Clinical Trial Conundrums: More Art Than Science?

By Vicki Brower

In a recent study comparing proton therapy and intensity-modulated radiation therapy (IMRT), both of which spare surrounding tissues from excess radiation, patients with locally advanced lung cancer who received combination proton therapy and chemotherapy suffered less bone marrow toxicity and other side effects than those who received IMRT and chemotherapy. This phase II trial, conducted by Ritsuko Komaki, M.D., professor of radiation oncology at the University of Texas M. D. Anderson Cancer Center in Houston, lends credibility to the claim that proton therapy produces fewer side effects than radiation with photons because of its precision. The results, which were presented at the 2008 Chicago Multidisciplinary Symposium in Thoracic Oncology in November, also indicate a difference in survival between the two groups, which will be detailed in a forthcoming phase III randomized controlled trial (RCT), Komaki said. The new study is one of relatively few in which proton therapy is being tested, although proton therapy was introduced in the 1990s, before RCTs were performed.

Whether or not new technologies such as proton therapy need testing in RCTs is debated among radiation oncologists (see JNCI, 100;1496-8). Similarly, which clinical trials should be conducted to test carbon ions, the newest type of radiation therapy, is a pressing question in Europe, where this technology will be rolled out early next year (see JNCI, current issue).

Although RCTs are considered the “gold standard” for testing new treatments, a rapidly changing regulatory landscape, new targeted therapies, trials that test endpoints ranging from efficacy to superiority to noninferiority, and an increasing number of phase II trials being conducted in their stead for U.S. Food and Drug Administration review mean that, in practice, many treatments are now approved on the basis of trials that are not randomized or controlled. Also, sometimes RCTs may not be performed for rare medical conditions for which sufficient patient accrual is unlikely.

“The question of when RCTs should be conducted, and under what conditions they are not needed, has no easy answer and depends on so many different factors,” said Steve Pearson, M.D., president of the Institute for Clinical and Economic Review at Harvard Medical School in Boston. Although RCTs may be the gold standard, trials may be designed in a variety of ways to give many types of information, Pearson said. “In some cases, observational studies may be better than RCTs for their ‘real world’ quality,” he said.

Real-world patients often have several medical conditions, for which they take multiple medications, a factor that is not addressed by strictly controlled studies, said Paul Applebaum, M.D., professor and director of the division of psychiatry, law, and ethics at Columbia University in New York City. “The research community is beginning to recognize that ‘effectiveness’ trials may be better designed [than some RCTs] to provide cleaner answers for patients in the real world,” he added.

But RCTs have often exposed the weaknesses of other trial designs. One example is the case of autologous bone marrow transplantation (BMT) for metastatic breast cancer. In the mid-1980s, BMT gained many proponents who reasoned that if higher chemotherapy doses could be given to patients getting BMT, cancer cells would be killed more effectively and that would translate into a survival benefit. The first study on efficacy, a phase II uncontrolled trial, appeared in 1988 and showed a 58% response rate, noted Gilbert Welch, M.D., professor of medicine at Dartmouth College in Hanover, N.H. A few months later a similar study with an 80% response rate was published. At the time, study authors were cautious about these data, noting that controlled studies were needed and that improved response rates were not yet associated with better survival. But press reports were encouraging, and by 1990, because patients sought insurance coverage for the procedure, the National Cancer Institute finally began an RCT. On that basis, one insurer moved to cover the costs of the trial. But by the mid-1990s, results from RCTs were in: Four of five trials did not support the use of BMT and high-dose chemotherapy for treating metastatic breast cancer, and so insurance coverage was revoked.

“Creeping Phase II-ism”

Since the mid-1980s, there has been a growing trend of replacing RCTs with phase II trials that are randomized, non-blinded, non-placebo-controlled studies, said J. Jack Lee, Ph.D., of the department...
of biostatistics and applied mathematics at the University of Texas M. D. Anderson Cancer Center. But because of the inferiority of these trials, better designs are needed.

In an editorial in the *Journal of Clinical Oncology*, Andrew Turrisi, M.D., chairman of radiation oncology at Detroit’s Wayne State University School of Medicine, called the trend “creeping phase II-ism” and warned that caution is needed in interpreting phase II trial results, which can be misleading. Turrisi cites a phase II study of paclitaxel, radiotherapy, and cisplatin plus etoposide in lung cancer that indicated a survival advantage after 1 year but which, in RCTs, did not show the same benefit.

Turrisi observed that phase II studies are often used prematurely to guide treatment before more data are available. And phase II trials are not powered to reach statistical significance, Benjamin Djulbegovic, M.D., Ph.D., professor of medicine and oncology at the H. Lee Moffitt Cancer Center in Tampa, noted. Often, particularly for industry-sponsored trials, they do not compare a new treatment with standard therapy, which he called “ethically questionable.”

Another critic of the widespread use of phase II trials to guide clinical practice called this phenomenon “misguided or even dangerous.” Marcie Tomblyn, M.D., assistant professor of medicine at the University of Minnesota in Minneapolis, cited a study comparing outcomes in phase II trials that found response rates exaggerated by nearly 13% when compared with subsequent phase III RCTs. “These issues must be weighed against the reality, however, that in certain diseases or therapies a definitive phase III study is either unlikely to be done, or cannot be done due to limited numbers of patients,” Tomblyn wrote in a 2007 *Hematology* article.

**Equipoise Needed for RCTs?**

Exactly when and under what circumstances RCTs should be performed is a longstanding and ongoing debate among clinicians and bioethicists. “Ethically, RCTs should be conducted when clinical equipoise—genuine uncertainty or disagreement—exists as to the relative merits of two or more therapies within the medical community,” said Djulbegovic. Known also as the “uncertainty principle,” equipoise is achieved when the intervention and control group are understood to be equivalent by both physician and patient, he said.

But not everyone agrees that equipoise is an appropriate criterion for designing an RCT. According to Franklin G. Miller, Ph.D., bioethicist at the National Institutes of Health, clinical equipoise is a fundamentally flawed concept. “The underlying ethical idea is that no patient in need of treatment should be randomized to an intervention under evaluation in an RCT that is known to be inferior to the established standard of care. Clinical equipoise rules out placebo-controlled trials for conditions that have proven effective treatments. But clinical equipoise inappropriately applies the ethics of the doctor–patient relationship to the fundamentally different context of clinical research, which is focused on gaining knowledge, not doing what is best medically for particular patient volunteers,” Miller said.

Good research methodology can conflict with standard patient care, and randomization to placebo may be justified even though an effective treatment may exist, Miller added.
Despite conflicting with the principle of clinical equipoise, placebo-controlled trials can be ethically justified, Miller said, if placebo controls are necessary to produce answers to clinically important questions, if the risks to “patient subjects” from withholding proven treatments are relatively minor, and if informed consent is given. “We are better off dispensing entirely with clinical equipoise, as it confuses the ethics of patient care with those of clinical trials.”

Steven Joffe, M.D., assistant professor of pediatrics at the Dana-Farber Cancer Institute in Boston, sought to discover whether most trials are in fact conducted according to the uncertainty principle. In one study, he examined 93 cooperative group RCTs and found that most did. But Djulbegovic found one major exception while examining myeloma trials testing the drug erythropoietin. He discovered that industry-sponsored studies violated equipoise more often than publicly funded trials, by using placebo, no drug, or an inferior drug as a control.

But Do They Work?
It is the hope of benefit from a new treatment, however, and not altruism, that motivates many patients to participate in a clinical trial. Joffe wanted to find out whether participating in clinical trials actually benefits patients. In one study, he observed a modest advantage for patients in the trials’ active arm. In another study, Joffe compared outcomes of cancer patients who were treated within clinical trials and those who were not, and he found little good evidence to support the idea that patients in clinical trials benefit from participation. About half the studies he examined showed some evidence of a trial effect, or inclusion benefit, and none found that participation harmed patients—but most of the trials in the study had methodological problems that made interpretation difficult.

Others have examined and tried to quantify the claim that the clinical trial system helps identify new, effective treatments. Djulbegovic recently found that successful cancer therapies were identified in phase III RCTs conducted by the National Cancer Institute from 1955 to 2006 nearly 50% of the time. “This percentage represents a good return on [society’s] investment and is fair to patients as well,” he noted. “This is also an ethically welcome finding, because if every RCT found that the new treatments were better, it would destroy the system of RCTs because people would not accept randomization if it meant that they would only get the better treatment if they were in the 50% of patients allocated to the new treatment.”

In another study published in *BMJ* in 2005, Djulbegovic examined 126 RCTs and found that new treatments were as likely to be inferior as superior to standard treatments. There was no strong evidence that overall patients were either harmed or benefited by participating in RCTs.

In an update of this research, presented at the 2008 annual meeting of the American Society of Clinical Oncology, Djulbegovic examined how often in the past 50 years breakthrough interventions have been discovered in RCTs. He and his colleagues found that about 15% resulted in real innovation. Of those, 23% were in pediatric cancer, most notably in leukemia. Although only 2% of studies examined resulted in treatments that reduced the death rate by more than 50%, 27% of treatments tested prolonged life, 23% were adjuvant treatments, and 14% were curative.

“No identifiable pattern [for discovering specific treatments] had emerged, indicating unpredictability in treatment discoveries,” he said. “It is impossible to predict the results of any particular trial when it begins. … However, we can predict the overall statistical pattern of the treatment successes and expect that 25%–50% of all treatments tested in RCTs will turn out to be successful.” Djulbegovic emphasized that this predictable proportion of success is directly derived from the uncertainty, or equipoise, that underpins the ethics of clinical trials. “Uncertainty determines a pattern of successes and drives clinical discoveries.”

Clinic-Driven Practical Trials
But potential commercial sponsors may not have an incentive to do certain types of trials that will help guide clinical practice. Often, NIH-sponsored studies focus more on discovery and proof of concept than how drugs can be optimally used to help best help patients, said Sean Tunis, M.D., director of the Center for Medical Technology Policy, a private, nonprofit group in Baltimore that works with clinicians, health insurance payers, researchers, and drug companies to design and fund prospective, real-world studies to inform health care decisions for new medical technologies. Tunis calls these studies—which are designed to guide clinical and health care policy decision making—“practical clinical trials.”

“Too often, one looks to evidence from trials to guide decisions in clinical practice, and it’s not there,” Tunis said.

The goal of practical trials is to fill in the gaps in evidence-based knowledge, according to Tunis. Working with the American Society for Therapeutic Radiation Oncology and several leading radiation oncology researchers, the Center for Medical Technology Policy has designed a parallel, nonrandomized, prospective cohort 10-year study to test toxicity of IMRT and of protons in patients with early-stage, low-risk prostate cancer. The study will examine how changes in bowel function differ between patients treated with protons and IMRT after 6 months and 2 years after treatment, differences in second malignancies at 10 years, time to progression, and survival.

Whether new therapies such as proton and carbon ion therapy are proven to be safe and effective for patients depends on a collaborative effort in designing well-conceived clinical trials that can answer pressing questions and an effective public–private partnership dedicated to answering questions about treatments that benefit patients.