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Phase II Studies of Modern Drugs Directed Against New Targets: If You Are Fazed, Too, Then Resist RECIST

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There is no question that the treatment of cancer 10 years from now will be very different from that employed 10 years ago. Are we at the beginning of a series of rapid breakthroughs, or are we making slow progress? Only time will tell. We have many new "druggable" targets, and maybe the results really will be different from the past, with major advances in the treatment of traditionally refractory malignancies.

Let us first briefly recapitulate the history of anticancer agents, to understand that the more things change, the more they stay the same. The pharmacologic management of cancer can be traced back to the Manhattan Project (1945), with a number of laboratories developing alkylating agents.[1,2] These were clearly targeted agents, directed toward alkylating DNA, albeit in a diffuse manner.

The next drugs were the antimetabolites, including the antifols, such as methotrexate,[3] and the purine and pyrimidine analogs, such as 6-mercaptopurine and fluorouracil.[4,5] Again, these drugs were clearly targeted against specific pathways and even specific enzymes, such as dihydrofolate reductase for methotrexate. Even then, we implicitly understood the concept of biomarkers, and myelosuppression was considered to be pharmacodynamic evidence of effects on the target—DNA.

Now, approximately a half century (and hundreds of drugs) later, we are engrossed in a new era of oncology therapeutics, that many call "targeted therapies." To paraphrase one perennially asked question, why are these drugs different from all other drugs? They are meant to be different because we believe that we can preferentially target the tumor rather than normal tissue. This belief is partially supportable, as particularly exemplified by the fantastic results achieved in chronic myelogenous leukemia with imatinib.[6] The drugs are different because we have identi-

fied new signaling pathways and tumor biology, which we must learn and understand. They are different because we can't remember or spell the generic names. They are not different, however, in that we have always had targets, and we have generally known that we have hit a target (which may be different from the intended target). As one example, estramustine was developed as an estrogen-receptor targeted–alkylating agent. However, it was subsequently demonstrated to be an antimitotic agent with activity in prostate cancer independent of the estrogen receptor.[7] Furthermore, we have demonstrated that targeted agents, both old and new, can exhibit mechanism-based effects on normal tissue (myelosuppression, skin rash, diarrhea) that may or may not be associated with a beneficial effect on the patient.

With a plethora of new targets, we also have a plethora of new drugs and sponsors, some of whom only have one drug to develop. There is immense competition among companies for patient resources, particularly in the United States and Europe, though many investigators in Asia and South America are equally inundated with requests for trials. Thus, many sponsors and investigators have attempted to minimize the number of patients treated in early clinical trials because of concerns relating to imbalances in patient resources, and financial incentives to move quickly toward phase III trials.

Phase I trials have become smaller, in large part because of the recognition that newer targeted agents are less toxic, and are therefore less likely to result in serious toxic effects. This has led to the widespread adaptation of a variety of accelerated titration designs, which have in common, aggressive dose escalations and small patient cohorts, in the absence of toxicity.[8] Such designs are very efficient for defining the maximum-tolerated dose, but are less useful for obtaining a full understanding of a new agent's clinical pharmacology. In

particular, smaller phase I studies do not often permit an analysis of pharmacokinetic-pharmacodynamic relationships, or the effects of doses well below the maximum-tolerated dose, which may have a better therapeutic index than higher doses.

In our opinion, one of the biggest challenges in modern oncology drug development is phase II testing, which should be the primary indicator of antitumor efficacy. In the past, it was easy to prioritize agents for phase III trials based on their ability to induce objective tumor regression. However, a drug may be active without consistent achievement of high-level tumor regression, as illustrated by the development of gefitinib, bevacizumab, and cetuximab— all agents that have definitive, but minimal, single-agent effects using traditional Response Evaluation Criteria in Solid Tumors (RECIST) criteria. This level of activity is considered more acceptable with agents that exhibit a relatively mild toxicity profile, and are administered over prolonged periods. But what is the optimal phase II design for such agents? Can we really establish the activity of these agents with trial designs developed principally to detect a substantial rate of tumor regression?

One approach that many companies have taken to avoid this problem is to rapidly proceed into phase III trials. Unfortunately, most that have utilized this approach have been disappointed, resulting in high profile failures, including matrix metalloproteinase inhibitors, farnesyl transferase inhibitors, tyrosine kinase inhibitors, and antisense oligonucleotides. Interestingly, phase III trials in other therapeutic areas fail infrequently and are intended to confirm phase II findings rather than to refute activity altogether. These areas also routinely use randomized phase II trials, often evaluating a range of doses, including a placebo.[9] Such trials can be designed to test readily ascertainable end points, such as time to progression, and can utilize crossover or randomized discontinuation designs to enhance the attractiveness of the trial to patients and physicians. Randomized phase II studies can also address questions other than activity, such as biomarkers and pharmacokinetic-pharmacodynamic relationships.

Will we find another imatinib anytime soon, or will we have to settle for drugs that have a more subtle effect, but are clearly active, such as the epidermal growth factor tyrosine kinase inhibitors (gefitinib and erlotinib) or the multiple new agents targeting the vascular endothelial growth factor pathway (eg, bevacizumab, SU11248, PTK787, sorafenib)? The key point is to understand the pharmacology of the agent and the expected effect of treatment so that the trial can be designed to detect that effect. If the anticipated outcome is significant tumor regression, then our standard phase II designs are fine, though randomization across dose levels may be desirable, as was utilized for gefitinib and bevacizumab.[10-12]

Overall, we need to be more flexible in our end points and our definitions of antitumor activity, as long as the effect is distinguishable from no treatment or a placebo. This is really an issue to be addressed in phase II, as a mechanism to avoid failures in phase III. The RECIST criteria for response (and its predecessors) were designed primarily for cytotoxic agents and are not applicable to all new agents.[13] For example, these criteria do not consider durable modest regressions or prolonged disease stability as activity, which we now know is an effect of several agents such as gefitinib, erlotinib, and bevacizumab. On the other hand, we should not rush to falsely define drugs as active on the basis of stable disease, since stable disease is a composite outcome consisting of inherent tumor growth kinetics and potential drug effect.

This was the rationale for the randomized discontinuation trial design, which sought to differentiate drug effects from intrinsic growth patterns in patients with stable disease, which has now been utilized for two new agents in patients with metastatic renal cell cancer.[14,15] Another important study was the randomized placebo-controlled dose-ranging study of bevacizumab in metastatic renal cell cancer, with cross-over at progression.[12] The latter trial resulted in a very low response rate by RECIST criteria, but clearly demonstrated the potential activity of bevacizumab in this disease. The key point is that all of the above trials are much larger than the traditional single-arm phase II oncology trial, as larger sample sizes are necessary to obtain a more robust answer on which decisions about phase III trials may be based. Lastly, as has been recently illustrated by the discovery of the association of somatic mutations in epidermal growth factor receptor (EGFR) with response to gefitinib, a clearer understanding of the target of agents may eventually lead to better patient selection and the ability to enhance clinical benefit, even when using traditional measures.[16,17]

So, how do we manage this dilemma? As noted above, the clinical trial system is already stretched to its limit, particularly in the United States and Europe. If we are going to perform larger phase II trials, one approach is to do fewer of them, as illustrated by the study of CI-1040 by Rinehart et al[18] in this issue.

This study is novel because it does not follow the entrenched dogma of phase II oncology trials of one protocol per disease site. This seems appropriate given the broad relevance of the MEK pathway to aberrant signaling in many cancers. The investigators could also have considered a waiver of restrictions on prior therapy, given that the investigational drug bears little resemblance to any marketed agent, with the exception of gefitinib.

Although this study included patients with carcinomas of four different organ sites, each was analyzed separately. Is organ site the most important determinant of response, or might it be a particular molecular lesion, such as EGFR-activating mutations? In trying to identify an active drug, is it most efficient to have broad or

narrow eligibility criteria? The answer clearly depends on the hypothesized effect, leading to the specific design of the trial. But, if the hypothesized effect is a partial response, one could argue that the net should be tossed far and wide to demonstrate proof of activity.

In the study by Rinehart et al,[18] the hypothesized effect was either a partial response, or stable disease of at least 3 months duration. No partial responses were observed, but stable disease was observed in eight patients. However, it is not possible to ascertain from this uncontrolled trial whether the stable disease was the result of a drug effect or was due to the inherent growth characteristics of the disease.

A significant concern regarding this study is the authors' use of a modified Simon design, incorporating stable disease as a measurement of activity, when stable disease in a patient does not imply that the drug has activity.[19] Specifically, the drug would be considered of no interest if there were five objective responses in 43 patients with a particular "disease," even though that frequency of objective responses would suggest that this agent was as active as other recently approved EGFR- and vascular endothelial growth factor–targeted agents, and worthy of phase III study. Conversely, would we really believe the drug is active if there were 13 of 43 patients with stable disease, but no objective responses? We also would challenge the authors' analysis relating pERK expression to stable disease. If we don't know whether stable disease represents drug effect, why perform such a correlation? Clearly, the clinical benchmarking of gefitinib, cetuximab, and bevacizumab has indicated that, at some level, tumor regression continues to be a predictor of successful clinical development. As newer agents come along that may be of interest without anticipation of disease regression, we will certainly require well-controlled randomized phase II studies to minimize failure in phase III.

What can we conclude? The authors have certainly demonstrated that multidisease phase II trials are feasible and efficient. They have also demonstrated that CI-1040 has an objective response rate of less than 5%, whereas any conclusions regarding whether or not the drug induces stable disease are suspect, due to the diverse diseases represented in the eight patients and the lack of a control group. We also cannot draw any conclusions regarding pERK as a predictive marker for this or other MEK-targeted drugs, though this should be investigated in larger studies, but only when there is clear evidence of activity.

What is the future of this agent? The authors imply that its development is being discontinued in favor of a more potent second-generation compound with the potential advantage of a decreased likelihood of mechanism-independent toxicities and drug interactions. It may also exhibit more favorable pharmacodynamics such as a longer duration of target inhibition.

Thus, we would like to provide some advice to the sponsor, as well as to other sponsors and investigators who might read this editorial. First of all, carefully define your expectations for your compound. Do you expect objective responses (by RECIST criteria), minor responses, disease stabilization, or combinations of these? Then use a design appropriate to detect the expected effect in early clinical trials. This may mean that randomized phase II studies are required, which may provide substantive evidence of activity, as well as information regarding optimal dose and schedule. Incorporation of readily obtainable biomarkers may also be useful. Most importantly, a well-conducted phase II trial should minimize the risk of failure in phase III. Incorporating expensive studies of predictive markers will probably not enhance your likelihood of detecting activity unless you are lucky enough to have both an active agent and an accurate assessment of the population most likely to respond. Alternatively, these studies can be deferred until after demonstration of activity, as was done for gefitinib.

Reducing the risk of phase III oncology trials needs to be a goal of all concerned parties. In theory, a reduced risk in phase III should eventually lead to a greater incentive to develop oncology drugs, as well as a reduction in costs. In particular, sponsors with drugs in phase III trials without substantive proof of activity should be openly criticized, as they are ultimately increasing the long-term societal costs of oncology drugs.

Authors' Disclosures of Potential Conflicts of Interest

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