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In the era of molecular-targeted therapy, "effective" dose is sometimes measured through the inhibition of the intended target, which can prove to be problematic.

Risks and Benefits of Phase 1 Clinical Trial Participation

Amit Mahipal, MD, and Danny Nguyen, MD

Background: *The results from phase 1 clinical trials can allow new treatments to progress further in drug development or halt that process altogether. At the forefront of phase 1 clinical trials is the safety of every patient participant, which is particularly true when testing new oncologic treatments in which patients may risk potentially toxic treatments in the hope of slowing the progression of or even curing their disease.*
Methods: *We explore the benefits and risks that patients experience when participating in phase 1 clinical trials.*
Results: *Rules and regulations have been put into place to protect the safety and interests of patients while undergoing clinical trials. Selecting patients with cancer who will survive long enough to accrue data for these trials continues to be challenging. New prognostic models have been validated to help health care professionals select those patients who will likely benefit from participation in phase 1 trials. There also are long-lasting positive and negative impacts on those patients who choose to participate in phase 1 clinical trials.*
Conclusions: *Modern phase 1 clinical trials represent a therapeutic option for many patients who progress through frontline therapy for their malignancies. Recent phase 1 clinical trials testing targeted therapies have increased responses in many diseases in which other lines of therapy have failed. Patients still face many risks and benefits while enrolled in a phase 1 trial, but the likelihood of treatment response in the era of rational, targeted therapy is increased when compared with the era of cytotoxic therapy.*

Introduction

Results from clinical trials help to answer questions and provide guidance for practicing health care professionals. The regimented clinical trial design was not standardized until the twentieth century[1]; however, physicians have been employing concepts of modern clinical trials for centuries. An ancient medical text, *The Canon of Medicine*, established guidelines for the proper conduct of medical experimentation.[2] In this text, the principles for testing the efficacy of a new medication were laid out, including that the drug must be free from any extraneous accidental quality and that the experimentation must be performed with the human body.[2] The essence of these guidelines became the scientific method for testing of medications, and, for the most part, the medical field regulated itself when it came to new medications, elixirs, "cure-alls," panaceas, and the like.

The turning point in medication development that resulted in the rigorous, regimented development of clinical trials in the United States occurred in 1937 when pharmaceutical manufacturer S.E. Massengill Company (Bristol, Tennessee) released the first elixir

From the Clinical Research Unit at the H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida.

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Address correspondence to Amit Mahipal, MD, Clinical Research Unit, H. Lee Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33647. E-mail: Amit.Mahipal@Moffitt.org

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formulation of sulfanilamide, an antibiotic that, at the time, had been shown to have activity against streptococcal throat infections.[3] The elixir was available to consumers without undergoing animal or human testing of any kind prior to its release. However, the antibiotic was suspended in diethylene glycol, also known colloquially as antifreeze. The product was so extensively disseminated into US stores that the US Food and Drug Administration (FDA) and S.E. Massengill could not fully recall the product, which had caused the deaths of at least 100 people.[1] Even then, the FDA was empowered to recall the drug only because the label was misleading (ie, it was labeled as an "elixir" and, therefore, had to contain alcohol, but this "elixir" did not have any). Due in part to this series of deaths, the FDA was granted new powers in 1938 under the Federal Food, Drug, and Cosmetic Act, which required drug sponsors to submit safety data to the FDA for it to evaluate prior to marketing of the drug, thus planting the seed for the modern clinical trial structure[4]; this was later modernized by Hill in 1948.[1] Hill, who was a British statistician, performed one of the first randomized controlled studies that showed that streptomycin could cure tuberculosis.[5]

However, in 1962, thalidomide, a drug popular as a hypnotic in Europe and suspected to cause birth defects, was supplied to US physicians who subsequently gave the drug to expectant mothers as a remedy for morning sickness.[6] This act resulted in nearly a dozen infants being born with birth defects, far less than the approximately 10,000 infants worldwide born with thalidomide-related defects. The smaller impact of thalidomide in the United States was due in part to the efforts of the FDA, which denied the thalidomide application on grounds that more evidence of safety was required.[1] The amendments in 1962 that followed on the heels of the thalidomide incident further strengthened the control of the FDA over new investigational drugs, thus requiring pharmaceutical companies to demonstrate that their investigational drug could be safely given to patients in the preclinical setting, thereby setting the stage for the formation of phase 1 clinical trials (Table 1).[1,7]

Purpose of Phase 1 Trials

Historically, the focus of phase 1 clinical trials has been to demonstrate that a new drug can be safely given to humans at the maximum tolerated dose (MTD),[8] which is associated with dose-limiting toxicities (DLTs). The MTD, which could be a therapeutic dose or the maximum dose that can safely be administered, is then carried on to further phases of clinical trials. In the era of targeted agents, the biologically effective dose is now frequently used rather than the MTD. Because the primary purpose is not efficacy, maintaining patient population homogeneity and obtaining measurable tumor response is not required; however, many investigators include these factors in their protocols.[9] Understanding the emphasis on safety in phase 1 studies requires an understanding of the history of drug development in the United States and why the FDA is concerned with establishing safety followed by efficacy.

The field of oncology has matured during the last 20 years due in part to the understanding of the various molecular pathways involved in tumorigenesis. Because of the advent of molecularly targeted therapies due to this evolution, the standard dosing regimen, which consists of "cycles" of chemotherapy at the MTD, may need to be reconsidered.[10] In fact, se-

Table 1. — Phases of Clinical Trials

Phase	Primary Goal	Primary Researcher	Subject Type	Comment
Preclinical	Nonhuman efficacy Toxicity PK	PhD, MD, PharmD, or any researcher	Cell lines (animal)	
0	Determining PK and PD	Clinical researcher	Human	Focuses on determining oral bioavailability and half-life Often combined with phase 1
1	Evaluation of safety and adverse events	Clinical researcher	Human	May be expanded or combined with phase 2
2	Examine efficacy and dose range	Clinical researcher	Human	May help in optimizing dose, schedule, and select disease types
3	Expanded study to substantiate efficacy and safety	Clinical researcher	Human (N = large range)	Generally includes multiple sites and investigators
4	Postmarketing surveillance	Primary physician	Human (N = all patients taking the drug)	Determines long-term effects

PD = pharmacodynamic, PK = pharmacokinetic.

lected molecularly targeted therapies such as tyrosine kinase inhibitors (eg, imatinib, ibrutinib, sorafenib) are not given in cycles but instead are given orally every day.[10] The goal in such cases may not be tumor regression but rather tumor control. As such, dosing at the MTD may not be the dose associated with the most effectiveness. As in the case of ibrutinib, the MTD was never reached because the drug was well-tolerated and the dose selected for further clinical trials was based on the dose that caused near complete occupation of all Bruton tyrosine kinase receptors.[11] This calls into question whether toxicity can continue to be the primary goal for phase 1 trial design.[10] For a particular agent, its effects on its purported molecular target may serve as another marker for efficacy. Logistically, this may become a complicated matter, such as repeatedly obtaining tissue or routine blood work. For the patient, this may result in more invasive procedures, which carry their own inherent risks, or more frequent blood work, which one may expect to negatively impact patient enrollment. However, study results indicate that patients are willing to undergo multiple biopsies if needed.[12]

Study Design

The difficulty in designing a phase 1 clinical trial is the decision of whether to escalate the dose of the study drug quickly (such that patients develop toxicities sooner) or whether to escalate the dose slowly (such that patients are treated at subtherapeutic doses for longer).[13] However, study design protocols that attempt to answer this question are out of the scope of this review article, but they may be of interest because investigators must consider the impact of the study design on patient safety. For instance, one study examining phase 1 patients enrolled between 2002 and 2004 demonstrated that aggressive dose-escalation schemes did not have a response advantage for cytotoxic agents but were associated with more toxicity when compared with conservative dose-escalation schemas.[14] In

Table 2. — Selected Dose Escalation Designs

Dose-Escalation Method	Description	Advantages	Disadvantages
Rule-Based Designs			
3 + 3 (including 2 + 4, 3 + 3 + 3, and 3 + 1 + 1)	Dose escalation follows a modified Fibonacci sequence (dose escalation sequence 100% → 67% → 50% → 40%, and so on) If 1 patient has a DLT, 3 more patients are added (+ 3) Escalation continues until 2 patients among the same cohort experience a DLT	Simple Safe Adding 3 more patients per dose level supplies more PK data	Excessive number of escalation steps means more patients potentially treated at subtherapeutic doses
Accelerated titration	Assignment of patients to dose levels follows specific rules according to observed toxicities at each dose level Allows intrapatient dose escalation	Reduces the amount of patients treated at subtherapeutic doses Eventual phase 2 dose can be interpreted from data from all patients	May mask cumulative toxic effects of treatment if model does not fit data
Pharmacologic-guided dose escalation	Assumes that DLT is predicted by plasma drug concentrations and an animal model Area under the curve predicted from preclinical data	Reduces the amount of patients treated at subtherapeutic doses (100% dose increment escalation) Provides PK data	Logistics behind obtaining real-time PK data Interpatient variability in drug metabolism may affect results
Model-Based Designs			
Continual reassessment	Based on the Bayesian model Initial dose based on preclinical data All patients treated at predicted maximum tolerated dose Probability of reaching DLT updated for every patient who enters the study at every dose level Stopping rules vary (eg, when 6 patients are assigned to the same dose level)	Reduces amount of patients treated at subtherapeutic doses Uses all data gathered from all patients Phase 2 dose estimated with a confidence interval Late toxicities are accounted for	Logistics and manpower behind calculations for every patient for every cohort Requires strong support from a statistician for dose escalation

DLT = dose-limiting toxicity, PK = pharmacokinetic.

Adapted from Le Tourneau C, Lee JJ, Siu LL. Dose escalation methods in phase I cancer clinical trials. *J Natl Cancer Inst.* 2009;101(10):708-720. Published in its adapted form by permission of Oxford University Press.

this study, investigators reported a death rate of 1.1%,[14] which, in general, is more than double the typically accepted risk of death for phase 1 studies.[15]

Innovative, more efficient, and safer designs are being developed compared with the traditional 3 + 3 dose-escalation design,[16] which was designed in the era of cytotoxic therapy. During this time, higher doses were assumed to result in higher efficacy rates, but these doses also resulted in higher toxicity rates. Another main drawback of the traditional 3 + 3 design is that each escalation step may represent a group of patients treated with subtherapeutic levels of a particular medication. An analysis of 21 trials of cancer therapies using the 3 + 3 design between 1992 and 2008 (therapies eventually approved by the FDA) revealed that more than one-half of these designs had at least 6 dose-escalation levels.[17]

Many different dose-escalation schemes exist, although the predominant scheme used is the 3 + 3 design. Table 2 lists the advantages and disadvantages of selected dose-escalation designs.[17] Ultimately, the primary goal of newer dose-escalation schemes is to maximize the number of patients receiving the most efficacious dose.

In the era of molecular-targeted therapies, new questions arise as to what constitutes an "effective" dose. Oftentimes, this concept is measured through the inhibition of the intended target, which can pose several obstacles, such as access and assessment of tissue (eg, tumor, peripheral blood) and the determination of the level of inhibition required to obtain a clinical response.[17] In these situations, dose-escalation designs may not be as relevant as during the era of cytotoxic therapy. However, generally speaking, toxicity is still used as an end point for molecular-targeted therapies. In addition, emphasis is placed on the preclinical setting and the so-called phase 0 trial in which the demonstration of a targeted effect is the primary goal. Pharmacokinetic and pharmacodynamic data are also obtained during phase 0 trials. The advantage of phase 0 trials is that having data upfront helps expedite new drugs through other phases of clinical testing.[7]

Patient Selection

From our experience, the largest risk to patients who participate in phase 1 trials is death; secondary risks include adverse events associated with the study drug that may or may not be reversible. Our experience also suggests that oncologists generally offer patients with progressive, refractory malignancies the opportunity to participate in phase 1 studies as a "last ditch effort." Consequently, many patients may be frail and will have experienced end-organ dysfunction and have short life expectancies. Early reports suggested that approximately 20% of patients passed away during the first 90 days of entry into a phase 1 trial.[18] Because of this, modern phase 1 studies use arguably biased stringent inclusion criteria, which exclude approximately 33% of participants screened for entry.[19] Moreover, criteria are so stringent that a study published by Seidenfeld et al[20] concluded that 93% of participants of phase 1 trials nearly matched the performance status (PS) of the general population. Other inclusion criteria, along with Eastern Cooperative Oncology Group (ECOG) PS, Karnofsky PS, or both, generally look at organ function (eg, creatinine, liver enzymes), age, lactate dehydrogenase (LDH), and other comorbidities.[21] In an effort to select which patients might reasonably survive long enough to accrue safety data for phase 1 studies, many scoring systems have been formulated to help select patients with the lowest risk of mortality.[22,23]

For instance, Wheler et al[24] retrospectively determined that a history of thromboembolism, the presence of liver metastasis, and thrombocytosis predicted a shorter survival rate in patients enrolled in phase 1 clinical trials, with each parameter bearing comparable risk of death and weighed equally. From these data, they developed a risk score with corresponding risk groups and 6- and 12-month survival rates (low risk = 73%, 51%; intermediate risk = 65%, 34%; high risk = 35%, 6%, respectively).[24] This study was the first to report the survival rate of phase 1 participants in the era of biologically and molecularly targeted therapy. A median overall survival (OS) rate of 9 months was reported in this study,[24] which is in contrast to the median OS rate of 5 months in the era of cytotoxic therapy and ECOG PS and LDH levels.[21]

Arkenau et al[22] from the Royal Marsden Hospital (RMH) developed a prognostic score using retrospective data of 212 patients enrolled in their phase 1 program (Table 3). In this study, 3 variables associated with poor outcomes were isolated, including an elevated level of LDH (> upper limit of normal), low

Table 3. — Royal Marsden Hospital Prognostic Score

Variable	Score	Hazard Ratio
Lactate Dehydrogenase		1.85
< ULN	0	
> ULN	1	
Albumin (g/dL)		1.83
> 3.5	0	
< 3.5	1	
Sites of Metastases		1.54
0–2	0	
> 2	1	

Scores 0–1 = good prognosis, 2–3 = poor prognosis.
ULN = upper limit of normal.
Data from reference 22.

level of albumin (< 3.5 g/dL), and more than 2 sites of metastasis. Patients with a score of 0 to 1 had a median OS rate of 74.1 weeks, whereas patients with a score of 2 to 3 had a median OS rate of 24.9 weeks across all tumor types.[22] These data were prospectively studied at the same institution and validated in a follow-up study.[25] Using the RMH score, Arkenau et al[25] demonstrated that nearly 90% of patients who died within the first 90 days of entry into a phase 1 trial had a prognostic score of 2 to 3. At the time of the study, those with a score of 0, 1, 2, or 3 had a median OS rate that was not reached: 25.7 weeks, 15.7 weeks, and 14.1 weeks, respectively. This scoring system was further modified and validated at the phase 1 clinic at the University of Texas MD Anderson Cancer Center in Houston.[23] Wheler et al[23] added gastrointestinal tumor type and ECOG PS (≥ 1) to the RMH score as factors associated with a poor prognosis (Table 4). Using their prognostic score, they found that median survival rates for the low-risk (0), low-intermediate (1), intermediate-risk (2), high-intermediate risk (3), and high-risk (4–5) groups were 24.0 months, 15.2 months, 8.4 months, 6.2 months, and 4.1 months, respectively.[23] The relative risk of having more than 2 sites of metastasis and ECOG PS of at least 1 was lower than the other variables, a finding likely due to stringent inclusion criteria and clinical judgment. Also of note is the median survival rate of 10 months, with 86% patients having received a targeted therapy/biological agent and 32% having received a cytotoxic agent. These results further demonstrate the increased clinical benefit of phase 1 clinical trials in the era of targeted therapies.

Table 4. — MD Anderson Clinical Center Prognostic Score

Variable	Score	Relative Risk for Death
Lactate Dehydrogenase		1.74
< ULN	0	
> ULN	1	
Albumin (g/dL)		1.58
> 3.5	0	
< 3.5	1	
Sites of Metastases		1.26
0–2	0	
> 2	1	
ECOG PS	0	1.32
0	1	
≥ 1		
Tumor Type		1.42
Non-GI	0	
GI	1	

Scores: 0 = low risk, 1 = low-intermediate risk, 2 = intermediate risk, 3 = high-intermediate risk, 4–5 = high risk.

ECOG PS = Eastern Cooperative Oncology Group performance status, GI = gastrointestinal, ULN = upper limit of normal.

Data from reference 23.

Phase 1 Trial Participation as a Therapeutic Option

Although the goal of phase 1 studies has primarily focused on safety profiles, most patients with cancer participate in these trials with the hope of deriving clinical benefit, and health care professionals are beginning to integrate participation in a phase 1 study as part of a patient's plan of care.[26] Historically, health care professionals expected that phase 1 studies would yield a response rate of approximately 6% and a death rate due to the study drug of approximately 0.5%.[27] With the advent of molecular targets and immunotherapy, this expectation of efficacy has changed. Horstmann et al[15] updated these findings using data from the Cancer Therapy Evaluation Program, which consisted of data from 10,402 participants of phase 1 trials that took place between 1991 and 2002. They found an overall response rate of 10.6% and partial response and complete response rates of 7.5% and 3.1%, respectively. They reported that 0.49% of patients died while participating in a trial (0.21% of patient deaths were attributed to the study drug).

Italiano et al[26] reviewed the efficacy of phase 1 trials from their own institution between the years 2003 and 2006. The researchers found an objective response rate of 7.2%, a rate of stable disease of 41%, a progression-free survival rate of 2.3 months, and a median OS rate of 8.7 months.[26] In addition, 56.6% of participants went on to pursue different treatment options after exiting the phase 1 study, demonstrating that clinicians at that institution were incorporating participation in a phase 1 study as part of treatment pathways, particularly for malignancies without a clear, preferred treatment option with good effectiveness.[26] Moreover, in some malignancies (eg, progressive head and neck cancers), participating in a phase 1 clinical trial could potentially mean that patients would have progression-free survival rates similar to those seen in third-line therapies already approved by the FDA.[28]

Considering the evidence of efficacy behind selected approvals by the FDA,[29,30] these results are significant. For instance, the addition of cetuximab to leucovorin/fluorouracil/irinotecan compared with leucovorin/fluorouracil/irinotecan alone in *KRAS* wild-type patients increased the progression-free survival rate from 8.7 months to 9.9 months[29] and the addition of nab-paclitaxel to gemcitabine increased the progression-free survival rate from 3.7 months to 5.5 months.[30]

Further expanding on the benefit of targeted therapy, one study found that the risk of death during a phase 1 trial testing a cytotoxic agent was nearly quadruple that of a trial testing a targeted agent.[31]

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