

CLINICAL TRIALS

Accrual to Cancer Clinical Trials in the Era of Molecular Medicine

Richard L. Schilsky

Enrollment of patients in a clinical trial is difficult as a result of a host of well-documented barriers. In the field of oncology, molecularly targeted treatments have demonstrated considerable therapeutic promise. At the same time, clinical testing of these targeted agents has introduced new complexities in the decision-making process by patients or providers on whether to participate in clinical trials. Explored in this Commentary are challenges of and potential solutions for the clinical testing of modern cancer therapies.

MISSING PERSONS

Annual enrollment of adult cancer patients in clinical trials (accrual) sponsored by the U.S. National Cancer Institute cooperative groups (1) has ranged from 25,000 to 30,000 over the past decade. The majority of these patients are enrolled by only a small fraction of the 14,000 oncologists who participate in the cooperative group program (2). While this level of accrual is considerable, it has been recognized for many years that only 3 to 5% of adult cancer patients enroll in clinical trials even though many indicate an interest in doing so if asked (3). The barriers to enrollment are well documented (Table 1). Some, such as the ability to prescribe drugs for off-label use and the variable insurance coverage for the care of patients in clinical trials, are likely unique to the United States.

The potential for oncologists in the United States to prescribe Food and Drug Administration (FDA)-approved drugs for off-label uses provides strong incentives for both doctors and patients to forgo trial enrollment if the drug being studied can be prescribed and reimbursed outside of the trial. Off-label prescribing guarantees a patient's access to the new agent while eliminating, for the physician, the complexities of the clinical trial administrative process. Oncologists who participate in clinical trials also face considerable regulatory liability for doing so; such liabilities may range from potential violations of human subjects protections and patient privacy to possible allegations of fraudulent billing practices or data handling that may result from inaccurate or incomplete documentation in the research record. Trials that compare substantially

different treatment approaches, such as radiation therapy compared with surgery, are notoriously difficult to complete because of the lack of equipoise—a condition in which there is genuine uncertainty whether or not a treatment will be beneficial—and important clinical questions, such as the optimal therapy for localized prostate cancer, have remained unanswered as a result.



Fig. 1. Patient empowerment. Patient advocate groups help individuals to play an active role in finding clinical trials for which they are eligible. For example, the aim of the Love/Avon Army of Women initiative is to recruit 1 million women—breast cancer survivors and women at risk for breast cancer—to participate in breast cancer-related studies.

Despite various attempts to remedy the accrual problem, such as awareness campaigns, establishment of clinical trial registries, and the development of search engines to match patients to trials, annual enrollment on cooperative group clinical trials has remained essentially unchanged throughout the past decade. Moreover, as the cooperative group bureaucracy has become more complex and trial start-up times have lengthened to an average of 2 years or longer, up to 40% of cooperative group phase III trials have failed to complete accrual and closed without achieving study endpoints, wasting the contribution of those patients willing to enroll in the trial (4).

CLINICAL CHALLENGES OF TARGETED THERAPIES

In the era of molecular medicine and targeted cancer therapy, a host of additional issues must be considered that have the potential to further complicate the decision by patients or providers to participate in clinical trials. Among these are the need for biospecimen donation by patients to screen for molecular targets, greater use of randomized phase II trials to assess the activity of drugs likely to produce disease stabilization rather than regression, and more frequent use of placebo controls that may discourage patient enrollment. Indeed, a considerable ethical dilemma may occur when patients are asked to accept randomization to a targeted agent that has high activity in a biomarker-selected population compared with a placebo or a modestly effective standard-of-care agent (5). Furthermore, sponsors increasingly develop products for a global marketplace and must consider issues such as pharmacogenomic variation in toxicity or efficacy across populations. Addressing such issues requires enrollment of an ethnically diverse study population to demonstrate the drug's optimal effect; an example of this phenomenon is the case of the much higher prevalence of epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer in Asian compared with Caucasian patients and the corresponding increase in efficacy of gefitinib in the Asian patient population (6). The challenge is that many patients may need to be screened if the biomarker used for patient selection is of low prevalence in the tumor type under study. For example, in a recent trial to assess the effectiveness of trastuzumab in patients with HER2⁺ gastric cancer, investigators from 122 centers in 24 countries collaborated to screen 3803 pa-

Section of Hematology-Oncology and Comprehensive Cancer Center, University of Chicago, Chicago, IL 60637, USA.

E-mail: rschilsk@medicine.bsdu.uchicago.edu

Table 1. Barriers to enrollment in clinical trials.

• Insufficient physician time/interest
• Lack of dedicated research staff
• Lack of equipoise in clinical trial design
• Increasing protocol eligibility requirements and protocol complexity
• Lack of reimbursement for physician management of patients in trials
• Off-label prescribing of drugs
• Lack of insurance coverage for patients participating in clinical trials
• Regulatory liability and burden
• Insufficient patient awareness/demand

tients with gastric cancer in order to enroll 594 HER2⁺ patients in the study (7).

Fortunately, the advent of molecular medicine also offers potential new strategies to enhance clinical trial enrollment and speed the completion of studies. Promising targeted therapies that offer a high probability of response with limited toxicity are, of course, in high demand, and trials testing such agents have the potential to rapidly complete accrual. Furthermore, the use of biomarkers to identify patients likely to respond to the treatment being tested offers the potential for higher effect sizes in clinical trials that, therefore, require enrollment of fewer patients.

Indeed, even early-phase clinical trials have begun to reveal considerable antitumor activity of many targeted agents, such as PLX4032 in metastatic melanomas that harbor a B-Raf valine-to-glutamate mutation at amino acid 600 (8) or crizotinib in non-small cell lung cancers with an *EML4-ALK* genetic translocation (9). Novel adaptive clinical trial designs are also now being introduced into oncology drug development; these protocols appeal to patients and physicians because they vary rates of enrollment or assignment of treatment on the basis of the probability that the treatment being tested will demonstrate antitumor activity (10).

Ultimately, the factor that most greatly influences a patient's decision to enroll in a clinical trial is his or her oncologist's recommendation to do so. Patients, however, are increasingly well informed, supported, and empowered by advocacy and support groups, and the potential exists for patients themselves to take a more active role in finding trials, assessing their eligibility, and even submitting their biospecimens and clinical data to facilitate their enrollment. As an example, the Love/Avon Army of Women initiative is attempting to recruit 1 million women (including breast cancer survivors and women at risk for breast cancer) to participate in breast cancer-related studies and maintains a database with basic demographic information on volunteers (Fig. 1). To date, more than 337,000 women have registered online, and 34 studies have been launched after successful matches were made between interested women and researchers. To initiate the process, researchers fill out a standardized online application that an outside board reviews in coordination with an institutional review board. If approved, Army of Women sends an e-blast to everyone in the database, and women choose the studies in which they would like to participate.

Clinical trials remain the primary vehicle by which to translate promising laboratory observations into products, drugs, or devices that directly benefit patients as well as to directly compare existing standard-of-care treatments. Procedural changes that must be made in order to stimulate and facilitate patient accrual include better support for physicians who are committed to trial enrollment; harmonized regulation across oversight agencies and limited regulatory liability; improved awareness of trials by patients and physicians; expanded eligibility criteria; and better access and insurance coverage for patients of all ethnic and socioeconomic groups (2). Proper attention to and investment in these areas by policymakers and funding agencies will accelerate our ability to deliver on the promise of molecular medicine.

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