Never Too Old? Age Should Not Be a Barrier to Enrollment in Cancer Clinical Trials

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ABSTRACT

Throughout Europe and the U.S., over 60% of the total incidence of cancer occurs in the elderly (≥65 years) population, a patient group that requires particular consideration when making treatment decisions due to a number of factors. Despite this, elderly patients are generally under-represented in clinical trials such that study data should be interpreted with caution because results in younger cancer patients may not always extrapolate to the typical elderly cancer patient.

Reports suggest that elderly cancer patients represent around 22% of patients enrolled in phase II clinical studies. Barriers to the accrual of elderly patients to clinical trials include lack of appropriate trials, high burden of comorbidity, study-imposed restrictions, and attitudes of physicians. There is a belief that elderly patients may be unable to tolerate various cancer therapies, which may result in this patient population being excluded from prospective trials. However, clinical data demonstrate that age alone is not a sufficient reason to withhold treatment.

Lack of clinical trial data and the associated lack of evidence-based guidelines for elderly patients mean physicians have little to guide them, with the result that patients may not receive the optimal therapy. As clinical trials are the primary method of evaluating the efficacy and safety of adjuvant and palliative cancer therapies, trials that specifically target the elderly cancer patient are required to adequately assess the risks and benefits of treatment in this vulnerable population. This review
aims to assess the clinical reality and clinical trial age mismatch to evaluate implications for elderly cancer patients and to identify how this situation may be addressed. Possible reasons for the disparity, and the resulting clinical consequences, are also considered. *The Oncologist* 2005;10:198–204

**INTRODUCTION**

In Europe and the U.S., over 60% of new cancer cases and over 70% of cancer mortalities occur in elderly people (often defined for regulatory purposes as those aged 65 years or older) (Table 1) [1–4]. There is much variation in what is considered elderly, and this is based on chronological rather than physiological age. However, physiological age is a better predictor of patient health status and should, therefore, be used as an indicator of who is elderly. For example, in studies of the treatment of acute myeloid leukemia (AML), patients over 60 are considered elderly because the prevalence of multidrug-resistant protein increases after the age of 60 years, while elderly is classed as 70 years of age or older in patients with solid tumors [5]. Since the biology of tumors may differ with age (as indicated for AML), age can be a prognostic factor for disease outcome; however, treatment decisions may also affect disease outcome. As a classic example, survival in elderly patients with lymphoma is compromised by the decision to not treat with standard chemotherapy because of an expected poor tolerance, which could be overcome with appropriate measures, as discussed later.

Elderly patients are generally under-represented in clinical trials; only about 22% of patients are over 65 years of age [6–9], and only 8%–13% are over 70 [6, 9]. This contrasts with the composition of the U.S. cancer population, in which 63% of patients are older than 65 years of age and 47% are over 70 years old. In a study by Hutchins et al. [6], this difference was apparent for all types of cancer analyzed (including breast cancer, colorectal cancer, myeloma, pancreatic cancer, bladder cancer, and leukemia) with the exception of lymphoma (Fig. 1). The problem of under-representation of the elderly in clinical trials also applies to supportive therapies. Yee et al. [8] found that only 21% of participants in National Cancer Institute of Canada Clinical Trials Group supportive care trials were elderly. Thus, clinical trials have rarely been representative of typical cancer patients.

The results from clinical trials in younger patients are not directly applicable to the treatment of the elderly. Younger cancer patients comprise a comparatively homogenous population of otherwise fit individuals. Conversely, the diverse effects of aging on organ function and the variety of possible comorbid diseases result in a heterogenous elderly population. Pharmacokinetic differences between young and elderly patients, and indeed among elderly patients, could result in considerable variability in the efficacy and safety of cancer treatments. This may be particularly pertinent for oral therapies, which could have diverse bioavailabilities depending on variability in gastrointestinal absorption and first-pass metabolism, which is common among the elderly with declining organ function. Additionally, drugs requiring activation by hepatic enzymes may be less effective in elderly patients with diminished hepatic function. Furthermore, without performing the necessary studies, one cannot be certain that the end points used to measure outcomes in younger patients are appropriate to the elderly. The impact of chemotherapy on daily functioning during treatment, or its long-term impact on comorbidities, may be more important than overall survival in many of these patients.

These observations raise several questions, including: Why are clinical trial populations not representative of clinical reality? Should elderly patients be treated differently from younger patients? And how can we optimize treatment in the elderly? This review attempts to answer some of these questions.

**WHY THE MISMATCH?**

There are several possible reasons why relatively few elderly patients are enrolled into clinical trials. These include:

- trial exclusion criteria that filter out older patients.
- the reluctance of doctors to put older patients forward for entry into clinical trials.

### Table 1. Crude incidence of death for all cancers in young (<65 years) and elderly (≥65 years) patients per 100,000 population in Europe and the U.S. in 1998. Adapted with permission from the WHO Cancer Mortality Database [1].

<table>
<thead>
<tr>
<th>Country</th>
<th>≥65 years</th>
<th>&lt;65 years</th>
<th>% ≥65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>85.30</td>
<td>1,169.95</td>
<td>70.4</td>
</tr>
<tr>
<td>Germany</td>
<td>90.60</td>
<td>1,221.55</td>
<td>70.5</td>
</tr>
<tr>
<td>Greece</td>
<td>70.75</td>
<td>957.35</td>
<td>72.3</td>
</tr>
<tr>
<td>Hungary</td>
<td>150.95</td>
<td>1,519.15</td>
<td>61.2</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>78.05</td>
<td>1,241.35</td>
<td>71.4</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>77.60</td>
<td>1,339.40</td>
<td>71.8</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>106.75</td>
<td>1,008.60</td>
<td>53.8</td>
</tr>
<tr>
<td>Spain</td>
<td>76.25</td>
<td>1,075.70</td>
<td>71.9</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>76.15</td>
<td>1,305.90</td>
<td>75.4</td>
</tr>
<tr>
<td>United States</td>
<td>66.70</td>
<td>1,159.90</td>
<td>70.9</td>
</tr>
</tbody>
</table>
Stringent exclusion criteria can make elderly patients ineligible on several counts: clinical trials may (often arbitrarily) include only patients aged 18–65 or 70 years; elderly patients often have comorbidities; elderly patients may be taking drugs that might interact with the investigational drug; elderly patients may have declining organ function or cognitive impairment.

COMORBIDITIES
Comorbidity as an exclusion criterion will undoubtedly result in a large proportion of elderly patients being ineligible for clinical trials. The use of comorbidity evaluation scales, such as the Cumulative Illness Rating Scale-Geriatric or the Charlson scale, enables the assessment of the potential impact of comorbidities on patient outcome, by considering both the number of comorbidities and the effect they have on the patient. It should be noted, however, that the type of comorbidity may have more of an impact on therapy outcome than the score for a particular condition. For example, the presence of severe coxarthrosis, although having a high score on the evaluation scale, will not affect chemotherapy performance as much as the presence of cardiac heart failure. Thus, such scales should be viewed as predictors of survival but not be used globally to render patients ineligible.

Elderly patients have an average of five coexisting medical conditions [10]. In a survey of 3,841 women aged 65–101 years in Baltimore, MD, 81% reported two or more chronic conditions and 18% reported five or more [11]. The most common conditions were reported to be cardiovascular (Table 2) [12]. Due to the under-representation of elderly patients in clinical trials, it is not known to what extent the results of trials apply to this subgroup [13]. Increasing enrollment of elderly patients into clinical trials will provide physicians with a better understanding of appropriate therapies for this patient population [14]. However, comorbidity need not be a barrier to inclusion: studies in elderly patients with high incidences of comorbidities have been completed successfully [12].

Figure 1. Percentage of elderly patients (aged over 65 years) enrolled in Southwest Oncology Group (SWOG) trials (1993–1996) compared with the percentage of elderly patients in the U.S. population of individuals diagnosed with the specific cancer. Reproduced with permission from Hutchins et al. [6].

Elderly patients (%)

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>60.3</td>
</tr>
<tr>
<td>Respiratory</td>
<td>35.6</td>
</tr>
<tr>
<td>Digestive/hepatobiliary</td>
<td>31.6</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>26.6</td>
</tr>
<tr>
<td>Osteoarticular</td>
<td>21.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11.3</td>
</tr>
<tr>
<td>Neurological/psychiatric</td>
<td>6.0</td>
</tr>
</tbody>
</table>
MEDICATIONS AND DRUG—DRUG INTERACTIONS
Hand in hand with a high incidence of comorbidities comes polypharmacy and the risk for drug—drug interactions. Around 80% of people older than 65 years take one or more prescription medications on a daily basis, with most taking two or more [15]. In one study, nursing home residents were shown to use an average of six different medications daily, with over 20% using 10 or more [16], and a recent study reported that patients on an oncology ward were receiving a median of eight drugs (range 1–20) [17]. Not surprisingly, the risk for drug—drug interactions increases with the number of medications being taken [18], and patients taking five different agents have been estimated to have a 50% chance of an interaction occurring, rising to 100% with seven or more drugs [18]. A recent study on 135 elderly cancer patients receiving five or more medications reported 30 cases of dangerous drug—drug interactions [19]. Nevertheless, polypharmacy need not be a barrier to entry into clinical trials. It may be possible to rationalize a patient’s medications to reduce the numbers taken and/or to change those most likely to interact with the study drug. Potential interactions could be evaluated by pharmacokinetic analysis. A recent example relates to elderly patients receiving weekly docetaxel (Taxotere®; Aventis Pharmaceuticals Inc., Bridgewater, NJ, http://www.aventispharma-us.com) therapy. The authors showed a wide variation in the area under the plasma drug concentration-time curve (AUC) in patients aged 58–80 years. In that study, two of the three patients with the highest AUCs experienced the most significant toxicities [20].

RENAL AND HEPATIC IMPAIRMENT
Patients with poor renal or hepatic function are often excluded from clinical trials, which results in many elderly patients being excluded. Declining renal function is an important contributor to drug toxicity in the elderly [21]. It is not, however, a reason to withhold therapy, but these patients should have their treatment adapted. A study by Gelman and Taylor [22] suggested that the effectiveness of chemotherapy with cyclophosphamide, methotrexate, and fluorouracil (CMF) was not compromised in women aged 65 years or older with metastatic breast cancer when the doses of chemotherapy were modified according to renal function. Therefore, if appropriate dose adjustments are made to account for expected pharmacokinetic changes, elderly patients could be included, perhaps forming a substudy to reveal important insights into the use of the study drug in elderly patients.

CHEMOTHERAPY CLINICAL TRIALS
Elderly patients may not be put forward for entry into clinical trials by their doctors: there is a strong correlation between age and enrollment fraction [23]. Benson et al. [24] found, in a survey of oncologists, that 50% declared patients unsuitable for clinical trials on the basis of age alone. A Cancer and Leukemia Group B (CALGB) study by Kemeny et al. [25] found that fewer eligible elderly patients were offered the trial compared with younger patients (34% versus 68%, respectively; \( p = .0004 \)). A survey of 156 participating physicians (85% oncologists) found that perceived barriers to accrual of older patients included the presence of comorbid conditions that may affect response to treatment (16%), the likelihood of poor compliance (16%), treatment toxicity (14%), and exclusion due to eligibility criteria (15%) [26]. Yee et al. [8] reported similar results, in that the main reasons for physicians’ reluctance to enroll elderly patients onto clinical trials in their study were comorbidities (28%), concern about toxicity (50%), and patient/family preferences (25%). In addition, doctors (and patients) may assume that older patients are less likely to benefit from entry into clinical trials. This may be because of a perception that the treatments may be “too toxic” or experimental to be appropriate for elderly patients. This is a particular problem in adjuvant trials, perhaps because the slower recovery of older patients from surgery is considered to make them too frail to participate [8]. Nonetheless, successful adjuvant trials have been conducted in elderly patients with breast [27, 28] and colorectal [29, 30] cancer, among others. Further, several studies in colorectal cancer, where diagnosis often does not occur until the patient is 70 years old and the median age of patients in trials is 65 years [5], have shown similar efficacy and safety in elderly and younger cancer patients with various chemotherapy regimens [13, 30]. Therefore, to improve the accrual of elderly patients to trials, patient and doctor education is paramount: personnel should be available to explain the trial to the patient, and educational materials should be provided to physicians concerning treatment toxicities in the elderly [26].

A further barrier to participation may be the perceptions of the patients about the toxicity of cancer treatments. They may remember “old-fashioned” chemotherapy and radiotherapy regimens coupled with few and ineffective support measures that resulted in severe side effects. However, Monfardini et al. [9] found that, after adjustment for previous chemotherapy, there was no difference in toxicity between younger and older patients (with the exception of oral toxicity) among patients with solid tumors participating in single-agent drug-development trials. In the CALGB study, when elderly patients were offered participation in a clinical trial, an equal proportion of older and younger subjects accepted [25]. Furthermore, a survey of cancer patients aged 70 years and older found a large proportion of patients expressed a strong desire to receive strong chemotherapy
treatments [31]. Therefore, the principal barriers to accruing older patients appear to be due to physician-related rather than patient-related issues [25], indicating that physician education may be the key to enrollment of higher numbers of elderly patients into clinical trials.

**Supportive Care Clinical Trials**

Due to the effects of physiological aging on declining organ function, including hematopoietic stem cell reserve capacity, cytotoxic therapy in the elderly is more likely to result in declines in functional capacity. Therefore, these elderly patients require therapeutic strategies adapted to their individual risk profile and a more intensive supportive care regimen.

For example, the under-representation of elderly patients in antiemetic trials may perhaps reflect the observation that elderly patients are less likely to suffer nausea and vomiting than younger patients [32]. Yet, antiemetic therapy remains extremely important in elderly patients because the consequences of severe emesis are likely to be more serious than in younger patients. Protracted nausea and vomiting can result in life-threatening dehydration and electrolyte imbalance, which is particularly important in patients who may already have cardiovascular problems [33]. In addition, older patients tend to have a decreased thirst reflex and so are more at risk of dehydration than younger patients. Prolonged emesis may also damage the esophagus [33]. Nevertheless, it appears that many patients are not receiving adequate antiemetic therapy [34]. The 5-HT₃-receptor antagonists are currently the most commonly used antiemetic agents and are recommended by antiemetic guidelines as prophylaxis for moderately or highly emetogenic chemotherapy or radiotherapy regimens [35]. However, these guidelines neither provide recommendations specific to the elderly nor differentiate among the different 5-HT₃-receptor antagonists. Differences do exist among these agents, and a description of these differences would aid physicians in choosing the best agent to use in each patient.

The cardiovascular side-effect profile of antiemetics, which has been studied in fit younger patients, is one of the most important considerations in the elderly population in which 60% have cardiovascular comorbidities [12]. Therefore, the antiemetic that poses the lowest cardiovascular risk should be chosen, as some 5-HT₃-receptor antagonists (e.g. dolasetron [Anzemet®; Aventis Pharmaceuticals Inc.], tropisetron [Navoban®; Novartis International AG, Basel, Switzerland, http://www.novartis.com], and palonosetron [Aloxi®; MGI Pharma, Inc., Bloomington, MN, http://www.mgipharma.com]) carry cardiovascular warnings or precautions in their labeling. QTc interval prolongation can be associated with potentially fatal arrhythmias (torsades de pointes) [36], and cumulative cardiovascular insults in patients may precipitate this condition.

**Never Too Old?**

Despite the perceived barriers to including elderly patients in clinical trials, there are actually few data to support excluding them. As mentioned above, studies in elderly patients (those meeting study criteria, and thus generally fit) have shown them to suffer no more toxicity than, and to obtain efficacy equal to, their younger counterparts [5, 9, 27–30, 37]. Even when elderly patients are more susceptible to toxicity, they can gain benefit from chemotherapy regimens [38]. Further, the enormous advances in supportive treatments over recent years enable adverse effects to be minimized.

It may not be possible to overcome the barriers mentioned above in some patients, including the most elderly and frail patients or those who may not be compliant with therapy due to cognitive impairment or depression. However, there is no reason why a much greater proportion of the over 65-year olds should not be included in clinical trials in the future. Investigators are exploring practical means of improving the accrual of older patients into clinical trials. As mentioned previously, one possible intervention is physician education. This is likely to necessitate a large, sustained effort from the research community, as punctuated interventions appear to have a limited impact [39]. The most promising means of improving accrual may be broadening functional and comorbidity inclusion criteria, as shown by modelization studies [40]. Stratification and modelization methods could be developed to allow the inclusion of patients with larger functional and comorbidity diversity into clinical trials, while preserving the reliability of the effectiveness results. Additionally, coinciding with the drug development process, phase II clinical trials specifically targeted to older individuals to demonstrate evidence of efficacy and safety to determine pharmacokinetic variables in the elderly would be an invaluable means of addressing the issue of age. Furthermore, the analysis of subgroups of elderly patients in these trials would provide indications for how treatments could be more accurately customized to the individual.

An example of the need for specific trials is in the area of lymphomas. The elderly are at higher risk of bone marrow toxicity, and thus, numerous clinical trials have targeted these patients to investigate alternative treatment strategies. With the implementation of appropriate pretreatment strategies, including the use of growth factors [41], there is no valid reason why many elderly patients should not be treated with the most effective therapies available and enrolled in clinical trials. The application of a comprehensive geriatric assessment prior to the treatment of
elderly patients would enable a detailed assessment of their suitability for treatment and highlight any areas of concern that may require closer attention before or during treatment. Interestingly, despite the time and resources necessary for performing a comprehensive geriatric assessment, it has been shown that this does not increase the total treatment cost [42]. Therefore, a detailed understanding of the status and needs of the patient seems to result in the avoidance of subsequent treatment costs.

CONCLUSIONS
Clinical trials are considered the most reliable means of evaluating the efficacy and safety of new drugs. They should, therefore, endeavor to use populations that reflect clinical reality. Unfortunately, this has not been the case in cancer trials, in which the proportion of elderly patients included in trials is significantly lower than the proportion of elderly patients with cancer. This mismatch occurs across the board, affecting trials of primary and adjuvant chemotherapy agents and supportive care agents. This has resulted in no evidence-based guidelines being available for treatment of elderly patients. It is time, therefore, for clinical trials specifically aimed at elderly cancer patients, which address the issues of polypharmacy and comorbidity in these patients, to be performed. Age-related factors that must be considered when prescribing cancer treatment and supportive care include organ function, comorbidity, polypharmacy, and cognitive function.

- Assessments of renal and hepatic functions are critical to ensure that necessary dose adjustments can be made for agents whose pharmacokinetics are affected by renal or hepatic impairment [43].
- Assessments of bone marrow reserves and peripheral and central neural functions are important to avoid excessive treatment-related adverse effects [43].
- Assessments of comorbid conditions will allow an effective therapy that will not add significantly to the patient’s disease burden to be chosen.
- Chosen therapies should have a low underlying potential for drug–drug interactions.
- If cognitive function is reduced, and to aid compliance, simple drug regimens should be used.

Without the information available from clinical trials to enable more individual tailoring of drug prescription in elderly patients, the physician must attempt to choose therapies that have a low potential for drug–drug interactions, with no warnings for use in patients with common comorbid conditions. In addition, treatments should involve convenient, simple dosing regimens that are well tolerated and consider the unique needs of the elderly cancer patient.

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REFERENCES