EDITORIAL

Building Firm Foundations for Therapy Development

James J. Dignam, Theodore G. Karrison

Affiliations of authors: Department of Public Health Sciences, University of Chicago (JJD, TGK).

Correspondence to: James J. Dignam, PhD, Biostatistics, Department of Public Health Sciences, University of Chicago Biological Sciences, 5841 S. Maryland Ave., Room W259, MC2000, Chicago, IL 60637 (e-mail: jdignam@health.bsd.uchicago.edu).

The phase I trial in the oncology treatment development paradigm is supremely challenged on the one hand by being required to identify a satisfactory dose-regimen that will be carried forward in pilot and definitive efficacy evaluations and on the other hand to minimize patient’s exposure to ineffective doses. The result of this compromise is often scant data on which to base the entire subsequent program of evaluation, the failure of which at any juncture could lead to abandoning further development of what might be a promising treatment strategy. At times, it can seem that we are, as the parable warns against, attempting to build a sturdy structure with a foundation of sand.

In these necessarily small experiments, after the putative maximum tolerated dose (MTD) is identified, sometimes an additional group of patients, known as the dose expansion cohort (DEC), is enrolled. As Boonstra and colleagues point out, as a prelude to their comprehensive simulation investigation (1), the practice is becoming increasingly common, although specific elements related to the utility of this cohort (sample size justification, for example) are often absent (2–4). Furthermore, the role that the expansion cohort may play in estimating (or redefining) the MTD is often not clearly specified. We surmise that the main motivation for the DEC is simply because the most commonly used design (3+3) results in a maximum of only six patients treated at the terminal dose, which is inherently unappealing.

In their simulation studies, the traditional 3+3 approach and two variations on the continual reassessment method (CRM), a progressive dose-response curve model-based approach, are compared. Each was evaluated with and without a subsequent DEC, and the DEC was incorporated with the dose-escalation portion into re-estimation of the MTD. The investigators make several recommendations, supported by the observations and at odds with current phase I trial practice.

First, with respect to design choice, the 3+3 approach remains ubiquitous despite recognized shortcomings, perhaps owing to its simplicity (one needn’t even interact with a statistician during trial conduct, an attractive feature). Wider adoption of alternatives may be because of real and perceived complexity in implementation, as well as the assumption that the 3+3 design performs serviceably. Boonstra’s study illustrates again that too often this design does not arrive at the true MTD. The CRM naturally incorporates information from all patients (not just the terminal dose tier) in dose escalation decisions and MTD estimation and has better performance. For the cleverly conceived and widely useful original CRM (5), many modifications have improved operational practicability in diverse applications and allayed concerns that it may play out in ways jeopardizing safety or defying rational progression through dose tiers (6–7). Nonetheless, there is a certain amount of overhead involved in this model-based design, and it is incumbent upon statisticians to provide and maintain the machinery required. It is admirable that at the authors’ institution, a commitment has been made to use what is a proven superior approach, even if only nominally so in some cases. Continued dominance of the 3+3 design would seem to be an impediment to more reliable phase I testing, at least as far as determining the MTD is concerned.

Second, the DEC should serve a more efficient purpose of fully contributing to determination of the MTD. This means that, at a minimum, observations from the DEC be used to estimate whether the terminal dose or some other value is the best estimate of the MTD. How this is done for the 3+3 (described in the Supplemental Material, available online) when augmented by the DEC is based on underlying assumptions of that design that may not be familiar to many users (8). For the CRM, incorporation of additional observations more naturally follows the model-based approach used throughout the trial. In fact, rather than enroll to the DEC at fixed dose, the authors go further to advocate that dose adjustments per the algorithm remain in effect during the DEC, tantamount to continuing the dose-seeking experiment for all patients. This is what occurs by design in the “large” CRM they describe, an approach that largely prevails in their simulations at concurrently arriving at the true MTD and treating the largest number of patients at that dose.

Third, based on the probability of correct MTD determination, no phase I strategy seems to provide much reliable information beyond its principal purpose. Consequently, as they point out, the assumption that augmentation at the terminal dose with a DEC then provides reliable additional adverse event and preliminary response data at the MTD is not well supported, and more so in...
the case of the more prevalent 3+3 design. These findings should temper the over-optimism in anticipating evidence for response and other parameters from the latter entrants in phase I trials.

To shore up the foundation for the entire development process, investigators should heed the recommendations provided, and even partial adoption, such as use of DECs with full integration to inform the MTD irrespective of the design used, may yield more reliable results. One straightforward change in current practice would be to establish a requirement that the study protocol explicitly state the purpose and intended analysis plan for the DEC. Then, protocol reviewers could assess the plan and make recommendations accordingly. With the greater use of integrated phases of development (eg, phase I/II trials) for logistical efficiency, it is more likely that latter portions of phase I data and the DEC will be repurposed directly into expanded safety and pilot efficacy evaluations. An approach that more often identifies and accumulates patients at the true MTD provides a critical bridge to the rest of the development cycle. Improvements along these lines will have the equally important benefit of providing patients the greatest opportunity to benefit from their goodwill in participating in phase I trials (9).

Funding

This work was supported by the National Institutes of Health grants (P30 CA014599 to JJD, TGK, and U10 CA180822 to JJD).

Notes

The funders had no role in the writing of the editorial or the decision to submit it for publication.

The authors have no conflicts of interest to disclose.

References