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PANEL CONSENSUS STATEMENT

When is Intervention Warranted?

The rising incidence and death rate of prostatic carcinoma, coupled with emerging methods of improved detection, raises at least two important questions. First, can men with the propensity to develop prostate cancer be prevented from developing clinically significant disease? Second, can men with premalignant (PIN) or early cancer (low volume/low grade) be prevented from progressing locally (larger volume/higher grade/extracapsular invasion) or from developing metastatic prostate cancer?

There are many points to be considered prior to determining when to intervene: (1) selection of chemopreventive agents, doses, and schedules—perhaps related to their effectiveness at various points in the carcinogenic cascade; (2) toxicity of the drug chosen and potential interactions with drug treatment of coexisting non-malignant disease; and (3) endpoints of treatment—for example, when monitoring progresssion of known existing cancer, metastasis or death from prostate cancer, etc., may be appropriate endpoints. However, in premalignant or even high risk patients, intermediate endpoints relating to biomarkers of the presence or progression of prostate cancer would be desirable; otherwise the definitive endpoint may take many years (and perhaps many biopsies). Unfortunately, these biomarkers (possible examples are proliferating cell nuclear antigen, transglutaminase I, micronuclei, cytogenetic, molecular, etc.) are only now being described and very little relative to prostate cancer has been reported. Additional points to be considered include: (4) methods of monitoring treatment—there is a paucity of pharmacologic and pharmacokinetic data on most chemopreventive agents with which to assess biological activity of the drugs *in vivo* and to determine patient compliance (*i.e.*, serum or tissue levels); and (5) many other questions relating to statistical design of studies and interpretation of results.

If we assume the above concerns are answered, consideration of when to intervene could be discussed from at least three patient group perspectives, listed below.

I. MEN AT HIGH RISK OF DEVELOPING PROSTATE CANCER

It is now established that primary relatives of men known to have prostate cancer have an increased risk of developing prostate cancer themselves. Black men have the highest incidence of prostate cancer in the U.S. In addition, age alone is a factor in that advancing age has a direct correlation with prostate cancer prevalence. A pertinent clinical trial could prospectively randomize men between the ages of 45 and 60 who have a primary relative known to have prostate cancer or who are black, to receive either a chemopreventive agent or a placebo. Baseline studies would include digital rectal examination (DRE), serum prostate specific antigen (PSA), and transrectal ultrasound-guided quadrant core biopsies. These biopsies could be subjected to histologic study as well as to multiple biological marker probes. Patients could be followed by annual DRE and serum PSA with repeat biopsies and marker studies every three years. The endpoint of the study would be biopsy-proven prostate cancer (or development of an unequivocal marker of malignancy that has yet to be identified).

II. PATIENTS WITH PREMALIGNANT LESIONS, *i.e.*, PROSTATIC INTRAEPITHELIAL NEOPLASIA (PIN)

Patients with high grade PIN frequently have associated prostate cancer. A study designed to prevent progression would require that the subjects have only PIN at study initiation, yet it is currently problematic to completely eliminate the possibility that associated prostate cancer is present. Low grade PIN patients may be candidates for study; however, the lesions tend to be diploid, displaying a very long natural history with few progressing to clinically detectable cancer, and thus would require an extended and probably prohibitively large volume study.

III. PATIENTS WITH EARLY LESIONS

The classic definition of stages A and B prostate cancers is becoming obsolete; thus, a low volume/low grade cancer (<1.0 cm and GL<3) can be considered an early lesion for this discussion. An early lesion discovered by transurethral ultrasound may underestimate the volume of disease present and is not always correlated with the serum PSA value. An early lesion discovered by PSA, but not seen on transrectal ultrasound or felt on DRE may also underestimate the disease volume present. An early lesion discovered by

transurethral prostatic resection certainly may underestimate the volume unless, and perhaps even if, systematic TRUS-guided biopsies are done. While patients with pure transition zone cancers may be appropriate candidates, there are very few such tumors that would be expected to rapidly progress.

Several problems with the study of existing cancers seem evident: (1) inability to absolutely determine whether or not the early lesion is accompanied by adjacent (higher volume) cancer; (2) the number of identifiable patients and the progression rates too low to attain an answer in an acceptable time frame; and (3) the reluctance of physicians and patients to accept randomization to a no-treatment study group.

As an alternative to long-term studies, short-term treatment of patients with known cancer prior to radical prostatectomy may allow observation of various chemopreventive strategies as pilot studies preparatory to definitive trials. Such studies could provide biopsy material prior to chemopreventive treatment, with subsequent study of the whole organ following treatment to assess effects on morphologic, biochemical, cytogenetic, and molecular biomarkers. This approach has merit in that patients will receive definitive treatment previously assigned and accepted, and substantial information may be gained in this neoadjuvant setting. However, the information gained may only be obliquely relevant to the ultimate goal of determining a method to decrease the incidence and mortality of clinical prostate cancer.

SUMMARY

A chemoprevention trial in prostate cancer would be a formidable but potentially rewarding study. The current status of knowledge of drug interactions with, biomarkers of, and even the natural history of prostate cancer is insufficient to study all levels of men at risk. Currently, the most promising group to study is group I—those men with a high probability of developing prostate cancer but who do not currently have evidence of the disease. This could be a placebo-controlled, prospective and randomized study with the endpoint being clinically-detected prostate cancer.

In addition, much may be gained from short-term pilot studies of "chemo-active" agents on morphologic and other biomarkers of prostate cancer initiated immediately before surgical removal. It is hoped that such studies may provide rationale for future efforts directed at preventing progression of premalignant or early prostate cancer lesions.

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