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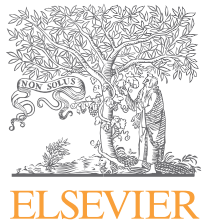

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# The EORTC Cancer in the Elderly Task Force, a Protostar for EORTC's future

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ABSTRACT

The EORTC Cancer in the Elderly Task Force (ETF) aims to develop, conduct, coordinate and stimulate research on elderly patients with cancer. Towards this goal, the ETF has established close interactions with disease-oriented EORTC groups by having representatives from most of these groups attend the ETF meetings. In addition, the ETF reviews every new protocol for elderly-specific questions within the protocol review process of the EORTC aiming to reduce ageism within study protocols. Since 2006, the ETF decided to focus on three aspects: open a discussion on specific methodology for clinical trials in the older population; create a common language for describing heterogeneity between older individuals, the EORTC minimal dataset for geriatric assessment in older cancer patients; and develop specific clinical trials in the older population. This article reports the achievements of the ETF in these three domains and discusses its future strategies.



## 1. 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. 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 underrepresentation of these patients in prospective clinical trials.

Geriatric oncology is a relatively recent field which probably dates to the early 1980's.[1] The European Organization for Research and Treatment of Cancer (EORTC) has currently defined senior adult oncology as one of its priorities and has established a Cancer in the Elderly Task Force (ETF). The ETF is one of

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the youngest research groups of the EORTC, and was officially established in 1992 under the name of 'EORTC Neoplasia in the Elderly Study Group' with Silvio Monfardini acting as the first chair. However, before this date there were initiatives led by EORTC members, among whom Ian Fentiman deserves to be mentioned with respect to his editorial on why older cancer patients are not receiving the therapy they need.[2] This was followed in October 1990 by a joint symposium with the United States National Cancer Institute organized by Monfardini and Chabner, where problems identified in elderly cancer trials were discussed. This resulted in a consensus paper with defined goals which remain relevant 20 years later.[3,4] Within the EORTC disease-oriented groups, a few clinical trials directed towards the older population were set up,[5–9] but there was no consistent global approach towards older cancer patients. The ETF initially had an advisory function towards the disease-oriented groups. Subsequent ETF Chairs were, respectively, Matti Aapro, Ulrich Wedding, and presently Hans Wildiers.

Currently, the ETF consists of 75 members and meets physically at least twice a year. The ETF aims for close interaction with disease-oriented EORTC groups by having representatives from most of these groups attend the ETF meetings. In 2006, the EORTC and the ETF decided to focus on three aspects: (1) open a discussion on specific methodology for clinical trials in the older population; (2) create a common language for describing heterogeneity between older individuals (both in older cancer patient specific trials and in general population trials); and (3) development of specific clinical trials in the older population.

In addition the ETF reviews every new protocol for elderly-specific questions within the protocol review process of the EORTC. With this approach ageism within study protocols is reduced.

We report here on the achievements of the ETF in these three domains and on future perspectives.

## 2. Development of specific methodology for clinical trials in the older cancer patients

Old age has often been perceived as a 'contraindication' for drug and treatment strategy development. In older patients comorbidity is often present. Certainly in unfit elderly, there is generally a decreased tolerance of therapy with higher risk of 'toxic deaths', and (sometimes unrelated) serious adverse events that can harm early drug development significantly. This contrasts with the fact that the majority of cancer patients are 'old'. Drugs and other treatments are thus generally developed in 'healthy young patients' (and a few fit older patients) but only administered to 'less healthy older patients' following registration.

An important concept is the fact that fit older patients can often tolerate and receive identical treatments as younger patients. On the other hand, vulnerable and frail patients have decreased capacity to tolerate treatments, and cannot receive identical treatments as younger patients in many oncological settings (e.g. high-dose cisplatin or anthracycline; concomitant radiochemotherapy; major surgery). If one designs clinical trials in older patients, the question often arises what would be the appropriate control arm. If one would take the 'standard treatment as in younger' as standard arm, this would probably bias the study towards dominant inclusion of fit older patients only who would be expected to tolerate standard therapy. If one would take 'less toxic treatments' as control arm, it could be argued that these are not really standard arms, and that the more fit patients might be 'undertreated'. It is quite difficult to escape from this "Catch 22" situation.

The ETF believes that older cancer patients provide specific opportunities for drug and treatment development. Specific drugs/regimens or study designs can be investigated in older patients that would not be possible/acceptable in the 'younger population'. Examples are: (1) monotherapy of new drugs can be acceptable in an early stage in older patients; (2) since there is no real standard therapy for (unfit) older patients in general, any new drug/combination with good safety profile and improved efficacy compared to 'one of the possible standard therapies' might become a new standard of care; (3) placebo arms without 'active' therapy can be more often acceptable in older patients. So there are big opportunities for drug development in the older population. Since the majority of cancer patients are old, there is a huge potential market for new drugs and strategies, and at present there is much less competition in 'older' patients than in younger patients (for instance: in HER2-positive breast cancer there are a multitude of upcoming drugs, but to date none of them has been studied specifically in unfit older individuals).

An important aspect is that new drugs and treatment strategies in older individuals should have limited toxicity; Quality of life (QoL) is important for cancer patients in general, but even much more for older individuals! If a therapy is too toxic and decreases QoL in a significant proportion of older patients, many would probably not choose such a treatment if they knew the pros and cons before deciding.

The first important achievement of the ETF is the development of specific methodology for clinical trials in the older cancer population. Two papers regarding standardization and unmet needs of clinical trials in older population were published in 2010.

The first publication was an EORTC Elderly Task Force Position Paper[10]: Approach to the Older Cancer Patient, published in *European Journal of Cancer*. The purpose of this paper was 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.

For the second, the EORTC ETF organized a workshop on clinical trial methodology in older individuals which was held at EORTC Headquarters in December 2009. A summary of this international multidisciplinary meetings is published in *Annals of Oncology*.[11] Focusing on improvement of cancer treatment in older patients, this workshop reached the following conclusions:

- Besides the "classical" efficacy end-points (overall survival, time to tumor progression, progression-free survival) cancer clinical trials in older patients should have an assessment of the impact of treatment on QoL, functional status and independence of the patient, key issues rated as priority by older cancer and non-cancer patients. These issues could be incorporated either as co-primary end-points or as composite end-points (in combination with efficacy end-points).
- The participants of the workshop agreed on the use of a Minimum Data Set for the assessment of global health status and functional status in older cancer patients (see below).
- The panel had three recommendations for designing and reporting clinical trials in the future:
  (1) Obligatory reporting of age related subgroup analysis (with a preplanned analysis).
  (2) Obligatory post marketing studies in vulnerable and frail older patients.
  (3) Obligatory inclusion of a minimum 'geriatric' data set for senior adult patients in registration trials and post-marketing trials.

The ETF will continue with this process and try to establish a worldwide dialogue on this topic with the goal of combining efforts and using comparable strategies in different parts of the world (allowing cross-trial comparisons). A second ETF multidisciplinary workshop with European and now also American representatives on clinical trial methodology will be held on 03 November 2011 during the SIOG (Société Internationale d'Oncologie Gériatrique) conference in Paris.

Awareness at the level of regulatory bodies is a key element in the development of more 'elderly directed' clinical trial methodology in the frail and vulnerable patients. The current chairman, Hans Wildiers, has recently been appointed as member of the EMA GEG (European Medicine Agency Geriatric Expert Group), where a strategy for better investigation of drugs in the older population will be on the agenda.

## 3. EORTC minimal dataset for geriatric assessment in older cancer patients

Over the last few years there has been a great deal of interest in the development of objective assessment tools to measure the "fitness" of older patients with cancer which may be used to enhance management decisions. Much of the research in this area has centered around the development of "Comprehensive Geriatric Assessments" which aims to describe the characteristics of a patient in a number of domains (such as functional status, co-morbidities, nutrition). However different groups with an interest in geriatric oncology have proposed different formats of the so-called Comprehensive Geriatric Assessment, meaning that it will be difficult to compare data and to apply findings to practices at a local level.

In response to this the EORTC ETF has established a standardized Elderly Minimal Dataset (MinDS) with the purpose of harmonizing the collection of data relevant to older patients and to enable cross-study/practice comparisons in the future. It was emphasized that the dataset does not need to be restrictive nor comprehensive but rather should form the backbone upon which individual investigators could add assessment tools pertinent to the particular study or local specific interests. It is also anticipated that this dataset will evolve over time with addition, removal, or refinement of tools as more data become available. A key aspect of the dataset is that it includes instructions for completion of the tools as there are some controversies in this area.

The MinDS includes four elements: Charlson Co-morbidity Index (CCI), G8 Geriatric Assessment Screening Tool, Instrumental Activities of Daily Living (IADL), and Social Situation. It is published (as an appendix) in the *Annals of Oncology* paper mentioned above.[11] The G8 is a geriatric screening tool initially developed and studied in France aiming to identify which patients require a full geriatric assessment.[12] The Oncodage study, a large multicenter French study, has prospectively validated the G8 with optimal cutoff at 14 (on a total score of 17) and is currently the only prospectively validated geriatric screening tool in oncological patients (submitted for publication). Detailed information on the G8 and other evaluation instruments can be found at http://siog.org/

## 4. Development of clinical trials in the older population

A few EORTC disease-oriented groups were pioneers in performing trials in older patients in the 1990's. The EORTC Lymphoma Group had innovative trials including a substantial number of frail elderly patients.[6,7] The EORTC Breast Cancer Group performed a randomized trial in older patients with early breast cancer comparing surgery with or without tamoxifen.[8] In 2002 an ETF working party concluded after review of existing data that for some specific cancers, dose intensification with the use of G-CSF improved survival in older cancer patients.[9] Despite these efforts, older patients have

generally been under-represented in clinical cancer trials, meaning that there is very limited evidence for the treatment of the population of patients in whom cancer is most prevalent. [13,14]

In order to directly address this problem the ETF has developed a number of clinical study proposals which have been submitted to the EORTC protocol review committee (PRC). It is not easy to find financing for clinical trials in older cancer patients, but the first trial of the ETF has obtained PRC approval in early 2011, and the trial is expected to open and recruit in the coming months. This study in colorectal cancer (EORTC 40085–75083) is a phase III randomized trial of 5-FU + cetuximab *versus* 5-FU alone in "unfit/frail" patients with metastatic colorectal cancer and wild-type k-ras status. Frailty or unfitness is defined as an age of 80 or over, or lower age (70–80) but with functional limitations or significant co-morbidities. The trial will be performed together with the EORTC Gastrointestinal Tract Cancer Group. The main objective is to determine if these patients derive benefit in terms of progression-free survival from a regimen consisting of chemotherapy plus a biological agent with limited toxicity. Accrual of 228 patients (136 k-ras wild type) is required. Other proposals in breast cancer and lung cancer are currently in advanced stage of development.

Within the framework of these trials, the ETF is planning to start a central biobank for peripheral blood to study potential ageing biomarkers. Given the paucity of large clinical trials currently running in the older population, it is of crucial importance to create a European biobank of biological samples which can be used for future research projects. In a first step this biobank will involve the collection and storage of blood samples. Ageing markers of interest are: telomere Length, expression of p16 in peripheral leukocytes, circulating IL-6, TNF-$\alpha$ and IL-10, CMV IgG and IgM and SNP's in FOXO3A and other ageing related genes. A template protocol for biobanking has been established that can be built into different clinical trial protocols. An FP7 grant on this topic has been submitted in October 2011 for this purpose.

The ETF has also collaborated with the EORTC Quality of Life Group in the development of tool specifically for older cancer patients, the QLQ-ELD15 scale. [15] This QoL scale will also be integrated in future older cancer patient studies. The ETF has also published guidelines on the treatment of lung cancer [16] and colorectal cancer [17] in older individuals.

The EORTC Clinical Research Groups are starting to see the added value of the ETF and its program of specific older cancer trials. Integration of the available elderly tools for an elderly subgroup in their general population studies is more often taken into consideration.

## 5. Conflict of interest statement

Hans Wildiers, Etienne Brain, Alistair Ring, Lazzaro Repetto, Silvio Monfardini, and Bjorn Penninckx, declare no conflicts of interest. Pierre Soubeyran consults for Roche, Janssen, Mundipharma, Celgene, Chugai and Hospira. Ulrich Wedding received lecture honoraria from Amgen, Sanofi, Janssen-Cilag, Novartis, and Roche, is on advisory boards for Roche, Shire, Fresenius Biotech, and Janssen-Cilag, and receives research support from Janssen-Cilag. Matti Aapro is consultant for and received honoraria from Celgene, Roche, Sandoz, Novartis, Pfizer, and Pierre Fabre, and received honoraria from Sanofi.

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