Temporal evolution of patient characteristics enrolled on phase I trials

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Summary Purpose Phase I trials serve a crucial role in anticancer drug development. Given the explosion in the number of both approved anticancer therapies and agents in development, we hypothesized that the characteristics of patients enrolling on phase I clinical trials is evolving. **Patients and Methods** We reviewed 476 published phase I trials over the past decade encompassing 15,100 patients and determined the following characteristics for patients enrolled: age; percentage with ECOG PS of 0, 1, or 2; sex; race; and number of prior chemotherapeutic therapies received: 0, 1, 2 or ≥ 3 . We also identified the major tumor types enrolled: colorectal, lung, renal, breast, head/neck or “other”. The change of patient characteristics over time as well as between the first half of studied period (period 1 = 1998–2001) and the second half period (period 2 = 2002–2006) was analyzed. **Results** Colorectal and lung cancer patients together comprise ~35% of all patients enrolled on phase I trials and this has not changed over the past decade.

The contribution of “other” malignancies has however significantly increased over time. The proportion of patients with PS2 has declined while that of PS1 has increased. The proportion of patients with ≥ 3 prior therapies prior to study enrollment has also significantly increased. **Conclusion** The shifting of patient characteristics especially as related to tumor types enrolled and number of prior therapies has important implications for future design of studies and inadequate attention to these issues may slow the accrual process.

Keywords Phase I · Patient characteristics · Cancer

Introduction

Phase I clinical trials serve an important role in anticancer drug development [1]. Their main goal is to establish the maximum tolerated dose, dose-limiting toxicities and a recommended phase II dose. Classically, patients with a good Eastern Cooperative Oncology Group (ECOG) performance status (PS) (generally 0, 1 and 2) that are refractory to standard therapy are eligible. Also, the number of permitted prior therapies is stipulated in the eligibility criteria of the trial. This restriction in number of prior therapies serves a dual role. First it is to prevent highly pretreated patients from enrolling because of the fear of potential toxicity in this group. This has traditionally been applied to agents that cause myelosuppression, as pretreated patients, especially those exposed to alkylating agents, are more susceptible to bone marrow suppression. More recently limits on prior therapies are included to allow the sponsor and investigators to obtain preliminary efficacy data, in general a secondary endpoint for phase I trials. For example, phase I studies of novel antiangiogenic agents

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may exclude prior antiangiogenic drugs or HER2 targeting agents will exclude prior HER2 based therapies.

In recent years a number of new agents have reached the clinic for use in the treatment of the most common malignancies. This prompted us to hypothesize that given the number of new FDA approved anticancer agents over the past decade, the characteristics of patients enrolled on phase I trials has evolved. This in turn would have implications for the design of future studies.

Patients and methods

Data Acquisition We reviewed phase I trials published between January 1998 and December 2006 from two clinical cancer journals—Journal of Clinical Oncology and Clinical Cancer Research. Combined phase I/II trials were excluded from analysis. We identified the following components from each study as it pertains to patient characteristics: median age; percentage with ECOG PS of 0, 1, or 2; sex; race; and number of prior chemotherapeutic therapies received: 0, 1, 2 or ≥ 3 . We also identified the major tumor types enrolled: colorectal, lung, renal, breast, head/neck or “other”. The “other” category incorporated sarcomas, melanomas, gynecological malignancies and other less common tumors such as carcinoid. This database shows that 59% of published phase I trials during this period were sponsored by the pharmaceutical industry [2].

Statistical Evaluation The association between two continuous variables was estimated by Pearson correlation coefficient. The change of patient characteristics between the first half of studied period (period 1 = 1998–2001) and the second half period (period 2 = 2002–2006) was examined by T-test. The time points chosen were done to reflect a period before approval of most targeted therapies for cancer versus the period after. All statistical analyses were done using SAS (SAS Institute, Cary, NC) and p-value less than 0.05 is considered to be statistically significant.

Results

General We identified 476 trials that enrolled a total of 15,100 patients. Table 1 depicts the data on patient characteristics over 2 different time periods, 1998–2001 (period 1) and 2002–2006 (period 2). Table 2 shows the median and mean number of patients in each category along with the estimated Pearson correlation coefficient for change over time.

Patient Characteristics The median age remained the same over time at 57 ($p=0.751$). The percentage of female patients

Table 1 The change of patient characteristics between the first half of studied period (1998–2001) and the second half period (2002–2006) examined by T-test

Variable	Study period	Mean	std	p-value
Median age	1998–2001	57	5.76	0.751
	2002–2006	57.2	7.2	
Sex—Female (%)	1998–2001	44	13	0.902
	2002–2006	43	15	
Race—Black (%)	1998–2001	9.2	9.5	0.884
	2002–2006	9.7	10.4	
Performance status (PS)				
PS=0 (%)	1998–2001	35.6	19.4	0.333
	2002–2006	37.9	20	
PS=1 (%)	1998–2001	53.9	17.4	0.882
	2002–2006	54.3	19.5	
PS=2 (%)	1998–2001	10.5	10.8	0.045
	2002–2006	8	8.5	
Disease site				
Colorectal (%)	1998–2001	30	23.9	0.302
	2002–2006	27	20.2	
Lung (%)	1998–2001	13	16.1	0.873
	2002–2006	12.7	12.9	
Breast (%)	1998–2001	7	11.6	0.445
	2002–2006	6	10.7	
Renal (%)	1998–2001	6	8.4	0.827
	2002–2006	6.4	8.4	
Head & neck (%)	1998–2001	3	6.8	0.723
	2002–2006	3.3	6	
Others (%)	1998–2001	39	18.3	0.016
	2002–2006	44	16.7	
# of prior therapy				
0 (%)	1998–2001	16.5	19.8	0.865
	2002–2006	15.9	20.3	
1–2 (%)	1998–2001	56.5	20.7	0.016
	2002–2006	46.2	22.9	
≥3 (%)	1998–2001	28	23.2	0.034
	2002–2006	38	28.6	

also did not change (~43–44% participants, $p=0.902$). Similarly no change ($p=0.884$) in the percentage of black patients was seen representing nearly 9% of all patients enrolled. More than 50% of patients had an ECOG PS of 1 and approximately 1/3 had an ECOG PS of 0. A significant decrease in PS 2 patients was seen over time, comprising 10.5% of patients during period 1 and 8% during period 2 ($p=0.045$). A Pearson correlation coefficient suggested a progressive decrease over time (r value= -0.128 , $p=0.035$, Fig. 1). The percentage of PS 2 participants ranged from studies with 0 participants up to 50% comprised of PS2 patients. When general solid tumor phase I studies alone (285 of the 476 trials in this review) were analyzed a

Table 2 The association of patient characteristics and time of the studied period (year in publication) estimated by Pearson correlation coefficient

Variable	Mean	Median	Correlation coefficient with time
Median age	57.1	57	0.027 ($p=0.575$)
Sex			
Female (%)	43.4	42.9	-0.028 ($p=0.565$)
Race			
Black (%)	9.6	6.7	-0.039 ($p=0.797$)
Performance status (ps)			
PS=2 (%)	9	6.7	-0.126 ($p=0.035$)
Disease site			
Colorectal (%)	29	24	-0.084 ($p=0.161$)
Lung (%)	13	9	-0.056 ($p=0.349$)
Breast (%)	6	3	-0.063 ($p=0.297$)
Renal (%)	6	3	0.056 ($p=0.348$)
Head & neck (%)	3	0	0.05 ($p=0.4$)
Others (%)	43	43	0.144 ($p=0.016$)
# of prior therapy			
0 (%)	16	7	0.027 ($p=0.757$)
1–2 (%)	49	50	-0.095 ($p=0.274$)
≥ 3 (%)	35	31	0.044 ($p=0.61$)

significant rise in PS 1 patients was also seen from 52% to 59% of patients over the two time periods. There was no change over time in the number of patients with no prior therapy, prior to enrollment (15–16%, $p=0.865$). In terms of the number of prior therapies, we observed significant changes over time. A significant increase in patients with ≥ 3 prior therapies was seen with 28% during period 1 and 38% during period 2 ($p=0.034$, Fig. 2). This was associated with a concomitant decrease over the two time periods in patients with 1 or 2 prior therapies from 56.5% to 46.2% ($p=0.016$).

Fig. 1 Scatter plot of ps = 2 vs. studied period (year) **Fig. 2** Box plot of percentage of patients with 3 or more prior chemotherapies by studied period: black bar = median, red box = 25th to 75th percentiles, Bars = entire range, Whisker line = outliers

Tumor Types No significant differences were seen for the major tumor types enrolled over time. Colorectal cancer remains the most common group with a mean of 29% of all patients enrolled on phase I trials having colorectal cancer. Lung cancer patients comprise the second largest group at 13%. Only 6% of enrollees had breast cancer. A significant rise (5% between the 2 time periods) in patients with “other tumors” is seen.

Discussion

This is the largest review of phase I data and the first reported analysis focusing on changes of patients characteristics over time in the era new molecular targeted agents. The time periods chosen were done to reflect an era prior to approval of new targeted agents for cancer and a period immediately after. Given the explosion of new anticancer drugs in development and the approval of new therapies for previously treatment-refractory cancers, changes in this patient population are inevitable.

The under-representation of black patients is an important finding and has not changed over the past decade. Hypotheses regarding this include: less accessibility to phase I trials or patients choosing not to enroll. Most recently, it has been shown that black patients with advanced lung cancer [3] are more likely to present with poor PS, a factor that influences their eligibility for enrollment. Only 44% of enrolled patients were female. The most likely explanation for this finding is that breast and ovarian cancer patients comprise only a small percentage of participants. This probably reflects the number of therapeutic options available or it may reflect the restrictions on number of prior therapies in the eligibility criteria of these trials. In a prior review of phase I studies, a similar proportion of men and female was seen [4].

Despite therapeutic advances for colorectal and lung cancer over the past decade, these two patient populations contribute over 40% of all patients on phase I trials. We had speculated that given the number of new therapies for colorectal cancer that this group of patients would contribute less to phase I studies. This however was not the case as our data demonstrates. The increase in “other” category is reflective of mostly melanoma and sarcoma patients, for which little therapeutic advance has been made. In the Institut Gustave Roussy experience only 9% of patients had colorectal cancer, while sarcoma was the single highest group suggesting local differences in practice patterns [5]. Another important finding is the median age of 57 without change over the past decade. This may indicate either a poorer PS, lack of interest in phase I trials, or that physicians are less likely to offer these trials to elderly patients.

The decrease in PS2 patients with an increase in PS1 is noteworthy. However, the absolute difference over the two time periods is only 2% which is probably not clinically significant. Nevertheless, a possible explanation for this change is that more stringent eligibility criteria, excluding the PS2 group, are responsible for this finding. Investigators are concerned that PS2 patients lead to early withdrawal from study and increased toxicity. A recent study suggested utilizing a prognostic score encompassing LDH, albumin and number of metastatic sites to predict early withdrawal from study. PS2 patients may reflect this poor prognostic category [6]. A prior French review showed a PS 2 population of 1.1% of the total enrolled [5]. A review of CTEP studies showed 6% of patients had PS2. These differences are most likely due to practice patterns and eligibility criteria [7].

One of the main findings of our study is the observed increase in patients with ≥ 3 prior therapies. This is likely a consequence of better available cancer treatments. This may have profound consequences for study design and available patient population for phase I studies. It is our experience that many pharmaceutical-sponsored trials are restricting the number of prior therapies both of fear of toxicity but

also with hope of gaining evidence of antitumor activity which supposedly would be higher in patients who have been exposed to less anticancer therapies. We believe that this will result in slower accrual and thus hamper reaching the primary endpoint of phase I trials. Our analysis also showed 16% of enrollees had no prior chemotherapy. A review of CTEP trials [7] showed 8% of patients had no prior therapy. This difference in chemo-naïve patients between our analysis and CTEP studies may stem from the fact that over 50% of trials that we analyzed were sponsored by pharmaceutical companies. One again may hypothesize that pharmaceutical sponsors have an interest in accruing patients with minimal therapy with hope of minimizing toxicity and obtaining early efficacy data.

In conclusion, knowledge of patient characteristics enrolled on phase I studies is important in future design of trials. Inadequate attention to these trends may result in difficult accrual and exclusion of certain patient populations.

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