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Phase I Clinical Trials in Patients ≥80

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Abstract

Phase I clinical trials play a crucial role in development of therapeutics for cancer patients. During phase I clinical trials common toxicities are delineated, dose limiting toxicities (DLT) are determined and a dose for phase II studies is recommended. However, reviews of the phase I population indicate a younger group of participants with a median age of 50-55. No data exists on the performance of octogenarians on phase I trials. Concerns for enrollment of this patient population, relates to presence of comorbidities and possibly altered pharmacokinetics in the setting of unknown potential toxicities. We present herein the largest review of octogenarians on phase I trials. Twenty-two octogenarian patients with a median age of 83 were enrolled on phase I clinical trials. More than 50% of them were chemotherapy-naïve most likely indicative of the fact that treating physicians believed standard therapy to be potentially toxic to this population. These 22 patients were otherwise matched in terms of performance status and other parameters to a control group of participants < 80. This includes a similar number of cycles administered. Patients ≥80 had a 3 fold higher rate of achieving DLT (p=0.06) compared to the control group enrolled at the same dose level. The toxicities observed include cardiovascular, gastrointestinal and infectious complications. Three patients were enrolled on molecular targeted treatments with no significant toxicities. We conclude that enrollment of patients ≥80 on phase I trials of chemotherapy agents is most likely associated with higher risk of DLT.

INTRODUCTION

The goal of phase I oncology trials is to determine the dose limiting toxicities (DLT) and maximum tolerated dose (MTD) for an experimental agent or regimen and to recommend a phase II dose for subsequent testing. Standard eligibility criteria include locally advanced or metastatic cancer that are refractory to standard treatment regimens or where no standard therapy exists. Patients in general must have a good Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1 or 2.

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As the patient population in the United States is aging, a larger proportion of people will become candidates for clinical trials [1]. Although oncologists have more readily embraced the concept of treatment for advanced malignancies in elderly patients, there is still some reluctance because of concern for undue toxicity in this patient population [2]. In a survey of American oncologists, 80% of the respondents agreed with published data showing that patients have better outcomes when they receive treatment on clinical trials, but 50% indicated that they declare patients unsuitable for clinical trials on the basis of age alone [3]. Additionally elderly patients are often disproportionately excluded because of a higher incidence of co-morbidities. When the enrollment of patient's ≥ 70 years old in 164 Southwest Oncology Group (SWOG) treatment trials between 1993 and 1996 was evaluated, a significant discrepancy was found between the rates of enrollment (13%) verses those in the US population with cancer (47%). These figures indicated that patients who were 70 years of age or older accounted for much of the shortfall in enrollment [4].

Over the past few decades the median life expectancy in the United States has increased [5]. By 2030, the number of persons in the United States over the age of 65 years will have doubled, and the number of persons over the age of 85 years will have quadrupled. Therefore the definition of who is an “elderly patient” will continue to evolve. Generally patients aged greater than 80 have multiple co-morbidities and a suboptimal performance status so there is a disproportionately higher rate of exclusion from clinical trials. However, due to the increasing proportion of patients within this cohort the quandary of how aggressive one should be is becoming more commonplace. This dilemma is more pronounced in the phase I trial setting as the therapeutic dose and associated drug toxicity is yet to be established

So far there have been no studies which have addressed the tolerability and toxicity of patients enrolled in phase I trials in this age group. From our observations as a comprehensive cancer center with 17 years of experience conducting phase I clinical trials, we hypothesized that patients ≥ 80 years may experience an excess in dose limiting toxicity. We thus conducted a retrospective review and compared the degree of adverse events and other important parameters in 2 groups of patients: patients ≥ 80 years and their younger counterparts (age less than 80) who were enrolled on the same phase I trials.

MATERIALS AND METHODS

This was a retrospective review conducted after receiving Institutional Review Board approval. We reviewed patient records from phase I trials conducted at our institution between 1994 and 2009. Out of 1195 patients that were enrolled on phase I studies during this time period, 31 pts were aged 80 or above and deemed to be eligible for this study (2.6%). Eligibility was defined by patients aged 80 years or greater who had been enrolled in phase I trials for cytotoxic or targeted systemic anti-cancer agents. Out of the 31 elderly patients who were potentially evaluable, analysis was conducted on 22 patients. Six patients were excluded from 2 studies because they were treated with photodynamic therapy and topical chemotherapy respectively for cutaneous malignancies. There was insufficient information available from the archived records on 3 patients. The following data was obtained : age, gender, performance status, number of prior chemotherapy treatments, length of time on study, reason for termination of treatment, nature of dose-limiting adverse events, total number of cycles administered, dose level in which the patient was enrolled and MTD for the respective study. Dose limiting toxicity was defined as per the respective study protocols.

The 22 patients were enrolled in 15 different trials [6-19], 3 of which were for targeted agents. This information was compared to the 123 patients who were enrolled on the same

studies and at the same dose levels as the patients who were ≥ 80. Thus elderly patient adverse event and DLT data was matched for younger patients who were enrolled at the same dose level on the same trials. For the patients enrolled in organ dysfunction trials comparisons were made for patients enrolled on the same dose level within the individual treatment cohorts (mild, moderate and severe levels of organ dysfunction).

Elderly patients (age ≥ 80 years) and patients with age < 80 years that were treated at the same dose level as the elderly patients in the phase I trials were compared in terms of the DLT rate, number of treatment cycles, performance status (PS) and number of prior therapies. The difference of DLT rate between two age groups was examined by chi-square test. The difference in number of treatment cycles, PS, and number of prior therapies between two age groups was examined by Wilcoxon signed rank sum test. All statistical analyses were done using SAS (SAS Institute, Cary, NC) and a p-value less than 0.05 is considered to be statistically significant.

RESULTS

A total of 22 patients aged 80 years or older participated in 15 phase I clinical trials at the Ireland Cancer Center of University Hospitals Case Medical Center from 1994-2009. Table 1 shows the data on patient characteristics in regards to age, performance status, number of prior therapies and trial characteristics. The median patient age was 83 years old (55% were males and 45% were females). Ninety percent of the patients had a performance status of 0-1. The majority of the patients (59%) were treatment naïve whereas only 13% of patients had 3 prior treatments. None of the patients were treated with more than 3 prior regimens.

Four of the 22 (18%) elderly patients developed dose limiting toxicities (DLT) in cycle 1 of treatment. These adverse events were atrial fibrillation, gastric perforation, sepsis due to prolonged neutropenia and intractable nausea/vomiting. The significant grade 3 and 4 adverse events are summarized in Table 2. In contrast only 8 patients out of 123 (6.5%) under the age of 80 experienced DLTs (Table 3). This difference reached borderline statistical significance (P=0.067). The mean number of treatment cycles administered in the elderly population in comparison to the younger individuals was equivalent (3.39 vs. 3.16, p=0.88). Table 4 shows the differences between the study and control groups for number of treatments, baseline PS and number of prior therapies before study participation. There were no differences amongst the groups for either of these characteristics.

Three patients (14%) of the 22 were enrolled on trials of targeted agents. None of them experienced significant toxicity and they all went off study because of disease progression. They were on study for an average of 47 days compared to 94 days for the patients who were on trials with cytotoxic agents. There were no treatment related deaths in the elderly population.

DISCUSSION

In a large retrospective review of 460 Phase I trials, 11,935 patients were assessed for toxicity and response to therapy [20]. The overall incidence of grade 4 toxicity was 14.4%. Patients on cytotoxic regimens had a severe adverse event rate of 17.4% while the rate was only 4.8% for all other non-chemotherapy trials [20]. In comparison the overall toxicity rate amongst the elderly patients in our study was 18%.

The results of our study serve to highlight the potential risk for toxicity in the elderly patient group (≥80 years) on phase I trials. There was an increase in the number of DLTs in this patient population when compared to the younger patients enrolled on the same studies that trended toward statistical significance (P=0.067). This despite the fact that the elderly

patients were equivalent to the younger cohort in terms of the performance status at enrollment, number of prior therapies, dose level and median number of cycles received. The analysis showed no statistically significant difference for these variables. A significant proportion of the elderly patients (59%) were treatment naïve which may explain their relatively good performance status at enrollment.

These results are in contrast to those recently reported by LoConte et al. who published a retrospective review of 242 patients with a mean age of 57. A multivariate logistic regression model was used to incorporate variables pertaining to socioeconomic status, demographics, co-morbidities, ECOG performance status and laboratory values to help predict toxicity. They concluded that age and comorbidity did not predict for the development of DLT in phase I chemotherapy trials. However there were only 7 patients (3%) who were over 75 years and no patients over the age of 80 [21] . Therefore the sample of patients in this age range was likely insufficient to make the comparison for this cohort of patients valid.

Another retrospective study was conducted at Johns Hopkins Oncology Center where clinical and pharmacokinetic data for 344 patients enrolled in 13 phase I clinical trials for 9 different drugs were examined. Patients were stratified according to age, however, only 1.5% were ≥ 75 years old. There was no significant difference between the younger (< 65yrs) and older patients (≥ 65yrs) with regards to dose, drug clearance and toxicity, but the ≥ 80 years age group was again underrepresented[1].

Our data is the most comprehensive representation of this unique minority of patients so far. However this is still a relatively small sample size and the study was also limited by the fact that it is a retrospective review. Over time there has been an increased tendency at our institution to include elderly patients in phase I trials. This is reflected by the observation that only 2 patients were enrolled in the year 1999 and the rest were after 2000. This tendency to raise the age bar for enrollment parallels the rise in the number of trials with molecularly targeted agents/biologic therapies. It is presumed that trials of molecularly targeted agents have more favorable toxicity profiles and, in some cases, treatment convenience in the setting of oral agents [20].

Since enrollment of patients aged ≥ 80 in phase I clinical trials are very limited at present, larger prospective studies would be required to validate these findings. Additional information pertaining to socioeconomic, co-morbidity, laboratory data and most importantly pharmacokinetic data should be incorporated into the analysis. It is important to highlight that patients enrolled on phase I trials are a selected group of patients and it is likely that those greater than the age of 80 are even more highly selected. Patients greater than 80 years may be good candidates for phase I trials with molecularly targeted agents, immunomodulators, etc. given the generally lower adverse event rate.

In conclusion, our analysis of phase I trials enrolled at a single institution notes that only 2.6% of those enrolled were over the age of 80. A higher rate of DLT was seen in this patient population despite the fact that the majority of patients were treatment naïve with no prior chemotherapy history.

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Table 1

Patient Characteristics:

Characteristic	No. (%)
Total No of Patients	22
Age (years)	
Median	83
Mean	83.5
Sex	
Male	12 (55%)
Female	10 (44%)
ECOG PS	
0	5 (23%)
1	15 (67%)
2	0
Unknown	2
No of Prior Treatments	
0	13 (59%)
1	5 (23%)
2	1 (4.5%)
3	3 (13.5%)
Type of Trials	
Hematologic	3 (20%)
Gynecologic	4 (27%)
Solid Tumor	8 (53%)
Organ Dysfunction	4 (27%)

Table 2

Listing of Grade 3 & 4 Adverse Events in Elderly Patients

Toxicity	Adverse Events	Grade	Dose Limiting Toxicity
Atrial fibrillation	1	4	Y
Diarrhea	2	3	
		3	
Thrombocytopenia	1	4	
Hematuria	1	4	
Hypotension, weakness	1	3	
Sepsis	1	3	Y
Neutropenia without infection	1	4	
Intractable nausea/vomiting	1	4	Y
Perforated gastric ulcer	1	4	Y
Periorbital edema	1	Allergic Reaction	
Pulmonary embolus	1	3	
Stomatitis	1	3	
None	10	-	

Table 3

Comparison of DLT rate

	Without DLT (%)	With DLT (%)	p-value
Age ≥ 80 yrs	18 (81.8)	4 (18.2)	0.067
Age < 80 yrs	115 (93.5)	8 (6.5)	

Table 4

The comparison of mean number of treatment cycles, performance status, prior therapies between elderly patients (≥ 80 yrs) and younger patients (< 80 yrs)

	Number of treatment cycles		
	mean	**std**	**p-value**
Age ≥ 80 yrs	3.39	2.38	0.88
Age < 80 yrs	3.16	1.17	
	Performance Status		
Age ≥ 80 yrs	0.75	0.44	0.18
Age < 80 yrs	0.4	0.5	
	Number of prior therapies		
Age ≥ 80 yrs	0.73	1.08	0.26
Age < 80 yrs	1.38	1.19	