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SHORT COMMUNICATION

Eligibility criteria for phase I clinical trials: tight vs loose?

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Abstract

Purpose The purpose of the current study is to analyze a series of phase I cancer clinical trials, examine and compare trial protocols based on patients' eligibility criteria.

Methods We evaluated all dose escalation phase I trial protocols with accessible or published results performed at Institute for Drug Development, Cancer Therapy and Research Center (San Antonio) between 1991 and 2016. Study protocols were categorized as non-restrictive (NRP) or restrictive (RP) based on several eligibility parameters. Fisher's Exact and Chi-square tests were used to compare characteristics of NRP and RP.

Results Of 284 protocols screened, 231 dose escalation phase I trial protocols (with accessible results) of solid tumors were included in this review. There were 145 NRP (involving 3190 patients) and 86 RP (involving 1892 patients). The median number of exclusion criteria for NRP and RP were 14 and 23, respectively. The most common reasons that made trial protocol to be restrictive were ECOG ≤ 1, strict requirements for renal or hepatic function (≤ 2.5 times upper limit of normal) and exclusion of subjects with brain metastases. The median accrual time for NRP was significantly shorter as compared to RP (17 vs 26 months). The median number of dose levels explored in NRP and RP were 9 and 6, respectively. RP had a higher screen failure as well as premature closure rate. The rates of DLTs, SAEs, toxicity-related death and response were not different between the two groups.

Conclusions Our study findings are in support of devising well thought and justified phase I study eligibility criteria.

Keywords Trials · Eligibility · Criteria · Phase I

Introduction

The development of effective new agents in oncology is a slow, difficult and demanding process. This is often because of poor accrual to clinical trials leading to early termination and hence lack of meaningful results [1]. The landscape of phase I trials in oncology is undergoing a rapid and much-needed change. To improve efficiency of drug development process in oncology, it is high time to review several outdated dogmas that prevail in the current era of early phase clinical trials. One such practice is restrictive eligibility criteria that may not only threaten successful completion of phase I trials, but also limit the applicability of results to real-life patients. Complex eligibility requirement for phase I trials can ultimately impact timelines, costs and burden on patients as well as researchers.

Recent guidelines from American Society of Clinical Oncology recommend expanding eligibility criteria for early and late phase trials in oncology [2]. Phase I clinical trials in oncology should have broader eligibility criteria to allow rapid accrual, reduce cost, and improve generalizability of results. Obviously this should be achieved without compromising patient safety.

Here we have reviewed and compared the conduct, performance and outcomes of phase I trials that were run at our institution over a 25-year period to study any significant differences between trial protocols that were considered non-restrictive (NRP) and restrictive (RP).

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Materials and methods

We evaluated all dose escalation phase I trial protocols with accessible or published results performed at Institute for Drug Development, Cancer Therapy and Research Center (San Antonio) between 1991 and 2016 after receiving institutional review board approval. Both authors examined eligibility (inclusion and exclusion) features for each study protocol to identify presence of overly strict requirements including criteria for renal or hepatic function (≤ 2.5 times upper limit of normal); exclusion of subjects with brain metastases, ECOG ≥ 1, non-biopsible patients, non-measurable disease, history of second malignancy; overly restrictive cardiovascular requirements (systolic blood pressure < 160, history of myocardial infarction > 12 months, left ventricle ejection fraction > 45%); biomarker positive patients only; limit on prior lines of therapy; any other clinical or laboratory criteria that in the judgment (and with agreement) of both investigators is unnecessary and unusual (Table 1). A simple scoring strategy was adopted to categorize study protocols by assigning one point for each of above eligibility features. Study protocols were categorized as non-restrictive (total score ≤ 1) and restrictive protocols (total score ≥ 2). For both categories, information was extracted for each trial using a standardized form including screen failure, accrual time, protocol amendments, premature study closure, dose levels explored, number of DLTs, SAEs, death on study and treatment response rate. Responses were classified according to the description in each study (RECIST or WHO criteria) [3–5]. Fisher's Exact and Chi-square tests were used to compare characteristics of NRP and RP. *P* value < 0.05 was considered significant.

Table 1 Definition of restrictive criteria

Hepatic function < 2.5 times upper limit of normal
Creatinine clearance > 60 ml/min
Absence of brain metastases
Systolic blood pressure < 160
History of myocardial infarction > 12 months
Left ventricle ejection fraction > 45%
Patients only eligible if they are positive for a specific biomarker
Limit on prior lines of therapy
ECOG 0
Patients with only accessible biopsible tumor
Measurable disease (on imaging)
No other prior malignancy
Any other clinical or laboratory criteria that in the judgment of both investigators is restrictive

Study protocols were categorized as non-restrictive (if ≤ 1 criteria present) and restrictive protocols (if ≥ 2 criteria present)

Results

We included a total of 231 dose escalation phase I trial protocols (with accessible results) that were conducted at our institution over last 25 years. Fifty-three protocols of drug–drug interaction, QTc, bioequivalence, food effect and organ dysfunction studies were excluded due to inherent methodology restrictions. Most of the included studies were industry sponsored and of solid tumors. We reviewed the performance of 145 NRP involving 3190 patients as well as 86 RP involving 1892 patients (Table 2). The most common reasons that made protocols to be restrictive were ECOG ≤ 1, strict requirements for renal or hepatic function (≤ 2.5 times upper limit of normal) and exclusion of subjects with brain metastases. The median number of exclusion criteria for NRP and RP were 14 and 23, respectively. The median accrual time for NRP was significantly shorter as compared to RP (17 vs 26 months). The median number of dose levels explored in NRP and RP were 9 and 6, respectively. RP had a higher screen failure as well as premature closure rates when compared to NRP. The most common causes of study screen failure were poor performance status, organ dysfunction and use of prohibited medications. Furthermore, the rates of DLTs, SAEs and toxicity-related deaths were not different between the two groups. The objective response rate was low, but similar for both groups.

Discussion

This study showed that when compared to NRP, RP were slow to recruit, had a higher screen failure as well as premature closure rate. Furthermore, there were no differences in response rates and safety parameters (rates of DLTs, SAEs and toxicity-related death) between the two groups.

These results support the current notion to modernize clinical trial eligibility criteria. However, eligibility criteria of a clinical trial also relates to complexity of study to some extent. There is evidence that phase 1 trials have become more complex with substantially increased requirements over the last 20 years. Our recently published study showed that "procedures" in oncology phase I trials such as pharmacokinetic (PK) time points, non-PK tests, ECGs, functional imaging, molecular profiling, study medication dispensing, number of outpatient tests and subjective assessments had increased with time [6]. Hence with a more complex study protocol, there is more restriction to the type of patients who are expected to participate in these trials. On the other hand, the relationship between a trial complexity and eligibility criteria was not directly assessed in our study.

Table 2 Characteristics and outcomes of non-restrictive and restrictive phase I protocols ($n = 231$)

Protocol characteristic	Non-restrictive (NRP)	Restrictive (RP)	*P* value
Total number of protocols	145	86	
Total number of patients enrolled	3190	1892	
Number of screen failures (%)	478 (14.9)	491 (25.9)	0.048[a]
Age < 50	224 (46.8%)	218 (44.3%)	
Age > 50	254 (53.1%)	273 (55.6%)	
Studies closed premature number (%)	16 (11.0)	23 (26.7)	0.003[a]
Accrual time			
Median (months)	17	26	0.007[a]
Min, Max	11, 24	15, 36	
Number of protocol amendments			
Median	5	7	0.84
Min, Max	2, 8	5, 11	
Number of dose levels explored			
Median	9	6	< 0.001[a]
Min, Max	3, 12	2, 9	
Number of DLTs			
Median	6	5	0.3
Min, Max	2, 9	2, 11	
Serious adverse events (SAEs) Number (%)	421 (13.1)	286 (15.1)	0.4
Toxicity-related deaths number (%)	20 (0.62)	14 (0.73)	0.58
Objective response rate number (%)	18 (12.4)	10 (11.6)	0.2

[a]*P* value < 0.05

The patient participation rate in phase I clinical trials is known to be low [7]. Several studies have identified reasons for low accrual rate although only little effort has been made until now to address them [8]. The primary intent to define trial eligibility criteria is to exclude potential patients who are; at a high risk of adverse events; less fit and may not be able to tolerate study treatment; considered to have adverse prognostic factors at baseline. Although it is well understood that some patients will be more vulnerable to specific adverse effects and should be excluded. However, eligibility criteria should be revised for each trial and all the exclusions should be fully scientifically justified and not duplicated from other protocols. Many of the exclusion criteria in clinical trials are historically ill-conceived and poorly justified. There is emerging data that clinical trials reflexively exclude patients who may not pose any threat to its safety analysis or efficacy results. One such example is exclusion of patients with known prior malignant. Recently Gerber et al. showed that prior cancer history did not impact survival outcomes in lung cancer trials [9].

It is equally important to generate data in specific subgroups of patients as these new agents will eventually be used in a very heterogeneous real-world patient population. This can be achieved by enrolling high risk patients in separate expansion cohorts (such as seen in newer "basket trials") that could be monitored more carefully and cohorts immediately closed if needed: for example, recent guidelines recommend recruitment of patients with leptomeningeal disease in separate cohorts in early phase trials [2]. Hence, unless there is a strong scientific rationale for exclusion, it's high time to review current practice of using strict criteria for renal, liver and cardiac function as well as consider enrolment of geriatric, pediatric, and organ dysfunction patients in separate cohorts [10].

Our study has a few limitations. First, it is based on studies that were carried out at a single institution. We believe that investigator bias will be minimal as we extensively captured studies over a 25-year period. Second, we did not include trials that were either not published or were performed at multiple institutions, as retrieving data over such a long time was very difficult. Third, our study findings may not relate to investigator or cooperative group trials.

In conclusion, our study findings are in support of devising well thought and justified eligibility criteria for phase I trials. Future effort should focus on identifying criteria that could be relaxed or eliminated from phase I protocols. Other potential obstacles to broaden eligibility criteria should also be prospectively identified and addressed in the development and conduct of future studies, which may potentially lead to more robust data and rapid enrolment.

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Compliance with ethical standards

Conflict of interest The author(s) declare that they have no competing interests. All authors had full control of all primary data, which are available for review upon request.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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