

Advances in Drug Development

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Current Developments in Oncology Drug Research

Ethical Issues in Phase I Clinical Trials

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What are the main ethical issues in phase I clinical trials?

The main ethical issues in phase I research, apart from the overarching issue of patients as research subjects, relate to the involvement of a specific population of patients with advanced, incurable disease and to the fact that these patients are being enrolled in trials where the likelihood of clinical benefit, as this is generally measured in oncology, is exceedingly small. At the time of enrollment, the population of patients involved in phase I clinical trials has an average of 6–8 months to live, and 70–80% die within a year, presumably from their disease and not from participation in the trial. This population is appropriate for palliative care, perhaps hospice care, which presents a serious dilemma. Prior experience tells us that 97% of patients who participate in phase I trials experience no measurable clinical benefit.

Why is the likelihood of patients on phase I trials benefiting from therapy so small?

This lack of clinical benefit, defined as a complete eradication of the tumor (complete response) or a 50% reduction in tumor burden (partial response), is understandable. Patients with advanced-stage cancer generally have very resistant disease, they have a tumor type for which there is no identifiable standard of care, or they have received that standard of care for months or years and it is no longer effective. In addition, identifying new therapies is very difficult; the success rate of new agents coming out of the laboratory is very low.

There is another important reason why clinical success is so infrequent in phase I trials that is directly related to concerns about human subjects in research. The first step in the drug development process is to confirm that the agent can be given safely. Based on what is known from laboratory studies, an agent is started at a very small dose to ensure no harm is produced. Gradually, as each new group of patients comes into the trial, the dose is escalated until side effects are observed, or in other words, to the maximum tolerated dose (MTD). Generally, the MTD is the point at which one can expect to see clinical benefit. Because the MTD is reached only toward the end of a trial, the majority of patients receive doses below that level.

Clearly and with good reason, patients with advanced disease have an overwhelming motivation for wanting a clinical benefit. The challenge for phase I trial investigators is to ensure that patients are aware that the real purpose of these trials is to identify the MTD so that subsequent phase II trials can investigate whether or not the agent will shrink tumors.

In your experience, what are patients' motives for participating in phase I trials?

Typically, when a patient is asked why they are participating in a trial, they say that they are hoping for a clinical benefit, or even to be cured of their disease. We have conducted studies of patients entering phase I trials at our institution, which has the largest phase I trial program in the world, in which we asked patients about their goals and expectations. No patients speak about altruism as a motivating force; they speak about clinical benefit. This response does not imply the absence of altruistic feelings, and patients do note that perhaps if the therapy does not help them it will help someone else. However, this is not a motivating force for leaving the comfort of their home environments to travel to an academic medical center to receive an investigational agent.

How do investigators typically describe the purpose of phase I trials?

Investigators involved in drug development do not typically speak with patients about advancing future patient care. Rather, they speak about clinical benefit, although at a much smaller magnitude than what patients consider benefit. Clinical investigators may speak about palliating symptoms or extending life by some degree, and may also speak about having access to agents that other clinicians would not. In reality, although there is reason to hope that drugs showing anticancer activity in the laboratory will show the same effect in humans, efficacy is unlikely.

What are the challenges associated with informed consent?

Informed consent is very important because patients need to be aware that the likelihood of clinical benefit is exceedingly small. However, the process is also somewhat complicated. Disclosing and communicating information does not necessarily mean that patients are accepting the information and

using it to make decisions. We have interviewed over 600 patients over the last 10 years and have found that up to 50% of patients have already made their decision about participating in a particular trial before they have even entered the clinic. Whether or not information disclosure will have an impact on the patient's decision is not clear, but doctors are obligated to provide information to every patient, regardless of what the patient does with that information. It is often difficult to know how hard to push with ensuring patients understand the purpose of the trial, and also important that a doctor not become apathetic or assume that patients have already made up their minds.

Does the involvement of family members in the decision-making process raise ethical concerns?

Yes. Quite often patients learn about clinical trials from family members, and the motivating force to participate comes from not only the patient but also the family. Family members give patients information and often ask more questions of doctors than do the patients themselves. The involvement of family members complicates the process because it makes unclear whose preferences for information and treatment are being served.

Based on your studies, what do you think the correct process is for introducing a patient to a phase I trial?

From both a clinical and ethical standpoint, I think the conversation needs to begin by eliciting from patients their understanding about their disease. What do they know about it? What do they know about their prognosis? What is their source of information? What are their expectations, and why? Once these questions are thoroughly answered, then the doctor should fulfill the obligation to communicate what he/she knows about the patient's prognosis, the likelihood of benefit from the various treatment options available, and the notion that their disease is not curable. This process should be the foundation for any subsequent decision made.

After these aspects are made clear, then the doctor can elicit the patient's preference regarding how much other information they would like about the trials and therapy available at the particular medical center. How much does the patient want to know, beyond discussions about prognosis? Hopefully, the patient will want to know as much as possible about the purposes of the various clinical trials for which they are eligible.

How should a doctor respond if a patient does not want this information?

Patients who do not want information and simply want to be told which agent to take present a dilemma to phase I trial investigators. Medical ethics teaches us that people's preferences for information should be respected. Is it better to fulfill the ethical obligation to adhere to patients' preferences or to insist on disclosing as much information as possible? One solution is for a patient to indicate that they want the information in a way that the physician can provide. However, oftentimes the physician is unable or unwilling to become familiar enough with the patient to elicit these preferences, and it is then that problems may develop.

Are medical ethicists ever introduced as a third party to ensure the soundness of the process?

Introducing third-party observers and participants into the informed consent process has been discussed since the 1980s, but has rarely, if ever, been done. Federal regulations stipulate that institutional review boards may audit or observe the informed consent process as it takes place, but they generally do not have the time or resources to do so. To some extent, the nature of my involvement with phase I trials is as a third-party researcher. We observe the process and later query enrolled patients about the purpose of the trial, treatment alternatives, and their prognosis. We have also explored potential interventions to see if they facilitate the process.

What types of interventions have you explored?

We recently completed a study in which patients were randomized to receive standard-of-care disclosure alone or standard-of-care disclosure in addition to an interactive CD-ROM program about phase I trials. The CD-ROM employed touch-screen technology and embedded videos of patients and physicians discussing clinical trial participation. Patients were given this CD-ROM before entering the clinic, in order to determine whether it would empower them in some way. Would the program give them a better knowledge base from which to ask questions, so that they would leave the clinic more informed?

What were the findings of this study?

We found that the outcomes of the informed consent process were improved for those patients who used the CD-ROM, but only by 10–15%. A week after signing informed consent documents stating that the purpose of the trial is to identify a dose, that palliative comfort is an alternative option, over half of the patients on the CD-ROM arm said that the purpose of the trial was to see whether the agent could treat their tumor or cure their cancer.

Are the ethical dilemmas associated with phase I clinical trials thwarting drug development research?

No, I don't think so. There are some physicians and oncologists who consider phase I trials to be unethical. Others who consider it to be in society's best interest to develop drugs and improve care for future cancer patients acknowledge that the phase I process is the best system we've found so far. Everyone recognizes that the system needs continued improvement. Ideally, we would be able to identify active drugs more accurately in the laboratory and could develop a system within academic medicine or industry where the only motivations to develop an agent was cure of future patients, exclusive of the marketplace and the individual investigator's career. Some will argue that the market force is strong enough that only truly effective drugs will be allowed through the process, but issues still arise. However, I do not think that patients are not enrolling because they perceive the process to be unethical; I think slow or low enrollment is due to the time and effort required by both the investigators and the patients.

What impact might improved clarity have on drug development?

It is possible that if there were better clarity and more openness about the process, and also an improved understanding about how hard some clinicians work to ensure that patients are well informed and that trials are designed in the best way possible, individuals who are opposed to the notion of phase I trials might be more accepting. There are many assumptions made that patients are not informed or are taken advantage of, but in reality these circumstances are extremely rare.

In addition, as mentioned above, physicians may become resigned to the sense that no matter what they tell patients about the purpose of a trial, the information seems not to be absorbed. It can be difficult to recognize that this response does not change the obligation to the next patient.

Overall, studies of the ethics of phase I trials have contributed to our understanding not only about the advanced cancer patient population or the phase I trial process, but about what it means for a patient to enter any clinical research. We understand more about why patients enter trials and what challenges exist in ensuring they have the information they need and that doctors are required to provide.

Suggested Reading

Gordon EJ, Daugherty CK. 'Hitting you over the head': oncologists' disclosure of prognosis to advanced cancer patients. *Bioethics*. 2003;17(2):142-168.

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