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ORIGINAL ARTICLE

Amongst eligible patients, age and comorbidity do not predict for dose-limiting toxicity from phase I chemotherapy

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Abstract
Background There are no clear predictors clinicians can use to determine who is more likely to experience dose-limiting toxicity (DLT) in phase I chemotherapy clinical trials. Many providers are reluctant to refer older adults to phase I trials because of concerns about the development of toxicity. The goal of this study was to identify clinical and nonclinical factors which were associated with the development of DLT in phase I studies.
Methods Patients (pts) were included if they were treated at maximally tolerated dose (MTD) and above. Studies were included only if MTD was reached. Data collected included age, comorbidity (Cumulative Illness Rating Score-Geriatrics), labs at enrollment, height, weight, performance status, cancer type, duration of diagnosis, prior treatment, drug level, smoking status, marital status, mean income, percent of population high school educated as determined by ZIP code, and distance to the phase I trial hospital. Those who did and did not have DLT were compared by bivariate and then multivariate analysis.
Results A total of 242 charts were reviewed from 24 cytotoxic chemotherapy studies, and 27 different types of cancer were represented. On bivariate analysis, mean age, household income (higher), weight, body surface area, dose of drug, alkaline phosphatase, hemoglobin, and LDH were significantly associated with DLT ($P < 0.05$). CIRS-G score was not associated with DLT. In multivariate analysis, dose level ($P = 0.004$) and distance from the phase I trial hospital ($P = 0.04$) were still significant predictors of DLT. Age did not predict for severity of DLT.
Conclusions Age and comorbidity did not predict for development of DLT in phase I chemotherapy trials. Many of these pts were very fit, with relatively low CIRS-G scores, so the impact of comorbidity may not have been fully evaluated. Several social and clinical factors may predict for development of DLT. A prospective study is being planned to confirm these results.

Keywords Phase I · Chemotherapy · Predictors · Toxicity · Age · Comorbidity

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Introduction

Phase I clinical trials are early experimental trials of pharmaceuticals in humans. The goal of these studies is to determine toxicities and optimal doses in humans. Although many patients have been treated in phase I trials nationally, very little is known about patient characteristics that may predict the occurrence of dose-limiting toxicity (DLT) aside from performance status [1]. Although one prior study has analyzed common cancer-related variables related to experimental therapy toxicity [1], such as prior

radiation and chemotherapy, no published trials have jointly analyzed the impact of age and comorbidity, and none have utilized a measure of severity of comorbidity (rather than the more common, but less clinically useful method of counting number of comorbid illnesses). In addition, no trials have analyzed the impact of socioeconomic status (SES) or familial support on incidence of toxicity.

Although the number of older cancer patients is rapidly increasing, and a larger number of older cancer patients are being placed on clinical trials, the optimal ways to predict toxicity in the elderly patient are not known. It is assumed that the elderly do not tolerate phase I drugs as well as younger patients, presumably because of increased levels of comorbid illness [2]. It is known that performance status does not correlate with comorbidity [3], so our ability to determine which elderly patient might do well with a trial is minimal. Thus, oncologists are reluctant to place elderly patients on clinical trials because of concern for undue toxicity [4]. However, the majority of cancer patients are elderly, and although we base treatment decisions, in part, on clinical trial results, most trials do not include many elderly patients [5]. Additionally, there is a suggestion in the literature that several patient-related characteristics may be more significant than previously appreciated in predicting toxicity. Prior research has identified that patients of low SES are more likely to have toxicity from cancer treatments for cervical cancer [6] as well as higher non-Hodgkin lymphoma-related mortality [7]. In addition, married women with breast cancer have a better overall survival, thought to be from increased family support [8]. Smoking has been linked to increased toxicity in early phase trials at one academic institution [1].

We hypothesized that age and performance status would not predict incidence of DLT as well as comorbidity burden. In addition, we hypothesized that smokers and married or partnered patients would have lower rates of DLT.

Methods

A retrospective chart review of 242 patients treated in a phase I clinical trial at the University of Wisconsin was performed. Only studies where a maximally tolerated dose was reached were included, to not include patients who did not experience toxicity because dose intensity was not optimal. All charts were reviewed by a single person (LoConte). Data collected is presented in Table 1, and includes sociodemographic data (age at the time of enrollment on study, gender, 5 digit ZIP code used to determine mean income by 2000 census data and distance to the University of Wisconsin hospital, height, weight, smoking status and marital status), clinical data (cancer type, time since original cancer diagnosis, prior cancer therapies, past medical history, number of medications, Eastern Cooperative Oncology Group performance status), chemotherapy data (investigational agent and dose level at MTD or above MTD) and laboratory data (creatinine, alkaline phosphatase, lactate dehydrogenase, white blood cell count, hemoglobin, platelet count, albumin).

Analysis

Descriptive and bivariate statistics were calculated for all clinical and sociodemographic data. Table 1 reports descriptive statistics on the total sample. Means and standard deviations were calculated for continuous measures; percents and frequencies were calculated for categorical variables. Table 2 presents results from bivariate analyses testing for significant differences between patients with DLT and those without DLT on all study variables. Fisher exact tests were used to test for differences in categorical variables and exact P values are reported. For continuous data, one-way ANOVAs and F tests were performed. A Fisher exact test was also used to test for a significant association between type of cancer and DLT in Table 4.

Multivariate logistic regression was used to determine which clinical and sociodemographic variables are significant predictors of DLT. However, this multivariate analysis was complicated by the presence of a number of variables with significant amounts of missing data (see Table 1). Missing data problems are common in observational studies and can produce biased and inefficient estimates if not dealt with appropriately.

Multiple imputation (MI), proposed by Rubin [9], is an accepted and widely implemented procedure used to deal with missing data [10]. MI is a technique that replaces each missing value in the data set by $m > 1$ simulated values. Values are simulated from a conditional distribution based on observed data and the model subsequently used for analysis. Such a procedure creates m complete versions of the data which can then be analyzed using familiar complete data methods.

We imputed $m = 100$ equally plausible complete datasets. Though some researchers have reported that efficient estimates can be obtained with as a few as five to ten imputations [9–11], a recent simulation study found that many more imputations are necessary to avoid reductions in statistical power [12]. Separate logistic regression models were estimated from each of the 100 data sets, yielding 100 sets of results, which were then combined according to "Rubin's Rules." Rubin's combined estimate of a scalar parameter, such as a logistic regression coefficient, is the arithmetic mean of the $m = 100$ different estimates [9]. The

Table 1 Key characteristics ($N = 242$)

Characteristic	% or mean
Dose-limiting toxicity (%) (*N*)	
DLT absent	73.3 (173)
DLT present	26.7 (63)
Age (years) [mean (SD)]	57.1 (12.9)
Younger than 48 years	26
48–57 years	26
58–67 years	27
Older than 67	22
Gender (%) (*N*)	
Male	55 (133)
Female	45 (109)
Marital status (%) (*N*)	
Single	16.3 (38)
Married	83.7 (195)
Census zip code median household income in $1,000s [mean (SD)]	47.3 (11.5)
Percent of census block aged 25+ with a bachelor's degree [mean (SD)]	15.7 (6.9)
Distance to hospital (miles) [mean (SD)]	85.7 (73.9)
Smoking status (%) (*N*)	
Never a smoker	42.1 (88)
Former smoker	43.5 (91)
Current smoker	14.4 (30)
Number of pack years [mean (SD)]	18.3 (24.2)
Height (cm) [mean (SD)]	171 (10.9)
Weight (kg), [mean (SD)]	80 (19.3)
Body surface area (m^2) [mean (SD)]	1.9 (0.3)
Dose (%) (*N*)	
MTD	49.6 (120)
Above MTD	50.4 (122)
Duration of diagnosis in months [mean (SD)]	30.9 (36.5)
Number of prior therapies [mean (SD)]	2.5 (1.8)
Number of medications [mean (SD)]	4.4 (3.2)
CIR-G total score [mean (SD)]	7.5 (2.5)
ECOG-PS (%) (*N*)	
Restricted	73.5 (172)
Fully active	26.5 (62)
Lab data [mean (SD)]	
Alk phos (U/L)	152.2 (128.4)
WBC (K/μL)	7.2 (3.8)
ANC (cells/μL)	4963.1 (2387.2)
HGB (K/μL)	12.5 (1.7)
PLT (K/μL)	269.2 (103.5)
Creat (mg/dL)	0.9 (0.2)
ALB (g/dL)	3.6 (0.5)
LDH (U/L)	351.2 (476.3)

variance of the combined estimate is based on both the variation of an estimate within an imputed dataset and also the variation in estimates between datasets, reflecting the uncertainty involved in imputing missing values. With MI combined estimates, Rubin showed that a *t* distribution can be used for constructing confidence intervals and significance tests [9].

Our initial logistic regression model included terms for gender, number of prior therapies and all variables that were related to DLT with a *P* value less than or equal to 0.2 in the bivariate analyses. Backward selection with an inclusion level of $P \leq 0.15$ was used to eliminate covariates that were not significant predictors of DLT, yielding the final parsimonious model reported in Table 3. Standard errors were adjusted using the Huber–White robust variance estimate. All analyses were performed with Stata MP, version 10 (StataCorp, College Station, TX).

Results

A total of 242 charts were reviewed, including 63 patients with DLT. Demographic data is presented in Table 1. The ages of patients ranged from 31 to 86 years, but most patients were under 65, and only 7 patients over 75 years. On bivariate analysis (Table 2), higher age ($P = 0.039$), higher 2000 census median household income as determined by 5 digit ZIP code ($P = 0.029$), lower weight ($P = 0.023$), lower body surface area ($P = 0.039$), higher alkaline phosphatase ($P = 0.029$), lower hemoglobin ($P = 0.044$) and higher lactate dehydrogenase ($P = 0.002$) were associated with increased odds of DLT. As expected given the 3 + 3 dose escalation design of most phase I studies, being treated at a higher dose level also predicted for DLT ($P = 0.002$). Notably, comorbidity did not predict for DLT, but the entire cohort was relatively healthy with a mean of only 4.4 medications, and a mean Cumulative Index Rating Scale-Geriatrics (CIRS-G) score of only 7.5. All patients were also ECOG-PS 0 (26.5%) or 1 (73.5%). Gender, marital status, educational level, smoking status, number of pack years, height, duration of cancer diagnosis, number of prior therapies, ECOG-PS, CIRS-G score, white blood cell count, absolute neutrophil count, platelet count, creatinine, and albumin were not predictive of DLT.

Using a multivariate logistic regression model (Table 3) incorporating all of the variables found to be associated with DLT in the bivariate analysis, higher median household income (OR 1.030, $P = 0.038$), lower body surface area (OR = 0.279, $P = 0.029$), higher dose level (OR 2.403 for dose above MTD, $P = 0.007$), and higher LDH

Table 2 Key characteristics of cancer patients by presence or absence of DLT ($N = 242$)

Characteristic	DLT present ($N = 63$) % or mean	DLT absent ($N = 173$) % or mean	P value
Age (years) [mean (SD)]	**60.2 (13.4)**	**56.2 (12.6)**	**0.039**
Gender (%) (*N*)			
Male	55.6 (35)	56.7 (98)	0.883
Female	44.4 (28)	43.4 (75)	
Marital status (%) (*N*)			
Single	9.8 (6)	19.3 (32)	0.110
Married	90.2 (55)	80.7 (134)	
Census zip code median household income in $1,000s [mean (SD)]	**50.4 (11.7)**	**46.4 (11.3)**	**0.029**
Percent of census block aged 25+ with a bachelor's degree [mean (SD)]	15.5 (6.5)	15.8 (7.1)	0.748
Distance to hospital (miles) [mean (SD)]	72.5 (47.9)	91.2 (81.8)	0.091
Smoking status (%) (*N*)			
Never a smoker	47.3 (26)	40.5 (60)	0.375
Former smoker	43.6 (24)	42.6 (63)	
Current smoker	9.1 (5)	16.9 (25)	
Number of pack years [mean (SD)]	18.7 (27.8)	18.3 (23.2)	0.915
Height (cm) [mean (SD)]	170.5 (11.5)	171.3 (10.8)	0.621
Weight (kg) [mean (SD)]	**75.4 (15.4)**	**81.9 (20.5)**	**0.023**
Body surface area (m^2) [mean (SD)]	**1.88 (0.23)**	**1.96 (0.28)**	**0.039**
Dose (%) (*N*)			
MTD	**31.8 (20)**	**54.9 (95)**	**0.002**
Above MTD	**68.3 (43)**	**45.1 (78)**	
Duration of diagnosis in months [mean (SD)]	25.5 (26.7)	32.3 (38.3)	0.196
Number of prior therapies [mean (SD)]	2.4 (1.9)	2.5 (1.7)	0.825
Number of medications [mean (SD)]	4.5 (3.7)	4.4 (3)	0.927
CIR-G total score [mean (SD)]	7.3 (2.5)	7.5 (2.6)	0.651
ECOG-PS (%) (*N*)			
Restricted	80.3 (49)	71.3 (119)	0.179
Fully active	19.7 (12)	28.7 (48)	
Lab Data [mean (SD)]			
Alk phos (U/L)	**184.6 (165.5)**	**141.7 (113.2)**	**0.029**
WBC (K/μL)	7 (2.5)	7.2 (4.1)	0.692
ANC (cells/μL)	5030.1 (2349.3)	4931.8 (2398.3)	0.783
HGB (K/μL)	**12.1 (1.5)**	**12.6 (1.7)**	**0.044**
PLT (K/μL)	268.6 (113.6)	267.8 (99.4)	0.960
Creat (mg/dL)	0.9 (0.2)	0.9 (0.2)	0.680
ALB (g/dL)	3.5 (0.5)	3.7 (0.5)	0.056
LDH (U/L)	**537 (854.9)**	**290.9 (234)**	**0.002**

Bold indicates $P < 0.05$

(OR = 1.009, $P = 0.32$) remained significant predictors of DLT. The remaining variables no longer predicted for DLT (including hemoglobin and alkaline phosphatase).

No group of cancer type was more predictive of DLT (Table 4). The most common type of DLT was hematologic (34.8%), followed by gastrointestinal (28.3%) and musculoskeletal (10.9%). Most DLTs were grade 3 (55.3%), followed by grade 4 (36.2) and grade 5 (2.1%). Age was also not predictive of grade of DLT (see Table 5, P value = 0.284).

Discussion

This retrospective controlled study demonstrated that few patient characteristics are predictive of dose-limiting toxic-

Table 3 Odds ratios (OR) and 95% confidence intervals (CI) for risk factors predicting presence of at least 1 DLT ($N = 242$)

Characteristic	OR	95% CI[a]	*P* value
Age (years)	1.028	(0.999, 1.058)	0.056
Census zip code median household income ($1,000s)	**1.030**	**(1.002, 1.06)**	**0.038**
Distance to hospital (miles)	0.996	(0.99, 1.001)	0.134
Body surface area (m^2)	**0.279**	**(0.089, 0.879)**	**0.029**
Above MTD	**2.403**	**(1.27, 4.548)**	**0.007**
CIR-G total score	0.903	(0.793, 1.027)	0.121
LDH (U/dL × 1/10)	**1.009**	**(1.001, 1.018)**	**0.032**

ORs and CIs are based on 100 imputed datasets, yielding 100 sets of results that were combined using Rubin's rules of combination. Results obtained from backward selection procedure

Bold indicates $P < 0.05$

[a] Standard errors adjusted for clustering of observations using the Huber–White robust variance estimate

Table 4 Cancer diagnosis by presence or absence of DLT ($N = 242$)

Cancer type	Total ($N = 242$) (%) (*N*)	DLT present ($N = 63$) (%) (*N*)	DLT absent ($N = 171$) (%) (*N*)	Exact *P* value
GU	15.4 (37)	19.1 (12)	14 (24)	0.870
GI	38.8 (93)	38.1 (24)	40.4 (69)	
GYN	11.7 (28)	11.1 (7)	11.1 (19)	
Thoracic	13.3 (32)	14.3 (9)	12.9 (22)	
Heme	2.1 (5)	0 (0)	2.9 (5)	
Head and neck	4.6 (11)	4.8 (3)	4.1 (7)	
Other	14.2 (34)	12.7 (8)	14.6 (25)	
N missing	2	2	0	

Table 5 Relations with between age and DLT

Severity of DLT	Age category			Total
	Less than 50	50–60	Over 60	
Grade 2	0	3	0	3
Grade 3	7	10	13	30
Grade 4	5	5	7	17
Grade 5	0	0	1	1
Total	12	18	21	51

Pearson chi-squared = 7.412, *P* value = 0.284

ity for patients in a phase I clinical trial. Perhaps most surprisingly, a social characteristic (distance from the sponsoring hospital) was predictive, though this finding has been noted in curative intent phase II clinical trials as well [13]. Age, up to age 75 does not seem to be a risk factor; no statements can be made about the influence of more advanced ages. The CIRS-G score was not predictive of dose-limiting toxicity. However, this was a relatively young and healthy cohort, which likely represents a selection bias. In general, phase I trials require good or excellent performance status, normal lab values and motivation and ability to make frequent visits to the academic hospital for treatment. This, in effect, may select for younger, higher SES, educated patients unintentionally. Prior work has identified that longer distance to the academic center correlates with better outcomes, and is thought to represent improved functional abilities beyond what can be measured with stage of cancer, performance status and income [13]. There were no pre-specified protocol requiring upper age restrictions on any of the phase I studies included in this analysis. Age was predictive of DLT in the bivariate analysis but not the logistic regression analysis. Age did not predict for severity of DLT. Lower weight, lower body surface area, higher alkaline phosphatase, lower hemoglobin, and higher lactate dehydrogenase all predicted for toxicity in bivariate analyses. Many of these determinants likely reflect a higher tumor burden rather than a unique risk factor for dose-limiting toxicity.

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