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PANEL CONSENSUS STATEMENT

Chemoprevention of Prostate Cancer: Guidelines for Possible Intervention Strategies

Abstract The "natural history" of prostate cancer may bedevil the development of guidelines for chemoprevention interventions. Can strategies be designed to direct agents to those lesions which have the potential to develop localized extension that may become symptomatic or metastatic disease? Of necessity our interventions will focus on the identification and quantification of appropriate biomarkers as intermediate endpoints, although no reliable endpoints for prostate cancer have yet been identified. The reduction of prostate cancer incidence may be the ultimate objective, but a decrease in the progression of microfocal or "latent" cancer may well be just as effective as prevention when the age of the target population and competing causes of death are taken into account. Early intervention strategies must focus on the analysis of the interactions of the chosen chemopreventive agents upon precancerous and cancerous cellular dynamics in the prostate. Whether the requirements of such molecular epidemiology necessitate a more deliberate strategy of Phase II studies or a high risk-high gain strategy of a broad Phase III study is open to debate. Factorial designs for proposed randomized chemoprevention trials may be desirable to test multiple chemopreventive agents simultaneously, provided knowledge of the biochemical synergism of the agents is solid. Stratification of study participants by degree of risk will ameliorate concerns regarding the precision targeting of lesions at different stages in the precancer/cancer continuum.

Key words: biomarkers, chemoprevention, premalignancy, prostate, randomized trials, risk stratification

The ideal chemoprevention strategy for prostate cancer (PCa) would be possible if initiating and promoting agents and processes were understood and countervailing agents and processes were demonstrated to be efficacious with no toxicity or side effects [1–4]. Chemoprevention of prostatic premalignancy would ideally proceed if: (a) premalignant lesions [*i.e.*, prostatic intraepithelial neoplasia (PIN) and atypical adenomatous hyperplasia (AAH)] were known to develop into either localized extension that would become symptomatic or into metastatic disease; (b) methods to assess the impact of chemopreventive agents on premalignancies were identified; and (c) clinicians possessed the knowledge and incentive to prevent progression by appropriate drug dosage and duration protocols.

INTEGRATION OF STUDY METHODOLOGIES

The confluence of descriptive and analytical epidemiology, laboratory studies, and randomized trials would similarly provide sufficient momentum for a definitive approach to PCa chemoprevention [5]. Unfortunately, as this conference has demonstrated, such integration awaits further (perhaps considerable) research. Our debates on (a) the sequence and comprehensiveness of such studies and (b) the degree of scientific certainty necessary to embark on primary prevention trials of PCa reflect the dynamic potential in all areas of research. Molecular and genetic epidemiology will provide critical insight into PCa risk [6–8]. Molecular biology will elucidate prostate carcinogenesis. Model systems will demonstrate the impact of chemopreventive agents on the initiation and promotion of PCa. Cooperative clinical research networks will expand to design and implement randomized trials for the prevention of prostate cancer. The question "When?" has been addressed in the preceding paper. In this paper we first present various guidelines for PCa chemoprevention (the "How?") and conclude with a discussion of the two major conceptual strategies for PCa chemoprevention debated at the conference.

TOXICITY LEVELS OF CHEMOPREVENTIVE AGENTS

In chemoprevention research, toxicity standards are established prior to the implementation of efficacy studies; however, investigational results of an agent's potential efficacy will have been indicated prior to any toxicity testing [2,3]. **Toxicity levels must be established in relation to the study population.** The risk of cancer development needs to be balanced against the known toxicities and therapeutic indices of potential chemopreventive agents when designing trials for testing their efficacy. Where *high toxicity* is accept-

able to treat an **established malignancy**, only a *slightly elevated degree of toxicity* is tolerable and acceptable if the target population is at **elevated risk** (*i.e.*, among patients cured of an initial malignancy at higher risk of developing a second cancer). Populations with an **intermediate risk** of developing cancer (*e.g.*, evidence of a preneoplastic lesion which would progress to malignancy if ignored) would require *even less toxicity*. To reduce overall risk in large populations, chemopreventive agents must be entirely free of any side effects.

Toxicity testing will continue to assess potential long-term adverse effects.

EFFICACY AND SELECTION OF CHEMOPREVENTIVE AGENTS

Hypotheses on the initiation, promotion and progression of PCa would suggest the appropriate point at which to intervene and the biochemical impact necessary to prevent or halt the carcinogenic process. Premalignant lesions are presumed to lead inexorably to malignancy but can be thwarted in that process [9]. An anti-promoting agent(s) would halt this either permanently or temporarily. Is there a continuum of progression from normal prostatic epithelium into microscopic prostatic lesions and the further progression of these premalignant lesions into clinically evident lesions? The consensus of this conference suggests that current scientific knowledge is not adequate to answer that question for PCa, even though it may be adequate for other epithelial neoplasms [10]. Should we then consider potential anti-initiating agents as well? That is, in addition to anti-androgens, should chemoprevention strategies for PCa consider retinoids, nonsteroidal anti-inflammatory drugs (*e.g.*, prostaglandin synthesis inhibitors), Vitamin D_3 analogs, CAB and DFMO, or combinations of these agents in factorial designed randomized trials [11–13]? Studies are needed to establish the most efficacious agent or the best combination of agents [14]. Efficacy would include measurements of the biochemical prevention, retardation or reversal of carcinogenesis by the study drug (or drugs), as well as the cost-efficiency of the intervention. With regard to the synergism of activity by combinations of chemopreventive agents that act by different mechanisms, knowledge of inhibitors at various stages and intermediate markers may permit the process to be analyzed in steps. These data might then be related to host and environmental factors which may (have) influence(d) the various stages.

Quantitative techniques are recommended to assess **both** the potential of prostatic premalignancies to progress and the relative impact of the chemopreventive agent(s) on this potentiality of malignancy [15–17]. Bostwick *et al.* [18] have addressed in detail the range of biomarkers to be considered for such assessment. Fine needle aspiration (FNA) would be the recommended sampling modality by which to secure cell samples for various quantitative methods of analysis. However, core biopsies performed by the traditional method of Six Random Systematic Core Biopsies (SRSCB) are likely to remain the common practice because of tissue needs, despite low probabilities of pinpointing cancerous or precancerous foci. Such procedures are based on the *"field cancerization" theory* [19]: an area of epithelium has been preconditioned by an as-yet-unknown carcinogenic agent/process. If the carcinogenic influence is operative long enough in time and intense enough in exposure, it will produce an irreversible change in cells and cell groups in the prostate, so that change of the process toward cancer becomes inevitable. *Whether any currently practiced method of prostate biopsy can assure representative sampling of premalignancy* ***and*** *the potential impact of chemopreventive agents remains highly problematic.* Research is urgently needed in the development of biopsy methods more mathematically precise than SRSCB.

Reduction of PCa incidence would be the critical endpoint measure, but an equally valid measure could be the slowing down or reversal of progression of microfocal or "latent" PCa. The incidence of PCa escalates dramatically at ages when men confront other competing causes of mortality, and simply to prolong the nonclinical manifestation of prostatic neoplasia may be a more suitable and more cost-effective chemoprevention strategy.

Toxicity levels have been established for many potential agents of prostate cancer chemoprevention, including retinoids and 5α-reductase inhibitors; but the efficacy of such agents has not been satisfactorily substantiated. The evidence of efficacy of the latter group, specifically **finasteride**, is only circumstantial. It is based on the drug's actions to reduce: (a) benign hyperplastic growth; (b) levels of dihydrotestosterone (DHT) in the prostate; and (c) levels of prostate specific antigen (PSA), and on the assumption that such reduction retards (or prevents) the growth of cancerous prostate cells [20–22]. In a Memorial Sloan-Kettering Cancer Center study of patients with D_2 PCa, the PSA decrease with finasteride did not come close to what would be expected with conventional hormonal manipulation. At 12 weeks, the overall PSA decrease was on the order of 15%. A drop of this magnitude in a slightly elevated PSA (*e.g.*, 4.5 ng/ml) would put PSA in the "normal" range. If this reflected a decrease in the progression rate of PCa with a marked delay in the development of clinical cancer, this may be exactly the desired marker of PCa chemoprevention [23]. Scientific evidence for such a conclusion is not yet available. Currently, it does not appear that

finasteride is near equivalent to conventional endocrine manipulation in the therapy of metastatic PCa.

Even with fragmentary results, however, it may be appropriate to design a prostate cancer chemoprevention strategy, to identify intervention populations, and to test appropriate recruitment methods.

SELECTION OF APPROPRIATE POPULATIONS

When appropriate toxicity levels have been established and efficacy has been indicated, pilot studies are inaugurated prior to the implementation of an actual cancer incidence reduction trial in a suitably selected population. In cancer chemoprevention trials, it has been considered appropriate to begin with patients at risk of a second cancer or with premalignancies known to progress if not treated. However, these conditions are not applicable to what is currently known about the natural history of PCa, its prognostic indicators, and its accepted modes of treatment.

Stratification of study participants by degree of risk has been agreed upon, but the specific risk factors upon which a chemoprevention trial should be based remain problematic. Premalignant and early malignant prostate lesions may be the best markers for chemoprevention intervention, but research is necessary to verify this for PCa. A family history of PCa, race and age may be the most reliable PCa risk factors; but consensus on their validity for a chemoprevention trial has yet to be established. How would these risks be ranked? Would sufficient at-risk subjects remain eligible after definitive screening was conducted to rule out the presence of PCa among potential participants?

Can another risk stratification schema be considered? The following has been adapted from Rao *et al.* [16] (from highest to lowest risk) and is presented for further consideration:

- subjects with histologically proven disease (*e.g.*, local PCa which would be subject only to "expectant management" or neoadjuvant therapy);
- subjects with prior PCa, abnormal DNA ploidy, and cytology but currently with undetectable disease;
- subjects with no currently detectable disease or prior PCa and negative cytologies, but having a family history of PCa;
- subjects who either have a family history of PCa or are African-American or both;
- subjects from the general population.

DESIGN OF RANDOMIZED CLINICAL TRIALS WITH ESTABLISHED SCIENTIFIC HYPOTHESES AND BIOCHEMICAL MARKERS AS INTERMEDIATE ENDPOINTS

Byar and Freeman [24] have characterized the stages of cancer prevention trials as **primary** if they precede initiation, **secondary** if they are presumed to act on already initiated cells during the promotional phase of carcinogenesis, and **tertiary** when the targets of intervention are precancerous lesions. A randomized chemoprevention trial can be adapted to a wide variety of uses because the design is under the control of the investigators and thus can be tailored to address the specific hypotheses formulated for the study [25].

While primary and secondary prevention trials are designed for subjects at normal or high risk, tertiary prevention trials require the identification and recruitment of individuals with specific precancerous conditions. The identification and recruitment of men with established premalignancy (and no PCa) may be more difficult and time-consuming than if normal subjects were to participate, but fewer participants will be required in a tertiary prevention trial for statistical power and efficiency. In tertiary prevention trials, the disappearance or regression of precancerous lesions, or a demonstrated delay in their recurrence after removal, are useful endpoints that could provide clear results in relatively short time periods. The duration of such trials might range from 6 months to 5 years, depending on the presumed mode of action of the preventive agent(s). Because the incidence of PCa rises sharply with age, surprising gains in statistical efficiency may be achieved by rather modest increases in the total duration of a chemoprevention trial among older men. The calculation of sample size for tertiary prevention trials is similar to methods used extensively for cancer treatment trials [24].

Human intervention studies in PCa chemoprevention should follow a stepwise progression of Phase I, II, and III studies [26]. The endpoint in a Phase I trial is to determine the dose-related safety and toxicity of the intervention agent. Acceptable doses may be different for various study populations. In a Phase I treatment trial the maximum tolerated dose is required, but little or no toxicity is appropriate in a Phase I chemoprevention trial. Efficacy is addressed after safety is established, although efficacy may not be definitively established until a Phase II or Phase III chemoprevention trial. Phase II chemoprevention trials (a) determine whether the agent has biological activity affecting some aspect or stage of the carcinogenesis process, (b) are concerned with the modulation of biological or surrogate endpoints, and (c) are screens for biological activity and thus have all the imperfections of any screening process. In the

startup of a Phase II trial, safe doses (as per Phase I studies) are chosen to test in selected "high risk" cohorts. A risk-benefit analysis determines if Phase III studies should be conducted. An important function of the analysis of intermediate endpoints is establishing methods to identify populations at risk and assessing their risk of developing PCa. Some maintain that Phase III trials are aimed at reducing incidence, but some investigators allow for an outcome of regression of preneoplastic changes and changes in the cellular or biochemical parameters associated with tumor progression [26,14]. These studies are placebo-controlled and double-blinded.

If premalignancy is targeted for chemoprevention, the importance of consistency and uniformity in properly identifying the targeted premalignant lesions cannot be overstated. Likewise, standards for categorizing changes that occur in these lesions will need to be recognized and established. What are the expectations for the actions of one or more chemopreventive agent(s) upon the target lesions? Establishment of a reference laboratory must be given serious consideration.

The consensus of this conference is that chemoprevention directed at premalignant lesions must await further scientific investigation. *However, this panel considers it appropriate to design a neoadjuvant strategy that would compare the effect of hormonal manipulation by a 5α-reductase inhibitor or another anti-androgen agent (or any other chemopreventive agent) on premalignant lesions.*

IDENTIFICATION OF EFFICIENT MEANS TO ACCESS TARGET POPULATIONS

(Will clinical settings be the most appropriate settings from which to accrue study participants?) The answer will depend upon the target population(s) and the selected chemoprevention strategy. Men with premalignancies or early malignancies would likely be recruited through a clinical setting. Would this fact bias their participation in, and expectations, of a chemoprevention trial? First-degree male relatives of PCa cases could be identified through documented family histories. Men who have personal experience with a family member being treated for or dying from PCa may have a greater incentive to participate in a chemoprevention trial for PCa. Disease-free subjects would be recruited from nonclinical community settings. Senior citizen centers, local AARP organizations, African-American churches, and community centers, for example, could be locations from which eligible subjects are recruited. However, administrative structures within existing cooperative group mechanisms may make these approaches too unwieldy. The breast cancer chemoprevention trial with tamoxifen is administered by National Surgical Adjuvant Project for Bowel and Breast Cancer (NSABP). Recruitment of participants is managed through the Community Clinical Oncology Program (CCOP) and the Cooperative Group Outreach Program (CGOP). Local CCOPs and CGOPs had to make applications to demonstrate access to populations and "recruitability" of sufficient numbers to satisfy protocol needs. Chemoprevention trials of PCa may be required to use the same methodology.

When African-American males become the target population for PCa chemoprevention studies, we strongly recommend that African-American urologists be immediately recruited to assist with trial design and recruitment strategies. Focus groups may need to be conducted to validate incentives and identify barriers to African-American participation.

DESIGN OF EFFECTIVE RECRUITMENT AND RETENTION METHODS

Regardless of the environments from which study subjects are recruited, recruitment and retention of "healthy" subjects will nevertheless be difficult. Appropriate educational and promotional efforts would accrue eligible subjects who would presumably undergo some form of "screening" to determine suitability (*i.e.*, premalignancy without malignancy, satisfactory functional status, family history of PCa, etc.). Informed consent would also require informing an individual as to his possession of a marker of uncertain significance (if such is a criterion of eligibility) or informing him of the possession of a marker that will be "under observation only" while he continues on the chemoprevention protocol. Retention of compliant, healthy subjects over the course of several years will be perhaps the greatest challenge of chemoprevention studies in PCa.

Will **compliance** among trial subjects be an issue [27]? In a cancer *treatment* trial, even a blinded or double-blinded study, a natural incentive exists for patients to comply with a drug regimen. Toxicity or treatment failure usually causes a patient to drop out of a study. However, in a prevention trial where "healthy" individuals are required to follow some regimen or protocol, the issue of compliance becomes relevant and drop-out rates are a major design issue. Over-recruitment is often the most appropriate strategy. A PCa chemoprevention trial must be monitored carefully throughout its course (a) to assure that recruitment of target subjects is proceeding as required; (b) to ascertain the level of compliance with the drug regimen or examination protocol; and (c) to end the trial after either clear benefit or harm has been demonstrated. A placebo run-in is usually advisable. That is, prior to randomization subjects are given a placebo and tested for compliance with the drug regimen. An

estimated 10–15% will not comply with the protocol, but these will have been identified prior to randomization. Statistical power will have been preserved [28].

INCLUSION OF PSYCHOSOCIAL DIMENSIONS IN CHEMOPREVENTION CLINICAL TRIALS

As cancer prevention trials reach further into "healthy" populations, the range of related psychosocial issues expands exponentially. A pretrial assessment of knowledge, attitudes, and practices of randomly sampled men in the target population (and perhaps their physicians) could provide clues of ultimate success by identifying potential barriers to compliance and by making allowances for these barriers through trial implementation. Similar assessments during the course of the trial would monitor the prospects for adequate retention so that statistical needs are achieved.

A PARADIGM OF PROSTATE CANCER INTERVENTION

This conference has not resolved the issue of whether to implement Phase II chemoprevention trials of patients with histologically proven PCa or to proceed in a Phase III trial with **finasteride** of men at high risk of developing PCa. The majority of the panel members are opposed to such a Phase III trial at this time because we have no basis which suggests this drug's chemopreventive effectiveness. A possible Phase II strategy would target patients who are radical prostatectomy candidates with small measurable lesions (B_1–B_2 lesions; and A_1–A_2 lesions if PSA levels are not affected by the study chemopreventive agents). Multiple biopsies would be performed to establish baselines of certain biochemical dynamics, and a 3–4 month chemoprevention protocol would be followed. Evaluation of the therapeutic effect would be done not only on the "index lesion" but also on clinically undetected microfocal carcinoma. Studies are conclusive that most patients who appear to have a solitary nodule will have at least one, and frequently multiple, latent carcinomas on careful examination of the rest of the gland. Similarly, familial syndromes appear to be characterized by multifocality. If a marked reduction in the incidence of these latent carcinomas in patients receiving the neoadjuvant therapy is evident when compared with patients who have radical prostatectomies without neoadjuvant therapy, a chemopreventive effect of the study drug would be more strongly indicated. In addition, after the prostatectomy is performed, a panel of intermediate endpoint biomarkers would be evaluated to further document chemopreventive activity. Proponents argue that this strategy follows more closely the "protocol" of cancer prevention studies, while opponents claim it to be only a "fishing expedition."

A Phase III intervention strategy, supporters claim, moves the chemoprevention agenda more quickly to where it will otherwise be at some (indeterminate) future time. High-risk, disease-free individuals (based on family history, race and/or age) would not only benefit immediately, but the same knowledge of biochemical markers could presumably be gained in the process. Critics claim that no known agent possesses the necessary clinical efficacy and lack of toxicity to be used as a chemopreventive for PCa. More carefully controlled studies of the effects of various agents on PSA synthesis and secretion are needed before we can assume that PSA is an appropriate biochemical marker to guide efforts to prevent PCa. A large-scale Phase III chemoprevention trial could then be initiated, but it would have a more solid and acceptable scientific basis.

In sum, consensus on the question of which of the above strategies is more important to pursue at this time will come when some common ground is identified by those who advocate "all deliberate speed" to assure satisfactory answers to scientific questions posed at this conference and others who seek "action now" to preclude unnecessary temporizing. Both strategies may in fact proceed concurrently when that common ground is found.

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E. David Crawford, M.D. (chair)
William R. Fair, M.D.
Gary J. Kelloff, M.D.
Michael M. Lieber, M.D.
Gary J. Miller, M.D., Ph.D.
Peter T. Scardino, M.D.
Edward P. DeAntoni, Ph.D.

Division of Urology
University of Colorado Health Sciences Center
Denver, CO 80262

Urologic Surgery Service
Memorial Sloan-Kettering Cancer Center
New York, NY 10021

Chemoprevention Branch
National Cancer Institute, NIH
Bethesda, MD 20892

Department of Urology
Mayo Clinic
Rochester, MN 55905

Department of Pathology
University of Colorado Health Sciences Center
Denver, CO 80262

Department of Urology
Baylor College of Medicine
Houston, TX 77030

Division of Urology
University of Colorado Health Sciences Center
Denver, CO 80262