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Criteria for Implementation of Large and Multiagent Clinical Chemoprevention Trials

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Abstract If one were to wait for the perfect set of experimental results before launching a multi-agent chemoprevention or large risk reduction study, the trial would never be launched. On the other hand, non-scientific considerations have led to the premature launching of at least three prominent studies (CARET, Carotene and Retinol Efficacy Trial; ATBC, Apha Tocopherol Beta Carotene; PCPT, Prostate Cancer Prevention Trial) and the much delayed start-up of another, BCPT, the Breast Cancer Prevention Trial. Strong epidemiologic data by itself should not be adequate to justify starting a large trial; experimental and/or clinical data should be developed. On the other hand fear of secondary adverse events that are of low incidence should not be enough to delay a trial if the overall health benefit could be high. The development of multiagent chemoprevention trials requires that each agent is active and additively or synergistically so in combination in preclinical models. Additionally, side effects of each agent should be non-overlapping and low to non-existent, preferably a feature determined in formal phase IIa and IIb trials. These principles will be discussed in the context of prior (CARET, ATBC) and ongoing (EUROSCAN, acetylcysteine/retinol), as well as proposed future trials (difluromethyl/sulindac). J. Cell. Biochem. Suppl. 34:115–120, 2000.

Key words: chemoprevention; trials; multiagent

This paper will focus on two major areas: a consideration of criteria for launching large clinical chemoprevention studies and reasonableness of starting multiagent clinical trials.

The time from the detection of preclinical activity of a candidate agent to the completion of the definitive randomized phase III chemoprevention trial takes from 10 to 20 years, depending on whether the agent is being developed de novo (e.g., difluoromethylornithine, 4-hydroxyphenylretinamide) or has a clinical track record in other situations (e.g., Tamoxifen, NSAIDs, non-steroidal antiinflammatory agents). Most of the initial large phase III/IV studies did not go through rigorous clinical trials development [Kelloff, 1994; Goodman, 1992; Meyskens et al., 1998], and the mixed results to date [review in Meyskens, In press] indicates that phase III/IV studies should not be started until careful assessment of the candidate compound has been made in pilot, phase I, and phase II trials. The initial success of some compounds in large chemoprevention trials [Hong, 1990; Meyskens, 1994a, Moon, 1997; Wickerham, 1998] has prompted a renewed interest in multiagent trials since the side effects in single agent trials have been considerable. Numerous investigations in animal models indicate that combinations of two or more compounds at doses lower than either agent is consistently equal or greater in effectiveness to either single compound [Kelloff, 1996]. The anticipation is that a strategy of using lower doses of multiple agents will result in fewer side effects and higher acceptability without compromising efficacy.

LARGE CHEMOPREVENTION TRIALS

Two major questions were asked. The first was: "When should a large risk reduction trial be mounted?" The answer is simple: When it is politically acceptable to do so and there is enough money available. The second and more difficult question to answer was: "When is it

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appropriate to mount a large population risk reduction cancer prevention trial?"

LESSONS FROM THE PAST AND PRESENT

Looking through the retrospectroscope is always dangerous but a brief look at the readiness of several large trials is informative (Table 1). I have designated readiness as a composite score of five categories (maximum of 20 points each): experimental evidence, epidemiologic data, sponsor enthusiasm, political will, and principal investigator stature and effectiveness. Comparisons between 1980 and 1990 are made. The basis for the launching of several large beta-carotene trials in the mid-1980s is of particular interest. Although the epidemiologic data was strong (although indirect), there was no supporting experimental evidence for any of the trials. However, the agent was thought to be non-toxic and enthusiasm for initiating the study was high. Unfortunately beta-carotene produced no effect on health outcomes in normal physicians [Hennekens,1996] and increased the number of lung cancers and total mortality in smoking participants in two large studies [ATBC, 1994; Omenn, 1996]. Whether this outcome would have been avoided by systematic development of beta-carotene through the clinical trials process is problematic since it is unlikely that a change in the definitive endpoint (lung cancer) would have been detected in phase II studies. Since there was some evidence that beta-carotene could function as a prooxidant under certain conditions perhaps experimental data in human systems would have been developed that would have dictated caution [Burton and Ingold, 1994].

A breast cancer prevention trial was proposed by several groups (including our own at the Arizona Cancer Center) in the late 1970s and early 1980s. Although the experimental data supporting the use of Tamoxifen as a chemoprevention agent was nearly as strong in 1980 as in 1990, no epidemiologic evidence (e.g., reduction in incidence of contrataleral breast cancers) was available, the investigators were junior, the National Cancer Institute was not supportive, and the potential pharmaceutical sponsor actively fought the proposed studies (hence minus 10 score). In contrast, by 1990 the support in all areas for the implementation of a trial was strong, the study was implemented quickly, and extremely important results were recently reported [Wickerham, 1998]. Since two other smaller negative randomized trials have been subsequently reported [Veronesi, 1998; Powles, 1998], the issue has become somewhat clouded. The implementation of the Women's Health Initiative was even more political since the scientific evidence did not change substantively between 1980 and 1990. The logjam was finally broken when a prior NIH director worked with Congress to allocate dedicated funds to this $500 million effort. Finally, the readiness of the Prostate Cancer Prevention Trial as assessed by our evaluation is high, but the relatively low scores for experimental and epidemiological evidence for the agent is of concern. The conduct of a phase II study before launching

TABLE I. Large Chemoprevention Trials: A Tale of Key Agents

Agent	Organ	Readiness						Comments	Results
		Agent		Sponsor					
		Epidem-iology	Experi-mental	enthu-siasm	Political will	PI[a]	Total		
B-carotene	ALL	15	0	20	20	20	75	No experimental data	Null result
B-carotene	Caret (ATBC)	20	0	20	20	20	80	SAME	Adverse Result
Tamoxifen	Breast								
1980		0	15	−10	10	10	25	DOA	Not Launched
1990		15	20	20	20	20	95	Launched	Positive Result
WHI	Multiple[b]								
1980/5		10	10	10	5	15	50	Huge Fights	Not Launched
1990		10	10	20	20	20	80	Women's cause celbre	Launched
Finasteride	Prostate	5	10	25	25	20	85	Little Experimental data	Pending

[a]Fat/Diet, HRT, Ca/Vit D.
[b]PI, Principal investigator status and effectiveness.

into the full phase III trial probably would have been prudent.

The message from the retrospectroscope would say that in the implementation of phase III/IV chemoprevention trials: scientific data is not enough; the political will must be there. Of more concern is that prior experience indicates that scientific enthusiasm can overcome the lack of data if the political will and sponsorship is present.

GUIDELINES FOR THE FUTURE

Based on my experience and those of others the following should serve as guidelines for the implementation of large phase III/IV chemoprevention trials. First, the disease should be medically important. Second, since these trials are so expensive, lengthy, and time-consuming a priority system will probably need to be developed to triage funding of approved studies. Thirdly, compounds should probably not be developed solely from epidemiologic data or mechanistic considerations. Experimental and/or clinical studies need to be done. Additionally, favorable modulation of a biochemical/molecular marker of agent action should be demonstratable in the tissue of interest in phase IIa and/or IIb trials. Side effects in these trials should be absent, minimal, or if present, reversible and with a low risk/benefit ratio. Fourth, the agent-appropriate placebo should be available in sufficient quantity to conduct the trial and the enthusiastic participation of the sponsor (pharmaceutical and/or NIH) must be present.

Hong and colleagues have systematically developed oral retinoids for the chemoprevention of aerodigestive cancers [Hong 1986, 1990; Lippman, 1993] and we have done so for topical Beta-trans retinoic acid and cervix chemoprevention [Graham, 1986; Meyskens, 1983, 1994a]. Additionally, we as well as the Wisconsin group, have taken difluoromethylorthine from an orphan (treatment) status to one of the most promising agents in chemoprevention [Love, 1993; Meyskens, 1994a, 1998b]. An important consideration in the phase III/IV studies is whether surrogate endpoints biomarkers markers (SEBMS) are worth doing since these assays add considerable cost [Meyskens, 1992a,b]. My own bias is that measurement of the relevant biochemical parameter (e.g., polyamines for DMFO, prostaglandin's for non-specific anti-inflammatory agents, retinoic acid receptors for retinoids) in the tissue of interest is critical in the phase II studies so that an estimate of agent effectiveness can be made and dose responsiveness determined. Whether SEBMs should be prospectively incorporated into Phase III trials is a complex issues. At the very least a specific question, not dependent solely on the final definitive outcome (e.g., polyps, cancer), should be asked. In contrast, measurement of a variety of markers connected to the carcinogenesis process in only a general way is unlikely to be informative.

MULTIAGENT TRIALS

Lessons From the Past and Present

If the development of single agents for chemoprevention is so lengthy, arduous, and expen-

TABLE II. History of DFMO Development

1978–1988	Treatment trials
<1990	Not on NCI's List (Linear Array for Development)
1991	Analysis of ototoxicity (reversible) and relationship to total cumulative dose shown.
1998–1992	Several animal studies show anti-cancer activity, including the colon.
1992	*Pilot Study* Polyamine contents in rectal and buccal mucosae in humans treated with oral diflouromethlornithine. (Boyle, 1992)
1994	Phase IIa Dose de-escalation chemoprevention trial of α-diflouromethylornithine in patients with colon polyps. (Meyskens, 1994b)
1996	Phase IIb nearly complete
	OR
6/96	Phase III Combination (RFP)
1997	Phase IIb Effect of Diflouromethylornithine on Rectal Mucosa Levels of Polyamines in a Randomized Double-blind Trial for Colon Cancer Prevention [Meyskens, 1998]

sive is it reasonable to develop chemoprevention trials that use more than one compound? There are two compelling reasons to do so. 1) The experimental data is clear that multiple agents are more effective than single compounds in inhibiting or suppressing carcinogenesis in all animal models examined to date. 2) A major limitation of most chemoprevention compounds is their side effects and the risk/benefit ratio must be low for any agent to be acceptable. Since the side effects of most agents is dose related the opportunity to use a lower dose of both agents in combination decreases the potential for toxicity.

Additionally, the positive protective effects of fruits and vegetables against cardiovascular diseases and cancer and the difficulty in demonstrating that any one compound is protective suggests that it is the additive or synergistic effect of low doses of many chemicals that produces this favorable effect [Omenn, 1995]. At least one large randomized trial with multiple antioxidants supports this viewpoint as well [Blot, 1992].

Our own development of the combination of DFMO plus sulindac is a case history for the development of multiagent trials. A brief history of the development of DFMO is shown in Table 2.

A major decision point occurred in 1996 when we had the choice of doing a phase III study using DFMO alone or to combine DFMO with another agent. Our phase II trials allowed us to select a dose of DFMO which suppressed polyamine content in rectal mucosa without producing side effects. Rapidly emerging positive epidemiologic and experimental data about the potential of NSAIDs caused us to look hard at

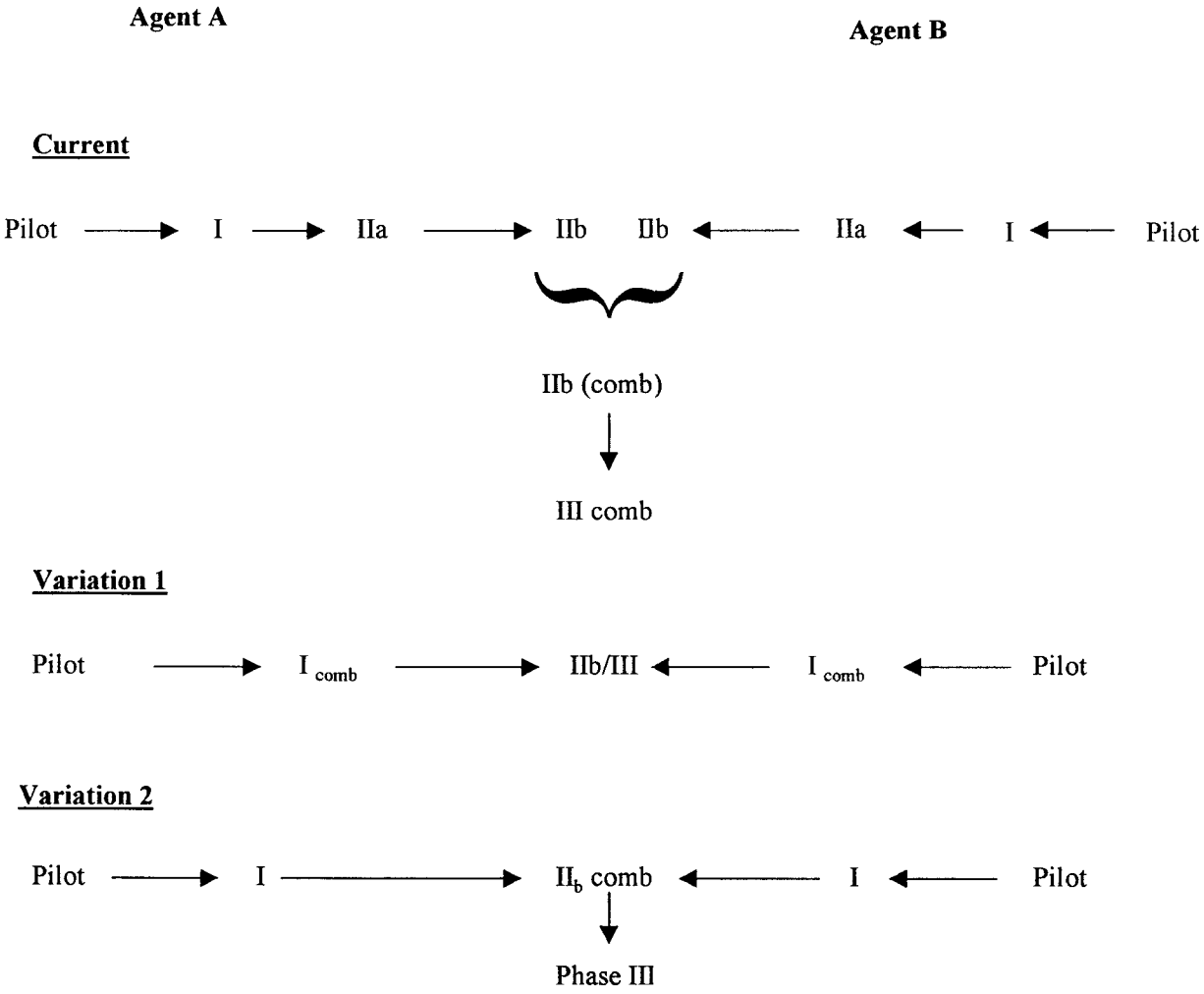

Fig. 1. Evolution and design of combination trials.

this compound Although none of the NSAIDs had been developed as a chemoprevention agent in as rigorous a fashion as DFMO, we carefully considered the options and elected to use sulindac at a low dose (150 mg per day). The dose of sulindac is 50% that of used for therapy and may well be above the lowest effective dose since detailed phase IIa/b studies have not been done.

DIRECTIONS FOR THE FUTURE

Designs for the logical development of chemoprevention agents is shown in Figure 1. Currently, each agent is developed separately and only come together in combination in the late IIb trial stage. Many other designs need to be considered. The design in variation 1 is probably efficient, but is likely to not determine the lowest effective dose (and side effects will be higher) as the phase IIa trial is omitted and phase IIb/phase III is continuous. The design in variation 2 represents a hybrid of the current practice and the extreme variation shown in variation 1. The phase IIa trial is omitted and a full phase IIb trial is done before entering phase III. There are many other designs that could be considered and a major effort needs to be launched to reconsider the design options so that chemoprevention agents can be developed more efficiently and at low risk but in a shorter time span and at lower cost.

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