

Critical Role of Phase I Clinical Trials in Cancer Treatment

Adopted on November 8, 1996 by the American Society of Clinical Oncology*

PHASE I clinical trials are the essential gateways to the development of new cancer therapies. The process of translating basic research findings into clinical applications necessarily commences in small phase I trials that lead to larger investigations and eventual regulatory approval and widespread usage. Despite the centrality of these early-phase trials to the process of medical discovery, they are not well understood and are indeed subject to significant misconceptions, particularly as they relate to clinical oncology research.¹

Traditionally, phase I trials have involved the administration of usually subtherapeutic doses of a new agent to healthy volunteers to assess toxicity. In contrast, phase I cancer trials can represent a real therapeutic option for some patients who have failed to respond to other treatment or for whom no other therapies exist. Because of the importance of phase I trials for both research and treatment purposes, the American Society of Clinical Oncology (ASCO) convened a subcommittee of the Public Issues Committee to review current issues that are related to these trials and to draft a policy statement regarding their role in cancer treatment and research.

WHAT ARE PHASE I CLINICAL TRIALS?

Phase I trials classically are considered "first in human" studies. For most drugs outside oncology, such phase I studies are conducted in healthy volunteers in specially dedicated clinical pharmacology units. However, because of the toxicity that generally is observed in preclinical studies, phase I studies of new anticancer agents almost always are conducted in patients with refractory cancers.

Most phase I studies are cohort studies, in which patients are treated at increasing doses according to chronological entry into the study.^{1,2} Thus, results in early patients greatly influence dosing of subsequent patients. The starting dose is based on preclinical testing, and is usually quite conservative. A standard measure of toxicity of a drug in preclinical testing is the percentage of animals (rodents) who die because of treatment. The dose at which 10% of the animals die is known as the LD₁₀, which has in the past often correlated with the maximal-tolerated dose (MTD) in humans, adjusted for body-surface area.³ Thus, the standard conservative starting dose is one tenth

the murine LD₁₀, although it may be even lower if other species (ie, dogs) were more sensitive to the drug.

Extensive preclinical testing is required prior to initiating the first phase I study. The candidate drugs may either be synthesized, which often results in a group of analogs to choose from, or identified by screening extracts of natural products. Then, a lead candidate is selected based on its relative activity in a variety of experimental tumor models. These models may include tumor cells that are grown in tissue culture and/or animals who are bearing tumors. Subsequent studies generally will include preclinical efficacy studies, which show beneficial activity, and preclinical toxicology studies, which suggest that the drug will likely be safe at effective doses. As noted previously, such studies also determine the human starting dose. In addition, preclinical pharmacology studies often provide extensive information about pharmacokinetics.

It is common for drug discovery and development to be directed based on experience with another drug. The recent development and approval of two camptothecin analogs, topotecan and irinotecan, exemplify such directed development. Camptothecin was developed more than 20 years ago, but was abandoned because of severe bladder toxicity, diarrhea, and myelosuppression.⁴ Because of its marked preclinical activity, there was a long search for acceptable analogs, which culminated in the approval this year by the Food and Drug Administration (FDA) of topotecan and irinotecan for refractory ovarian and colorectal cancers, respectively.

In the United States, there may be extensive regulatory

See Appendix for Subcommittee on Phase I Clinical Trials member affiliations.

From the American Society of Clinical Oncology.

Submitted November 27, 1996; accepted November 27, 1996.

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**ASCO sincerely appreciates the contributions of the ASCO Subcommittee on Phase I Clinical Trials, which devoted much time and effort to this project. Chair: Mark J. Ratain; Subcommittee Members: Deborah Collyar, Barton A. Kamen, Elizabeth Eisenhauer, Theodore Steven Lawrence, Carolyn Runowicz, Sam Turner, and James L. Wade III.*

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0732-183X/97/1502-0055\$3.00/0

review prior to the first phase I study. The sponsor must file an Investigational New Drug (IND) application, to include all the preclinical data and the initial clinical protocol(s). The FDA has 30 days in which to decide whether such protocols may proceed without additional preclinical data or modification of the clinical protocol. There are other levels of review, which often occur prior to submission to the FDA. Most large pharmaceutical companies have their own internal protocol review committees that examine the protocols for both ethical and scientific issues. Compounds under development by the National Cancer Institute (NCI) have extensive review through the NCI Decision Network, and each protocol undergoes detailed ethical and scientific scrutiny prior to FDA filing. In addition, there is extensive review at the institutional level that must include approval by an Institutional Review Board, and often a cancer center scientific review committee also.

It is important to recognize that phase I studies are not limited to "first in human" studies. Subsequent phase I studies often evaluate new schedules or combinations with established drugs or radiation. In addition, these secondary phase I studies may evaluate toxicity and pharmacokinetics in patient populations that were excluded in prior studies, such as children.

Phase I studies represent the critical transition point from the laboratory to future improvements in cancer care and outcomes. All drugs that are currently marketed first showed activity in phase I studies.⁵ Two of today's most commonly prescribed drugs, cisplatin and paclitaxel, exemplify these successes.

Cisplatin was best known for its toxicity during its initial clinical evaluation. It induced severe nausea and vomiting in an era of only modestly effective antiemetics. It induced acute renal failure prior to the development of hydration strategies to prevent such complications. And it induced major responses in patients with chemotherapy-resistant testes cancer.⁶ In the absence of these responses, cisplatin probably would have been abandoned.

Paclitaxel, then known as taxol, also was an extremely difficult agent for its phase I investigators. The major toxicity to be reckoned with was hypersensitivity reactions, which since have been improved by pretreatment with corticosteroids and antihistamines. Again, there was great enthusiasm for further development, despite its toxicity, because of responses observed in women with refractory ovarian cancer.⁷

COMMON MISCONCEPTIONS REGARDING PHASE I TRIALS

Because phase I studies are unfamiliar to most physicians and patients, there are many popular misconceptions

about these trials. It is commonly misstated that such trials are nontherapeutic toxicology studies, that phase I studies pose high risk of extreme toxicity, that cancer patients are too vulnerable to give informed consent, and that the sponsor of the drug covers all costs of such studies.

Misconception. Phase I Trials Are Not Therapeutic

As noted previously, phase I studies of most drugs are conducted in healthy volunteers. However, almost all phase I studies of new anticancer agents are conducted in patients with malignancies that are refractory to standard therapy or for which there is no standard therapy. The development of a new agent has traditionally consisted of its sequential study in trials that have different major endpoints. Although the goals for each phase of development may shift, the hope in the treatment of individual patients on such trials is that the new therapy will offer therapeutic benefit. These subjects are patients who are seeking palliation of their disease and who recognize the investigational nature of phase I studies. It should not be relevant whether the scientific goals of the study are to determine toxicity and pharmacokinetics (phase I) or to ascertain the response rate (phase II) because the patient is receiving an appropriate treatment for his or her disease.

Phase I trials represent the first translational step from the laboratory into patients. The decision to move an agent into phase I evaluation is based on extensive preclinical evaluation, as detailed previously. The central criterion is the observation of sufficient preclinical antitumor activity, such that a therapeutic effect in human cancer is anticipated. Thus, although the goal of a phase I study is to identify the recommended dose for future trials, there is reasonable expectation that antitumor effects will be noted in some patients in the trial.

There is a tension that is inherent in phase I design between the need to balance the concern for patient safety when being treated with an unknown agent, as reflected in careful dose escalation, and the desire to treat at doses that will be close to the recommended phase II dose, thus increasing the likelihood of benefit. This has led to number of proposals that permit more rapid dose escalation, some of which investigators are now implementing.^{1,18} Unfortunately, translating animal studies to humans is sometimes difficult, such that the necessity of starting low is appropriate. Accelerating the dose escalation through pharmacodynamically driven studies may help to optimize therapy.

The usual measurement of therapeutic benefit during phase I trials has been the assessment of objective tumor regression (response). Evidence from the literature sug-

gests that, although response rates in phase I trials can be low, they very often are helpful in identifying which agents subsequently will be of benefit and in directing subsequent phase II investigations.⁵ In fact, it has been suggested that *failure* to observe responses in phase I trials is predictive of subsequent failure of the agent and should be considered in the decision of moving the agent into phase II development.⁹

Aside from response, other measures of therapeutic benefit may be documented in clinical trials. These include improvement in disease-related symptoms, tumor markers, and global quality of life. Unfortunately, little is known about the success of phase I agents in inducing changes in these measures.¹⁰ Nevertheless, the growing interest in endpoints in clinical trials that overall are related to quality of life may have an impact on phase I studies.

In summary, although the goal of a phase I trial is to determine the toxic effects, pharmacologic behavior, and recommended doses for future study of a new agent, there is a strong preclinical rationale for bringing the drug into the clinic with the expectation of positive clinical outcomes for some patients. In fact, Institutional Review Boards would not permit the administration of potentially toxic treatments to patients unless there was some reasonable prospect of antitumor effect.¹¹

Misconception: Patients Participating in Phase I Trials Must Expect Severe Toxicity

A major endpoint of phase I trials of a new agent is the definition of the MTD that causes dose-limiting toxicity (DLT). As described previously, the trials usually begin at a conservative dose that is expected to cause no toxicity. In the classic design, it is expected that there will be four to six escalations of dose before reaching the MTD. Therefore, the subsequent phase II trial of an agent usually results in more toxicity than the phase I because more patients will be treated at the presumed MTD.¹

Toxic deaths especially are rare in phase I trials, occurring in only 0.5% of adult patients.¹² Similar results have been shown in children.¹³ Phase I trials have not shown an adverse impact on either patients' quality of life or survival.^{10,14}

Sometimes, second-generation phase I trials of particularly promising agents specifically may aim to develop approaches to circumvent toxicities. This particularly was critical for the development of paclitaxel, which engendered severe hypersensitivity reactions in initial trials.¹⁵ Subsequent phase I studies showed that premedication with corticosteroids and antihistamines, as well as prolon-

gation of the infusion, could reduce toxicity and maintain activity.¹⁶

Misconception: Phase I Trials in Patients with Advanced Cancer Are Ethically Questionable

Patients who are offered treatment in the context of a phase I trial are informed that the purpose of the study is to find the optimal drug dose and that some patients will be treated at a dose that is too low or too high (above the MTD). Investigators also inform them that there is a possibility, although small, that the treatment will be beneficial, as important new drugs have always been active in phase I testing in refractory cancers. The Institutional Review Board, the sponsor, and the FDA (when applicable) approve the written consent forms.

The misconception seems to center around the belief that phase I trials are ethically questionable because of the "vulnerable" population that is considered in these trials.¹⁷ These patients are "vulnerable" to the extent that they know they are going to die from their disease. With that knowledge, and following an informed discussion, they may then consider which course of action they may want to take. Such action may be no treatment, treatment with chemotherapy (or other conventional approaches) outside of a clinical trial, treatment with unorthodox therapies, or participation in a clinical trial. Many of them will decide not to enroll in a trial, but some will. And such patients who participate in phase I trials appear to have adequate (self-perceived) knowledge of the risks of investigational agents.¹⁸ The only time these patients may be considered incapable of analyzing their risks is when their death is imminent. At this point in their illness, they would certainly not be eligible for any clinical trial.

Misconception: All Costs of Phase I Trials Are Covered by Sponsor

Third-party payors seek to justify denial of coverage for routine patient care costs in clinical trials, perhaps especially phase I trials, on the ground that such costs are the responsibility of the pharmaceutical sponsor or other entity who is conducting the research. This is a widespread misconception that reflects the views of third-party payors, but has no basis in historical fact. For as long as clinical research has been conducted, payment for routine patient care costs, such as physician and hospital charges, has been borne by insurers or individual patients.

One exception to this rule is the Clinical Center of the National Institutes of Health, where an explicit policy of providing patient care free of charge has always been in effect. However, even the Clinical Center is now under pressure to collect third-party payment where it is avail-

able, either through private insurance or public programs such as Medicare.

Although third-party payors customarily cover routine patient care costs, the research sponsor is responsible for the costs of the investigational agent and its incremental costs, and of data collection, management, and analysis. Responsibility for patient-care costs has become an item of contention only over the past decade, when sometimes expensive new therapies (such as high-dose chemotherapy and autologous bone marrow transplant for breast cancer) administered in a research setting have attracted the attention of claims reviewers and resulted in reimbursement denials.¹⁹ Undue focus on bone marrow transplant, with its atypical costs, has distorted the perception of third-party payors about clinical research in general.

Third-party payors also take the position that they have no contractual obligation to cover treatment that is given in a clinical trial because such treatment is "experimental" or "investigational." Such experimental exclusion clauses originally were inserted to prevent patients from being subjected to unorthodox approaches to serious illness, and were intended for the patient's protection. Now, such exclusions are used to prevent patients from receiving therapies that are recommended by leading physicians, thereby protecting payors' finances but placing patients' health at risk. In fact, for many cancer patients who have failed other therapy, clinical trials, especially phase I trials, may represent not only the best, but one of the few justified therapeutic treatment options. In that context, if insured patients are to receive the value of their insurance policy or their eligibility under public programs such as Medicare, exclusions for experimental treatment should not be automatically applied. Investigational therapy is widely accepted as part of the standard of care in oncology, and insurance plans that fail to recognize this fact are depriving their policyholders and beneficiaries of significant treatment alternatives.

CONSEQUENCES OF MISCONCEPTIONS

Decreased Availability of New Drugs for Phase III/III Development

Because the progress of new agents into phase II and III has, as an absolute requirement, the successful completion of (usually) more than one phase I trial, it follows logically that a restriction in access to phase I agents by whatever means inevitably will result in a decrease in the availability of agents for phase II and III development. Furthermore, a restriction on the number of phase I trials carried out with any individual drug may limit the opportunities to observe evidence of therapeutic activity, which

help guide the selection of tumor types for subsequent phase II and III testing.

Patients May Be Treated With Relatively Ineffective and/or More Toxic Therapies

Systemic chemotherapy for most metastatic solid tumors provides only temporary palliation. When disease progression occurs during treatment, patients and their doctors have three options: continue the current ineffective regimen; stop systemic treatment altogether; or try a different regimen. Many patients who have a good performance status will select the third option. Although some patients may benefit from second-line or even third-line treatment regimens, there are some chemotherapeutic drugs that are used in this setting that have no measurable clinical benefit. One example of such a treatment is the use of mitomycin for patients with colorectal cancer. Some clinical trials of this drug for this disease have measured a response rate of 0%.²⁰ Therefore, it is clear that, in at least some common clinical situations, phase I trials have a greater probability of benefit than nonexperimental options.

Patients May Be Treated With More Costly Therapies

Patients who have failed all standard therapies and who wish to enroll in, but who are denied access to, a phase I trial continue to require medical care. Such patients may receive treatment with an alternative commercially available regimen or supportive care, either of which may be more expensive than the therapy in the denied phase I trial.²¹

Decreased Pharmacologic Knowledge About Anticancer Drugs

Phase I studies provide the best opportunity to elucidate the often complex clinical pharmacology of a potentially effective agent. These studies generally involve administering a broad range of doses, which allows elucidation of dose-toxicity relationships. Furthermore, issues, such as drug excretion and metabolism, can be analyzed via detailed studies in small numbers of patients in a single institution. After completion of phase I, studies often are conducted at multiple sites, which complicates the collection and analysis of pharmacologic data. Further studies often are conducted in combination with established agents, which makes assessment of information about the new agent especially difficult. Any decrease in the number of phase I trials and, as a consequence, the amount of pharmacologic data accumulated, may hinder subsequent rational development and safe use of the drug.

Advances in laboratory techniques have facilitated

measurement of plasma concentrations of potent anticancer drugs, which has led to an improvement in their use.²² Moreover, our understanding of the genetics of drug-metabolizing enzymes is creating new paradigms in treatment.²³ It may be possible to test a patient for a particular drug-metabolizing gene prior to treatment and then prescribe an individualized dose, rather than our current approach of prescribing an average dose to everybody. Such an approach has been shown to be feasible.²⁴

Curtailed Development to Minimize Number of Phase I Trials

All phase I trials have limitations on patient eligibility. Some of these limitations are in the interest of patient safety, whereas others are included to ensure a relatively homogeneous patient population. As a consequence, some patient populations are excluded and optimal dosing in these patients may be unknown, even after full FDA approval. Specific populations include children, the very old, and patients with marked organ dysfunction secondary to either the disease or complications of prior therapy. One approach to resolving this is additional phase I trials in special populations. If phase I trials were more costly to sponsors (because of no reimbursement for patient care costs), such trials would not be performed. Instead, patients in these special populations would have to be treated based on the experience of their oncologist, rather than on the basis of scientific data.

Another area in which phase I trials are helpful but not always pursued is in the development of new schedules or new combinations. Such approaches can be applied directly in phase II trials, but if the doses are incorrect, such trials may be useless (if at too low a dose) or lethal (if at too high a dose). Specific phase I trials that address these issues can rapidly provide reliable data, but are unlikely to be performed if the costs of such studies are too high.

PROPOSED IMPROVEMENT IN PROCESS (AND RAMIFICATIONS)

Increased Public Awareness Regarding Therapeutic and Societal Value of Drug Development

There is a widespread misunderstanding among the public concerning the nature of clinical trials, and more specifically, the manner in which patients are able to participate in clinical cancer research for treatment purposes. A fully informed public would support clinical cancer research, not just for the purpose of advancing knowledge about cancer, but also to provide optimal treatment opportunities. The lack of public knowledge is par-

ticularly acute with respect to early phase trials, which are shrouded in misconceptions about both toxicity and potential therapeutic benefit. The goal of the clinical research community should be to enhance public awareness and understanding about the pivotal role of phase I trials in the overall research enterprise and in the comprehensive treatment of people with cancer. Fulfillment of this goal would lead to greater research funding, a more efficient drug-development process, and more widespread acceptance of early phase trials as valid treatment options.

Increased Access to Phase I Trials as a Legitimate Therapeutic Option in the Context of Managed Care

The impact of managed care on clinical research is of substantial concern in the oncology community. Patients and physicians alike believe that decision-making by managed care organizations may be driven more by considerations of cost than in the fee-for-service system. Moreover, those who have organized managed care plans often do not seem to place a great premium on the capacity to conduct clinical research.

With greater education and public awareness of the value of clinical research, this situation may be reversed. Managed care plans will eventually come to compete not merely on cost, but also on quality of care. If potential enrollees and other purchasers of managed care products are convinced that quality cancer care requires access to clinical trials, including phase I trials, access to investigational therapy may become a marker for quality in comparison of different plans. In addition, cost-conscious plans will value the data that are made available to them by their participation in clinical research.

Reimbursement for All Patient Care Costs Associated With Phase I Clinical Trials

Beginning with the health care reform debate of 1993-1994, a number of legislative proposals have been introduced in the United States Congress to require coverage of patient care costs in clinical trials. An important feature of all these proposals is that they fail to distinguish among different phases of clinical research. Instead, the proposals recognize that, in appropriate circumstances, all phases of clinical research may represent treatment options for people with life-threatening diseases such as cancer. Although these proposals have yet to become law, they are redefining the manner in which third-party payors in both private and public plans are evaluating their coverage policies. If sympathetic legislators continue to place the question of reimbursement in a research setting before the American people, all phases of high-quality peer-

reviewed clinical research one day may be available to people with cancer and other life-threatening diseases.

Research Regarding Phase I Trial Designs That Maximize Likelihood Of Patient Benefit

There has been only limited research into design of phase I trials, and most published studies have used gradual dose-escalation schemes with three to six patients per cohort. However, in the past 5 years, there have been a number of published suggestions for modification of the standard trial paradigm.^{1,2,8} In the ideal phase I study, dose escalation will rapidly proceed to doses near the MTD, without drug-related fatalities. This will provide the maximal chance of therapeutic benefit to the subjects that are willing to take on the risks of such trials.⁵ It also appears feasible to empower patients to participate in the selection of their dose, where reasonable uncertainty

exists.²⁵ These efforts can be enhanced by targeting grant support to this important area.

SUMMARY

The physician/investigator must simultaneously manage the twin goals of patient benefit and knowledge acquisition. There are few fields with greater challenges than early clinical trials of anticancer agents, as all clinical protocols must be both scientifically and therapeutically valid. The task of the physician/investigator would be greatly facilitated if research is performed in an environment in which the public, which includes third-party payors, is adequately informed and sufficiently supportive of the role of clinical research in the treatment of cancer. Only through sustained and even enhanced support of early-phase testing will the health care system take full advantage of the many new basic science discoveries that are awaiting translation into clinical application.

APPENDIX

Subcommittee on Phase I Clinical Trials (As of 6/28/96)

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2624 '03 DEC 15 P3:46

FDA Docket #: 2003P-0274/CP1

Dear Frank:

Thank you for sharing the Jan 15, 2003 Abigail Alliance for Better Access to Developmental Drugs Proposal for Early Conditional Approval at the FDA (Tier 1 Initial Approval).

The Pancreatic Cancer Action Network is greatly concerned about improved access to developmental drugs. We support the need to work closely with the FDA, patients, industry and the research community in developing a more effective program for access and approvals.

Thank you for your efforts.

Sincerely,
Paula Kim

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