



Treatment of Castrate-Resistant Metastatic Prostate Cancer

Background

About 1 in 10 men will develop prostate cancer during their lifetime, and the incidence increases with age. Ten to twenty per cent of cases are locally advanced at the time of diagnosis (T3) and have substantial risk for late metastases¹. Metastatic progression is infrequent for men with low risk prostate cancer². Nevertheless, prostate cancer still is the second leading cause of cancer death among men in the U.S. In 2008 there were approximately 28,000 prostate cancer-related deaths, the majority in metastatic castrate-resistant disease³.

Outcomes are best when patients with advanced/metastatic prostate cancer are treated at the first sign of disease progression, rather than delaying treatment until the development of serious symptoms¹. When deprived of androgen by medical or surgical castration (ADT), about 95% of advanced prostate cancer patients usually respond⁴. Present guidelines recommend either orchiectomy or a luteinizing hormone-releasing hormone agonist alone for the treatment of metastatic prostate cancer^{1,7}, although some experts prefer to add antiandrogens as well⁷.

Nevertheless, androgen deprivation therapy has been found to be palliative, not curative. Eventually all metastatic cases will become resistant to androgen ablation and progress, a condition known as castrate-resistant prostate cancer (CRPC). The median time to death after biochemical (rising PSA) failure is 12-18 months, and once symptoms occur, median survival is less than 1 year¹.

Definition of Castrate-Resistant Prostate Cancer

Castrate-resistant prostate cancer (CRPC) is defined as the development of tumor growth despite castrate levels of testosterone. Tumor cells in CRPC are still dependent on activation of androgen receptor pathways even though the levels of circulating testosterone are in castrate range. It has been shown that in a significant percentage of CRPC cases androgen receptors are amplified and many androgen responsive genes upregulated. Intratumor and extra-gonadal (especially adrenal) androgens provide a means of continued stimulation of these androgen receptors with resultant growth of tumor. This indicates that many cases are not androgen independent and may still respond to further reduction of circulating androgens or suppression of intracellular androgen activity³.

Secondary Hormone Therapy for CRPC

The ideal candidates for secondary hormonal therapy are those with rising PSA only relapses ("CRPC-biochemical recurrence"), or those with low volume metastatic disease experiencing signs of progression³. Three options are available: antiandrogens that directly block androgen receptors, corticosteroids and ketoconazole which inhibit adrenal androgen production, and estrogens, which may act via negative feedback on the hypothalamic-pituitary axis. Estrogens are powerful secondary agents but have been associated with significant adverse medical effects and are not often used. Each secondary hormonal treatment unfortunately produces modest, short-lived responses, although there is evidence of survival benefit for certain antiandrogens and ketoconazole. These agents usually are administered sequentially while maintaining castrate levels of testosterone.

Skeletal Metastases

Bone is the most frequent site of prostate cancer metastases, which usually appear first in the axial and later in the appendicular skeleton. Metastatic bone disease is the main source of morbidity and reduction in

quality of life. Radiation therapy is an essential aspect of treatment for local pain relief and specific complications such as pathological fractures and spinal cord compression. In addition, to prevent skeletal complications, bisphosphonates such as zoledronic acid (Zometa) or pamidronate (Aredia) are recommended in conjunction with standard anti-cancer agents. This class of drugs blocks bone resorption by inhibiting osteoclastic activation and proliferation and has been shown to reduce skeletal events by 25%⁶.

Another agent, the monoclonal antibody denosumab, targets RANK Ligand (RANKL), a member of the tumor necrosis family found on marrow, stromal cells, and osteoblasts. Overproduction of RANKL is a crucial factor for stimulating osteoclastic bone resorption in skeletal metastases. Denosumab, by inhibiting RANKL, has been shown in phase III trial data to be superior to Zometa for the treatment of bone metastases from breast cancer, and currently is also under study for CRPC³.

Chemotherapy

Patients with CRPC are candidates for chemotherapy when they have rapid PSA doubling times, symptomatic moderate to large volume metastatic disease, or visceral metastases. Patients with a slow PSA doubling time and/or asymptomatic low volume disease may be followed carefully, until symptoms develop. The indications for chemotherapy should not be based on a very slowly rising PSA alone³.

In 1996 the standard of care for chemotherapy was established as mitoxantrone and prednisone based on studies showing superior pain relief, although overall survival was not improved³.

In 2004 the standard became docetaxel (Taxotere) plus prednisone. Several clinical trials of Taxotere-based regimens reported for the first time significant improvement in overall survival. The most important trial was the phase III TAX 327 for CRPC with metastatic disease, which compared TAX every 3 weeks, to TAX weekly, to 3 weekly mitoxantrone; low dose prednisone was administered in each arm. The group given docetaxel every 3 weeks demonstrated improved median overall survival (19.2 months vs. 16.3 months) with a 24% reduction in mortality risk, and more patients with a > 50% decrease in PSA and pain relief than those on mitoxantrone. Weekly TAX also was better than mitoxantrone in terms of survival, but slightly inferior to the 3 weekly regimen³.

Options after Docetaxel Failure

Mitoxantrone/prednisone is the most commonly used second line systemic therapy, but neither this nor any other chemotherapy salvage regimen has been shown to improve survival⁶. NCCN guidelines recommend that the best management for Taxotere-resistant CRPC is enrollment in a clinical trial⁷. A large number of drugs currently are being tested in clinical trials. One of the most interesting is a suppressor of adrenal androgen synthesis known as abiraterone acetate⁸. A new taxane called cabazitaxel, in the same drug class as Taxotere, was compared to mitoxantrone and demonstrated a 30% improvement in overall survival⁹. Other chemotherapy drugs, vaccines, monoclonal antibodies, tyrosine kinase and mTOR inhibitors currently are showing promise in clinical trials.

References

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This publication is a review and not meant as a guideline for medical treatment.