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Strategy and Planning for Chemopreventive Drug Development: Clinical Development Plans

Gary J. Kelloff, MD[1], James A. Crowell, PhD[1], Charles W. Boone, MD, PhD[1], Vernon E. Steele, PhD[1], Ronald A. Lubet, PhD[1], Peter Greenwald, MD, DrPH[2], David S. Alberts, MD[3], Joseph M. Covey, PhD[4], Linda A. Doody, PhD[5], Gene G. Knapp, MS[5], Susan Nayfield, MD, MSc[6], David R. Parkinson, MD[7], V. K. Prasad, PhD[8], Phillip C. Prorok, PhD[9], Edward A. Sausville, PhD[10], and Caroline C. Sigman, PhD[5]

[1] Chemoprevention Branch, Division of Cancer Prevention and Control (DCPC), National Cancer Institute (NCI), Bethesda, MD 20892
[2] Director, DCPC, NCI, Bethesda, MD 20892
[3] University of Arizona Cancer Research Center, Tucson, AZ 85724
[4] Pharmacology Branch, Division of Cancer Treatment (DCT), NCI, Bethesda, MD 20892
[5] CCS Associates, Mountain View, CA 94043
[6] Early Detection and Community Oncology Program, DCPC, NCI, Bethesda, MD 20892
[7] Investigational Drug Branch, DCT, NCI, Bethesda, MD 20892
[8] Ogden Bioservices Corporation, Rockville, MD 20850
[9] Biometry Branch, DCPC, NCI, Bethesda, MD 20892
[10] Laboratory of Biological Chemistry, DCT, NCI, Bethesda, MD 20892

Abstract At the National Cancer Institute, Division of Cancer Prevention and Control, the Chemoprevention Branch and Agent Development Committee develop strategies for efficiently identifying, procuring, and advancing the most promising drugs into clinical trials. Scientific expertise is applied at each phase of development to critically review the testing methods and results, and to establish and apply criteria for evaluating the agents for further development. The Clinical Development Plan, prepared by the Chemoprevention Branch and the Agent Development Committee, is a summary of the status of the agent regarding evidence for safety and chemopreventive efficacy in preclinical and clinical studies. It also contains the strategy for further development of the drug that addresses pharmacodynamics, drug effect measurements, intermediate biomarkers for monitoring efficacy, toxicity, supply and formulation, regulatory approval, and proposed clinical trials. Sixteen Clinical Development Plans are presented here: *N*-acetyl-*l*-cysteine (NAC), aspirin, calcium, β-carotene, 2-difluoromethylornithine (DFMO), DHEA analog 8354, 18β-glycyrrhetinic acid, *N*-(4-hydroxyphenyl)retinamide (4-HPR), ibuprofen, oltipraz, piroxicam, Proscar®, sulindac, tamoxifen, vitamin D_3 and analogs, and vitamin E. The objective of publishing these plans is to stimulate interest and thinking among the scientific community on the prospects for developing chemopreventive drugs.

At the National Cancer Institute, Division of Cancer Prevention and Control, the strategy and planning for clinical chemoprevention studies is carried out through the Prevention Trials Decision Network. The Decision Network has three operating committees—Endpoints and Biomarkers Committee, Large Trials Committee, and Agent Development Committee. The Chemoprevention Branch, working with and through the Agent Development Committee, provides scientific and administrative oversight for chemopreventive drug development. Its scope ranges from drug discovery and preclinical evaluation through conduct of clinical trials.

The Agent Development Committee is charged with developing efficient strategies for identifying, procuring, and advancing the most promising drugs into clinical trials. Scientific expertise of the committee is applied at each phase of development to critically review the testing methods and results, and to establish and apply criteria for evaluating the agents for further development.

The Clinical Development Plan, prepared by the Chemoprevention Branch and the Agent Development Committee, is a summary of the status of the agent regarding evidence for safety and chemopreventive efficacy in preclinical and clinical studies. It also contains a strategy for further development of the drug that addresses pharmacodynamics, drug effect measurements, intermediate biomarkers for monitoring efficacy, toxicity, supply and formulation, regulatory approval, and proposed clinical trials. A significant aspect of the evaluation is complying with FDA[1] guidelines for drugs to progress to clinical trials and for marketing approval. Although no formal FDA regulations exist specifically for cancer chemopreventive drugs, the Chemoprevention Branch and FDA have worked together to draft consensus guidance [1].

Sixteen Clinical Development Plans are presented following this paper:

- *N*-Acetyl-*l*-cysteine (NAC)
- Aspirin
- Calcium
- β-Carotene
- 2-Difluoromethylornithine (DFMO)
- DHEA Analog 8354
- 18β-Glycyrrhetinic Acid
- 4-HPR
- Ibuprofen
- Oltipraz
- Piroxicam
- Proscar®
- Sulindac
- Tamoxifen
- Vitamin D_3 and Analogs
- Vitamin E

These agents showed significant promise when their development was undertaken and have made progress in clinical studies. That is not to say that they are the best or the only candidates of their class to be developed; some may be replaced or dropped. New drugs are being evaluated continually. In many of the Clinical Development Plans, the strategies presented include evaluation of newer agents with improved properties—that is, greater efficacy and reduced toxicity.

For example, the nonsteroidal antiinflammatory drugs (NSAIDs) under development (aspirin, ibuprofen, piroxicam, and sulindac) have demonstrated considerable efficacy in preclinical studies against colon and bladder cancers [2–12]. A primary mechanism of action of these drugs is inhibition of the cyclooxygenase activity in prostaglandin (PG) synthesis. This inhibition may contribute to chemopreventive efficacy. However, PGE_2 in the gut promotes protective mucosal secretions, and the lowered gut PG levels resulting from NSAID administration are associated with one of the major side effects of longterm NSAID treatment, gastrointestinal ulceration and bleeding [*e.g.*, 13]. Likewise, PGs in the kidney and thromboxanes in platelets are important to normal physiological function, and their inhibition is associated with renal tubule toxicity and excessive bleeding, respectively [14]. Thus, the development of chemopreventive agents which retain the ability to inhibit the carcinogenesis-associated activities of PG synthesis without depressing its protective effects is an attractive strategy. The discovery of an inducible form of cyclooxygenase (COX-2), which is predominant at inflammation sites and in macrophages and synoviocytes, suggests that such an approach is feasible. In contrast to COX-2, constitutive cyclooxygenase (COX-1) predominates in the stomach, gastrointestinal tract, platelets, and kidney. The NSAIDs currently under development inhibit both forms of the enzymes, but other compounds inhibit COX-2 selectively—for example, a newly synthesized NSAID, NS-398 [15,16]. Such agents may

[1]Please see Appendix A: Abbreviations at end of this Supplement.

prove to be desirable alternatives for the NSAIDs currently being developed.

A second example is the development of more potent carotenoids acting by mechanisms different from β-carotene, which may derive its efficacy partially from bioconversion to vitamin A. For instance, α-carotene has only half the provitamin A activity of β-carotene, but is 10 times more efficacious than β-carotene in preventing lung, liver, and skin carcinogenesis in animal models [17]. Third, the development of the antiestrogen tamoxifen as a chemopreventive drug for breast cancer has been well-publicized, along with the increased risk for endometrial cancer that may be associated with its partial estrogen agonist activity [18]. Other antiestrogens devoid of or with less agonist activity may be considered for development.

A development strategy that may be particularly productive is the use of combinations of agents. Lower doses of two agents with complementary mechanisms of action may provide equal or greater efficacy with reduced risk of side effects. Several combinations are now being considered for development on this basis. Examples are the NSAID piroxicam with the ornithine decarboxylase inhibitor DFMO for prevention of colon and bladder cancers, and tamoxifen with 4-HPR for prevention of breast cancer. Combinations of a chemopreventive agent with a second drug specifically chosen to prevent known toxicity of the chemopreventive agent are also being considered. One such combination would be a chemopreventive NSAID with an antiulcer agent.

The Clinical Development Plans presented here are the first of a series to be published. The Chemoprevention Branch and the Agent Development Committee will continue to prepare plans on new agents as well as update this first set of plans. The objective of this publication is to stimulate interest and thinking among the scientific community on the prospects for developing chemopreventive drugs. Comments on these agents and strategies for development are welcome, as are suggestions for additional agents to be evalulated.

EXPLANATION OF DATA COVERED IN CLINICAL DEVELOPMENT PLANS

The Clinical Development Plans represent the work of the Chemoprevention Branch and Agent Development Committee through September 30, 1994. The plans are reviewed and updated approximately every six months. The elements comprising the plans are described below.

Drug Identification

The chemopreventive agent is usually identified by the USAN name for the drug substance or the registered name of the drug product being developed. Other identifiers are the Chemical Abstracts Service (CAS) Registry Number and the CAS 9th Collective Index Name. Also listed are any synonyms, such as common names, registered drug names in which the agent is an active ingredient, and alternate chemical names. Other salt forms and closely-related derivatives are cited. The chemical structure of the agent is also included.

Executive Summary

The first part of this section is a brief statement of the regulatory status and indications of the agent, if applicable. If the agent is an approved drug or in clinical trials, the human therapeutic dose range is included. The reasons for developing the drug as a chemopreventive agent are then summarized. These may include relevant mechanism(s) of action, the tissues in which it modulates carcinogenesis (including intermediate biomarkers), and pharmacokinetic, pharmacodynamic and safety considerations. Comparisons with other drugs under development also may be made.

The progress to date in the agent's development as a chemopreventive drug is reviewed. The models in which preclinical efficacy was demonstrated are summarized. A conclusion regarding the adequacy of these studies in supporting FDA requirements and the Chemoprevention Branch/FDA consensus guidance for clinical trials is then reached. Both NCI-sponsored and published studies are included in this evaluation. Any assays showing modulation of intermediate biomarkers of carcinogenesis by the agent are noted, since this is an important aspect for the future development of chemopreventive drugs.

Preclinical toxicity data from the Chemoprevention Branch testing program, the manufacturer's *Investigator's Brochure*, other IND or NDA filing information, and the literature are summarized. The relevant results are stated, plus an evaluation of their adequacy in fulfilling FDA requirements for approval to start clinical trials and complete development of the drug.

Next, any completed, existing, or planned NCI-sponsored clinical trials are summarized. Any relevant published epidemiological or clinical trial data may also be included.

Finally, information on the drug supply and formulation is provided. This may include the status of the drug supply, patent status, the means of acquiring the drug, the source, the formulation type, and the availability of a suitable placebo.

Preclinical Efficacy Studies

This section evaluates the extent to which chemopreventive efficacy has been demonstrated in preclinical models/assays. A conclusion regarding the adequacy of these studies in supporting further development is reached. The most compelling evidence for efficacy is from *in vivo* tumor modulation studies. Relevant *in vitro* assay results may be included to strengthen the evidence. In keeping with the design of IND and NDA submissions, NCI-sponsored results are discussed separately from published data.

Chemopreventive efficacy may also be demonstrated by at least one *in vivo* study which shows statistically significant modulation of an intermediate biomarker of carcinogenesis. The biomarker should reasonably predict modulation of tumor incidence/multiplicity or latency. A dose-related effect should also be demonstrated. Information on modulation of intermediate biomarkers is an important component of this section. A significant effort in the Chemoprevention Branch program is to identify and validate intermediate biomarkers of carcinogenesis and the potential for chemopreventive agents to modulate these markers. Such studies may also identify biomarkers for future evaluation as surrogate endpoints in clinical trials. The identity of the intermediate biomarkers and the tissues in which they were measured should be included from both NCI-sponsored studies and published studies from other sources.

The effective plasma concentration is included, if available, for each assay type so that the Phase I dosing strategy can be pharmacologically guided. If this concentration is not available, the efficacious dose is stated in the appropriate units.

Preclinical Safety Studies

Safety In this section, the animal toxicity studies sponsored by the NCI are critically evaluated for compliance with FDA requirements. Preclinical toxicity studies required by the FDA for initiation of Phase I and II clinical trials include investigations of acute (single dose) and subchronic (30-day, 90-day dosing) toxicity (incorporating pharmacokinetics), reproductive performance and genotoxicity. The toxicity studies should be conducted in two species, rodent and non-rodent, and should be of equal or greater duration than the proposed clinical trials. The route of administration should be equivalent to that for the clinical trial, unless a rationale can be provided for another route. When possible, the drug substance should be administered in the same form as the clinical trial formulation. As is usual in FDA-required toxicology studies, clinical signs, clinical chemistry, hematology, urinalysis and pathology should be assessed. Segment I (rat) and II (rat, rabbit) reproductive studies should be performed before clinical trials of long duration. In addition, deficiencies in the results or performance of the studies are noted.

Relevant information from published subchronic or chronic toxicity studies can be included to give an indication of the agent's relative toxicity. If available, toxicity data from the manufacturer's previous IND or NDA filing are summarized. In some cases, however, this information may not be readily accessible. A manufacturer's IND or NDA can be cross-referenced if the toxicology studies are adequate and the manufacturer agrees. For a long-used, approved drug such as ibuprofen, it may not be necessary to formally make reference to previous regulatory filings. Instead, the Summary Basis of Approval for such drugs is obtained and reviewed for this information. The MTD and the NOEL from the toxicity studies are listed if available. This information may be useful in determining the human dose range.

ADME This section summarizes the pharmacokinetics of the agent. ADME represents what the body does to the drug. Estimates of plasma $t_{½}$, AUC, C_{max}, C_{min}, C_{ss}, V_d, Cl_r, Cl_p and t_{max} are included, if available. These parameters provide a dose-concentration profile of the drug for guiding clinical dosing regimens. Species similarities and differences in the ADME of the agent are evaluated. The pharmacokinetics in certain species may also be relevant to the applicability of their toxicity or efficacy results to humans. For example, in both rodents and humans, approximately 50% of a DFMO dose is absorbed; the rest is excreted through the colon [19]. The absorbed DFMO is excreted primarily *via* the urine. DFMO inhibits carcinogenesis in the colon and bladder of both rats and mice [2,6,12,20–27]. The similarity of the pharmacokinetics in rodents and humans suggests colon and bladder as targets for chemoprevention by DFMO. In contrast, the identity of the major

metabolite of tamoxifen differs between humans and most experimental animals (rats, dogs, mice, monkeys). In the latter, the metabolite is 4-hydroxytamoxifen, a more potent antiestrogen (efficacy) with partial estrogenic effects (uterine toxicity) [18]. In this case, it is difficult to predict the effective dose level in humans.

Clinical Safety: Phase I Studies

All NCI-sponsored Phase I studies, which have been completed, are in progress, or planned are described in this section. Relevant information from Phase IIa studies also is included. This is a narrative summary of the information contained in the data table (Table I) accompanying each clinical development plan. Information from manufacturer-sponsored or published studies may be included as necessary, but is clearly designated as such.

Drug Effect Measurement Drug effect measurements are tissue, plasma and urine indicators of the pharmacological activity of the drug. A biochemical change related to the drug should be correlated to an effective tissue, plasma or urine concentration of the active drug form. This also serves to estimate compliance. It should be noted that this measurement may be unrelated to tissue effects producing efficacy (*i.e.*, intermediate biomarkers) or toxicity. In this section, the identity and applicability of the drug effect measurement are assessed. Some of the criteria include correlation of the measurement level to dose, stability of the measurement with chronic drug intake, ease of obtaining a tissue/fluid sample, and accuracy and precision of the assay method for the drug effect measurement. For example, DFMO is an irreversible inhibitor of the activity of the enzyme ODC. The drug effect measurements for DFMO have been under evaluation in NCI-sponsored Phase I/II trials. Those which show potential include polyamine levels in urine or colorectal mucosa, or TPA-induced ODC activity in skin punch biopsies. In contrast, measurements of ODC activity and polyamine levels in leukocytes, lymphocytes and erythrocytes proved to be too low and too variable for consideration in future trials.

Safety Single- and multidose Phase I clinical trials are designed to investigate the dose-related pharmacokinetics and safety of the chemopreventive drug in a single-arm trial. The major endpoints are identification and incidence of the spectrum of adverse effects, including determination of a dose-response relationship. Ideally, dose-escalation should continue until minor side effects are seen in the majority of subjects at the highest dose [28]. In this section, the results of any Phase I trials are presented and evaluated based on the above functions.

Phase IIa trials may also produce safety data, although the primary endpoint is to identify the minimum dose at which a measurable biological effect occurs (*i.e.*, using a drug effect measurement or intermediate biomarker).

ADME As for preclinical safety studies, values for pharmacokinetic parameters are identified. Distribution to the target tissue, drug metabolism, and the best dosing interval are addressed as appropriate. The pharmacokinetic profiles after acute and chronic dosing are compared for impact on the dosing schedule in future trials. Finally, validation of assays for the drug and its metabolites in body fluids/tissues are assessed.

Clinical Efficacy: Phase II/III Studies

As mentioned above, the minimum safe dose at which measurable biological effects can be observed has usually been determined in a non-randomized, shorter Phase IIa trial. Phase IIb trials are randomized, placebo-controlled trials with modulation of intermediate endpoints and drug effect measurements as endpoints. A significant aspect of these trials is to identify intermediate biomarkers with the potential to serve as surrogate trial endpoints, to establish a dose-biomarker response relationship, and to select a safe dose for a Phase III trial. Also, potential side effects with chronic treatment may be more closely evaluated with standardized criteria for degree and frequency.

In this section, completed and ongoing Phase II trials are reviewed and evaluated for the characteristics and results described above. For Phase II trials in progress, the cohort, endpoints, and rationale are summarized. Epidemiological evidence of chemopreventive efficacy can be sufficient to support Phase II development of a drug. Examples are β-carotene, vitamin E and calcium. Some published clinical evidence may be available, such as the case histories of the effect of the NSAID sulindac on colonic adenomatous polyps. Proposed Phase II trials are also reviewed, with a discussion of the rationale.

Pharmacodynamics

The pharmacodynamics of the chemopreventive agent are described. Influences of the interaction of

the drug with a receptor (used in its widest definition) to produce a biological effect (toxicity or efficacy) are evaluated. Considerations include the concentration of the drug required to produce an effect in a target tissue, or the length of time the receptor-drug interaction lasts. As an example, systemic metabolism of 4-HPR to 4-MPR contributes to the chemopreventive activity of this drug. 4-MPR has been shown to accumulate in the mammary glands [29] of humans and animals; cancer inhibition has been demonstrated in this tissue in mice and rats [30]. It is unknown if the metabolite binds to retinoic acid receptors, or if this is necessary for efficacy. If this could be determined, the clinical dose of 4-HPR might be lowered to produce only the level of 4-MPR necessary for the pharmacologic effect. In turn, a lower dose could reduce the potential for the ophthalmic toxicity associated with 4-HPR.

An important aspect of this section is a comparison between the effective doses in animals and humans. When blood levels are available from preclinical assays, they are also compared with human data. Critical evaluation of these data can allow pharmacodynamically guided prediction of the effective human dose. AUC is considered the most appropriate predictor of biological effects across species [31]. When blood levels are not available, the magnitude and range between the toxic and effective doses are compared between animals and humans. For example, the lowest effective dietary dose of DFMO against AOM-induced colon cancer in the rat was 1/20 of the one-year rat NOEL. This suggested that the tolerated human dose of 0.5 g/m^2/day could be titrated to lower doses against ototoxicity while retaining efficacy.

Proposed Strategy for Clinical Development

This section recommends strategies for continued development of the drug, as well as approaches to solving identified problems or insufficiencies.

Drug Effect Measurement Issues The applicability and reliability of drug effect measurements identified in animal and human studies are issues addressed here. Consideration is given to the sensitivity, reproducibility, and standardization of the analytical method for an acceptable drug effect measurement. Other issues discussed include tissue sampling and handling. A plan for addressing any inadequacies is included, if necessary.

Safety Issues Strategies for overcoming any obstacles to clinical development of a drug with regard to toxicity are addressed in this section. This may involve special studies in preclinical models to characterize the adverse effect and its relationship to the administered dose. For example, the effect of DFMO on hearing acuity was evaluated in special rat and dog studies. Another consideration is the best method to measure any potential adverse effect in clinical trials. For DFMO, future trials will have standardized criteria for reporting and characterizing hearing loss.

Pharmacodynamic Issues Any issues related to the drug-receptor interaction and the resulting biological effects are discussed in this section. Special consideration is given to the adequacy of the estimated therapeutic ratio. For example, as noted above, both the gastrointestinal toxicities and the efficacy of NSAIDs may result from inhibition of PG synthetase (cyclooxygenase). Strategies to decrease the interaction between the drug and the enzyme in the upper gastrointestinal tract while retaining effective drug concentrations in target tissues would be addressed here.

Regulatory Issues The fulfillment of FDA requirements for clinical testing is assessed in this section. Any additional toxicology studies needed are noted; the timing of these studies relative to the proposed clinical trials is also discussed.

Intermediate Biomarker Issues Intermediate biomarkers are biological alterations in tissue occurring in carcinogenesis before malignant invasion. They include histological changes, and differentiation, proliferation, and genetic biomarkers. Preclinical studies identify potential biomarkers, standardize/validate assays for biomarkers (*e.g.*, sampling procedures, analytical techniques, parameters measured, data collection and data interpretation), demonstrate modulation by a chemopreventive agent, and evaluate intra/intersubject variability. The next step is to demonstrate that intermediate biomarker modulation correlates with decreased cancer incidence/multiplicity or increased latency. For epithelial cancers, the closest causal association exists between intraepithelial neoplasia (*i.e.*, histological/premalignant lesions) and increased cancer risk. After the intermediate biomarker has been established, chemopreventive efficacy can be measured as modulation of this endpoint. Phase II clinical trials then explore similar aspects in human populations. Demonstrating the correlation between intermediate biomarker modulation and decreased cancer risk in longer Phase II chemoprevention trials will begin to validate the biomarker as a surrogate endpoint for future trials; final validation will be part of Phase

III trials. All the aspects mentioned above which are related to identification, modulation, and validation of intermediate biomarkers are issues evaluated in this section.

Supply and Formulation Issues The availability of bulk, finished dosage form, and placebo drug supply is reviewed in this section. Finished dosage forms can be procured by several methods, such as direct purchase, or free from the manufacturer in an acceptable formulation. Potential problems which affect supply of the drug for existing and planned preclinical and clinical studies include cessation of manufacture by the drug company, expiration or instability of present drug supply, and necessity to change formulations. When formulations are prepared from bulk drug, the process can take up to 12–14 months. All these issues affect the timing of proposed clinical trials.

Other formulation issues include palatability, odor, and bioavailability. For example, NAC formulated as a powder to be dissolved in fruit juice was found too distasteful by patients in Phase I trials. In further trials, a capsule formulation will be used. In cases where the formulation changes, it is necessary to incorporate a time period for preparation and testing the dosage forms into the Clinical Development Plan.

Clinical Studies Issues This section includes the strategy for the clinical phase of development. The acceptability of the completed and existing clinical trials is assessed from a regulatory viewpoint. Additional proposed and planned Phase II trials are evaluated critically for relevance, priority, and need. The final goal of the development plan is to place chemopreventive drugs in Phase III trials to validate intermediate biomarkers as surrogate endpoints and to demonstrate cancer incidence reduction or extend the period until cancer onset or recurrence. These planned Phase III studies are reviewed in this section.

References

Full bibliographic references to information contained in the plan are cited.

Data Table (Table I)

This table shows completed, existing, proposed, and planned NCI-sponsored/funded Phase I, II, and III clinical trials. The first column includes the study contract or grant number, the title of the study, the Principal Investigator, the period of performance, and the IND number and sponsor. The second column lists the target organ (which is not generally applicable to Phase I trials). The third column includes a description of the cohort and its size. Next, the doses of the agent are listed with the duration of the study, including follow-up. The fifth column contains a description of all the study endpoints, including drug effect measurements, intermediate biomarkers, efficacy, and toxicity. If any of the endpoints have not fulfilled the criteria described above, this is noted. In the final column, the status (*i.e.*, complete, in progress, *etc.*) and adequacy of the study are indicated. If completed, the findings are listed, including pharmacokinetics parameters, efficacy measurements, and adverse effects. References to publications arising from the study are also listed.

Development Schedule Chart

This Gantt chart represents the development plan for the drug. The duration and timing of all preclinical efficacy, toxicology, and clinical trials are displayed graphically as bars stretched over a time period. Completed studies or portions of a study are differentiated from proposed studies or uncompleted portions of a study by different fill patterns in the bar(s). Also, critical time points for making decisions or completing tasks such as a new formulation may be indicated.

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