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Review article

Treatment options in castration-resistant prostate cancer: Current therapies and emerging docetaxel-based regimens

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Abstract

Background: Docetaxel-based chemotherapy remains the standard of care for metastatic castration-resistant prostate cancer (mCRPC) and it is the only globally approved first-line therapy. Although docetaxel offers improved survival for this patient population, it is also associated with toxicity and resistance in many patients, representing a need for more efficacious therapies. Preclinical advances have led to improved understanding of the molecular biology of prostate cancer, and targeted therapies that exploit the signaling pathways and molecular targets that underscore the disease are being clinically investigated in combination with docetaxel.

Design: This article briefly highlights recent data from phase III trials in mCRPC that have led to agent approval. This article also reviews phase II and III trials in which docetaxel-based regimens have been investigated in mCRPC.

Results: Recently approved agents, including sipuleucel-T, cabazitaxel, abiraterone acetate, and enzalutamide, have diversified the mCRPC treatment landscape. Phase III trials evaluating docetaxel in combination with targeted therapies, including potent oral tyrosine kinase inhibitor, dasatinib, in the READY trial and clusterin inhibitor, custirsen, in the SYNERGY trial, are currently ongoing.

Conclusions: In combination with docetaxel, targeted agents dasatinib and custirsen will likely expand the existing treatment paradigm for mCRPC if results from phase III trials are positive.

Keywords: Custirsen; Dasatinib; Docetaxel; Prostate cancer; Review; Targeted therapy

1. Introduction

1.1. Epidemiology

Prostate cancer is the second most commonly diagnosed cancer in men worldwide [1]. With an estimated 258,000 deaths projected in 2008, prostate cancer is the sixth leading cause of death from cancer in men [1]. Prostate cancer represents a large therapeutic area of unmet medical need.

1.2. Overview of disease course

Initial therapies for prostate cancer, including radiotherapy and prostatectomy, aim to eliminate tumor burden [2]. Most patients diagnosed with early disease (local or regional stages) have positive disease outcomes with 5-year survival rates approaching 100% [3]; however, some patients progress to advanced or metastatic disease [4]. Additionally, ~10% to 20% of the patients are diagnosed with advanced or metastatic disease [4]. For these patients, androgen deprivation therapy is often performed by either pharmacologic or surgical castration [5]. Androgen deprivation therapy results in decreased serum prostate-specific antigen (PSA) as well as tumor regression and relief of symptoms in many patients, but the response to treatment is often not durable in patients with advanced cancer. Over time, PSA levels will rise, indicating a transition to a castration-resistant state, often through a reactivation of androgen receptor (AR) signaling that is unfortunately fatal [6].

Castration-resistant prostate cancer (CRPC) is defined as prostate cancer that has progressed despite castrate levels of testosterone (<50 ng/ml) [7]. Approximately 90% of the men with metastatic CRPC (mCRPC) are clinically characterized by rising PSA levels prior to symptoms of pain and progression of metastatic lesions in bone tissue [8,9]. Bone metastases are a hallmark of mCRPC as well as a

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cause of morbidity and poor quality of life (QoL) among men with mCRPC [10]. Therefore, goals of therapy for mCRPC include improvement in overall survival (OS) in addition to reductions in pain and skeletal-related events (SREs).

2. Current treatment guidelines for CRPC

2.1. First-line treatment for symptomatic mCRPC

Globally, the gold standard first-line therapy for mCRPC includes docetaxel (TAXOTERE), a member of the taxane family of anticancer agents, which induces apoptosis by suppression of microtubule dynamics, disruption of the cell cycle, and phosphorylation of bcl-2 [11,12]. Standard of care (SOC) first-line therapy for symptomatic mCRPC in the United States, Europe, and Canada is docetaxel administered every 3 weeks in combination with corticosteroids [2,8,13]. This SOC is based on results from the Southwest Oncology Group (SWOG) 9916 and Taxotere (TAX) 327 studies that both demonstrated a significant survival benefit, as discussed later [14–16].

In the SWOG 9916 trial, 770 men with mCRPC received docetaxel/estramustine and showed improvement in OS compared with a regimen of mitoxantrone/prednisone (median OS 17.5 mo vs. 15.6 mo, respectively; hazard ratio [HR]: 0.80, 95% confidence interval [CI] 0.67–0.97; $P = 0.02$) [14]. In the phase III TAX327 study, docetaxel/prednisone every 3 weeks prolonged OS by 2.9 months in 1,006 men with mCRPC compared with a schedule of mitoxantrone/prednisone (median OS 19.2 mo vs. 16.3 mo, respectively; HR: 0.79; $P = 0.004$) [15,16]. Improvements in pain response rates (35% vs. 22%, respectively; $P = 0.01$), decline in serum PSA levels of at least 50% (45% vs. 32%, respectively; $P < 0.001$), and improvements in QoL also were observed [15–17]. As a regimen of docetaxel/estramustine was associated with greater toxicity and less efficacy compared with docetaxel/prednisone every 3 weeks [14–17], the latter was adopted as the preferred SOC in symptomatic mCRPC patients.

For symptomatic CRPC patients for whom docetaxel cannot be tolerated, mitoxantrone is an alternative, palliative option [2,13]. Bisphosphonates, including zoledronic acid [8] or the receptor activator of nuclear factor-kappa B ligand inhibitor denosumab, may be considered for patients with bone metastases for the prevention or reduction of bone complications, and to relieve bone pain [2,13]. Furthermore, radioisotope therapy with strontium-89 or samarium-153 may be an effective alternative for patients with bone metastases [2,8,13].

2.2. Alternative first-line treatments for mCRPC

In the United States, sipuleucel-T (PROVENGE) has been approved by the Food and Drug Administration (FDA) as a first-line treatment option in patients with chemotherapy-naive, asymptomatic or minimally symptomatic advanced CRPC [2,18]. Sipuleucel-T is an immunotherapy comprised of autologous peripheral-blood mononuclear cells, including antigen-presenting cells, that have been activated ex vivo with a recombinant fusion protein (PA2024) [19]. This vaccine was approved following the results of the phase III IMmunotherapy for Prostate AdenoCarcinoma Treatment (IMPACT) trial, which revealed a 4.1-month improvement in OS relative to placebo (median OS 25.8 mo vs. 21.7 mo, respectively; HR: 0.78, 95% CI 0.61–0.98; $P = 0.03$) in asymptomatic or minimally symptomatic mCRPC patients ($n = 512$; randomized 2:1, experimental to control) [19]. Sipuleucel-T was found to be well tolerated; adverse events (AEs) such as chills, fever, and headache were more commonly reported with treatment relative to the placebo group [19]. However, the lack of surrogate markers of response, such as PSA decline or Response Evaluation Criteria In Solid Tumors (RECIST) response, makes it difficult to assess if the patient truly is benefiting from the treatment.

More recently, abiraterone acetate (ZYTIGA), a selective inhibitor of androgen biosynthesis, was approved by regulatory agencies in the United States and Europe for chemotherapy-naive mCRPC [20,21]. Approval came following positive results from the phase III COU-AA-302 trial, in which 1,088 chemotherapy-naive men with mCRPC who were treated with abiraterone acetate/prednisone experienced prolonged OS relative to a regimen of placebo/prednisone (median OS not reached vs. 27.2 mo, respectively; HR: 0.75, 95% CI 0.61–0.93; $P = 0.01$) [22]. COU-AA-302 results also revealed that abiraterone acetate improved radiographic progression-free survival (PFS) relative to placebo (median radiographic PFS 16.5 mo vs. 8.3 mo, respectively; HR: 0.53, 95% CI 0.45–0.62; $P < 0.001$) [22]. Adverse events, such as fatigue, arthralgia, and peripheral edema, were more frequently reported in the abiraterone acetate treatment group than in the placebo group [22].

2.3. Second-line treatment for mCRPC

Second-line systemic therapy for symptomatic mCRPC patients, following docetaxel failure, includes cabazitaxel (JEVTANA) [23], a second-generation tubulin inhibitor, and abiraterone acetate [2,20]. Both agents have demonstrated improvements in OS postdocetaxel in phase III trials [24,25], leading to health authority approvals in the United States and Europe [20,23,26,27]. More recently, enzalutamide (XTANDI) [28], an oral AR-signaling inhibitor, was also approved by the FDA for the treatment of patients with mCRPC postdocetaxel.

Cabazitaxel was approved in the second-line for mCRPC treatment [23] following results from the phase III TROPIC study, in which 755 men with mCRPC were randomized to receive either cabazitaxel/prednisone or mitoxantrone/prednisone [24]. Patients who received cabazitaxel experienced