Current status of treatment for patients with metastatic prostate cancer

Celestia S. Higano, MD

Seattle Cancer Care Alliance, University of Washington, Seattle, Washington, USA

HIGANO CS. Current status of treatment for patients with metastatic prostate cancer. The Canadian Journal of Urology. 2005;12(Supplement 2):38-41.

Introduction: *Men with advanced prostate cancer now have many treatment options which include first and second-line hormonal therapy, chemotherapy, radiation therapy, (either directed external beam or systemic radioistotope), and investigational agents on protocols. Additional adjunctive therapy with the bisphosphonate, zoledronic acid, to reduce skeletal complications should be considered.*

Discussion: *This review will discuss appropriate timing of many of these options and summarize the randomized trials demonstrating survival benefit for docetaxel and decreased skeletal morbidity for zoledronic acid.*

Conclusion: *The clinical trials conducted to date do not address the question of when to give chemotherapy in the course of hormone refractory disease and the role of chemotherapy earlier in advanced disease remains to be defined. For the present, clinicians must consider many factors in determining what treatment is appropriate for the individual patient with advanced prostate cancer.*

Key Words: metastatic, prostate cancer, treatment

Introduction

Treatment options for advanced prostate cancer have changed dramatically over the last 20 years. In 1993, Yagoda and Petrylak reviewed the literature and reported that there was a 9% response rate for single-agent chemotherapy.[1] At that time, many concluded that there was no role for chemotherapy in prostate caner. Several years later, however, Tannock et al[2] in 1996 and then Kantoff et al[3] in 1999 both reported on the palliative benefits of mitoxantrone and prednisone for the treatment of patients with symptomatic disease. However, neither randomized trial showed a survival benefit for chemotherapy. During the ensuing years, numerous phase II trials showed activity of taxane (docetaxel and paclitaxel) based regimens and these trials formed the rationale for two phase III studies in which taxotere-based therapy was compared to mitoxantrone and prednisone. In 2004, results of both trials were presented at the American Society of Clinical Oncology in the plenary session and were ultimately published back to back in the New England Journal of Medicine.[4,5] Both of these landmark trials demonstrated that compared to mitoxantrone or to weekly docetaxel, docetaxel-based chemotherapy given every 3 weeks improved survival in men with metastatic hormone-refractory prostate cancer (HRPC). In the United States, the Food and Drug Administration (FDA) approved docetaxel and prednisone for the treatment of hormone-refractory

Address correspondence to Dr. Celestia Higano, Seattle Cancer Care Alliance, University of Washington, 825 Eastlake Avenue East, Mailstop G3-200, Seattle, WA 98109 USA

disease, although docetaxel is still not approved for this use in many countries.

In 2002, a phase III placebo controlled trial in men with HRPC showed that there were fewer skeletal complications in men who received zoledronic acid in addition to other anticancer therapies for prostate cancer.[6] This trial was the basis for approval of zoledronic acid by the FDA in the United States for use in patients with HRPC metastatic to bone, and in other countries for use in any patient with bone metastases, regardless of disease status. Thus, the positive results from this trial as well as from the docetaxel studies now afford new therapeutic options for men with HRPC who might otherwise have been offered palliative therapy that did not impact survival. In the following discussion, the timing of the use of these agents during the course of advanced prostate cancer is addressed.

Discussion

In men with newly diagnosed, untreated metastatic prostate cancer to the bone, medical or surgical androgen deprivation therapy (ADT) continues to be the gold standard. Whether to add zoledronic acid for patients with bone metastases who are still hormone sensitive has not yet been answered in clinical trials. However, if a patient has a skeletal related event such as fracture or spinal cord compression or if the DEXA scan indicates the presence of osteoporosis even before starting ADT, treatment with zoledronic acid would be logical. As discussed below, skeletal related events are delayed or prevented by zoledronic acid and, although zoledronic acid is not approved for use in the United States in this setting, use in the setting of a skeletal event to prevent or delay further skeletal complications is reasonable. In a randomized trial of men who were starting ADT, zoledronic acid administered every 3 months not only prevented loss of bone mineral density but actually increased bone density compared to placebo.[7] It should be noted, however, that at this time, alendronate is the only drug that has FDA approval for treatment of osteoporosis in men.

Whether chemotherapy should be added to hormonal therapy in men with newly diagnosed, untreated bone metastases, especially in certain high-risk patients, is still unknown and is the subject of numerous on-going trials. In general, outside of a clinical trial, chemotherapy is reserved for patients with hormone-refractory disease.

When patients with metastatic disease have a rising PSA level on ADT, patient specific factors listed in Table 1 should be taken into consideration. Usually treatment is dictated by the presence or absence of symptoms. If a patient does not have symptoms, most clinicians offer second line hormonal manipulations listed in Table 2. Alternatively, such patients are excellent candidates for clinical trials of new agents. Patients should probably remain on gonadotrophin-releasing hormone (GnRH) analog or chose to have an orchiectomy unless testosterone levels are carefully followed as administration of exogenous testosterone has been shown to exacerbate symptoms.[8]

In addition to other anti-cancer therapy, zoledronic acid is commonly started when patients with bone metastasis become hormone refractory. In a randomized, placebo controlled trial, continuous administration of zoledronic acid for up to 2 years has been shown to both delay and reduce the incidence of skeletal events.[6,9] Of note, the randomized docetaxel trials did not permit concurrent use of bisphosphonate therapy. While a randomized trial of docetaxel with or without zoledronic acid for men with HRPC would determine the impact of the combination, such a trial may be difficult to conduct in the United States at this time, as many patients with HRPC already receive zoledronic acid routinely.

TABLE 1. **Issues to consider in patients with HRPC**

Presence or absence of symptoms
Performance status
Extent of disease
Non-metastatic or metastatic
Location(s) of disease
Bone, nodal, visceral
Co-morbid diseases
Cost of therapy
Logistics

TABLE 2. **Second-line hormonal manipulations**

Anti-androgen withdrawal
Anti-androgen addition
Estrogens
Ketoconazole
Aminoglutethimide
Corticosteroids

Baseline renal function based on actual or calculated creatinine clearance needs to be considered for the initial dose of zoledronic acid. Subsequent dosing is also based on renal function and serum creatinine levels must be checked prior to each administration. The details of these dosing guidelines are shown in Table 3. Patients should be told about possible side effects as up to 25% of patients experience an acute phase reaction consisting of myalgias that may be accompanied by a fever.[6] These symptoms usually last less than one day and can be treated with non-steroidal medication for symptomatic relief. This reaction tends to be less bothersome with each subsequent infusion.

Patients starting zoledronic acid should also be educated about osteonecrosis of the jaw, a complication that appears to be associated with the use of bisphosphonate therapy. Good dental hygiene should be encouraged in all patients receiving chemotherapy. If receiving zoledronic acid, a patient who develops symptoms suggestive of a "toothache" should notify his dentist and, if the dentist is not familiar with osteonecrosis of the jaw, information from the oncologist's office should be provided. Dental extractions are generally discouraged in this setting, but sometimes cannot be avoided. Antibiotic therapy is usually prescribed. It is our practice to give patients written material and instructions about this potential problem.

Although docetaxel based chemotherapy has been shown to improve survival, the timing of chemotherapy in the course of HRPC was not addressed in the randomized trials referenced above. Patients who have symptoms should be offered chemotherapy even though there are some reports of symptomatic responses with second line hormonal manipulation. Most patients should be offered docetaxel (every 3 weeks with prednisone), since it is

TABLE 3. **Dosing guidelines for zoledronic acid**

Initial dosing

Baseline Cr Cl (ml/min)*	Zoledronic acid dose (mg)
> 60	4
50-60	3.5
40-49	3.3
30-39	3.0

***Creatinine clearance (CrCl) using Cockcroft-Gault formula:**

$$CrCl = \frac{(140 - \text{age in years}) \times \text{weight in kilograms}}{72 \times \text{serum creatinine (mg/dL)}} \quad \text{-or-}$$

$$CrCl = 1.2 \times \frac{(140 - \text{age in years}) \times \text{weight in kilograms}}{\text{Serum creatinine (}\mu\text{mol/L)}}$$

Subsequent dosing

Baseline serum creatinine < 1.4 mg/dL or < 123 μmol/L		Baseline serum creatinine ≥ 1.4 mg/dL or ≥ 123 μmol/L	
New serum creatinine			
< 0.5 mg/dL or < 44 μmol/L over baseline	≥ 0.5 mg/dL or ≥ 44 μmol/L over baseline	< 1.0 mg/dL or < 88 μmol/L over baseline	≥ 1.0 mg/dL or ≥ 88 μmol/L over baseline
Give baseline dose	Hold dose until serum creatinine within 10% of baseline	Give baseline dose	Hold dose until serum creatinine within 10% of baseline

this dose schedule that has been shown to improve both survival (by approximately 2 months) and quality of life.[4,5] However, the every 3-week docetaxel dose schedule is clearly more myelosuppressive than weekly dosing or mitoxantrone therapy. For patients with compromised hematological function who may not tolerate receiving docetaxel every 3 weeks, weekly docetaxel or mitoxantrone should be considered for palliation. The weekly docetaxel schedule and mitoxantrone appear to be equally effective for pain control.[5] While some patients are not good candidates for chemotherapy due to multiple co-morbidities and poor performance status, patients who are otherwise healthy but with a poor performance status may derive very significant clinical benefit in quality of life from chemotherapy.[2-5,10]

When treating patients with metastatic prostate cancer, the most important consideration is to improve or maintain of quality of life. The concept of a "chemotherapy vacation" allows some patients to discontinue chemotherapy after a significant response is achieved and to remain off chemotherapy, sometimes for months, until there is symptomatic or other progression. However, the latter approach remains an art for which there is no data derived from clinical trials.

Conclusion

Current research now focuses on taxane-based therapy in combination with other chemotherapy or novel targeted agents. It is hoped that these trials will result in improved survival with less toxicity for patients with advanced prostate cancer. □

References

1. Yagoda A, Petrylak D. Cytotoxic chemotherapy for advanced hormone-resistant prostate cancer. *Cancer* 1993;71(3 Suppl):1098-1099.
2. Tannock IF, Osoba D, Stockler MR et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. *J Clin Oncol* 1996;14:1756-1764.
3. Kantoff PW, Halabi S, Conaway M et al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the cancer and leukemia group B 9182 study. *J Clin Oncol* 1999;17:2506-2513.
4. Petrylak DP, Tangen CM, Hussain MH et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004;351:1513-1520.
5. Tannock IF, de Wit R, Berry WR et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;351:1502-1512.
6. Saad F, Gleason DM, Murray R et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2002;94:1458-1468.
7. Smith MR, Eastham J, Gleason DM, Shasha D, Tchekmedyian S, Zinner N. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. *J Urol* 2003;2008-2012.
8. Fowler JE, Whitmore WF. The responses of metastatic adenocarcinoma of the prostate to exogenous testosterone. *J Urol* 1981;126:372-375.
9. Saad F, Gleason DM, Murray R et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst* 2004;96:879-882.
10. Tannock IF, Osoba D, Stockler MR et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. *J Clin Oncol* 1996;14:1756-1764.