Journal of Cellular Biochemistry Supplement 27:1–6 (1997)

Protocol Design Considerations That Relate to Demonstrating the Safety and Effectiveness of Chemopreventive Agents

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Abstract As with other drugs, applications for marketing approval of new chemopreventive agents in the United States must include data from adequate and well-controlled clinical trials that demonstrate effectiveness and safety for the intended use. Knowledge of a drug's pharmacologic actions and metabolism may benefit protocol design, by identifying the patient populations and dosing schedules associated with a favorable risk/benefit profile. With availability of appropriate preclinical data, including standard assessments of an agent's toxicology, effects on reproductive performance, and genotoxicity, initial Phase I studies of 1–3 months may be performed in normal volunteers or an appropriate higher-risk population. For chronic dosing studies of longer duration, preclinical toxicology studies of longer duration are relevant. Enrollment in chemoprevention studies should be directed toward individuals at sufficient risk of developing cancer so that potential benefit may counterbalance the unpredictable and possibly serious adverse effects that may be observed with prolonged administration of a study drug. Phase I and II studies with clinical dosing lasting up to 12 months often afford opportunities to assess drug effect on surrogate endpoint biomarkers that may correlate with endpoints of clinical effectiveness. Phase III and late phase II chemopreventive investigations should routinely utilize a prospective, randomized study design (double-masked and placebo-controlled, when possible). To support marketing approval, there must be evidence that a chemopreventive agent significantly delays or prevents the occurrence of malignancy, with acceptable safety. In some circumstances, modulation of a surrogate marker may provide a basis for marketing approval, before more definitive endpoint data become available. However, the acceptability of a surrogate depends on the nature and quality of the data supporting its predictive value. Given the considerations of large study size, long duration, and high cost that may hamper development of potential agents, studies designed to examine the predictive value of surrogate endpoint biomarkers are of great importance to the future development of chemoprevention research. J. Cell. Biochem. Suppl. 27:1–6.

Key words: cancer; chemoprevention; clinical trial; surrogate endpoint biomarker; protocol design; safety; efficacy; FDA

Expeditious and scientifically sound clinical development of cancer chemopreventive agents that may reduce the burden of cancer in specific consumer populations is a matter of high priority for the United States Food and Drug Administration (USFDA). Development of such products has been the subject of an ongoing dialogue between the USFDA and other groups in the United States such as the National Cancer Institute (USNCI), and representatives of the pharmaceutical industry and various academic and consumer organizations. This overview will address a variety of issues relevant to the approval of agents for chemoprevention in the United States. Many of these issues have been considered in a joint publication from the USFDA and the USNCI [1]. In general, the issues considered in this reference also merit consideration in clinical studies of chemopreventive agents that might be conducted in countries other than the United States and by groups performing collaborative international trials.

In spite of extensive efforts to design and implement protocols to assess chemopreventive agents and identify surrogate endpoints, an ongoing discussion of these issues is clearly worthwhile, since methods to evaluate cancer chemoprevention trial outcomes are constantly evolving. An exchange of information and ideas among international investigators will help to pave the way for future international collaborations.

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Received 3 March 1997; Accepted 6 November 1997

Pharmaceutical development ventures involving international cooperation have been facilitated by International Conferences on Harmonization (ICH) [2], which have led to regulatory agreements specifying uniform technical approaches for registering pharmaceuticals for human use. At the first of several harmonization conferences, safety, efficacy, and quality were identified as issues of primary importance to the harmonization process. Basic harmonization issues related to safety include long-term toxicity testing and the evaluation of reproductive toxicology, carcinogenic potential, and genotoxicity. Issues related to efficacy include agreement on selection of the appropriate population to assess clinical safety and effectiveness, clinical data management, good clinical practice, the demonstration of dose response, and concerns about international variation in drug response suggested by observations of biologic variation such as those described at this conference by Dr. Zhau et al. [3]. Beyond safety and efficacy, issues related to the quality of pharmaceutical products include stability testing, validation of analytical methods, and detection of impurities in bulk substances and final products. While progress has been made toward international agreement on standardizing approaches to safety, efficacy, and quality, marketing approval activities still occur at the national level. However, harmonization has made it easier for sponsors to use an international approach to developing pharmaceutical products. When harmonization principles are followed, the authorities who regulate the development and marketing of pharmaceutical products in a specific nation are more likely to accept the results of clinical trials performed in other countries.

The framework used in the harmonization process addresses the same issues that are central to the development of potential chemopreventive agents: safety, effectiveness, and quality. Applications to the USFDA for marketing approval of chemopreventive agents have requirements similar to applications for approval of other drugs. In the United States, federal regulations require a demonstration of product safety and effectiveness as the basis for marketing approval. Since safety and effectiveness usually cannot be defined in absolute terms, the assessment of clinical usefulness is based on net clinical benefit as reflected by the relationship between risk and benefit in specific clinical situations.

An application to the USFDA for marketing approval must provide proof of overall clinical benefit to a patient population, based on data from adequately sized and well-controlled clinical investigations that provide statistically sound evidence demonstrating the effectiveness and safety of the agent for its intended use. Usually, data from at least two well-controlled clinical Phase II/III studies are provided in marketing applications for new drugs. Under certain circumstances, data from a single, adequately sized, multi-institution, randomized clinical trial might provide sufficient evidence of a new agent's safety and effectiveness. For example, if the multi-institution study findings strongly demonstrate a net clinical benefit from the new agent, and the findings are consistent across study centers, then the results from this kind of single trial supported by results from prior studies might be interpreted as adequate for full marketing approval. Replicated or substantiated evidence of safety and effectiveness, and other data from the process that leads into Phase II/III clinical trials, provides the foundation for the pivotal studies upon which USFDA marketing approval is based. To receive such approval, a demonstrable benefit under defined conditions, and an estimate of the magnitude of that benefit, must be available. Common risks and their frequency of occurrence during the clinical trials for safety and effectiveness are also taken into account. However, long-term consequences of a drug are typically unknown at the time of approval, so its eventual usefulness may be determined by experience after the approval process.

The early evaluation of a drug for cancer chemoprevention is expected to follow a typical process. Information about preclinical efficacy is needed to justify the initiation of Phase I and II clinical trials of chemopreventive agents. Suitable preclinical evidence of efficacy may be based on either epidemiologic evidence or investigations of in vivo tumor modulation. The ideal results from a preclinical, in vivo tumor modulation study would be a statistically significant, dose-related increase in the length of time to tumor development or a significant reduction in tumor incidence or multiplicity. Confirmation of these results in a second animal model sys-

tem, demonstrating delay or reduction in tumors of the same organ or in a different organ, could provide important supportive evidence. Even without statistically significant results, a dose-related trend showing a decrease in tumor incidence or an increase in latency could be acceptable, particularly when this trend was also supported by in vitro data. Additional confirmation of such a trend in a second animal model system could be helpful. Alternatively, another acceptable set of evidence supporting the initiation of Phase I and II clinical trials for the chemoprevention of cancer would consist of statistically significant findings provided by an appropriate in vivo surrogate endpoint modulation study supported by in vitro data. Confirmation of these results in a second in vivo model of the surrogate endpoint biomarker would be desirable.

In addition to the preclinical studies that provide a rationale for effectiveness, additional standard preclinical studies are needed to assess toxicology, genotoxicity and the effects on reproductive performance, before clinical trials are initiated [4]. Preclinical safety studies that are generally pertinent can be summarized as follows:

1. Toxicity studies in two species (rodent and non-rodent) utilizing the route, schedule, and duration of administration relevant to the proposed clinical trial.
2. A battery of genotoxicity assays (according to ICH recommendations) [5].
3. An assessment of Stage A-B (also known as Segment I) reproductive performance and fertility in the rat in accordance with ICH guidelines [6].
4. An assessment of Stage C-D (also known as Segment II) teratology in both rodent and non-rodent, which should be initiated as early as possible and prior to large-scale testing consistent with ICH recommendations [5].

A detailed discussion of the development of the preclinical pharmacology/toxicology data set needed to support applications to the USFDA is available in guidance documents published in the Federal Register and available on the Internet from the home page of the Center For Drug Evaluation and Research (CDER): http://www.fda.gov/cder/.

When preclinical data are acceptable, USFDA approval can be given for starting initial studies of 1 to 3 months, performed in normal volunteers or in an appropriate population at higher than normal risk of developing cancer. Phase I chemoprevention studies of investigational drugs are performed to understand the pharmacokinetic profile of the drug, and the pharmacodynamics when characterization of pharmacologic effect is technically feasible. Single-dose, fasting and non-fasting studies are followed by repeated daily dose studies at multiple dose levels that serve to establish pharmacokinetics and chronic toxicity. At the time of these studies, it is operationally desirable to develop biomarkers that indicate drug effect and dose response.

If the initial preclinical toxicology studies are short–term, additional preclinical toxicology studies will be needed to evaluate prolonged, chronic dosing to justify subsequent clinical studies of longer duration. Enrollment in longer-term clinical studies should be limited to individuals who might obtain significant benefit from the study drug should it prove to be effective. In this instance, the potential benefit would serve to counterbalance the increasing risks for unpredictable and possibly serious toxicities that might result from prolonged administration of the drug. Compared to studies of 3 months or less, Phase I and II studies where clinical dosing lasts up to 12 months provide needed information about adverse effects associated with chronic dosing and opportunities to assess the effect of extended drug exposure on surrogate endpoint biomarkers that may be correlated with clinical effectiveness. At the conclusion of Phase II chemoprevention studies, the common adverse effects of chronic dosing should be identified and the effect of the agent on candidate surrogate biomarkers, including any evidence of a dose-response relationship and/or tolerance to marker modulation by the agent, should be well established. Standardized biomarker assays and established quality control procedures are critical to this effort.

Phase III as well as late Phase II chemoprevention interventions should routinely use a prospectively randomized study design with double-blinding and placebo controls whenever possible. These measures help to assure balance in both known and unknown factors predictive of outcome, avoiding bias and also the error that may be introduced by time trends. Marketing approval from the USFDA requires evidence from such well-controlled trials to demon-

strate that a cancer chemopreventive agent significantly delays or prevents the occurrence of malignancy with acceptable safety. The key objective of studies of chemopreventive therapy is a reduction in site-specific cancer incidence, ideally demonstrating a corresponding decrease in site-specific cancer mortality. However, it is also important to look beyond cancer incidence and mortality to overall mortality, since it is possible that benefits from a reduction in site-specific cancer mortality could be eroded by increased mortality from other causes. Although less desirable than never developing cancer, a delay in the development of cancer at a specified organ site is also a favorable outcome, which may lead to a reduction in age-specific cancer incidence and, in turn, a subsequent reduction in age-specific mortality at that organ site in a treated population.

In North America, two especially large chemoprevention trials sponsored by the USNCI are broadening the agenda of the cooperative group clinical trials network. The resources needed to conduct these trials illustrate the magnitude of resources required to mount chemoprevention trials based on primary cancer incidence endpoints and subsequent mortality. It has been estimated that the Breast Cancer Prevention Trial (BCPT) with tamoxifen has an 80% power to detect a minimum 30% reduction in breast cancer incidence at 8 years of follow-up [7]. The design of the BCPT uses randomization, double-blinding, and placebo controls. A sample size of 13,000 is estimated to be sufficient to achieve the goals of the trial. The cost of this endeavor was estimated to be $60,000,000 at start-up. Like the BCPT, the Prostate Cancer Prevention Trial (PCPT) is a large randomized, double-blind, placebo-controlled chemoprevention trial [8]. The sample size of the PCPT is 18,000 men, and the study is estimated to have 90% power to detect a minimum 25% reduction in prostate cancer prevalence after 7 years of finasteride intervention. The estimated cost of this trial is similar to the cost of the BCPT. These trials are but two of many examples that might be given.

By 1993, the USNCI had provided the resources to support at least 9 major (more than $1 million per trial per year) chemoprevention trials [9], including BCPT, PCPT, and several trials with beta-carotene. The ATBC [10] (Alpha- Tocopherol, Beta-Carotene) and the CARET [11] (Carotene and Retinol Efficacy Trial) trials were informative, but illustrate the point that extensive prior developmental work may not automatically guarantee that drug effectiveness will be observed in the later phase trials of agent development. The number of trials that can be performed on this scale is obviously limited. The desire to optimize the efficiency of clinical evaluation of chemopreventive agents has stimulated interest in surrogate biomarkers, which may have the potential to reduce the resources needed to demonstrate the effectiveness of a chemoprevention intervention based on endpoints that are predictive of cancer incidence, but determined earlier or more readily than the actual occurrence of malignancy.

A surrogate marker for cancer prevention is defined as an observable event shown to be a highly significant and predictably accurate correlate of the risk of subsequent malignancy. Although a definition is easily provided, the scientific acceptability of a surrogate endpoint for cancer is more difficult to define. At this moment, the surrogate markers closest to being accepted in lieu of a cancer endpoint may be precursor lesions such as the adenomatous colorectal polyp in which colorectal cancer may develop, or oral leucoplakia, which may give rise to a subsequent malignancy. The investigation and characterization of potential surrogate endpoint biomarkers has been the subject of numerous articles [12–15]. In some circumstances, the favorable effects of a chemopreventive agent on a surrogate marker might be used as a basis for marketing approval, even before there is final proof that the agent is delaying or preventing the occurrence of a malignancy. However, such a decision would depend on the nature and quality of the data regarding the predictive value of the surrogate marker, including the data supporting the value of a favorable effect from the drug on the surrogate marker as a predictor of reduced risk of malignancy.

A surrogate endpoint is more likely to be persuasive when it represents an obligate step in the pathway to cancer and shows consistent association with cancer development. Surrogate endpoints with an unproven or inconsistent association with cancer development are less likely to persuade. For the USFDA, accelerated approval using a surrogate endpoint is based on the Code of Federal Regulations, Title 21, Section 314.500. According to the regulations, the accelerated approval mechanism applies when certain conditions prevail:

1. The new drug is intended to treat a serious illness and offers meaningful therapeutic benefits compared with existing treatment as documented by an effect on a surrogate endpoint.
2. The surrogate endpoint is "reasonably likely" to predict clinical benefit.
3. Controlled studies will be carried out with "due diligence" to eventually verify the net clinical benefit to patients (e.g., reduced cancer incidence, improved survival).
4. If post-approval controlled studies fail to show a net clinical benefit, there is provision for accelerated withdrawal of the drug.

The implementation of these concepts will be assisted by the actual submission of applications with surrogate endpoint cancer biomarkers and by working through the questions raised by those submissions.

Given the considerations of study size, duration, and cost that hamper development of potential cancer chemopreventive agents, studies designed to examine the predictive value of surrogate endpoint biomarkers are of great importance to the future development of chemoprevention research. However, optimism about the use of intermediate markers should be tempered with a certain amount of caution. There are examples of investigational cardiovascular medications that favorably affect intermediate markers without a corresponding effect on final endpoints [16]. Another potential pitfall of relying on an effect predicted by a surrogate marker would be the possibility of unexpected toxicity from a long-term drug exposure not anticipated from the relatively brief period of observation during the agent's clinical development. A third possibility with a surrogate marker would be the occurrence of a false-negative outcome, if an active chemoprevention drug failed to produce a postulated effect on a candidate surrogate biomarker.

Though underutilized, factorial design may maximize the scientific reward from clinical chemoprevention trials. Such a design was used in the Linxian study [17]. With a factorial design, the participants simultaneously contribute data to the analysis of more than one study intervention. Admittedly, the results from a study with a factorial design may present difficulties with data interpretation, especially if there are interactions.

As this conference has demonstrated, much progress has been made in developing cancer chemopreventive agents and surrogate markers that offer promise for accelerating the future development of cancer chemopreventive agents. This presentation has reviewed some of the developmental activities that precede and follow the filing of an IND and lead to a technical basis for filing a New Drug Application (NDA) or a supplemental NDA for a drug that has gained prior approval for another indication. Investigators who work to develop cancer chemopreventive agents may wish to stay informed about the most recent regulatory guidance or guidelines available from the USFDA. These documents are routinely published in the Federal Register, which is available on the Internet. Electronic versions, including those with information about INDs and NDAs, are also available via Internet by connecting to the CDER FTP server at the USFDA using the address: CDVS2.CDER.FDA.GOV.

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