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Early-phase Development of Cancer Prevention Agents, Challenges and Opportunities

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Abstract

Chemoprevention is the administration of agents (drugs, biologics, dietary supplements, or nutrients) to reduce the risk of developing cancer or prevent the recurrence of cancer. The National Cancer Institute, Division of Cancer Prevention (NCI, DCP) is a major sponsor of cancer preventive preclinical and clinical research. As such, it has developed a comprehensive drug development program specifically designed to meet the requirements needed for cancer preventive drugs to achieve initial regulatory approval. Clinical development of cancer prevention agents presents unique challenges not encountered with most cancer therapeutic agents. To meet these challenges, NCI, DCP has implemented new approaches and programs, including Phase 0 clinical trial designs and microdose studies. In addition, the PREVENT Cancer Program was recently implemented by NCI, DCP to offer a formalized structure for moving drugs forward in the prevention pipeline using a continue/not continue decision process. Likewise, DCP has implemented a clinical trials Consortium to further develop these agents. These and other approaches will be discussed in this commentary.

Keywords

Chemoprevention; Agent Development; PREVENT; Exploratory IND; Clinical Trials

Introduction

Early-phase Clinical Development of Cancer Prevention Agents

The NCI formally included cancer prevention in its research portfolio in 1971 [1]. Large numbers of candidate chemopreventive agents have subsequently been identified and evaluated by a combination of in vitro and in vivo studies in NCI-sponsored and independent investigations (reviewed in [2]). In some cases there is little or no previous human experience with a candidate agent (e.g., new chemical entities identified through a rational drug design, or new analogues designed to improve the safety or efficacy profile of known compounds), and in some cases there is ample previous human experience with a compound of interest (e.g., re-purposing of over-the-counter or prescription medications). Other candidates fall in between these extremes (e.g., some evidence of safety and efficacy of an isolated compound or extract based on previous consumption as a food or dietary supplement). The goal of early-phase trials depends on the compound's history and availability of previous human data (see Table 1). For agents with no previous human data, early clinical trials must address evaluation of safety and pharmacokinetics (PK) in a first-

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in-human setting. For agents with prior human experience, there may be limited need for additional PK evaluation. In all instances, however, the potential applicability of available data, from both preclinical and human studies, must be considered in a chemoprevention setting.

One tool that may offer improved development efficiency in instances where there is no previous human experience is the conduct of exploratory (Phase 0) Investigational New Drug application (IND) studies. Exploratory IND studies were proposed by the FDA in 2006 as a means to reduce the time spent on development of agents that are unlikely to succeed [3, 4]. Phase 0 trials involve fewer subjects, lower doses, very limited human exposure, and have no therapeutic or diagnostic intent as compared to Phase 1 trials.

They require less initial pharmacologic and toxicology testing than traditional Phase 1 studies, allowing a go/no-go decision point for further agent development to be reached quicker and at less expense. It has been estimated that 40% of agents dropped during Phase 1 testing fail due to undesirable PK characteristics that are not consistent with the predictions derived from preclinical models (reviewed in [5]). Clearly, it would be of great value to reach this decision point with minimal expenditure of time and resources. While the concept of moving quickly into human studies may raise concerns, it is also true that animal data cannot always be considered a valid predictor of PK in humans [6]. The important question is not whether human studies should be initiated earlier in the agent development process, but how this can be done safely.

In order to enable sponsors to move ahead more efficiently with the development of promising candidate agents while maintaining needed human subject protection, FDA issued Guidance for Industry, Investigators and Reviewers: Exploratory IND Studies in January 2006 [7]. These Phase 0 studies administer a single dose or multidose (typically less than seven days) of the trial drug at low, nontherapeutic, nontoxic doses to a few subjects. Tissue and/or blood sampling is used to generate a PK/PD profile of the agent. Because the drug is administered at sub-pharmacologic and thus likely nontoxic doses, initial clinical testing can begin with less extensive preclinical data and at lower cost in a shorter timeframe with fewer subjects. Exploratory IND studies also offer the promise of more rational selection of agents for further development as well as molecular identification of potential therapeutic failures early in the process.

Exploratory IND studies present several opportunities in the cancer prevention setting. These include determining whether a biochemical effect identified during in vitro screening is also observed in humans, evaluating PK, and selecting a lead formulation candidate based on PK and/or PD properties. The first-ever Phase 0 cancer prevention trial was recently completed with the AKT inhibitor SR13668 under a NCI, DCP-sponsored exploratory IND [8]. The study was designed to evaluate whether preclinical PK of the compound are predictive of behavior in humans, determine the dosing condition (fed vs. fasted) best suited for future human studies, and identify which of several formulation candidates shows the best bioavailability in human. The trial took only five months to complete and identified a lead formulation of SR13668 for further clinical testing. Several pharmaceutical companies have also conducted exploratory IND studies; however, the ability of Phase 0 trials to have a positive impact on development efficiency remains to be seen [3]. For example, the poly (ADP-ribose) polymerase (PARP) inhibitor ABT-888 was one of the first compounds to be investigated using the Phase 0 clinical trial design [3, 5, 9]. This phase 0 trial was a success, in that important biochemical and PK data were obtained that eliminated the need for a traditional phase 1 monotherapy study, and guided the design of efficient phase 1 combination studies. Whether this ultimately translates to a quicker time to market will depend on the outcome of pivotal clinical trials. Unfortunately, the use of PD endpoints in

Phase 0 studies, as was the case for ABT-888 and which is of particular interest for the development of cancer prevention drugs, has been limited [10].

Other tools are available that could be applied to make early-phase human PK trials more efficient. The development of assays to detect drugs and metabolites in biological specimens can be a very time-consuming and difficult task — especially for microdose studies, as might be used in an exploratory IND trial where the amount of analyte present is likely to be very small. Techniques such as functional magnetic resonance imaging (MRI) and single photon-emission computed tomography (SPECT) can be used in conjunction with very low dose human studies to allow accurate, sensitive, and efficient analysis of biological specimens [6, 11]. Accelerator mass spectrometry (AMS) is several orders of magnitude more sensitive than liquid chromatography, and can detect radiolabeled drugs at very low concentrations (10^{-18} moles) and with great precision. Nuclear magnetic resonance (NMR) spectroscopy and positron emission tomography (PET) spectroscopy are other techniques that can be used in a setting of minimal chemical or radiation exposure to subjects. Use of these techniques in exploratory and Phase 1 studies would allow rapid collection of accurate PK/PD data for drugs in humans, even at microdose levels, and has logistical advantages over more invasive technologies [11]. By administering a constant low dose of radiolabeled drug with increasing doses of unlabeled drug, the effects of dose level on bioavailability and biodistribution could rapidly be assessed and with minimal need for assay development. Use of these techniques would likely yield more accurate data in a shorter time and with less error due to assay variability than is seen in more common assays used in human PK studies (e.g., specimen collection and extraction, followed by separation and analysis by HPLC). The ability to collect accurate data using microdoses in a small sample set could ultimately translate to lower human exposure, both in terms of the total number of subjects required and total exposure per subject. In addition, data obtained using sensitive isotope detection techniques could be used as a reference for development of more traditional biological assays since method validation must address both the practical matters (whether the method is robust and reproducible) and application (whether the method generates accurate data).

Determining the maximum tolerated dose is of virtually no value for cancer prevention applications, (although it may be a critical step in selecting doses for later-stage cancer treatment trials). Higher doses are often associated with a higher incidence and/or greater severity of side effects, which must be avoided for chronic administration to be clinically acceptable [12]. What is of great import, however, is the lowest dose that is effective, and the side effects associated with chronic administration of that low dose. Once initial safety and PK has been established, early-phase cancer prevention studies could be designed to verify modeled predictions of low-dose PK, safety, and biological activity, with the ultimate goal of identifying a PD endpoint that is predictive of efficacy.

Streamlining and Optimization of Preclinical Drug Development

While there is an acute need for a focused development pathway designed based on knowledge of a particular agent's mechanism of action and predicted pharmacological activity, some areas of early development would still benefit from utilization of more molecularly oriented processes. With the wealth of information now available on potential targets of interest in cancer, as well as the biochemical processes of normal cells, a profile of cellular processes affected by a drug candidate can be generated. We have a great advantage in cancer prevention, since a large number of agents have already demonstrated efficacy in preclinical models [2]. For example, the rat mammary tumor model for ER positive breast cancer accurately identified tamoxifen as an effective chemopreventive agent. Since these preclinical models are not validated, a predictive value project is currently underway to study this correlation. Through rational mechanism selection, we can use these active agents to generate statistical models of what does and does not translate to a viable cancer

prevention agent in humans. Focusing on single molecular pathways or biomarkers affected by an agent will only give a partial picture. Many of these agents affect multiple pathways with an unknown hierarchy of importance [12]. Preclinical testing could theoretically be tailored to evaluate concerns early in the development cycle, and at dose levels reflective of the predicted minimal effective doses in humans.

Once a viable cancer prevention drug candidate has been identified, predicted efficacy must be verified through additional whole animal preclinical testing. Taking advantage of existing protocols and facilities with experience in conducting standard preclinical efficacy and toxicology tests on cancer prevention agents is another opportunity for streamlined development. To better meet the emerging challenges of cancer preventive drug development, DCP has implemented the PREVENT Cancer Program [13]. This program provides all the necessary preclinical testing, documentation, and strategic planning required to move agents from discovery up to but not including Phase I clinical studies. The PREVENT Cancer Program is a process to develop new agents with strategies to optimize its available resources. This program invites academia, small businesses and pharmaceutical to collaborate in chemopreventive agent development efforts. Two areas of high interest are the development of drugs that target the inflammatory microenvironment and vaccines that target precancer. The DCP PREVENT Cancer Program receives input and guidance from FDA on various subjects including exploratory IND studies (Phase 0), development of risk, safety and efficacy biomarkers, and in vitro diagnostics. An important feature of the PREVENT Cancer Program is a formalized structure for moving drugs forward in the prevention pipeline using a continue/not continue decision process. This process is modeled on benchmarks used by biotechnology and pharmaceutical industries, as well as NCI's Experimental Therapeutics (NExT) Program. It lays out a defined set of guidelines and milestones to support go/no go decisions along the critical path for drug development. The stage gate process is a key governance component of PREVENT Cancer Program and is designed to maximize the utilization of DCP's resources.

Practical considerations should be made to quickly eliminate candidates with little development potential. A drug being developed to prevent cancer should have adequate bioavailability when administered by non-invasive means (e.g., oral or topical). Theoretically, cost should not be a primary consideration for agent development, however, a drug that will be administered chronically for cancer prevention must be affordable. Drugs that require expensive manipulations in order to achieve a stable formulation or to improve bioavailability are unsuited for development for prevention applications. Identification of a standard panel of acceptable, cost-effective strategies to resolve formulation and bioavailability issues would be a very useful contribution to streamlining the cancer prevention agent development.

Summaries and Conclusions

Drug development is a time-consuming and costly process. Efficiency can be improved by increasing communication in the cancer prevention effort. It would be a great advantage to identify and/or develop centers with experience in conducting early-phase clinical studies of cancer prevention agents, possibly utilizing some of the non-invasive PK and PD imaging tools discussed above. DCP has also implemented a clinical trials consortium [14], established in 2003 and reissued in 2012. This Consortium is responsible for conducting clinical trial efforts in cancer prevention and provides an opportunity for the clinical development of new agents. An increased level of productive communication among prevention-oriented clinical scientists would result in more experienced input on effective adaptive designs for early-phase cancer prevention studies. To increase efficiency in these studies, a great deal of administrative time and effort could be eliminated through formation

and adoption of a centralized IRB, made up of a panel of individuals knowledgeable about the specific challenges and needs affecting cancer prevention studies.

Special challenges confront development of agents for cancer prevention; they must be convenient, affordable, and safe for administration over long periods. Overwhelming epidemiological and experimental evidence shows that a variety of agents plays a role in cancer chemoprevention. In addition, the past decades have seen massive growth in our scientific understanding of cancer biology, as well as major advances in our technical abilities in cellular and molecular biology. The combination of these factors should result in increased ability to bring cancer prevention agents to the market.

Early-phase clinical development for cancer prevention trials perhaps should best be pictured as a multi-faceted approach encompassing mechanism-based PK/PD modeling in preclinical systems, results of which are used to guide clinical trial design, subject identification, and dose selection. By using the tools available to us now, and the vast array of promising agents identified in preclinical testing, we can begin to generate a better, more comprehensive model of the biological actions of putative cancer prevention agents. Initial human testing, perhaps in an exploratory setting and using minimally invasive PK and PD technologies, can be utilized for hypothesis testing and biomarker verification. Continued clinical development could then focus on establishing the correlation between the proposed biomarker and late-stage endpoints or outcomes. Once safe and effective doses and adequate biomarkers have been identified, we will need the patience and resources to conduct long-term studies under intended conditions of use.

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Table 1

Level of Previous Human Experience for a Selection of Candidates Being Evaluated in NCI, DCP-sponsored Cancer Prevention Studies

Level of Previous Human Experience	Possible Avenue of Discovery	Examples	Goals of Initial Clinical Development in Cancer Prevention Setting
None	NCE or analogue discovered during rational drug design or high-throughput screening	SR13668 (synthetic AKT pathway inhibitor); 9-cis-UAB30 (retinoid analogue)	Establish first-in-human safety and bioavailability; verify applicability of preclinical safety, PK, and PD data; choose variant with best profile for continued development
Little or Some	Purified compound (isolated or synthetic) found in food; botanical extracts; new formulation of existing compound designed to have altered bioavailability; existing food or dietary supplement being evaluated as a drug; continued development of chemopreventive agent of interest	Polyphenon E® (green tea extract); indole-3-carbinol (found in cruciferous vegetables); G-2535 (genistein-rich isoflavone mixture)	Investigate dose effect and dose response; establish lowest effective dose; establish human safety and ADME at lowest effective dose; generate early evidence of efficacy
Substantial	Re-purposing of over-the-counter or prescription drug for new indication; food component	Pioglitazone; celecoxib; aspirin; ursodiol	Establish lowest effective dose; establish safety and ADME with long-term administration; generate early evidence of efficacy

ADME: absorption, distribution, metabolism and excretion; NCE: new chemical entity; PD: pharmacodynamics; PK: pharmacokinetics