EORTC workshop on clinical trial methodology in older individuals with a diagnosis of solid tumors


Background: Due to the aging of the population, the number of older patients diagnosed with a malignant disease is increasing. A multidisciplinary approach to the senior adult cancer patient is mandatory, to assure optimal diagnosis and therapeutic management.

Design: European Organisation for Research and Treatment of Cancer (EORTC) has currently defined senior adult oncology as one of its priorities and has established an active Elderly Task Force (ETF). Under the auspices of the EORTC, the ETF organized a workshop on clinical trial methodology in older cancer patients and in this article, we present the conclusions of this workshop.

Results: Besides the ‘classical’ efficacy end points, quality of life, functional status and independence of the patient should be assessed in clinical trials in older patients. The participants of the workshop agreed on the use of a minimum dataset for the assessment of global health and functional status in older cancer patients. The panel also recommended that optimization of collaboration with pharmaceutical industry requires reporting of age-related data (subgroup analyses of clinical trials, age-related pooled analyses and obligatory post-marketing studies in vulnerable and frail older patients).

Conclusion: The identification of proper clinical outcomes and the validation of geriatric screening tools are needed for conducting sound and comparable clinical trials.

Key words: clinical trials, EORTC workshop, geriatric oncology, solid tumors

introduction

Due to the aging of the population in the Western world, the percentage of the European population aged ≥65 years is projected to increase from 17.1% (84.6 million) in 2008 to 30.0% (151.5 million) in 2060 [1]. As a consequence, the number of older patients diagnosed with a malignant disease will increase. Indeed, cancer incidence is 11-fold higher in persons over the age of 65, than in younger ones [2]. More than 60% of diagnosed cancer cases and nearly 80% of cancer deaths are observed in people ≥60 years of age [3]. Approximately, 27% of male and 32% of female cancer deaths occur in people aged ≥80 years in the United States [3]. However, despite this high incidence of cancer and cancer-related mortality in the older population, these patients are frequently underrepresented in clinical trials evaluating new cancer treatments [4]. For this reason, our knowledge about aging, cancer and optimal design of clinical trials in this special population is still far from adequate.

The European Organisation for Research and Treatment of Cancer (EORTC) has currently defined senior adult oncology as one of its priorities and has established an active Elderly Task Force (ETF). The ultimate goal of the ETF is to improve the standards of cancer care in older people, through improving awareness and early diagnosis and the evaluation of innovative...
drugs and new regimens, to establish more effective therapeutic strategies and to develop valid tools and methods for the evaluation of older patients. Under the auspices of the EORTC, the ETF organized a workshop on clinical trial methodology in older cancer patients that was held at the EORTC headquarters in December 2009. This workshop was attended by 23 specialists from all over Europe interested in the treatment of cancer and clinical trials in the older population and 5 representatives from EORTC. The main topics that were discussed were clinical trial methodology (selection of end points, trial design and eligibility criteria for clinical studies in older individuals), geriatric assessment (standardization of data collection for trials in the elderly such as functional status and comorbidity) agreement on a minimum dataset, and proposing strategies for optimizing collaboration with governmental agencies and industry in the field of clinical trials in older patients.

**clinical trial methodology**

The first purpose of this workshop was to reach a consensus on what the most appropriate end point for clinical trials in older patients should be. Until recently, the ‘gold standard’ of outcome measurement in most cancer clinical trials has been overall survival. However, overall survival might not be the most appropriate end point for many cancer patients, and specifically for older cancer patients. It might not reflect the true benefit of therapy, especially for cancers with an indolent course or in case of patients with significant comorbidities who are likely to die of causes other than cancer. Other factors like health-related quality of life (QoL), maintenance of functional independence, absence of serious therapy-related side-effects and burden of treatment are equally important in the older population. Indeed the question ‘quantity versus QoL and maintenance of independence’ are fundamental in the older population who may be traded for some loss of quantity of life to maintain quality and independence [5, 6]. Researchers, clinicians and health care providers should be aware of this and have lower thresholds for treatment efficacy outcomes if QoL is superior. Competent authorities should consider clinical trials in older cancer patients as positive if significant health-related QoL improvement is demonstrated despite slightly inferior efficacy. Currently, reflecting practice in research involving younger patients, longer survival counts more than better QoL with slightly shorter survival. There are known to be significant differences in the outcome priorities of younger and older patients, which means that simply using these same outcome thresholds may not be appropriate in older patients. Participants agreed that changes in social situation, functional status and health-related QoL should be measured and documented in all research involving older patients. Two approaches of incorporating efficacy, QoL and toxicity measures as primary criteria for success of a new therapeutic strategy were proposed, either as composite end points or as co-primary end points. Trials based on composite end points will be declared successful if the new treatment is an adequate trade-off between efficacy, QoL and toxicity; the drawback is that no statement can be formulated in terms of efficacy or toxicity or QoL separately. Trials based on co-primary end points will be declared successful if the new treatment is successful on each of the primary end points; the drawback is that more patients are needed for such trials. Adaptive (Bayesian) trial design is also a useful design in frail populations, as one can adapt procedures early to data produced in the trial itself. Older patients not qualifying for standard treatment regimens might be candidates for early evaluation of less toxic innovative drugs. It was also recognized that trials evaluating treatments that are known to have mild toxicity can be designed based on a single efficacy end point. The importance of qualitative research and user input into the evaluation of new treatment strategies should be encouraged.

There was a discussion about whether criteria of inclusion should be based on chronological age, on medical criteria (thus allowing the inclusion of younger patients with impairments) or on a geriatric assessment. Although it is acknowledged that functional status cannot be predicted solely on the basis of chronological age, there was an agreement to use age >70 as a reference point for the definition of ‘older’ patients for participants in clinical trials in oncology. Obviously, this cut-off is arbitrary but it is widely used in cancer clinical trials [7]. Although in some specific situations current high-level evidence extents to 60–65 years of age (e.g. concurrent chemoradiotherapy in non-small-cell lung cancer, glioblastoma), to avoid an ‘age-knowledge gap in the young-old’ age limit for an older cancer patient group might even be 60 or 65. Additionally, there was a wide agreement that some kind of geriatric assessment should be used because it will clarify the prognostic value of geriatric assessment and facilitate the distinction between fit, vulnerable and frail patients and therefore allow stratification and/or different treatment approaches and suitable tailored trials and drug development plans.

**evaluation of older patients: the comprehensive geriatric assessment**

Among older cancer patients of the same chronological age, there is wide heterogeneity in physical and psychological functioning. A major issue confronting oncologists treating elderly cancer patients is how to effectively select patients for therapies with significant potential toxicity such as major surgery or chemotherapy. Currently, uncertainty exists about the optimal tools and strategies for geriatric assessment and the second purpose of this workshop was to propose a common approach to evaluate older cancer patients in clinical trials and to reach a consensus among European oncologists.

Comprehensive geriatric assessment (CGA) is a procedure developed by geriatricians to evaluate the elderly patients’ functional and global health status, to identify and manage age-related problems allowing clinicians to select patients more appropriately for therapy and avoiding futile therapy/ overtreatment as well as undertreatment [8].

However, full CGA is a time- and manpower-consuming procedure that is difficult to use in everyday clinical practice and a more feasible approach should be adopted. Among participating oncologists and geriatricians, there was a consensus on a minimum dataset data (MinDS) (supplemental Appendix 1, available at *Annals of Oncology* online) to be collected in older cancer patients. This proposed dataset consists of the G8 questionnaire [9], the Instrumental Activities of Daily Living (IADL) questionnaire [10], information about social situation and the Charlson Comorbidity Index (CCI) [11]. These factors would comprise the EORTC Elderly MinDS (supplemental Appendix 1, available at *Annals of Oncology* online).

The G8 questionnaire is a very simple screening tool, which includes seven mini nutritional assessment items and age (>80, >85), for a total score ranging from 0 (poor score) to 17 (good score) and in an exploratory study has already shown significant sensitivity and specificity [9]. It is currently being validated prospectively in a large French study (Oncodage) and in a national Belgian study.
The IADL questionnaire assesses advanced self-care activities (ability to prepare meals, do housework, use the telephone, take medications, manage finances and use transportation means) [10]. Fit seniors are independent in IADL. It was decided to use this questionnaire because in cancer patients IADL dependence has been associated with poorer survival in lung cancer patients [12] and in patients with hematological malignancies [13, 14], risk of chemotherapy toxicity in patients with ovarian cancer [15] and with more postoperative complications [16].

All participants considered information about available social support as essential for the treatment planning of the older patient. Social support is crucial for several aspects of treatment of older cancer patient (coordination of patient’s treatment, recognition of treatment complications, practical issues such as transportation and physical assistance) [17]. Another question was suggested (Which of the following statements best describe where you live?) to discriminate between three groups, i.e. living at home with and without help and institutionalized care (supplemental Appendix 1, available at Annals of Oncology online).

Finally, it was considered necessary to collect information about comorbidities. Comorbidities are a frequent problem and a competing source for mortality in older cancer patients [18]. These comorbid medical conditions may often lead to death from causes other than cancer, thus nullifying any possible benefit of treatment. Comorbidity is reported to have a negative impact on survival in cancer patients [19–26] and treatment tolerance [27, 28]. The CCI is one of the most widely used questionnaires for estimating the number and the severity of comorbidities [11] and has been clearly shown to predict mortality.

This proposed MinDS would take no more than 5 min to complete and would be feasible to use in all settings. Being only a brief geriatric evaluation it was strongly recommended to provide further assessment if this initial screen detects problems, preferably in collaboration with geriatricians and other health care workers.

The MinDS should be used at least as baseline assessment in order to evaluate the patients’ global and functional status and facilitate treatment decisions. It might also be used for the detection of hidden health problems in the older cancer population, which then should be taken care of. Furthermore, G8, IADL and social support questionnaires could be reassessed during treatment and be used as an evaluation instrument of treatment tolerance and efficacy. The exact method of analysis and reporting these data is still under evaluation by ETF members at EORTC headquarters. One other potential benefit of the use of a standardized minimum dataset is that it will permit comparison between different studies or facilitate meta-analysis, so strengthening effect sizes by pooling data. This is especially relevant in studies in older age groups where recruitment rates may be poor. Another potential benefit is that it will permit categorization of patients into groups with different age-related conditions (fit, vulnerable and frail) and different risks of toxicity/drop out.

**Collaboration with industry**

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’. Therefore, drugs are tested in ‘young’ and ‘fit’ patients but are later used in clinical practice in a wide range of older less fit patients. It is obvious that in order to recommend a treatment for older patients it has to be tested in an adequate number of such patients representative of the general older population.

Special attention must be given to drug–drug interactions and issues like absorption of oral drugs or renal function.

The panel had three recommendations for designing and reporting clinical trials in the future:

1. Obligatory reporting of age-related subgroup analysis including number of patients, efficacy and toxicity data and, if possible, pooled analysis of different trials with the same drugs in similar settings.

   Selection bias will very often be present in registration trials, certainly in oncology, where strict exclusion criteria and physician/patient preference automatically lead to the inclusion of only ‘fit’ older patients. Although this obviously leads to a bias in the evaluation of a drug in the senior adult population, we believe it is convenient that unfit patients are excluded from this type of trial. Indeed, since most anticancer drugs have a significant side-effects and a narrow therapeutic index, unexpected events/toxicity (related but can be unrelated as well) can obscure the true benefits in a fit population (defined by the inclusion and exclusion criteria) and can lead to slower registration and availability of new drugs for the ‘fit’ population (young and fit elderly). In addition, some new drug combinations are expected to be too toxic for vulnerable or frail elderly, and it would be unethical to expose patients to an excessive degree of toxicity.

   But even in ‘fit’ elderly entered in clinical trials, age-related effects can be present. We propose that a ‘subgroup analysis of efficacy and safety’ based on age is preplanned and that the results should be presented in not only registration documents but also in the Summary of Product Characteristics (SmPC) and in scientific publications (at present, this information, if negative for the drug, may not be easily accessible to the scientific audience and may be only available in registration documents that are not often read by physicians). It is important that data from different studies with the same drug in the same setting are ‘pooled’ and that a pooled analysis to evaluate the effect of age on efficacy and safety is carried out and displayed. This might detect age effects that cannot be detected within single trials. The Food and Drug Administration currently requests this kind of pooled analysis, both for age-related efficacy and toxicity. These analyses should be presented together with a description of the population in terms of concomitant therapies and comorbidities in order to be able to characterize the elderly population included in the trials, and the proposed MinDS will facilitate such combined analysis.

2. Obligatory post-marketing studies in vulnerable and frail older patients, with age-specific trial design if applicable.

   Besides fit elderly, it is crucial to have data on the new drug/ regimen in vulnerable and frail elderly, as these treatments will be used in these groups. The question is how this can be best achieved.

   A label stating that the new drug/regimen can be used only in fit elderly (as in most registration studies), is probably discrimination, could lead to decreased opportunity to prescribe drugs to seniors in general.
As only fit elderly patients will tend to enter clinical trials with no age limit, ‘elderly-specific trials’ with elderly-specific regimens should also be requested. Certain regimens, not only in the palliative setting but also in other circumstances, would be poorly tolerated by frail older patients, and adapted strategies with new drugs should be investigated in older cancer patients. Moreover, the goals of therapy can be quite different: prolonging survival is probably the most important goal for young cancer patients whereas for older patients maintenance of functional independence and QoL might be more important than survival. Longer survival at the price of significantly increased toxicity, hospitalization and dependence may not be the preferred option for the majority of older cancer patients.

3. Obligatory inclusion of a minimum dataset for geriatric patients in registration trials and post-marketing trials.

One of the problems with older patients is that they form a very heterogeneous population, and the most important age-related parameters (functional status, comorbidity, social situation, QoL) are not routinely evaluated although they have major impact on prognosis and QoL. The EORTC workshop on clinical trial methodology in older cancer patients defined a consensus on a ‘minimum dataset’ for age-related topics that could be analyzed in all future senior-specific cancer trials. The EORTC ETF endorses this dataset and concept.

conclusions

In order to reach evidence-based clinical recommendations that apply to the treatment of the older cancer patients, we need to have meaningful clinical trials specifically for older patient populations. However, we believe clinical trial methodology in older cancer patients needs to be optimized. The identification of proper clinical outcomes and the validation of geriatric screening tools are needed for conducting sound and comparable clinical trials. Standardization of assessment and of clinical study report should be proposed to facilitate intertrial comparisons of results. This work will hopefully lead to the identification of more appropriate treatment strategies for senior cancer patients and will allow a tailored treatment approach. Adequate information on optimal treatment strategies for the general older population will permit oncologists to offer properly tested therapies to older cancer patients. It will save these patients not only from undertreatment but also from overtreatment by selecting patients who are suitable for therapy while sparing toxicity to others who are not likely to benefit from treatment.

Focusing on improvement of cancer treatment in older patients, this workshop reached the following conclusions:

- The participants of the workshop agreed on the use of a minimum dataset for the assessment of global health status and functional status in older cancer patients. This dataset will consist of the following:
  - G8 questionnaire,
  - IADL questionnaire,
  - CCI and
  - data about social situation

- The panel had three recommendations for designing and reporting clinical trials in the future:
  - obligatory reporting of age-related subgroup analysis (with a preplanned analysis),
  - obligatory post-marketing studies in vulnerable and frail older patients and
  - obligatory inclusion of a minimum dataset for senior adult patients in registration trials and post-marketing trials.

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