The Role of Age on Dose-Limiting Toxicities in Phase I Dose-Escalation Trials


Abstract

**Purpose:** Elderly oncology patients are not enrolled in early-phase trials in proportion to the numbers of geriatric patients with cancer. There may be concern that elderly patients will not tolerate investigational agents as well as younger patients, resulting in a disproportionate number of dose-limiting toxicities (DLT). Recent single-institution studies provide conflicting data on the relationship between age and DLT.

**Experimental Design:** We retrospectively reviewed data about patients treated on single-agent, dose-escalation, phase I clinical trials sponsored by the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute. Patients’ dose levels were described as a percentage of maximum tolerated dose, the highest dose level at which <33% of patients had a DLT, or recommended phase II dose (RP2D). Mixed-effect logistic regression models were used to analyze relationships between the probability of a DLT and age and other explanatory variables.

**Results:** Increasing dose, increasing age, and worsening performance status (PS) were significantly related to an increased probability of a DLT in this model ($P < 0.05$). There was no association between dose level administered and age ($P = 0.57$).

**Conclusions:** This analysis of phase I dose-escalation trials, involving more than 500 patients older than 70 years of age, is the largest reported. As age and dose level increased and PS worsened, the probability of a DLT increased. Although increasing age was associated with occurrence of DLT, this risk remained within accepted thresholds of risk for phase I trials. There was no evidence of age bias on enrollment of patients on low or high dose levels. Clin Cancer Res; 20(18): 4768–75. ©2014 AACR.

Introduction

While more than 60% of all cancers and more than 70% of cancer-related deaths occur in the elderly, the enrollment of geriatric patients in clinical oncology trials is substantially lower and not reflective of the prevalence of cancer in the elderly (1–4). A review of NCI-sponsored clinical trial cooperative group studies reported a significant inverse relationship between age and enrollment fraction, with patients ages 30 to 64 years representing 3% of the general age-matched population, compared with 1.3% for patients ages 65 to 74 years and 0.5% for patients ages 75 or older (5). Only 20% of patients enrolled in FDA registration trials of investigational oncology agents were ≥70 years of age (6).

Overall response rates (OR) on phase I trials have been reported to be around 10% and drug-related toxic death rates have been reported to be less than 0.5% (7). Overall survival (OS) on phase I trials varies but has been reported to be, on average, more than 6 months; according to a retrospective review of patients ages ≥65 years who presented for consideration of phase I trial, patients who enrolled on phase I trials, when compared with those who did not, had longer OS (8). Because early oncology clinical trials study investigational agents before regulatory approval, the underrepresentation of elderly patients reflects reduced access of geriatric patients to new agents that may have tumor efficacy and may improve survival.

By definition, most phase I trials are designed to determine a recommended phase II dose (RP2D) and they have dose-escalation schemes usually until the occurrence of serious drug-related toxicities (SDRT). Inappropriately strict selection criteria, such as age bias contributing to low enrollment of elderly patients in phase I oncology clinical trials, may delay the detection of SDRTs, which may not be detected until the oncologic agent is administered to a more diverse population of patients reflective of the age-related prevalence of cancer. In a retrospective review of nonpediatric phase I oncology trials, 73% of phase I trials successfully predicted RP2D as the dose used in later phase trials; furthermore, there was a significant relationship between increasing number of patients in phase I trials and the ability to describe future clinically relevant toxicities (9). The study of outcomes of geriatric patients on phase I trials should yield important information on the use of investigational agents in this growing patient population.
Translational Relevance

More than 60% of all cancers occur in the elderly; however, the enrollment of geriatric patients in clinical oncology trials is substantially lower and not reflective of the prevalence of cancer in the elderly. We analyzed hematologic and solid tumor phase I dose-escalation trials involving more than 500 patients older than 70 years of age. Our model showed that as age and dose level increased and ECOG performance status worsened, the probability of a dose-limiting toxicity (DLT) increased; however, this risk remained within accepted thresholds for phase I trials. Our findings can be used to inform patients, patient families, and health professionals about the risks that geriatric patients, enrolled in phase I trials, have for developing drug-related adverse events. Advanced age, by itself, does not justify exclusion of older patients from phase I cancer trials.

Reasons for the low geriatric enrollment on clinical trials are unproven but may include an underlying fear of excess toxicity by elderly patients, their families, primary care physicians, and oncologists. Physicians may not inform elderly patients about trials because of their perception that elderly patients will not tolerate experimental agents or the procedures mandated by trials as well as younger patients (10). Several studies have shown that healthcare workers have concerns of SDRTs when treating elderly patients with breast cancer using full-dose chemotherapy; similarly, healthcare professionals may be particularly reticent to enroll such patients on phase I trials (11–13).

Studies of phase I trials have evaluated the effect of baseline patient characteristics on OS to create prognostic models. Investigators at Royal Marsden Hospital (RMH) identified elevated lactate dehydrogenase (LDH), decreased albumin, and >3 metastatic sites as negative predictors for OS (14, 15). Age, which was analyzed as a bivariate variable, <65 versus ≥65 years, was not determined to be an independent factor predictive of OS. Researchers at the University of Texas MD Anderson Cancer Center validated the RMH prognostic criteria for overall survival and in addition, found gastrointestinal tumor type, and ECOG performance status (PS) ≥1 to be independent predictors of shorter OS (16). In contradistinction, analysis of predictors of 90 day mortality demonstrated increased mortality in younger patients (17). However, these studies have been limited by analysis of relatively small numbers of geriatric patients, with median age 58 to 60.

Because appropriate inclusion of geriatric patients in phase I trials may more closely mirror the age demographics of a drug’s ultimate intended target population with cancer, evaluation of the effect of age on the occurrence of dose-limiting toxicities (DLT) is of interest. Prior single-institution studies evaluating the effect of age on the occurrence of DLTs in phase I trials have reported different findings. A retrospective analysis of phase I trials conducted at Centre Léon Bérard (18) evaluated 154 patients whose average age was 54 (range, 21–74) years and found that age >65 predicted for increased risk of toxicity (18). Gaddipati and colleagues (19) conducted a retrospective review of phase I patients enrolled at Case Comprehensive Cancer Center from years 1994 to 2009. Twenty-two patients ages ≥80 years who experienced DLTs were compared with 123 patients ages <80 years enrolled on the same dose level cohorts. The rate of DLTs in the first cycle was 18% for patients ages ≥80 compared with 6.5% of patients ages <80 years. LoConte and colleagues (20) reviewed 242 patient records of phase I participants enrolled at the University of Wisconsin and analyzed the relationship of patient factors to incidence of DLTs; they found that age was not a significant predictor of the risk of DLTs. Noteworthy, however, was that the average age was 57 years with only 7 patients older than 75 years of age. These studies, while important, were single-institution studies that may not have given an accurate picture of the relationship between age and DLT that could have been achieved by analyzing a larger database.

In this study, we focus on determining whether the probability of DLTs is higher in the elderly and evaluate the impact of other patient factors on the probability of DLTs. We conducted a multiinstitutional meta-analysis of the National Cancer Institute Cancer Therapeutics Evaluation Program (CTEP)–sponsored adult phase I dose-escalation trials to describe the distribution of age and other patient characteristics across dose levels (described as %MTD), i.e., the percentage of the highest dose level at which <33% of patients had a DLT; and analyzed the effect of age on DLTs while controlling for other risk factors. It was also of interest to determine whether older patients were systematically assigned to lower dose levels. Therefore, we analyzed whether there was a relationship between age and dose level to which patients were assigned.

Materials and Methods

Eligibility criteria

The study population consisted of adult patients, generally ≥18 years of age, who were enrolled on phase I oncology trials sponsored by CTEP from 1995 to 2011. CTEP-sponsored trials were conducted in North America and protocol-specific baseline and follow-up trial data were monitored and recorded. The trials analyzed had to fit two criteria: (i) dose-escalating single-agent trials (multiple drugs could be administered in a trial; however, only one was permitted to be dose-escalated); and (ii) trials in which MTD or RP2D was determined. The following trials were excluded from the analysis: (i) pediatric trials; (ii) trials with local, intratumoral therapy only; (iii) trials that were not complete or had been administratively closed early. All administered dose levels were defined as %MTD or RP2D. If the database was unclear about the MTD or RP2D, a literature review was conducted to provide this information.
Database source
CTEP is responsible for supporting North American clinical trials that involve investigational agents for which CTEP has an investigational new drug (IND). It receives trial data at regular intervals from investigators. Theradex Systems is responsible for phase I monitoring using the Clinical Trials Monitoring System (CTMS). Data are submitted for quality control and maintained in an Oracle database. Each institution participating in a CTEP-sponsored clinical trial is audited for quality assurance three times a year.

Trial characteristics
An initial interrogation of the CTEP database of NCI-sponsored clinical trials from 1995 to 2011 resulted in a total of 412 trials. We reviewed every protocol summary and trial history; trials were removed if they did not meet our criteria for analysis. Eighty-six trials were excluded because they lacked drug-escalation schemes, were primarily pediatric, or involved premalignant conditions; 77 trials were not completed or were still ongoing; 55 trials did not meet prespecified criteria of escalating only one agent on trial; and 32 trials lacked a clearly identified MTD or RP2D. There were a total of 162 phase I trials that met our criteria for analysis; 108 of these trials were single-agent studies, whereas 54 trials were multiagent with dose escalation of only one agent (Fig. 1).

Data acquisition and extraction
The following information about each trial was extracted from CTEP database: trial protocol number, dates trial was conducted, antineoplastic agent(s), investigational agents and number of patients enrolled. The following patient characteristics were obtained: baseline age; ECOG PS; hematologic and metabolic laboratory values, including complete blood count (CBC), electrolytes, renal and liver function tests, and LDH; prior history including the number of previous treatments; presence or absence of brain metastases; and number of metastatic sites. For each patient, the dose of the investigational agent administered, time on trial, and DLTs were obtained.

Statistical analysis
Mixed-effect logistic regression models were used to determine if there was a relationship between the probability of a DLT and age, dose, and other potentially explanatory variables (21). The explanatory variables examined were LDH, albumin, creatinine, bilirubin, alanine aminotransferase (ALT), white blood count (WBC), lymphocytes, platelets, absolute neutrophil count (ANC), number of metastases, and ECOG PS. These models included study as a random effect. Univariate mixed-effect logistic regression was used to determine the relationship between DLT and each variable. The explanatory variables were included in the univariate model in two ways, first as continuous variables and, then, with the values for each variable grouped into four categories according to the 25, 50, and 75 percentiles. Age and dose were left as continuous variables and we explored whether squared and cubic terms should be included in the model to allow for nonlinear effects of age and dose.

We performed a series of multivariate logistic regressions. Explanatory variables from the univariate logistic regression model with $P < 0.15$ were included in the multivariate

![Figure 1. CONSORT diagram of trial selections and patient exclusions.](image-url)
model. Similarly, squared, cubic, and interaction terms with $P<0.15$ were included in the multivariate model. We first ran a model with squared terms and then, if the squared terms met the inclusion criteria, we ran a model with cubic terms. Once the main effects model was determined, we analyzed the data for first-order interactions of age and dose and the explanatory variables that were included in the model.

We performed a $\chi^2$ test to see if there was an association between age and dose. For this analysis, age was grouped according to the following categories: less than 40, 40–59, 60–69, 70–79, and 80 and older. Dose levels were grouped according to the following categories: 33% or less of MTD, greater than 33% to 66% or less of MTD, greater than 66% to 100% of MTD. Twenty-two percent of patients were treated at dose levels between 66% and 100% of MTD. The probability of DLTs was increased with increasing dose level (%MTD). As ECOG PS worsened, there was an increased probability of DLT. Serum chemistry values and hematologic parameters did not meet our criteria for being included in the final analysis model.

### Results

#### Patient characteristics

There were 5,401 patients enrolled on 162 trials; 27% were 60–69 years of age, 16% were 70–79 years of age, and 2% were 80 years of age or older (Table 1). Patients over age 80 were represented in all eligible PS categories, including 13 patients ages 80 years or older with PS of 2. Fifty-two percent of patients were treated at dose levels between 66% and 100% of the MTD. Twenty-two percent of patients were treated at dose levels higher than the MTD. There was no evidence of an association between dose and age ($P = 0.57$). This suggests that there was no bias in entering patients, i.e., older patients did not seem to be systematically placed on lower dose levels.

There were 5,401 eligible patients from the studies that met the inclusion criteria; 2,496 patients had missing values on the covariates of interest in the final model and were excluded from the final analysis. The proportion of DLTs in the patients excluded and included in the analysis was 0.066 versus 0.085, respectively. The mean age in each group was 56.2 versus 57.3 years; and the mean dose levels were 95% and 97% of the MTD, respectively. It seems that the excluded group is similar to the included group based on the variables in the final model.

#### Univariate analysis

Baseline laboratory values, when analyzed by quartiles or as continuous variables, were not associated with DLT in univariate analyses (Table 2). For univariate logistic regression models of the explanatory variables, only age, PS and number of metastatic sites (both defined as a continuous measurement), and dose level met our criteria for including in the final model ($P = 0.023$ and $P = 0.107$, respectively).

#### Mixed-effect logistic regression model

There were 2,905 patients in this analysis (2,496 patients with missing PS and number of metastatic sites were omitted). The squared and cubed term for dose met the 0.15 level of significance. The first-order interaction terms between age, dose, and the explanatory variables did not meet the criteria to be included in the model. Increasing dose ($P < 0.001$), increasing age of patient ($P = 0.0058$), and poor baseline PS ($P = 0.047$) were significantly related to the probability of a DLT in this model (Table 3).

Table 4 and Fig. 2 show the relationship between the probability of a DLT and age, dose, and PS. As age increased, the probability of a DLT increased. For example, for a 40 year old patient who had one metastatic site and a PS of 0 and who received 33% of the MTD, the probability of a DLT was 0.011; had the patient been 85 years old, however, the probability of DLT would have been 0.023. Furthermore, as the dose of drug administered increased, the probability of DLT increased. Thus, for a 40 year old patient with a PS 0 and one metastatic site, the probability of a DLT was 0.011, 0.022, and 0.037 for dose levels 33%, 66%, and 100% of MTD. The probability of DLTs was increased with increasing age, worsening PS, and increasing dose levels (%MTD). As PS worsened, there was an increased probability of DLT. Serum chemistry values and hematologic parameters did not meet our criteria for being included in the final analysis model.

#### Discussion

In this study, we investigated the role of age in phase I trials by conducting a large multiinstitutional meta-analysis of CTEP-sponsored, adult, phase I, single-agent dose-escalation trials. Multivariate analysis of both constitutional and laboratory baseline patient characteristics identified increasing age, worsening PS, and increasing dose levels as independent factors predictive for increased risk of DLTs on phase I trials. By using mixed-effects modeling, we demonstrated that the increased probability of DLTs in elderly patients was 0.011; had the patient been 85 years old, however, the probability of DLT would have been 0.023. Furthermore, as the dose of drug administered increased, the probability of DLT increased. Thus, for a 40 year old patient with a PS 0 and one metastatic site, the probability of a DLT was 0.011, 0.022, and 0.037 for dose levels 33%, 66%, and 100% of MTD. The probability of DLTs was increased with increasing dose levels (%MTD). As PS worsened, there was an increased probability of DLT. Serum chemistry values and hematologic parameters did not meet our criteria for being included in the final analysis model.

### Table 1. Percentage of patients by age and dose

<table>
<thead>
<tr>
<th>Dose level (%MTD)</th>
<th>Age groups (y)</th>
<th>Number of patients</th>
<th>Proportion of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;33</td>
<td>(40–60)</td>
<td>(60–70)</td>
<td>(70–80)</td>
</tr>
<tr>
<td></td>
<td>Age groups (y)</td>
<td>Number of patients</td>
<td>Proportion of patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>556</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>(40–60)</td>
<td>2,438</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>(60–70)</td>
<td>1,481</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>(70–80)</td>
<td>836</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>&gt;80</td>
<td>90</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5,401</td>
<td></td>
</tr>
</tbody>
</table>
patients with ECOG PS equal or better than 2 remained below generally accepted patient safety thresholds of 33% risk of SDRT on phase I trials (22).

Unlike prior studies that evaluated for prognostic factors for OS of patients enrolled in phase I trials, we did not find that abnormal baseline chemistry or hematologic values were predictive for DLTs (14, 16, 23). This finding is consistent with other single-institution studies of phase I predictors of DLT that failed to show that baseline laboratory values predicted for DLTs (20). Molife and colleagues (24) evaluated 687 phase I patients at RMH and determined that worsening ECOG PS and increasing dose level predicted for increased risk of DLTs, whereas components of the RMH score prognostic for OS, including decreased albumin and elevated LDH, did not predict for DLTs. Furthermore, our analysis did not find characteristics consistent with increased tumor burden, such as number of metastatic sites or elevated LDH to be predictors of DLTs; this is consistent with factors that generally predict for SDRT in phase I trials (25).

Not surprisingly, baseline patient PS was identified by us as well as by others to be predictive of increased risk of DLTs and or decreased OS on phase I trials (26). Karnofsky and ECOG performance scales have been shown to correlate with some geriatric assessments (27). Possible geriatric evaluations performed in the trials were not captured in the phase I database and, thus, any additional assessments were unknown and could not be explored in this study. The extent to which oncology performance scales reflect the functional and physiologic status of geriatric oncology patients is a robust area of research in geriatric oncology; geriatric assessments may be equally or more important than PS in determining the risk of DLT in the elderly.

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Table 2. Percentage of DLTs in each percentile defined category for each explanatory variable (quartile value)

<table>
<thead>
<tr>
<th>Explanatory variable</th>
<th>0 to &lt;25 percentile (25 percentile)</th>
<th>25 to &lt;50 percentile (50 percentile)</th>
<th>50 to &lt;75 percentile (75 percentile)</th>
<th>75 to 100 percentile</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDH</td>
<td>7.89 (174)</td>
<td>7.16 (258)</td>
<td>7.75 (497)</td>
<td>7.55</td>
<td>4,363</td>
</tr>
<tr>
<td>Alb</td>
<td>8.11 (3.3)</td>
<td>7.96 (3.7)</td>
<td>7.01 (4.1)</td>
<td>7.16</td>
<td>5,015</td>
</tr>
<tr>
<td>Creat</td>
<td>6.69 (0.7)</td>
<td>8.15 (0.9)</td>
<td>7.74 (1.1)</td>
<td>7.42</td>
<td>5,389</td>
</tr>
<tr>
<td>Bil</td>
<td>7.72 (0.4)</td>
<td>6.36 (0.5)</td>
<td>7.52 (0.7)</td>
<td>8.36</td>
<td>5,370</td>
</tr>
<tr>
<td>ALT</td>
<td>8.56 (16)</td>
<td>7.58 (25)</td>
<td>7.93 (37)</td>
<td>7.00</td>
<td>4,950</td>
</tr>
<tr>
<td>WBC</td>
<td>7.72 (4.8)</td>
<td>6.94 (6.6)</td>
<td>7.25 (8.9)</td>
<td>8.46</td>
<td>5,387</td>
</tr>
<tr>
<td>Lym</td>
<td>8.06 (10.0)</td>
<td>7.43 (16.8)</td>
<td>7.12 (24.1)</td>
<td>7.73</td>
<td>5,301</td>
</tr>
<tr>
<td>Plat</td>
<td>7.99 (157)</td>
<td>7.78 (234)</td>
<td>6.07 (311)</td>
<td>8.36</td>
<td>5,374</td>
</tr>
<tr>
<td>ANC</td>
<td>11.67 (2.9)</td>
<td>11.47 (4.4)</td>
<td>11.45 (6.7)</td>
<td>12.45</td>
<td>2,729</td>
</tr>
<tr>
<td>PS</td>
<td>= 0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>= 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>= 2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3,910</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>118</td>
<td>3,278</td>
<td>514</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mets</td>
<td>7.52 9.12</td>
<td>8.77 8.06</td>
<td>6.93 2.08</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>1,743 1,220</td>
<td>593 248</td>
<td>101 48</td>
<td>28</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Alb, albumin; Creat, creatinine; Bil, total bilirubin; Lym, total lymphocyte count; Plat, platelets; N, number; Mets, metastases.

<sup>a</sup>Not percentile; these are the value categories.

Table 3. Parameter estimates from the logistic regression model

<table>
<thead>
<tr>
<th>Model with dose and age and PS</th>
<th>Parameter estimates from logistic regression model</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear</td>
<td>3.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Squared</td>
<td>-1.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cubed</td>
<td>0.108</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>0.017</td>
<td>0.0058</td>
</tr>
<tr>
<td>PS</td>
<td>0.38</td>
<td>0.047</td>
</tr>
<tr>
<td>Number of metastatic sites</td>
<td>-0.10</td>
<td>0.11</td>
</tr>
</tbody>
</table>
that have demonstrated that of patients who were success-
fully screened for phase I trials and who met eligibility
criteria, age was not an independent factor of enrollment (28, 29).

There are several strengths of our study. First, we were able
to expand greatly upon the previous single-institution trials
that predicted for DLTs. These trials contained far less
patients, and particularly fewer geriatric oncology patients;
our study contained more than 500 patients who were ages
>70 (18–20). Second, it is noteworthy that we investigated
factors, as shown in Fig. 2, that predict for any DLT at all; this
is an interesting addition to the work of Hyman and
colleagues (25) who devised a nomogram for predicting
serious toxicities in cycle one. Our work provides a general
educational tool applicable to most adult phase I studies for
healthcare professionals to visualize and describe possible
risks of DLT associated with age and PS. Whereas most other
large studies have explored phase I variables primarily as
they relate to overall survival, this study focused on DLTs as
the outcome that occurred while enrolled in phase I trial.

However, our study also has some limitations. Because of
the structure of our database, we were unable to examine the
relationship between patient comorbidities and the inci-
dence of DLTs. Although comorbidities affect tolerability of
therapy, we could not determine whether the presence of
comorbidities was independently associated with increased
risk of DLTs (30, 31). In addition, concomitant medications
were generally self-reported, and may not have been
completely reliable. We were unable to assess whether
having received more concomitant medications predicted
for more DLTs. A third relative limitation was that the extremely
robust phase I database provided 2,905 patients who met our
study eligibility, but we excluded 2,496 other patients in the
database because they did not meet our eligibility criteria
(Fig. 1). Our goal was to determine which factors predicted for
DTLs regardless of whether the DLTs were due to hematologic
versus nonhematologic adverse events. We did not determine
whether there would have been a difference in our results had we
considered cytotoxic and targeted therapies separately. When
we designed the study, we did not think that this was necessary
because hematologic toxicities, nausea, and even death may have
occurred more commonly with cytotoxic agents, but toxic-
ities such as palmar-plantar erythrodysesthesia, protein-
uria, and hypertension were likely more common with
targeted agents (25, 32). Part of the explanation for more
deaths associated with cytotoxic agents may have been that
cytotoxic agents were generally tested at an earlier date than
supportive care improved markedly during the intervening years.
Another limitation of our study is that we could not account for
the role that the number of prior lines of therapy may have had
on DLT incidence. Although data about prior lines of treatment
were collected, they were not collected in a systematic
fashion and, therefore, they were neither amenable to
evaluation nor interpretation. Finally, we do not know how
many older patients in the general population of patients
with cancer who were eligible for our phase I studies actually
failed to be enrolled in phase I trials. If the number and
characteristics of such patients differed substantially, and

### Table 4. 95% CIs around the estimate of the probability of a DLT for different combinations of dose levels and PS

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose = 33%</th>
<th>Dose = 66%</th>
<th>Dose = 100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>(0.005, 0.010, 0.012)</td>
<td>(0.011, 0.020, 0.036)</td>
<td>(0.020, 0.034, 0.058)</td>
</tr>
<tr>
<td>50</td>
<td>(0.006, 0.012, 0.023)</td>
<td>(0.014, 0.024, 0.041)</td>
<td>(0.024, 0.040, 0.066)</td>
</tr>
<tr>
<td>60</td>
<td>(0.007, 0.014, 0.026)</td>
<td>(0.016, 0.028, 0.047)</td>
<td>(0.028, 0.047, 0.076)</td>
</tr>
<tr>
<td>70</td>
<td>(0.008, 0.016, 0.031)</td>
<td>(0.019, 0.033, 0.056)</td>
<td>(0.033, 0.054, 0.090)</td>
</tr>
<tr>
<td>80</td>
<td>(0.010, 0.019, 0.038)</td>
<td>(0.022, 0.039, 0.068)</td>
<td>(0.037, 0.064, 0.108)</td>
</tr>
<tr>
<td>PS 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>(0.009, 0.015, 0.025)</td>
<td>(0.020, 0.029, 0.044)</td>
<td>(0.034, 0.049, 0.069)</td>
</tr>
<tr>
<td>50</td>
<td>(0.010, 0.017, 0.028)</td>
<td>(0.025, 0.035, 0.049)</td>
<td>(0.042, 0.057, 0.077)</td>
</tr>
<tr>
<td>60</td>
<td>(0.012, 0.020, 0.033)</td>
<td>(0.029, 0.041, 0.056)</td>
<td>(0.051, 0.067, 0.088)</td>
</tr>
<tr>
<td>70</td>
<td>(0.014, 0.024, 0.039)</td>
<td>(0.034, 0.048, 0.067)</td>
<td>(0.058, 0.078, 0.104)</td>
</tr>
<tr>
<td>80</td>
<td>(0.016, 0.028, 0.047)</td>
<td>(0.038, 0.056, 0.082)</td>
<td>(0.064, 0.091, 0.127)</td>
</tr>
<tr>
<td>PS 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>(0.011, 0.021, 0.039)</td>
<td>(0.026, 0.043, 0.069)</td>
<td>(0.044, 0.070, 0.110)</td>
</tr>
<tr>
<td>50</td>
<td>(0.014, 0.025, 0.044)</td>
<td>(0.032, 0.050, 0.078)</td>
<td>(0.054, 0.082, 0.122)</td>
</tr>
<tr>
<td>60</td>
<td>(0.017, 0.029, 0.051)</td>
<td>(0.038, 0.059, 0.090)</td>
<td>(0.064, 0.095, 0.140)</td>
</tr>
<tr>
<td>70</td>
<td>(0.019, 0.034, 0.061)</td>
<td>(0.044, 0.068, 0.106)</td>
<td>(0.073, 0.110, 0.163)</td>
</tr>
<tr>
<td>80</td>
<td>(0.022, 0.040, 0.073)</td>
<td>(0.049, 0.080, 0.127)</td>
<td>(0.082, 0.128, 0.193)</td>
</tr>
</tbody>
</table>

NOTE: Number of metastatic sites is always 2, which is the median number of sites (lower CI, estimate, upper CI). Dose is represented as %MTD.
they would have been at high risk of DLTs, then this study would have underestimated the probability of DLTs in the elderly. This scenario could occur if oncologists and internists excluded otherwise technically eligible elderly patients because of "clinical judgment." It is well known that elderly oncology patients have more immune-senescence, decreased bone marrow and organ reserve, increased numbers of comorbidities, polypharmacy, and worsening functional status than younger oncology patients and that elderly patients with cancer have experienced more falls, depression, and osteoporosis (as well as hearing loss and urinary incontinence) relative to age-matched patients without cancer (33–36).

Even after accounting for the relative limitations of our study, we believe that the information presented here will inform referring physicians and phase I trialists of the risks for DLTs associated with enrolling elderly patients on dose-escalation trials. Our model predicted for increased DLTs with increasing age and worsening PS. On the basis of the patients evaluated in our study, the overall clinical significance of increased risk of DLTs with increased patient age is small and within the range of generally accepted patient safety risk of 33% for DLTs on phase I trials (22). Our findings help to further refine evidence-based patient selection criteria for phase I trials to correctly identify patients at elevated risk of DLTs with the concurrent goals of decreasing the overall number of patients required by minimizing the need for dose expansions due to early trial DLTs, and reducing the possibility of halting a phase I dose-escalation scheme early with determination of RP2Ds at an otherwise lower, possibly less effective, dose. In our opinion, advanced age of a patient alone should not justify the general tendency to globally exclude the elderly from phase I trials. The robustness of this study, due to the inclusion of a wide variety of phase I trials, investigational agent types, and both hematologic and solid tumor types, allows our findings to be incorporated into discussions of risks of drug-related adverse events on phase I trials with geriatric oncology patients.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: A. Schwandt, P.J. Harris, S. Hunsberger, G.L. Smith, B.D. Anderson, S.P. Ivy
Development of methodology: A. Schwandt, S. Hunsberger, S.P. Ivy
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A. Schwandt, G.L. Smith, S.P. Ivy

Figure 2. The 95% CIs presented graphically show predicted probability of DLT given a patient’s age and ECOG PS at various dose levels (% MTD).
Role of Age on DLTs in Phase I Dose-Escalation Trials

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References

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