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Participation and survival of geriatric patients in Phase I clinical trials: the Karmanos Cancer Institute (KCI) experience.

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Abstract

Background—Geriatric cancer patients (age 65 or older) comprise a majority of cancer cases in the United States, yet they are underrepresented in therapeutic clinical trials. It is therefore important to increase our understanding of their participation, survival outcomes, and recruitment barriers. This study aims to describe the demographics, treatment, toxicity, and overall survival (OS) of all patients ≥ 65 years of age who presented to the Phase I Clinical Trials service at Karmanos Cancer Institute (KCI).

Methods—A retrospective chart review was performed of all referred and seen patients ≥ 65 years of age at Phase I clinical service at KCI between 1995–2005. Data on demographics, comorbidities, tumor type, reason not enrolled, toxicities and OS were obtained.

Results—A total of 216 patients met the study criteria. The median age was 71 years. 114 (59%) patients were performance status 1. 102 (47%) patients were enrolled and of those 95 (44%) patients were treated. More than half of the patients failed to enroll with predominant reasons being protocol ineligibility (30%), loss to follow up (12%), patient refusal (8%), or unavailability of trial (2%). The median OS duration of treated patients was 8.4 months (95% CI: 6.2–10.5). This was significantly longer than the patients who failed to enroll or did not receive treatment ($p < 0.0001$).

Conclusion—This study suggests that elderly patients who were treated on a Phase I clinical trial(s) at our institution survived significantly longer than our elderly patients who did not receive treatment.

Keywords

Elderly; Phase I clinical Trials; Barriers; Survival

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1. Introduction

Geriatric cancer patients (age 65 or older) account for approximately 63% of cases of cancer in the United States (1). Despite a projected increment in the prevalence of cancer in the elderly population (2), there is a dearth of corresponding robust studies in the area of geriatric oncology. There is also a lack of reliable data on issues specific to cancer treatment in this population, such as pharmacokinetics, efficacy, and toxicity of treatments (3). This discrepancy originates from a substantial underrepresentation of elderly in both early and late phase clinical trials of therapy (4-6). While adults age ≥ 65 years comprise $> 60\%$ of the US population with cancer, their enrollment in registration trials is only 36% (4).

Phase I clinical trials in oncology are crucial to evaluate the safety of novel antineoplastic agents. These trials should determine the toxicity, maximum tolerated dose, and recommended dose for future evaluations and pharmacokinetics of either a new drug or a new combination regimen (7). Phase I trials therefore, serve as an essential link between the preclinical setting and subsequent trials evaluating efficacy.

Attempts have been made to identify barriers to the accrual of elderly patients to clinical trials in order to improve our understanding of elderly participation (8). Studies have analyzed general survival outcomes of a Phase I service although there is a lack of descriptive data that specifically addresses survival outcomes of elderly patients in Phase I clinical trials. For that reason, we assessed survival outcomes, demographics, treatment, and toxicity of geriatric patients (≥ 65 years of age), to describe our experience. Herein, we report our analysis of 216 geriatric patients who were seen in consultation by the Phase I Clinical Trials Program of KCI.

2. Materials and Methods

This was a population based retrospective review of all patients ≥ 65 years old who presented to the Phase I clinical trials service at KCI between 1995-2005. KCI is a Comprehensive Cancer Center with an established Multidisciplinary Phase I Clinical – Pharmacology Team located in Detroit, MI. The program is one of sixteen National Cancer Institute funded phase I clinical pharmacology programs in the United States. Our program has been successful in the clinical development of several new cytotoxic chemotherapy and biologic agents currently utilized in clinical practice. Wayne State University Human Investigation Committee and Institutional Review Board approval was obtained to review patients' medical records. We performed a thorough review of both outpatient clinic based and hospital based medical records of KCI. Demographic data (age, gender, race), pertinent oncologic data [tumor type, performance status (PS), treatment status, enrollment status, type of chemotherapy, number of cycles, toxicity, referring physician], medical information (cardiovascular, hematological, endocrine co-morbidities, medication profile), trial participation details (enrollment, refusal, eligibility, follow up) were extracted from physician's clinic notes. . RECIST criteria were used to assess response. Response status was described as complete remission (CR), partial remission (PR), stable disease (SD), progressive disease (PD), or not evaluable (NE). The patients were divided into three mutually exclusive groups: patients considered (PC) but not enrolled; patients enrolled (PE) but not treated; and patients treated (PT). We will refer to this categorization as the Phase I patient groups.

2.1 Statistical Methods

Patient characteristics were summarized with descriptive statistics. Categorical variables were compared by Phase I patient group using Fisher's exact test. Overall survival (OS) was

measured from the date each patient was first considered for a Phase I trial until their death from any cause. Patients were censored for OS as of the most recent date on which it had been confirmed that they were still alive. Standard Kaplan-Meier estimates of the censored OS distributions were computed. Due to the modest sample size of the PE group, survival statistics (e.g., median, and confidence interval (CI) estimates) were estimated more conservatively using linear interpolation (9) among successive event times on the Kaplan-Meier curves. Censored time to progression (TTP) and OS distributions were compared via the log-rank test (9). To control for PS confounding of the relationship of patient group and OS, stratified log-rank tests were also performed using PS (levels 0-2 only) as the stratification factor (10).

3. Results

A total of 216 patients met the study criteria. Patient demographics are detailed in Table 1. The median age was 71 years (range 65-87) with 87% Caucasians and 63% males. PS at baseline (i.e., at the time of first consideration for a Phase I trial) was known for 192 patients. PS was: 0-1 in 71% of patients; 2 in 16%; 3 in 11%; and 4 in 2%. Colorectal (27%), lung (15%) and prostate (8%) were the three most common cancers. More than 60% of patients had a history of concurrent cardiovascular disease whereas renal, hepatic and hematological disease was found in less than 7% of patients at baseline.

Of the 216 eligible patients, 114 were PC, 7 PE, and 95 PT. Figure 1 describes the follow up pattern of the patients that were seen in consultation with the Phase I service. More than 20% of patients were considered more than once for enrollment into a Phase I clinical trial. A total of 102 (47%) patients finally enrolled of whom 95 (44%) patients were finally treated. More than 20 patients were treated at least two or more times. Twenty-five of the 95 treated patients (26%) *completed* at least one cycle, followed by 2 cycles completed (27%), 3 cycles completed (9%), and 4 cycles completed (9%). Lack of enrollment was mainly due to patient ineligibility (30%), no follow up (12%), patient refusal (8%), or unavailability of trial (2%).

Among the 95 PT, 54% received a cytotoxic agent(s), 62% received a biologic agent(s), and 17% received a combination therapy. 69% of patients were eventually found to have PD, followed by 15% SD, 11% who were NE, 3% PR, 1% CR.

The three most common Grade 3-4 toxicities were: leucopenia (15%), electrolyte abnormalities (11%), and anemia (4%). 23% of PT were hospitalized at least once during their treatment course.

The OS data are very mature, since the censoring rate is extremely low (12/216 = 6% of patients were still alive). Median follow-up among the 12 censored patients was 25.8 months. The median OS for PC, PE and PT was 3.9 months (95% CI: 3.3-4.8), 2.2 months (95 % CI: 0.3-4.2), and 8.4 months (95% CI: 6.2-10.5). OS duration (see Figure 2) was highly significantly different across the 3 patient groups (PC, PE, PT), with $p < 0.0001$. Multiple comparisons revealed that OS duration of PT was significantly longer than that of either PC or PE ($p < 0.0001$ in each case), and that OS duration of PC was significantly longer than that of PE ($p < 0.001$).

Comorbidity prevalence was a potential confounder of the relationship of Phase I patient group and OS. Consider the distribution of 5 specific comorbidities by Phase I patient group (see Table 2). The prevalence rates of each of the 5 comorbidities did not differ significantly by Phase I patient group ($p > 0.22$ in each case). Moreover, since the variation by Phase I patient group in each set of prevalence rates was deemed not clinically significant, we disregarded comorbidity prevalence as a potential confounder.

PS was another potential confounder of the relationship of Phase I patient group and OS. Consider the distribution of PS by Phase I patient group (see Table 3). PS 3-4 patients would be ineligible for nearly all Phase I trials, hence there are none of them among the PE or PT subgroups. The imbalance in PS across PC, PE, and PT is perhaps best indicated by the observation that PS 0-1 patients comprised 47%, 75% and 73% of those 3 subgroups, respectively. The association of PS with Phase I patient group was highly statistically significant ($p < 0.0000001$, by Fisher's exact test). In addition, PS (in 4 groups, PS 0, 1, 2, and 3-4) was very strongly associated with duration of censored OS ($p < 0.0001$). Hence, PS was clearly a confounder of the Phase I patient group and OS relationship.

To control for this confounding, we first focused on only the 169 patients with PS 0-2, as they are present in all 3 Phase I patient groups. We then performed a PS-stratified log-rank test of OS by Phase I patient group which revealed that censored OS duration was still highly statistically significantly different across the 3 Phase I patient groups ($p = 0.0003$). Thus, it appears that our elderly patients who got treated on a Phase I trial(s) survived significantly longer than our elderly patients who did not get treated on a Phase I trial(s), even after adjusting for the influence of PS.

4. Discussion

Geriatric cancer patients may require more thorough care when instituting systemic therapy because of the biological changes of aging and the uncertainty of pharmacokinetic and pharmacodynamic profile of chemotherapy and other medications. This concern is common among oncologists whose perceived incapacity of elderly patients to undergo therapy in an early phase clinical trial may hinder participation and therefore enrollment. Hence, it is imperative to study the outcome of elderly patients in early phase clinical trials, specifically Phase I, to address this qualm.

To our knowledge, this is the first report on survival of geriatric patients treated on Phase I clinical trials. OS duration of PT was significantly longer than that of either PC or PE. This is comparable to results obtained from an M.D. Anderson study where median OS was reported to be 9 months in the Phase I clinic with approximately half of the studied patient population aged ≥ 60 years (11). Aligned with this, another study reported a 5 month median OS of patients treated with cytotoxic agents on Phase I clinical trials, where age over 65 years was independently associated with the risk of toxicity (12). The difference in the median survival can be explained partly by the type of agent used, as our study consisted predominantly of biologics and this is consistent with the M.D Anderson report. In a clinical outcome evaluation of patients in Phase I trials at Royal Marsden Hospital, median OS in elderly (≥ 65 years) patients was noted to be approximately 60 weeks (approx. 14 months) (95% CI 25.6 - 94.6 weeks). The elderly comprised approximately 31% of their entire study population (13).

These results suggest that the prognosis of elderly patients referred to a Phase I clinic is comparable to the rest of patient population presenting to such a clinical service. Although the prognosis remains poor overall, it still presents an optimistic view of the role of elderly in Phase I cancer clinical trials. At least 20 (21%) of our 95 PT were well enough to participate in more than 1 clinical trial. Our study presents a more positive view of elderly participation in Phase I clinical studies than is generally assumed, suggesting a more robust population than previously considered.

There is a general perception among health care providers that the elderly may not be strong enough to participate in clinical trials, thus leading to lower enrollment into clinical trials. However, most elderly people show willingness to consider participation in cancer clinical

trials, although they may not be actively seeking trials (14). It should be noted that 72% of the 192 patients with known PS in our study had PS 0-1, which suggests a more functional elderly population with perhaps a more indolent disease course. However, Phase I clinical trials generally enroll patients with $PS \leq 2$. Therefore interpretation of these results should be made in the proper context of patient selection by relatively healthier performance status. Nonetheless, the final assessment of OS by Phase I patient group (using the PS-stratified log-rank test) was limited to only the 169 patients with $PS \leq 2$, and still identified a highly significant association of Phase I patient group with OS.

It is important to understand barriers to enrollment in Phase I trials in order to characterize interventions to improve patient accrual. Analyzing elderly underrepresentation and recruitment failure is crucial to design effective accrual strategies. Patient ineligibility (30%), loss to follow up (12%), refusal (8%), and lack of trial (2%) were the most common reasons for enrollment failure. In a study from Princess Margaret Hospital in Canada, patient ineligibility (24.7%) was reported to be the predominant reason for recruitment failure, followed by refusal (14.4%), pursuit of other treatments (12.6%), no trials available (8.4%), and loss to follow up (5.4%) (15). Another report from Royal Marsden also identified various reasons for recruitment failure highlighting deteriorating performance status, availability of other treatment options, patient uncertainty, and refusal as important reasons (16). Other studies have described barriers related to logistics and knowledge (4). There is some similarity among the aforementioned reports with regards to the nature of barriers reported. Although the mean age documented in the Canadian study was 56.6 (SD 11.1) and the median age reported in the UK study was 59 (range 19-78), age per se was not observed to be a significant barrier. Nevertheless, the Canadian group did mention that elderly patients (> 70 years of age) appeared less likely to be eligible for Phase I trials (15).

Our report suggests similar barriers to enrollment that are encountered in other Phase I settings. More focused effort is required to decipher the relationship between chronological age and recruitment in early Phase clinical trials. Age, in essence, may merely be a perceived barrier as opposed to a true impediment. In addition, the potential for achieving some therapeutic benefit remains the most important motivator for trial participation (17). Multiple parameters have to be taken into consideration including patient characteristics, type of therapy, and referral pattern in order to estimate an impact on response. Nevertheless, our study represents an optimistic view of survival pattern which can potentially affect patient perception for trial participation.

In our review of 216 elderly patients, the overall accrual rate onto Phase I trials was 47%, which is higher as compared to other centers. The Canadian and the UK groups reported accrual rates of 29.5% and 32%, respectively (15-16). Multiple factors contributed to our higher accrual rate including a dedicated Phase I service, a strong referral pattern, and possibly healthier patient characteristics. Contemplating necessary steps to overcome our observed barriers will help further improve our accrual to clinical trials. Approximately 20% of our patients failed to enroll because of loss to follow up or refusal, which suggests that better logistical support, follow up methods and patient education, can potentially improve our accrual rate.

The limitations of our study include its retrospective nature, review of patients over a long (11 year) period of time, relatively small number of patients, and the possibility of residual confounding by PS despite our statistical efforts to control for it. Our study period may not truly reflect the current status of drug development and its impact on response rates and patient survival. Our results need to be interpreted with caution when compared to other studies as the type of therapy administered in other centers may have been different. Further elaboration of the agents used may be useful to address this bias. Another weakness of our

study is the lack of objective parameters to analyze patient response rates and its effect on median survival. The OS duration of our patients should also be interpreted carefully, considering their performance status.

In conclusion, we have demonstrated that PS is a strong confounder of the principal relationship of interest in our study: Phase I patient group with OS. Nonetheless, we have demonstrated via PS-stratified log-rank testing that the significant univariate relationship persists even after controlling for confounding by PS. Thus, it appears that our study suggests that elderly patients who got treated on a Phase I trial(s) at our institution survived significantly longer than our elderly patients who did not get treated on a Phase I trial(s), even after adjusting for the influence of PS. This observation lends support to the hypothesis that patients age ≥ 65 can tolerate and benefit from being treated on a Phase I cancer clinical trial.

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Biographies

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This figure describes the flow of the 216 study eligible patients from the first time they were considered for a Phase I trial, then to possible enrollment, and then to possible treatment.

Figure 2. Kaplan-Meier graph of overall survival (OS) by Phase I patient group

The median OS for PC, PE and PT was 3.9 months (95% CI: 3.3 - 4.8), 2.2 months (95% CI: 0.3 - 4.2), and 8.4 months (95% CI: 6.2 - 10.5), respectively. The 6-month OS rate for PC, PE and PT was 36% (95% CI: 27 - 45%), 13% (95% CI: 0 - 43%), and 60% (95% CI: 51 - 70%), respectively. The 12-month OS rate for PC, PE and PT was 12% (95% CI: 6 - 18%), 0% (95% CI: not available), and 35% (95% CI: 25 - 45%), respectively. Since no PE patients survived to 12 months, the 95% CI of their 0% 12-month OS rate cannot be calculated.

Table 1Patient Characteristics ^a (N=216)

Characteristics	Total (%)
Age, median (years)	71 (range 65-87)
Sex	
Male	136 (63)
Female	80 (37)
Race	
Caucasian	181 (87)
African American	26 (12)
Other	2 (1)
Performance Status (PS)	
0	24 (13)
1	114 (59)
2	31 (16)
3	21 (11)
4	2 (1)
Tumor Types	
Head and Neck	5 (2)
Thyroid	1
Breast	12 (6)
Lung	33 (15)
Esophagus	5 (2)
Stomach	2 (1)
Colorectal	57 (27)
Pancreas	17 (8)
Other GI	11(5)
Prostate	18 (8)
Bladder	4 (2)
Kidney	16 (7)
Other GU	1
Melanoma	17 (8)
Sarcoma, soft tissue	3 (1)
Hodgkins Lymphoma	1
NHL	1
Other Misc	11 (5)
Co-morbidities ^b	
Cardiovascular	143(66)
Renal	14(6)
Hepatic	1(1)
Hematologic	6(3)
Endocrine	65(30)

^aThese characteristics were recorded at baseline, i.e., at the time the patient was first considered for a Phase I trial.

^bCardiovascular disease was defined as any history of hypertension, coronary artery disease, or cerebrovascular disease.

Renal disease was defined as any presence of chronic kidney disease with GFR < 90.

Hepatic disease was defined as presence of an abnormal liver function panel (AST, ALT, bilirubin, or hepatitis profile).

Hematologic disease was defined as the presence of abnormal hemoglobin, white blood count, and/or platelets.

Endocrine disease was defined as presence of diabetes mellitus and/or thyroid dysfunction.

Table 2Distribution of all 216 study eligible patients by comorbidity ^a prevalence and by Phase I patient group ^b

Comorbidity	Phase I patient group			
	PC	PE	PT	p-value ^c
Cardiovascular	79	5	59	0.5349
	(69%)	(71%)	(62%)	
Renal disease	7	0	7	0.8668
	(6%)	(0%)	(7%)	
Hepatic disease	0	0	1	0.4722
	(0%)	(0%)	(1%)	
Hematologic	5	0	1	0.3645
	(4%)	(0%)	(1%)	
Endocrine disease	40	2	23	0.2243
	(35%)	(29%)	(24%)	
Total patients	131	7	91	

^a Comorbidities are defined in Table 1 footnotes. Percentages shown are of the column totals.^b Patients considered (PC) but not enrolled; patients enrolled (PE) but not treated; and patients treated (PT).^c From Fisher's exact test.

Table 3Distribution of 192 patients by PS and by Phase I patient group ^a

PS	Phase I patient group			Total
	PC	PE	PT	
0	8	0	16	24
	(8%)	(0%)	(18%)	
1	47	3	64	114
	(47%)	(75%)	(73%)	
2	22	1	8	31
	(22%)	(25%)	(9%)	
3	21	0	0	21
	(21%)	(0%)	(0%)	
4	2	0	0	2
	(2%)	(0%)	(0%)	
Total	100	4	88	192

PS was unknown for 24 of the 216 patients. Percentages shown are of the column totals.

^aPatients considered (PC) but not enrolled; patients enrolled (PE) but not treated; and patients treated (PT).