Barriers to Study Enrollment in Patients With Advanced Cancer Referred to a Phase I Clinical Trials Unit

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Key Words. Phase I trial • Enrollment • Consults • New patients • Patient referral • Barrier

Learning Objectives

Assess barriers for advanced cancer patients to participate in phase I trials.

Discuss strategies to improve the rate of enrollment of cancer patients in phase I trials.

ABSTRACT

Background. We conducted this retrospective study to identify reasons that patients referred to a phase I clinical trial failed to enroll or delayed enrollment onto the trial.

Materials and Methods. Outcome analyses were conducted independently on data collected from electronic medical records of two sets of consecutive patients referred to a phase I clinical trial facility at MD Anderson Cancer Center. Data from the first set of 300 patients were used to determine relevant variables affecting enrollment; data from the second set of 957 patients were then analyzed for these variables.

Results. Results from the two sets of patients were similar. Approximately 55% of patients were enrolled in a phase I trial. Patients referred from within MD Anderson were more likely to be enrolled than patients seen originally outside the insti-

tution ($p = .006$); black patients were more likely than white patients to enroll (69% vs. 43%; $p = .04$). The median interval from the initial visit to initiation of treatments was 19 days. Major reasons for failure to enroll included failure to return to the clinic (36%), opting for treatment in another clinic (17%), hospice referral (11%), early death (10%), and lack of financial clearance (5%). Treatment was delayed for three weeks or more in 250 patients; in 85 patients (34%), the delay was caused by financial and insurance issues.

Conclusion. Failure to return to the clinic, pursuit of other therapy, and rapid deterioration were the major reasons for failure to enroll; lengthy financial clearance was the most common reason for delayed enrollment onto a phase I trial. *The Oncologist* 2013;18:1315–1320

Implications for Practice: Early drug development is essential as a first step in guiding the development of cancer therapies. Therefore, sufficient enrollment of patients into phase I clinical trials in a timely fashion is key to facilitating cancer drug investigation. We present the results of a study designed to investigate barriers to study enrollment in patients with advanced cancers referred to a phase I clinical trials unit. Careful coordination between referral and phase I services may result in the referral of appropriate patients, thus increasing the rate of study enrollment. In addition, overcoming potential financial hurdles may significantly help facilitate rapid enrollment.

INTRODUCTION

Patients with advanced refractory cancer are eligible to participate in phase I trials [1]. Recently, we demonstrated that patients who were referred to the phase I clinical trials program at MD Anderson Cancer Center had a median overall survival of approximately 10 months after referral [2]. Sick patients may do considerably worse (median survival of 3.2 weeks after initial intensive care unit admission and one day after receiving cardiopulmonary resuscitation) [3]. Options for

patients whose disease has failed to respond to conventional treatments may include seeking complementary approaches [4], hospice care, or participating in a clinical trial [5–7].

A meta-analysis spanning eleven years of patients with cancer enrolled in a phase I trial reported an overall combined complete and partial response rate of 11%. An additional 34% of patients demonstrated less than a partial response or stable disease [1, 6]. Despite the potential benefit of participating in

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a phase I trial, patients who are seen in a facility conducting phase I clinical trials may have enrollment delayed or may not be able to participate in a trial or may choose not to participate [8, 9]. Enrollment delay may result in ineligibility of patients for a specific phase I trial because of continuous tumor progression-related systemic effect. To investigate timelines and factors affecting enrollment into phase I clinical trials after referral, we undertook the present study.

MATERIALS AND METHODS

Patient Selection

Two sets of consecutive candidate patients with cancer who were referred to or came as new patients to the Department of Investigational Cancer Therapeutics (phase I clinical trials program) at The University of Texas MD Anderson Cancer Center (MDACC) were included in this retrospective chart-review study. Data from the first set of 300 patients were reviewed from December 31, 2010, backward, followed by the other set of 957 patients who were referred to the phase I clinical trials program from August 1, 2011, to February 29, 2012. Two separate reviewers reviewed the charts independently for each set of patients. Approximately 5% of the patients were randomly selected for cross review to confirm accuracy. Any disagreement between the reviewers or any uncertainty was brought to a joint chart review with the corresponding author to reach an agreement. Data from the first set of patients were used as a training dataset to determine variables that might affect enrollment. Data from the second set of patients were validated using the same variables. This study was conducted in accordance with the MD Anderson institutional review board guidelines.

Data Collection

Clinical information was extracted from the electronic medical records at MDACC. All patients were followed until July 31, 2012, or death. Variables collected included age, gender, race, residence, time of the initial phase I clinic visit, time of the therapy under the first phase I clinical trial, reasons for lack of participation, and time of death. Reasons for lack of participation in a trial were categorized as follows: (1) death before starting protocol treatment or before enrollment; (2) need for referral to hospice care; (3) patient declined participation for any reason; (4) ineligibility for a phase I study because of poor performance status, comorbidity, and/or abnormal laboratory tests; (5) financial reasons for lack of participation (e.g., insurance would not cover or lack of adequate insurance); (6) perceived preferable treatment options, including standard therapy or phase II or III trials; (7) off-protocol treatment in the phase I clinic; (8) patients did not return, preferred to be treated outside MDACC, or unknown. If more than one category applied, the patient was assigned to the single best category using the following rule: If the patient had reasons 2, 4, and 5, the patient was assigned to category 2 (the smallest number). The data were entered into a Microsoft Excel data sheet for further statistical analyses.

Statistical Analyses

Categorical data were described using contingency tables. Continuously scaled measures were summarized with descriptive statistical measures (i.e., median with range), whereas overall survival rates were estimated using the Kaplan-Meier method and compared using the log-rank test. Patients still alive at the

time of data analysis were censored at that time (July 31, 2012) if they had not been enrolled into a phase I trial. All patients referred to the phase I clinical trials facility during the allotted time were included in the analysis, regardless of whether they received treatment. The chi-square test or Fisher exact test were used to examine the association between two categorical variables. Statistical inferences were based on two-sided tests at a significance level of $p < .05$. Statistical analyses were carried out using GraphPad Prism 5 software (GraphPad Software, Inc., San Diego, CA, <http://www.graphpad.com>).

RESULTS

Study Patient Population

Between August 1, 2011, and February 29, 2012, a total of 957 patients with advanced cancer were seen at the phase I clinic at MDACC (Table 1). Of these, 803 (84%) were referred from inside MD Anderson, and 154 (16%) were new patients referred from outside the institution. All patients were evaluated and then given information about a potential phase I trial if they were eligible. Their median age was 58 years old; 12.5% of patients were 70 years or older ($n = 120$), and 0.6% were children 18 years or younger ($n = 6$). There were more women ($n = 527$; 55%) than men. In this cohort of patients, 76% were white ($n = 728$), 10% were Hispanic ($n = 99$), 9% were black ($n = 89$), and 5% were other ($n = 41$). The majority of patients had gastrointestinal cancer ($n = 281$; 29%), gynecologic malignancies ($n = 160$; 17%), breast cancer ($n = 94$; 10%), sarcoma ($n = 87$; 9%), head and neck cancer ($n = 82$; 9%), lung cancer ($n = 82$; 9%), or melanoma ($n = 50$; 5%). Significantly more patients with gastrointestinal cancer and melanoma were referred to the phase I clinical trials facility as new patients than those with other malignancies, who were mainly referred from the inside MD Anderson ($p < .0001$).

Enrollment of the Referred Patients Into Phase I Trials

Initially, we reviewed data from 300 patient charts from December 31, 2010, backward as a pilot study to identify various factors that contribute to delay in or lack of participation in phase I trials and to determine the time lag from initial office visit (time of initial phase I clinic visit) to the first dose on a phase I trial (time of therapy). Among these 300 patients, 151 (50.3%) received therapy in a phase I trial. Median time from referral to first dose was 21 days. Patients who received therapy under a phase I clinical trial after referral had a median survival of 282 days, compared with 161 days for those who had not enrolled in a phase I trial ($p = .01$). This was true (289 days vs. 196 days; $p = .007$) even when patients who died within 30 days of the initial visit to the phase I trials facility were removed from the analyses.

After exploratory analysis of data from the above 300 patients, we conducted an independent chart review of data from 957 patients seen at the phase I clinical trials facility between August 1, 2011, and February 29, 2012. Of 957 referred patients, 527 patients (55%) were enrolled into phase I trials. The median time from the first visit to the first treatment in a phase I trial was 19 days (interquartile range of 14–30 days). Further analyses showed no significant differences in age, gender, pathologic diagnosis, and geographic residence between patients who enrolled in a phase I trial and those who

Table 1. Patient characteristics (*n* = 957)

Characteristic	Enrolled	Not enrolled	<i>p</i> value ^a
	<i>n</i> = 527 (55%)	<i>n</i> = 430 (45%)	
Age (years)	58	57	
Median (range)	(17–84)	(17–79)	
Gender			
Men	234 (54%)	196 (46%)	.74
Women	293 (56%)	234 (44%)	
Race distribution			
White	387 (53%)	341 (47%)	.05
Black	61 (69%)	28 (31%)	
Hispanic	56 (57%)	43 (43%)	
Others	23 (56%)	18 (44%)	
Cancer diagnoses by subspecialty			
Gastrointestinal	154 (55%)	127 (45%)	.46
Gynecologic	90 (56%)	70 (44%)	
Breast	51 (54%)	43 (46%)	
Sarcoma	55 (63%)	32 (37%)	
Thoracic	48 (59%)	34 (41%)	
Head and neck	47 (57%)	35 (43%)	
Melanoma	22 (44%)	28 (56%)	
Genitourinary	23 (59%)	16 (41%)	
Endocrine	14 (50%)	14 (50%)	
Neurologic	11 (44%)	14 (56%)	
Dual primary	7 (58%)	5 (42%)	
Unknown primary	3 (30%)	7 (70%)	
Hematologic	2 (29%)	5 (71%)	
Status of patients			
Referred from inside MD Anderson	458 (57%)	345 (43%)	.006
New patients ^b	69 (45%)	85 (55%)	

^a *p* values are for enrolled versus nonenrolled patients.^b New patients are those referred from outside MD Anderson.

did not. Significantly more patients referred from inside MD Anderson (458/803; 57%) participated in phase I trials than those referred from outside (69/154; 45%; *p* = .005). White patients were less likely to be enrolled in phase I trials than nonwhites (*p* = .04), and black patients were more likely to be enrolled (61/89; 69%) in phase I trials than nonblacks (46/868; 54%; *p* = .007). Eight of the nine patients who were ≥80 years old were referred from inside MD Anderson; all nine patients were enrolled in phase I trials.

Reasons for Lack of Participation in a Phase I Trial

The initial chart review of data from 300 patients revealed the following reasons for failure to enroll in a phase I trial: (1) patient did not return to the phase I trial clinic (23%); (2) patient was treated in another department at MD Anderson (21%); (3) patient was not eligible for a phase I clinical trial (20%); (4) patient received planned hospice care (11%); (5) financial issues (10%); (6) patient was not interested in participating in a phase I trial (7%); (7) patient was treated off protocol in the phase I trial clinic (7%); or (8) patient died before starting a phase I trial (2%). A total of 957 consecutive patients were referred to a

Reasons that Cancer Patients Did Not Participate in Phase I Trials (*n* = 430)

Figure 1. Pie chart shows percentages of patients with cancer who were first seen in the phase I clinical trials facility at MD Anderson Cancer Center from August 1, 2011, to February 29, 2012, according to reason for failure to enroll onto a phase I clinical trial. A total of 430 of 957 patients failed to enroll.

phase I clinical trial; 430 of these did not participate in a phase I trial. The following were the most frequent reasons for failure to enroll: (1) patient did not return to phase I trials clinic (36%), (2) patient opted for treatment in another MD Anderson clinic (17%), (3) patient accepted hospice referral (11%), or (4) patient died (10%) (Fig. 1). Only 5% of the patients who were not enrolled in a phase I trial failed to enroll because of financial issues, and only 6% were not enrolled because they were ineligible.

Reasons for Delayed Enrollment and Treatment in a Phase I Trial

Further analyses of data from our cohort of 957 patients identified 250 patients in whom treatment was not initiated for three weeks or longer. The median interval from the first visit to the phase I trial clinic to the first dosing in a phase I clinical trial in this cohort of patients was 30 days. Compared with those who received their first dose in a phase I trial within three weeks after their initial phase I clinic visit, the cohort of patients who received their first dosing three weeks from the first office visit or beyond showed no significant differences with regard to age, gender, race, or pathologic diagnoses. We found that the major reason for enrollment delay was that the business office needed extra time for financial clearance (*n* = 85; 34%) (Fig. 2). Additionally, enrollment was delayed if the patient required extra time if initial tests were abnormal (*n* = 25; 10%), if the patient was admitted for acute medical illness (*n* = 24; 10%), or if the patient was receiving concurrent therapy that did not allow the initiation of the phase I trial (*n* = 21; 8%). Finally, the need for additional time to arrange traveling and/or relocation delayed enrollment for 19 patients (8%).

DISCUSSION

The objective of phase I trials is to define dose levels and toxicity of new agents or combinations, describe responses, and evaluate pharmacokinetics and pharmacodynamics of new agents. Phase I trials are associated with a toxicity-related mortality of only 0.49%, and objective response rates generally range from 4% to 10% [1, 6, 10]; however, higher response

Figure 2. Pie chart shows percentages of patients with cancer who were first seen in the phase I clinical trials facility at MD Anderson Cancer Center from August 1, 2011, to February 29, 2012, classified by reasons for delay in enrollment for ≥ 3 weeks (from first visit to first dose on trial). A total of 250 of 957 patients had delays of ≥ 3 weeks.

rates of more than 20% to 30% can be seen with molecular matching of patients with drugs [7, 11–14]. Therefore, participating in a phase I trial may provide an appropriate option for a person with cancer who desires further intervention after the standard of care has failed to control disease.

Enrollment in cancer clinical trials is low; approximately 1.7% of those with cancer. Enrollment rates are even lower for those 75 years and older and for nonwhites [15]. Accrual rates into phase I clinical trials are much higher when patients are referred to a dedicated phase I clinical trials facility, with rates ranging from 14% to 29.5% [9, 16–18]. Factors affecting enrollment may include the patient's attitude about phase I trials, the availability of suitable trials, other treatment options, patient ineligibility because of poor functional status, patient comorbidities, rapid tumor progression, and financial issues [15, 19–24]. Factors that enhance enrollment in phase I trials might be therapeutic misconception and therapeutic optimism when patients run out of treatment options [25].

In this retrospective study, approximately 55% of the referred patients were enrolled in a phase I clinical trial. These enrolled patients received their first dose of therapy under a phase I clinical trial within a median interval of 19 days from the first visit to the clinic. Major reasons for failure to enroll included failure to return, opting for therapies at other clinics, and rapid clinical deterioration. Difficulty with financial issues was a barrier for only 5% of those who were not enrolled; however, this might be underestimated because a significant number of patients ($\sim 36\%$) did not return after their initial visit. Financial issues were a major reason for delay for 34% of those who delayed enrollment beyond three weeks after the initial phase I clinic visit.

Previous studies have reported phase I trial enrollment rates of 14% to 44% [9, 16–18, 26]. Our enrollment rate was 55%, which might be the result of one or more factors. A high percentage of enrolled patients were referred from inside MD Anderson. Of these, 86% enrolled in a phase I trial versus 49% of those referred from inside Princess Margaret Hospital in To-

ronto, which reported an enrollment rate of 29% [9], and 51% of patients referred from inside Daniel den Hoed Cancer Center in Rotterdam, which reported an enrollment rate of 44% [26]. Patients referred from inside the institution were more likely to be enrolled into a phase I trial, perhaps because of physicians' familiarity with the requirements of these phase I trials. Other possible reasons include that the clinic was highly specialized, with physicians engaged exclusively in phase I clinical trials, and the presence of dedicated ancillary assistance, including nurses, study coordinators, and business office personnel, who focused exclusively on supporting patients on these trials. Furthermore, patients were prescreened by a nurse, who helped them understand the demands of these trials and tried to ensure that patients who were too ill to participate knew it was unlikely that they would be eligible. Our pre-referral screening process ensured that patients who were unlikely to meet eligibility criteria were not referred to our phase I trial facility; thus, our participation rate was higher than centers where more significant numbers of patients did not enroll because of ineligibility.

Our findings should include several considerations. As is always inherent to retrospective methodology, selection bias may limit the generalization of our findings. Furthermore, the actual reasons for failure to enroll or delays in enrollment might not be identifiable from the electronic medical record. Unfortunately, a significant percentage of patients ($\sim 36\%$) did not return after their initial visit, and their information was not available for data analysis. In addition, these results were obtained from a single comprehensive cancer center, and they may not be applicable to another institution where there is not a dedicated phase I clinical trial facility.

Despite these limitations, several lessons were learned from this retrospective study. Many factors contributed to the high accrual rate onto our phase I cancer clinical trials, but preselection of patients who were prepared and able to participate in a phase I trial was thought to be one of the key steps [4, 27]. In general, prior studies suggested that racial and ethnic minorities, women, and the elderly were less likely to be enrolled into cancer clinical trials than whites, men, and younger patients [15, 28–30]. However, in our clinic, the above phenomena did not hold true, which is worthy of further investigation. Nonwhites, especially blacks, were more likely to be enrolled into a phase I clinical trial. Women and men had similar rates of enrollment (56% vs. 54%). Approximately 59% of patients aged 70 years or older were enrolled after referral, which was similar to the rate for younger patients (54%; $p = .38$).

In our study, only a small percentage of patients failed to enroll because of financial reasons (5%) or ineligibility (6%). However, lengthy financial issues were the most common factor delaying enrollment, affecting 34% of patients who were delayed by three weeks or more between the first clinic visit and receipt of the first dose of drug. Several factors might be relevant here. First, legislation in the United States mandating coverage of trials with therapeutic intent has undoubtedly helped enrollment. Nevertheless, it is our experience that a robust and specialized business office is needed to gain financial clearance for trials, and that the business office must communicate closely

with physicians and study coordinators. The low rate of failure to enroll because of ineligibility is of interest. It has been well documented that there has been a rapid rise in eligibility criteria for phase I trials (31). The low rate of ineligibility and high enrollment rate might be the result of several factors: (1) high rate of referral of patients from within MD Anderson, a tertiary care center where physicians were familiar with phase I trials; (2) presence of a nurse in the business office who prescreened patients referred from other institutions using a simple but effective questionnaire to ensure that patients who were too ill and/or who had insufficient financial support understood that a phase I trial was unlikely to be an appropriate option; (3) the availability of a large menu of phase I trials ($n = 128$ in 2012) so that openings were available on multiple trials; (4) a high number of investigator-driven trials (about 50% of open trials) with relaxed eligibility criteria; (5) pre-referral discussion with patients regarding the requirements and intensity of phase I trials as a routine of practice; (6) social service personnel who assisted patients with appropriate hotel and travel recommendations; (7) the presence in the clinic of experienced doctors of pharmacy who were knowledgeable about drug interactions that could affect eligibility; (8) dedicated phase I physicians who had the time and experience to enroll and manage patients on trials; and (9) well-trained research nurses and study coordinators who were able to recognize and resolve enrollment barriers and delays.

CONCLUSION

Our data suggest that financial issues may be the major hurdle that delays enrollment onto phase I trials. Because these pa-

tients usually have rapid disease progression, it may be worthwhile to reduce financial barriers to participation in studies. We anticipate that careful coordination between referring and phase I trial physicians, as well as a robust infrastructure suitable to phase I trials, can be associated with a high rate of study participation and timely enrollment of patients referred to a phase I clinical trial facility.

AUTHOR CONTRIBUTIONS

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Provision of study material or patients.

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DISCLOSURES

Filip Janku: Biocartis, Novartis, Roche, Transgenomic, Trovogene (RF); **Ralph G. Zinner:** Eli Lilly, GlaxoSmithKline (RF). The other authors indicated no financial relationships.

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