Adaptive Clinical Trial Design: Has Its Time Come?

By Nancy J. Nelson

One of the most talked-about cancer clinical trials last spring was BATTLE—a phase II trial that did not change practice or introduce a new drug. What got all the attention was the non-small cell lung cancer trial’s “adaptive” design.

In adaptive trials, data gathered as the trial progresses are used to change some aspect of the trial midstream. These trials have increased over the past decade, a trend fueled by the need to improve the poor success rate of conventional clinical trials and one that the U.S. Food and Drug Administration supports. The adaptations can be to drop a treatment arm that isn’t effective, alter dose levels, or increase the trial size if a drug proves less responsive than predicted.

In BATTLE (Biomarkers-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination), about 40% of the patients were randomly assigned to receive one of four treatments in the first phase of the trial. In the second phase, the adaptive phase, treatments were based on the results of biomarker testing; that is, the remaining patients were assigned to drugs that had proven effective in first-phase patients with similar tumor biomarkers.

The trial showed that adaptive design could work in a complex trial that assessed multiple drugs and biomarkers and required tissue collection and biomarker analysis. “This is the first time in lung cancer that we have collected real-time tissue during a trial and incorporated real-time assessment of biomarkers to help direct therapy,” said BATTLE principal investigator Edward S. Kim, M.D., from the M. D. Anderson Cancer Center in Houston. Kim presented the results at the annual meeting of the American Association for Cancer Research in April (see sidebar).

Buoyed by their success, the BATTLE researchers are now planning BATTLE-2, also a phase II trial, which will test whether certain drugs produce a response in non–small cell lung cancer patients with certain biomarkers (see sidebar). The new trial, which already has institutional review board approval, is just one of several signs that adaptive trial designs may be gaining popularity and acceptance. Nevertheless, experts say, hurdles remain and many issues with adaptive design still have to be worked out.

Adaptive Trials Increasing

One recent study suggests that adaptive trials, although still few, are on the rise. Judith Quinlan, vice president for adaptive clinical trials at Cytel in Cambridge, Mass., reported on a survey of 13 pharmaceutical companies and three statistical consultants in Clinical Trials this year. Quinlan and her colleagues found that between 2003 and 2006, three or fewer adaptive design studies started per year. That number jumped to 13 in 2007.

One reason for the increase may be a growing acceptance of the Bayesian statistical framework, which is used to analyze data from adaptive trials. According to a recent report by Swati Biswas, Ph.D., from the department of biostatistics at the University of North Texas Health Science Center in Fort Worth. 5%–10% of the medical devices that the FDA recently approved used Bayesian designs and analyses, compared with none 10 years ago (Clinical Trials 2009;6:205–16).

Greater computing power and efficient computation algorithms have also cleared the way for adaptive trial design and analysis, according to J. Jack Lee, Ph.D., in the
department of statistics at M. D. Anderson. “In the early days, we didn’t have the computer power to run the computations for Bayesian trials,” he said. To run a simulation study would easily take a week on a fast computer. Even now, he added, the calculations can be challenging. In the last decade, 20% of protocols have used Bayesian adaptive trial designs at M. D. Anderson, where Donald A. Berry, Ph.D., head of the division of quantitative sciences, has promoted their use.

Some of the encouragement to use adaptive trials has come from the FDA. In 2004, it issued a report saying that the usual medical product development process could no longer keep pace with scientific discoveries. The report called for new trial designs that incorporated adaptive designs and Bayesian methods. And last February, the agency published guidance regarding the regulatory implications of adaptive trial design.

**Extra Time, Infrastructure**

But adaptive design has some drawbacks. Quinlan, who is also a statistical and clinical consultant to pharmaceutical and biotech companies, said that it takes 3 months’ extra time to plan an adaptive trial, working with all the stakeholders in the process: clinicians, biostatisticians, IT people, project managers, drug providers.

Moreover, she said, adaptive design demands creating an infrastructure to facilitate real-time learning, a flexible drug supply, and frequent data intake. Organizing information flow to prevent data leakage takes special attention, and documenting the information that comes from monitoring is important, she said. Finally, to educate research and development staff, including senior management, takes time and attention.

Another barrier, according to Berry, is that few biostatisticians have extensive training in Bayesian theory and methods. And statisticians don’t all agree that Bayesian design is a good thing: “It’s still debated in the statistical community because there’s some subjectivity in the design,” said Lee.

And then there are the limitations of the trials themselves. “Adaptive trials are great for learning but are not a panacea,” Lee said. “BATTLE is a phase II trial, not a phase III trial. We’re not going to solve all the problems. We learned a lot, which helped us to plan future trials, but we don’t have a big enough sample size to get a definitive result based on the BATTLE trial.”

**I-SPY 2 Trial**

Another adaptive trial attracting attention, I-SPY 2, is designed with an eye toward more definitive results. Although a phase II trial, it will facilitate the transition to phase III, according to Berry, who is the trial’s co–principal investigator along with Laura Esserman, M.D., at the University of California, San Francisco.

Launched in February, I-SPY 2 is testing whether adding drugs to traditional chemotherapy improves outcomes in women with locally advanced breast cancer. The trial will examine which biomarker subtypes will benefit from various therapies. As in BATTLE, I-SPY 2 will test biopsied tissue for key biomarkers involved in breast cancer pathways.

All women will be treated with paclitaxel, doxorubicin, and cyclophosphamide. Initially, 80% of the women will be randomly assigned to one of five drugs designed to interact with specific breast cancer biomarkers. As the trial progresses, the investigators will evaluate the success of each drug–biomarker combination. Eventually, more women with specific biomarkers will be assigned to the drugs shown to be effective with those biomarkers. Drugs that are ineffective with all biomarkers will be dropped from the trial.

Drugs more effective than standard therapy will graduate to a small phase III trial focused on the subpopulation of patients who benefit from the drug.

A main difference between I-SPY 2 and BATTLE, according to Berry, is that I-SPY 2 is more a process than a trial. “It allows for therapies to come and go,” he said. Whereas BATTLE considered four therapies that were fixed throughout, I-SPY 2 might go on forever.”

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**BATTLE and BATTLE-2**

The adaptive phase II trial known as BATTLE involved 255 patients with advanced non–small cell lung cancer. The research team, led by M. D. Anderson’s Edward S. Kim, M.D., tested whether various drugs will respond to tumor biomarker subtypes. Fresh core needle biopsies at the beginning of the trial were analyzed for four biomarker subtypes: epidermal growth factor receptor (EGFR), KRAS/BRaf, vascular endothelial growth factor (VEGF), and cyclin D1/RXR.

In the first phase of the trial, 40% of the patients were randomly assigned to one of four treatment groups: erlotinib, an EGFR inhibitor; vandetanib, a VEGF inhibitor; sorafenib, a multi kinase inhibitor; and erlotinib–bexarotene, an RXR receptor activator.

The second phase was the adaptive phase. The decision as to how to treat the remaining 60% of the participants was based on which biomarker subtypes in the random phase benefited from the drugs. For example, many patients with increased EGFR expression showed improved benefit with erlotinib but not with sorafenib. Many with increased VEGF expression improved with vandetanib treatment.

At the end of the adaptive phase, when the trial ended, the erlotinib arm had 59 patients; the vandetanib arm, 54; the sorafenib arm, 105; and the erlotinib-plus-bexarotene arm, 37. The final results showed that patients with both EGFR mutations and amplified expression of EGFR were 100% responsive to erlotinib but 100% nonresponsive to sorafenib. On the other hand, patients with KRAS mutations responded better to sorafenib than to any of the other drugs; sorafenib was effective in 61% of patients with KRAS mutations. The erlotinib–bexarotene combination showed an improved benefit in patients with tumors with increased cyclin D1 expression.

Overall, 46% of patients had their disease in check after 8 weeks of treatment, compared with 30% of late-stage lung cancer patients after 8 weeks of traditional chemotherapy. More patients in the adaptive phase had the disease in check than in the randomized phase (42% vs. 37%).

The M. D. Anderson team is now planning BATTLE-2 on the basis of what they’ve learned. Although not all details are available, J. Jack Lee, Ph.D., statistician for the BATTLE trial, said that BATTLE-2 will also be a multistatic randomized phase II trial with advanced non–small cell lung cancer, testing whether certain drugs will respond to biomarker subtypes. So far, erlotinib and sorafenib are contenders, and more drug combinations will be tested. BATTLE-2 will not include patients with EGFR mutations and EML4–ALK gene fusion because there are drugs known to be effective in people with these mutations. KRAS mutations will be included. The protocol has received institutional review board approval and is being amended.