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Original article

A multicenter phase I study of cabazitaxel, mitoxantrone, and prednisone for chemotherapy-naïve patients with metastatic castration-resistant prostate cancer: A department of defense prostate cancer clinical trials consortium study

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Abstract

Background: Cabazitaxel plus prednisone has significant activity in patients with chemotherapy-naïve and pretreated metastatic castration-resistant prostate cancer (mCRPC). Mitoxantrone has antitumor activity in mCRPC and nonoverlapping mechanism of action and toxicity profile.

Objective: To establish the maximally tolerated dose of the combination of cabazitaxel, mitoxantrone, and prednisone.

Methods and materials: Patients with chemotherapy-naïve mCRPC were prospectively enrolled in a multicenter phase 1 trial. Cabazitaxel 20 and 25 mg/m^2 were each evaluated in combination with escalating doses of mitoxantrone (starting dose 4 mg/m^2), given with prednisone 5 mg twice daily.

Results: A total of 25 patients were enrolled, with median age of 67 (range: 51–78) and prostate-specific antigen of 66.8 ng/ml (range: 3–791.2). There were 4 dose-limiting toxicities (febrile neutropenia, $n = 3$; sepsis, $n = 1$). The maximally tolerated dose was cabazitaxel 20 mg/m^2 plus mitoxantrone 12 mg/m^2. The most common treatment-related grade ≥ 3 related adverse events included neutropenia ($n = 8$; 32%), febrile neutropenia ($n = 5$; 20%), and thrombocytopenia ($n = 4$; 16%). The median number of treatment cycles was 8 (range: 2 to 19+). Decline in prostate-specific antigen to $\geq$50% from baseline was observed in 15 patients (60%). Objective responses were observed in 10/14 (71%) evaluable patients. The median radiographic progression-free survival was 14.5 months (95% CI: 8.0-not reached (NR)), and median overall survival was 23.3 months (95% CI: 14.3-NR).

Conclusions: The approved single-agent doses of mitoxantrone and cabazitaxel were safely combined. The combination led to durable tumor responses in most patients. Further study of the combination is warranted.

Keywords: Cabazitaxel; Castration-resistant; Chemotherapy; Clinical trial; Metastatic; Mitoxantrone; Phase 1; Prednisone; Prostate cancer

1. Introduction

Metastatic castration-resistant prostate cancer (mCRPC) is the fifth leading cause of cancer death among men worldwide, with an estimated 307,000 deaths in 2012 [1]. Taxane-based chemotherapy remains a cornerstone of treatment for advanced prostate cancer. In contrast to the substantial survival benefit observed with taxane-based chemotherapy in the metastatic hormone-sensitive setting [2], treatment with single-agent docetaxel in mCRPC has demonstrated only a modest survival benefit compared to

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older chemotherapeutic regimens such as mitoxantrone [3]. Additionally, multiple attempts to combine docetaxel with investigational agents have failed to improve survival compared to docetaxel monotherapy [4–11]. Thus, new combination treatment approaches, including potentially combining agents with proven single-agent activity, are needed to improve outcomes with front-line chemotherapy in mCRPC.

Cabazitaxel is a semisynthetic taxane derivative that has significant antitumor activity in mCRPC at both the 25 and 20 mg/m^2 dose levels, with the former approved for use in mCRPC that has progressed on prior docetaxel [12]. Front-line and second-line phase 3 studies comparing cabazitaxel 25 mg/m^2, 20 mg/m^2 cabazitaxel, and docetaxel 75 mg/m^2, all delivered on an every 3-week interval, have recently been reported to demonstrate similar survival outcomes [13,14]. Mitoxantrone is an anthracenedione approved for use in mCRPC on the basis of pain palliation, which has also demonstrated significant antitumor activity including prostate-specific antigen (PSA) and objective tumor responses in prior clinical studies [15,16]. Given the largely nonoverlapping mechanisms of action and toxicity profile of these 2 agents, aside from potential additive myelosuppression that may be managed with prophylactic use of growth factors, and demonstrating single-agent activity with both agents, additional antitumor activity may be achieved with combination therapy with an acceptable safety profile.

Consequently, a multicenter phase 1 trial was conducted through the Prostate Cancer Clinical Trials Consortium to determine the maximally tolerated dose (MTD) and recommended phase 2 dose of cabazitaxel, mitoxantrone, and prednisone in patients with chemotherapy-naïve mCRPC.

2. Patients and methods

2.1. Study population

Eligible patients had histologically confirmed prostate adenocarcinoma with evidence of progressive, metastatic, castration-resistant disease by PCWG2 criteria and a minimum serum PSA level of 2 ng/ml [17]. An Eastern Cooperative Oncology Group performance status of 0 to 2 was required, as was adequate hematologic, renal, and hepatic function. Patients were required to have a castrate level of testosterone ($<$50 ng/dl). Cardiac ejection fraction was required to be greater than institutional lower limit of normal. Key exclusion criteria included prior chemotherapy or radiopharmaceuticals for mCRPC, history of New York Heart Association class III or IV congestive heart failure or myocardial infarction within the past 6 months, grade 2 or higher peripheral neuropathy, and radiation treatment or other systemic therapies within 28 days before study treatment. The washout from prior anticancer therapy, including antiandrogen treatment, was a minimum of 4 weeks, with progression required following antiandrogen withdrawal.

The protocol was approved by the local institutional review board of all participating centers, and written informed consent was obtained from all patients.

2.2. Treatment and study assessments

The starting dose level was cabazitaxel 25 mg/m^2 + mitoxantrone 4 mg/m^2, both administered intravenously on day 1 of 21-day cycle, in combination with prednisone 5 mg orally twice daily. At the time of study design, cabazitaxel 25 mg/m^2 was the standard approved dose for use in mCRPC [12]. Prophylactic pegfilgrastim 6 mg was administered subcutaneously every cycle. Mitoxantrone was escalated in 2 mg/m^2 increments up to the approved single-agent dose of 12 mg/m^2. An alternative, prespecified, dose-escalation schema using cabazitaxel 20 mg/m^2 was investigated upon reaching MTD at the 25 mg/m^2 dose level, as prior studies had indicated comparable activity with potentially improved toxicity profile at the 20 mg/m^2 dose level [18] (Supplementary Table 1). Dose reductions or interruptions or both were required for toxicities as per package insert for both agents. No intrapatient dose escalation or reescalation was permitted.

Adverse events (AEs) and physical examination were performed on day 1 of each cycle. Complete blood count with differential was measured weekly and metabolic panel including liver function tests on day 1 of each cycle. Ejection fraction assessment by multigated acquisition scan or echocardiogram was performed at baseline, every 4 cycles, and additionally as clinically indicated. Tumor assessments including cross-sectional imaging of the chest, abdomen, and pelvis, as well as whole-body bone scan, were performed at baseline and every 12 weeks.

Study treatment was continued until the first occurrence of radiographic progression by PCWG2 criteria, clinical progression, unacceptable toxicity including delays of treatment for $>$21 days, patient withdrawal from study (including patients who opted for break from chemotherapy in the absence of progression), or the use of nonprotocol therapy. Treatment discontinuation for PSA progression alone in the absence of clinical or radiographic progression was discouraged. There was no prespecified maximum number of chemotherapy cycles. Mitoxantrone could be continued beyond cumulative dose of 140 mg/m^2 at the discretion of the investigator.

2.3. Study design and statistical analysis plan

The time window for assessing dose-limiting toxicities (DLTs) was days 1 to 21 of the first treatment cycle. DLTs were defined using CTCAE v4.0 as any grade 3 or higher treatment-related nonhematologic toxicity, with the exclusion of the following: fatigue lasting $<$72 hours, any grade alopecia, and hypersensitivity infusion reactions. Hematologic DLTs included grade 4 thrombocytopenia, grade 3