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ORIGINAL ARTICLE

Phase 0 clinical trials in oncology: a paradigm shift for early drug development?

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Abstract
Purpose To review the potential impact of Phase 0 trials conducted under the United States Food and Drug Administration (FDA) exploratory IND guidance on oncology drug development.
Methods The FDA's exploratory IND guidance document is examined in detail and its practical application to specific first-in-human proof of concept clinical studies called Phase 0 trials is discussed.
Results Phase 0 trials represent a novel strategy for accelerating the development of the next generation of anticancer treatments. Phase 0 studies are conducted prior to conventional toxicity-defined dose-escalation studies and these trials do not explore maximum toxicity levels and by definition are devoid of any therapeutic or diagnostic intent. They require less extensive formulation and non-clinical toxicity testing than conventional first-in-human Phase I trials. This pathway may be valuable in reducing the time and resources required to initiate clinical testing and it may also be useful in guiding the later stages of drug development. Alternatively, the early termination of a less than promising lead compounds could help in selecting the best agents for later clinical development. Possible disadvantages include the ethical challenge of testing non-therapeutic drug regimens in cancer patients and the need to conduct standard dose-escalation Phase I studies later in development.
Conclusions The potential of this novel pathway to accelerate drug development makes it worthy of further exploration, and National Cancer Institute has recently completed a Phase 0 trial demonstrating its applicability to targeted anticancer agents.

Keywords Phase 0 · Exploratory IND · Drug development

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The problem: innovation or stagnation?

In 2004, the FDA released an influential white paper entitled "Challenge and Opportunity on the Critical Path to New Medical Products" [2]. This important document highlighted some disturbing trends. First, the number of new chemical entities (NCE) beginning clinical testing in each year from 1996 to 2002 steadily declined instead of increasing. Second, the success rate of new compounds entering into first-in-human testing also decreased. In 2000, a new chemical entity entering into a first-in-human a Phase I clinical trial had an 8% chance of reaching the market, compared with a historical success rate of 14% in 1985. One of the FDA's conclusions was that the "…medical product development process is no longer able to keep pace with basic scientific innovation" [2]. Furthermore, the report conceded that "[w]e must modernize the clinical development path that leads from scientific discovery to the patients," and it went on to add that "…a better product development toolkit is urgently needed" [2]. These blunt statements provide strong warnings about the need to "innovate" rather than "stagnate" [2, 17].

One new instrument in the toolkit of the drug development scientist is the exploratory IND. This innovation, first described in an FDA draft guidance issued in April 2004,

was later published in finalized form in January 2006 [3]. The exploratory IND guidance describes the requirements for a new class of first-in-human studies that have collectively been referred to as Phase 0 clinical trials. The specific term, Phase 0, is not used in the document; instead, it was introduced by others to refer to clinical trials conducted under this mechanism [16]. Phase 0 trials represent an innovative attempt to change our traditionally conservative approach to drug development by accelerating the clinical testing of experimental therapeutic agents. In oncology circles, this out-of-the-box thinking has stimulated large amounts of debate and discussion on the utility of Phase 0 clinical trials in accelerating drug development [16]. However, there are still many misconceptions about the exploratory IND mechanism and Phase 0 trials that cloud the debate and may hinder its more widespread adoption. The goal of this review is to analyze the types of studies outlined in the FDA's exploratory IND guidance and to discuss their potential applications to oncology drug development.

The exploratory IND

The exploratory IND forms the basis for conducting a Phase 0 clinical trial. Thus, any thorough discussion of this topic requires a careful reading of recommendations that contained in the FDA exploratory IND guidance document [3]. The exploratory IND is not the result of new federal regulations; instead, it is based upon existing guidelines with an emphasis on their adaptability when applied to specific types of clinical trials. In a fine example of bureaucratic magnanimity, the FDA guidance states that "existing regulations allow a great deal of flexibility in the amount of data that needs to be submitted with an IND application" [3]. In addition, the "agency believes that sponsors have not taken full advantage of that flexibility and often provide more supporting information in INDs than is required by regulations" [3]. Finally, the exploratory IND guidance does not outline a firm set of statutes or stipulations; instead, it provides a series of recommendations based upon the FDA's current thinking.

As defined by the FDA, an exploratory IND study is a clinical trial conducted early in Phase I that involves very limited human exposure, and has no therapeutic or diagnostic intent. These Phase 0 trials are conducted prior to the typical dose-escalation, safety, and tolerance studies (classical Phase I trials) that ordinarily initiate clinical testing. Phase 0 trials can be conducted in patients or normal volunteers, but by definition, the duration of dosing must be limited. As an example, the exploratory IND guidance suggests a temporal limit of 7 days of dosing [3]. These guidelines apply to drugs, small molecules, and certain well-characterized therapeutic biological products such as recombinant proteins and monoclonal antibodies. It does not apply to other biological reagents such as human cell or tissue products, blood, blood proteins, vaccines, or devices. Another important concept is that Phase 0 trials are not meant to supplant or replace traditional Phase I dose-escalation studies that strive to define toxicity profiles, dose limiting toxicities, and the maximally tolerated dose level. If such endpoints are important for a specific therapeutic agent, then a traditional Phase I trial will still be required.

Examples of exploratory IND Phase 0 trials

The FDA guidance describes three types of representative Phase 0 trials as specific examples of the clinical application of an exploratory IND (Table 1) [3]. All of these have potential relevance to oncology therapeutics. These trial types include: (1) studies of pharmacokinetics or imaging endpoints after administration of microdoses of drug, (2) studies pharmacologically relevant doses, and (3) studies of mechanisms of action related to efficacy.

Phase 0 microdose studies of pharmacokinetics or imaging

These studies are designed to evaluate the pharmacokinetics, metabolism, and/or imaging distribution of specific agents in the absence of any planned pharmacological effect. They are sometimes referred to as microdose studies and, in the terminology of the exploratory IND, a microdose is strictly defined as less than 1/100th of the dose calculated (based upon animal data) to yield a pharmacological effect of a test substance, with a maximum dose

Table 1 Types of phase 0 trials described in the FDA exploratory IND guidance from Ref. [2]

Type of Phase 0 Trial	Comments
Microdose	Pharmacokinetic or imaging study endpoints
Pharmacologically relevant dose	Higher doses than microdose studies, more extensive safety testing required. Pharmacodynamic endpoints
Mechanism of action related to efficacy	Higher doses than microdose studies, more extensive safety testing required. Pharmacodynamic biomarker endpoints (may require tumor biopsies)

limit of ≤100 μg [3]. For imaging studies, the maximal 100 μg limit also applies; however, for protein products, the maximum limit is 30 nanomoles. In these studies, current Good Manufacturing Practices (cGMP) material is not absolutely required if the risk to human subjects is limited. Instead, a graded approach to chemistry, manufacturing, and controls (CMC) can be utilized [3, 4]. In this case, the level of supporting CMC information regarding the identification, strength, quality, purity, and potency of an agent will vary with the clinical trial proposed. Furthermore, the batch of drug product used clinically does not have to match with that used in the non-clinical studies if the sponsor can demonstrate by analytic testing that any given sample is representative of earlier batches. Finally, multiple related compounds may be studied clinically under a single exploratory IND, which can represent a major savings of preclinical resources.

For single dose microdose studies, the FDA will accept extended single dose toxicity studies conducted in a single animal species, if justified by in vitro metabolism and comparative in vitro pharmacodynamic data [3]. A possible preclinical toxicology experiment could be designed as follows. After drug administration by the same route planned for clinical use, an observation period of 14 days is required with interim necropsy performed on a subset of animals on day 2 that includes chemistry, hematology, and histopathology endpoints. The goal is to establish a minimal toxic effect for determination of a margin of safety. The formal margin of safety demonstration requires that 100-fold higher dose than the proposed human dose should not induce adverse effects in the experimental animals after appropriate interspecies body surface area scaling. Routine genetic toxicology and safety pharmacology studies are not required.

Specific examples of microdose studies include the administration of multiple related but different agents at extremely low doses for evaluation of their pharmacokinetic characteristics. One possibility is to administer a cassette of microdoses of several related agents with pharmacokinetic monitoring. In this case, a number of related compounds under consideration for further clinical development could be examined collectively or individually in a Phase 0 pharmacokinetic study under a single exploratory IND. Microdose pharmacokinetic studies require the use of highly sensitive analytical instruments and the development of technologies such as accelerator mass spectroscopy (AMS) have led to an increase in the feasibility of these types of studies [10]. Another microdose Phase 0 trial is a study of trace amounts of a novel imaging agent, which by definition will not have any pharmacological effect when used at the doses anticipated for clinical use. Reducing the amount of preclinical testing required for studies of this type is both logical and wise, because of the large anticipated safety margins of microdose regimens.

The European EMEA regulatory position on microdose studies has been outlined in a June 2004, position paper on non-clinical safety studies required to support clinical microdose studies [1]. The basic definition is comparable to the US FDA's exploratory IND guidance with a microdose defined as 1/100th of the dose calculated to yield a pharmacological effect. However, the EMEA requires a greater safety factor of 1,000-fold is required for the demonstration of a margin of safety dose, and once again the duration of dosing cannot extend beyond 7 days. The European regulators also allow for multiple, closely related test substances to be administered and single dose toxicity studies in a single species may be justified. Genotoxicty studies should be performed but may be abridged if justified. Finally, the EMEA requires that all non-clinical safety studies should be conducted under current Good Laboratory Practice (cGLP) standards.

Phase 0 trials to study pharmacologically relevant doses

The second Phase 0 trial type described in the FDA guidance is a pharmacological endpoint study. This trial is designed to examine the pharmacological effects of the candidate product, but it does not attempt to define the maximum tolerated dose. An example might be a repeat dosing study over a defined dose range designed to examine a specific pharmacodynamic effect such as lowering blood pressure or elevating a predefined laboratory test parameter. Obviously, the doses used will be much higher than in a microdose trial, and as a consequence, more extensive preclinical safety data are required. However, the amount of preclinical information is still less extensive than that needed to support a traditional Phase I trial. The suggested duration of dosing is still limited to 7 days, and once again, no therapeutic or diagnostic intent is permitted.

For a pharmacological endpoint Phase 0 trial, the non-clinical studies necessary to support a 7-day planned clinical treatment regimen might include 2-week repeat dose animal toxicology studies [3]. This information should be used to define safe starting and stopping doses and the maximum dose allowed. Typically, rodents are the most common toxicology species used; however, additional confirmatory studies in a second non-rodent species (most often dogs) are still required. Safety pharmacology studies examining the pulmonary, cardiovascular, and central nervous systems are also required. However, genotoxicity experiments may be waived for clinical studies performed in patients with terminal diseases such as cancer. An example of the recommended starting and stopping dose toxicology experiments recommended for a planned Phase 0 study

examining pharmacologically active doses are outlined in Fig. 1 [3]. Thus, the requirements for non-clinical safety testing for pharmacological endpoint Phase 0 trials are not inconsequential.

Phase 0 trials of mechanisms of action related to efficacy

The third Phase 0 study described in the FDA guidance is designed to evaluate the specific mechanisms of action of a novel agent. These trials are similar to the pharmacological endpoint Phase 0 studies, but they focus on the target tissue and on an agent's proposed mechanism of action. These studies have the greatest relevance to targeted therapy drug development in oncology. Endpoints related to the mechanism of action could include the degree of receptor saturation in target tissue, the inhibition of an enzyme or signaling pathway in tumor cells, the altered expression of a specific gene product, or other molecular biomarker endpoints. In these trials, specific pharmacodynamic biomarkers that are validated in preclinical experiments become the primary endpoints for the clinical study. For example, a clinical study of a new monoclonal antibody might monitor its degree of binding to tumor expressed antigens or surface membrane receptor. Alternatively, the primary endpoint might be the down regulation of an activated phospho-tyrosine kinase in a specific signaling cascade downstream from the targeted receptor.

Preclinical support studies for these Phase 0 trials should include short-term toxicity studies performed in at least two animal species. In some cases, "a single species could be used if it were established as the most relevant species" [3]. The dosing strategy should be designed to achieve the maximally desired pharmacodynamic effect related to the mechanism of action. The preclinical studies are of paramount importance for defining the starting and stopping doses, and for validating the mechanisms of action biomarker endpoints. Finally, production of frank toxicity is not the primary goal, but informative safety endpoints such as hematological or histopathological assessments must still be monitored.

The NCI Phase 0 trial of a novel PARP inhibitor, ABT 888

In May, 2007, the US National Cancer Institute Experimental Therapeutics (NExT) program presented their preliminary results of a pioneering mechanism of action Phase 0 oncology trial [9]. This prototype study examined the mechanism of action of ABT-888, a novel oral poly (ADP-ribose) polymerase (PARP) inhibitor. The enzyme, PARP, senses DNA damage and catalyzes covalent binding of poly (ADP-ribose) (PAR) units to DNA repair enzymes and histones to facilitate DNA repair [14]. Inhibition of PARP results in the persistence of DNA damage ultimately leading to apoptosis. Anticancer therapies such as platinum derivatives, topoisomerase poisons, and DNA alkylating agents show synergistic antitumor activity in preclinical models when combined with PARP inhibitors.

The primary goals were to determine the non-toxic dose ranges at which ABT-888 inhibits PARP in tumor tissues

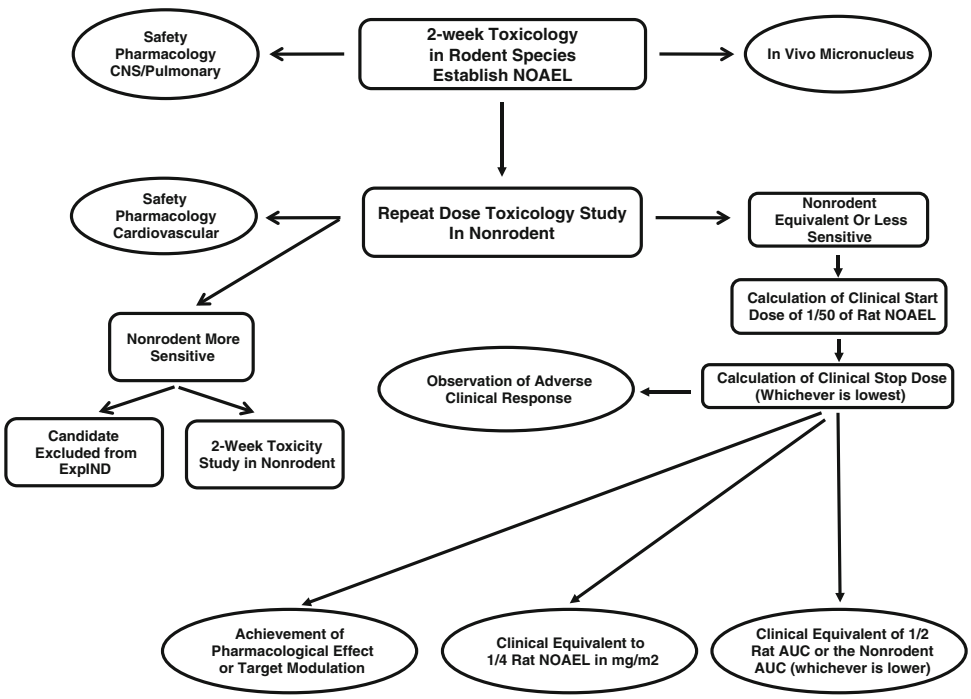

Fig. 1 Preclincial toxicology testing for exploratory INDs desgined to administer pharmacologically active doses in a Phase 0 trial. *NOAEL* no adverse effect level, *CNS* central nervous system, *ExpIND* exploratory investigation new drug application, *AUC* area-under-the-curve. Adapted from Ref. [3]

and in peripheral blood mononuclear cells (PBMC), to define ABT-888 pharmacokinetics, and to examine the time course of PARP inhibition in PBMC. A secondary goal was to define the safety of a single dose of ABT-888, but not to explore the MTD. Patients with a diagnosis of cancer, chronic lymphocytic leukemia, or non-Hodgkin's lymphoma were eligible and had to agree to extensive pre-treatment blood sampling for PARP analysis in PBMC. Other tests included pharmacokinetic monitoring of ABT-888 blood levels after a single dose administration and, in a subset of patients, tumor biopsies were performed pre-treatment and 3–6 h post-treatment. Extensive preclinical experiments were conducted prior to study initiation to validate the assay procedures and to determine the optimal timing of tumor biopsies and PBMC collection for PAR expression [7, 12]. Impressively, pharmacokinetic and pharmacodynamic analyses were run in real time with data available within 72 h of sample collection. Patients were enrolled in cohorts of three at increasing dose levels until at least a twofold reduction in PAR expression was seen in the tumors from two out of three patients at two different dose levels [15].

From July 2006 to May 2007, ten patients were enrolled and were treated at three dose levels [8]. Down modulation of PAR expression in PBMC was seen at the very first dose level, and in five patients with serial tumor biopsies, all had greater than 95% reduction in PAR expression after ABT-888 therapy. Thus, the trial achieved its ambitious goal of demonstrating the inhibition of the molecular target at clinically achievable doses. Furthermore, it demonstrates the feasibility of validating complex tissue-based assays preclinically and instituting rigorous standard operating procedures (SOPs) prior to the initiation of a first-in-human Phase 0 trial. The NCI's Phase 0 team was successful in generating valuable information for the design of subsequent Phase I combination chemotherapy trials of ABT-888 that are now being launched.

Critical path critics

The ultimate goal of the exploratory IND and Phase 0 trial is to accelerate the development of novel therapies for human disease. However, despite the early impressive results from the NCI team, a number of criticisms have also been raised regarding the widespread implementation of this pathway [16]. Some of these concerns have scientific validity. For example, microdose pharmacokinetic experiments may not always predict drug behavior at higher pharmacological doses because of deviations from dose proportionality due to non-linear kinetics. Making go or no-go decisions based on microdose kinetics could be problematic for some agents. This issue was examined prospectively in a microdose study of five agents selected for potential non-linearity in kinetic behavior [11]. These included diazepam, midazolam, erythromycin, warfarin, and a failed experimental agent, ZK253. Microdose pharmacokinetics were predictive of full pharmacological dose kinetics for three of the agents (diazepam, midazolam, and ZK253). However, erythromycin concentrations were not detectable, even with a sensitive AMS analytical method, and warfarin had a highly non-linear distribution profile; although, clearance predictions were comparable to higher doses. Despite these shortcomings, the authors concluded that "when used intelligently, microdosing is a useful additional tool to assist in the decision making during drug development" [11]. Whether a three out of five average is robust enough for most drug discovery and development programs is debatable, although these agents were chosen for their potential to cause problems. Nonetheless, studies of this type should be interpreted with a critical eye and it is uncertain how applicable these data are to unselected experimental agents in actual development pipelines.

A distinct advantage of a microdose Phase 0 study is the reduced preclinical testing requirements necessary prior to the initiation of a clinical trial. However, as previously described, the savings in resources may not be substantial for the more complex Phase 0 studies such as the pharmacological effect or mechanism of action trials (Fig. 1). Furthermore, the FDA guidance is not explicit on when non-clinical toxicity must meet full cGLP compliance, stating that "all preclinical safety studies supporting the safety of an exploratory IND application will be performed in a manner consistent with cGLP" [3], but "sponsors must justify any non-conformance with GLP provisions" [3]. Thus, any attempt to deviate from cGLP guidelines must be discussed with the FDA in advance.

Another misconception is that Phase 0 studies might obviate the need for additional Phase I dose-escalation trials. If the MTD is important for a particular agent, then a traditional Phase I study will still be required to define the full toxicity profile. In such cases, the exploratory IND must be withdrawn and further studies conducted under a standard IND mechanism.

Another frequently raised issue is the ethical implications of conducting Phase 0 trials in cancer patients [6]. Most cancer patients participate in clinical studies with the hope, albeit quite small, of obtaining some degree of therapeutic benefit. Because of the strict limitation in duration and dosing and the mandatory lack of therapeutic or diagnostic intent, some have questioned whether cancer patients will agree to participate in these types of intensive clinical trials. However, the NCI experience demonstrates that patient accrual, while challenging, can be successful with a motivated health care team that is highly communicative with patients and their families [5]. In a Phase 0 study, the

major inducement for participation is the desire to further cancer research, thereby helping future patients with a similar diagnosis. This altruistic instinct is quite strong in many research subjects with cancer [6].

Another limitation of a pharmacological effect or mechanisms of action Phase 0 trial is that the conclusions will only be as good as the biomarker assay used as an endpoint. The cold hard truth is that many biomarker assays used in oncology, early clinical trials, are not well validated. The scientific rigor required for accurate biomarker validation and for consistency in processing of clinical specimens collected at multiple times is challenging. The NCI's prospective effort to validate its biomarker Phase 0 laboratory is highly commendable. However, these problems are not limited to just Phase 0 trials, but apply equally to any biomarker-guided study.

Conclusions

Whither the Phase 0 trial in oncology drug development? Will it "become a routine part of early Phase oncological drug development in the future" as predicted by the NCI Phase 0 team [9], or will it occupy a specialized niche in the pantheon of clinical trial designs? At this point it is premature to draw any definitive conclusions, at least until the collective experience with these trials increases. In selected situations such as microdose imaging studies, the exploratory IND mechanism offers compelling advantages in shortening the time to human testing. The planned clinical use of these reagents will be at or near the microdose level. However, microdose studies have less direct relevance to early therapeutics in oncology where the most pressing proof of principle question is the effect of the treatment on the tumor target. As a drug discovery tool for weeding out poor therapeutic candidates, Phase 0 trials may help to select the optimal agent for further development using the traditional pathways. But Phase 0 trials are unlikely to be a common pathway for all drugs and all classes in clinical development. Instead, selected targeted agents with well-characterized mechanisms of action may be most amenable to the Phase 0 trial approach, as exemplified by the NCI's fine work with the ABT-888 PARP inhibitor [8].

Overall, the pharmaceutical industry and the cancer research community appear to be taking a cautious approach to Phase 0 trials [16]. Until at least one agent tested in a Phase 0 trial receives regulatory approval, there is unlikely to be a huge groundswell of change despite the large numbers of targeted agents in development. For this reason, the pioneering and influential Phase 0 trial conducted by the NCI is essential for spearheading this new approach. Innovators must lead by example, and the growth of high-quality biomarker-driven clinical trials in oncology is to be applauded. Furthermore, even when the Phase 0 approach is not utilized, the principles discussed are applicable to pharmacodynamic biomarker endpoints incorporated into standard Phase I first-in-human trials. Increasingly, Phase I first-in-human trials of targeted cancer treatments are incorporating biomarker endpoints, hopefully with the same rigor as demonstrated by the NCI [13]. The courageous cancer patients who volunteer for these early clinical trials in oncology deserve nothing less.

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