Early Cancer Clinical Trials: Safety, Numbers, and Consent

Michael J. Hawkins*

In this issue of the Journal, Ratain and his colleagues (1) revisit a number of issues that are of considerable importance to physicians who conduct early clinical trials of new anticancer agents and to the patients who participate in these trials. Because anticancer agents typically have a low therapeutic index, the initial dose level in phase I trials for most agents has been equivalent to 10% the dose lethal to 10% of mice (the murine equivalent of LD_{10}, which is MELD_{10}). This starting dose has been found to be safe for patients in almost all instances (2,3).

Several modifications to the standard phase I trial design have been proposed to address the counterconcern that, because these initial dose levels are too safe and thus subtherapeutic, many dose escalations have often been required to reach the maximum tolerated dose (4). These suggestions have included treating fewer than three patients at nontoxic dose levels, increasing dose levels in individual patients, increasing the dose increment between cohorts, and using pharmacokinetics to guide the rate of dose escalation. Ratain et al. (1) expand on these proposals by suggesting that only one patient be studied at nontoxic dose levels or that patients be allowed to choose the dose level at which they are treated.

In general, the investigators and regulatory personnel who are most familiar with the data on a drug determine what they feel will be a safe starting dose after careful evaluation and extrapolation of preclinical data. However, the lack of benefit for patients treated at subtherapeutic dose levels has not always received comparable emphasis. In retrospective analyses, a safe initial dose has proven to be substantially higher than the MELD_{10}; thus, ethical concerns have arisen regarding the large number of patients in phase I trials who are treated at biologically inactive dose levels. For example, starting doses that were 30% and 70% of the MELD_{10} were equal to or less than the maximum tolerated dose for, respectively, 12 and 11 of 13 drugs reviewed by Collins et al. (2). Since all patients treated on phase I trials have advanced, incurable malignancies, it is important to select the highest starting dose that can be administered with reasonable, but perhaps not complete, safety. Given the recent improvements in supportive care, a critical re-evaluation of the “standard” starting dose for many anticancer agents seems appropriate. While a higher starting dose would be associated with a higher rate of toxicity, many fewer patients would be treated at subtherapeutic doses. Increased awareness of species differences, the use of in vitro testing on human cells, and characterization of metabolic pathways may assist in more accurately predicting safe but biologically active starting doses.

Ratain et al. (1) also propose to modify the method of determining the recommended phase II dose by developing a model-guided dosing schema based on pharmacokinetic analyses conducted during the phase I trial. Model-guided dosing is particularly useful if dosing per body surface area results in highly variable toxicity. Only six patients in a phase I study are typically treated at what is to become the recommended phase II dose, but the variability of drug metabolism can only be determined after larger numbers of patients have been treated. The potential problems associated with this approach have been demonstrated by the recent experience with the investigational agent amonafide. Not until this drug was in broad phase II testing did it become apparent that the distribution of pharmacokinetic parameters and toxicity were bimodal and that dosing needed to be based on acetylator phenotype (4,5). Hence, one could argue, as Ratain and his colleagues have, that considerably more patients should be treated at the recommended phase II dose in the typical phase I evaluation of an agent to better characterize the distribution of toxicity and pharmacokinetic parameters. When considerable variability in pharmacokinetics and toxicity exist at the recommended phase II dose, more complicated dosing regimens based on limited sampling of pharmacokinetic data and/or characterization of patients’ metabolic pathways will probably need to be developed.

The issue of how much information is required for a patient to give informed consent to participate in any clinical trial is complex. Ratain et al. (1) suggest that patients should be provided with data from patients already treated in the trial. Clinical investigators are well aware of the dangers in making decisions based on limited data. Due to patient heterogeneity, standard clinical trial designs have utilized predetermined protocols and have prospectively specified the number of patients who will be treated in a given manner. Investigators who are uncomfortable with these numbers for whatever reason should clearly consider modifications. For instance, perhaps in certain phase II trials, it would be sufficient to rule out a 20% response rate with 90% or 80% confidence (instead of 95%) or to set the response rate of interest at 30% (instead of 20%), thereby reducing the number of patients treated with ineffective agents. However, no matter how sophisticated and empowered the patients, an unlimited supply of scientifically uninterpretable data can quickly become counterproductive to making an informed decision. Ultimately, at some level, physician investigators

*See "Notes" section following "References."
Screening for Breast Cancer: What Should National Health Policy Be?

Thomas C. Chalmers*

For decades, it has been assumed that the lives of women with breast cancer could be prolonged if their tumors could be diagnosed early, before metastasis to other parts of the body. The addition of effective technology, in the form of radiological mammography, to supplement routine physical examinations and breast self-examination has been viewed as an inherently attractive program, and mammography has become widely used in the last 20 years.

By 1977, there was general agreement that women older than age 50 should have an annual breast physical examination and mammography. This consensus was codified by the National Cancer Institute (NCI) and the American Cancer Society (ACS) (1). However, there were serious doubts about the wisdom of encouraging annual mammograms for women younger than 50. Was the apparent lengthening of life merely a shortening of the prediagnosis lead time? Could the exposures to x rays at a younger age be harmful (2)? In 1980, undaunted by these worries, the ACS encouraged mammography for women under 50.

In 1988, led by the American College of Radiology, most organizations involved with cancer treatment agreed to a more stringent recommendation, which stated that beginning at age 40, annual or biannual mammography should be performed in addition to a yearly clinical examination. In 1991, the ACS reiterated its support of radiological screening in women under 50.

The landmark Health Insurance Plan (HIP) of New York study that began 30 years ago was the first of eight long-term clinical trials in which women were selected at random or randomly assigned either to a group receiving mammography or to a control group with no mammography. Results of that trial and those from the other six studies, which have been published during the last 8 years, have been combined in a meta-analysis by Elwood et al. (3) presented at an international workshop on screening for breast cancer summarized in this issue of the Journal (4). A representative of each trial was present and participated in the deliberations.

The charge to the workshop was not to make recommendations regarding mammography, but to seek a consensus on the data from the eight studies for the benefit of an advisory committee of the NCI, which would, in turn, make recommendations. The report from the workshop summarizes data on women aged 40–49 in the trials as follows: "The randomized trials of women ages 40 to 49 are consistent in

References


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Correspondence to. Michael J. Hawkins, M.D., Departments of Medicine and Pharmacology, Georgetown University Medical Center, Lombardi Cancer Research Center, 3800 Reservoir Rd., Washington, DC 20007. Manuscript received September 13, 1993; accepted September 14, 1993.

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