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New Drugs

Second-line treatment options in metastatic castration-resistant prostate cancer: A comparison of key trials with recently approved agents

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SUMMARY

Standard first-line treatment for metastatic castration-resistant prostate cancer (mCRPC) is docetaxel plus prednisone; however, patients will usually experience disease progression during or after docetaxel treatment due to inherent or acquired resistance. Before 2010, second-line options for mCRPC were limited. However, cabazitaxel, abiraterone acetate and enzalutamide have since been approved for patients with mCRPC whose disease has progressed during or after receiving docetaxel, based on the Phase III trials TROPIC, COU-AA-301 and AFFIRM. In all three trials, an overall survival benefit (primary endpoint) was seen in the experimental arm compared with the control arm: 15.1 vs. 12.7 months for cabazitaxel plus prednisone compared with mitoxantrone plus prednisone in TROPIC (hazard ratio [HR] 0.70; $P < 0.0001$); 14.8 vs. 10.9 months for abiraterone acetateplus prednisone compared with placebo plus prednisone in COU-AA-301 (HR 0.65; $P < 0.001$); and 18.4 vs. 13.6 months for enzalutamide compared with placebo alone in AFFIRM (0.63; $P < 0.001$). However, differences in patient populations, comparators, and selection and/or definition of secondary endpoints make it difficult to draw direct cross-trial comparisons. Radium-223 dichloride has also been approved for patients with mCRPC with metastases to bone but not other organs. To date, no comparative trials or sequencing studies with newer agents have been performed. Without such data, treatment decisions must be based on evaluation of the existing evidence. This commentary compares and contrasts study designs and key data from each of these Phase III trials, and also discusses recent and ongoing clinical trials with new agents in the first- and second-line settings in mCRPC.

Introduction

Globally, prostate cancer is the second most frequently diagnosed cancer in men and is a major cause of mortality, representing 258,000 deaths in 2008 [1]. Although localized prostate cancer may be successfully treated with radiotherapy or surgery, many patients will develop metastatic disease [2–4]. Standard treatment for patients with metastatic prostate cancer is androgen-deprivation therapy; however, most patients will eventually develop resistance leading to disease progression (metastatic castration-resistant prostate cancer [mCRPC]). The introduction of highly effective novel therapies has resulted in increased overall survival (OS) in patients with mCRPC, from approximately 9–18 months [4] to >30 months in patients enrolled in recent clinical trials and expanded-access programs [5].

For patients with mCRPC, docetaxel (75 mg/m^2 every 3 weeks) was the first agent to demonstrate a survival benefit, and docetaxel plus prednisone (10 mg orally, daily) is the standard first-line therapy recommended by international guidelines for patients with symptomatic mCRPC who are suitable candidates for chemotherapy [2–4]. In randomized Phase III trials, docetaxel-based treatment showed a median OS benefit compared with mitoxantrone of 2–3 months, which was similar across subgroups (including both ⩽68 and ⩾69 years, both presence and absence of visceral

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metastases, and both low and highperformance status) [6]. In addition, prostate-specific antigen (PSA) response rates of 45–50%, an objective tumor response rate of 12–17% and an improvement in quality of life (QoL) compared with mitoxantrone were observed ($P < 0.01$) [6–8]. However, patients will usually experience disease progression either during or after receiving docetaxel regimens, due to resistance, either inherent or acquired through a number of different mechanisms [9,10]. In one study investigating a docetaxel-based regimen, the median time from first docetaxel dose to disease progression was 6.3 months [9].

Before 2010, second-line treatment options for mCRPC werelimited, with no benefits observed in terms of OS. Since 2010, however, three therapies have been approved for patients with mCRPC whose disease has progressed during or after receiving docetaxel: cabazitaxel, a novel tubulin-binding taxane (FDA approval in 2010; EMA approval in 2011) [11,12]; abiraterone acetate (AA), an oral androgen biosynthesis inhibitor (FDA and EMA approval in 2011) [13,14]; and enzalutamide, an oral androgen receptor antagonist (formerly known as MDV3100; FDA approval in 2012) [15]. Currently, cabazitaxel and AA are recommended in the European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) guidelines as second-line options in this setting [2,4]. In addition, radium-223 dichloride, a novelalpha-emitting radiopharmaceutical agent that targets bone metastases owing to its chemical similarity to calcium, has recently been approved by the FDA for use in patients with mCRPC with symptomatic bone metastases and no known visceral metastatic disease. This agent demonstrated positive results compared with placebo in the Phase III ALSYMPCA trial in patients with mCRPC with bone metastases [16,17]. Based on the enrollment criteria for the ALSYMPCA study and efficacy data currently available, it is likely that radium-223 dichloride will be used both in patients with prior docetaxel therapy and in those who are not sufficiently fit to receive chemotherapy [16,17]. However, because this agent is not approved specifically in the second-line setting, it is not discussed in detail within this manuscript.

To date, no comparative trialsor sequencing studies with newer agents have been performed. In their absence, comparison of study designs and data from the pivotal Phase III trials can help to determine which agents are suitable for patients with different characteristics in second-line mCRPC. However, direct comparisons of studies are difficult when there are subtle differences in patient populations and in definitions of either treatment response or failure. This commentary compares and contrasts study designs and key data from each agent in patients with mCRPC whose disease has progressed during or following treatment with docetaxel.

Overview of Phase III trials of agents recently approved for second-line treatment of mCRPC

Cabazitaxel, AA and enzalutamide were evaluated in patients with mCRPC with disease progression during or after docetaxel treatment in separate randomized Phase III trials – TROPIC, COU-AA-301 and AFFIRM, respectively (Table 1).

Cabazitaxel (TROPIC)

Cabazitaxel was the first agent to demonstrate improved survival post-docetaxel in mCRPC patients. The approval of cabazitaxel was based on the TROPIC study, a randomized, open-label, Phase III trial in 755 patients with mCRPC whose disease had progressed during or after treatment with a docetaxel-containing regimen (TROPIC; Table 1) [18]. Patients were randomized (1:1) to cabazitaxel (25 mg/m^2 1-h intravenous [IV] infusion every 3 weeks) plus prednisone (10 mg daily) or mitoxantrone (12 mg/m^2 IV infusion every 3 weeks) plus prednisone (10 mg daily). Eligible patients had pathologically proven prostate cancer, previous and ongoing castration by orchiectomy or luteinizing hormone-releasing hormone agonists, or both, and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2. Patients with measurable disease were required to have documented disease progression by Response Evaluation Criteria in Solid Tumors (RECIST) with $\geqslant 1$ visceral or soft-tissue metastatic lesion. Patients with non-measurable disease were required to have rising serum PSA concentrations (at least two consecutive increases relative to a reference value measured at least a week apart) or the appearance of at least one new demonstrable radiographic lesion. The primary endpoint was OS; secondary endpoints included progression-free survival (PFS), tumor response rate, PSA response rate and time to tumor progression (Table 1). For PFS, progression was indicated by any of PSA progression, tumor progression (radiologic evidence by RECIST) or pain.

Abiraterone acetate (COU-AA-301)

AA was evaluated in COU-AA-301, a randomized, double-blind, Phase III trial in 1195 patients with mCRPC who had previously received docetaxel and had progressive disease (Table 1) [19]. In this trial, patients were randomized (2:1) to AA (1 g orally, once daily) plus prednisone (5 mg twice daily) or placebo plus prednisone (5 mg twice daily). Eligible patients had histologically or cytologically confirmed prostate cancer, ongoing androgen deprivation, with a serum testosterone level of 50 ng per deciliter or less ($\leqslant$2.0 nmol per liter), and an ECOG PS of 0–2. Disease progression was defined according to the criteria of the Prostate Cancer Clinical Trials Working Group (PCWG2) [20] (two consecutive increases in PSA concentration over a reference value) or radiographic evidence of disease progression in soft tissue or bone with or without disease progression on the basis of the PSA value. The primary endpoint was OS; secondary endpoints included PFS, PSA progression, PSA response rate and QoL measures (Table 1). Before completion, the study was unblinded at the request of the Independent Data Monitoring Committee (IDMC) and patients receiving placebo were crossed over to receive active treatment [19].

Enzalutamide (AFFIRM)

Most recently approved by both the FDA (August 2012) and EMA (June 2013), enzalutamide (160 mg orally, once daily) was evaluated in AFFIRM, a randomized, double-blind, placebo-controlled, Phase III trial, which included 1199 patients with mCRPC who had previously been treated with docetaxel and had progressive disease, and who were randomized (2:1) to enzalutamide or placebo (Table 1) [21]. Patients had a histologically or cytologically confirmed diagnosis of prostate cancer, castrate levels of testosterone (<50 ng per deciliter [1.7 nmol per liter]) and an ECOG PS of 0–2. Progressive disease was defined according to PCWG2 [20] criteria and included three increasing values for PSA or radiographically confirmed progression with or without a rise in the PSA level. The primary endpoint was OS; secondary endpoints included PFS, time to first skeletal-related event (SRE), tumor response, PSA response and QoL measures (Table 1). After initial positive results from this trial, the study was terminated early at the request of the IDMC in order to cross patients over from placebo to active treatment [21].

Evaluation of the TROPIC, COU-AA-301 and AFFIRM trials

Study designs

Both the COU-AA-301 [19] and AFFIRM [21] trials were placebo controlled, in contrast to the TROPIC study [18], which compared cabazitaxel with mitoxantrone (a palliative chemotherapy). This