MAURIE MARKMAN, MD
Dr. Markman is chairman of the Department of Hematology/Medical Oncology at the Cleveland Clinic, head of the Cleveland Clinic Cancer Center, and an associate editor of the *Cleveland Clinic Journal of Medicine*.

Ethical issues in clinical trials in oncology

In the gray area where clinical research may cross the line of ethical practice, physicians must act in the patient's best interest

To protect patients and ensure scientific integrity, clinical trials must conform to ethical guidelines. Patients must give informed consent to participate, and must be told if alternative treatments exist. Trials must be approved by institutional review boards. Despite these measures, gray areas persist in the ethics of clinical trials, posing questions for which there are no easy answers.

DESIGN OF CLINICAL TRIALS

Progress in clinical medicine depends on clinical trials. Only through well-designed and well-conducted studies can we critically evaluate the efficacy and safety of new treatments—especially in oncology, where experimental drugs and new treatment strategies can cause considerable morbidity.

Clinical trials in cancer, as in many other areas of medicine, follow a logical, systematic progression. Phase I studies examine the safety of new treatments and, for antineoplastic agents, their pharmacokinetics and appropriate dose levels for further testing.

Phase II studies evaluate efficacy, often using the response rate (ie, the percent of patients in whom tumors shrink) as a measure of effectiveness. These studies, which are not randomized, also generate additional data about the side effects of the treatment.

If a particular drug or strategy appears promising in phase II, it undergoes a randomized, controlled phase III trial to compare it with a standard treatment, which patients in the control group receive. If there is no known effective treatment for the condition, control patients receive no additional treatment.

A phase III trial need not always be conducted before a new regimen or drug is accepted in clinical practice. However, unless several phase II studies convincingly demonstrate that the new treatment is superior to standard treatment (eg, many more patients who receive it survive than do historic controls), a randomized trial is required to confirm that the therapeutic ratio (risks vs benefits) of the new strategy is indeed superior to that of conventional therapy.

WHAT IF YOU BELIEVE THAT ONE TREATMENT IS BETTER?

Ethical questions can arise in a number of situations in clinical trials. For example, in obtaining a patient's informed consent for a randomized controlled clinical trial, the investigator must state the rationale for the study, the known benefits of the different treatments, their potential toxic effects, and the possible outcomes of the study.

The experimental treatment might prove more effective than the control treatment, or equally effective, or less effective. At the same time it might prove more toxic, equally toxic, or less toxic. However, at the start of the trial, there must be no valid reason to believe that one treatment is better than the other, and the patient must be so informed.[1] Otherwise, how can the study be ethical?

But what if an investigator believes, on the

basis of the results of phase II studies, that either the experimental or the control treatment is actually superior—either more effective or less toxic? Should that investigator enter patients into the study, or give patients what his or her clinical judgment suggests is best for them?

The question is far more than academic. One of the questions that patients and their families ask most often when considering treatment options is: "What would you do if the patient were your mother, father, sister, or brother?" How one answers this question should strongly influence whether it is appropriate to enter a patient into a particular trial.

If the experimental treatment is a new drug not yet approved by the Food and Drug Administration (FDA), this situation poses no ethical dilemma. Even if the investigator believes the new drug is superior, the only way for the patient to receive it is by participating in the trial, in which he or she has a 50% chance of receiving it, assuming the trial has two study groups. However, if the drug or investigational strategy can be given anyway, the clinical researcher has an obligation to address this issue directly.

In randomized trials, there must be no valid evidence that either treatment is superior to the other

Case in point: paclitaxel in ovarian cancer

Initial phase II studies demonstrated that paclitaxel possessed more activity in cisplatin-refractory ovarian cancer than any previous cytotoxic agent. This information generated considerable enthusiasm for using this drug as part of the initial chemotherapeutic regimen in ovarian cancer.

At first, the only way patients with ovarian cancer could receive paclitaxel was to participate in a randomized trial conducted by the National Cancer Institute (NCI), in which half of the patients received it. Now, paclitaxel is commercially available. Should physicians simply have given paclitaxel to women with ovarian cancer, on the basis of phase II data, before the NCI trial was completed? Or should all eligible women have been required to enter the NCI study, in which only 50% received paclitaxel in the initial regimen?

WHAT IF BETTER TREATMENTS EXIST?

A second question arises when the patient's best interest conflicts with what the FDA requires for licensing a new drug.

Consider oral ondansetron, a new agent given to prevent chemotherapy-induced nausea and vomiting.[2] When this drug was undergoing testing, there was no oral drug that was FDA-approved for this indication with which it could be compared. Several well-designed randomized trials[3,4] had documented that oral corticosteroids are highly effective in this situation, although corticosteroids had never received FDA approval for this indication, nor was such approval required. However, physicians routinely used oral corticosteroids to prevent vomiting. Ignoring the data from the randomized trials of oral corticosteroids, the FDA required that the new oral agent be compared with an oral placebo control, rather than an oral corticosteroid.

Thus, half the patients in this study were denied treatment with a known effective prophylactic antiemetic agent, simply to meet regulatory requirements. Was this an ethical study design? Would any patients have agreed to participate in this study if they had been informed that they would not be permitted to receive treatment with a drug for which effectiveness had been established? If not, should the study have been allowed to proceed?

WHY SHOULD PATIENTS VOLUNTEER FOR PHASE I TRIALS?

Patients enter phase I trials of new antineoplastic agents for a variety of reasons, but most say they volunteer because they hope the new drug will make them feel better or live longer. Unfortunately, the chances of a major or even minor response are very small, generally less than 5%.

Are phase I trials ethical, given the unrealistic hopes that patients typically have, the limited chances of benefit, and the potential for harm? Three arguments favor the ethicality of phase I trials:

- Toxicity in phase I trials is not necessarily excessive. In fact, it is the physician's

responsibility to remove any patient from treatment if the side effects are unacceptable. In addition, the study must be stopped if the overall incidence of toxicity is excessive.

- Patients who participate in such studies may benefit emotionally, although this benefit is hard to measure. Many patients feel the need to do something, even if the chances of achieving objective clinical benefit are severely limited.
- Patients participating in clinical trials often receive valuable additional benefits, including seeing a health care provider regularly. In this way, they may receive better overall medical care, such as better pain management. ■

REFERENCES

1. Hellman S, Hellman DS. Of mice but not men: problems of the randomized clinical trial. N Engl J Med 1991; 324:1585–1589.
2. Beck TM, Ciociola AA, Jones SE, et al. Efficacy of oral ondansetron in the prevention of emesis in outpatients receiving cyclophosphamide-based chemotherapy. The Ondansetron Study Group. Ann Intern Med 1993; 118:407–413.
3. Cassileth PA, Lusk EJ, Torri S, DiNubile N, Gerson SL. Antiemetic efficacy of dexamethasone therapy in patients receiving cancer chemotherapy. Arch Intern Med 1983; 143:1347–1349.
4. Markman M, Sheidler V, Ettinger DS, Quaskey SA, Mellits ED. Antiemetic efficacy of dexamethasone: randomized, double-blind, crossover study with prochlorperazine in patients receiving cancer chemotherapy. N Engl J Med 1984; 311:549–552.

ADDRESS REPRINT REQUESTS to Maurie Markman, MD, Department of Hematology/Medical Oncology, T33, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.