A NEW ERA IN HORMONE-REFRACTORY PROSTATE CANCER

Optimal treatment requires multidisciplinary approach

Fred Saad, MD, FRCS et al.

Prostate cancer is the most common cancer in North American males and the third leading cause of death due to cancer. Androgen deprivation therapy (ADT) was introduced in the 1940s, but few meaningful therapeutic advances have been made since then.

Palliative chemotherapy with mitoxantrone and prednisone was introduced in 1996, zoledronic acid in 2002, and docetaxel in 2004. Although docetaxel is the first agent to demonstrate a survival advantage in this setting, improving survival may not be feasible for many elderly prostate cancer patients who cannot tolerate chemotherapy.

Androgen deprivation therapy has been and continues to be the most common treatment for men with advanced prostate cancer. It is now used earlier in the continuum of care, before bone metastases develop, based on rising prostate-specific antigen (PSA) following primary therapy. Earlier treatment has been shown to 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.

Further, recent evidence has demonstrated that ADT is often associated with bone loss. Bone loss in patients with prostate cancer may be attributed both to the disease itself, which is a risk factor for osteoporosis, and to ADT. Bone loss associated with ADT has been shown to increase the risk for fractures. Moreover, approximately 70% of patients with advanced prostate cancer will develop bone metastases, which cause local decreases in bone integrity. All of these disease-associated factors lead to a fragile bone state and significant risk of skeletal complications, including pathologic fractures, debilitating bone pain and spinal cord compression. The patient’s quality of life (QOL) is affected by these complications. Symptom control and maintaining QOL are thus priorities for patients with HRPC.

TREATMENT OF HRPC

Treatment options for patients with metastatic HRPC include second-line hormonal manipulations, chemotherapy, bisphosphonates and/or radiation or radioisotope therapy to reduce
skeletal morbidity and improve pain control. Second-line hormonal manipulation may sometimes transiently lower PSA levels, but these regimens have not been shown to improve survival, and it is now standard of care to stop anti-androgens when disease progresses on hormone therapy. Whether there is any clinical benefit to changing anti-androgens or increasing the dose of a given anti-androgen remains unknown.

Chemotherapy
In 1996, chemotherapy (mitoxantrone + prednisone) demonstrated significant palliative benefits in HRPC, significantly reducing pain (p < 0.0001) and improving QOL compared with prednisone alone.2 While overall survival did not improve, this treatment regimen was subsequently approved for HRPC based on palliative benefit. Next, in 2004, docetaxel + estramustine was compared to mitoxantrone + prednisone every 3 weeks,3 demonstrating the first survival benefit in this patient population: median survival increased by 2 months (p = 0.01) in patients receiving docetaxel + estramustine. This group had a significant increase in PSA response (p < 0.0001), but significant added toxicity attributed to estramustine.

A similar international trial compared 2 different schedules of docetaxel (administered either every 3 weeks or weekly) + prednisone vs mitoxantrone + prednisone for 30 weeks. This trial demonstrated a significant 2.5-month survival advantage (p = 0.009) in patients treated with docetaxel given every 3 weeks compared to those receiving mitoxantrone + prednisone.12 In contrast, docetaxel + prednisone administered weekly did not significantly improve survival. Docetaxel + prednisone also significantly improved pain (p = 0.01) and PSA response rates (p = 0.0005) compared with mitoxantrone + prednisone. In general, docetaxel was well tolerated. Grade 3–4 toxicities included neutropenia, with 3% of the patients in the every 3-week docetaxel group being hospitalized with febrile neutropenia compared with 2% of those in the mitoxantrone + prednisone group. Common non-hematologic adverse events included alopecia, fatigue and nausea. Because it significantly improves survival and reduces both PSA and pain levels, docetaxel has now become the first-choice chemotherapy in HRPC.

Bone-targeted therapy
Radiation or radioisotope therapy and bisphosphonates are palliative treatments for patients with bone metastases. Radiation therapy to metastatic sites can provide rapid relief of pain and improvements in quality of life, and is the preferred treatment modality in cases of spinal cord compression due to prostate cancer. It is most effective when applied before the onset of paralysis. Radioisotopes are less frequently used in the era of chemotherapy, given the possibility of bone marrow suppression, but remain an option for treatment of painful widespread metastases. Bisphosphonates are inhibitors of osteoclast-mediated bone resorption. They can prevent bone loss in patients with prostate cancer receiving ADT, and zolendronic acid can increase bone mineral density in this setting.13,14 This agent has demonstrated significant clinical benefits, including delay and prevention of skeletal complications and durable pain palliation in patients with bone metastases from HRPC.15 Bisphosphonates can be combined with chemotherapy, and clinical trials have used zolendronic acid safely with a variety of cytotoxic chemotherapies. Adverse events reported during bisphosphonate treatment did not appear to increase with concomitant chemotherapy.

Based on the available evidence, several guidelines, including National Comprehensive Cancer Network (NCCN), European Association of Urology (EAU) and International Consultation on Urologic Diseases (ICUD) have recommended that bisphosphonates be used to preserve bone health and to prevent skeletal complications in patients with bone metastases from HRPC, whether asymptomatic or symptomatic.16 Zolendronic acid is presently the only bisphosphonate that has shown efficacy in prostate cancer. The combination of docetaxel and zolendronic acid has demonstrated additive antitumour activity in a human prostate cancer cell line, PC-3:17 the addition of zolendronic acid increased the antitumour activity of docetaxel in a dose-dependent manner. These results suggest that combination therapy with docetaxel and zolendronic acid could be especially active in patients with HRPC.18

FUTURE HRPC THERAPIES
Novel agents are also being investigated. A placebo-controlled Phase III trial has shown that the endothelin receptor antagonist atrasentan has activity in bone metastatic HRPC.39 Although the study did not achieve its primary endpoint, patients with bone metastases who received atrasentan experienced significant delay in disease progression. Results from ongoing Phase II and III studies will further help to define the role of this agent in clinical practice. Vaccines, Vitamin D analogs and antisense oligonucleotides are currently investigational in the HRPC setting, and Phase II studies appear to show promising results.

Research in second-line therapy after primary chemotherapy for HRPC is another active area of research. In patients who respond to first-line docetaxel it is reasonable to rechallenge with the same agent. Other agents are presently being investigated in this setting, and to date satraplatin appears to show activity.38 Given the promising preclinical proof of principal, antisense clusterin is presently being studied in the second-line setting in combination with chemotherapy.

COOPERATION OF MULTIPLE SPECIALISTS
Advanced HRPC is a multifaceted problem and requires a multidisciplinary approach. Urologists should remain...
involved from the time of diagnosis throughout the continuum of care and should be familiar with the challenges that this disease presents. Medical oncologists and radiation oncologists have to take up the challenge of actively contributing to decision making earlier than they have done in the past. All specialties involved need to be aware that hormone therapy diminishes bone health, that chemotherapy with docetaxel can provide a survival benefit in HRPC, and that zoledronic acid reduces and delays skeletal complications. Building on these positive results is necessary to further improve survival, symptom management and QOL in these poor-prognosis patients.

Now that prostate cancer has progressed from being a disease with limited options into an era where new options have become available — with much more to come — interaction between different specialties needs to increase. Learning from other tumour models (especially breast cancer) tumour boards and multidisciplinary clinics are some of the means many centres are using to meet the challenge of optimizing patient care in prostate cancer. We are optimistic that through teamwork, prostate cancer patients will have a much brighter future.

Disclosure
Dr. Saad reports being on advisory boards of Abbott, GlaxoSmithKline, Merck, Novartis and Sanofi-Aventis.

References