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Phase 0 Trials: Expediting the Development of Chemoprevention Agents

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Abstract

Phase 0 trials are first-in-human clinical trials performed under the Exploratory IND [investigational new drug] Guidance of the US Food and Drug Administration. Unlike traditional phase I trials, these studies have no therapeutic or diagnostic intent but instead aim to provide only pharmacokinetic and/or pharmacodynamic data to inform the next step in developing an agent. We discuss the role that such trials, including one reported by Reid et al. (beginning on page ***XXX*** in this issue of the journal), can play in expanding the number of drugs that are evaluated for chemoprevention while compressing the drug-development timeline.

Keywords

Phase 0; pharmacokinetics; pharmacodynamics; chemoprevention; oncology

Chemoprevention has been defined as “the prevention of cancer or treatment of identifiable precancers (intraepithelial neoplasia, IEN)” (1). The potential to intervene prior to the development of cancer is very attractive and confers obvious advantages to both patients and clinicians. Unfortunately, drug development for cancer prevention imposes distinct challenges beyond those associated with drug development for cancer therapy. The scale of chemoprevention trials is often much greater than that of standard treatment trials because of the large number of subjects and long duration of their participation necessary to obtain statistically useful results. For example, the Study of Tamoxifen and Raloxifene (STAR), a randomized, double-blind trial in postmenopausal women at a high risk for developing breast cancer, entered over 19,000 participants over five or more years (2,3). Enrolling healthy individuals, even though at a high risk for developing cancer, raises questions about the long-term safety of the intervention and compliance. Therefore, given the cost and logistics of successfully completing a chemoprevention trial, strategies for the early identification of promising compounds that will expedite getting them into definitive clinical trials could represent a significant advance.

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Potential cancer chemopreventive agents must have a high therapeutic index. This requirement enhances these drug's suitability for evaluation in trials conducted under the U.S. Food and Drug Administration (FDA) Exploratory IND [investigational new drug] Guidance, conceived as part of the FDA's “Critical Path” initiative (4). Phase 0 trials are first-in-human clinical studies performed under this guidance. Unlike traditional phase I trials, these studies have no therapeutic or diagnostic intent but instead aim to inform, to enhance the efficiency of, and to increase the chance of success of the subsequent development of the agent (5). Phase 0 objectives are to develop human pharmacodynamic (PD) and/or pharmacokinetic (PK) data (including biodistribution), information that may form the basis for rational drug development decisions (Fig. 1). Only drugs showing sufficient promise are to be evaluated for safety and tolerability in traditional phase I trials. For phase 0 trials, a single dose or a short course (typically fewer than seven days) of low, non-therapeutic, non-toxic doses is administered to a few patients, with tissue and/or blood sampling to evaluate target modulation and the PK profile of the agent. It is therefore essential that the drugs being considered for a phase 0 trial have a high therapeutic ratio in preclinical toxicity models *in vivo* so that the desired PK or PD effect may be observed without substantial toxicity.

The Exploratory IND Guidance includes examples of three types of phase 0 trials that allow, respectively, the determination of biodistribution (via imaging technologies), determination of pharmacokinetics and bioavailability, and evaluation of the mechanism(s) of drug action (Box 1). These trials provide an opportunity to examine a new agent in humans earlier than traditional dose-finding, toxicity-driven phase I trials (Fig. 2). The amount of preclinical toxicology needed to support a phase 0 trial is determined by the dose and schedule intended to be administered to humans. Therefore, because a limited number of sub-therapeutic doses (microdoses or non-microdoses) are administered in the phase 0 setting, the preclinical toxicology can also be limited, saving precious time and resources. Phase 0 trials permit identification of potential therapeutic failures earlier in the drug-development process, allowing resources to be reallocated and permitting expeditious evaluation of only the most-promising agents.

A lack of predictive (drug sensitivity/resistance) models has hampered drug development across the field of oncology, including chemoprevention. This lack has contributed to the high failure rate for agents in clinical drug development trials, with regulatory approval rates of only 5%–10% for cancer therapeutics (6). Overall, unfavorable PK, including low bioavailability, accounts for only approximately 10% of oncologic drug-development failures, with the vast majority of the remaining failures due to poor response or sensitivity to drugs with adequate PK. In the process of development, multiple analogs are routinely produced; and the lead compound is determined based on animal data that may not always predict how a molecule will behave in humans. Full-scale toxicology evaluations, manufacturing, and clinical development are often implemented only for the lead compound. Thus, potentially promising compounds may be overlooked because resource constraints limit the ability to evaluate back-up molecules if the lead compound is not initially successful in the clinic. The major advantage of phase 0 trials is their feasibility for assessing in a single trial up to five chemical entities or formulations (the maximum number allowed by the FDA) sharing a common biologic target. The specific aim of such studies is to identify the lead compound based on effects in an early human trial rather than in animal models (which may not predict clinical effects), thus helping to combat the lack of predictive models. Under the Exploratory IND Guidance, this identification is permissible within the purview of a single trial in a few patients, thus bypassing the need for full-scale toxicology and manufacturing for all the analogs being evaluated.

Applying the Exploratory IND Guidance in identifying the most bioavailable analog is highlighted by the report of Reid et al. in this issue of the journal (7). These investigators tested multiple formulations of SR 13668 (an indole-3-carbinol analog that inhibits the Akt pathway), assessing plasma exposures following oral administration of a single 38 mg dose, which is an easily measured, non-microdose, in 20 healthy volunteers. This first-in-human trial evaluated five different formulations, as well as the effect of food on one formulation, using the area under the plasma concentration-time curve (indicating systemic exposure) as the primary endpoint. In light of the small number of patients (three) in each treatment arm, the highest systemic exposure *per se*, rather than degree of statistical significance versus the control formulation, was prospectively defined as the major criterion for selecting a lead formulation for further development.

The study demonstrated that taking SR 13668 with food (the fed state) versus without food (the fasted state) led to optimal oral bioavailability (albeit requiring eight capsules to deliver the protocol drug dose of 38 mg); furthermore, a lead compound for future development as a chemopreventive agent was clearly identified. Of particular note, the entire study was completed in five months. Although no PD endpoints were examined in this trial, its rapid completion and definitive identification of an agent for further study provide support for applying the Exploratory IND in developing new agents for chemoprevention.

Unlike the approach taken by Reid and colleagues, which utilized a dose of SR13688 that approaches the range of doses that would be therapeutic, microdose studies administer $1/100^{th}$ of the pharmacologically active dose, or a maximum of 100 μg of study drug, and are allowed by both the U.S. FDA and European regulatory agency (European Medicines Agency). By definition, however, drug levels and PK parameters obtained in such studies must be determined using advanced analytic techniques that are not routinely available in academic medical centers. One of the controversies surrounding the non-pharmacologic microdosing approach to the assessment of PK is whether it is possible to extrapolate the PK data obtained from a microdose to the PK of pharmacologically active doses. This concern has been raised specifically (and especially) for agents with a non-linear PK profile. The literature suggests that a concordance between PK profiles following a microdose versus a therapeutic dose occurs for approximately 70%–80% of the drugs that have been evaluated in microdose studies (8–10).

Although microdosing is an option for the determination of PK under the FDA's Exploratory IND, the guidance also allows pharmacologically active doses (as used by Reid and colleagues) to be administered for assessing PD parameters, which are not assessed in microdose studies, in addition to PK parameters. The starting dose for these phase 0 studies is defined as $1/50^{th}$ of the “no observed adverse effect level” (NOAEL) dose in a rodent two-week toxicology study. Dose escalation in a phase 0 trial is also permitted to determine the dose range for target modulation and/or dose-plasma exposure relationships from PK studies using active drug concentrations. Therefore, real-time results of PK and PD analyses need to be available to allow decisions regarding dose and sampling during the conduct of the trial. This methodology requires close communication between the laboratory scientists and clinical investigators and the formation of a multidisciplinary drug-development infrastructure dedicated to the development and conduct of the preclinical and early clinical phases of the drug-development process.

In 2006, an American Association for Cancer Research Task Force highlighted the concept of prevention or regression of molecular IEN (determined by assessing molecular alterations in the histopathology of the IEN; ref. 1). Stimulated by the feasibility Reid et al. demonstrated for the use of pharmacologically active doses in a chemopreventive phase 0 trial, future studies could be directed toward demonstrating target modulation in IEN very

early in the development process, thus identifying promising agents at a molecular level while establishing potential endpoints for subsequent trials. The prerequisites for conducting a PD-driven phase 0 chemoprevention trial would be that *1)* chemopreventive effects are, in fact, based on the ability of the drug to modulate a specific target, *2)* the agent has a wide therapeutic index with target modulation occurring at non-toxic doses and relatively short exposures, and *3)* the PD effect is robust enough to be reliably measured in small numbers of patients.

Designing phase 0 trials to measure statistically significant target modulation following administration of low doses of a drug in very few patients is challenging (11–13). It requires that rigorously qualified, robust assays for determining the target drug effect be developed early in the drug development process (12); these assays must be capable of use with small tissue samples that contain limited numbers of cells of interest (e.g., premalignant cells), which are typical of chemoprevention. Optimal time points for obtaining tissue or blood samples and standard operating procedures for sample handling and processing that mirror clinical procedures all need to be developed prior to initiating the clinical trial. Questions such as “What defines a PD response in a given patient?” and “What will be considered a promising PD response rate for a dose level?” need to be prespecified and addressed up front in these trials. The tissue of interest also needs to be carefully defined since there is no assurance that effects of an agent in surrogate tissues such as easily accessed normal skin or peripheral blood lymphocytes will, for example, have any relationship to effects in a premalignant lesion at less-accessible sites.

The website Clinicaltrials.gov lists multiple ongoing chemoprevention trials of molecularly targeted agents given for relatively short periods of time (in the range of 3–6 months) to assess effects on premalignant lesions. These studies are being done with agents that have already been developed for other indications, including cancer therapy. Phase 0 trials offer the opportunity to evaluate potentially preventive agents, including molecularly targeted and other agents, much earlier in development, addressing questions related to the drug's effect on IEN and to its pharmacologic properties. Given their early stage and limited preclinical toxicology requirements, phase 0 trials could potentially expand the number of agents that are evaluated for chemoprevention while compressing the drug development timeline.

Box 1 Three types of phase 0 studies are supported by the US FDA Exploratory IND Studies Guidance

1. Pharmacokinetics (PK) or imaging: Evaluate human biodistribution and target-binding (to molecular target and target tissue) characteristics using sensitive imaging techniques and microdoses ($1/100^{th}$ of the pharmacologically active dose [up to a maximum of 100 μg] or 30 nmol for protein products). Preclinical toxicology studies should demonstrate that a dose 100 times the proposed human dose does not induce adverse effects.
2. Pharmacologically relevant doses: Evaluate human PK (e.g., bioavailability) of two or more analogues to select a lead agent. Preclinical toxicology studies must establish the no observed adverse effect level (NOAEL) in a rodent two-week toxicology study; the clinical starting dose is generally 1/50th of this dose (and is not a microdose).
3. Pharmacodynamic end-point studies: Evaluate whether the new molecular entity modulates its intended target. Supporting preclinical toxicology studies are generally short-term, modified-toxicity or safety studies in two species. Dosing levels for these studies are not specified.

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References

1. Kelloff GJ, Lippman SM, Dannenberg AJ, et al. Progress in chemoprevention drug development: The promise of molecular biomarkers for prevention of intraepithelial neoplasia and cancer - A plan to move forward. Clin Cancer Res. 2006; 12:3661–97. [PubMed: 16778094]
2. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes. JAMA. 2006; 295:2727–41. [PubMed: 16754727]
3. Vogel VG, Costantino JP, Wickerham DL, et al. Update on the national surgical adjuvant breast and bowel project study of tamoxifen and raloxifene (STAR) P-2 trial: Preventing breast cancer. Cancer Prev Res (Phila). 2010; 3:696–706. [PubMed: 20404000]
4. US Food and Drug Administration. Guidance for industry, investigators, and reviewers: exploratory IND studies. 2006 [cited 2010 6 Dec]. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078933.pdf
5. Kummar S, Kinders RJ, Rubinstein L, Parchment RE, Murgo AJ, Collins J. Compressing drug development timelines in oncology using phase '0' trials. Nat Rev Cancer. 2007; 7:131–9. [PubMed: 17251919]
6. Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? Nat Rev Drug Discov. 2004; 3:711–5. [PubMed: 15286737]
7. Reid JM, Walden C, Qin R, et al. Phase 0 clinical chemoprevention trial of the AKT inhibitor SR13668. Cancer Prev Res (Phila). 2011; 4 ***XXX*** — **[Ed: Please complete once issue is paginated]**.
8. Boyd RA, Lalonde RL. Nontraditional approaches to first-in-human studies to increase efficiency of drug development: will microdose studies make a significant impact? Clin Pharmacol Ther. 2007; 81:24–6. [PubMed: 17185993]
9. Lappin G, Kuhnz W, Jochemsen R, et al. Use of microdosing to predict pharmacokinetics at the therapeutic dose: Experience with 5 drugs. Clin Pharmacol Ther. 2006; 80:203–15. [PubMed: 16952487]
10. Lappin G. Microdosing: current and the future. Bioanalysis. 2010; 2:509–17. [PubMed: 21083258]
11. Murgo AJ, Kummar S, Rubinstein L, et al. Designing phase 0 cancer clinical trials. Clin Cancer Res. 2008; 14:3675–82. [PubMed: 18559582]
12. Kinders RJ, Hollingshead M, Khin S, et al. Preclinical modeling of a phase 0 clinical trial: qualification of a pharmacodynamic assay of poly (ADP-ribose) polymerase in tumor biopsies of mouse xenografts. Clin Cancer Res. 2008; 14:6877–85. [PubMed: 18980982]
13. Rubinstein LV, Steinberg SM, Kummar S, et al. The statistics of phase 0 trials. Stat Med. 2010; 29:1072–6. [PubMed: 20419759]

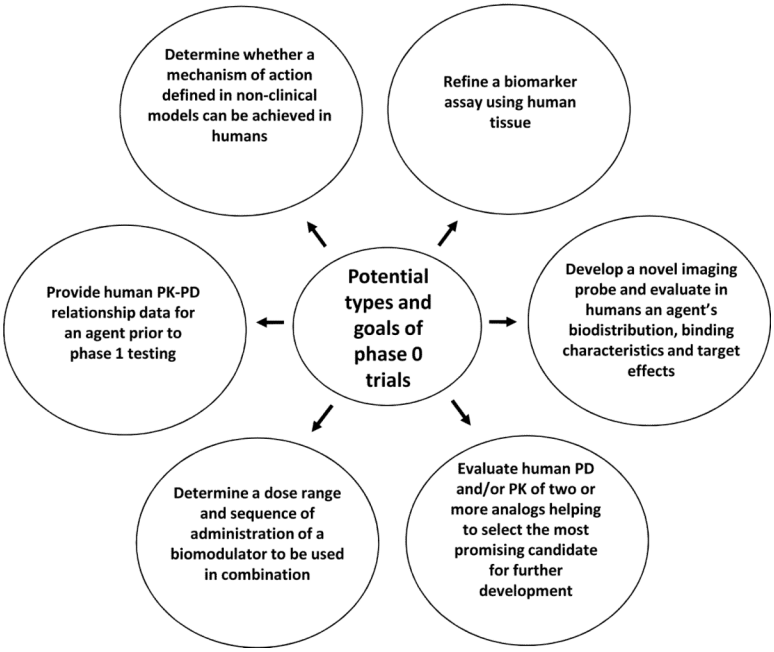

Fig. 1.
Different types and goals of phase 0 clinical trials.

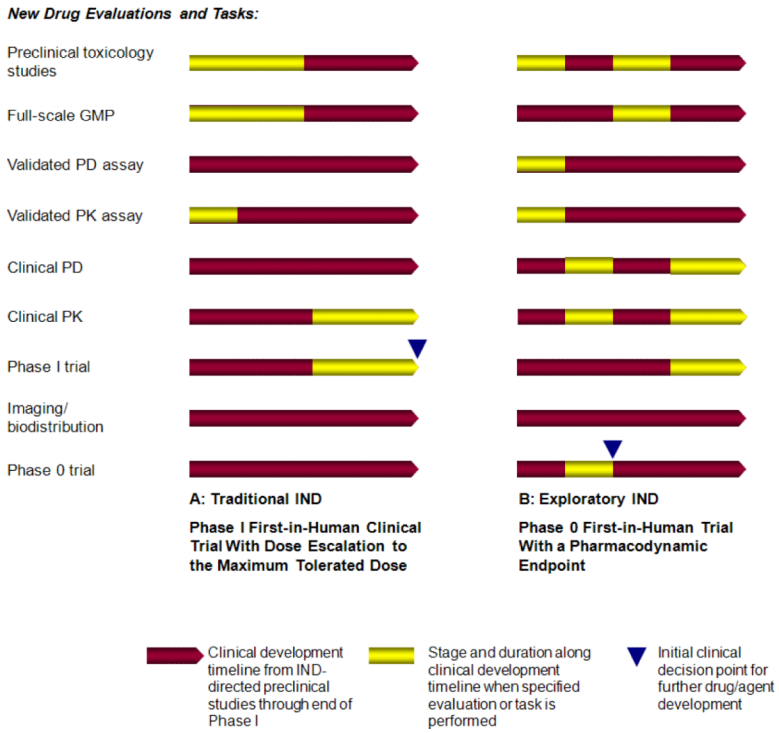

Fig. 2.

Phase 0 trials can potentially reduce the clinical development time for new agents and inform further clinical decision making. *A*, phase I trials conducted under a traditional IND require substantial preclinical toxicology studies and full-scale good manufacturing practice (GMP) production of the investigational agent prior to clinical administration; pharmacodynamic (PD) studies are generally not performed until phase II trials are initiated. The initial point of deciding on further drug development occurs relatively late in the process (blue dart above the “Phase I trial” bar). *B*, phase 0 trials (conducted under an exploratory IND) with a PD endpoint must have a validated PD assay prior to starting accrual. The decision to proceed to further clinical development in accelerated phase I/phase I combination (two investigational agents or one investigational plus one non-investigational agent) or phase I/II trials can be made relatively early in the process (blue dart above “Phase 0 trial” bar) based on whether the PD objective was met in the phase 0 trial. If the decision on further development following a phase 0 trial is a go, full-scale GMP production and further toxicology studies may be necessary (reflected in top two bars [at right]) before moving on to a phase I trial.