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# Clinical Trial Design for Target-Based Therapy

**ELIZABETH FOX, GREGORY A. CURT, FRANK M. BALIS**

Center for Cancer Research, National Cancer Institute, Bethesda, Maryland, USA

**Key Words.** *Clinical trials · Drug development · Pharmacokinetics · Pharmacodynamics · Molecular targets*

## LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Differentiate between cytotoxic and molecularly-targeted drug development in terms of drug discovery, mechanism of action, pharmacological effect, and specificity.
2. Define the primary objectives of phase I, II, and III clinical trials of cytotoxic and molecularly targeted anticancer agents.
3. Compare the end points used in clinical trials for cytotoxic agents to the proposed end points for target-based (cytostatic) agents.


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## ABSTRACT

**Anticancer drug discovery has shifted from an empiric random screening directed approach to a more rational and mechanistic, target-based approach, which reflects our rapidly expanding knowledge of the pathogenesis of a variety of forms of cancer at the molecular level, providing new targets for drug discovery and development. The clinical development of target-based anticancer drugs will require fundamental changes to the traditional clinical trial design and end points that have been used for conventional cytotoxic drugs. In the phase I and II settings, traditional end points (toxicity and response) may not be suitable for more selective, cytostatic target-based agents, and these end points may be replaced by biological or pharmacokinetic end points to define the optimal doses and the therapeutic effects of these drugs on their targets. For phase III trials, measurable clinical benefit will continue to be the primary end point. As our understanding of the complex pathways and networks controlling cell signaling, proliferation, and cell death expands, we must learn how and when to use agents to target specific steps in malignant transformation and proliferation, and we must adapt clinical trial design to test the clinical utility of this promising new class of anticancer drugs.** ***The Oncologist*** *2002;7:401-409*

## INTRODUCTION

Over the past decade, the emphasis in anticancer drug discovery has shifted from an empirical approach, characterized by random screening of a variety of natural and synthetic compounds using high throughput cell-based cytotoxicity assays, to a more rational and mechanistic, target-based approach [1]. The goal of this new target-based approach is to improve the efficacy and selectivity of cancer treatment by developing agents that specifically block the pathogenic mechanisms that account for malignant transformation. This new approach reflects our rapidly expanding knowledge of the pathogenesis of a variety of forms of cancer at the molecular level, providing new targets for drug discovery.

*Correspondence: Elizabeth Fox, M.D., Pediatric Oncology Branch, CCR, NCI, Building 10/Room 13C103, 10 Center Drive, MSC 1920, Bethesda, Maryland 20892-1920, USA. Telephone: 301-402-6641; Fax: 301-480-8871; e-mail: foxb@mail.nih.gov*
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The use of cytotoxicity as the end point for random screening assays evolved from the concept that the cure for cancer could be achieved by eradicating all cancer cells in the body, analogous to the successful treatment of bacterial infections with antibiotics. The cytotoxic anticancer drugs discovered through random screening have diverse mechanisms of action, but most target or damage DNA. As a result, the pharmacologic effects of most of these drugs are nonselective and, unlike classical drug-receptor interactions, their pharmacologic effects, which lead to cytoxicity, are irreversible.

The clinical development and subsequent clinical use of cytotoxic anticancer drugs also reflect the goal of cure (eradicating all cancer cells) as the treatment end point. The optimal dose is usually defined as the maximum tolerated dose in phase I trials, and the activity of a new drug is determined by whether it produces tumor shrinkage (response) in patients with advanced disease in phase II trials. In many front-line treatment regimens, conventional cytotoxic drugs are administered parenterally at their maximum tolerated dose in a pulsed fashion, which results in substantial toxicity in many patients and necessitates reiterative interruption of cycles of treatment to allow for recovery of normal tissues, usually bone marrow.

Target-based drug discovery selects agents for development based on their mechanisms of action. Validated targets are usually proteins that play a direct role in malignant transformation, such as the products of mutated genes that result in a gain of function (e.g., *ras, bcr-abl*), or normal receptors and signaling proteins in pathways that regulate apoptosis or the cell cycle and that are dysregulated by a mutation that results in the loss of protein function. For example, mutations or hypermethylation of the von Hippel-Lindau gene result in the loss of functional pVHL (protein product of the VHL gene), which acts as the substrate recognition component for the ubiquitination and degradation of hypoxia-inducible factors (HIFs) in the presence of oxygen. The constitutive activation of HIF transcriptional activity in the absence of pVHL leads to an increased production of the proangiogenic factor, vascular endothelial growth factor (VEGF), and a subsequent increase in microvessel density [2]. Many of the current molecular targets are proteins with enzymatic activity. Potential drugs to block these molecular targets may be designed and synthesized based on the three-dimensional structure of the target or identified by screening compound libraries for their ability to inhibit the target (target-based screening) [1].

Unlike cytotoxic drugs, the interaction of molecularly targeted drugs with their target (receptor) can be described by classical drug-receptor theory (Table 1) [3]. Their immediate pharmacological effects do not induce acute cellular damage, and therefore, are likely to be cytostatic rather than cytotoxic, although some agents can induce apoptosis. Cytostatic agents are more likely to be effective when they are administered continuously rather than in pulses, and oral formulations are preferred for continuous dosing schedules. Ideally, molecularly targeted drugs will interact with proteins that are specific to tumor cells or that are upregulated during malignant transformation. Under these conditions, target-based therapies hold the promise of being more selective and less toxic to normal tissues. As target-based therapies are developed, the common toxicities of cytotoxic therapy, such as bone marrow suppression and mucositis, may be replaced by unique and agent-specific toxicities, such as pseudotumor cerebri in children who are treated with retinoids, arthralgia associated with the matrix metalloproteinase inhibitors, and the cardiac toxicity of herceptin.

Drugs that validate the molecularly targeted approach to anticancer drug development include tretinoin (all-*trans*-retinoic acid), which targets the PML-RARα fusion protein in acute promyelocytic leukemia (APL) [4, 5], and imatinib mesylate (STI571, Gleevec™), which targets the BCR-ABL fusion protein in chronic myelogenous leukemia [6, 7] and the mutated KIT receptor in gastrointestinal stromal tumors (GIST) [8]. These agents have high response rates as single agents in cancers with the targeted molecular defect and are less toxic than conventional combination cytotoxic chemotherapy for these diseases. However, unlike APL and chronic myelogenous leukemia (CML), the molecular pathogenesis of most solid tumors has not been linked to a single genetic defect or target.

**Table 1.** Empirical (random cell-based screening for cytotoxicity) versus target-based drug development

| | **Empirical** | **Molecularly Targeted** |
|---|---|---|
| Discovery | Cell based | Receptor based |
| Mechanism of action | Not determined by screening assay | Basis for selection |
| Pharmacological effect | Cytotoxic (irreversible) | Cytostatic (reversible) |
| Specificity | Nonselective (toxic) | Selective (less toxic) |
| Dose and schedule | Pulse, cyclical at MTD | Continuous at tolerable dose |

Abbreviation: MTD = maximum tolerated dose.

**Table 2.** Clinical drug development of cytotoxic agents

| | Phase I | Phase II | Phase III |
|---|---|---|---|
| Objective | MTD, toxicity spectrum, pharmacokinetics | Activity spectrum | Efficacy (clinical benefit) |
| Disease | All diagnoses | Disease specific | Disease specific |
| Dose | Escalated | MTD | MTD |
| End point | Toxicity | Response | Survival |
| Design | Dose escalation in small cohorts of patients | Two-stage (early stopping rule) | Randomized (± blinded) |

Abbreviation: MTD = maximum tolerated dose.

Preclinically, the number of potential molecular targets and new drugs that interact with these targets has expanded rapidly. The clinical development of this new class of anticancer drugs will require fundamental changes to the traditional clinical trial design and end points used for cytotoxic drugs. For conventional cytotoxic drugs, the design and end points are summarized in Table 2 [9]. In the phase I and II settings, traditional end points (toxicity and response) may not be suitable for more selective, cytostatic target-based agents (Table 3), and these end points may be replaced by biological or pharmacokinetic end points. For phase III trials, measurable clinical benefit will continue to be the primary end point.

## Phase I (Dose-Finding) Trials

Phase I trials are small dose-finding studies designed to rapidly identify the optimal dose of a new agent, which is administered on one or more dosing schedules that were shown to be effective in preclinical models of human cancer. For conventional cytotoxic anticancer drugs, the optimal dose has usually been defined as the maximum tolerated dose (MTD) rather than the dose that produces a quantifiable therapeutic effect. Cohorts of three to six patients are treated at gradually increasing doses, and the MTD is defined as the dose level below the dose at which unacceptable or dose-limiting toxicity occurs in two or more of the three to six patients who were treated at that dose. This toxicity-based dosing approach is founded on the assumption that the therapeutic anticancer effect and toxic effects of the drug increase in parallel as the dose is escalated (Fig. 1A). This assumption is sound if the mechanisms of action of the toxic and therapeutic effects are the same, as is often the case with cytotoxic agents.

Phase I trials of cytotoxic anticancer drugs, which are relatively nonspecific and nonselective in terms of their mechanisms of action, are usually open to patients with a broad spectrum of cancers that become refractory to standard therapy or for which no standard drug therapy exists. Enrolling patients with different forms of cancer in these trials is also feasible because the primary end point (identification of the optimal dose) of the trial is based on the drug's toxic effects rather than its therapeutic effects. The toxic effects of many cytotoxic agents are similar (e.g., hematological toxicity), and as a result, patients who have been heavily pretreated with conventional cytotoxic anticancer drugs may be less tolerant of a new agent in a phase I trial than would be a patient who was previously untreated.

The pharmacokinetics of new cytotoxic agents are also studied in patients who are treated in a phase I trial. Pharmacokinetic parameters are correlated with patient characteristics, such as age, gender, or excretory organ function, and with outcome measures, such as the severity of common toxic effects; but the results of the pharmacokinetic study of the new agent generally do not play a role in determining the optimal dose of a cytotoxic agent.

Determination of the optimal dose will remain the primary objective in phase I trials of new molecularly targeted agents, but the primary end point used to measure the dose-

**Table 3.** Drug development of target-based therapy

| | Phase I | Phase II | Phase III |
|---|---|---|---|
| Objective | OBD, pharmacokinetics, PK-PD relationship, toxicity spectrum | Activity spectrum | Efficacy (clinical benefit) |
| Disease | Target-bearing tumors | Target-bearing tumors | Target-bearing tumors |
| Dose | Escalated | OBD | OBD |
| End point | Inhibition of target | Time to progression | Survival |
| Design | Guided-dose escalation | Controlled | Randomized (± blinded) |

Abbreviations: OBD = optimal biological dose; PK-PD = pharmacokinetic-pharmacodynamic

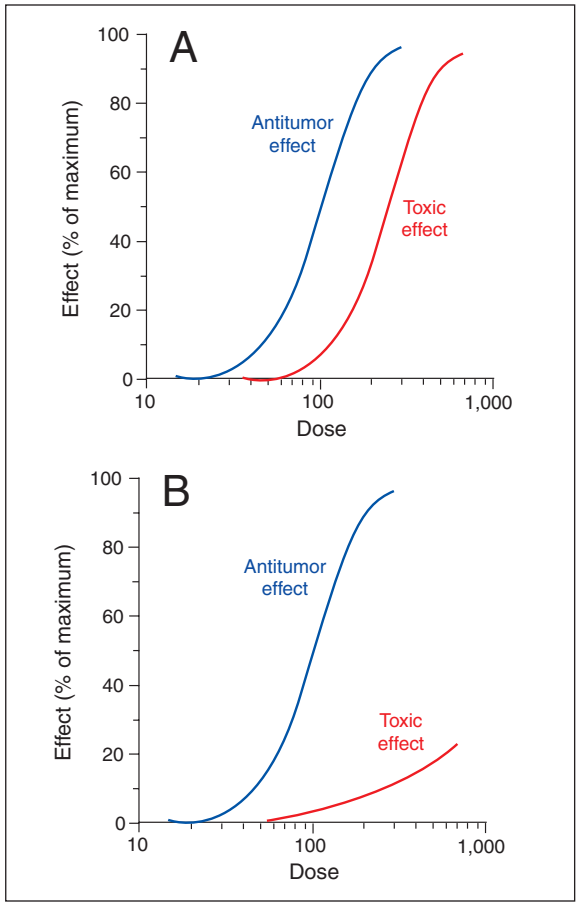


***Figure 1. (A) Hypothetical dose-effect curves for the therapeutic and toxic effects of a conventional cytotoxic agent.*** *The mechanisms of action of the antitumor effect and toxicity are the same, and the dose-effect curves are parallel. Therefore, the intensity of the dose-effect curve for the toxic effect is predictive of the therapeutic effect. (B) Hypothetical dose-effect curves for the therapeutic and toxic effects of a selective molecularly targeted drug. The mechanisms of action of the therapeutic and toxic effects are different (the toxicity arises from an interaction with a different receptor), and the intensity of the toxicity is not predictive of the therapeutic effect. Escalating the dose until dose-limiting toxicity is observed does not result in a substantial increase in therapeutic effect because the maximal effect was achieved with a nontoxic dose.*

effect relationship is likely to be a biological rather than a toxicity end point for many new agents, depending upon whether the biological end point is achieved at a nontoxic dose [10]. Most molecularly targeted drugs are expected to be more selective and less toxic than conventional cytotoxic drugs, and as a result, the maximum therapeutic effect may be achieved at doses that are well below the MTD. In addition, the toxic effects of these new agents may be produced through different mechanisms of action than the therapeutic effect, in which case, the toxic effects may not parallel the therapeutic effect (Fig. 1B), and therefore, may not be predictive of the therapeutic effect. For example, imatinib's therapeutic effect results from the inhibition of BCR-ABL tyrosine kinase activity (50% inhibitory concentration [$IC_{50}$] 0.025 $\mu$M). However, it also inhibits other receptor tyrosine kinases, such as platelet-derived growth factor ($IC_{50}$, 0.1 $\mu$M) and KIT ($IC_{50}$, 0.1 $\mu$M) [11]. If inhibition of the other receptors was responsible for one or more of the toxicities of imatinib, then the dose-response relationship for the toxic effect may not parallel the dose-response relationship for BCR-ABL inhibition because of the differing affinities of the receptors for the drug.

Ideally, phase I trials for new target-based drugs should be designed to determine whether the target can be inhibited in vivo at a tolerable dose and schedule and to estimate the dose or drug concentration required to achieve and maintain maximum inhibition of the target (define the dose-effect relationship) in vivo [12]. Drug effect on the target can be measured in tumor biopsy specimens obtained prior to and after the initiation of therapy in an easily obtainable surrogate tissue, such as peripheral blood mononuclear cells (PBMCs), or using functional imaging that quantifies the level of target function in vivo, when available. For example, dynamic enhanced magnetic resonance imaging and positron emission tomography (PET) have been used to assess changes in tumor blood flow after administration of antiangiogenic agents. Using PBMCs or functional imaging may provide an initial estimate of drug effect on the target; however, these surrogate measures must be validated and correlated with the effect of the drug on the target in the tumor prior to using them as primary end points in clinical trials [13]. Alternatively, if the drug concentration required to maximally inhibit the target can be accurately determined from preclinical studies, then the primary end point of the phase I trial could be determination of the dose required to achieve this therapeutic concentration in a defined fraction of the patients.

$O^6$-benzylguanine ($O^6$BG) is an irreversible inhibitor of $O^6$-alkylguanine-DNA-alkyltransferase (AGT), which is the DNA repair protein that can confer resistance to nitrosoureas and temozolomide. The primary end point of the dose-finding study for this modulating agent was inhibition of AGT in brain tumors [14]. Patients who were scheduled for surgery to remove a brain tumor had a single dose of $O^6$BG ranging from 40 to 100 mg/m$^2$ prior to surgery, and AGT levels were measured in tumor specimens removed at surgery. The optimal biological dose was defined as the dose achieving AGT levels <10 fmol/mg protein in at least 11 of 13 patients treated at that dose level. As shown in Figure 2, all 11 patients at the 100 mg/m$^2$ dose level had tumor AGT levels <10 fmol/mg protein. There was no toxicity from this dose. In a similar phase I study in adults with solid tumors [15], AGT levels in tumors and

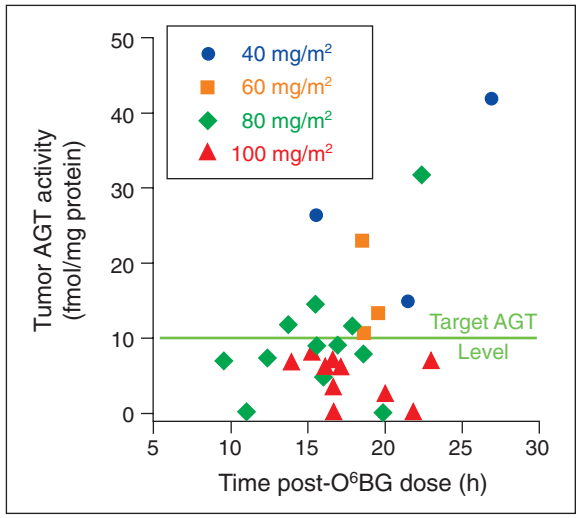


***Figure 2. $O^6$-alkylguanine-DNA-alkyltransferase levels in brain tumor surgical specimens from patients treated with escalating doses of $O^6$-benzylguanine ($O^6$BG) prior to surgery.*** *All 11 patients treated at the 100 mg/m² dose level had undetectable levels of the target enzyme in tumor specimens, and this dose of $O^6$BG was nontoxic. Data for this graph are from* Friedman et al. *[14].*

PBMCs were measured in patients receiving 10-120 mg/m² of $O^6$BG in combination with BCNU (carmustine). At baseline, AGT activity was detected in all tumor biopsies, and 18 hours after $O^6$BG administration, a greater than 87% depletion of AGT was observed at all dose levels. However, complete depletion of AGT activity was not observed until the 120 mg/m² dose level. AGT activity in PBMCs was not predictive of the depletion of AGT activity in tumor tissue.

The number of patients required to establish the optimal biological dose based on a therapeutic or pharmacokinetic end point and the dose escalation scheme used to reach the optimal biological dose must be individually assessed based in part on the sensitivity and variability of the assays used to measures these end points. The dose escalation may be guided by the results of biological or pharmacokinetic studies from the previous dose levels. Trials with primary laboratory end points such as these require real-time performance of assays that represent the primary end point, rather than batching samples and running them at the end of the trial. The assays used to measure the primary end point and the sample collection and processing procedures must be carefully validated prior to the initiation of the phase I trial. Trial designs with primary laboratory end points obviously require close coordination among the clinicians who are conducting the trial and the laboratory investigators who are measuring the primary end point.

Sequential tumor biopsies for pharmacodynamic evaluation of molecularly targeted therapies present significant challenges to the patient, clinician, and laboratory investigator. In seven clinical trials conducted at University Hospitals of Cleveland and Case Western Reserve University from 1989 through 2001 in which a biochemical or biological end point in human tumor tissue was planned, 81% of patients (87/107) had successful, paired biopsies with adequate tumor for analysis [16]. In a phase I study of the farnesyl transferase inhibitor BMS-214662 in patients with advanced solid tumors, farnesyl transferase activity was measured in tumor tissue, normal tissue, and PBMCs prior to and at multiple time points after BMS-214662 administration. The degree of farnesyl transferase inhibition in tumor tissue, normal tissue, and PBMCs related to BMS-214662 dose. Correlation of farnesyl transferase inhibition, pharmacokinetic parameters, and response is currently being investigated [17].

Measuring the effect of a molecularly targeted drug on its putative target in tumor tissue as the primary end point of a phase I clinical trial necessitates that the trial be restricted to patients whose tumors express the target. This may limit the potentially eligible patient population to those with a specific tumor type or even a subpopulation of patients within a specific histologic tumor type. This is also the population most likely to benefit from the new agent, and as a result, significant information about the clinical activity of the new agent may also be gleaned from the phase I trial, as was the case with the phase I trial of imatinib in patients with Philadelphia-chromosome-positive CML [7]. However, targeted agents, such as the farnesyl transferase inhibitors, which were originally developed to target signaling by the mutant *ras* gene product by interrupting the posttranscriptional modification of the RAS protein, may also have a broader spectrum of activity in in vitro and in vivo models or in the clinic than was anticipated from the target-based studies of their mechanisms of action [18, 19]. The complexity of the mechanism of action of farnesyl transferase inhibitors has been studied in p53 wild-type and p53 mutant human tumor cell lines after exposure to the farnesyl transferase inhibitor L-744,832. Both p53 and RAS status had an impact on growth inhibition and cell cycle arrest [20]. However, in studies using another farnesyl transferase inhibitor, the in vitro antitumor activity did not correlate with *ras* status [21].

The ability of a targeted drug to interact with and activate or block its target could be incorporated into early clinical trials, if targeted agents were administered to patients in a "window of opportunity." For example, a drug could be administered to patients after initial tumor biopsy and prior to definitive surgery, as was done with $O^6$BG. This strategy permits comparison of in vivo target inhibition of the tumor pre- and post-therapy but is only feasible if there is no detrimental effect on the patient from delaying definitive surgery to study an investigational agent [22].

Phase I trial design for molecularly targeted drugs could also incorporate both traditional toxicity end points and novel methods to measure target inhibition, as illustrated by the development of the proteasome inhibitor, PS-341. Proteasomes, which are cellular organelles that degrade intracellular proteins, regulate the activity of proteins involved in signal transduction, cell cycle regulation, and metastasis. PS-341 binds the active site on the proteasome leading to reversible inhibition of this degradative pathway. A sensitive, specific, and reproducible assay measuring proteasome proteolytic activity in whole blood or PBMCs has been developed for use in phase I clinical trials to measure the percent proteasome inhibition by PS-341 [23]. Using this assay, a dose-dependent reversible inhibition of proteasome activity can be demonstrated in patients' blood or PBMCs (Fig. 3) [24-26]. The recommended phase II dose, which was determined in part by the intensity of proteosome inhibition, was 1.3 mg/m$^2$, and proteasome inhibition at this dose was 65% [25, 26]. Preliminary data indicated that proteasome inhibition in tumor and blood samples was similar, and animal models had predicted dose-limiting gastrointestinal toxicity at ≥80% proteasome inhibition [25].

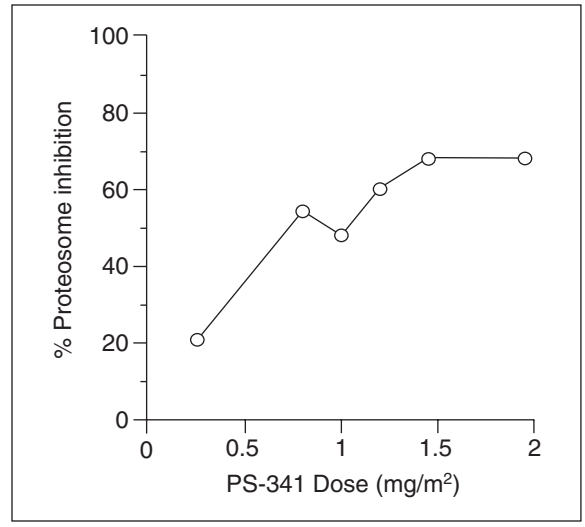


***Figure 3. Dose-effect curve for the proteasome inhibitor PS-341.*** *The drug effect end point is percent inhibition of proteasome proteolytic activity in PBMCs. The maximal effect (65% inhibition) is achieved at a dose of 1.3 mg/m$^2$ (the recommended phase II dose). Data for this graph are from* Aghahanian et al. *[26].*

For drugs administered on a daily chronic administration schedule, which may be the preferred schedule for many molecularly targeted drugs, the definition of "tolerable" toxicity will likely have to be adjusted from the standard definitions of dose-limiting toxicity used with cytotoxic agents that are administered in a pulse-cyclical fashion. A toxicity, such as nausea and vomiting, which is tolerable or manageable over 2 to 3 days of a 21-day cycle, would be unacceptable to most patients if it persisted indefinitely. For many toxicities, a grade 2 level of intensity may be dose limiting on a chronic basis. Clinical trials of orally administered drugs must also monitor adherence [27], which has not been an issue for parenterally administered cytotoxic drugs.

Pharmacokinetic studies are likely to assume an increasingly important role in the initial dose-finding trials with molecularly targeted agents. In addition to providing descriptive information about the disposition of the drug or serving as the primary trial end point as described above, the availability of quantitative data regarding the therapeutic effect of the drug on its target will allow for detailed analyses of pharmacokinetic-pharmacodynamic relationships and the definition of a therapeutic level, which would be useful for therapeutic drug monitoring. Additionally, pharmacokinetic studies allow the investigator to determine the duration of time that inhibitory concentrations are maintained on a given schedule of drug administration.

## Phase II (Activity) Trials

The primary objective of phase II trials is to define the spectrum of antitumor activity for a new agent administered at the optimal dose and schedule from phase I trials. These trials are restricted to patients with specific histologic types of cancer, which are selected based on activity of the drug in preclinical cancer models, the mechanism of action of the drug, and activity observed in phase I trials. For conventional cytotoxic drugs, the end point in a phase II trial is response, which is measured as the percent decrease in size of tumor nodules compared with the pretreatment tumor size. Therefore, patients enrolled in conventional phase II trials must have measurable tumors (advanced disease) that are refractory to standard therapy.

Until recently, individual tumor nodules were measured in two dimensions (the longest diameter and then the longest diameter perpendicular to the initial measurement), and the products of these two measurements for each measurable tumor were then summed. An objective response was defined as a ≥50% reduction in the sum of the products of the two longest perpendicular diameters. More recently, the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines were established and validated in an attempt to simplify and standardize the evaluation of response to treatment in solid tumors in clinical trials. With RECIST, the sum of the longest single diameter of measurable lesions is used to estimate overall tumor burden [28]. An object response in RECIST is a ≥30% decrease in the sum of the longest diameters from all target measurable lesions.

A number of phase II clinical trial designs have emerged, but most attempt to determine whether a new drug has a sufficient level of antitumor activity to warrant testing in a

randomized trial to evaluate efficacy. Traditional phase II trials are uncontrolled and attempt to minimize the number of patients enrolled if the drug turns out to be inactive by incorporating an early stopping rule. For example, using the optimum two-stage design [29] and assuming type I and II error probabilities of 0.10, if a response rate of 25% would justify further clinical development of a new drug, then nine patients with the specified type of cancer would be entered during the first stage of accrual. If no response was observed in the first nine patients, then the trial would be terminated. If one or more patients experience a response, then accrual would continue up to a total of 24 patients, and two or more responses in the 24 patients would be consistent with a response rate ≥25%. Trials with this two-stage design may require suspension of accrual after accrual to the first stage is complete until response data have been collected. Fortunately, response can be evaluated over a relatively short time (weeks to months).

Randomized phase II trial designs have also been proposed in order to reduce bias in treatment assignment, but the limited sample size of phase II trials does not provide sufficient statistical power to make formal treatment comparisons.

Cytostatic molecularly targeted agents may prevent further tumor growth without appreciably shrinking existing tumors, and as a result, response may not be an appropriate end point for assessing the activity of these agents. Possible end points for phase II trials with target-based agents might include changes in tumor markers, measures of target inhibition, PET scanning, time to tumor progression, or proportion of patients with evidence of tumor progression at a defined time point after the start of therapy. None of these end points have been well validated [30]. Serum, plasma, and urine angiogenic peptide (VEGF, basic fibroblast growth factor) concentrations have been monitored in patients who were treated with antiangiogenic agents, but substantial intrapatient variability has made interpretation difficult in some clinical trials [31, 32]. Measurement of target inhibition in tumor tissue is often limited by access to sequential tumor biopsies, and measurement of target inhibition in surrogate tissues, such as PBMCs, may not correlate with the effect of the drug on the target within tumors [15, 33]. Incorporation of functional imaging in early clinical trials is gaining acceptance as a means to assess activity or response. In patients with GIST treated with imatinib, early response assessed by $^{18}$fluorodeoxy-glucose PET correlated with clinical improvement and predicted objective response by computerized tomography scan [8]. Other functional imaging modalities, including doppler ultrasound and dynamic infrared imaging of vascular perfusion patterns, have been shown to detect changes in GIST tumors after imatinib therapy [34].

Time to tumor progression (a 25% increase in the sum of the products of the longest perpendicular diameters or a 20% increase in the sum of the longest diameters compared with pretreatment measurements) may be a more appropriate clinical end point for targeted agents. However, time to progression will depend on the frequency of scans or other end-point measurements used to assess tumor size. In addition, an historical control population for comparison may be lacking and, therefore, randomized phase II studies may be required to determine whether an agent prolongs the time to progression.

If the primary trial end point is time to progression, phase II trial design will need to be adapted. Response is measured as a change in tumor size from pretreatment measurements, so in essence, the patient serves as his or her own control. Defining activity of a new drug based on the time to progression requires an historical or concurrent control group in order to demonstrate that the new agent prolongs the time to progression. Additionally, the standard two-stage design with an early stopping rule may not be feasible, because it takes considerably longer to measure a time to progression end point than a response, and the trial may have to be suspended for a prolonged time after accrual to the first stage to determine whether accrual to the second stage is warranted. If the new molecularly targeted agent is well tolerated, consideration could be given to studying time to progression in the adjuvant setting rather than limiting the trial to patients with advanced measurable disease.

Novel trial designs, such as the randomized discontinuation design, have been proposed for cytostatic agents that are unlikely to produce objective responses with single-agent therapy. In the randomized discontinuation design, all enrolled patients receive drug for an initial 2-4 month period. Patients with progressive disease, toxicity, or nonadherence during this initial period are removed from the study. The remaining patients are randomized to continue treatment or discontinue treatment in a double-blind placebo-controlled portion of the study. The end point is the fraction of patients in each group who maintain stable disease during the randomization period [35]. The advantages of the randomized discontinuation design are that it may overcome the slow accrual often seen in trials that randomize patients to placebo or treatment upfront, eligibility criteria can be relatively nonrestrictive, and enrichment of the randomized population may increase the efficiency of the trial. Disadvantages of this trial design include the inability to conclude on the magnitude of antitumor activity, questions about carry-over effect, and development of resistance in the initial treatment period [36]. This design is being used in a Cancer and Leukemia Group B study of the antiangiogenic agent, carboxyamidotriazole (CAI), in metastatic renal cell carcinoma. Initially, all patients receive oral CAI daily for 4 weeks for four courses. Patients who achieve a partial or complete response after four courses continue CAI until their disease progresses or they experience unacceptable toxicity. For patients with stable disease after the initial four courses, therapy is then

blinded and randomized to continue CAI or receive placebo. When the patient's disease progresses, therapy is unblinded, and if the patient was receiving placebo, they will be offered CAI. Up to 335 patients will be required to complete this study and achieve the objectives to determine the toxicity and disease-stabilizing effect of CAI and to determine the objective response rate of CAI in renal cell carcinoma.

The difficulty in determining appropriate end points and designs for phase II trials does not imply that target-based therapy should bypass phase II studies. The resources required to conduct a phase III trial, including patients, time, and cost, demand that we develop only those agents that have a reasonable expectation of improving outcomes for oncology patients. We should not abandon phase II studies but invest the resources necessary to validate end points for phase II trials. Some matrix metalloproteinases moved from phase I trials directly to phase III trials. This did not speed the development of these agents; however, it left many unanswered questions about a class of promising agents [37].

### Phase III (Efficacy) Trials

Phase III trials are designed to determine efficacy or clinical benefit. They are typically large cooperative group trials that randomize patients to new regimens versus standard therapy. Patients and medical staff may be blinded to the treatment arm to reduce bias. The end points are time to progression or survival. With target-based therapy alone or in combination with cytotoxic agents, traditional phase III trial designs should remain relatively unchanged. The eligibility criteria should include only patients that demonstrate the target, and end points could be expanded to include quality-of-life measures [38].

### Conclusions

The results of molecular biological studies of cancer are changing the way we diagnose and treat cancer. Tremendous strides continue to be made in understanding the pathways and networks that control cell signaling, proliferation, metastasis, and cell death. We are developing agents and treating patients with drugs that act at individual points in these networks. As our understanding of these pathways and the complexity of their interaction develops, we must learn how and when to use agents to target specific steps in malignant transformation and proliferation, and we must adapt clinical trial designs to test the clinical utility of this promising new class of anticancer drugs.

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