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The Treatment Continuum in the Management of Prostate Cancer Patients: What's New?

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Abstract

Objectives: Symptom control is a priority in patients with hormone-refractory prostate cancer. However, since the approval of androgen deprivation therapy, there have been few meaningful therapeutic advances. Several current treatment options and novel agents are presented in this review.
Methods: Existing and novel therapies were identified and researched through PubMed and published guidelines.
Results: Treatment options include chemotherapy, second-line hormonal manipulations, radiation/radioisotope therapy, and bisphosphonates. Chemotherapy has demonstrated significant palliative benefits, and docetaxel has demonstrated a survival advantage. Hormonal manipulation lowers PSA levels, but has not significantly delayed the course of disease progression. Radiation/radioisotope therapy and bisphosphonates are palliative treatments for patients with bone metastases. Zoledronic acid significantly reduces skeletal morbidity in patients with bone metastases. Several novel treatments, including vaccines and vitamin D analogues, are currently being investigated.
Conclusions: Although improving survival is the optimal goal, it may not be feasible in elderly patients who may not tolerate some therapies. In addition, advanced HRPC is a multifaceted disease and needs a multidisciplinary approach. Urologists should be familiar with the new challenges that this disease presents and remain involved throughout the continuum of patient care.

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Prostate cancer is the sixth most common cancer in the world, with approximately 679,000 new cases annually [1]; however, since the introduction of androgen deprivation therapy (ADT) in the 1940s, there have been few meaningful therapeutic advances. Palliative chemotherapy with mitoxantrone was introduced in 1996, zoledronic acid in 2002, and docetaxel in 2004. Although docetaxel was the first agent to demonstrate a survival advantage in this setting [2], improving survival may not be feasible in some elderly patients with prostate cancer who cannot tolerate chemotherapy. ADT

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has been and continues to be the most common treatment for men with advanced prostate cancer and is now used earlier in the continuum of care for prostate cancer (often before bone metastases develop) based on rising PSA levels. Earlier use may improve survival and delay bone metastasis. However, ADT is associated with adverse effects such as fatigue, depression, increased fat mass, loss of libido, and hot flashes. In addition, recent evidence has demonstrated that ADT is associated with bone loss that may lead to osteoporosis, a phenomenon generally referred to as cancer treatment-induced bone loss or CTIBL [3].

In patients with prostate cancer, bone loss (which is a risk factor for osteoporosis) may be attributed to the disease and to ADT. Bone loss associated with ADT has been shown to increase the risk of fractures [4]. Moreover, approximately 70% of patients with advanced prostate cancer will develop bone metastases, which cause local decreases in bone integrity [5]. All these disease-associated factors lead to a fragile bone state and a significant risk of skeletal complications, including pathologic fractures, debilitating bone pain, and spinal cord compression. The patient's QOL is affected by these complications. Therefore, symptom control and maintaining QOL are priorities for patients with HRPC.

Treatment options for patients with metastatic HRPC include second-line hormonal manipulations plus bisphosphonates and/or radiation/radioisotope therapy to reduce skeletal morbidity and chemotherapy. Hormonal manipulation typically lowers PSA levels, but these regimens have not significantly delayed the course of disease progression in clinical trials.

In 1996, chemotherapy (mitoxantrone plus prednisone) demonstrated significant palliative benefits in HRPC, significantly reducing pain ($p < 0.0001$) and improving QOL compared with prednisone alone (Fig. 1) [6]. However, overall survival was not significantly improved. This treatment regimen was subsequently approved for HRPC based on palliative benefit. In 2004, docetaxel plus estramustine was compared with mitoxantrone plus prednisone every 3 weeks, and this trial demonstrated the first survival benefit in this patient population [2]. Median survival increased by 2 months ($p = 0.02$) in patients who were treated with docetaxel plus estramustine (Fig. 2) [2].

A significant increase in PSA response ($p < 0.0001$) was also observed in the docetaxel plus estramustine group [2]. A similar international trial that compared two schedules of docetaxel (either every 3 weeks or weekly) plus prednisone versus mitoxantrone plus prednisone for up to 30 weeks demonstrated a

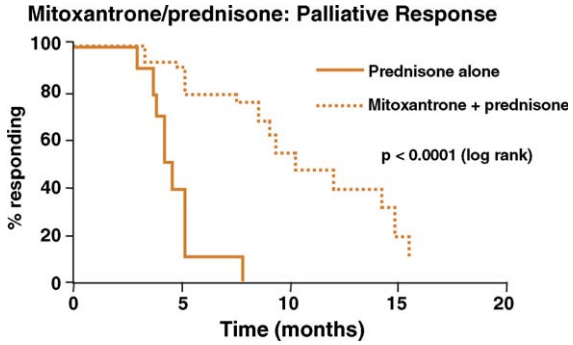

Fig. 1 – Percentage of patients with a palliative response. Palliative response was defined as a two-point decrease in pain assessed by a six-point scale without an increase in analgesic medication and maintained for two consecutive evaluations at least 3 weeks apart. From Tannock et al. [6], with permission.

significant 2.4-month survival advantage ($p = 0.009$) in patients treated with docetaxel (every 3 weeks) compared with the mitoxantrone plus prednisone group [7]. In contrast, docetaxel plus prednisone administered weekly did not demonstrate a significant improvement in survival. Results are shown in Fig. 3 [7]. However, despite the survival advantage, there was no significant difference in the tumor response rate between the two chemotherapy groups. Docetaxel plus prednisone also significantly improved pain response and PSA response rates compared with mitoxantrone plus prednisone ($p = 0.01$ and $p < 0.001$, respectively). Grade 3/4 toxicities included neutropenia; 3% of the patients in the docetaxel (every 3 weeks) group were hospitalized with febrile neutropenia compared with 2% of the patients in the mitoxantrone plus prednisone group. Common nonhematologic adverse events

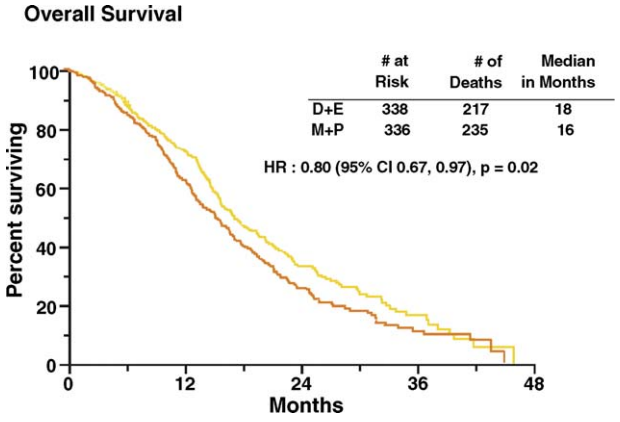

Fig. 2 – Kaplan–Meier estimate of overall survival. D + E = Docetaxel plus estramustine; M + P = Mitoxantrone plus prednisone; HR = Hazard ratio; CI = confidence interval. From Petrylak et al. [2], with permission.