Therapeutic approach to hormone-refractory prostate cancer

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Over 60 years ago, Huggins and Hodges discovered androgen deprivation as an effective first-line therapy for metastatic prostate cancer. This leads to significant cancer control but in almost all men prostate cancer ultimately progresses to a hormone-refractory (HRPC) state resulting in significant morbidity and eventual death. In 2004, two landmark studies using docetaxel based chemotherapy demonstrated, for the first time, a survival advantage in HRPC. This has set a new standard of care for this disease. In addition, treatment with the bisphosphonate zoledronic acid has been shown to significantly reduce bone complications in metastatic HRPC. Building on these advances, several new docetaxel/zoledronic acid based combinations as well as new targeted therapies are under development. Introducing these effective therapies earlier in high risk patients is also under investigation to further improve outcomes.

Key Words: hormone refractory prostate cancer, docetaxel, zoledronic acid

Introduction

Prostate cancer is the most common cancer in North American males and the second 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

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survival may not be feasible in 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 and is now used earlier in the continuum of care for prostate cancer (before bone metastases develop) based on rising prostate-specific antigen (PSA). 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 and osteopenia, a phenomenon generally referred to as cancer treatment-induced bone loss or CTIBL.[1]

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.[2,3] 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 pathologic 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 HRPC.[4,5]

Treatment of HRPC

Treatment options for patients with metastatic HRPC include chemotherapy and second-line hormonal manipulations plus bisphosphonates and/or radiation/radioisotope therapy to reduce skeletal morbidity. Hormonal manipulation typically lowers PSA levels, but these regimens have not significantly delayed the course of disease progression in clinical trials. It is now standard of care to stop anti-androgens when patients progress on hormone therapy. Whether there is clinical benefit to changing anti-androgens or increasing the dose of a given anti-androgen remains unknown.

Chemotherapy

In 1996, chemotherapy (mitoxantrone plus prednisone) demonstrated significant palliative benefits in HRPC, significantly reducing pain ($P < .0001$) and improving QOL compared with prednisone alone.[6] However, overall survival was not improved. This treatment regimen was subsequently approved for HRPC based on palliative benefit. Subsequently, 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.[7] Median survival was increased by 2 months ($P = .01$) in patients treated with docetaxel plus estramustine.

A significant increase in PSA response ($P < .0001$) was also observed in the docetaxel plus estramustine group. A similar international trial comparing two different schedules of docetaxel (either every 3 weeks or weekly) plus prednisone versus mitoxantrone plus prednisone for 30 weeks demonstrated a significant 2.5-month survival advantage ($P = .009$) in patients treated with docetaxel (every 3 weeks) compared with the mitoxantrone plus prednisone group.[8] In contrast, docetaxel plus prednisone administered weekly did not demonstrate a significant improvement in survival, Figure 1. 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 ($P = .01$ and $P = .0005$, respectively). In general, docetaxel was well tolerated. Grade 3/4 toxicities included neutropenia with 3% of the patients in the docetaxel (every 3 weeks) group being hospitalized with febrile neutropenia compared with 2% of the patients in the mitoxantrone plus prednisone group. Common

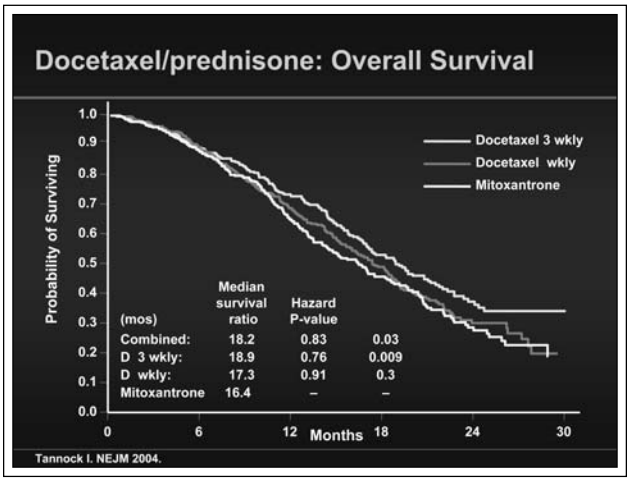

Figure 1. Overall survival of docetaxel/prednisone vs mitoxantrone/prednisone. A statistically significant median survival with q 3 weekly docetaxel was observed in the study.

nonhematologic adverse events included alopecia, fatigue and nausea. Therefore, docetaxel 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 resoprtion. They can prevent bone loss in patients with prostate cancer receiving ADT, and zoledronic acid can increase bone mineral density in this setting.[9,10] Zoledronic acid has demonstrated significant clinical benefits, including the delay, Figure 2, and prevention of skeletal complications, Figure 3, and durable pain palliation in patients with bone metastases from HRPC.[11] 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, an International 2002 Consensus Meeting recommended that bisphosphonates be used to preserve bone health and to prevent skeletal complications in patients with bone metastases from HRPC, whether

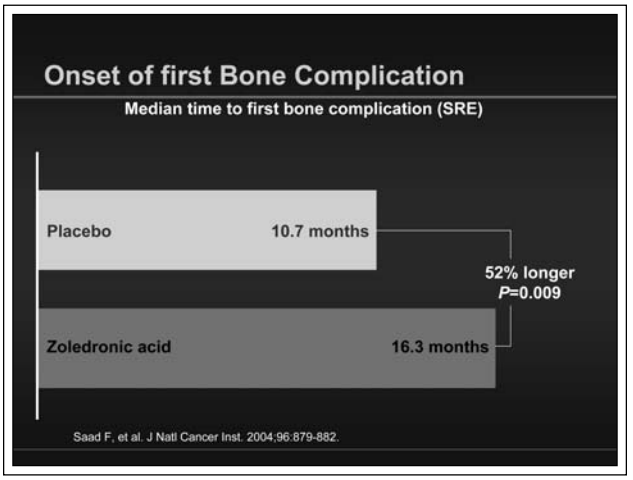

Figure 2. The time to the first SRE was significantly prolonged in patients receiving Zoledronic acid compared with patients receiving placebo. it was 488 days to the median time to the first SRE for patients in the zoledronic acid arm vs 321 days for patients in the placebo arm (P=0.009).

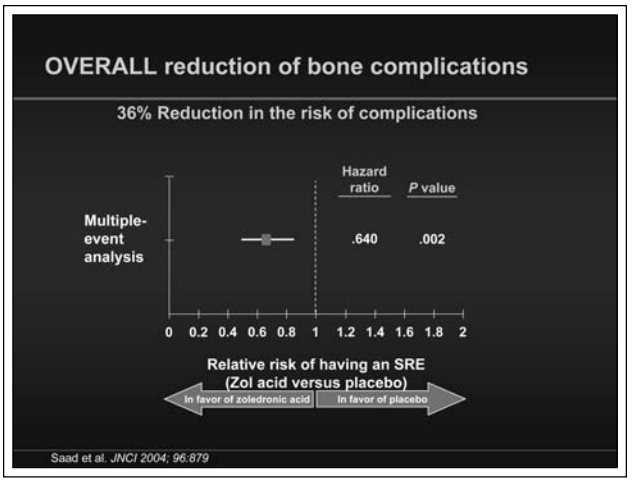

Figure 3. There is a significant (36%) reduction in the risk of developing an SRE for the zoledronic acid treatment group compared with placebo.

asymptomatic or symptomatic.[12] Zoledronic acid is the only bisphosphonate approved for this indication.

The combination of docetaxel and zoledronic acid have demonstrated additive antitumor activity in a human prostate cancer cell line, PC-3.[13] 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.[14]

Future therapies

Novel agents are also being investigated in this setting. Several different treatment modalities such as the endothelin receptor antagonist, Atrasentan, has shown activity in bone metastatic HRPC in a placebo controlled phase 3 trial. Although the study did not achieve its primary endpoint, in patients with bone metastases there was a significant delay in progression in patients receiving atrasentan. Results from an ongoing phase 3 study in preventing metastases will further help in defining the role of this agent in clinical practice.

Vaccines, vitamin D analogues, and antisense oligonucleotides are currently investigational in the HRPC setting, but appear to show interesting results in phase 2 studies.

Conclusion

Advanced HRPC is a multifaceted problem and needs

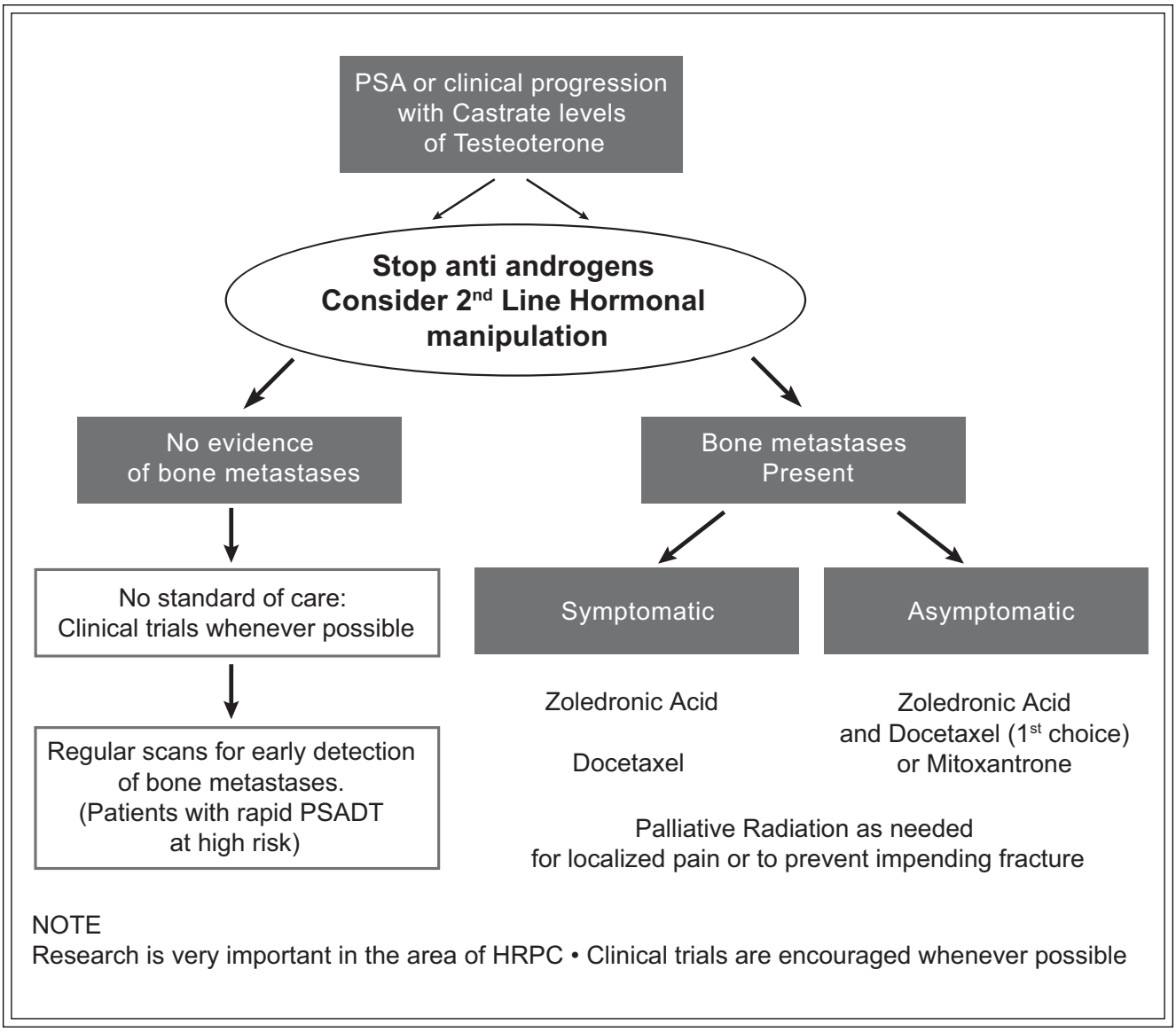

Figure 4. Proposed algorithm for treating HRPC.

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. Based on the data availabe, an algorithm for treating HRPC is proposed, Figure 4. Urologists 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. □

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