Sequencing Systemic Therapies in Metastatic Castration-Resistant Prostate Cancer

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Background: Men with prostate cancer will not die of the disease until it progresses to the metastatic castration-resistant stage. At that stage, the median survival is 9 to 30 months.

Methods: Recently approved and emerging treatments for metastatic castration-resistant prostate cancer (mCRPC) were reviewed based on their mechanisms of action, as well as sequencing and combining these treatments with existing options.

Results: Advances in androgen deprivation therapy, immunotherapy, bone-targeted therapy, and chemotherapy have led to approvals of abiraterone acetate, sipuleucel-T, denosumab, and cabazitaxel for the treatment of mCRPC. Despite improvements in patient survival and quality of life, mCRPC remains incurable.

Conclusions: With the emerging new therapies, this is an unprecedented time in treating mCRPC. A better understanding of their mechanisms of action, the genetic makeup of each mCRPC, and the development of new prognostic and predictive biomarkers will help determine sequencing or different combination treatments for each individual patient.

Introduction

Prostate cancer is the most common cancer among North American men, with approximately 238,590 new cases diagnosed and 29,720 deaths expected in 2013 in the United States. Prostate cancer is not deadly until it progresses to the metastatic castration-resistant stage, defined as progressive prostate cancer despite a castrate level of serum testosterone (< 50 ng/dL). Patients with metastatic castration-resistant prostate cancer (mCRPC) have a progressive and morbid disease process, with a median survival of 9 to 30 months. Although the survival period will likely be improved with newly approved and emerging therapies, mCRPC remains an incurable disease. Based on the palliative nature of systemic therapies, the goals of treatment are to improve survival and to maintain patient quality of life with minimum toxicities. In this article, we review newly approved and emerging therapies for mCRPC, dividing them into four strategies: antiandrogen therapy, immunotherapy, cytotoxic chemotherapy, and bone-targeted therapy.
We also discuss how to sequence these treatments to maximize survival benefits.

**Antiandrogen Therapy**

Second-line androgen deprivation therapies with antiandrogens, estrogen, or ketoconazole in combination with hydrocortisone have been widely used in patients with mCRPC, but with limited response rates and duration of response. Furthermore, these therapies do not improve survival for mCRPC.³ Over the last 3 years, a paradigm shift in mCRPC treatment occurred with the clinical confirmation that a significant proportion of mCRPCs are dependent on the androgen axis despite the castrate level of testosterone in the serum.⁴ Several new agents were developed to more potently block androgen synthesis or inhibit androgen binding to the androgen receptor. Among them, abiraterone acetate and enzalutamide improve survival rates of patients with mCRPC in the post-docetaxel setting.⁵,⁶

Abiraterone acetate is a selective inhibitor of androgen biosynthesis that potently blocks cytochrome P450c17 (CYP17, 17-α-hydroxylase and C17, 20-lyase), a critical enzyme in testosterone synthesis in the adrenal glands, in the testes, and within the prostate tumor.⁷⁻¹⁰ It is more potent and less toxic than ketoconazole.⁷ A phase III trial comparing abiraterone plus prednisone with placebo plus prednisone studied 1,195 patients with mCRPC who had progressive disease after docetaxel chemotherapy.⁵ This trial excluded patients who were previously treated with ketoconazole. Based on a 4-month improvement in the rates of overall survival (OS) during the interim analysis (14.8 vs 10.9 months; hazard ratio [HR] = 0.65; P < .001), the US Food and Drug Administration (FDA) approved abiraterone in April 2011 for mCRPC following docetaxel treatment. All secondary and exploratory end points were met and favored the abiraterone treatment group, including time to prostate-specific antigen (PSA) progression (10.2 vs 6.6 months; P < .001), rate of progression-free survival (PFS; 5.6 vs 3.6 months; P < .001), PSA response rate (29% vs 6%; P < .001), time to skeletal event (9.9 vs 4.9 months), and rate of pain palliation (44% vs 27%; P = .002).⁵ Adverse events associated with elevated mineralocorticoid levels due to CYP17 blockade were fluid retention, edema, hypokalemia, and hypertension. Abnormal liver function test results were more common in the abiraterone group than in the placebo group.

The approval of abiraterone marked the beginning of a new era of antiandrogen therapy, with a wide array of agents undergoing phase III clinical trials for mCRPC. The second preplanned interim analysis of the phase III COU-AA-302 trial was recently reported at the 2012 American Society of Clinical Oncology annual meeting. The trial tested the safety and efficacy of abiraterone in combination with prednisone chemotherapy-naïve mCRPC patients who were asymptomatic or mildly symptomatic.¹¹ Compared with the prednisone arm, abiraterone significantly improved OS and radiographic PFS, co-primary end points of this phase III study. TAK-700 (Orteronel) is a selective nonsteroidal inhibitor of C17,20-lyase. After encouraging data from a phase I/II trial,¹² TAK-700 plus prednisone vs placebo plus prednisone is being tested in two phase III studies for men with mCRPC in both the chemotherapy-naive setting (NCT01193244) and the post-docetaxel setting (NCT01193257).

MDV3100 is a potent antiandrogen that inhibits androgen binding to androgen receptor, translocation of androgen receptor to the nucleus, and the subsequent DNA binding.¹³ The results from an interim analysis of the phase III AFFIRM trial were reported at the 2012 ASCO annual meeting.⁶ The trial evaluated MDV3100 (formerly enzalutamide) vs placebo in 1,199 men with advanced prostate cancer who were previously treated with docetaxel-based chemotherapy. It demonstrated a clinically meaningful and statistically significant improvement in OS compared with placebo (18.4 vs 13.6 months, HR = 0.63; P < .001). Fatigue (34% vs 29%), diarrhea (21% vs 18%), and hot flush (20% vs 10%) were the most common events in the MDV3100 arm, with an incidence higher than that reported in the placebo arm. Of note, 5 patients (0.6%) in the MDV3100 arm developed seizure vs 0% in the placebo arm. The ongoing phase III PREVAIL trial is testing MDV3100 in the chemotherapy-naïve mCRPC patients (NCT01212991).

**Immunotherapy**

Prostate cancer cells express a number of tumor-associated antigens that can serve as targets for immunotherapy. The limited immune response to prostate cancer in vivo has been attributed to impaired immune system recognition by decreased immunogenicity of surface antigens or blunted effectiveness of the immune response. Sipuleucel-T is an active cellular immunotherapy¹⁴,¹⁵ designed to stimulate an immune response to a widely expressed prostate cancer antigen, prostatic acid phosphatase fused with granulocyte-macrophage colony-stimulating factor (GM-CSF).¹⁶ The phase III IMPACT trial, in which sipuleucel-T was compared with placebo, showed a 4.1-month median survival benefit (25.8 vs 21.7 months) and a 22% reduction in the risk for death compared with placebo (HR = 0.775; P = .03) in patients with asymptomatic or minimally symptomatic mCRPC.¹⁷ Similar improvements in OS were supported by two smaller previous phase III trials with similar design (D9901 and D9902A).¹⁸ However, improvement in OS was not associated with improvements in PFS. In the IMPACT trial, no significant difference occurred in
time to objective response (3.7 vs 3.6 months; \( P = .63 \)), time to clinical progression (\( P = .4 \)), or PSA response (2.6% vs 1.3%; \( P > .05 \)) in the sipuleucel-T group vs the placebo group. Patients with poor performance status (ECOG 2 or above) or visceral metastasis were excluded, and 25% of patients in the IMPACT trial had Gleason sum of 8 or more. The most common adverse events reported were chills, fatigue, fever, back pain, nausea, joint ache, and headache.\(^{17} \)

The FDA approved sipuleucel-T for the treatment of asymptomatic or minimally symptomatic men with mCRPC in April 2010.

Other immunotherapies such as anti-CTLA immunotherapy and therapies using gene transfer approaches for mCRPC are also being evaluated in phase III studies. Ipilimumab is a human monoclonal antibody that blocks CTLA-4, a negative regulator of T cells.\(^{19-22} \)

It was recently approved by FDA for treating metastatic melanoma.\(^{23} \)

In a randomized phase II trial, 108 patients with advanced prostate cancer treated with ipilimumab plus androgen ablation were more likely to have undetectable PSA levels by 3 months compared with those treated with androgen ablation alone (55% vs 38%), and significant clinical responses were also seen.\(^{24} \)

Ipilimumab is now being investigated in two phase III clinical trials targeting chemotherapeutic-naïve and docetaxel-treated patients (NCT01057810 and NCT00861614, respectively). Another emerging immunotherapy approach uses PSA-targeted poxviral vaccines (PROSTVAC-VF). In a randomized phase II trial, 125 men with mCRPC who were minimally symptomatic were randomly assigned to a PROSTVAC-VF plus GM-CSF or to an empty vector with a GM-CSF placebo for 24 weeks.\(^{25} \)

PROSTVAC-VF immunotherapy was associated with a 44% reduction in the death rate and an 8.5-month improvement in median OS.\(^{5} \)

A phase III trial (PROSPECT) to reevaluate these results has been open for accrual since November 2011 (NCT01322490).

**Cytotoxic Chemotherapy: Beyond Single-Agent Docetaxel**

Since the publications of the TAX 327 and SWOG-9916 phase III studies,\(^{26,27} \)
docetaxel in combination with prednisone has become the standard first-line chemotherapy for mCRPC on the basis of improvement in survival compared with mitoxantrone plus prednisone. Several agents have been studied in combination with docetaxel and prednisone to improve the efficacy and survival. The phase III Cancer and Leukemia Group B study (CALGB 90401) evaluated docetaxel plus prednisone with or without bevacizumab.\(^{28} \)

Regardless of the significant improvement in PFS (9.9 vs 7.5 months; \( P < .0001 \)) and response rate (53.2% vs 42.1%; \( P = .01 \)), the trial was negative for the primary end point of OS (22.6 vs 21.5 months; \( P = .91 \)). Another phase III clinical trial, MAINSAI, evaluating docetaxel combinations with lenalidomide was halted at interim analysis due to lack of efficacy.\(^{29} \)

Despite these early disappointments, combination strategy continues to be tested. Dasatinib, a potent inhibitor of the Src (sarcoma) family of kinases that targets stromal-epithelial interactions, was tested in the phase III READY trial. Despite its promising phase II results, the addition of dasatinib to docetaxel failed to improve survival of patients with mCRPC compared to docetaxel alone when the results of the READY trial were presented at the genitourinary symposium in February 2013 (NCT00744497).\(^{30} \)

In summary, no combination to date has been shown to triumph docetaxel and prednisone in phase III evaluation to enhance the activity of docetaxel and prednisone as first-line chemotherapy for men with mCRPC.

By contrast, the effort of developing second-line chemotherapy after docetaxel has led to the FDA approval of cabazitaxel in 2010. Compared with mitoxantrone plus prednisone, cabazitaxel and prednisone led to a 30% reduction in risk of death (HR = 0.70; \( P < .0001 \)) and a 2.4-month improvement in median OS (15.1 vs 12.7 months) in the phase III TROPIC trial.\(^{31} \)

Grade 3/4 toxicities included neutropenia (81.7%), febrile neutropenia (7.5%), infections (10.2%), vomiting (1.9%), and diarrhea (6.2%). Deaths resulting from adverse events were 4.9% with cabazitaxel (primarily because of neutropenic infections) compared with 1.9% with mitoxantrone. Of note, the dose of cabazitaxel in the TROPIC trial was higher than what was recommended from phase I evaluation (25 vs 20 mg/m\(^2\)), and a follow-up phase III trial (PROSELICA) is now planned to directly compare cabazitaxel 25 and 20 mg/m\(^2\) (NCT01308580). Another phase III trial (FIRSTANA) will compare cabazitaxel with docetaxel in the first-line setting (NCT01308567).

**Bone-Targeted Therapy**

Skeletal complications are major causes of morbidity in patients with mCRPC. Bisphosphonates, which inhibit the bone resorbing activity of osteoclasts by binding to the mineralized bone surface,\(^{32} \)

are an established treatment for patients with mCRPC. Based on the results of three randomized controlled trials, intravenous zoledronic acid was approved in 2002 to treat patients with bone metastases from multiple myeloma and solid tumors like prostate cancer.\(^{33-35} \)

The prostate cancer-specific trial was in the setting of mCRPC and showed that the zoledronic acid arm had significant reduction in the frequency of skeletal-related events (33% vs 44%; \( P = .021 \)) and prolongation of the median time to develop skeletal-related events (16 vs 11 months).\(^{35} \)

Pain and anaglesic scores were significantly lower in the group treated with zoledronic acid, but there were no differences in disease progression or OS.
In addition to bisphosphonates, osteoclast inhibition can be achieved by targeting the receptor activator of nuclear factor kappa B (RANK) ligand, a key component in the pathway for osteoclast formation and activation. Denosumab is a human monoclonal antibody against the RANK ligand; it inhibits osteoclast-mediated bone destruction. When compared against zoledronic acid in a phase III trial of 1,904 men with mCRPC, denosumab improved median time to first on-study skeletal-related event by 3.6 months (HR = 0.82; \( P = .008 \) for superiority). The two groups were similar with regard to OS and time to disease progression. Rates of adverse events were similar, except for an increased incidence of hypocalcemia (13% in the denosumab group vs 6% in the zoledronic acid group; \( P < .0001 \)). The incidence of osteonecrosis of the jaw was 2% in the denosumab group and 1% in the zoledronic acid group. Denosumab was approved for the treatment of mCRPC patients with bone metastases in November 2010.

The role of denosumab in preventing bone metastasis or death in nonmetastatic CRPC has been examined. In a study protocol that randomized 1,432 men with CRPC at high risk for bone metastases (PSA \( \geq 8 \) μg/L, PSA doubling time ≤ 10 months, or both) to denosumab or placebo, denosumab significantly increased median bone-metastasis–free survival by 4.2 months compared with placebo (29.5 vs 25.2 months; HR = 0.85; \( P = .028 \)). Denosumab also significantly delayed time to first bone metastasis (33.2 vs 29.5 months; HR = 0.84; \( P = .032 \)). However, OS did not differ between the two groups (denosumab 43.9 vs placebo 44.8 months; \( P = .91 \)). Of note, 33 patients (5%) on denosumab developed osteonecrosis of the jaw compared with none on placebo. Hypocalcemia occurred in 12 patients (2%) on denosumab and in 2 patients (< 1%) on placebo. The rates of other adverse events and serious adverse events were similar in both groups. Denosumab is not approved by the FDA for preventing bone metastasis in nonmetastatic CRPC.

Men with multifocal painful bone metastases and those with persistent or recurrent pain despite receiving external palliative radiation therapy may achieve palliation of their symptoms by treatment with bone-targeted radioisotopes such as samarium-153 and strontium-89. Among the bone-targeted radioisotopes, radium-223, an alpha emitter, was the only one that has been shown to improve survival by a phase III trial. In the ALSYMPCA phase III trial, 922 men with symptomatic bone metastases from CRPC were randomly assigned to radium-223 or placebo. The majority of the 922 subjects had previously been treated with docetaxel. A planned interim analysis observed a statistically significant reduction in the risk of death with radium-223 compared with placebo (median survival 14 vs 11.2 months; HR = 0.695; \( P = .002 \)). There was also a significant delay in the time to first skeletal event by 5.2 months (13.6 vs 8.4 months; HR = 0.61; \( P = .00046 \)). The incidence of bone pain was numerically lower compared with placebo (43% vs 58%), and the incidence of toxicities was similar in both groups except increased mild hematologic toxicity in the group treated with radium-223.

**Treatment Sequencing and Combination Strategy**

Significant advances have been made in prostate cancer drug development in the past decade (Tables 1 and 2). Several new challenges now confront physicians treating mCRPC. These challenges include identifying the best sequencing of the approved agents for individual patients and determining how to combine these agents in a rational way to maximize survival and minimize toxicity.

The division of patients with mCRPC into chemotherapy-naive and docetaxel-treated populations for evaluation of androgen-targeting agents has been driven mostly by the motivation to select a trial population that will minimize the time for obtaining regulatory approval for a novel agent. With its convenient oral administration, efficacy in disease and symptom control, survival benefit, and acceptable tolerability, androgen pathway inhibition with abiraterone acetate and the upcoming enzalutamide can be a desirable option at any point in the continuum of mCRPC treatment. Both agents, as well as TAK-700, have activity in chemotherapy-naive mCRPC based on early phase clinical trials and are being tested in the phase III setting. The combination of agents with different mechanisms of action, namely androgen synthesis inhibition and androgen receptor blockade, for maximal antiandrogen effect is an area to be explored. Antiandrogen therapy combined with immunotherapy or chemotherapy and continuous maximal androgen deprivation beyond disease progression are potentially beneficial strategies to be tested. Most importantly, these strategies need to be tailored to the biology of the patient’s cancer. Of note, a significant portion of mCRPC patients did not respond to newer androgen-targeting agents, and none of these agents are curative. Developing predictive biomarkers and investigating the mechanisms of resistance are areas of active research.

As the first approved immunotherapy, sipuleucel-T is indicated for minimally symptomatic or asymptomatic patients with mCRPC. It is currently the only FDA-approved treatment that can be given in the prechemotherapy setting and has been shown to improve survival of mCRPC patients. Given the fact that immunotherapy requires time to work and will likely work the best with low disease burden, sipuleucel-T is probably a superior choice as a frontline treatment when cancer has progressed to the mCRPC stage and...
remains asymptomatic or minimally symptomatic.

Due to the immunosuppressive nature of corticosteroids and the fact that prednisone is a component of approved combinations with abiraterone, docetaxel, and cabazitaxel, the option to use sipuleucel-T requires reviewing immediate prior therapy and estimating the time to next therapy.

As the first agent approved for mCRPC with survival benefit, docetaxel has the longest track record for symptom control and survival prolongation. It remains the treatment of choice for symptomatic mCRPC in the chemotherapy-naive setting. For progression after docetaxel, theoretically, patients now have three options: sipuleucel-T, abiraterone, and cabazitaxel. Enzalutamide could be another option after its approval by the FDA. For patients with mCRPC that progresses on docetaxel within the first 3 months, abiraterone is a more acceptable choice due to its suggested taxane resistance. For those who have poor performance status or residual bone marrow suppression from prior chemotherapy, abiraterone is currently the best option based on its proven efficacy and favorable safety profile. For patients who have responded to docetaxel before and have progressive mCRPC while on chemotherapy break, we favor utilizing cabazitaxel rather than reintroducing docetaxel.

When managing mCRPC in patients with newly approved agents such as abiraterone, it is important to know that criteria developed by the Prostate Cancer Working Group 2 (PCWG2) were used to define disease progression in recent phase III clinical trials. In terms of progression of measurable soft-tissue lesions by RECIST, the PCWG2 recommends a confirmation second scan 6 or more weeks later. For prostate cancer biological therapies or immunotherapy, a target lesion may increase in size before it decreases. Bone metastasis, which occurred in ≥ 90% of mCRPC cases, is not measurable by RECIST. Bone progression is defined as ≥ 2 new lesions by bone scan. If ≥ 2 new lesions are present at the first reassessment, a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions is recommended by the PCWG2 to define disease progression in the bone. In terms of symptoms, the PCWG2 recommends ignoring early changes (≤ 12 weeks) in pain or health-related quality of life in the absence of compelling evidence of disease progression. These recommendations by the PCWG2 aim

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to ensure a sufficient window of drug exposure and reduce the reliance on early changes in PSA.

In general, the toxicity profiles of the newly developed antiandrogen therapies — immunotherapy and bone-targeted therapy — are superior compared to taxane-based chemotherapy. This advantage allows testing of the combination of different treatment modalities to improve the outcome of mCRPC. One example is a phase II randomized, open-label trial of sipuleucel-T with concurrent compared with sequential administration of abiraterone acetate plus prednisone in men with mCRPC (NCT01487863). This trial aims to study how concurrent vs sequential use of abiraterone would affect the immune response to sipuleucel-T, and the primary objective is to evaluate cumulative sipuleucel-T CD54 upregulation. Another approach would be combining effective treatments earlier in the disease stage to improve the margin of benefits. The STAMPEDE trial is one example, and the hormone therapy plus abiraterone combination arm was recently added to version 8 of the STAMPEDE protocol.

In addition to the underlying tumor biology and the mechanisms of action for different agents, patient comorbidities, performance status, and life expectancy are other important factors in determining how to sequence or combine different treatment modalities for mCRPC. Based on the average wholesale price, the cost of sipuleucel-T for 5 weeks (3 treatments) is $93,000, 12 weeks of abiraterone is $18,000, 12 weeks of denosumab (3 injections) is $5,940, and 12 weeks of docetaxel (4 cycles) is $12,000. Therefore, the decision-making process should incorporate cost-benefit analyses to determine whether a combination treatment approach is justified for patients with mCRPC.

**Conclusions**

This is an unprecedented time in the history of clinical development for patients with metastatic castration-resistant prostate cancer. In the last 2 years, several large phase III trials demonstrated improvements in survival rates using novel therapeutic agents with diverse mechanisms of action (Table 1, Figure). As our understanding of this heterogeneous disease improves, defining effective combination and sequencing strategies for these active agents will further improve patient outcomes.

**References**


