ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

Next Generation Clinical Trials

Donald A. Berry, PhD
Professor, Department of Biostatistics
The University of Texas MD Anderson
Cancer Center
Houston, Texas

H&O What is the current method that is used to design clinical trials, and what are its limitations?

DB There are many approaches and many types of clinical trials. Generally, cancer drugs are developed sequentially and in phases, from phase I to II to III. Phase I trials address questions of toxicity and maximum tolerated dose (MTD). However, many modern agents do not have an MTD. Moreover, the usual toxicity that results from cytotoxic chemotherapy is hematologic, and of course nausea and vomiting can be limiting as well. Such toxicities tend to manifest in the first cycles and sometimes with the first dose. The biologic agents that are increasingly common today tend to not have these kinds of toxicities. Rather, their toxicities are usually longer term (rashes, heart failure, etc) and may not show up until later cycles and even later phases of development. Phase II trials are designed to determine whether the drug has efficacy, some indication of anti-cancer effect. Historically, oncology phase II trials have had a single arm, with the drug given at the MTD, and the historical endpoint has been tumor response. Phase III trials are randomized comparisons usually against standard of care, placebo, or active polychemotherapy, and sometimes the study drug is added to standard therapy. The dose and schedule are usually chosen on the basis of limited information regarding the endpoint of the trial.

In regard to limitations, and speaking empirically, over the last 7 years, 66% of phase III oncology trials have failed, the most among all therapeutic areas. This high and very costly failure rate reflects the weaknesses in the earlier phases of development. Too often it takes huge phase III trials to demonstrate that we got it wrong. Perhaps the dose was wrong, the schedule was wrong, the concomitant therapy was wrong, or the population was wrong. Or perhaps the drug had no role in any cancer, which we should have discovered long before. Failing late breaks the bank. We should learn as early as possible that a drug is a dud so we can utilize precious patient resources more wisely.

H&O What is adaptive design, and why should it be used over traditional study designs?

DB An adaptive design is one in which the data accumulating in the trial are used to modify the trial's course. Adaptive designs are particularly useful for addressing many questions in the same trial. For example, they can address the appropriate dose, the appropriate patient population, and whether the agent works best with concomitant therapies all in the same trial. If one study arm is not doing well, we might change the randomization or drop it entirely to focus on other arms.

A goal in personalized medical research is to identify patients who are not benefiting and drop them from the trial. This has the effect of not exposing them to therapies that do not help them. It also makes the trial more efficient and potentially much smaller. Patients who do not benefit dilute the therapy's effects. It is not just that including such patients does not add anything, it subtracts. For example, suppose a therapy doubles median survival in a patient population, from 6 to 12 months. To show this with 80% statistical power in a randomized trial requires a sample size of slightly more than 100 patients total. Now suppose that these patients are mixed with an equivalent number of other patients who do not benefit. Now, the study size that is required is about 300 patients. Not only is this almost 3 times as large, it requires about 50% more

patients of the subpopulation that benefits. The reason is that the benefit of the subpopulation is diluted by the patients who do not benefit.

H&O What is the role of the Bayesian approach in adaptive design?

DB Both the Bayesian and the frequentist approaches to clinical trial design can be adaptive, and they can be complementary. The Bayesian approach is being used increasingly because it is exquisitely tuned to adapting to information that accumulates during an experiment, including during a clinical trial. The Bayesian approach is naturally adaptive because it enables and indeed requires continually updating what is known based on the available information, and because it can be constructed around a theme. The frequentist approach is based on a fixed design, where at the end of the day one evaluates the data in the context of the design used. The frequentist can accommodate adaptations. However, while the Bayesian can assign the next patient to an arm that maximizes the expected number of successful treatments of the remaining patients to be included in the trial, the frequentist cannot. On the other hand, one can evaluate the standard frequentist characteristics for any given Bayesian design. Because the Bayesian design is complicated, with many "if-then" statements, such an evaluation requires simulation. Quite generally, when we build a trial using the Bayesian approach, we use simulation to find the false positive rate, the statistical power, and other conventionally frequentist characteristics. Based on these characteristics, we might revisit the design and modify it to control type I error, for example.

H&O What are the main goals of using adaptive clinical designs?

DB The goal of an adaptive approach is to learn efficiently. The principle is fundamental and intuitive: when walking from A to B, it is most efficient to keep your eyes open. As but one example, non-adaptive trials are either unnecessarily big or too small. For successful trials it is the former and for unsuccessful trials it more likely the latter. Sometimes a trial ends without a definitive conclusion and a modest increase in sample size might have resolved the issue. In any case, it is better to have one's eyes open to know when the sample size is sufficient. Also, non-adaptive trials usually address a single question. Keeping one's eyes open makes it possible to learn about many things, and enables follow-up to ensure that an observation was not a fluke.

H&O How does the Bayesian method fit in with the targeted agents being developed today?

DB The Bayesian approach is not the only way to address a problem, but its inherent flexibility helps in addressing more questions and doing so efficiently. In the case of targeted agents, many that have been developed either hit targets other than those planned or do not hit any target at all. My use of Bayesian design with targeted therapies is to adaptively randomize patients who are target negative as well as those who are target positive. The biology can be incorporated into the prior distribution. The same data might mean different things in the different groups. Should the data show that target-negative patients are not really benefiting, we can lower the probability of assigning them to the agent under consideration. And we might eventually drop them from the trial completely. This design answers not only the question of whether the agent is effective in the target-positive patients, but also gives some information about whether there are markers in the target-negative population that carry a drug effect.

H&O In which ways can study designs be adaptive?

DB All phases of clinical trials can be adaptive, and indeed an entire drug development program can be adaptive. There are many kinds of adaptations. The simplest types are stopping a trial early or extending its accrual beyond the planned sample size. Other adaptations include assigning patients to different doses to more effectively assess a dose-outcome relationship, to focus on subpopulations that apparently benefit, and to evaluate drug schedules to determine how the drug is best delivered. It is also possible to adaptively change randomization proportion, add arms or doses, and include different phases of drug development within the same trial, seamlessly moving from one phase to another. Quite generally, if something about a drug is less than perfectly known, that aspect may be addressed in an adaptive trial. I am not saying that every such issue should be included in an adaptive design, only that they may be considered for inclusion. How well they can be answered can be assessed, usually by simulation.

H&O What are some studies utilizing this method?

DB In my first 5 years at MD Anderson Cancer Center, my colleagues and I designed about 200 Bayesian trials. We described them in the journal *Clinical Trials*. The Bayesian

designs most commonly used were the continuous reassessment method in phase I trials, adaptive randomization in phase II trials, and designs to simultaneously monitor efficacy and toxicity in phase I/II trials. A large and complicated adaptive trial that is currently ongoing is I-SPY 2 (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And molecular Analysis 2). It is sponsored by the Foundation for the National Institutes of Health. The goal is to identify types of tumors that respond to a variety of experimental drugs, drugs that come from different pharmaceutical company sponsors. It is more a clinical screening process than it is a conventional clinical trial. The patients have newly diagnosed locally advanced breast cancer treated neoadjuvantly. The primary endpoint is pathologic complete response. The control therapy is 4 cycles of a taxane followed by 4 cycles of doxorubicin/cyclophosphamide followed by surgery. Randomization is adaptive across the treatment arms based on biomarker subsets, with therapies that are performing better within a subtype being assigned with greater probability to patients having that subtype. The goal of this phase II trial is to enable smaller, focused phase III trials. Not including patients who do not benefit from the experimental therapy can make a phase III trial more positive while decreasing its sample size and cost by an order of magnitude.

H&O Are there any barriers to implementing adaptive designs?

DB There are barriers to every major change. In this case, researchers (including me) worry that we will lose some of the advances that have been made in the science of clinical trials. For example, randomization changed clinical research from an imperfect art to a science. No one wants to lose that. Most researchers understand that we could do better, but some worry about throwing the baby out with the bathwater, and appropriately so.

One of the barriers has been a perceived opposition from regulatory agencies. That concern was largely eliminated in 2010 when the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research of the US Food and Drug Administration issued a draft guidance for industry pertaining to the use of adaptive designs in "adequate and well controlled trials." Also in 2010, the National Institutes of Health joined with the FDA to fund a regulatory science grant to address potential barriers in using and implementing adaptive designs and ways to overcome them. The grantee is a collaboration between the Neurological Emergency Treatment Trials network and a company of which I am part owner. Barriers can exist with investigators, patients, regulators, Institutional Review Boards, statisticians, and journals. My assessment at this early stage of the grant is that educating statisticians and clinicians is critical. And the best education is experience. With experience comes comfort. So far, the experiences associated with adaptive designs have been very positive.

Suggested Readings

Biswasa p, Liub D, Leeb JJ, Berry DA. Bayesian clinical trials at the University of Texas M. D. Anderson Cancer Center. *Clinical Trials.* 2009; 6:205-216.

Breast Cancer I-SPY 2 Trial. http://ispy2.org/about.

Johnson V, Cook J. Bayesian design of single-arm phase II clinical trials with continuous monitoring. *Clin Trials.* 2009;6:217-226.