Prostate Cancer Update: 2004

Highlights from the 4th International Prostate Cancer Congress, Grand Bahama Island, Bahamas, July 15-18, 2004

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The 4th International Prostate Cancer Congress was held July 15-18, 2004, in the Bahamas. The conference was moderated by co-chairmen Drs. Oliver Sartor, from Louisiana State University Medical School, New Orleans, LA, and David McLeod, from Walter Reed Army Medical Center, Washington, DC, and included a faculty composed of leading world experts in medical, radiation, and urologic oncology. The meeting provided a comprehensive update on the biology, screening, diagnosis, and management of prostate cancer and was attended by medical oncologists, urologists, and radiation oncologists.

Reviewed by Stephen J. Freedland, MD, Alan W. Partin, MD, PhD, The James Buchanan Brady Urological Institute and the Department of Urology, The Johns Hopkins Medical Institutions, Baltimore, MD

The meeting began with an opening discussion by Dr. Robert Stephenson, from the University of Utah School of Medicine, Salt Lake City, UT, on the epidemiology of prostate cancer. Dr. Stephenson nicely laid out recent data on prostate cancer incidence and mortality, showing that the number of prostate cancer diagnoses rose sharply after the introduction of prostate-specific antigen (PSA) testing in the late 1980s and has been relatively steady since the mid-1990s. In contrast, mortality rates rose until 1991 but have declined by 27% since then. Dr. Stephenson used these numbers to suggest that the rate of prostate cancer overdiagnosis is on the rise. The talk was not geared to provide data on specific means to counter these

trends, but rather to bring these trends to the general awareness.

Prevention

Dr. Oliver Sartor discussed new developments in hormonal therapy, with a special emphasis on chemoprevention. He began with an overview of data from the now well-discussed Prostate Cancer Prevention Trial (PCPT).[1] He showed some interesting data from an open-label study of dutasteride for benign prostatic hyperplasia conducted by Dr. Gerald Andriole of Washington University School of Medicine, St. Louis, MO. This was an open-label extension of 3 randomized, placebo-controlled trials. Entry criteria for these trials included age 50 years or older, prostate volume 30 cc or greater, and a PSA level between 1.5 and 10 ng/mL. During a little more than 2 years of follow-up, there was a reduction in prostate cancer incidence among men taking dutasteride (approximately 2.5% in the placebo arm vs 1.2% in the dutasteride arm).[2]

Dr. Ian Thompson, from the University of Texas at San Antonio, San Antonio, TX, also gave an update on the PCPT.[1] He mainly focused on results of their most recent paper comparing the incidence of prostate cancer detection relative to the serum PSA concentration in men in the placebo arm, using data from the end-of-study biopsy. The conclusion from this was that even among men with a "normal" PSA value, the incidence of prostate cancer on biopsy is not trivial and rises with increasing PSA, even within the "normal" range. For example, men with PSA levels between 3.1 and 4.0 ng/mL had a 27% incidence of prostate cancer, of which 25% were high-grade (Gleason score ≥ 7).[3] Dr. Thompson concluded by discussing 2 case scenarios to illustrate that the decision to start finasteride treatment to prevent prostate cancer is a very personal decision and that it is not the right choice for all men.

The first case was that of a 50-year-old, recently married white man with no family history of prostate cancer and no urinary symptoms. Given this patient's low risk of prostate cancer and greater risk of sexual side effects from finasteride, he may not be a good candidate for chemoprevention with finasteride. In contrast, Dr. Thompson presented the case of a 60-year-old impotent man with a positive family history of prostate cancer, moderate urinary obstructive symptoms, an elevated PSA level, and a negative biopsy result. This man is at higher risk, and because he is impotent he will not be as affected by the sexual side effects of finasteride. In addition, he will likely receive urinary relief from finasteride. Therefore, for this man it may be reasonable to begin chemoprevention with finasteride.

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Radical Prostatectomy

Dr. Stephen Freedland, from the Johns Hopkins University, Baltimore, MD, presented data on the association between obesity and prostate cancer. Using the multicenter SEARCH Database, he examined the risk of an elevated PSA level after radical prostatectomy as related to preoperative body mass index (BMI). He found that men with a BMI > 35 kg/m^2 (for example, a 5'11" man weighing > 250 lbs) were at increased risk for a positive surgical margin, which was thought to be a possible result of iatrogenic positive margins due to technical difficulties in operating on obese men.[4] However, even after adjusting for this higher rate of positive surgical margins as well as other preoperative clinical characteristics, men with a BMI > 35 kg/m^2 were at increased risk for PSA level progression.

Even when men with only organ-confined disease and negative surgical margins were considered, a BMI > 35 kg/m^2 remained a significant predictor of PSA progression.[5] In addition, Dr. Freedland showed data that height (≤ 69 in vs > 69 in) was a significant predictor of PSA level progression following radical prostatectomy—although this was seen only among black men, not white men.

Radiotherapy

Dr. Michael Zelefsky, from the Memorial Sloan-Kettering Cancer Center, New York, NY, presented some interesting data regarding the role of intensity-modulated radiotherapy (IMRT). IMRT is a newer technology that allows the radiation beam to be more closely sculpted to fit the contours of the prostate. As a result, the dose given can be increased with fewer side effects. He showed data that the incidence of any grade 2 or higher rectal bleeding was less than 3% in the IMRT arm at 81 gray, compared with more than 15% using 3D-conformal radiotherapy. Finally, he showed some data suggesting that as the radiation dose is increased, cancer control is improved. Therefore, he suggested that IMRT with doses ≥ 81 gray would be expected to result in both lower morbidity and improved oncologic outcomes, although longer follow-up is needed.

Dr. John Blasko, from the Seattle Prostate Institute, Seattle, WA, presented long-term results following

brachytherapy. He reviewed a series of 123 men treated with ^{125}I monotherapy between 1988 and 1990. Most patients had clinical stage T2 disease; all had Gleason score < 7; and 21% had PSA values > 10 ng/mL. Fifteen-year overall survival was 42%, whereas disease-specific survival was 96%. Overall biochemical relapse-free survival was 85% to 86%, independent of pretreatment risk group. He noted 2 cases of possibly radiation-induced secondary malignancy, for a rate of 2%, and no cases of late complications. He went on to say that, given improvements in technique and patient selection that have occurred in more recent series, he anticipated that long-term outcomes would also continue to improve among more recently treated patients.

Alternative Treatments

Two different and newer alternative treatments for prostate cancer were discussed: cryotherapy and high-intensity focused ultrasound (HIFU). Dr. Fletcher Derrick, of the Medical University of South Carolina, Charleston, SC, reviewed recent data regarding cryotherapy for primary treatment and for salvage treatment in men with a radiation treatment failure. He explained that for sufficient tissue necrosis, temperatures must be in the range of –20°C to –40°C. His current preferred approach involves placing 4 to 6 cryotherapy probes, using a brachytherapy-like ultrasound-guided grid. A urethral warming device is placed and 5 thermal probes are also placed to follow intraprostatic temperatures. The method involves 2 freeze/thaw cycles.

Dr. Derrick presented data from multiple small studies, which together suggested that the cumulative 5-year biochemical disease–free survival following cryotherapy was 60% to 92% for low-risk patients and 36% to 89% for high-risk disease. Dr. Derrick stated that he thought these numbers were superior to the results from surgery or radiation and that the unique tumor-killing mechanism of cryotherapy was more effective than radiation for high-grade tumors. He finished with a brief discussion regarding data on salvage cryotherapy for radiation treatment failures, which, he suggested, showed outcomes similar to those for salvage prostatectomy, but with a lower rate of incontinence.

Dr. Michael Koch, from Indiana University Medical Center, Indianapolis, IN, presented an overview of HIFU for prostate cancer. This involves an ultrasound probe in the rectum, which utilizes an elliptical focusing dish to concentrate the high energy, similar to shock-wave lithotripsy. The energy is then swept through the prostate, heating the prostate to 70°C to 90°C to provide tissue necrosis. A rectal tube is placed for cooling to prevent rectal injury.

Dr. Koch presented the results of a small trial of 20 patients treated at his institution. All men had low- or intermediate-risk disease (PSA level ≤ 10 ng/mL, Gleason score ≤ 7, tumor stage ≤ cT2) with a prostate volume < 40 cc. Patients were followed prospectively with quality-of-life questionnaires and follow-up biopsy at 6 months. Major complications were few, although transient urinary retention was nearly universal. The PSA responses were disappointing, with only 42% of patients achieving a PSA level < 1.0 ng/mL following 1 treatment. Many patients required re-treatment. However, after 2 treatments nearly 50% of patients still had a positive biopsy result at 18 months following treatment. Dr. Koch discussed various technical issues that might contribute to the poor outcomes, and suggested modifications that have been undertaken that he expects will improve results in the future.

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Hormonal Therapy

Dr. Judd Moul, from the Center for Prostate Disease Research, Rockville, MD, presented data regarding the timing of hormonal therapy for men with a PSA elevation following radical prostatectomy.[6] In a dataset of nearly 5000 men treated with surgery during the PSA testing era, 1352 men with a biochemical recurrence were identified. In this retrospective study, timing of the initiation of hormonal therapy was assessed by PSA level at the time of hormone treatment. The majority of men (997) did not receive hormonal therapy; there was a mean of 5 years of follow-up after surgery. The primary endpoint examined was time to metastatic disease.

Among the entire cohort, the timing of hormonal therapy had no effect on time to metastatic disease. However, among the high-risk cohort (pathological Gleason score > 7 or PSA doubling time < 12 months), earlier hormonal therapy (starting when the PSA level was < 10 ng/mL) was associated with a delay in the time to metastasis. Dr. Moul emphasized that because of the retrospective nature of the study and the lack of overall survival data, it was difficult to draw firm conclusions from this study. However, he stressed that a risk-stratification approach to identify high-risk men who stand to benefit the most from hormonal therapy was reasonable,

given the lack of data from randomized controlled trials.

Chemotherapy

The most exciting and significant data presented at this meeting were those on chemotherapy and prostate cancer. Specifically, the results of 2 phase 3 clinical trials demonstrated the benefit of chemotherapy, namely docetaxel, in prolonging survival of men with hormone-refractory prostate cancer (HRPC).[7,8]

Following the opening talk, the first session of the meeting focused on various chemotherapeutic agents for prostate cancer. Dr. Daniel Petrylak, from Columbia-Presbyterian Medical Center, New York, NY, discussed results from 2 recent phase 3 clinical trials investigating the use of docetaxel for men with metastatic HRPC. The first study, TAX 327, compared 2 different schedules of docetaxel (weekly and once every 3 weeks) to mitoxantrone and prednisone, the current standard and United States Food and Drug Administration (FDA)–approved treatment for HRPC.[7] The study involved 1006 men randomized to one of the 3 arms. The groups were well matched for baseline characteristics. The overall rate of grade 3 or 4 toxicity was highest in the docetaxel every-3-weeks arm (45%) and lowest in the mitoxantrone arm (35%). The primary endpoint of the study was survival. Median survival in the mitoxantrone arm was 16.4 months, compared with 17.3 months in the weekly docetaxel and 18.9 months in the docetaxel every-3-weeks arm (P = .009).

The second study examining docetaxel was SWOG 9916, run by the Southwest Oncology Group (SWOG).[8] This study involved 674 eligible men who were randomized to either mitoxantrone and prednisone or docetaxel every 3 weeks plus oral estramustine. The docetaxel and estramustine arm showed an increased risk of thromboembolic events, necessitating a change in the protocol to include routine prophylactic warfarin, 2 mg orally, and aspirin, 325 mg daily. The overall rate of grade 3 or 4 toxicity was higher in the docetaxel/estramustine arm (54%) than in the mitoxantrone arm (34%). Median survival in the mitoxantrone arm was 16 months, whereas in the docetaxel/estramustine arm median survival was 18 months (P = .01).

Both studies on docetaxel had similar entry criteria, and both showed a significant prolongation of survival of approximately 2 months associated with docetaxel use. Treatment with docetaxel plus estramustine did not appear to be any better than treatment with docetaxel alone. The clinical significance is that this is the first treatment approach that has shown a survival benefit in phase 3 trials for men with HRPC. Based on these studies, the FDA has now approved docetaxel for the treatment of HRPC. Dr. Petrylak commented that because of the toxicity associated with estramustine and the lack of improvement in efficacy, the role of estramustine in future trials is questionable. Thus, he concluded that the standard of care for men with HRPC should be docetaxel and prednisone.

Risk Stratification

Dr. Anthony D'Amico, from Harvard Medical School, Boston, MA, discussed surrogate and intermediate endpoints for prostate cancer–specific mortality. He reviewed results from his recent study showing that among men who had a biochemical failure after surgery or radiation, those men with a PSA doubling time < 3 months are at very high risk for death from prostate cancer.[9] Indeed, in this subset all deaths were attributed to prostate cancer. On the contrary, men with slower doubling times had improved prostate cancer survival and had competing mortality from non-prostate cancer causes.

Dr. D'Amico's talk ended with a

Main Points

- Two phase 3 studies have shown a survival advantage with docetaxel treatment for men with metastatic hormone-refractory prostate cancer. The agent is now FDA-approved and the standard of care.
- Early data suggest that dutasteride, like finasteride, may decrease the number of prostate cancer cases.
- One study found that men with a body mass index greater than 35 kg/m^2 were at increased risk for biochemical progression following radical prostatectomy.
- Intensity-modulated radiotherapy allows greater radiation doses with less toxicity, which appears to improve biochemical control.
- Long-term (15-year) prostate cancer control with brachytherapy monotherapy is beneficial in appropriately selected patients.
- Men who have a biochemical failure after radical prostatectomy and are at high risk for progression (Gleason score > 7 and/or prostate-specific antigen [PSA] doubling time < 12 months) may benefit from early hormonal therapy.
- Men with a PSA rise > 2 ng/mL in the year before diagnosis are at increased risk for prostate cancer death following radical prostatectomy.

review of his latest findings, also recently published, looking at a highly screened population of men with prostate cancer who went on to have a radical prostatectomy by Dr. William Catalona, from Northwestern University, Chicago, IL.[10] He found that men whose PSA concentration increased by > 2 ng/mL in the year before diagnosis had a significantly increased risk of prostate cancer death. Indeed, among men with a PSA rise < 2 ng/mL, there were no prostate cancer deaths in up to 10 years of follow-up. He explained that the evidence linking this PSA rise to prostate cancer death was not sufficient to call it a "surrogate," but rather he suggested that these men, many of whom would have been considered low-risk by PSA value and Gleason score, should in fact be considered high-risk and offered aggressive treatment, possibly in the context of a clinical trial. ■

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