Innovations in Phase 1 Trial Design: Where Do We Go Next?

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In this issue of Clinical Cancer Research, Dees et al. (1) describe the use of PGDE (2) in a Phase 1 trial of CI-958. PGDE was proposed (2, 3) as a more informative and efficient alternative to the standard design for Phase 1 studies (“modified Fibonacci”). Compared with the modified Fibonacci design, the authors estimate that the use of PGDE in this trial required 15–18 fewer patients. All of these additional patients would have been entered at dose levels far below the MTD. The authors state that this trial was the most successful use of PGDE ever reported. The principal reason for the efficiency of PGDE in this case was the 170-fold range between the starting dose, 5.2 mg/m², and the MTD, 875 mg/m².

This report adds to the collection of positive experiences with PGDE as an innovation in Phase 1 design. However, despite encouraging reports from Europe (4), Japan (5), and the United States (6), the success of PGDE has been more academic than practical. As noted by Dees et al., PGDE requires real-time pharmacokinetic monitoring, and this element has been considered a drawback by many investigators. Consequently, PGDE has failed to be widely accepted, and has generally faded from regular use.

PGDE is not the only alternative to the modified Fibonacci escalation procedure, and other strategies don’t require plasma concentration monitoring. Dees et al. mention both the accelerated titration and continual reassessment methods, and experiences have been recently surveyed for a wide range of trial designs (7). These methods have improved Phase 1 trials in a number of important ways. It’s particularly noteworthy that fewer patients are exposed to completely inactive doses because of two innovations: (a) reducing the cohort size at early stages from three patients to one; and (b) encouraging intrapatient escalation of doses.

The loss of real-time pharmacokinetics information translates into missed (or delayed) opportunities for early identification of interspecies differences, active and/or toxic metabolites, as well as preliminary hypotheses regarding dosage adjustment for impaired organ function. For example, during a Phase 1 study from the same institution for penclomedine (8), a metabolite was identified that was less toxic and more active than the parent molecule.

Phase 1 Design without Determination of the MTD

Until recently, it was expected that dose escalation for all anticancer drugs would continue until limited by toxicity. Although clinical monitoring for adverse events will always be an essential element for first-in-human studies, it is no longer expected that determination of the MTD will be the universal end point of a Phase 1 investigation. Indeed, there are already several classes of molecules undergoing clinical evaluation for which the MTD was not determined and/or not relevant to the drug’s use. What is the impact of this new paradigm on Phase 1 designs? Specifically, what is the end point for dose escalation? As the MTD fades in importance, what replaces it?

Ironically, in many cases, plasma concentration has served as the alternative end point. A target concentration is defined from in vitro studies or in animals. Doses are escalated until plasma concentrations reach this target level. Plasma concentrations are usually reliable as a measure of extracellular drug delivery but are completely uninformative about variations in the intrinsic sensitivity of the tumor to a particular drug. When intracellular target events can be monitored directly, the optimal dose might be lower than the MTD, e.g., in the work of Gandhi et al. (9) for leukemic patients.

Some studies examine peripheral WBCs as surrogates for inaccessible solid tumors, particularly for a biochemical end point, such as enzyme inhibition. This strategy provides some qualitative indication of bioactivity but is catastrophic for cases in which WBC response is more sensitive than tumor response. In this worst-case scenario, escalation of the drug is prematurely terminated, before achieving sufficient action at the tumor target. As reported by Spiro et al. (10), the dose of O6-benzylguanine that inactivates alkyltransferase in WBCs is lower than that required for inactivation in tumors.

Currently, a major effort is under way to use noninvasive imaging as a supplement or replacement for biopsies of tumors. In the ongoing Phase 1 evaluations of antiangiogenic agents, dose escalation is being assisted via monitoring of blood flow/perfusion by both magnetic resonance imaging and positron emission tomography (11, 12).

Stakeholders in Efficient Phase 1 Trials

All parties involved in a Phase 1 study have a desire for efficient determination of a dose that might help patients. A compelling humanitarian motivation underlies the participation of patients, investigators, and pharmaceutical sponsors. Of course, there are also various forms of self-interest. Individuals volunteer with a hope for the best chance in a desperate situation. No one’s career or economic prospects are enhanced by lengthy Phase 1 trials.

An individual patient’s chances of deriving any personal direct benefit are very small; nonetheless, we have an obligation to maximize this slim opportunity. Because the patients at
higher doses are more likely to obtain benefit than patients at lower doses (13), a primary goal of improved Phase 1 designs should be to move quickly toward bioactive doses.

Ultimately, Phase 1 trials are studies of, for, and (increasingly) with patients. Patients have become better informed and more involved in medical decision-making. Anecdotally, while considering trial options, some patients inquire about whether an “active dose” has been reached. Trials have been designed to include patients’ preferences for balancing risk-taking versus the probability of benefit (14).

**Blurring the Phase 1 Boundary: Antitumor Activity and Proof-of-Concept**

Determination of safety will always be a necessary part of Phase 1 trials, and work should continue on fine-tuning the efficiency of attaining this goal. However, many factors are pushing the boundary of Phase 1 into the realm normally considered to be part of Phase 2. As it becomes more common to seek “proof-of-concept” or mechanistic evaluations during Phase 1, an increased emphasis on antitumor activity isn’t far over-the-horizon.

For most Phase 1 studies, the population has usually included any patient without proven therapeutic alternatives. Of course, there have always been isolated trends to extrapolate activity profiles from preclinical data and to conduct “disease-specific” studies, with a blurring of Phase 1 and Phase 2 goals. There are some pitfalls to this approach, but this trend can only be expected to accelerate. By monitoring the target, both “proof-of-concept” and dose determination might be achieved simultaneously. Further, by selecting patients with favorable expression profiles of the target for entry to the trial, an “enriched” population is obtained with a higher likelihood of response, if the therapeutic concept has merit.

STI-571, an inhibitor of the tyrosine kinase (Bcr-Abl) associated with Philadelphia chromosome in chronic myelogenous leukemia (15), could be considered as the prototype for specialized first-in-human trials. Because of the distinctive staging criteria, patients on this study were even more homogeneous than most Phase-2 populations. Instead of a search for the MTD, the dose ranging could be driven by response rates! Most gratifying, nearly all of the patients in this study derived direct benefit. This trial had the substantial advantages of well-defined phenotypic and molecular targets, as well as convenient access to the leukemic cells for direct observation. The challenge for solid tumor trials is to find ways to translate targeting concepts into molecular and functional assays suitable for clinical application.

Phase 1 trials are not often considered as the most glamorous part of drug development. However, over the course of about a decade, we’ve witnessed an exciting progression from empirical determination of dose-limiting toxicity, to concentration-oriented designs, to the monitoring of molecular targets, and culminating in dramatic proof-of-concept for the STI-571 trial. We should not underestimate the amount of effort required to bring more of these examples to fruition. Nonetheless, in addition to our longstanding motivations for efficient Phase 1 trials, we now are further stimulated by a spectacular demonstration of the rewards.

**References**

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