Nontoxicity Endpoints in Phase I Trial Designs for Targeted, Non-Cytotoxic Agents

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Phase I trial designs for cytotoxic agents are based on the assumptions that (a) the clinical benefit of the agent increases with increasing dose, (b) the toxicity of the agent increases with increasing dose, and (c) there is a dose with acceptable toxicity that offers clinical benefit. For a targeted, non-cytotoxic agent, researchers and clinicians still obviously use the third assumption, but the first and second assumptions require additional consideration. When the first or second assumptions are not reasonable for an agent, one might want to consider using a dose escalation design that is not based on occurrences of toxicity, as in a standard phase I trial, but is based on some other endpoint. In this issue of the Journal, Parulekar and Eisenhauer (1) explore this possibility for targeted, non-cytotoxic agents and report the results of a survey of trial designs of completed phase I trials using such agents. They find that, in determining the recommended phase II dose from a phase I trial, the primary basis for the recommendation is still toxicity in the majority of trials, with pharmacokinetic data being used as the primary basis for the recommendation approximately 20% of the time. In only two trials (out of 60) was a targeted endpoint or surrogate tissue finding used as the primary basis for determining the recommended phase II dose.

Why are so few phase I trials using nontoxicity endpoints? As noted by Parulekar and Eisenhauer (1,2) and others (3–5), there are several challenges in using these nontraditional endpoints because it may be difficult to define the desired target effect. There may also be practical difficulties in measuring these effects once they have been defined because of the lack of reliable assays and because of the difficulty in obtaining the required tumor specimens. Here, I discuss two additional considerations in the choice of a phase I trial endpoint.

First, consider the assumption that the clinical benefit of an agent increases with increasing dose (assumption [a] above). The failure of this assumption is the reason for choosing a nontoxicity endpoint in a phase I trial. But what does it mean for this assumption to fail? Because it would only rarely be expected that the clinical benefit would decrease with increasing dose (assuming no toxicity of the agent over the relevant dose range), the concern is that the clinical benefit plateaus with increasing dose. But if a benefit plateau is the concern, then why not recommend the maximum dose administered with acceptable toxicity, or the maximum dose level that is practical to administer if no toxicity is seen?

One reason for not using a maximum dose of an agent is that the agent might be in short supply [as in the reported endostatin trials (6–8)], although typically the shortage would probably be only a temporary problem. Another reason is that for some targeted, non-cytotoxic agents, the agent will require longer-term treatment than the relatively short-term treatment of cytotoxic agents. If this is the case, then there would be more impetus to find a sufficiently biologically active dose level that is below the maximum dose tolerated because phase I trials typically incorporate only short-term toxicity. However, long-term administration may not be required for some of these agents, and even if long-term administration is required, a superior strategy to choosing a sufficiently active dose for further study might be to choose a dose that is one or two levels below the maximum dose. One should make sure that the chosen dose is sufficiently active, but note that this would only have to be done at this single-dose level if required tumor specimens were hard to obtain.

A second consideration in the choice of a phase I trial endpoint is whether the agent is going to proceed to phase II trials or go directly to large multi-institutional phase III trials. For example, agents belonging to categories of drugs that are expected to shrink tumors (e.g., inhibitors of cell surface receptors) would typically be tested in one or more standard phase II trials that use objective tumor response as an endpoint. These relatively small phase II trials allow for modifications of the dose level, if necessary, on the basis of the experience of additional patients receiving the agent and possibly receiving it for longer periods of time than would be possible in the phase I trials. On the other hand, if the agent is skipping standard phase II development and proceeding directly to a large, randomized phase III trial, then it might be wise to allocate more time and resources in the phase I design to choosing an appropriate dose and population for further testing. This would be the case with agents that are expected to offer clinical benefit without shrinking tumors (e.g., some matrix metalloproteinase inhibitors). Another possibility for these types of agents (and for agents with expectations of very low response rates) would be to have an expanded phase II trial of approximately 100–300 patients to refine and validate the molecular assays by comparing assay values of patients who do well on therapy with those who do not. In addition, one might be able to use data from the larger number of patients in the phase II trial to identify a subgroup of patients who are especially sensitive to the agent, based on the molecular characteristics of their tumors. A recent example is given by the identification of a mutation in the epidermal growth factor receptor (EGFR) gene that was found to lead to high susceptibility to the EGFR kinase inhibitor ZD1839 (gefitinib [Iressa]) (9,10).

The type of empirical survey performed by Parulekar and Eisenhauer (1) is important because it highlights the fact that...

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there may be practical reasons for not using nontoxicity endpoints. As noted by these authors, whether a standard phase I toxicity-driven trial design should have been used is not answered by recording what types of endpoints were used. In fact, even following the clinical development of the agents further may not answer this question because negative trials may be the result of an inactive agent (regardless of dose), and positive trials do not imply that a lower dose would not have been as effective. Instead, knowing whether the right dose and population were chosen may require a careful study of the biology of the agent–tumor–host interaction.

**REFERENCES**


