Abstract

Advances in our knowledge of the molecular mechanisms involved in cancer biology have contributed to an increase in novel target-specific oncology therapeutics. Unfortunately, clinical development of new drugs is an expensive and slow process, and the patient and financial resources needed to study the vast number of potential therapies are limited, requiring novel approaches to clinical trial design and patient recruitment. In addition, traditional efficacy endpoints may not be adequate to fully determine the therapeutic worth of the new classes of targeted agents. In this new era of drug development, it has become increasingly clear that new clinical trial design paradigms that examine nontraditional endpoints have become necessary to assist in prioritizing the development of the most promising agents. It is also vital that individual patient management be considered, and the subpopulations of patients most likely to derive benefit or experience harm from a new therapy be identified as early as possible. Phase I and II clinical trials allow investigators doing clinical research the opportunity to define these critical endpoints and subpopulations early on, before conducting large-scale randomized phase III clinical trials, which require an abundance of financial and patient resources.

Principles driving oncology clinical trial design were primarily developed in the 1970s, during the introduction of many cytotoxic anticancer therapies. In the current era of molecularly targeted therapy, these traditional clinical trial design principles and trial endpoints are being reconsidered. At present, the most widely accepted metric for therapeutic utility remains improvement in the length of survival. However, alternate endpoints, such as time to disease progression, durable overall response rate, or improvement in disease-related symptoms, may be more appropriate endpoints for different classes of agents being evaluated. A major goal in clinical cancer drug development is to obtain regulatory approval for an efficacious agent and, to reach this goal, developers must often evaluate a novel therapy through a pivotal randomized control trial (RCT). As the proliferation of molecularly targeted agents has increased, it is important to refine the critical steps that lead to RCT design and execution. This article proposes innovative approaches to earlier phase I and II trials, which may ultimately yield change in how we design, conduct, and inform RCTs as we advance into the next generation of oncology clinical trials.

Phase I Trials: Novel Designs and Impact on Patient Outcome(s)

Currently, nearly 900 novel cancer agents are undergoing investigation in more than 6,000 clinical trials (1-3). Owing to this large number of investigational agents, a critical lack of financial and patient resources significantly reduces the chances for adequate development of many of these agents. As a result, clinical drug developers require continual innovation in their approaches to best determine which drugs to develop further, in which patient populations to test the novel agents, and how to maximize resources. One example of such innovation was the development of the accelerated titration design by Simon and colleagues, with the purpose of treating fewer patients at lower, ineffective doses, while more rapidly identifying a recommended phase II dose (4). Another, more recent, innovation is the "phase 0 study," clinical trials involving very limited human exposure with no therapeutic or diagnostic intent, which are conducted prior to traditional phase I dose-escalation safety and tolerance studies (5). Although initial phase 0 studies have shown promise and have the potential benefit of expediting or accelerating selective elements of phase I trials (6), their use is not yet widespread, and phase I trials still often represent the first step in clinical drug development and the earliest opportunity to define go-no-go drug development decisions. As such, phase I studies require continuing novel drug development strategies as paradigms in the field shift.
Primary objectives of phase I trials

The two most common primary objectives of a phase I trial are the identification of a recommended phase II dose range and the determination of whether a drug is safe enough to move forward in clinical development. However, the perspective of at least four stakeholders with somewhat divergent objectives must be considered in the design of a phase I trial. First and foremost among the stakeholders are the patients, who bring their own unique perspective to early phase clinical trials. Despite the current low chance of benefit that is explicitly stated by investigators to the clinical trial participant, many patients participate because they hope to live longer. It is an obligation for the treating physician to help the patient identify the most appropriate agent(s), whenever possible, to allow informed decisions about whether a clinical trial may be appropriate. The second set of stakeholders are the investigators, who wish to define the true potential of the agent. The third set of stakeholders are the trial sponsors, which are typically the companies producing the experimental agents; their primary interest is in determining which drugs have the highest potential to reach the market while identifying those that are most likely to fail as soon as possible. Finally, the fourth stakeholder that must be kept in mind in designing and defining the objectives of an early clinical trial are third-party payers. As discussed elsewhere within this CCR Focus series by Klamerus and colleagues, even if a patient has health insurance, their plan may not cover all costs related to receiving treatment in a clinical trial, in large part because of the experimental nature of the study and the lack of efficacy endpoints, which severely limit their ability to participate in an early phase trial. Even in circumstances in which the insurer does cover some or all of the costs, the coverage is frequently associated with a copay that makes the treatment a financial strain for the patient. To optimize output from phase I trials, it is critical to consider the objectives of all stakeholders in both trial design and conduct.

Managing novel toxicity in phase I studies

Although targeted agents as a group are often considered to be associated with a less severe toxicity profile, this is not always the case. Toxicity profiles from targeted therapies tend to be different than their chemotherapeutic counterparts. For example, epidermal growth factor receptor (EGFR) inhibitors are often associated with severe dermatologic side effects that are a challenge to manage. Monoclonal antibodies against VEGF or small molecule VEGF receptor (VEGFR) tyrosine kinase inhibitors can cause hypertension and proteinuria. These examples are telling us that targeted agents may affect normal tissues as well as the tumor. The clinical investigator must pursue strategies to circumvent these toxicities whenever possible without compromising efficacy, and find better ways to manage and classify them when they cannot be avoided.

Rational and novel designs of phase I trials

In the contemporary era of drug development, one must consider whether defining success of a phase I trial on the basis of identification of a maximum tolerated dose (MTD) actually meets the objectives of all stakeholders. Although one must keep in mind that ultimate tumor effect relates to the drug dose delivered to the target, the assumption in traditional phase I clinical trials of cytotoxic agents is that tumor effect increases with increasing dose administered to the patient. Unfortunately, this effect is often accompanied by a parallel increase in drug toxicity. Therefore, the goal is to reach the often narrow therapeutic window in which clinical benefit exists along with acceptable toxicity. Hunsberger and colleagues proposed that this relationship may differ for the molecularly targeted agents for which a plateau exists on the dose efficacy curve where higher doses may not necessarily improve benefit, especially if the patient population is properly selected. In addition, toxicity for these agents may not necessarily increase with increased doses, or it may occur beyond doses that are actually yielding sufficient clinical benefit. This new paradigm has challenged investigators to come up with innovative phase I clinical trial designs that are rational and more efficient.

A critical question in the era of molecularly targeted therapy is whether treatment effect is proportional to dose of drug delivered in phase I trials. Postel-Vinay and colleagues recently reviewed 135 patients enrolled onto 15 monotherapy phase I trials of differing targeted agents. Patients were classified into three groups according to the dose they received, which was defined as a percentage of the final MTD level (A, 0–33%; B, 34–66%; and C, >67% of the MTD). The authors found no significant difference in the nonprogression rate between the three groups. However, these data must be interpreted cautiously as they represent a small sample set derived retrospectively from a single institution with a unique patient population relative to patients typically recruited into U.S.-conducted phase I studies. In contrast, we recently reported outcome results of 1,908 patients treated on 53 eligible clinical trials of molecularly targeted agents at multiple institutions throughout North America sponsored by the National Cancer Institute’s (NCI) Cancer Therapy Evaluation Program (CTEP), which suggest that potential clinical benefit in terms of overall response, nonprogression rate, and overall survival significantly correlates with the administered dose level, with increasing benefit for patients treated at doses at or near the MTD. These data suggest that dose-ranging studies must still be considered for molecularly targeted agents.

As discussed elsewhere in this CCR FOCUS series by Fojo and Parkinson, in an effort to maximize the efficiency and benefit of clinical trials, even early in phase I, proper patient selection is becoming increasingly important. Promising results for the EGFR tyrosine kinase inhibitor gefitinib (Astra Zeneca) observed in phase I and II trials led to accelerated approval by the U.S. Food and Drug Administration as treatment for patients with refractory advanced non–small cell lung cancer (NSCLC, ref. 12). However, as the subsequent pivotal randomized phase III trial failed to show a survival advantage in unselected patients, the drug has largely disappeared from clinical use in the United States.

Recent experience with gefitinib strongly suggests the
outcome of this particular pivotal trial might have been different had these early clinical signals been incorporated into its study design and patients rationally selected (14–16). This example illustrates the importance of addressing such questions and incorporating data learned in early studies not only to maximize outcome for the patients enrolled, but also to assist the investigational drug community in possibly saving considerable patient and financial resources, while enhancing the probability of a more favorable clinical trial outcome. Several recent clinical trials show the advantage of selecting specific tumor types, as well as specific biomarkers and/or genetic mutations, earlier on in the clinical development of novel agents. Examples include a phase I study of PLX4032 (Plexxikon Inc.), a novel, highly selective drug that targets the BRAFV600E cancer-causing mutation, which occurs in most melanomas and about 8% of all solid tumors (17, 18); and a study of GDC-0449 (Genentech), a novel inhibitor that targets the Hedgehog signaling pathway and has been shown to be effective in patients with basal-cell carcinoma (19). Finally, a phase I monotherapy trial of PF-02341066 (Pfizer), a selective, small molecule dual inhibitor of c-Met and Alk tyrosine kinases, illustrates how effective trial design can result in an extremely quick transition from first-in-human to large-scale efficacy testing. The first dosing study of PF-02341066 began enrollment in May of 2006 and showed effectiveness in patients with tumors harboring ALK fusion genes (20, 21). A subsequent pivotal phase III study enrolling ALK fusion gene—positive patients began enrolling in late 2009 (3, 20), showing that, by preselecting the right patients on the basis of robust and compelling preclinical data, clinical proof of concept can be reached very quickly and risk associated with ongoing drug development may be significantly diminished.

Another example of efficiency in using early clinical trials to help define the population most likely to benefit and help shape future trials was observed in the recent phase I clinical trial of the oral MAP/ERK kinase MEK 1/2 inhibitor GSK1120212 (GlaxoSmithKline; ref. 22). Although other studies of drugs in the same class have been recently conducted in unselected populations of patients with solid tumors with modest results (23, 24), investigators in the trial of GSK1120212 used preclinical data and knowledge of more than a decade of experience with inhibitors of MEK to rationally design a study that enriched for selected tumor types (melanoma, pancreatic, NSCLC, and colorectal) to evaluate the recommended phase II dose in populations considered to have the best chance of benefit. Notably, of the 20 patients with BRAF-mutant melanoma treated with GSK1120212, two complete responses and six partial responses were observed, resulting in an impressive preliminary response rate of 40% in this population (95% CI, 19–64%; ref. 22).

These examples show proof of concept for using targeted therapies and also show that a phase I patient population, in select situations, can indeed derive benefit with proper upfront selection. In addition, it shows that proper study design can result in an experimental agent being placed on fast track from phase I to phase III, potentially reducing time and costs associated with drug development. It must be noted that not all targeted drugs will be appropriate for upfront preselection of patients; agents without exquisite specificity (i.e., “dirty” drugs) interact with several possible targets, making a definitive biomarker assessment a prerequisite to enrolling onto a study difficult. However, by targeting therapies to select populations in early trials when preclinical and early clinical evidence is in support and a carefully validated assay exists, we may be able to suggest proof of principle with novel agents in terms of response, molecularly targeted effect, and pharmacodynamics. Pharmacodynamics is especially important if proven to correlate with a tumor-matched response. However, if no such correlation is observed, one must take into account possible causalities, including lack of a carefully validated assay, problems related to specimen acquisition and handling, and the presence of feedback mechanisms, to make sure these possibly confounding factors are not the reason that tumor response is not shown prior to making crucial early go-no-go decisions for future development of these agents. The need for reliable pharmacodynamic assays to validate that the correct target is being hit must be emphasized; if investigators do not see evidence of target effects, they should be confident in declaring a “no-go” rather than spending critical resources pursuing a lower chance of success.

The future of phase I trials

With the vast quantity of oncology drugs in the development pipeline and limited resources to evaluate them, it is vitally important to increase efficiency in the evaluation process. Prior to reaching the clinic, better preclinical models and more organized development of key targets and/or inhibitors (rather than several similar phase I trials of different agents targeting the same target) might improve drug development efficiency. Once in the clinic, the phase I community must consider how to better understand the mechanism of response and resistance of experimental therapeutics and toxicity as early as possible in the development process. Practical guidance addressing many of these issues has been provided by both the Task Force on Methodology for the Development of Innovative Cancer Therapies (MDICT) and the NCI Investigational Drug Steering Committee (NCI-IDSC; refs. 1, 25). However, we must continue to address how the new era of molecularly targeted agents will redefine the endpoints of phase I clinical trials. Most importantly, we must understand what our obligation is to each of the four stakeholders, with the foremost being the patient. As discussed by Dalton and colleagues (26) elsewhere in this CCR FOCUS series, the enactment of the 2010 United States Health Care Reform Act offers potential opportunities for realizing the promise of translational research and personalized medicine. By helping to define select patient subsets, which may allow a candidate drug to either move forward or halt development early on, investigators and patients may be able to contribute much more to the treatment of the cancer patient population, while also satisfying the financial stakeholders who stand to benefit.

The full text of this article can be found in the Clin Cancer Res publication. The citation for this article is: "The future of phase I trials" by [Authors]. Clin Cancer Res; 16(24) December 15, 2010.
from more efficiently executed studies. Perhaps a major goal of phase I trials in the future will not be simply to define recommended phase II doses, but to better understand which patient subpopulation we should move forward into randomized trials. Predicting as early as possible which patients will not respond is just as important as predicting those who will, and may well result in benefit to all of the stakeholders involved in drug development.

**Phase II Trials in Oncology: What Really Matters?**

The purpose of phase II trials is to provide information that will allow investigators to (1) confirm observations from phase I trials about dose, safety, and efficacy; (2) further define efficacy in a chosen population; (3) refine study design for phase III, such as inclusion criteria and patient enrichment strategies; and (4) improve understanding of mechanisms of action from correlative translational studies. In the context of drug development, perhaps the most important purpose of the phase II trial is to inform decisions that reduce the number of failures in late development and thereby reduce development costs.

Historically, the success rate of oncology drug development has been poor. Data from 2002 to 2006 across the pharmaceutical industry show a high attrition rate among oncology drugs from preclinical to market approval, yielding only a 12% success rate (27). Beginning with phase III, the success rate to market approval is only 50% (27). These failures translate into thousands of patients and millions of dollars expended toward an outcome with little to no tangible benefit. With nearly 900 novel cancer agents under investigation, constrained financial resources, finite patient resources, and increasing pressures on the clinical investigational infrastructure, the historic track record for drug development is unsustainable.

Learning more about a new molecule in the context of the intended patient population prior to phase III will undoubtedly reduce the risk of drug development failure. Therefore, the phase II trial represents a critical intersection of new knowledge integration with risk of drug development failure occurring downstream at the end of a large, randomized clinical trial.

**Novel endpoint selections in the context of new treatments**

Careful selection of endpoints in well-designed phase II trials does have the potential to contribute meaningfully to phase III considerations. Using robust overall survival or validated surrogate endpoints in phase II would be optimal to predict for primary outcomes in phase III (28). However, phase II trials have often failed to accurately predict phase III outcomes in oncology for several reasons. First, open-label single-arm phase II trials are subject to patient selection and data interpretation biases that can misinform subsequent phase III trials. Efficacy endpoints traditionally used in oncology, such as pharmacodynamic biomarkers, objective response rate, time to progression, and progression-free survival, are imperfect predictors for a survival outcome in phase III (29).

Tumor burden is typically measured using categorical criteria, such as Response Evaluation Criteria in Solid Tumors (RECIST) or RECIST 1.1 (30, 31), and the data are grouped according to complete or partial response, stable disease, or progressive disease on the basis of arbitrary cut-off values. These criteria also contribute to time-to-tumor-progression and nonprogression rate endpoints. However, given that new, molecularly targeted agents may not invariably cause shrinkage of measurable tumor that is predictive of survival, there is increasing interest in understanding tumor volume as a continuous measure. This interest has led to the development of waterfall and spider plots as representative displays of individual patient tumor responses (32). Waterfall plots only show the best on-study change in tumor burden relative to baseline for each individual patient (Fig. 1A). However, if maximum change in tumor burden relative to nadir is evaluated, a different picture may emerge (Fig. 1B). Waterfall plots can, therefore, misrepresent the kinetics of tumor growth over time by focusing on a single static measurement relative to a single point of reference. An alternative that addresses this limitation is the spider plot that shows a change in tumor volume over time longitudinally from a normalized baseline of zero (Fig. 2). Spider plots suffer because of missing information that is not necessarily random. Most of the missing information is in patients who progressed or died early in the trial and for whom data are not captured on a case report form. Both waterfall and spider plots allow only visual (qualitative) assessments, not formal statistical inference. Alternative approaches have been proposed that address some of these limitations by jointly considering tumor volume and time parameters while accounting for informative censoring (33–36). Finally, new mechanistic approaches to cancer treatment may require novel measurement criteria to address observed biologic effects. Recently, novel immune-related response criteria have been proposed to reflect the unique antitumor activity of immunotherapy (37). Whether any of these new alternative methods can reliably predict for phase III outcomes remains to be determined.

**Design considerations to increase efficiency in phase II to III transition**

In this *CCR FOCUS* series Booth discusses the importance of proper design and interpretation of the next generation of phase III trials (38). Numerous phase II trial designs to choose from have the potential to optimally inform a subsequent phase III trial. Although single-arm trials may still have a role in very select cases, a randomized phase II design is much more likely to be useful prior to phase III. Among different randomized trial designs, the comparative screening design provides the best opportunity to align factors that are more informative to make phase III decisions (28). The phase II trial needs to be large enough to support the proof of concept, and small enough to be a measured step before phase III.
For illustration, suppose a 6- versus 8-month overall survival improvement is the smallest benefit of clinical significance desired from a randomized phase III trial. This effect size translates into a hazard ratio of 0.75 as the threshold for both statistical and clinical significance. Therefore, the trial should have 90% power to detect a true hazard ratio of not 0.75, but 0.65, that is, a 6- versus 9.2-month difference. If the trial were powered at 90% to detect a true hazard ratio of 0.75, then a hazard ratio of 0.84 would be statistically significant and the 6- versus 7.1-month difference may not be clinically important. In the phase III setting, we often assign the power of 90% because we want to reduce the probability of a false negative outcome, and the false positive threshold is usually assigned a two-sided value of 5%.

These assumptions for phase III provide for the phase II construct whereby some fraction of the anticipated phase III population sample size, such as a third or a fifth of that sample size, will be defined. As a result, there will be differences in false negative and false positive rates. Typically, to avoid rejecting an efficacious drug, the power is set high at 90%, so the sacrifice is on the false positive rate, which may be set at a 10% or 20% false positive rate. Because the goal for such a phase II trial is for informing a decision whether to go to phase III, it is legitimate to assign all of the α to one side rather than having to split the α.

The use and limitations of this randomized phase II construct was illustrated in the early 1990s. A randomized phase II trial conducted by the North Central Cancer Treatment Group (NCCTG) showed that both the combination of 5-fluorouracil (5-FU) and levamisole or levamisole alone provided improved overall survival with long-term follow-up (39). Had there been two negative outcomes, a phase III trial would not have been pursued, whereas these observations were sufficient to generate a phase III trial recognizing that there was a relatively high probability for the phase II observation to be a false positive. In an appropriately sized and powered phase III, the 5-FU leva-misole combination was superior, whereas single agent levamisole was no different from control (40). Thus, there was one “true” positive and one “false” positive outcome from this three-arm randomized phase II trial that enabled an appropriately designed and sized phase III experiment to reveal “truth” on the basis of statistical probability. The development of bevacizumab in advanced colorectal cancer is another often cited example of how a well-designed dose-finding randomized phase II trial guided the eventual success of the landmark phase III study.
that was the basis for bevacizumab approval and its widespread use in clinical practice (41, 42). Of course, as discussed above with respect to false positive rates in randomized phase II trials, there have been and there will continue to be phase III trials that fail despite positive phase II results (43). The hope is that the number of these failures will be reduced.

In summary, several factors can help get the most relevant information in phase II: (1) Apply novel assessments of antitumor activity of targeted molecules (e.g., waterfalls and spiders) carefully, understanding what information they provide and what their limitations are; (2) Design randomized phase II trials to make decisions for phase III, paying attention to the design and trial size for phase II in the context of what the goals for the phase III trial are; (3) Depending on the tumor type and molecule being investigated, select phase II endpoints that provide the highest confidence for predicting for phase III benefit; (4) Select the same relevant patient population for phase II that will be defined in phase III; (5) Most importantly, whereas showing a minimum threshold of efficacy in the primary endpoint is a necessary condition for proceeding to phase III, it is not by itself a sufficient condition, as it is critical to evaluate all of the data with emphasis on the consistency of all the endpoints, both quantitatively and directionally, as well as a positive benefit-risk profile. Applying these principles to the design and conduct of phase II trials in oncology is likely to reduce the risk of failure in phase III, thereby bringing effective therapies to patients sooner and at a lower cost.

Conclusion

Since the 1970s, there have been tremendous improvements in the management and outcome of patients with cancer. Traditional phase I-III clinical trials are responsible for many of these advances. Each phase in the drug development strategy requires continual reassessment and is faced with its own unique challenges. Highly selective molecularly targeted agents showing high levels of activity in phase I may allow for a paradigm shift for more efficient phase I-III development strategies. As illustrated with the example of erlotinib in the overview article in this CCR FOCUS series by LoRusso and colleagues, identification of select patient subsets most likely to respond or fail to an investigational therapy may be critical to determining its true worth, and doing it in early phase I-II studies may save subsequent patient and financial resources (44). As we look forward to the next generation of clinical trials and therapeutics it will be critical to keep clinically relevant end-point and patient-centered outcomes at the forefront. Clear communication of study methodology and benefit of therapy is essential to convey to patients and other stakeholders the true benefit of novel therapies. Innovative phase I and phase II study designs are needed to reduce development failures and facilitate and expedite the number of effective therapies that move into phase III testing and eventually into clinical practice.

Disclosure of Potential Conflicts of Interest

P. LoRusso, commercial research grant, consultant, GlaxoSmithKline, Pfizer, Genentech; honoraria, Genentech. S. Averbuch, A. Anderson, employment, Bristol-Myers Squibb. The other authors declared no potential conflicts of interest.

Received 08/27/2010; revised 10/04/2010; accepted 10/15/2010; published online 12/15/2010.

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Making the Investigational Oncology Pipeline More Efficient and Effective: Are We Headed in the Right Direction?

Patricia M. LoRusso, Aparna B. Anderson, Scott A. Boerner, et al.


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