COMMENTARY

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The needs of science vs the needs of patients: Ethical concerns in cancer clinical trials

Patients in clinical trials are not data points, they are vulnerable people

TO ADVANCE the science of medicine and improve the care of patients, we need the objective data that can only be gained from clinical trials, in which outcomes are dispassionately analyzed.

But the patients in cancer trials are not data points; they are vulnerable people who often view a clinical trial as perhaps their last hope. And where the needs of science intersect with the needs of patients, ethical issues arise, especially when researchers stand to gain both financially and professionally from the outcomes of these trials.

This review, an update of a paper that appeared 6 years ago in the *Cleveland Clinic Journal of Medicine*,[1] discusses these highly relevant issues and highlights areas in which problems may arise in the various phases of clinical investigation.

ISSUES IN PHASE 1 TRIALS: ARE PATIENT EXPECTATIONS REALISTIC?

In phase 1 trials, a new drug, combination of drugs, or novel procedure undergoes its initial evaluation in patients. At this phase in testing, we are trying to find out:

- Is the new treatment safe?
- If the treatment is a new drug, what are its pharmacokinetic properties?
- What dose and schedule should be used in subsequent testing—how high a dose can be given without causing excessive toxicity?

At this point in testing we are not trying to determine if the treatment has any effect on cancer—that kind of testing comes later.[2–4]

Do patients understand the low chance of benefit?

When asked in surveys, cancer patients in phase 1 trials clearly indicate that their major motivation for participating is the opportunity to experience clinical benefit, often when no other effective alternative exists.[5]

Herein lies the ethical dilemma. Although, in theory, these patients may experience some clinically relevant benefit from the treatment such as improvement in symptoms or prolongation of survival, the realistic chances of this are slim in most (though certainly not all) phase 1 trials. How well do patients understand this?

Do patients understand the high chance of harm?

Moreover, the chance is great that the therapy may decrease the patient's quality of life. Particularly vulnerable are patients with advanced cancer and marginal function who may have already undergone chemotherapy, radiation therapy, or both. Such patients may have limited bone marrow reserve, which increases their risk for toxicity. Furthermore, since a major goal of phase 1 oncology drug trials is to define the optimal dose and schedule, patients treated during the later stages of a phase 1 study may be at considerable risk for toxicity.

Are clinical investigators truly disinterested?

Understandably, in their desire to maintain hope in the face of a devastating illness, patients with advanced cancer often focus on the positive aspects of a new strategy, even if the chances are slim. This tendency—termed

"therapeutic misconception"—raises the question of whether true informed consent been obtained when the patient either does not understand or ignores the objectives of the study.[5]

Even if the patient enthusiastically signs the consent form, if the physician does not feel the patient truly comprehends the limited chances for benefit and the realistic potential for harm associated with participation in a phase 1 clinical oncology trial, is it ethically acceptable to enter that patient into the trial?

Before answering, we physicians had better examine our own motives in this situation. A physician investigator may directly or indirectly benefit from the patient's participation. If the study is successful, the physician may publish an important paper, gain academic advancement, and even make a little money on the side if he or she owns stock in the company that makes the drug in question. In such a case, we have an even higher obligation to be certain the patient fully understands the implications of treatment in the study.[6]

Information and misinformation abounds

The task of obtaining appropriate and ethically valid informed consent for phase 1 oncology trials has been made more difficult in recent years by the widespread dissemination of information (and misinformation) to the public about every novel therapeutic strategy entering clinical trials.[7–9] Whether through Internet chat groups or public announcements from biotech companies regarding their drugs, the extraordinary and unrealistic hype surrounding these trials has, in many circumstances, made the process of explaining the fundamental nature of phase 1 oncology trials and the minimal chance for benefit an even more stressful experience for the patient, the family, and the physician.[7–9]

Case in point. In 1998, a newspaper quoted a Nobel Prize winner as saying that a leading proponent of antiangiogenesis will "cure cancer within 2 years."

It must have been quite difficult for a patient who read this and was considering entering a phase I antiangiogenesis trial to be told that antiangiogenesis agents are not known to have any meaningful impact on human cancer.

A proposal: VIP treatment for study patients

One proposal to deal with the extremely complex and often competing responsibilities of the physician to provide detailed and objective data within the context of the informed consent process, while at the same time remaining compassionate and providing some element of hope, is for the physician and entire health care team to pay particular attention to the needs of patients participating in such studies.[10]

For example, patients who develop treatment-related toxicity or symptoms due to progression of the cancer should be given expedited access to services (eg, pain clinic, social service support). Perhaps this special or "VIP" status can provide some measure of reward for what study patients are providing to future cancer patients by agreeing to participate in studies that offer them little, if any, direct benefit.

ISSUES IN PHASE 2 TRIALS: CAN PATIENTS BE HARMED BY NOT GETTING STANDARD THERAPY?

Phase 2 trials *are* designed to evaluate efficacy, so they might be expected to provide participants some measure of benefit. Unfortunately, this is not always the case. Many phase 2 trials examine new cytotoxic or biologic agents that have not previously demonstrated any evidence of activity in phase 1 studies, or specifically in the tumor type being tested in the phase 2 trial.

Physician investigators stand to benefit from enrolling patients in trials

Can a new drug be tried first?

In this situation—a phase 2 trial of a new agent with unknown activity in the disease in question—is it ethical to enroll a patient before offering him or her other treatments that are known to be useful in the disease?

Case in point. This question has been discussed extensively in regard to trials of initial chemotherapy for advanced-stage small cell lung cancer.[11] Although standard chemotherapy for this disease produces a reasonably high response rate, the response usually lasts less than 1 year, and the available second-line treatments are generally not very effective.

Some argue that we can never develop

better treatments for this disease if new drugs are studied only as second-line treatments (ie, after first-line or standard treatments have failed), as once a patient's disease becomes refractory to one treatment it is likely refractory to others, and clinical activity may be hard to observe.

Conversely, we could argue that it is not justifiable to initially use an agent with unknown activity in a tumor that may grow rapidly, if an alternative strategy is available that has a reasonable chance of producing even short-term tumor regression or delaying symptomatic disease progression.

In a disease like small cell lung cancer, for which at least moderately effective therapy is available, it is unlikely that a drug previously tested only in a phase 1 trial will possess greater activity than standard treatment. Thus, patients in a phase 2 trial of such a novel agent given as first-line chemotherapy will be participating more to generate information to help others than to help themselves. In fact, if the tumor progresses and produces symptoms during initial chemotherapy with the experimental drug, the patient actually may have been harmed by not receiving standard therapy first, even if ultimate survival is not influenced.

Can entry criteria be too strict?

Another ethical issue arises when an experimental drug or strategy appears quite promising in phase 1 trials and begins to undergo phase 2 testing, but with strict criteria for who can be enrolled in the study.

Strict entry criteria are appropriate from a scientific point of view, but they might be *too* strict if they keep out patients who might benefit from the treatment and if they are arbitrary and not relevant to patient safety. An example might be a rule that no patient can get in who has received more than one prior treatment.

There is no simple solution to this issue, but there is a lot to be said for good science. Early trials rarely give conclusive results about the efficacy of a new treatment. Thus, it is critical that well-designed and well-conducted studies be rapidly completed so that the new program can assume its appropriate place in clinical practice. If a promising therapy is made widely available before such testing is complete, then we may never determine its true clinical utility (as has occurred with high-dose chemotherapy and bone marrow transplantation for breast cancer).[9] We may also never know its true dangers.

Case in point. The early mania for the "wonder drug" paclitaxel in the treatment of ovarian cancer led the National Cancer Institute to release it for compassionate use in far-advanced disease long before its true clinical impact and toxicity were established.[12] There is little evidence this strategy had a pronounced influence on survival in this patient population (which has highly refractory disease and poor performance status), and many people died from toxicities of treatment.[13]

ISSUES IN PHASE 3 TRIALS: AMONG THE MOST DIFFICULT IN CLINICAL MEDICINE

The ethical issues in phase 3 oncology trials are among the most difficult faced in clinical medicine. Phase 3 trials are randomized studies designed to compare an investigative strategy with standard treatment in a particular condition. The goal is to determine if the new approach is associated with a superior outcome, such as longer survival or less toxicity.

The standard of care is sometimes not FDA-approved

Why should a patient agree to enter a phase 3 cancer trial?

- It may be the only way to receive a promising new treatment. For example, at first the only way patients in the United States with ovarian cancer could receive paclitaxel was in its initial phase 3 trial.[14] This trial filled up and was completed faster than any other trial in ovarian cancer in history, because patients wanted this drug.
- Many phase 3 trials provide the best care available for the malignant condition, in both the experimental group and the control group.
- Participating in a randomized trial helps future patients through the information gained in the study.

Do investigators really have no opinion?

Some observers note that the act of enrolling patients into a randomized phase 3 trial implies that the physician has no opinion

about whether one treatment is superior to the other.[15–17] For if the physician believes one treatment is better, he or she has an ethical obligation either to inform the patient of this personal belief, or not to present the study to the patient.

The role a physician's experience or bias should play in the decision to enter patients into clinical trials has been hotly debated.[15–17] Randomized controlled trials are supposed to exclude clinical bias. But patients go to doctors precisely to avail themselves of physicians' excellent clinical judgment.[18] I can testify that one of the questions most often asked of an oncologist after he or she has presented a patient with the option of participating in a randomized trial is "Doctor, what would you do if this was a member of your family?" The patient is not interested in whether the study is scientifically valid, but rather what the doctor thinks is best.

If the physician cannot honestly answer that he or she would participate in the trial (or let a family member participate), is it ethically acceptable to enter the patient into the study? And would it influence the physician's decision if his or her institution is a member of a cooperative group conducting the trial, or if he or she is receiving critically important funds to carry out the study?[6]

Is it ethical to induce excessive toxicity, just so it can be treated in a trial?

Does the control group get optimal care?

Ethical issues can also arise if the treatment in the control group is, for some reason, not what has previously been demonstrated to be the most effective therapy for the specific condition.

This situation might arise when a governmental regulatory body such as the US Food and Drug Administration (FDA) decides that the control treatment in a randomized trial of a new drug must be a drug previously approved by the agency for that specific indication. Cancer drugs often find new uses after their initial FDA approval, which is often for a very narrow clinical indication. Furthermore, pharmaceutical companies are rarely inclined and not required to spend the time, effort, and money necessary to obtain formal approval for these new uses.

Thus, a decision by the regulatory body to allow only approved drugs as treatment in the control group may lead to the ethically unacceptable situation that half of the patients in trial (the control group) will be given treatment that is not the current standard of care in the community.

Case in point. A randomized controlled trial in the United States examined the clinical utility of ondansetron, a new oral serotonin antagonist, in controlling vomiting during cancer chemotherapy.[19] Patients in the control group received no prophylactic antiemetic therapy. The apparent justification for this decision was that there were no drugs approved by the FDA at that time for this specific purpose.

However, several previous randomized trials had unequivocally demonstrated that short-term use of the corticosteroid dexamethasone was safe and highly effective in preventing emesis in this situation.[19] Unfortunately, dexamethasone, long available as a generic preparation and inexpensive, had never received FDA approval for the control of chemotherapy-induced emesis and was not considered an appropriate control treatment for this study.

Does either group receive standard care?

A final ethical issue in phase 3 trials is the use of nonstandard treatments in both treatment groups.

This issue might arise, for example, in a trial of a bone marrow growth factor in reducing the toxicity of a particular chemotherapeutic regimen. Unfortunately, for such a trial to have a statistically valid end point (ie, an acceptable *P* value), it may be necessary to substantially increase the concentration of chemotherapy to purposely produce a high level of toxicity, which the experimental drug may or may not ameliorate.

It is appropriate to criticize the ethical design of such a trial if there is no evidence the higher doses of chemotherapy are justified on the basis of the known efficacy of the regimen in the particular condition. In this circumstance, patients in the control group (without the growth factor) will be subjected to the potential for greater toxicity without any evidence the higher-dose regimen is superior to a lower-dose one, simply to determine if the agent given in the experimental group is

effective in reducing toxicity.

Case in point. Dunphy et al[20] examined the use of recombinant erythropoietin to reduce the severity of chemotherapy-induced anemia in 30 patients with advanced cancer of the lung or of the head and neck who were receiving intensive chemotherapy: carboplatin 7.5 mg/mL/minute every 21 days and two courses of paclitaxel 230 mg/m^2 given over 3 hours.

This regimen is highly toxic, potentially causing bone marrow suppression and peripheral neuropathy, and when this trial was started there was no evidence that the regimen was better than lower-dose and less-aggressive regimens for these types of cancer.

The study concluded that erythropoietin was clinically useful in reducing the incidence of severe anemia and the need for red blood cell transfusions. Yet it must be asked whether it was appropriate to subject patients to this level of toxicity with an unproven treatment program to demonstrate the benefits of this supportive care agent. Further, were the patients informed of the highly experimental nature of the chemotherapy regimen used in both treatment groups?

WHO IS RESPONSIBLE FOR PATIENT SAFETY?

The ethical concerns arising from these and other studies raise the critically important question as to the role and responsibilities of individual investigators, trial sponsors, governmental regulatory agencies, institutional review boards, the publication peer-review process, and editors of medical journals in ensuring patient safety in the conduct of clinical trials.

REFERENCES

1. **Markman M.** Ethical issues in clinical trials in oncology. Cleve Clin J Med 1997; 64:275–276.
2. **Von Hoff DD, Turner J.** Response rates, duration of response, and dose response effects in phase I studies of antineoplastics. Invest New Drugs 1991; 9:115–122.
3. **Decoster G, Stein G, Holdener EE.** Responses and toxic deaths in phase I clinical trials. Ann Oncol 1990; 1:175–181.
4. **Estey E, Hoth D, Simon R, Marsoni S, Leyland-Jones B, Wittes R.** Therapeutic response in phase I trials of antineoplastic agents. Cancer Treat Rep 1986; 70:1105–1115.
5. **Daugherty C, Ratain MJ, Grochowski E, et al.** Perceptions of cancer patients and their physicians involved in phase I trials. J Clin Oncol 1995; 13:1062–1072.
6. **Levinsky NG.** Nonfinancial conflicts of interest in research. N Engl J Med 2002; 347:759–761.
7. **Eysenbach G, Powell J, Kuss O, Sa E-R.** Empirical studies assessing the quality of health information for consumers on the World Wide Web. JAMA 2002; 287:2691–2700.
8. **Henson DE.** Cancer and the Internet. Cancer 1999; 86:373–374.
9. Demand grows for early access to promising cancer drugs. J Natl Cancer Inst 2002; 94:1668–1670
10. **Markman M.** The ethical dilemma of phase I clinical trials. CA-A Cancer J Clin 1986; 36:367–369.
11. **Markman M.** Revisiting the debate: The use of new agents in previously untreated patients with small cell lung cancer; quality versus duration of survival. J Cancer Research Clin Oncol 1994; 120:693–694.
12. **Trimble EL, Adams JD, Vena D, et al.** Paclitaxel for platinum-refractory ovarian cancer: Results from the first 1,000 patients registered to National Cancer Institute Treatment Referral Center 9103. J Clin Oncol 1993; 11:2405–2410.
13. **Markman M, Hakes T, Barakat R, Curtin J, Almadrones L, Hoskins W.** Follow-up of Memorial Sloan-Kettering Cancer Center patients treated on NCI Treatment Referral Center protocol 9103: Paclitaxel in refractory ovarian cancer. J Clin Oncol 1996; 14:796–799.
14. **McGuire WP, Hoskins WJ, Brady MF, et al.** Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med 1996; 334:1–6.
15. **Hellman S, Hellman D.** Of mice but not men: Problems of the randomized clinical trial. N Engl J Med 1991; 324:1585–1589.
16. **Emanuel EJ, Patterson WB.** Ethics of randomized clinical trials. J Clin Oncol 1998; 16:365–371.
17. **Marquis D.** How to resolve an ethical dilemma concerning randomized clinical trials. N Engl J Med 1999; 341:691–693.
18. **Markman M.** The importance of distinguishing "clinical judgment" in cancer management from "selection bias" in clinical trials. J Cancer Research Clin Oncol 1996; 122:573–574.
19. **Markman M.** When regulatory requirements conflict with ethical study design: The case of oral ondansetron. Cancer Invest 1994:654–656.
20. **Dunphy FR, Harrison BR, Dunleavy TL, Rodriguez JJ, Hilton JG, Boyd JH.** Erythropoietin reduces anemia and transfusions. A randomized trial with or without erythropoietin during chemotherapy. Cancer 1999; 86:1362–1367.

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