REVIEW

Castration-resistant prostate cancer: systemic therapy in 2012

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Prostate cancer is the most common non-cutaneous neoplasm in the male population worldwide. It is typically diagnosed in its early stages, and the disease exhibits a relatively indolent course in most patients. Despite the curability of localized disease with prostatectomy and radiation therapy, some patients develop metastatic disease and die. Although androgen deprivation is present in the majority of patients with metastatic prostate cancer, a state of androgen resistance eventually develops. Castration-resistant prostate cancer, defined when there is progression of disease despite low levels of testosterone, requires specialized care, and improved communication between medical and urologic oncologists has been identified as a key component in delivering effective therapy. Despite being considered a chemoresistant tumor in the past, the use of a prostate-specific antigen has paved the way for a new generation of trials for castration-resistant prostate cancer. Docetaxel is a life-prolonging chemotherapy that has been established as the standard first-line agent in two phase III clinical trials. Cabazitaxel, a novel taxane with activity in cancer models resistant to paclitaxel and docetaxel, is the only agent that has been compared to a chemotherapy control in a phase III clinical trial as a second-line therapy; it was found to prolong the overall survival of patients with castration-resistant prostate cancer previously treated with docetaxel when compared to mitoxantrone. Other agents used in this setting include abiraterone and sipuleucel-T, and novel therapies are continually being investigated in an attempt to improve the outcome for patients with castration-resistant prostate cancer.

KEYWORDS: Drug Therapy; Antineoplastic Agents; Prostate Neoplasms.

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INTRODUCTION

Prostate cancer is the most common non-cutaneous neoplasm in the male population worldwide (1). The vast majority of cases are diagnosed in the early stages (2), and the disease exhibits a relatively indolent course in most patients (3). In the United States, prostate cancer remains the most common malignancy in men (2), despite the recent trend of decreasing mortality from the disease (4). Likely as a result of the early diagnosis through prostate-specific antigen (PSA) testing, the clinical behavior of prostate cancer, and the age of patients with this disease, there is a large difference between incidence and mortality rates from prostate cancer in the United States and Europe (2,5). Recently, prostate cancer has become the most common cancer in Brazil, surpassing breast cancer with an estimated 52,000 new cases each year (6).

Despite the indolent course of the disease and the curability of localized disease with prostatectomy and radiation therapy, some patients develop metastatic disease, frequently involving the bones and other organs (7). Once metastatic disease is diagnosed, the likelihood of dying from prostate cancer surpasses death from other causes (8). For these patients, treatment is performed with a palliative intent, often involving androgen deprivation through pharmacological or surgical orchiectomy. As a general rule, androgen deprivation is present in 80% to 90% of patients with metastatic prostate cancer. These patients have a median progression-free survival (PFS) ranging from 12 to 30 months after treatment is initiated (9,10). However, a state of androgen independency eventually emerges, historically leading to a median overall survival (OS) of only 8 to 16 months from the time of its appearance (9,10). The terms 'androgen-independent,' 'hormone-refractory', and 'castration-resistant' have been used interchangeably over the years – not without some controversy (11) – to denote the progression of disease despite castration levels of testosterone (12). However, many recent studies and guidelines in metastatic disease have used the term castration-resistant prostate cancer (CRPC) (13-16), which will be used in the following review, based on the available therapeutic modalities for patients whose disease progresses after the use of standard hormone therapy.

DEFINING THE CASTRATION-RESISTANT STATE

Although most patients with metastatic prostate cancer initially respond to androgen deprivation due to testosterone dependence in prostate cancer cells, and despite the fact the secondary hormonal manipulations are active in some

patients (17), prostate tumor cells eventually acquire the capacity to survive and proliferate in an androgen-depleted environment (7,18). Mechanisms that underlie the transition from an androgen-sensitive to an androgen-resistant phenotype have been elucidated to some extent, and a variety of cellular pathways are implicated in this phenomenon (7,9,18-20). As a result, androgen-receptor mutations and alterations in the androgen-signaling cascade are considered to be responsible for the androgen-withdrawal response that is observed in a minority of patients being treated with antiandrogens (21).

In clinical practice, it is important to identify the patients with metastatic prostate cancer that require treatment as opposed to those whose disease is only manifested by a rising serum PSA level (22). Likewise, it is important to determine when an initially sensitive disease is no longer responsive to androgen deprivation, and improved communication between medical and urologic oncologists has been identified as a key component in achieving this goal (23). There is anecdotal evidence that many patients continue to receive hormone therapy, despite the failure of previous treatments, before being referred to a medical oncologist. For practical purposes, it is useful to consider patients as having progressive CRPC if their disease progresses during androgen-deprivation therapy, including the withdrawal of antiandrogens, and if at least 4-8 weeks have elapsed after the withdrawal of antiandrogens (24,25) The progression can be confirmed by a PSA elevation alone, a bone scan with measurable disease, or clinical progression (symptomatic progression). It should be noted that patients with CRPC may benefit from continued androgen deprivation, as androgen-sensitive clones are thought to play a role in disease progression after discontinuing hormone therapy (18).

FIRST-LINE TREATMENT OF CRPC

Historical development of and assessment of response to chemotherapy

Until the late 1980s, prostate cancer was considered a chemoresistant tumor (26). Several authors noted that the response rates to the available agents were typically low but also varied widely in different studies (26-28). In addition, authors postulated that the documentation of responses in prostate cancer was complicated by a lack of established criteria to assess the effects of the drugs, as nearly 80% of patients with CRPC have no measurable soft-tissue lesions (29). Thus, the response rates could only be determined in the minority of patients with measurable disease before the PSA era. In the early 1990s, PSA became widely available and was used in clinical trials as a measure of response (7,30). In 1999, a consensus conference suggested that a decline in PSA of at least 50% could represent a partial response in clinical trials as long as there was confirmation at least four weeks later and no clinical or radiographic evidence of disease progression (31). The use of PSA has allowed for a new generation of trials of CRPC treatments, and PSA responses have been used as surrogates for objective responses in this setting for early drug development (31). However, the PSA response has not been validated as a surrogate for OS in androgen-sensitive disease or in CRPC, and OS remains the most relevant endpoint in phase III clinical trials (32,33). In addition, other time-dependent endpoints, such as PFS and the time to tumor progression (TTP), have been increasingly used in clinical trials (12), and recent data from nearly 600 patients with CRPC suggest that PSA progression is able to predict OS in CRPC (25). Of note, PSA levels are not independent predictors of OS in CRPC when other clinical or laboratory parameters are considered (34).

Several chemotherapeutic agents, such as the anthracyclines, alkylating agents, antimetabolites, platinums, and topoisomerase inhibitors, have been assessed in numerous phase II clinical trials over the years (26,27). In a review of 26 different drugs before the PSA era, the average response rate was only 8.7%, but the combination of vinblastine plus estramustine was regarded as promising (27). This combination was assessed in randomized trials, but the results at the time did not establish a reference regimen, and toxicity remained a concern in the setting of palliative therapy for typically elderly men (35,36). In combination, both mitoxantrone and low-dose prednisone had displayed modest single-agent activity and good tolerability in phase II clinical trials (37,38). In randomized trials, mitoxantrone and a corticosteroid relieved pain and improved the quality of life more frequently than with the same corticosteroid alone (39-41). Therefore, before the advent of docetaxel, mitoxantrone eventually became the reference chemotherapeutic agent for the treatment of patients with CRPC (24). However, this approach was not associated with gain in OS (approximately 12 months) or gains in quality of life, and improved regimens were sought.

Docetaxel as the standard of care in the first-line treatment of CRPC

After the demonstration of its single-agent activity (42,43), docetaxel was assessed in two phase III clinical trials published in 2004 (24,44). In the first study, 1,006 patients with CRPC were randomized to receive mitoxantrone (12 mg/m^2 every three weeks), docetaxel (75 mg/m^2 every three weeks), or weekly docetaxel (30 mg/m^2), all combined with prednisone (5 mg twice daily) (24). As the primary endpoint of the study, OS improved in both docetaxel arms compared to mitoxantrone; however, these improvements were statistically significant when docetaxel was administered every three weeks (hazard ratio [HR] = 0.76; $p = 0.009$), but not weekly (HR = 0.91; $p = 0.36$). The median OS times were 16.5 months with mitoxantrone, 18.9 months with docetaxel every three weeks, and 17.4 months with weekly docetaxel. The secondary endpoints of predefined reductions in pain (22% vs. 35% vs. 31%), PSA response (32% vs. 45% vs. 48%), and improvements in quality of life (13% vs. 22% vs. 23%) were all significantly superior for both docetaxel schedules. However, docetaxel led to more adverse events than mitoxantrone – mainly neutropenia. In the second study, 674 eligible patients with CRPC were randomized to receive estramustine (280 mg three times daily on days 1 through 5), docetaxel (60 mg/m^2 on day 2), and dexamethasone (in three divided doses before docetaxel), or mitoxantrone (12 mg/m^2) plus prednisone (5 mg of twice daily), both regimens given every three weeks (44). The median OS, the primary endpoint, was longer with docetaxel and estramustine than with mitoxantrone (17.5 months vs. 15.6 months; HR = 0.80; $p = 0.02$). Likewise, the TTP (median of 6.3 months vs. 3.2 months) and decline in PSA (50% vs. 27%) significantly favored the docetaxel-containing regimen, but it was also more frequently associated with adverse events. The results of these two

studies established docetaxel as the new standard agent for first-line treatment of CRPC, and the toxicity of this agent was considered acceptable. However, the role of estramustine remained uncertain, and docetaxel every three weeks plus prednisone was accepted as a reference for future studies and for clinical practice.

SECOND-LINE TREATMENT OPTIONS FOR CRPC

Cabazitaxel

Cabazitaxel, a novel member of the taxane class of antimicrotubule agents, demonstrated effectiveness in preclinical models resistant to paclitaxel and docetaxel (45,46). Furthermore, cabazitaxel is able to cross the blood-brain barrier, a potential advantage in the treatment of some malignancies (47). On the basis of phase I and II clinical trials, the dose of cabazitaxel recommended for future studies ranged from 20 to 25 mg/m^2, and the effects were observed in docetaxel-refractory prostate cancers and in other tumors (46,48). Thus, a phase III clinical trial was launched with the aim of comparing cabazitaxel to mitoxantrone in docetaxel-refractory CRPC (13). In this study, 755 patients were treated with prednisone (10 mg daily) and randomized to receive either cabazitaxel (25 mg/m^2) or mitoxantrone (12 mg/m^2) every three weeks, with OS as the primary endpoint. The median OS was 15.1 months in the cabazitaxel group and 12.7 months in the mitoxantrone group (HR = 0.70; $p<0.0001$). Cabazitaxel was associated with a higher incidence of adverse events than mitoxantrone. The most common toxicities associated with cabazitaxel were neutropenia, anemia, and diarrhea. Of note, peripheral neuropathy was uncommon and typically mild or moderate in severity (13). The results of this phase III clinical trial led to the approval of cabazitaxel for the second-line treatment of CRPC in many countries, including Brazil. To date, cabazitaxel is the only agent that has been compared with a chemotherapy control in a phase III clinical trial in this disease setting. Although not based on phase III data in the second-line setting, mitoxantrone was chosen as a control arm in this study due to its frequent use in the community practice. Recently after the Food and Drug Administration (FDA) approved cabazitaxel on June 2010, the drug was approved in Brazil by the National Agency of Health Surveillance (ANVISA) to be administered in association with prednisone or prednisolone in the treatment of docetaxel-refractory metastatic CPRC. In addition to the United States, cabazitaxel had been approved for marketing in Israel, Curaçao and in the European Union, along with Iceland, Lichtenstein and Norway.

Abiraterone

Abiraterone is a selective inhibitor of androgen biosynthesis through its action on cytochrome P450 17 (17α-hydroxylase-17,20-lyase), the key enzyme in androgen and estrogen biosynthesis (49). Based on the evidence that CRPC remains sensitive to androgens derived from the adrenal gland or by endocrine synthesis, preclinical studies have suggested that abiraterone is effective in CRPC (19). Moreover, a phase I/II clinical trial has found a PSA response in nearly two-thirds of the 42 patients with chemotherapy-naïve CRPC (50). In a phase III trial, abiraterone (1000 mg/day) was compared to placebo, both combined with prednisone (5 mg twice daily), in 1196 patients with docetaxel-refractory metastatic CRPP (51). The primary OS endpoint was significantly different between the two groups: there was a 35% reduction in the risk of death (HR = 0.65; $p<0.0001$) and a median OS of 14.8 months with abiraterone vs. 10.9 months with placebo. Secondary efficacy endpoints, such as PFS, TTP, and PSA responses, consistently favored the abiraterone group, and the toxicities of this agent were primarily hypokalemia and fluid retention. Based on the results of this study, the FDA approved abiraterone in combination with prednisone as a treatment for docetaxel-refractory metastatic CPRC patients in April 2011.

Sipuleucel-T

Immunological mechanisms likely influence the behavior of prostate cancer and other malignancies. Sipuleucel-T, a type of therapeutic cancer vaccine, is able to elicit active immunologic cellular responses by autologous peripheral-blood mononuclear cells that have been activated ex vivo with a recombinant fusion protein consisting of prostatic acid phosphatase and the immune-cell activator granulocyte–macrophage colony-stimulating factor (14). The use of sipuleucel-T involves harvesting peripheral blood mononuclear cells from the patient, culturing them with the fusion protein, and then infusing the antigen-presenting cells back into the patient. The combined analysis of two relatively small randomized trials have shown that sipuleucel-T produced a survival benefit in 225 patients with CRPC compared to those treated with placebo; it had an acceptable toxicity profile consisting mostly of chills, fever, and headache (52). Thus, a third placebo-controlled phase III clinical trial was launched, and 512 patients were randomized in a 2:1 ratio to receive sipuleucel-T or placebo intravenously every two weeks for a total of three infusions (14). The study revealed a 22% relative reduction in the risk of death with the use of sipuleucel-T (HR = 0.78; $p = 0.03$), which represented a 4.1-month improvement in the median OS (25.8 months vs. 21.7 months in the placebo group). However, the TTP was similar in the two study groups; this relatively uncommon finding in medical oncology (i.e., survival prolongation with no accompanying delay in tumor progression) has been identified as surprising and worthy of further investigation, likely related to the mechanism of action of the vaccine, which could change the natural history of disease progression (52). Nevertheless, sipuleucel-T has been approved by the FDA for the treatment of patients with asymptomatic or minimally symptomatic CRPC.

OTHER AGENTS

Novel antitumor therapies

Several novel agents are currently being investigated for the treatment of patients with CRPC (19). MDV3100 is an androgen-receptor antagonist with no agonistic activity that allows for the exploitation of the continued reliance on androgen-receptor signaling by CRPC. In a phase I/II clinical trial conducted in the United States, antitumor activity was noted at all dosage levels with a PSA response in 56% of 140 patients with CRPC (53). Such promising results have prompted the continued development of this agent in larger trials. Bevacizumab, the anti-vascular endothelial growth factor antibody, has been added to standard docetaxel therapies but has not been shown to

improve the OS in patients with CRPC, despite an improvement in PFS; it was also associated with a higher morbidity and mortality than docetaxel alone in a large phase III clinical trial published in abstract form (54).

Bone-targeting agents

There are several potential explanations for the marked predisposition of prostate cancer to metastasize preferentially to bones (55). Both osteoblasts and osteoclasts appear to play a critical role in the interactions between prostate cancer cells and bone, and the receptor activator of nuclear factor kappa-B ligand (RANKL) is a key element in osteoclastogenesis, bone resorption, and chemoattraction of tumor cells (56). The prominent role of bone metastases in the natural history of metastatic prostate cancer has prompted investigators to target this site of metastasis in hopes of palliating symptoms and prolonging survival through the use of androgen ablation, bisphosphonates, radiopharmaceuticals, focal radiation, chemotherapy, and targeted agents (55). Successful results from these efforts have included the demonstration that zoledronic acid reduces the rate of skeletal-related events in patients with CRPC (57) and that radiopharmaceuticals may have a role as a consolidation therapy in patients treated with antitumor agents (58). More recently, targeting RANKL with the monoclonal antibody denosumab has been found to be more efficacious than treatment with zoledronic acid in terms of skeletal-related events in patients with CRPC, as observed by a significant delay in the time to first and subsequent on-study skeletal-related events (HR 0.82; $p = 0.004$) compared to zoledronic acid. Additionally, the median time to the first on-study skeletal-related event was 20.7 months for the denosumab group compared with 17.1 months for the zoledronic acid group (59).

Bone-seeking agents

Although the use of bone-seeking radiopharmaceuticals is currently approved for the palliation of bone pain, a randomized phase II study using sequential ketoconazole plus doxorubicin and strontium-89 showed a prolonged survival (16.8 to 27.7 months) compared to chemotherapy alone (58). More recently, a phase I study evaluated the effect of samarium-153 ethylenediamine tetramethylene-phosphonate (153Sm-EDTMP) administered repetitively in a docetaxel chemotherapy regimen in patients with castration-resistant metastatic prostate cancer (60). The results from this study demonstrated that this combination led to a greater than 50% decline in prostate-specific antigen without significant bone marrow toxicity.

Endothelin receptor antagonists

The endothelin pathway has been implicated in promoting osteoblastic activity, a feature of bone metastases in prostate cancer (61). Two selective endothelin-A antagonists have been evaluated in this population: atrasentan and zibotentan. Data from a study in 809 CRPC patients demonstrated that atrasentan (10 mg/day) did not reduce the TTP compared to placebo, although a significant decrease in the molecular markers of disease progression was observed. The same result for the TTP was observed with zibotentan, despite the improvement in OS, in a phase II clinical trial. These preliminary findings highlight the need for further evaluation in this group of patients.

Calcitriol

There is no consensus among clinical oncologists on the utility of calcitriol in the treatment of CRPC, although preclinical data have demonstrated it has potent antitumor activity with antiproliferative, antiangiogenic, and apoptosis-induction effects. Calcitriol also appears to synergistically act with dexamethasone.

In 2010, Chadha et al. (62) published the results of a phase II clinical trial using intravenous calcitriol and dexamethasone in patients with CRPC. The results from this study indicated that this combination did not produce a clinical or PSA response. More recently, a phase III study evaluated the efficacy of docetaxel plus high-dose calcitriol compared to docetaxel plus prednisone (ASCENT 2) in 953 patients with CRPC; it reported a higher number of deaths, shorter overall survival and shorter duration of treatment in the ASCENT arm compared to the control arm. These findings led to the termination of the trial, and the clinical development of the formulation of calcitriol used in this study was discontinued (63,64).

CONCLUSIONS

The introduction of docetaxel in 2004 began a new era in the management of CRPC. Over the past few years, additional progress has been made in the development of novel agents with activity against docetaxel-refractory disease and with the potential to improve docetaxel-based first-line therapies in the near future. At present, cabazitaxel is the only agent that has been compared to a chemotherapy control in a phase III clinical trial in patients with docetaxel-refractory CRPC, and sipuleucel-T is available in some countries for asymptomatic patients. Abiraterone appears to be a new treatment option for docetaxel-refractory CPRC patients. Over the next few years, results from studies on these and other novel agents will likely increase the therapeutic arsenal used to treat CRPC.

Conflicts of interest: We certify the financial support by Sanofi-aventis and disclose our interest statement. Fernando C. Maluf is a consultant for Janssen Cilag and Sanofi-aventis. Daniel Herchenhorn is an investigator in the TROPIC trial. Óren Smaletz is a recipient of honoraria as a speaker and consultant for Sanofi-aventis and receives research funding from Janssen-Cilag. All authors are members of the advisory board of Sanofi-Aventis. This work represents the opinions of the authors.

AUTHOR CONTRIBUTIONS

Maluf FC conceived and designed the study, and was also responsible for the manuscript writing, and final approval of the manuscript. Smaletz O and Herchenhorn D were responsible for the manuscript writing and final approval of manuscript.

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