Re: Dose Escalation Methods in Phase I Cancer Clinical Trials

The review by Le Tourneau et al. (1) missed some important references that contradict a number of their main findings. For example, they found that the widely used standard 3 + 3 design is simple to implement and safe. It is simple, no argument. However, several studies (2–6) have shown that the standard design is not safe. Worse, given that the purpose of a phase I clinical trial is to estimate the maximum tolerated dose to be used in further studies, the standard method is very inaccurate in terms of dose level estimation. Reiner et al. (2) showed that over a wide set of possibilities, the standard design incorrectly estimated the maximum...
tolerated dose in more than 66% of clinical trials. The standard design is known to both overdose and underdose more frequently than modern designs while failing to accurately indicate effective doses.

We (3) have pointed out that a major feature of the standard design is that it is a “memoryless” design, that is, the selected dose level is based on observation from at most six patients at one dose level and all previous information concerning other dose levels, and the distribution of toxic effects is ignored. Although it is widely thought that the standard design can select a dose level and come to a conclusion by using few patients, that information comes at a high cost in that the probability of an incorrect recommendation is unacceptably high (2).

Iasonos et al. (6) compared the performance of the standard design with the continual reassessment method (7). They found that continual reassessment method–based methods outperform the standard method in accurately finding the true maximum tolerated dose and in treating more patients at optimal dose levels. In addition, in a retrospective analysis of phase I clinical trials that were performed using the standard design with continual reassessment method–based designs, we (3) showed that the continual reassessment method–based designs would have included approximately twice as many patients at the optimal dose and fewer patients at unsafe dose levels compared with the standard method (3). Finally, in more complex situations, such as within-patient escalation, the use of combinations of drugs where the order of administration is not known, or the inclusion of different subgroups in a single trial, can be handled to great advantage using innovative designs. So can studies that simultaneously take into account outcome measures of toxicity and efficacy. In these more complex situations, the standard design fails almost entirely.

In conclusion, the most ethical design possible would treat each patient at his or her own specific optimal dose. If we were in a position to do that, of course, no actual trial would be necessary. It is the lack of more precise knowledge about the optimal dose level that requires us to carry out the dose-finding study. Nevertheless, such an objective, even if wholly idealized and theoretical, can shed light on our endeavor to find the dose level for further studies. Specifically, as our knowledge improves, and it will do so in the course of any study, such knowledge should be used efficiently to deliver a more accurate dose to the patient.

The standard design cannot achieve this.

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References


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