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Bone loss in patients with prostate cancer may be attributed 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.1,2 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 a significant risk of skeletal complications,
including pathological fractures, debilitating bone pain, and spinal cord
compression. The patient’s quality of life (QoL) is affected by these
complications. Therefore, symptom control and maintaining QoL are
priorities for patients with hormone-refractory prostate cancer (HRPC).1,3

Presently, zoledronic acid is the only
bisphosphonate that has shown efficacy
in prostate cancer.

A similar international trial comparing two different schedules of
docetaxel (either every three weeks or weekly) plus prednisone versus
mitoxantrone plus prednisone for 30 weeks demonstrated a significant
2.5-month survival advantage (p=0.009) in patients treated with
docetaxel (every three weeks) compared with the mitoxantrone plus
prednisone group.4 In contrast, docetaxel plus prednisone administered
weekly did not demonstrate a significant improvement in survival.
Docetaxel plus prednisone also significantly improved pain response
and PSA response rates compared with mitoxantrone plus prednisone
(p=0.01 and p=0.0005, respectively). In general, docetaxel was well tolerated.
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Prostate cancer is the most common cancer in North American males and the
third leading cause of death due to cancer. However, since the introduction
of androgen deprivation therapy (ADT) in the 1940s, there have been few
meaningful therapeutic advances. 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 in many elderly prostate cancer patients who cannot tolerate
chemotherapy. ADT 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 (before bone metastases develop),
Based on rising prostate-specific antigen (PSA) following primary therapy.
Earlier use 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 flushes. In addition, recent
evidence has demonstrated that ADT is often associated with bone loss.1

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Treatment of Hormone-refractory Prostate Cancer
Treatment options for patients with metastatic HRPC include second-line
hormonal manipulations, chemotherapy, bisphosphonates, and/or
radiation/radioisotope therapy to reduce skeletal morbidity. Second-line
hormonal manipulation may sometimes temporarily lower PSA levels, but
these regimens have not been shown to improve survival. It is now the
standard of care to stop antiandrogens when patients progress onto hormone
therapy. Whether there is any clinical benefit to changing antiandrogens or
increasing the dose of a given antiandrogen remains unknown.

Chemotherapy
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.4

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(p=0.01 and p=0.0005, respectively). In general, docetaxel was well tolerated.
Grade 3/4 toxicities included neutropenia, with 3% of the patients in the
docetaxel (every three weeks) group being hospitalized with febrile neutropenia compared with 2% of the patients in the mitoxantrone plus prednisone group. Common non-hematological adverse events included alopecia, fatigue, and nausea. By significantly improving survival and reducing both PSA and pain levels, docetaxel has now become the first-choice chemotherapy in HRPC.

**Bone-targeted Therapy**

Radiation/radioisotope therapy and bisphosphonates are palliative treatments for patients with bone metastases. Bisphosphonates are inhibitors of osteoclast-mediated bone resorption. They can prevent bone loss in patients with prostate cancer receiving ADT, and zoledronic acid can increase bone mineral density in this setting. 

Zoledronic acid has demonstrated significant clinical benefits, including the delay and prevention of skeletal complications and durable pain palliation in patients with bone metastases from HRPC. Moreover, bisphosphonates can be combined with chemotherapy. Indeed, zoledronic acid has been used safely with a variety of cytotoxic chemotherapies in clinical trials. Adverse events reported during bisphosphonate treatment did not appear to increase with concomitant chemotherapy.

Based on the available evidence, several guidelines, including those of the National Comprehensive Cancer Network, the European Association of Urology, and the International Consultation on Urological Diseases, recommend that bisphosphonates be used to preserve bone health and to prevent skeletal complications in patients with bone metastases from HRPC, whether asymptomatic or symptomatic. Presently, zoledronic acid is the only bisphosphonate that has shown efficacy in prostate cancer.

The combination of docetaxel and zoledronic acid has demonstrated additive antitumor activity in a human prostate cancer cell line, PC-3. The antitumor activity of docetaxel was increased with the addition of zoledronic acid in a dose-dependent manner. These results suggest that combination therapy with docetaxel and zoledronic acid could be especially active in patients with HRPC.

**Future Therapies**

Novel agents are also being investigated in this setting. Several treatment modalities, such as the endothelin receptor antagonist atrazen, have shown activity in bone metastatic HRPC in a placebo-controlled phase III trial. Although the study did not achieve its primary end-point, in patients with bone metastases there was a significant delay in progression in patients receiving atrazen. Results from an ongoing phase III study in preventing metastases will further help in defining the role of this agent in clinical practice. Vaccines, vitamin D analogs, and antisense oligonucleotides are currently under investigation in the HRPC setting, but appear to show promising results in phase II studies. Second-line therapy after primary chemotherapy for HRPC is an active area of research. In patients who respond to first-line docetaxel, it is reasonable to re-challenge with the same agent. Other agents are presently being investigated in this setting and, to date, satraplatin appears to show activity. Antisense clusterin is presently being studied in the second-line setting in combination with chemotherapy, given the promising pre-clinical proof of principle.

**Conclusion**

Advanced HRPC is a multifaceted problem and needs a multidisciplinary approach. Urologists should remain involved from the time of diagnosis throughout the continuum of care and should be familiar with the new challenges that this disease presents. Medical oncologists will have to take up the challenge of being actively involved in decision-making earlier than they have been used to. All specialties involved need to be aware that hormone therapy diminishes bone health, chemotherapy with docetaxel can provide a survival benefit in HRPC, and 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.