

The Next Phase of Chemoprevention Research

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Abstract

Phase 0 clinical trials are meant to explore mechanism of action, pharmacokinetics, pharmacodynamics, or biodistribution of investigational compounds in an efficient manner with relatively few subjects. Phase 0 designs have been applied sparingly in cancer research, but this issue of the journal provides an example of their utility reported by Reid and colleagues (beginning on page 347). Indeed, aspects of the phase 0 design lend themselves well to chemoprevention research, suggesting that this approach will become more common in the near future. *Cancer Prev Res*; 4(3); 293–5. ©2011 AACR.

The great majority of chemoprevention studies are conducted through cancer centers or medical oncology departments, where they borrow many of the paradigms traditionally employed in developing cancer therapeutics. Yet, when one considers the population to be treated with these agents, it is apparent that alternative drug development strategies are both necessary and feasible. Chemoprevention, by design, is meant for people who may be at risk for but do not have a diagnosis of current cancer, and, at least thus far, chemopreventive agents require long-term administration because their effects appear to wane after discontinuation. Patient adherence to the prescribed regimen is critical to achieve the goals of chemoprevention and may be influenced by the schedule, route, interactions, tolerability, and cost of the agent(s) used. Ideally, a chemopreventive drug would be taken orally and no more than twice daily, without interactions with food and other drugs, with few side effects, and inexpensive to the patient. Optimizing these factors is the cornerstone of drug development in many areas of medical therapeutics, where patients are asked to self-administer drugs for asymptomatic conditions, often to avert serious illness, for years or the remainder of their lives. Atorvastatin became the best-selling drug in the world partly because it was maximized for these qualities. Therefore, before embarking on developing a drug for chemoprevention, it makes sense to optimize the drug's formulation toward producing an agent that meets these criteria.

In this issue of the journal, Reid and colleagues report work in developing the AKT inhibitor SR13668 as a chemopreventive agent with a twist—the novel approach of a

"phase 0" trial (1). Faced with an agent with limited solubility and poor bioavailability, the investigators sought to develop a formulation that would be pharmacologically suitable and would optimize oral bioavailability; the phase 0 trial included a preliminary assessment of the effects of food intake on SR13668 pharmacokinetics.

The exploratory investigational new drug (IND) phase 0 trial grew out of U.S. Food and Drug Administration (FDA) efforts to decrease the overall duration and improve the efficiency of drug development by facilitating the movement of new agents from the lab to the clinic (2). The primary goal of such trials is to determine the pharmacokinetics and pharmacodynamics of a new agent in assessing its suitability for further development. Because subpharmacologic, and thus likely nontoxic, drug doses are administered, initial clinical testing can begin with less-extensive preclinical data. Such an approach may be particularly advantageous for compounds that have a complex or expensive synthesis, are in short supply, or are developed by sponsors with limited resources, such as academic investigators. As the FDA recommended (nonbindingly) in 2006 (2):

The common theme throughout this guidance is that, depending on the study, the preclinical testing programs for exploratory IND studies can be less extensive than for traditional IND studies. This is because for the approaches discussed in this guidance, which involve administering sub-pharmacologic doses of a candidate product or products, the potential risks to human subjects are less than for a traditional phase 1 study.

Thus, the phase 0 trial, which theoretically precedes traditional phase 1 studies, has been advocated as a means to assess the pharmacodynamic effects of a compound on targets of interest, help define mechanism of action, provide biodistribution characteristics through noninvasive imaging, or, as in the case of Reid and colleagues., determine important pharmacologic information that is necessary for continued drug development. Unlike traditional phase I studies, phase 0 trials are designed with limited or subtherapeutic dosing to minimize risk to participants. Because the endpoints are specifically designed not to

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doi: 10.1158/1940-6207.CAPR-11-0012

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address efficacy or toxicity, statistical designs and assumptions can be liberalized and call for fewer patients—an average of approximately 10–12 in a phase 0 study compared with 20–25 in a phase 1 trial (and with 40–80 in a phase 2 and 200 to greater than 2,000 in a phase 3 trial; Fig. 1).

SR13668 was chosen for clinical development because it was the most stable and active condensation product of the naturally occurring Akt inhibitor indole-3-carbinol (3). Akt itself and the phosphoinositol-3-kinase/Akt/mammalian target of rapamycin pathway, in general, have been provocative targets for chemoprevention because many of the proteins in this pathway have either been associated with genetic cancer syndromes or are activated early in carcinogenesis (4–6). The oral bioavailability of SR13668 was clearly low in animal studies, and the optimal oral formulation for human bioavailability has been completely unknown. It would be senseless and potentially futile to move forward with clinical development of SR13668 without determining the formulation to maximize its bioavailability. This was the right setting for a phase 0 trial; researchers would be able to eliminate the formulations that were not producing desired pharmacokinetic profiles and avoid studying these in later stage trials.

The phase 0 trial has advantages that, when properly applied, can enhance drug development. As mentioned earlier, and shown successfully by Reid and colleagues, (1), these studies can be completed in less time with fewer subjects than those of a phase 1 trial. Moreover, the results of phase 0 testing are meant to inform phase 1 and later trials as, for example, Kummar and colleagues have reported (7). These investigators designed a phase 0 study to assess increasing doses of the PARP inhibitor ABT-888 for pharmacodynamic effects in tumor tissue and peripheral blood monocytes of patients with advanced malignancies. They found that both 20 and 50 mg of ABT-888 produced the desired target inhibition, giving them a reasonable starting dose for phase 1 studies after a phase 0 study requiring only 14 subjects and 5 months. Furthermore, the investigators were able to validate a biomarker of putative target inhibition while ascertaining minimal plasma concentrations associated with this effect.

In a clever design, Reid and colleagues undertook a two-stage approach to first discover whether a high-fat, high-calorie meal had an effect on the bioavailability of one of

the lead formulations of SR13668 and then to determine which of 5 different formulations maximized bioavailability in healthy volunteers, who received a one-time 38-mg dose of SR13668. Calculating area under the curve (AUC) of plasma concentration time, the investigators concluded that the bioavailability of SR13668 was significantly improved when the agent was given with food than without food and that the formulation Solutol HS15 displayed the greatest AUC of the 5 that were tested. Moreover, the study required only 5 months and 18 subjects to complete, supporting the hypothesized efficiency of the phase 0 design.

In contrast to other early-phase cancer trialists, Reid and colleagues enrolled healthy subjects rather than cancer patients, which proved to be advantageous in two ways. One of the major criticisms of the phase 0 design is the *de facto* administration of doses that are not meant to be therapeutic. This has posed both an ethical dilemma in exposing patients with life-threatening diseases to treatments that will not offer any chance of efficacy and a practical issue of finding participants willing to enroll. Indeed, the study by Kummar and colleagues has been criticized for just this ethical dilemma, and the investigators went to great lengths to ensure that subjects understood the purpose and risks of the study. By enrolling healthy volunteers, Reid and colleagues avoided the problem of a lack of therapeutic benefit. Phase 0 studies in this population might need to incentivize subjects with monetary or other compensation but would likely still find that enrolling healthy volunteers is less difficult than enrolling cancer patients seeking active treatment.

The second intrinsic advantage of the Reid and colleagues design is that a healthy patient population mimics the intended-use (chemoprevention) population more closely than a cancer patient population. As mentioned, patients who are candidates for chemoprevention often do not have an acute, serious illness or active cancer. Therefore, it makes even more sense to study healthy volunteers in phase 0 studies, as the eventual intent of a drug's development is disease prevention.

As the investigators point out, this study was not designed to assess toxicity, efficacy, or inhibition of putative targets that would be addressed in future trials. In the end, however, Reid and colleagues may have done more than demonstrate the efficiency of the phase 0 design; they

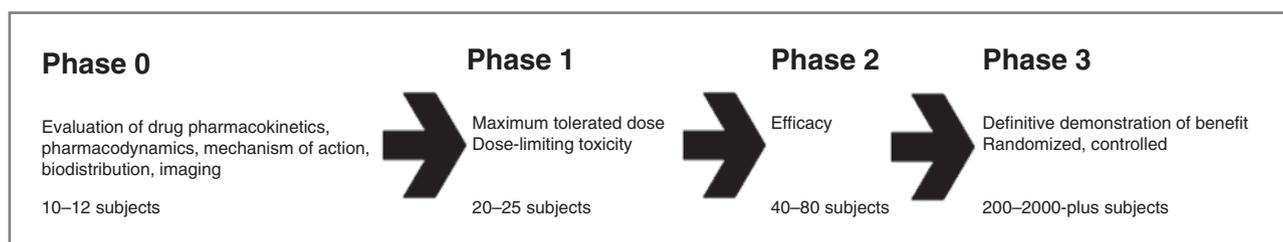


Figure 1. Phases of clinical cancer-prevention or cancer-therapy trials with the primary purpose and estimated usual number of subjects required to conduct them.

may have validated its utility. Insofar as SR13668 is being developed as a chemopreventive agent, this study shows that this is not a viable approach for this agent, at least not with the tested formulations. The requirement of 8 capsules per day to deliver a dose that is likely to be a fraction of the efficacious human dose will not be feasible for chemoprevention. A limitation of this study, however, is that it provides no information on whether the achieved drug concentrations have biological activity. The fact that the phase 0 dose was only 1 of 50 of the no-adverse-event-level dose in rats suggests that the phase 0 dose and achieved plasma concentrations are not biologically active. Inclusion of a biomarker of target inhibition measured in an easily accessible tissue, for example, peripheral blood mononuclear cells, would have been helpful in this study design. Therefore, although the study has defined which of the 5 formulations is optimal, it is likely that none is adequate for further development.

Methods to further increase the bioavailability of the drug through formulations that can concentrate the agent into fewer dosing units, increase absorption, or limit metabolism should be undertaken before its further study in chemoprevention. We utilized the last strategy to inhibit metabolism and thus increase plasma concentrations of rapamycin, which is another naturally occurring drug with poor bioavailability, in patients with advanced cancer. In two phase 1 studies, we found that coadministration of rapamycin with either ketoconazole or grapefruit juice, two profound CYP3A inhibitors, significantly and dramatically

increased blood levels of rapamycin, allowing once-weekly administration to achieve active concentrations (8, 9). Depending on the metabolism of SR13668 or related compounds, a similar strategy could be undertaken within a phase 0 design.

In oncology, less than 10% of the INDs filed for new molecular entities advance beyond the investigational stage. Although the phase 0 design may not change this statistic, it is advantageous to patients, investigators, and drug developers to discover early in the process, before investing a lot of blood, sweat, and tears, that a compound will land in the IND graveyard. Reid and colleagues have shown that the current formulation of SR13668 is not viable for chemoprevention, thus saving a great deal of time and resources that could have gone into its future development. In this case, the phase 0 design served the research community well, and if definitive conclusions to proceed or not to proceed with clinical development continue to be drawn from phase 0 trials, we should expect to see dramatic growth in the use of phase 0 designs for developing cancer-prevention and cancer-treatment drugs.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received December 16, 2010; revised December 24, 2010; accepted January 6, 2011; published online March 3, 2011.

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Cancer Prev Res 2011;4:293-295.

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