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Original Research

Weekly cabazitaxel plus prednisone is effective and less toxic for 'unfit' metastatic castration-resistant prostate cancer: Phase II Spanish Oncology Genitourinary Group (SOGUG) trial

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KEYWORDS
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Abstract ***Aim:*** Cabazitaxel (CBZ), a novel tubulin-binding taxane, improves overall survival in metastatic castration-resistant prostate cancer (mCRPC) that progresses during or after docetaxel treatment. We have designed a phase II study to evaluate the efficacy and safety of CBZ as a weekly schedule for 'unfit' mCRPC patients after docetaxel failure.

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prostate cancer;
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Dosing schedule;
Toxicity

Methods: In this single arm phase II study. CBZ was weekly administered in 1-hour infusion on days 1, 8, 15 and 22, every 5 weeks at 10 mg/m^2 to eligible 'unfit' patients; oral prednisone (5 mg) was administered twice a day. Circulating tumour cells (CTCs) were also collected. New treatment scheme was considered effective if at least 65% of patients met a clinical benefit criteria based on prostate-specific antigen (PSA)-progression-free survival (PFS) values at week 12.
Results: Seventy patients (median age: 73.9 years) were enrolled; overall, 71.4% had an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 2; and 84%, 16% and 11% had bone, liver and lung metastases, respectively. Objective partial response or stable disease was achieved in 61% of patients, while PSA responses of ≥50% and ≥80% were observed in 34.8% and 10.6%, respectively. The median PSA-PFS was 4.8 months; and 68.6% of patients had no progression at week 12. The most frequent grade 3/4 toxicities were neutropenia (2.8%), leukopenia (5.7%) and thrombocytopaenia (9%); no cases of febrile neutropenia were reported. Early CTC response was significantly correlated with PSA-PFS.
Conclusions: CBZ/prednisone administered weekly to 'unfit' mCRPC patients appears to be as effective as classical standard 3-week scheme (TROPIC study) but with significantly lower toxicities and better tolerance. Early CTC response appears to be valuable as an early end-point of therapeutic efficacy.

1. Introduction

Cabazitaxel (CBZ) is a novel tubulin-binding taxane that exhibits good antitumour activity in patients with prostate cancer (PC) tumours resistant to docetaxel (DTX) therapy [1] and new androgen receptor targeted agents [2–5]. Its administration at 25 mg/m^2 intravenously (IV) every 3 weeks (q3w) improves overall survival (OS) over mitoxantrone treatment (hazard ratio: 0.70, 95% confidence interval [CI]: 0.59–0.83, $p < 0.0001$) [3] and reduces mortality risk by 30% in patients who develop Progressive Disease (PD) during or after DTX-based therapy (the TROPIC trial) [7]. However, toxicities such as neutropenia (>80%) or diarrhoea (approximately 47%) were reported [7,8].

CBZ dose reduction and prophylactic granulocyte colony-stimulating factor (G-CSF) administration are employed to reduce toxicity, particularly in high-risk patients [9]. The tolerability of CBZ appeared to improve at 20 mg/m^2 dose per FIRSTANA and PROSELICA trials [10,11], but toxicity remained rather high, especially for vulnerable higher-risk patients.

We aimed to evaluate the efficacy and safety of weekly CBZ treatment plus prednisone in patients considered as 'unfit' (later described), based on the schedule previously reported by Fumoleau *et al.* [12] in a phase I study in solid tumours. In addition to evaluating serum biomarkers and radiological findings, we investigated the role of circulating tumour cells (CTCs) levels as a measure of treatment response.

2. Patients and methods

2.1. Study population

This open-label phase II trial was performed at 12 Spanish Oncology Genitourinary Group (SOGUG) sites. The main inclusion criteria were: pathologically proven PC, age >18 years, Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0–2, testosterone levels in the castration range (<50 ng/ml), previous treatment with DTX, documented progressive disease (PD) following previous treatment according to the Prostate Cancer Clinical Trials Working Group-II criteria [13], prostate-specific antigen (PSA) elevation (at least two consecutive increases relative to the reference value measured at least one week apart), PD according to Response Evaluation Criteria In Solid Tumours (RECIST), version 1.1 [14], or bone metastasis progression as detected by scintigraphy. Adequate haematological, hepatic, renal and cardiac functions were required. Patients were also required to satisfy at least one of the 'unfit' criteria: ECOG-PS 2, previously experienced dose reduction of DTX due to febrile neutropenia, or previous radiotherapy affecting >25% of their bone marrow reserve (BMR). All patients provided written informed consent; the protocol was approved by the local ethics committees.

2.2. Treatment

Patients received CBZ 10 mg/m^2 via 1-hour IV infusion on days (d) 1, 8, 15 and 22 of a 5-week cycle. Prednisone (5 mg) was continuously administered orally twice a day. A single IV dose of an antihistaminic, corticosteroid (dexamethasone 8 mg or equivalent), and H2-antagonist (ranitidine or equivalent) was administered at least 30 minutes before CBZ. Antiemetics were administered if warranted. Treatment was maintained until PD, unbearable toxicity or withdrawal of consent. Weekly doses were administered only if neutrophils were >1500/mm^3, platelets were >100,000/mm^3, and in the absence of major treatment-related toxicity. Dose reduction was permitted to 8.4 mg/m^2 in case of grade 4