

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Controversies in Multi-institutional Phase I Clinical Trials

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H&O What are some of the issues with multi-institutional phase I clinical trials?

AD Performing multi-institutional trials is the norm for the oncology world; however, this concept is best utilized in the setting of phase II and III clinical trials. The goal of performing studies in multiple sites is to enhance and accelerate patient accrual to studies, as no single institution can accrue enough patients to any given study that is large enough to complete the study in a reasonable timeframe. The cooperative groups—the Eastern Cooperative Oncology Group, the Southwest Oncology Group, and the Cancer and Leukemia Group B—solely perform multi-institutional studies in order to enhance accrual and obtain a better patient representation. For example, patients that may go to a tertiary care center at an institution may not be truly representative of that patient population; he or she may instead represent a highly selected group of people who can travel to that specific institution to get treatment. However, with multiple institutions, the results obtained from the clinical trial are more applicable to the general population. Although multi-institutional trials are very important, in the phase I setting, they lose their appeal because the primary goal is to find out the dose and schedule of a new anticancer drug.

There are a few problems that arise from phase I multi-institutional clinical trials, the main problem being the difficulty of obtaining early experience and expertise in these new drugs. Phase I clinical trials generally accrue anywhere between 20 and 40 patients on average, and therefore the number of patients who get the experimental

drug is somewhat limited. When a study is performed at only 1 institution, the investigator or group of investigators become experts in that drug very early on in the research process. They are able to recognize side effects and are able to closely follow patients. However, when a study is conducted in multiple sites, their experience becomes diluted among multiple institutions. Thus, if there are 30 patients in a trial with 3 participating institutions, each investigator will only have direct experience with 10 patients rather than 30, and therefore will not acquire enough experience with that drug before it goes to a phase II trial.

One of the other issues with phase I multi-institutional trials is the amount of coordination that is required between sites. Study data are important in real time and what happens at one institution needs to be reported to other participating institutions rather quickly, as these are ongoing trials with very limited experience. The main challenge in sharing data is the communication of minor toxicities between sites. There is an efficient mechanism—through regular scheduled conference calls amongst the institutions—that transmits major toxicities between study sites; however, minor toxicities are more difficult to convey to other sites. This issue is important because these minor adverse events may be a prelude to a more serious toxicity in the future.

H&O How do we balance the ethical concerns with the possible advantages that these studies confer?

AD One of the ethical issues related to trials that are multi-institutional is something we concluded in our analysis of phase I clinical trials: the number of patients being accrued to multi-institutional phase I studies is greater than the number of patients being accrued to single institution trials. This may be good and bad. One of the findings from our analysis showed that multi-institutional phase I studies do not complete their study faster than single institution studies and, therefore, offer little advantage over single institution studies. Moreover,

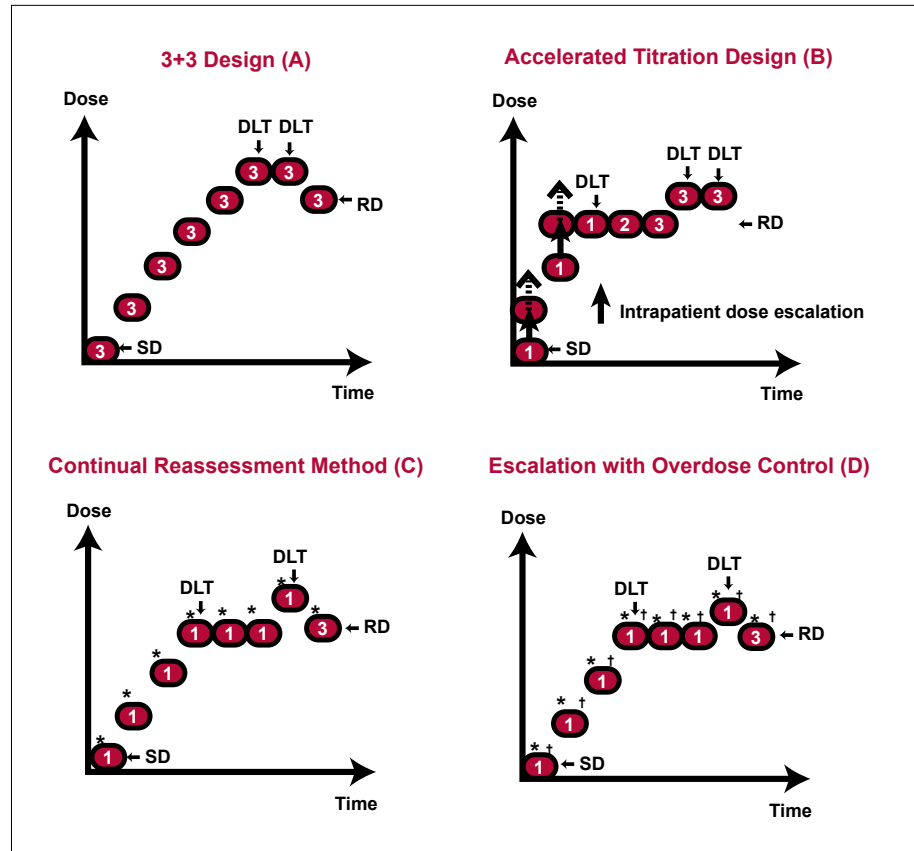
Figure 1. Dose Escalation Methods for Phase I Clinical Trials

*Probability of developing a dose-limiting toxicity (DLT) is estimated.

†Probability of administering a dose exceeding the maximum tolerated dose for each higher dose level is determined.

RD=Recommended dose;
SD=Starting dose

Adapted from Le Tourneau et al.
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they may provide a disadvantage because putting more patients on a study costs much more when multiple sites are involved. Therefore, if the goal is to reach a conclusion with the least amount of patients, conducting multi-institutional studies defeats the purpose. We basically need to strike a balance between decreasing patient exposure to toxic or subtherapeutic doses and maintaining efficiency and rapid accrual. Various study designs have been developed with this goal in mind.

H&O What are some of the different designs being applied to phase I studies?

AD Phase I clinical trials are necessary for the development of new anti-cancer therapies. The main goal of these studies is to determine the best dose and schedule of new drugs for phase II trials. Currently, there are a variety of designs being applied to phase I trials in order to minimize the number of patients who receive subtherapeutic dosing (Figure 1).¹ These trials aim to improve the efficiency of the study and determine the maximum tolerated dose (MTD) as quickly as possible with the least amount of patients. There are 2 main methods being applied to phase I trials: the rule-based dose escalation method and the model-based dose escalation method.

The most commonly used rule-based design is the standard 3+3 design. In this design, cohorts of 3 patients are added per dose level, with the first cohort given a starting dose and subsequent cohorts treated at increasing dose levels. If none of the patients in the cohort develops a dose-limiting toxicity (DLT), an additional 3 patients are treated at the next higher dose level. If, however, one of the 3 patients develops a DLT, 3 more patients are added to the same dose level. When at least 2 patients in a cohort (3–6 patients) experience a DLT, dose escalation is discontinued. The MTD is defined as the dose level right below the toxic level.

Another type of design, first described by Dr. Simon from the National Cancer Institute in 1997, is the accelerated titration design; its goal is to reach the recommended phase II dose as quickly as possible by putting the least amount of patients at the subtherapeutic level and escalating the dose more rapidly. The accelerated titration method is a variation of the 3+3 design and incorporates attributes from model-based designs as well. There are several types of accelerated titration designs and they are being implemented by some investigators; however, at this time they are uncommonly used. The 3+3 design remains the most frequently used rule-based method.

The other type of method, the model-based dose escalation method, uses statistical models to determine a dose level that creates a probability of DLT by using safety data from all study participants. This type of design produces models for the dose-toxicity curve and provides a confidence interval for the MTD for phase II trials. One of the model-based designs is the continual reassessment method. The original design treated all patients at the dose thought to be closest to the MTD. The probability of developing a DLT was estimated for each new patient who was enrolled in the study at any dose level until a prespecified condition was met, at which time the trial was stopped. This design has not been frequently used because of the possibility of exposure to toxic doses of the investigational drug if the prespecified model is incorrect. Modifications to this design have been made and implemented in practice. In the modified design, patients start on the lowest dose level and subsequently receive increasing prespecified dose levels, with up to 3 patients included per dose level.

The escalation with overdose control (EWOC) method is another model-based design; it is basically a continual reassessment method with modifications such as additional safety measures (in order to avoid exposing patients to doses that are potentially too toxic). The major difference between EWOC and the modified continual reassessment method is that in the EWOC method, the probability of giving a dose that is higher than the MTD for each increasing dose level is evaluated after each patient. The problem with the EWOC and the modified continual reassessment methods is that they require a real time statistician to continuously model the toxicities in order to provide the investigators with an idea of how to escalate the dose. Thus, because of this need for real time statisticians and statistical input, the implementation of these designs is very difficult, and for that reason they have not been widely applied in phase I clinical trials.

H&O Can you discuss the findings from the analysis you and your colleagues performed on phase I studies published in *Journal of Clinical Oncology* and *Clinical Cancer Research*?

AD My colleagues and I analyzed all published phase I studies between January 1998 and June 2006 in these 2 journals.² We looked at several components of each of these studies: number of participating sites, the sponsor, the continent where the trials were performed, whether the MTD was reached/determined, the number of

patients accrued, the study duration, the types of tumors being studied, and the mechanism of action of the drugs. We identified 463 clinical trials and found that 56% of them were performed in single institutions. When we attempted to evaluate how fast the studies accrued patients, only 30% of the studies provided information on the duration of accrual.

The main goal of the multi-institutional concept is to decrease the study time and/or to speed up accrual, and one of the major findings in our analysis of the 30% of studies that provided accrual data was that the studies did not do either. We also found that the number of patients in single institution studies was significantly lower than in multi-site trials. Our evaluation showed no increase in the percentage of multi-institutional studies from 1998 until 2006, which shows that the multi-institutional concept is not a recent phenomenon; however, its problems are starting to be recognized at this time. When analyzing the type of sponsor, we hypothesized that pharmaceutical sponsorship of multi-institutional studies would be higher; however, we established that pharmaceutical companies and the National Institutes of Health sponsor multi-institutional phase I trials to the same extent.

H&O Have we seen a shift in the study approach away from multi-institutional trials?

AD I do not think that there is a shift occurring away from multiple study sites to single institutions. The change that I have observed in the past 2–3 years since we have approached this topic and raised issues about multi-institutional phase I studies is the decline in the number of sites used in multi-institution studies. Several years ago, it was not uncommon to see multi-institutional studies that incorporated 4–6 sites. There are still multi-institutional studies being conducted today; however, the number of sites is no longer 4, 5, or 6. Instead, we see study sponsors limiting trials to 2 or a maximum of 3 sites. In my opinion, it is better to have 2 or 3 institutions involved rather than 6, but again the question gets raised: “Why 3 institutions? Why not 2?” Clearly, the cost of conducting research in 2 institutions would be less than doing that same research in 3 institutions.

References

1. Le Tourneau C, Lee JJ, Siu, LL. Dose Escalation Methods in Phase I Cancer Clinical Trials. *J Natl Cancer Inst.* 2009;101:708–720.
2. Dowlati A, Manda S, Gibbons J, Remick SC, Patrick L, Fu P. Multi-Institutional Phase I Trials of Anticancer Agents. *J Clin Oncol.* 2008;26:1926-1931.