The Role of Age on Dose Limiting Toxicities (DLTs) in Phase I Dose-escalation Trials

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**Statement of Translational Relevance**

Over 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 over 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 1 trials, have for developing drug-related adverse events. Advanced age, by itself, does not justify exclusion of older patients from phase 1 cancer 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 (DLTs). 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 percentage of maximum tolerated dose (%MTD), 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 over 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. While 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.
Introduction

While over 60% of all cancers and more than 70% of cancer-related deaths occur in the elderly, the enrollment of geriatric patients in clinical oncolgy 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 aged 30-64 years representing 3% of the general age-match population, compared with 1.3% for patients aged 65-74 years and 0.5% for patients aged 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 (mos); according to a retrospective review of patients aged ≥ 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) Since early oncology clinical trials study investigational agents prior to regulatory approval, this underrepresentation of elderly patients reflects reduced access of geriatric patients to new agents which may have tumor efficacy and may improve survival.

By definition, most phase I trials are designed to determine a recommended phase 2 dose (RP2D) and they have dose escalation schemes usually until the occurrence of serious drug-related toxicities (SDRTs). Inappropriately strict selection criteria, such as age bias contributing to low enrollment of elderly patients in phase I oncology clinical trials, may delay 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 non-pediatric phase I oncology trials, 73% of phase I trials successfully predicted RP2D as the dose employed 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.

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, health 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 vs ≥ 65 years, was not determined to be an independent factor predictive of OS. Researchers at M.D.Anderson 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 58-60.

Since 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 (DLTs) 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, Bachelot, et al (2000), 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, et al (2011) conducted a retrospective review of phase I patients enrolled at Case Comprehensive Cancer Center from years 1994 to 2009.(19) Twenty-two patients aged ≥ 80 years who experienced DLTs were compared with 123 patients aged < 80 years enrolled on the same dose level cohorts. The rate of DLTs in the first cycle was 18% for patients aged ≥ 80 compared with 6.5% of patients aged < 80 years. LoConte, et al (2010) 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.(20) 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 institutions studies which 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 multi-institutional 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 patients characteristics across dose levels (described as %MTD), i.e. the percent 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.

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 the National Cancer Institute’s Cancer Therapy Evaluation Program (CTEP) from 1995 – 2011. CTEP sponsored trials were conducted in North America and protocol-specific baseline and follow-up trial data was monitored and recorded. The trials analyzed had to fit two criteria: 1) dose-escalating single agent trials (multiple drugs could be administered in a trial, however only one was permitted to be dose-escalated); and 2) trials in which MTD or RP2D was determined. The following trials were excluded from the analysis: 1) pediatric trials; 2) trials with
local, intratumoral therapy only; 3) trials which were not complete or had been administratively closed early. All administered dose levels were defined as a percentage of MTD (%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 which 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 1995-2011 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 pre-specified 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, while 54 trials were multi-agent with dose escalation of only one agent (Figure 1).

Data acquisition and extraction
The following information about each trial was extracted from CTEP database: trial protocol number, dates trial was conducted, anti-neoplastic 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.

Statistics

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 4 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
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-square 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% or less of MTD, and greater than 100% of MTD.

**Results**

Patient characteristics

There were 5401 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 aged 80 years or older with PS of 2. 52% of patients were treated at dose levels between 66% and 100% of the MTD. 22% of patients were treated at dose levels higher than the MTD. There was no evidence of association between dose and age ($p = 0.57$). This suggests that there was no bias in entering patients, i.e. older patients did not appear to be systematically placed on lower dose levels.

There were 5401 eligible patients from the studies that met the inclusion criteria; 2496 patients had missing values on the covariates of interest in the final model and were
excluded from the final analysis. The proportion of DLT’s 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 appears 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 measurements) 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 2905 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 Figure 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 1 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. Further, as the dose of drug
administered increased, the probability of DLT increased. Thus, for a 40 year old patient with a PS 0 and 1 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 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.

**Discussion/Conclusion**

In this study, we investigated the role of age in phase I trials by conducting a large multi-institutional 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 employing mixed effects modeling we demonstrated that the increased probability of DLTs in elderly 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 which 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 which failed to show that baseline laboratory values predicted for DLTs. (20) Molife, et al (2012) evaluated 687 phase I patients at RMH and determined that worsening ECOG PS and increasing dose level predicted for increased risk of DLTs, while components of the RMH score prognostic for
OS including decreased albumin and elevated LDH did not predict for DLTs.\(^{(24)}\) 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 which 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 physiological 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. In a separate analysis, we assessed whether an age-related bias exists by examining the relationship of patient age and dose level. There was no association between assigned-dose cohort level and age. In other words, there was no evidence to indicate that investigators at CTEP-sponsored trials unsymmetrically assigned older patients to lower vs higher treatment doses. This is consistent with prior studies which have demonstrated that of patients who were successfully 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 which predicted for DLTs. These trials contained far less patients and, particularly fewer geriatric oncology patients; our study contained more
than 500 patients who were age > 70. (18-20) Secondly, it is noteworthy that we investigated factors, as shown in Figure 2, that predict for any DLT at all; this is an interesting addition to the work of Hyman, et al (2014) who devised a nomogram for predicting serious toxicities in cycle one. (25) Our work provides a general educational tool applicable to most adult phase I studies for health professionals to visualize and describe possible risks of DLT associated with age and performance status. While most other large studies have explored phase I variables primarily as they relate to overall survival, this study focused on DLTs as the outcome which 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 co-morbidities and the incidence of DLTs. While co-morbidities affect tolerability of therapy, we could not determine whether the presence of co-morbidities was independently associated with increased risk of DLTs. (30, 31) Additionally, 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 2905 patients who met our study eligibility but we excluded 2496 other patients in the database because they did not meet our eligibility criteria (Figure 1). Our goal was to determine which factors predicted for DLTs regardless of whether the DLTs were due to hematologic versus non-hematologic 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 toxicities such as palmer-plantar erythrodysesthesia, proteinuria 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 targeted therapies and 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 not 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 they would have been at high risk of DLTs, then this study would have under-estimated 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 co-morbidities, 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 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. Based on 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.
References

Table 1 Percent of patients by age and dose

<table>
<thead>
<tr>
<th>Dose level (%MTD)</th>
<th>Age groups (years)</th>
<th>Number of patients</th>
<th>Proportion of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;40</td>
<td>[40,60)</td>
<td>[60,70)</td>
</tr>
<tr>
<td>≤ 33</td>
<td>0.81</td>
<td>1.57</td>
<td>5.67</td>
</tr>
<tr>
<td>(33,66]</td>
<td>6.59</td>
<td>23.22</td>
<td>10.42</td>
</tr>
<tr>
<td>(66,100]</td>
<td>14.68</td>
<td>5.74</td>
<td>1.52</td>
</tr>
<tr>
<td>&gt;100</td>
<td>3.63</td>
<td>0.15</td>
<td>0.20</td>
</tr>
</tbody>
</table>

| Number of patients | 556 | 2438 | 1481 | 836 | 90 | 5401 |
| Proportion of patients | 0.10 | 0.45 | 0.27 | 0.16 | 0.02 |
Table 2 Percent of DLT’s in each percentile defined category for each explanatory variable (quartile value).

<table>
<thead>
<tr>
<th>Explanatory variable</th>
<th>0 to &lt;25%tile (25%tile)</th>
<th>25 to &lt;50%tile (50%tile)</th>
<th>50 to &lt;75%tile (75%tile)</th>
<th>75 to 100%tile number</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 4363</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 5015</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 5389</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 5370</td>
</tr>
<tr>
<td>ALT</td>
<td>8.56 (16)</td>
<td>7.58 (25)</td>
<td>7.93 (37)</td>
<td>7.00 4950</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 5387</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 5301</td>
</tr>
<tr>
<td>Plat</td>
<td>7.99 (157)</td>
<td>7.78 (234)</td>
<td>6.07 (311)</td>
<td>8.36 5374</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 2729</td>
</tr>
<tr>
<td>PS</td>
<td>7.63</td>
<td>7.69</td>
<td>9.73</td>
<td>7* or more 3910</td>
</tr>
<tr>
<td>N</td>
<td>118</td>
<td>3278</td>
<td>514</td>
<td></td>
</tr>
<tr>
<td>Mets</td>
<td>7.52</td>
<td>9.1</td>
<td>8.77</td>
<td>8.06 6.93 2.08 0</td>
</tr>
<tr>
<td>N</td>
<td>1743</td>
<td>1220</td>
<td>593</td>
<td>248 101 48 28</td>
</tr>
</tbody>
</table>

*Not percentile; these are the value categories.

Abbreviations: LDH, lactate dehydrogenase; Alb, Albumin; Creat, Creatinine; Bil, total bilirubin; ALT, Alanine transaminase; WBC, white blood count; Lym, total lymphocyte count; Plat, platelets; ANC, absolute neutrophil count; PS, performance status; N, number; Mets, metastases
Table 3. Parameter estimates from logistic regression model

<table>
<thead>
<tr>
<th>Model with dose and age and performance status</th>
<th>Parameter estimates from logistic regression model</th>
<th>P-value</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>Performance status</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>
Table 4. 95% confidence intervals (CI) around the estimate of the probability of a DLT for different combinations of dose levels and performance status.

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose=33%</th>
<th>Dose=66%</th>
<th>Dose=100%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Performance Status 0</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></td>
<td>Performance Status 1</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></td>
<td>Performance Status 2</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>

Number of metastatic sites is always 2 which is the median number of sites (lower CI, estimate, upper CI). Dose is represented as percent of maximum tolerated dose (%MTD).
Legends for Figures:

Figure 1

CONSORT diagram of trial selections and patient exclusions.

Figure 2

The 95% confidence intervals presented graphically show predicted probability of DLT given a patient’s age and ECOG performance status at various dose levels (%MTD).
Figure 1. CONSORT diagram of trial selection and patient exclusions

412 Trials phase I (1995-2011)

-77 trials - not completed
-86 trials - no drug escalation, pediatric, local therapy, premalignant, pharmacodynamic study
-55 trials - more than 1 drug escalated
-32 trials - MTD or RP2D not identified in publication or communication

162 phase I single agent escalation trials eligible
108 trials with one agent
54 trials with multiple agents (only one agent escalated)
Resulting in 5401 eligible patients

-415 patients missing both metastases and PS
-1005 patients missing only metastases
-1076 patients missing PS

2905 patients final sample size
Clinical Cancer Research

The Role of Age on Dose Limiting Toxicities (DLTs) in Phase I Dose-escalation Trials

Anita Schwandt, Pamela Jo Harris, Sally Hunsberger, et al.

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