Should We Preclude Phase 1 Clinical Trials From Enrolling Elderly Individuals?

A review by Mahipal and colleagues of phase 1 trial enrollment among patients 65 years and older at the H. Lee Moffitt Cancer Center & Research Institute in Tampa, Florida, appears in this issue of Cancer Control. The study provides a recent and extensive — albeit not exclusive — exploration of the subject, encompassing 39 clinical trials (31 no-transplantation and 8 transplantation studies) conducted within a 10-year period involving 1,162 study participants, 380 of whom were between the ages of 65 and 91 years.

In their research, Mahipal and coauthors confirmed previous findings, including that:

- The mean age of individuals involved in phase 1 trials is approximately 10 years younger than the mean age of the general cancer population.
- Age between 65 and 75 years does not appear to affect the effectiveness or toxicity of drugs used in the no-transplantation setting.

In addition, they reported that the risk of toxicity increases with age in the transplantation setting. This finding is new but not unexpected because age is a recognized risk factor for toxicity and treatment-related mortality in patients receiving bone marrow transplantation.

The results of the review by Mahipal and colleagues are robust because they are based on the experience of 1 institution, which keeps carefully recorded data relating to outcomes and toxicities. The Cancer Control editors decided to publish this contribution as a reminder that chronological age — at least up to the age of 75 years — should not represent an impediment for patients to enroll in phase 1 clinical trials.

Like all retrospective analyses of data, the review of Mahipal and coauthors has several limitations, many of which the authors have acknowledged, including an inadequate assessment of age-related prognostic factors (eg, function, polymorbidity) and, more generally, an under-representation of the older population. In addition, the authors did not include study participants enrolled in cooperative phase 1/2 trials.

However, an additional limitation not mentioned was a failure to account for polypharmacy that, by itself, could represent a risk factor for chemotherapy-related toxicity. Popa et al reported that the risk of chemotherapy-related toxicity was increased when the risks of potential drug interactions were present, even when such an interaction was not associated with chemotherapy agents. Drug interactions can typically be expected in any patient who takes at least 8 medications every day. Another limitation is the absence of data related to phase 1 studies of targeted therapy, which is posed to be the most promising form of cancer treatment in the next decade. Yet another limitation is that the authors stopped their review at the year 2007 because they wanted to limit their analysis to studies involving cytotoxic chemotherapy. Some readers may question whether these old data are still relevant to the evolving landscape of cancer treatment.

Despite these limitations, the Cancer Control editors elected to publish this study for 3 reasons: (1) reaffirm the importance of physiological — rather than chronological — age for the enrollment of older individuals in clinical trials of cancer chemotherapy, (2) discuss which provisions would render more meaningful results from clinical trials with elderly participants, and (3) address the discussion as to whether a number of positions in phase 1 trials should be reserved for older individuals.

Undoubtedly, targeted therapy has produced significant improvement in the prognoses of numerous malignancies, but predicting the demise of cytotoxic chemotherapy would be premature because this treatment modality currently represents the only curative treatment for germ cell tumors, some forms of lymphoma and leukemia, and a number of breast, colorectal, and pulmonary cancers. It is reasonable to expect that cytotoxic agents will be the main bulwark against the spread of cancers with complex genomic alterations that may vary from cell to cell. Thus, phase 1 trials of cytotoxic chemotherapy agents are still relevant to individuals of all ages. When these trials are conducted in patients of advancing age, a wealth of desirable information may help contextualize the effects of a new drug.

All clinical cancer trials in the elderly, including phase 1 trials, should provide an estimate of physiological age (ie, life expectancy and tolerance of stress). This estimate may be obtained from a comprehensive geriatric assessment validated for this purpose. A reconciled list of medications may be important so that toxicities and unsuspected drug interactions can
be accounted for and documented. Although the comprehensive geriatric assessment currently provides the most reliable assessment of physiological age, some laboratory assays may help such determination in the near future. Among the most promising are the so-called inflammatory index and the leukocyte telomeres length.\textsuperscript{13-15}

One may ask whether second or third malignancies should exclude patients from enrolling in a phase 1 clinical trial. In approximately 20\% of patients with cancer 70 years of age or older, a second primary malignancy will be present.\textsuperscript{16} In the majority of cases, the second neoplasm may be indolent (eg, localized prostate cancer, low-grade lymphoma) and may not compromise patient survival for several years. Therefore, in my opinion, it is difficult to justify excluding these patients from enrolling in either phase 1 or 2 clinical trials. As the US population continues to age, one may consider a change in the recruitment criteria for clinical trials so that they more realistically represent the demographics of patients with cancer. It is also desirable to examine the circumstances that may prevent older individuals from enrolling in phase 1 trials and to study how these barriers can be reversed.\textsuperscript{17} In addition to the increased prevalence of medical conditions that could potentially disqualify patients from trial participation, other barriers may include limited availability of transportation and health care professional and family prejudices.

Data are also needed related to the effects of phase 1 clinical trials in individuals 75 years of age or older. A single report of phase 1 studies collected data from 28 individuals aged 80 years and older, and found that, in this small patient population — the majority of whom was chemotherapy naive — dose-limiting toxicities were higher than in younger individuals.\textsuperscript{18} Likewise, Schwandt et al\textsuperscript{19} reported that dose-limiting toxicities increased with age in patients older than 70 years but remained within an acceptable threshold. These limited findings should make us question whether a chronological age threshold exists beyond which we can expect a reduction in dose-limiting toxicities in the majority of patients. For more than 20 years, health care professionals have advocated that physiological age should supersede chronological age in the care of older patients and in clinical trials of cancer treatment.\textsuperscript{12} While I still stand by this principle, I recognize that the prevalence of the so-called oldest old is ever increasing,\textsuperscript{20} so it is legitimate to ask whether chronological age accurately reflects a critical reduction of physiological reserve in the majority of individuals older than 85 years of age. Should we have phase 1 trials reserved for older participants? This question may sound more philosophical than practical. Personally, my position has been and continues to be that older individuals should not be excluded from phase 1 trials; however, at the same time, they should not receive special treatment. The goal of a phase 1 trial is to establish the maximum tolerated dose of a drug, and that is best accomplished without having to accommodate a special population such as the elderly. Thus, I would recommend that researchers reserve an adequate number of enrollment positions to individuals 70 years of age or older for phase 2 trials to establish how age may affect the pharmacology of a drug and whether a dose reduction may obtain similar results with less toxicity. One may argue that reserving a number of positions in phase 1 trials to older individuals, to those with a poor performance status, or those with significant comorbidity may produce a plethora of adverse events among the different populations and, thus, prevent the drug from misuse in clinical practice. I believe that the terms of the controversy should be exposed, but I doubt they can be solved in this context.

From time to time, the editors of Cancer Control publish studies with methodological flaws when the results of such studies are robust and important enough not to be ignored. I hope that the readership appreciates access to this information as well as the opportunity to discuss the important topics emerging from these studies.

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References


