Phase II Cancer Trials: Out of Control?

Commentary on Michaelis et al., p. 2400

Bruce Chabner

In this issue of Clinical Cancer Research, Michaelis and Ratain raise the issue of why phase II clinical trials in oncology lack controls (1). In their assessment of all published phase II trials from the year 2002, 703 in number, they found that an impressive 83% were from the field of oncology. Comparing the design of those oncology trials to trials from other fields, they observed a significant difference in approach. Oncologic trials were significantly less likely to use comparative trial designs. This is not surprising, as drug testing for an incurable disease is likely to differ from testing against a chronic nonlethal illness, in which a period of placebo or control treatment would carry minimal risk of serious consequence. The nononcologic studies more often used some form of control, either a randomized population or a carefully chosen historical comparison group. In conclusion, the investigators argue that the lack of controls might easily lead oncologists to discard the cancer drugs and that more thoughtful designs, such as their own randomized discontinuation approach, as used in the recent trial of sorafenib in renal cancer (2), might improve the efficiency of cancer drug development at this crucial early step in the life cycle of the new cancer agent.

There are certainly some drawbacks to the Michaelis analysis. As the investigators point out, perhaps oncologists tend to report all trials, whereas others might publish their best and most convincing, randomized trials. Second, the investigators did not read the full papers and might have missed more subtle aspects of trial design that would have changed the analysis. Third, an unstated number of the trials were published in non–peer-reviewed journals and may have had essential flaws in their conduct or analysis that should disqualify them from inclusion in this study. Fourth, half of the oncology papers reported trials of new combination therapies, and the objective in these studies might simply have been to confirm safety of the combination, as the decision to proceed to phase III had already been made. There was no compelling reason to control these studies. Further, because the Michaelis article examined publications from the year 2002 and therefore covered trials conducted in prior years, only a quarter (47 of 228) of the publications from the year 2002 and therefore covered trials in the recent trials might not accurately reflect the current state of oncological trials.

Nonetheless, the results of the study are worthy of discussion and reflection. The investigators are certainly right in arguing for greater emphasis on informative design in phase II. As Roberts and this author have pointed out in an earlier publication, the “go or no go” decision at the end of phase II is perhaps the most difficult one to make in the drug development cycle. Data are limited, the future investment required for a phase III trial is vast, and the success of the company may depend on the drug in question (3). An informative phase II trial is crucial. At the completion of phase II, the decision makers need to understand toxicity and pharmacokinetics, should have strong indications of activity in a specific kind of cancer, and should have a clear sense of an approval strategy. All too often, there are gaps in this knowledge, and the decision is guided by both fact and intuition. The decision becomes easier when the drug is being developed for treatment of an otherwise unresponsive tumor, such as melanoma, for which there are few, if any, effective drugs. Renal cancer used to be such a disease. Increasingly, there is competition in treating the more common solid tumors, such as breast, lung, or colon cancer, and the judgment requires stronger evidence of clinical benefit than in the past.

Not only do we need more complete data at the end of phase II, but that data may be harder to come by for the new generation of molecularly targeted compounds. The best of these drugs, such as Herceptin (3), Erbitux (4), and Avastin (5), may have only modest activity as single agents and produce few clinical responses. Their value may only be obvious in more subtle trial designs, in which they delay time to progression or recurrence or enhance response rates to standard cytotoxic agents (5, 6). The traditional single-agent phase II trial, with response as the end point, may lead to the abandonment of a valuable drug. Larger trials, and more complex phase II designs with time-to-progression end points, may be required to show effectiveness of the new agent. In this sort of trial, concurrent controls, treated with standard agents or randomized either to discontinue the experimental drug or perhaps to begin the drug after a period of placebo treatment, might show valuable aspects of the toxicity and effectiveness of the new agent. Such is the case with sorafenib, in which the University of Chicago group randomized stable patients to continued therapy versus drug discontinuation, with strikingly positive findings for patients who continued to receive the experimental drug (2). In other settings, in which a standard cytotoxic is an alternative to a new targeted drug, the choice of appropriate end points may be complicated. Although time to progression might be most appropriate for the cytostatic agent, partial or complete remission might be a clearer end point for the cytotoxic drug.

The use of controls for phase II studies is only one approach to improving and adapting phase II studies in the era of targeted therapies. The best design for any given agent in phase
II will depend on the nature of the agent, the early hints of activity in phase I, the disease setting, the degree of certainty about best dose and schedule coming out of phase I trials, and the competition faced by the new drug. A randomization involving two different doses of drug might show a dose-response relationship and a clear advantage for one and thereby might resolve questions that often persist even after approval. Even for effective drugs, such as imatinib, it is unclear whether escalation beyond the recommended 400 mg/d dose might have long-term benefit for certain patients. Other trial designs might evaluate target inhibition as an end point versus the maximum tolerated dose and thereby answer questions of the benefits and risks of escalating beyond the biologically effective dose (7, 8).

New molecular technologies offer remarkable insights that can inform unexpected development pathways. Increasingly, gene expression profiling and molecular studies have illuminated the existence of distinct subpopulations within pathologic categories of cancer and may be helpful in defining effective treatment for distinct subpopulations (9). The role of epidermal growth factor receptor mutations in predicting response to gefitinib and erlotinib offers an outstanding example of the value of a biomarker in defining a development strategy (10). Both the National Cancer Institute and the Food and Drug Administration have declared their intention to support the development of biomarkers to speed and inform drug development. The phase II setting, rather than phase I, may be the appropriate arena for addressing the question of how to identify the appropriate patient subpopulation for drug X (11) because this determination requires responses or other evidence of antitumor activity (such as delayed time to progression) to establish a correlation of activity with a biomarker. Thus, it might be useful to compare the molecular profile of responding patients or patients with stable disease beyond a defined time period, with the profile of nonresponders or those subjects who progress early after initiation of treatment. In the longer run, intensive molecular and immunologic characterization of the responsive subset of the phase II patient pool might provide more valuable information than randomization, with the potential for enrichment of the population for responders (12).

Returning to the specific plea for more controlled phase II trials, for many years, the field of oncology has wrestled with the issue of whether and when it is appropriate to do randomized clinical trials. Some have opposed this design categorically, even for phase III trials, based on ethical considerations (13), claiming that all patients with an incurable disease should be offered the opportunity to receive a potentially beneficial experimental treatment. For many patients with advanced disease who are approaching the end of their illness and enter phase II trials with a sense of desperation, the use of placebos is even more problematic. The U.S. Code of Federal Regulations states that “phase 2 studies are typically well controlled, closely monitored and conducted in a relatively small number of patients, usually no more than several hundred subjects,” but this statement seems much more appropriate for studies of new treatments for chronic, nonfatal diseases, for which a period of placebo might be acceptable. The proposal to subject 100 cancer patients to a no-treatment arm, as part of a phase II trial, is challenging, ethically and strategically. For cancer drugs, a more focused and laboratory-based phase II trial may better suit the current climate of drug development. Michaelis and Ratain have appropriately challenged our field to use the phase II opportunity to innovate. Whether innovation requires controls is not resolved, but we certainly can agree that this is the time to experiment in the design of experimental phase II trials in the cancer field.

References

Phase II Cancer Trials: Out of Control?

Bruce Chabner


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/13/8/2307

Cited articles
This article cites 13 articles, 7 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/13/8/2307.full#ref-list-1

Citing articles
This article has been cited by 3 HighWire-hosted articles. Access the articles at:
http://clincancerres.aacrjournals.org/content/13/8/2307.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.