Innovations and Challenges in Prostate Cancer: Summary Statement for the 6th Cambridge Conference

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The Sixth Cambridge Conference on Innovations and Challenges in Prostate Cancer, a symposium held in Cambridge, Massachusetts, October 30 and 31, 2006, was convened to review and discuss new data and recommendations related to prostate cancer. The forum addressed promising agents in development for treatment and prevention, and current approaches and recommendations for assessing and treating early stage disease as well as patients with biochemical failure (increasing PSA), castration resistant nonmetastatic, castration resistant metastatic and taxane refractory metastatic disease. The conference format combined brief presentations with extended periods of discussion. The conclusions and recommendations are summarized in this article and presented in more detail in the individual reports that follow.

CHEMOPREVENTION

Prostate cancer chemoprevention first attracted increased interest with the completion of the first phase III clinical trial, the Prostate Cancer Prevention Trial, reported in 2003 with more than 18,000 patients. The trial was closed early because of evidence that a decrease in prostate cancer risk was seen with the administration of finasteride.[1] Although a significant reduction in cancers was seen, an increase in the number and proportion of tumors with Gleason scores of 7 to 10 led to initial concern with the use of the drug for this purpose. A recent analysis shed light on this paradox, finding that finasteride significantly improved the sensitivity of PSA and biopsy for overall cancer and high grade cancer.[2] The results of ongoing studies will ultimately help guide us in making a recommendation regarding the use of 5α-reductase inhibitors as preventive agents. Vitamin E and selenium are now being assessed in an ongoing phase III study, the Selenium and Vitamin E Cancer Prevention Trial.

LOW RISK PROSTATE CANCER

Although curative therapy has been shown to decrease cancer specific and overall mortality for select men with prostate cancer,[3] all available therapies may have a significant negative effect on patient health related quality of life.[4] Furthermore, as more men are diagnosed with curable tumors at younger ages, the course of the disease is lengthening. Thus, patients and physicians must consider seriously the long-term implications of disease management decisions. Risk assessment at diagnosis based on available clinical data can help guide clinician-patient decision making with respect to the optimal treatment strategy. Patients with a PSA level of less than 10 ng/ml, a biopsy Gleason score of 6 and a clinical stage of T1c or T2a have typically been classified as low risk.[5]

On a national level the use of active surveillance (watchful waiting) decreased sharply among patients at low risk throughout the 1990s, even as low risk tumors accounted for a steadily increasing proportion of diagnosed tumors.[6] Current results show that the proportion of prostate cancer patients assigned to the low risk group as defined has stabilized at just less than half of patients with newly diagnosed prostate cancer in the first 6 years of the new millennium. However, in this group there are significant and ongoing trends toward lower risk at presentation. Rates of active surveillance in patients at low risk have increased since the start of this decade but, despite the ongoing downward trends in risk, a period of surveillance rather than immediate treatment is likely underused as a first management option for many such men. Standardized methods for surveillance are needed. Studies that critically assess optimal methods of followup (intervals of assessment, PSA kinetics, optimal use of biopsy, etc) and, moreover, methods for selecting out those appropriate for active surveillance using clinical and molecular markers are greatly needed.

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INTERMEDIATE AND HIGH RISK PROSTATE CANCER

The optimal treatment of intermediate and high risk prostate cancer is still debated. The subgroup of patients with a PSA level of greater than 10 ng/ml, a biopsy Gleason score of 7 or higher and clinical tumor category of T2b or T2c are at a higher risk for cancer specific death after standard treatment, suggesting that EBRT plus ADT or alternatively RP alone may be inadequate therapy for many men with such cancers. Patients with clinically organ confined disease may be considered for RP or high dose, well targeted radiation. Relapse rates can be significant and to our knowledge no evidence exists to date for combined modality treatment with surgery. Short-term ADT before surgery has not proved to be of clinical benefit. In contrast, dose escalation of EBRT appears to decrease relapse rates, although no evidence for a survival benefit yet exists. The addition of ADT to EBRT for patients at intermediate and high risk appears to be of benefit with respect to progression-free and overall survival in most studies. The optimal duration of this combination therapy is still under study. Whether higher doses of EBRT supplant the need for EBRT combined with ADT is not known. Chemotherapy has activity in those with prostate cancer but it is of uncertain clinical benefit. Ongoing trials are testing the role of chemotherapy in neoadjuvant and adjuvant settings with RP and radiotherapy.

INCREASING PSA AFTER LOCAL THERAPY

In patients with clinically localized prostate cancer who undergo focal treatment increasing serum PSA levels usually precede clinically detectable or metastatic disease by many years. Although many of these patients are unlikely to die of the disease, they may live with uncertainty and may be at risk for disease related morbidity.

In general increasing PSA values indicate recurrent disease after surgery. A PSADT that is short generally indicates clinically significant recurrence. A significant amount of work has been done in identifying relapsed patients at high risk for early metastases and prostate cancer specific mortality. PSA kinetics inform subsequent treatment strategies. Patients with low PSA values will have no detectable metastases. Local therapy after surgery, ie radiation, should be considered for select patients in the absence of metastases but the results are most satisfactory for those with later relapse and slowly increasing serum PSA levels, especially in those with positive surgical margins at initial surgery. The role of local salvage treatments for patients treated with primary radiation therapy has not been firmly established. Among the methods most often applied are surgery, cryotherapy and brachytherapy.

Patients with a Gleason score of 7 or less, who relapse after 2 years and who have PSADT longer than 10.0 months have a 3, 5 and 7-year probability of distant metastasis of 95%, 92% and 87%, respectively.[7] Patients who have relapse before 2 years, have a Gleason score of greater than 7 and have PSADT shorter than 10.0 months have a 3, 5 and 7-year probability of distant metastasis of 54%, 30% and 21%, respectively.[7] Although such patients are at higher risk for prostate cancer specific mortality, there is currently no consensus on the appropriate timing and form of systemic therapy for these patients. Thus, encouraging participation in clinical trials is essential to improving patient care.

The use of bisphosphonates in hormone naïve patients treated with ADT should be reserved for those with significant osteopenia or osteoporosis. No data are available to support their use as preventive agents against metastases and, moreover, long-term use may be associated with renal dysfunction, anemia and osteonecrosis of the jaw.

CASTRATION RESISTANT DISEASE

Castration Resistant Nonmetastatic Disease

In patients with an increasing PSA level after primary therapy a detectable PSA nadir is the earliest sign of impending androgen independent prostate cancer and a strong prognostic factor for death from prostate cancer. However, because of the low initial disease burden, the prognosis in these patients is better than the prognosis in patients with clinically advanced metastases.

Although a variety of therapies, eg secondary hormonal therapies, are used and are active for CRPC, adequately designed studies to detect a clinical benefit, ie a delay in the development of metastases or enhanced survival, have not been done. Ongoing randomized studies should enhance our understanding of the natural history of this disease state and future clinical trial design. One group reported that PSADT and PSA level predicted the time to clinical progression[8] and, therefore, these baseline measures may be useful for selecting and/or stratifying patients in clinical trials. Clinical trials should be designed to include conventional study end points, such as time to clinical metastasis and survival. Such trials will provide the necessary information on the relationship between potential intermediate end points, such as PSA dynamics, other clinical and laboratory variables, and time to clinically evident metastasis and survival that can be used in clinical practice decisions and clinical trial design.

Castration Resistant Metastatic Disease

The only therapy that has proven to prolong survival in this clinical context is docetaxel based chemotherapy. Whether all patients should be treated up front with docetaxel as soon as they enter this clinical state remains uncertain. The consensus is that chemotherapy for patients with rapidly progressive or symptomatic disease should be initiated early. There is scant evidence that asymptomatic patients with slowly progressive or otherwise low risk disease are at any disadvantage by trying additional hormonal or investigational maneuvers before initiating chemotherapy. Patients who are candidates for chemotherapy should be registered for a variety of trials that are under way to test the value of adding other agents to docetaxel. The results of randomized trials are pending.

The use of bisphosphonates in this setting is based on 1 study that demonstrated a decrease in skeletal related events.[9] The consensus of this group was that in the absence of a confirmatory study, the seemingly modest benefits associated with their use and the possibility of adverse effects, the indiscriminate use of bisphosphonates should be discouraged and further study identifying those most likely to benefit is needed. Moreover, the identification of more effective bone directed therapies is needed.