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REVIEW ARTICLE

Management of castration-resistant prostate cancer: a global approach

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ABSTRACT

Treatment options for castration-resistant prostate cancer (CRPC) have evolved since the start of the 2000s, with most of the new effective therapies appearing since 2010. In 2004, docetaxel was the first chemotherapeutic agent to improve survival in CRPC, but little else was available once patients recurred. Since 2010, four new options have been shown to improve survival in patients with refractory or recurring disease after docetaxel. In the management of bone metastases, two bone-targeted therapies have been shown to reduce the risk of bone complications, and they are part of the overall management strategy in CRPC patients. Therapeutic options before chemotherapy have shown promising results and may soon become available in Canada. The present article reviews the treatment options that have shown to be effective in CRPC and also some of the ongoing work in the field.

KEY WORDS

Castration-resistant prostate cancer, CRPC, prostate cancer, metastatic prostate cancer

1. DEFINITION OF CASTRATION-RESISTANT PROSTATE CANCER

Castration-resistant prostate cancer (CRPC) is defined by disease progression despite androgen deprivation therapy (ADT). That progression may present as any combination of a rise in serum prostate-specific antigen (PSA), progression of pre-existing disease, and appearance of new metastases[1].

2. MANAGEMENT APPROACHES

2.1 Hormonal

Because the androgen receptor remains active in almost all patients who develop castration-resistant disease, it is recommended that ADT be continued. Consequently, all clinical trials of patients with CRPC have mandated continued ADT. In terms of secondary hormonal manipulations, no study to date has shown definite benefits in terms of survival, but most trials have been smaller and heavily confounded by subsequent treatments used. In patients treated with luteinizing-hormone releasing-hormone agonist monotherapy or in those who have had an orchiectomy, it is reasonable to add an androgen receptor inhibitor such as bicalutamide. That approach can produce a PSA response in approximately 30% of patients.

For patients who are already receiving an antiandrogen and who are showing signs of progression, the antiandrogen should be discontinued, which may result in an antiandrogen withdrawal response. Other options may include a change to a different antiandrogen, to steroids, or to ketoconazole[2]. Transient PSA reductions have been reported in approximately 30% of patients with all of those modalities.

2.2 Systemic Corticosteroid Therapy

Corticosteroid therapy with low-dose prednisone or dexamethasone may also offer improvements in PSA values or palliative outcomes (or both) in up to 30% of both symptomatic and asymptomatic men[2,3]. Several studies have evaluated prednisone therapy in CRPC patients, although most addressed symptomatic patients. Prostate-specific antigen response rates, which are defined by a post-treatment decrease in PSA of 50% or more from baseline, have varied between 21% and 34%[4,5].

2.3 Novel Hormonally-Based Therapies

Novel agents that potently affect the androgen axis have recently been developed, renewing the enthusiasm for effective hormone manipulation. That approach is extensively reviewed by Leibowitz–Amit and Joshua[6] in this supplemental edition of *Current Oncology*.

Currently, phase III clinical trials in men with CRPC, evaluating whether, compared with prednisone and placebo, prednisone and abiraterone acetate—a potent and irreversible inhibitor of CYP17, which is a critical enzyme in androgen biosynthesis—can improve survival, have recently completed accrual[7]. In the post-docetaxel setting, abiraterone–prednisone (compared with placebo–prednisone) was shown to significantly prolong median overall survival by 3.9 months [14.8 months vs. 10.9 months; hazard ratio (HR): 0.64; $p = 0.0001$][8]. In light of those positive results, abiraterone was approved by the U.S. Food and Drug Administration (FDA) and Health Canada as second-line treatment in CRPC patients. The updated survival results, recently published in *Lancet Oncology*[9], show a 4.6-month advantage in overall survival. At the 2012 American Society of Clinical Oncology annual meeting, the results of the abiraterone pre-chemotherapy study in patients with metastatic CRPC were presented by Ryan *et al.*[10]. The study was halted early because of a very significant improvement in radiographic progression-free survival. Other important endpoints included improvements in time to chemotherapy and in opiate use. The co-primary endpoint of overall survival showed a strong trend toward statistical significance.

Enzalutamide is a potent multilevel inhibitor of the androgen receptor; it is described in more detail in the paper by Leibowitz–Amit and Joshua[6]. The results of the AFFIRM study of enzalutamide (previously called MDV-3100) compared with placebo in patients previously treated with docetaxel were recently published[11,12], demonstrating a significant advantage in overall survival of 4.8 months (18.4 months vs. 13.6 months; HR: 0.62; $p < 0.0001$) and very good tolerability. A recently completed phase III placebo-controlled study of enzalutamide in the pre-chemotherapy setting should report in the near future. Other androgen receptor and CYP17 inhibitors are also being evaluated in the pre- and post-docetaxel settings in international randomized trials[13].

2.4 Immunotherapy

In April 2010, sipuleucel-T became the first immunotherapeutic agent to be approved by the FDA, based on consistent observed improvements in overall survival. Sipuleucel-T is an autologous "vaccine" that requires the collection of white blood cells from individual patients to obtain antigen-presenting cells. The antigen-presenting cells are then exposed to the fusion protein prostatic acid phosphatase granulocyte–macrophage colony-stimulating factor and are re-infused into the patient. Patients entered into studies of sipuleucel-T have maintained an excellent to good performance status (Eastern Co-operative Oncology Group 0–1), have been asymptomatic or very minimally symptomatic, and have not developed visceral metastases. The confirmatory trial D9902B, which randomized 512 patients to sipuleucel-T or to placebo in a 2:1 ratio, also found a 22.5% improvement in mortality risk [median survival: 25.8 months vs. 21.7 months; HR: 0.775; 95% confidence interval (CI): 0.614 to 0.979; $p = 0.032$][14]. There was, however, no difference in PSA response or progression-free survival. The treatment appears to be well tolerated, and the most common complications included mild-to-moderate chills, pyrexia, and headaches, which are transient. Unfortunately, given the cost and the inability to predict who will actually benefit from sipuleucel-T, the drug is not approved in Canada. Another immunotherapeutic approach currently in phase III investigation is based on encouraging phase II data with a poxvirus-based PSA-targeted immunotherapy[15].

2.5 First-Line Systemic Chemotherapy

Docetaxel and prednisone are currently considered the standard of care for men with CRPC and detectable metastatic disease. This combination is based largely on the simultaneous publication of two large randomized controlled trials[16,17] that compared it with the previously established standard of mitoxantrone and prednisone.

Docetaxel is a taxane drug that induces polymerization of microtubules and phosphorylation of Bcl-2 protein. Tannock *et al.*[17] reported improved survival with every-3-weeks docetaxel–prednisone compared with mitoxantrone–prednisone (median survival: 18.9 months vs. 16.5 months; HR: 0.76; 95% CI: 0.62 to 0.94; two-sided $p = 0.009$). Petrylak *et al.*[16] reported a longer survival time with docetaxel–estramustine combination chemotherapy than with mitoxantrone (median survival: 17.5 months vs. 15.6 months; HR: 0.80; 95% CI: 0.67 to 0.97; two-sided $p = 0.02$). The latter trial also reported a median progression-free interval of 6.3 months compared with 3.2 months (HR: 0.73; 95% CI: 0.63 to 0.86; two-sided $p < 0.0001$) favouring docetaxel–estramustine.

Pain response was assessed in both the foregoing trials. Significantly more patients treated with every-3-weeks docetaxel achieved a pain response (35% vs. 22% with mitoxantrone, $p = 0.01$). Quality-of-life response, defined as a sustained 16-point or greater improvement from baseline on two consecutive measurements, was higher with docetaxel given every 3 weeks (22% vs. 13% with mitoxantrone, $p = 0.009$) or weekly (23% vs. 13% with mitoxantrone, $p = 0.005$). In both trials, PSA response rates were also statistically significantly higher with docetaxel than with mitoxantrone.

Based on the results of those two trials, it is now recommended that men with metastatic CRPC receive treatment with docetaxel 75 mg/m^2 administered intravenously every 3 weeks, combined with oral prednisone 5 mg twice daily to improve overall survival, disease control, symptom palliation, and quality of life.

2.6 Second-Line Systemic Chemotherapy

Until 2010, mitoxantrone was considered the *de facto* second-line chemotherapy, but published series suggest that it has limited activity and increased toxicity in that setting, with response rates from retrospective series in the range 9%–20%[18,19].

For patients who have not demonstrated definitive evidence of resistance to docetaxel, re-treatment with docetaxel can be considered[20,21].

Cabazitaxel is a potent taxane agent that has been selected in preclinical studies by virtue of its high cytotoxicity and low affinity for the adenosine triphosphate–dependent drug efflux pump P-glycoprotein 1, which can be responsible for resistance to docetaxel[22]. Results from a large phase III trial evaluating the efficacy of cabazitaxel were recently published. This randomized placebo-controlled trial recruited 755 docetaxel-pretreated CRPC patients. Patients were randomized to receive prednisone 10 mg daily, with either mitoxantrone 12 mg/m^2 every 3 weeks, or cabazitaxel 25 mg/m^2. Treatment caused high rates of grades 3–4 neutropenia (observed in 81.7% of patients in the cabazitaxel arm and in 58.0% of patients in the mitoxantrone arm), with incidences of febrile neutropenia of 7.5% and 1.3% respectively. A statistically significant and clinically relevant survival advantage emerged in favour of the cabazitaxel arm, with a median survival of 15.1 months compared with 12.7 months in the mitoxantrone arm (HR: 0.70; 95% CI: 0.59 to 0.83; $p < 0.0001$). In light of those positive results, cabazitaxel was approved by the FDA as second-line treatment in CRPC patients.

2.7 Bone-Targeted Therapy

Bone loss in patients with prostate cancer may be attributed to the disease itself, which is a risk factor for osteoporosis, and to ADT[23,24]. Bone loss associated with ADT and the presence of bone metastases lead to a fragile bone state and a significant risk of skeletal complications, including pathologic fractures, debilitating bone pain, and spinal cord compression. Bisphosphonates and denosumab, a human monoclonal antibody RANK ligand inhibitor, are inhibitors of osteoclast-mediated bone resorption that can prevent bone loss and increase bone mineral density in patients with prostate cancer receiving ADT[23–27].

Zoledronic acid and denosumab also reduce the risk of bone complications in patients with bone metastases[28–30]. In men with castration-recurrent prostate cancer and bone metastases, zoledronic acid (4 mg intravenously) and denosumab (120 mg subcutaneously) every 4 weeks is recommended to prevent disease-related skeletal complications including pathologic fractures, spinal cord compression, and surgery or radiation therapy to bone.

Results from a randomized study[29] showed that skeletal-related events occurred in fewer men receiving zoledronic acid than in men receiving placebo (38% vs. 49%, $p = 0.02$). Zoledronic acid also increased the median time to first skeletal-related event (488 days vs. 321 days, $p = 0.01$). An overall 36% reduction in the rate of skeletal-related events was observed in treated patients. In a randomized controlled study, denosumab demonstrated an 18% ($p = 0.001$) improvement in time to a first skeletal-related event (20.7 months vs. 17.1 months with zoledronic acid, $p < 0.008$)[30]. No dose modification for renal function is necessary in the case of denosumab, but the risk of hypocalcemia is greater than that with zoledronic acid. Both agents require calcium and vitamin D supplementation.

Zoledronic acid and denosumab are associated with 1%–2% risk of osteonecrosis of the jaw[30]. Most (but not all) patients who develop such osteonecrosis have pre-existing dental problems. Excellent oral hygiene, baseline dental evaluation for high-risk individuals, and avoidance of invasive dental surgery during therapy are recommended to reduce the risk.

A recently completed phase III study of patients with metastatic CRPC were randomized on a 2:1 basis either to ^{223}Ra (an alpha-emitting bone seeker) or to placebo. Overall survival was the primary endpoint. Median survival was 14 months for the treated patients and 11.2 months for patients who received placebo, conferring an approximate 30% improvement in overall survival (HR: 0.699; $p = 0.0022$). The study also showed a 5-month delay in time to a skeletal-related event. If approved by the FDA, this bone-targeted agent will be the first to demonstrate a survival advantage. The study is still unpublished; it was presented by Parker and colleagues at the 2012 American Society of Clinical Oncology genitourinary cancers symposium.

3. CLINICAL TRIALS AND FUTURE DIRECTIONS

Men with CRPC are living longer and with improved quality of life; however, most—if not all—will eventually succumb to their disease. Better treatments are still required. Several trials in the pre- and post-chemotherapy settings are ongoing, with the objective of delaying progression and the need for chemotherapy and of improving overall survival. Novel agents such as Src and clusterin inhibitors are also being tested in phase III trials in combination with docetaxel in the first-line setting[10,31–34]. Because CRPC remains an incurable and ultimately fatal illness, participation in clinical trials at all stages of the disease remain paramount.

4. CONFLICT OF INTEREST DISCLOSURES

FS serves as a consultant and has conducted research with Amgen, Astellas Pharma, Janssen, Novartis, and Sanofi–Aventis.

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