in older patients [1]. Furthermore, nearly 80% of cancer deaths are observed in people >60 years of age and approximately 30% of male and female cancer deaths in the USA occur in people aged ≥80 years of age [2]. Additionally, the number of older patients with cancer is expected to increase due to the aging of the western world's population [3] resulting in increased cancer-related morbidity and mortality among older persons [4].

However, the focus of cancer research does not tend to support this pattern of cancer burden. Despite the high incidence of cancer in older patients and the cancer-associated morbidity and mortality in this population, these patients are clearly underrepresented in clinical trials [5–8]. The age-related recruitment of cancer patients into registration trials of new drugs or new indications approved by the US FDA was evaluated by Talarico *et al.* [7]. This study evaluated data on 28,766 cancer patients from 55 registration trials and demonstrated that the proportions of the overall patient populations enrolled in trials who were aged ≥65, ≥70 and ≥75 were 36, 20 and 9% compared with the US cancer population as a whole, where the proportions were 60, 46 and 31%, respectively [7]. Statistically significant underrepresentation of older patients was noted in registration trials for all cancer treatment except for breast cancer hormonal therapies [7].

This underrepresentation results in a lack of evidence-based data and, consequently, hampers the development of treatment recommendations for

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these patients. This lack of recommendations results in undertreatment of these patients and thus to a poor clinical outcome, or to over-treatment and, therefore, to excessive toxicity. This fact clearly underlines the need for participation of older patients in clinical trials and the necessity of prospective data in everyday clinical practice. It is clear that without appropriate clinical research and prospective, well-constructed clinical trials for both fit and nonfit older patients we will not be able to provide optimal care for this growing population [9].

Definition of 'old'

The cut-off point at which an adult is considered 'old' has not been well defined. Aging is a highly individualized process and all the changes involved in this process cannot be predicted solely on the basis of chronological age. Patients of the same chronological age can have a completely different 'functional' age. Thus, the major challenge in geriatric oncology is to evaluate the patient's functional age rather than chronological age [10]. This is of crucial importance, especially in the field of cancer treatment, where many therapies have a palliative intent and are associated with substantial toxicity [10].

In some clinical trials, 70 years of age has been used as a cut-off point for the definition of 'old', whilst other studies have used 65 years of age [11,12]. Beyond this point, there is an increased incidence of age-related physiological changes, which result in altered pharmacokinetics and pharmacodynamics that could potentially lead to increased treatment-related toxicity. Furthermore, differences in efficacy of treatment are observed mainly in patients with hematological malignancies [13]. Hence, 70 years of age is a reference point commonly used in clinical trials in oncology, although this cut-off is arbitrary [14].

Selection of patients suitable for treatment: the role of geriatric assessment

One of the major challenges confronted by physicians in everyday clinical practice is how to effectively select older patients who are suitable for treatment. A general characteristic of the older cancer population is heterogeneity observed among older patients of the same chronological age [15]. Some patients are likely to tolerate and to benefit from standard cancer treatment in a similar way to their younger counterparts, while others who present with several comorbidities and significant functional impairment are at higher risk of experiencing severe treatment-related toxicity [15]. It is obvious that prediction of chemotherapy toxicity is crucial, especially in aggressive tumors (lung and pancreatic cancer), where the principal goal of treatment

is palliation [10]. Ambiguity in the selection of suitable patients may lead to severe, life-threatening toxicity induced by standard approaches in less-fit patients or inadequate treatment in fit patients in whom arbitrary treatment modifications are applied. This is an important issue in both clinical trial design and routine clinical practice. Therefore, a reliable tool that will allow the identification of patients who are likely to experience severe toxicity is of paramount importance for clinicians. This tool will allow physicians to better select patients, to apply treatment modifications, develop interventions to decrease the risk of toxicity and, in general, better tailor the treatment plan on an individual level, in both the clinical trials setting and routine clinical practice [16].

Geriatric assessment

Comprehensive Geriatric Assessment (CGA) is an approach developed and used in the field of geriatrics to set-up an individualized and proactive care plan for older patients. 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, nutritional status, polypharmacy and the presence or absence of geriatric syndromes [17].

CGA detects underlying health problems in the older cancer population and enlightens health parameters that are associated to severe chemotherapy-related toxicity in older cancer patients [18]. It provides more relevant information than chronological age and performance status [19]. The identification of clinical problems allows the design of interventions and more tailored therapeutic strategies and, thereby, improves clinical outcome and patients' quality of life. Two randomized trials evaluated the impact of implementing interventions in the outpatient care of older cancer patients on the basis of CGA results and demonstrated a statistically significant benefit in survival [20] and functional status [21].

Geriatric assessment allows the discrimination of patients into three broad categories: fit, older patients with no serious comorbidity or dependence (fit patients); frail patients who present with significant dependency and comorbidities; and the nonfit, nonfrail patients (vulnerable) who have some dependency with or without severe comorbidity. Patients in the first group are considered to be 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 [10]. Patients of the second group are usually offered only best supportive care or 'soft' treatments, while for the

Table 1. Comprehensive Geriatric Assessment measures and instruments used.			
Assessments	**Instrument**	**Administration**	**Ref.**
Dependency	Activities of daily living	Self-administered	[48]
Dependency	Instrumental activities of daily living	Self-administered	[49]
Depression	Geriatric depression scale	Self-administered	[50]
Cognition	Minimental state examination	Interviewer-administered	[51]
Comorbidity	Charlson comorbidity index Cumulative illness rating scale-geriatric	Self- or interviewer-administered or chart-based	[52,53]
Nutrition	Mininutritional assessment Body mass index	Interviewer-administered	[54]
Polypharmacy	n/a	n/a	
Geriatric syndromes	n/a	n/a	
Mobility/falls	Timed up-and-go test Tinetti	Performance test Performance test	[55,56]
n/a: Not applicable.			

third category of patients, individualized approaches and specific clinical trials are recommended [22].

Two very interesting papers dealing with the issue of toxicity prediction in the older cancer population were recently reported. The first was a model presented by Extermann *et al.* [23]. This model (CRASH score) was constructed along two subscores: hematological toxicity and nonhematological toxicity. For hematological toxicity, predictors were lymphocyte count, aspartate aminotransferase level, instrumental activities of daily living score, lactate dehydrogenase level, diastolic blood pressure, and chemotoxicity (according to MAX-2 index). Predictors of nonhematological toxicity were creatinine clearance, hemoglobin and albumin levels, self-rated health, Eastern Cooperative Oncology Group performance, minimental status score, mininutritional assessment score and chemotoxicity. The second report by Hurria *et al.* defined as risk factors for grade 3–5, toxicity age ≥73 years, cancer type (gastrointestinal or genitourinary), standard dose of chemotherapy, use of polychemotherapy, falls in the preceding 6 months, assistance with instrumental activities of daily living and decreased social activity [24]. The number of risk factors present was associated with the risk of severe toxicity (one risk factor: 23%; seven risk factors: 100%).

Despite the fact that CGA reveals extra information and a geriatric assessment-based approach is recommended by both the International Society of Geriatric Oncology [25] and the European Organization for Research and Treatment of Cancer [16], the best form of CGA for cancer patients is yet to be defined. Another significant issue in the feasibility of CGA implementation in everyday clinical practice, is that CGAs are time- and manpower-intensive procedures that are not always financially covered by healthcare systems. Furthermore, administering all of the questionnaires included in a CGA to all elderly cancer patients may not be possible in a heavy-loaded oncology department. This may explain why, outside geriatric medicine, it is often not used in routine clinical practice.

Due to these difficulties in the use of CGA in everyday practice, several shorter screening tools have been developed in cancer patients, such as the Vulnerable Elders Survey (VES-13) [26], the Groningen Frailty Indicator [27] and the G8 instrument [28]. These screening tools are used to select patients with impairment who need further multidisciplinary evaluation.

Why are so many older cancer patients excluded from clinical trials?

Despite the high frequency of cancer in the older population, older patients are frequently underrepresented in clinical trials evaluating new cancer treatments [5,6,29]. The reasons for this underrepresentation can be grouped into three general categories: physician related, clinical trial design/industry related and patient related [30,31]. Among physicians there is a widespread misbelief that older patients are, in general, incapable of tolerating the treatment toxicities and have limited expectations for long-term benefits. This was confirmed by a survey of 180 oncologists involved in the treatment of older cancer patients in Canada. Comorbities and functional status were reported as principal factors when making treatment decisions regarding chemotherapy [32]. 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 [33,34]. In addition,

although older patients are willing to participate in clinical trials [35], cultural, cognitive and physician-related issues might have an impact on a patient's treatment preference [36]. A systematic review of barriers to the recruitment of older patients to cancer clinical trials revealed barriers related to cancer-trial design (e.g., the majority of cancer trials in the past prohibited participation of older patients on the basis of restrictions on comorbid conditions or organ function requirements to optimize treatment tolerability) [30]. According to a survey by Van Spall *et al.,* a very high percentage of older patients, and those with common medical conditions were excluded from clinical trials [37]. Moreover, companies are quite reluctant to rapidly test their new compounds in the truly older population, since unexpected or even drug unrelated (side) effects might 'kill the drug'.

Age-specific versus age-unspecified clinical trials

An important issue is whether specific trials for older patients (age-specific trials) should be designed or if the conclusions extracted from clinical trials in the general population can be extrapolated to the older cancer population.

Younger cancer patients comprise a more homogeneous population compared with older patients. In fact, in the older population, aging results in different effects on organ function and, furthermore, several comorbidities that characterize the older population contribute to a significant heterogeneity [38]. This variance could result in considerable differences in the efficacy and safety of cancer treatments and, therefore, results from age-unspecified clinical trials cannot be directly applicable to the older population. Another major limitation of generalizing the observations of age-unspecified trials is that they are likely to suffer from selection bias, since only the 'healthiest' older patients would have been enrolled in these trials and, thus, are not applicable to the general older population.

Furthermore, these trials produce results that are more relevant and valid for older cancer patients, since they are focused on the geriatric population [39]. Another significant issue is that older patients who participate in age-specific trials experience significantly less toxicity compared with older patients who participate in age-unspecified trials [40]. Pros and cons of age-specific trials are presented in **Box 1**.

Design of drug clinical trials in older cancer patients

As differences in organ function between older and younger patients and also among older patients could result in differences in pharmacokinetics and pharmacodynamics of cancer drugs, pharmacokinetic studies and Phase I studies should be specifically designed for older patients [39]. Extermann *et al.* recently presented an interesting approach for early-phase studies [41]. Instead of progressively increasing the dose of a drug, as is common practice in Phase I studies, the level of comorbidities or functional dependence allowed could be increased. If dose-limiting toxicities are observed at the first cycle of chemotherapy, then the starting dose of chemotherapy is reduced (or a less-toxic regimen is used) in the next cohort of patients. Instead of three patients per cohort, six could be used, as older patients present multiple sources of heterogeneity.

Furthermore, as stated by the European Organisation for Research and Treatment of Cancer's Elderly Task Force, it is relevant to design separate specific trials at least for frail and vulnerable older patients [10]. Fit patients may be included in general-population studies. For frail patients, a 'soft therapy' versus best-supportive-care approach could be evaluated, while for vulnerable patients, standard versus 'softer' versus no-therapy approaches could be tested, depending on the setting. Given the difficulty of designing large, randomized Phase III trials, these issues could initially be assessed in the context of randomized Phase II trials. In these cases physical status (frailty and vulnerability) should be used as stratification factor [39].

Appropriate end points for older specific trials

It is likely that significant differences in the outcome priorities of younger and older patients exist, which means that the use of the same outcome thresholds may not be appropriate [16]. Therefore, one of the key elements of the design of a clinical trial in older cancer patients is the selection of the appropriate outcome measures and primary end points.

While overall survival is considered as the 'gold standard' of outcome measurement in cancer clinical trials, this may not be the most proper outcome for age-specific trials enrolling older cancer patients. This could be the case for tumor types with an indolent course [42] or in cases of patients with dependencies and/or comorbidities and could have a negative impact on cancer treatment outcome and/or life expectancy [43,44]. Therefore, some alternative end points in age-specific cancer trials [10] could be, among others, health-related quality of life, maintenance of functional independence, absence of serious therapy-related side effects and burden of treatment are equally important in the older population [45]. A very interesting end point, the so-called overall treatment utility was recently developed by Seymour *et al.* [46]. This end point incorporates patient-reported outcomes and patient opinion on whether his/her treatment has

been worthwhile. Moreover, as older patients are likely to die from causes other than cancer [47], the potential survival benefit from a new treatment is expected to be small and can possibly be best evaluated when considering disease- or treatment-specific events only. Therefore, a good alternative as an outcome measure could be disease-specific survival [10].

Conclusion

Despite the high incidence and prevalence of malignancies and cancer-associated morbidity and mortality in the older population, there is still a lack of evidence-based recommendations for the treatment of these patients. Treatment optimization in this special population will require age-specific clinical trials to be conducted. Thus, we need to optimize the manner in which clinical research is conducted in this special population. A number of important obstacles, such as the development of precise methods for patient evaluation and selection of appropriate outcomes for clinical trials regarding older cancer patients, remain to be addressed and should be areas of future research.

Future perspective

Future research in the field of geriatric oncology will need to address two major issues. The first is the development of precise methods and tools (both clinical and molecular markers of aging) to evaluate

Box 1. Pros and cons of age-specific trials.
Factors favoring separate trials
■ Improve accrual
■ Focus on toxicity and function
■ Integration of geriatric assessment
■ Determine which Comprehensive Geriatric Assessment domains are factors in outcome
■ Results focused on older population
■ Withdraw reluctance on the part of medical community to enrol older patients
■ Safer, with less toxicity
Factors against separate trials
■ Support current age bias
■ Limit participation in 'aggressive' trials or trials of new agents
■ Competitive trials
■ Add to trial expense

patients' 'functional' age. Several methods of comprehensive geriatric assessment are now available and are in the process of prospective validation. Similarly, a variety of biological markers of aging are intensively studied and implementation in clinical research and clinical practice is eagerly awaited. The second important issue is the selection of relevant end points for older patient-specific clinical trials. New end points are now being developed and tested in clinical trials and hopefully these will be

Executive summary
Definition of old
■ There is no well-defined cut-off point at which a patient is considered 'old'.
■ Aging is a highly individualized process and all the changes involved cannot be predicted solely on the basis of chronological age.
■ In clinical research, 70 years of age is usually used as a cut-off point, although this is an arbitrary distinction.
Selection of patients suitable for treatment
■ Among older patients there is great heterogeneity (those with no significant problems versus those with significant comorbidities and dependencies).
■ There is a need to effectively discriminate these categories in both clinical research and routine clinical practice. One such tool is the comprehensive geriatric assessment (CGA).
CGA
■ CGA is an estimate of a patient's functional status, presence of comorbidities, mental status and emotional conditions, social support, nutritional status, polypharmacy and presence or absence of geriatric syndromes.
■ It allows the discrimination of patients into three broad categories: fit older patients; frail patients; and nonfit, nonfrail patients (the vulnerable).
■ CGA provides more relevant information than chronological age and performance status.
Underrepresentation of older cancer patients in clinical trials
■ There is significant underrepresentation of older cancer patients in clinical trials.
■ The reasons for this underrepresentation can be physician related, clinical trial design/industry related or patient related.
■ One approach to address this issue is the use of age-specific clinical trials.
■ Age-specific trials usually produce more relevant and valid results for older cancer patients and are usually associated with less toxicity.
■ However, it should be kept in mind when designing an older-specific trial that significant differences in the outcome priorities of younger and older patients may exist.

applied in clinical practice in future and will guide treatment decisions in older cancer patients.

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