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PCa Commentary

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Contents

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PREVENTION AND DIET: Prostate Cancer Prevention Trial - Final Results At Seven Years

In July the NEJM published the final results of a seven year trial comparing 4369 men taking 5 mg finasteride with 4692 on a placebo. The study hypothesis: 1) by interrupting the enzyme 5 alfa-reductase, finasteride decreases the conversion of testosterone to the more potent dihydrotestosterone (DHT), a conversion which mainly takes place in the stromal cells surrounding normal prostate epithelium; 2) less DHT is then presented to the nearby epithelial cells thereby decreasing their intracellular DHT by 90%; 3) higher loads of DHT are thought to lead to an increase in the development of prostate cancer; 4) ergo: finasteride will decrease the prevalence of PC. [Prevalence: The total number of cases of a disease in a given population at a given time]. And it did - by 24.8% (18.4% developed cancer in the finasteride

group v. 24.4%, placebo). The eligibility criteria for trial participation were age >55, apparent good health, a normal digital prostate exam, and a PSA < 3 ng/ml. As expected finasteride effected a comparative decrease in urinary symptoms, but was associated with significantly more erectile dysfunction, loss of libido, and gynecomastia.

A thoughtful editorial by Scardino, however, raises some important issues. First, he notes that the accepted expected incidence of the diagnosis of cancer in this age group is 6% when a diagnosis results from customary clinical practice indications for biopsy - and he views both the 18.4% and 24.4% values as excessive and requiring explanation. [Scardino's usage of "incidence" is to be differentiated from "prevalence" because of the study's policy of performing biopsies for "no cause"] The NEJM study design did not require a prostate biopsy at entry. Presumably the number of undetected cancers in the men at entry was equal in the groups. Biopsies were performed in the course of the trial if a PSA rose above 4 ng/ml (2 ng/ml for men on finasteride) or clinical findings were abnormal. Participants who did not exhibit these indications for biopsy were asked to undergo biopsy at the end of their seven years - so called biopsies for "no cause". Examination of the study statistics reveals that in the finasteride group 9.9% (435/4368 = 9.9%) were diagnosed with PC as a result of a PSA rise above 4 ng/ml or clinical indications; and in the placebo group 12.1% (571/4692 = 12.1%) were diagnosed as result of meeting these clinical indications. In the category of "biopsy without cause" PC was diagnosed in 8.4% (368/4368 = 8.4%) in the finasteride group v 12.2% (576/4692=12.2%) for placebo. Scardino notes that autopsy studies on asymptomatic men >55 years old have revealed prostate cancer in 30 - 40%, and the NEJM study may have tapped into this subclinical pool of prostate cancer, thus contributing to an explanation of the high rate of PC detection in this study. Scardino discusses this issue of possible "overdiagnosis" of insignificant cancers - cancers that might not have clinical significance during a man's lifetime - that arises from the study schema that includes "no cause" biopsies.

Probably the most worrisome finding, however, was that cancers with Gleason sums >7 were found in 6.4% of the finasteride group v. 5.1% for untreated men. Scardino's concerns are sufficient to make him doubtful that finasteride will be widely used for prostate cancer prevention. If preventive treatment is offered, a full discussion of the details is required.

Bottom Line: Finasteride treatment decreases the prevalence of prostate cancer, but significant reservations exist about the usage of finasteride in prostate cancer prevention.

DIAGNOSIS: Improved MRI Technique for Detection of Lymph Node Metastases

The July 19 issue of the New England Journal of Medicine reported on "Noninvasive Detection of Clinically Occult Lymph-Node Metastases in Prostate Cancer." The technique combines MRI imaging with intravenously administered highly lymphotropic superparamagnetic nanoparticles (containing iron oxide) that are taken up in lymph nodes where the particles are internalized by macrophages. Metastatic deposits do not concentrate the particles and are thereby identified as an uptake "void."

Currently, information as to the likelihood of nodal metastases is principally dependent on correlation of clinical/pathological data as presented in the Partin tables, except for instances of clinical lymphadenopathy (usually defined as nodes > 1 cm.) that usually can be detected by current imagining techniques and confirmed by biopsy if indicated. However, estimates of lymph node positivity can vary widely. For example the new Partin tables (UROLOGY, Dec., 2001) would suggest a 5-18% risk of nodal metastases in a man with PC with Stage T1c, Gleason 8, and PSA >10 ng/ml, whereas Partin and Epstein (CANCER, Feb., 2002) would

estimate the risk at 45% if four or more core biopsies were positive and any core had a Gleason grade of 4, regardless of the PSA value. The recently reported radiation therapy Phase III trial (JCO, May, 2003) was essentially based on an *estimation* of a 15% risk of nodal positivity. Clearly, more accurate pretreatment information about the nodal metastatic status would be helpful.

A Chinese group reported results of 18-F-2 Deoxyglucose Positron Emission Tomography (PET) in men whose pelvic nodes were deemed *equivocal* on CT scanning (Urologia Internationalis, Vol 70, 2003). In their study of 24 men they were able to achieve a sensitivity of 75%, and 100% specificity based on histopathological correlation.

The NEJM report involved the study of 80 men with clinical stage T1, T2, or T3 PC who were preoperatively imaged, first with conventional MRI, and 24 hours later with the new technique. Nodes were considered malignant if the short axis exceeded 10 mm (or 8mm if rounded). The finding of interest relative to this PCa Commentary article is the ability of this technique to detect metastatic deposits in nodes that did not meet the criteria of malignancy. Their results: 1) for nodes with a short axis of 5-10mm (n=45) - accuracy 98.9% (sensitivity 96.4%, specificity 99.3%); 2) for nodes with short axis diameter <5 mm (n=17) - accuracy 90.4% (sensitivity 41.1%, specificity 98.1%)

Dr. Justin Smith, Seattle Radiologist, indicates that the new MRI technique, utilizing the contrast agent "Combidex" (Cytogen Corp), is under review by the FDA and that it is the manufacturer's hope that the agent will be available "soon", particularly owing to the strength of the findings in the NEJM article. At that time, Dr. Smith expects to offer the technique in conjunction with his ongoing interest in endorectal MRI at First Hill Diagnostic Imaging.

Bottom Line: If both PET and ferromagnetic augmented MRI can sustain these results with further testing, clinicians will be provided with an improved level of sensitivity for detection of nodal metastasis that will have an important clinical impact.

ANDROGEN INSENSITIVE DISEASE: Intermittent Chemotherapy for Chemotherapy Responders - An Early Trial

If a chemotherapy regimen fails to produce a response (or achieve an acceptable disease stabilization) after a reasonable trial period, physicians usually discontinue treatment and consider other options. However, there is no consensus regarding the proper duration of treatment for **responders**. Currently, treatment is continued until relapse or until unacceptable toxicity develops. An abstract in the ASCO Proceedings, June 2003, by Tomasz Beer and his Oregon colleagues (abst 1582) reported a trial of intermittent chemotherapy in metastatic androgen independent cancer using the Taxotere/Calcitriol regimen developed by that group (for analysis of that protocol see PCa Commentary, February 2003, archived on the seattleprostate.com web site). The new trial addressed the feasibility of intermittent treatment with the hope that benefit would not be lost and quality of life would be improved - in a sense, treating the disease as a chronic condition. Eleven of the thirty seven men (30%) in the trial met the response criteria and were offered a treatment break. Eight of them were suitable for analysis. The schema: if treatment led to a fall of PSA to <4 ng/ml a break in treatment was offered; and the "holiday" ended and treatment was resumed if the PSA rose by 50% (at least by 1 ng/ml) or symptoms developed. The median duration of the "holiday" for these men was 20 months (range 13 - 43 months). Four patients responded again to treatment and three others achieved PSA stabilization after restarting treatment. One is still on "holiday." These

eight men were at median follow-up of 20.4 months from the start of the trial at the time of this report.

Many medical oncologists will informally utilize "treatment breaks" for a variety of reasons, but this trial, small as it is, is the first reported formal evaluation of this strategy in prostate cancer and establishes feasibility and sets the stage for further evaluation of this commendable idea.

Bottom Line: If supported by additional trials, this is a strategy of merit.

CLINICAL TRIALS:

- An Online NCI Tool For Finding Clinical Trials For Patients: When a patient asks whether there is a clinical trial that he should consider, invite him to your computer and together review the clinical trials that are offered in your geographic area. You know the details of his clinical situation and are his best guide through this material. The most comprehensive and descriptive information for trials in your geographic area can be found at the following website which should be bookmarked for quick access.

  www.cancer.gov/search/clinical_trials/

  On this NCI page, select prostate cancer, the type of trial you are interested in and enter your ZIP code and the number of miles you are willing to send your patient to get to a study site. The many available trials in your area will appear, and, after selecting one, you can view information appropriate for patients or an expanded description for physicians. The information presents the details of the study and indicates which physicians in your area are participating in the trial. Most patients are not sufficiently informed to ask the question about available clinical trials, so it would be a service to them if you offered a review to them.

  NOTE: If you get lost, you can go to google.com and enter "NCI PDQ". Select the "Cancer.gov - PDQ®" listing. Scroll down to "Clinical Trials" and click on "Search for Clinical Trials" Then follow the instructions above

- Clinical Trials at Swedish: The trials in which **Swedish physicians** are participating can be viewed at "www.Swedish.com" - the home page. A side-bar menu offers "select a service"; choose "cancer institute". The next screen will offer "For more information...", select "clinical trials", and on the next page select "prostate cancer". Currently, eight trials are listed. Currently no additional data about a trial can be accessed (but the trial details could be checked at the NCI site).

Bottom Line: Patients will appreciate the review of applicable clinical trials and they will be impressed with your astuteness and the complete service you offer.

IN BRIEF

A Glimpse Of Things To Come - Utilizing DNA Microarray Data to Enhance Prediction : The addition of data indicating the number of prostate biopsy cores that are positive achieves a modest improvement in the accuracy of prediction of pathologic status and treatment outcome afforded by the Partin tables and the Kattan nomograms. However, with this improvement science is very likely approaching the limits of predictability that is achievable based on standard clinical/pathologic information. The next level of prediction of pathology, biologic behavior and outcome will very likely come from incorporating new science into the mix. An example: Cancer Research, July: "Successful Prediction of Prostate Cancer Recurrence by

Gene Profiling in Combination with Clinical Data: A 5-year Follow-up Study". The prostate pathology of 23 men was evaluated retrospectively with the knowledge of 5-year outcome. The researchers had previously identified eight metabolically related genes whose expression was involved in cancer progression. They first estimated the likelihood of cancer recurrence using standard data, i.e. Gleason score, PSA, clinical stage and prostate volume. A second prediction was based on the expression pattern of the eight genes. A final prediction was then constructed based on the combination of the two types of information - a "hybrid", so to speak. The results: using clinical/pathologic parameters the prediction accuracy was 87%; with gene profiling data, 82.6%. The combined data, however, produced an accuracy of recurrence predicition of 95.7%. And this is only the beginning of a new breed of information.

Two Reports From The April AUA Meeting:

- Ten-Year Brachytherapy Results: Ten-year Brachytherapy Results: Researchers from Mount Sinai School of Medicine reported ten-year follow-up data for high dose I-125 brachytherapy treatment in 146 low risk (PSA <10, Gleason sum ≤6; stage ≤ T2a) men with a median age of 67.2 years and T1-T2 tumors. The median follow-up for all participants was 6 years, and 93% of men who received radiation doses of ≥160 Gy were free of disease. Among those followed for ten years the disease-free rate was 78%. The optimal radiation dose was determined to be not less than 160 Gy and in this group the positive biopsy rate was 4.6%. Dr. Stone acknowledged that the goal is to obtain 15- and 20-year follow-up data.
- Adjuvant Casodex Delays Disease Progression: In Europe 150 mg bicalutamide (Casodex) is customarily substituted for an LHRH agonist in the treatment of early prostate cancer. Data from their prior Early Prostate Cancer (EPC) trials had shown that the 150 mg dose reduced the risk of progression by 42% compared to radiation therapy or surgery alone, or watchful waiting. A researcher from Plymouth Oncology Centre in Plymouth, England, presented data from a EPC trial wherein 1370 men received primary irradiation and then were randomized between 150 mg Casodex or placebo: at a median three years follow-up Casodex was associated with a 37% reduction in clinical progression and a lengthened progression free survival of 33%. Similar to the emerging USA consensus that significant benefit accrues to patients with T3 or locally advanced disease by early treatment with an LHRH agonist, the Plymouth researchers concluded that "Treatment benefits were most likely to be seen in those patients with the worst prognosis."

Percent Free PSA Values Less Reliable in Large Prostates: The report, "Factors Influencing the Ratio of Free to Total Prostate-Specific Antigen in Serum", Int. J. Cancer, Meyer, 1997, presents a conclusion of clinical relevance. In this study, prostate volume was found to be the most important factor to influence f-PSA%. The difference between the usually low f-PSA% observed in PCa patients and the higher normal values in BPH patients was lost when prostate volumes exceeded 40cm3. As the authors concluded, "Since PCa patients with an enlarged gland often have BPH as well, the typical decrease of f-PSA% values in PCa patients may be masked in patients with both conditions."