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Original Research

Weekly versus 3-weekly cabazitaxel for the treatment of castration-resistant prostate cancer: A randomised phase II trial (ConCab)

Jeffrey Yachnin [a,*], Bjørnar Gilje [b], Kristian Thon [c], Hemming Johansson [a], Yvonne Brandberg [d], Theocharis Panaretakis [d], Anders Ullén [a]

[a] *Theme Cancer, Karolinska University Hospital, 171 76 Stockholm, Sweden*
[b] *Department of Hematalogy and Oncology, Stavanger University Hospital, PB 8100, 4068 Stavanger, Norway*
[c] *Department of Oncology, Oslo University Hospital Ullevål, PB 4953 Nydalen, 0424 Oslo, Norway*
[d] *Department of Oncology-Pathology, Cancer Center Karolinska, Karolinska Institute, 171 76 Stockholm, Sweden*

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KEYWORDS
Castration-resistant prostate cancer;
Cabazitaxel;
Dosing schedule;
Dose intensity

Abstract ***Aim:*** Patients treated with cabazitaxel for metastatic castration-resistant prostate cancer (mCRPC) may experience dose delays and reductions or terminate treatment because of toxicity. A lower and more frequent dose of cabazitaxel could improve dose intensity.
Patients and methods: This prospective, multi-center, phase II study randomly assigned 101 patients to Arm A, cabazitaxel Q3W, 25 mg/m^2 or Arm B, Q1W, 10 mg/m^2 5 of 6 weeks. The primary end-point was dose intensity, and we hypothesised that the experimental arm (Arm B) would result in a 20% absolute increase in the relative cumulative dose by week 18. Secondary end-points were overall survival (OS), progression-free survival (PFS), pain progression, radiological and prostate-specific antigen (PSA) response rates, quality of life (Functional Assessment of Cancer Therapy Prostate) and tolerability.
Results: Median doses of cabazitaxel were 276 mg (45–320) and 257 mg (20–330) in Arms A and B, respectively, at week 18 ($p = 0.13$). More patients in Arm B stopped treatment because of toxicity. Median PFS in Arms A and B were 6.0 and 6.4 months (hazard ratio [HR] 0.73, 95% confidence interval [CI]: 0.47–1.13, $p = 0.156$) and for OS, 14.6 and 15.6 months (HR 0.95, CI: 0.58–1.58, $p = 0.85$), respectively. PSA responses ≥50% were seen in 52% and 46% of patients in Arms A and B, respectively. A higher incidence of febrile neutropenia was observed in the standard arm (10 events versus 1, $p < 0.008$). A grade V febrile neutropenia occurred in Arm A. Low-grade haematuria was more prevalent with weekly cabazitaxel

* *Corresponding author*: Center for Clinical Cancer Research, Theme Cancer, Karolinska University Hospital, 171 76 Stockholm, Sweden. Fax: +46 8 306989.
E-mail address: jeffrey.yachnin@sll.se (J. Yachnin).

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(15 events versus 5, $p = 0.003$). Three patients in Arm B experienced clinically significant inflammation of the ureters. A toxicity is not previously described for cabazitaxel.

Conclusion: Weekly cabazitaxel reduces the incidence of febrile neutropenia but does not increase the dose intensity compared with the standard therapy. Cabazitaxel has clinical meaningful efficacy in heavily pre-treated patients with mCRPC.

1. Introduction

In 2004, two pivotal studies showed that docetaxel/prednisone could prolong survival in patients with metastatic castration-resistant prostate cancer (mCRPC) [1,2]. Thereafter, the development of new therapies has been outstanding: second-generation androgen receptor (AR) axis inhibitors (abiraterone acetate, enzalutamide), radium-223, vaccines and a next-generation taxane, cabazitaxel. The median survival for a patient with mCRPC is now more than 3 years [3,4].

Cabazitaxel is structurally similar to docetaxel but has a different toxicity profile and shows activity in tumorus resistant to docetaxel and next-generation AR-targeted agents [5,6]. Marketing approval for cabazitaxel is based on the TROPIC study where there was a significant survival advantage (hazard ratio [HR] 0.7; 95% confidence interval [CI] 0.59–0.83, $p < 0.0001$) for cabazitaxel (25 mg/m^2)/prednisolone compared with that for mitoxantrone (12 mg/m^2)/prednisolone [7]. Patients in the cabazitaxel arm had a dropout rate of 18.3% because of toxicity and rates of dose reductions and dose delays of 12% and 28%, respectively. Clinically significant diarrhoea and bone marrow toxicity were common, 53% of patients experiencing any grade diarrhoea and 82% grade ≥III neutropenia [7].

The ConCab trial is a comparison of the standard dose and schedule of cabazitaxel (25 mg/m^2 every three weeks) with an experimental dose and schedule (10 mg/m^2 given weekly 5 of 6 weeks). The rationale for this study is to see if a novel dose and schedule could minimise dose reductions, dose delays and termination of treatment because of toxicity. If this could be achieved with unaltered efficacy, cabazitaxel would be a more attractive palliative treatment option. A higher dose intensity may result in greater drug efficacy. Dose intensities of the two treatment arms were designed to be similar (50 mg/m^2 over 6 weeks) given that no dose reductions, dose delays or stoppage of treatment occurred. Departure from planned treatment because of toxicity or lack of efficacy would be reflected in the dose intensity and thereby suggests which of the treatment arms is preferable.

2. Patients and methods

2.1. Patient eligibility

ConCab is a multi-center, randomised, open-label, phase II study (NCT01541007). The trial opened for recruitment on 19th April 2012 and completed its planned target of 100 patients on 21st October 2015. Median follow-up time is 21 months. The study was conducted at two sites in Norway (Stavanger and Oslo) and Sweden (Uppsala and Stockholm). The trial population consisted of patients with mCRPC who had previously received docetaxel and had progressive disease defined as an increase in measurable disease (Response Evaluation Criteria in Solid Tumours [RECIST] 1.1), the appearance of at least one new lesion for non-measurable disease or a rising prostate-specific antigen (PSA) on two consecutive occasions at least 1 week apart. Castration resistance was defined as a serum testosterone level ≤0.5 ng/ml. Patients had an Eastern Collaborative Oncology Group (ECOG) performance status of 0 or 1 and adequate haematological, renal and liver function. There was no upper age limit. Signed informed consent was obtained from all participants.

2.2. Study design

Patients were randomised 1:1 to Arm A (Q3W), cabazitaxel 25 mg/m^2 every 3 weeks and prednisolone 10 mg once daily or Arm B (Q1W), cabazitaxel 10 mg/m^2 weekly for 5 of 6 consecutive weeks and prednisolone 10 mg once daily. Subjects were stratified for skeletal-only disease and time since last treatment with docetaxel (≤3 months or >3 months). At the start of the trial, primary prophylactic haematopoietic stem cell agents (G-CSF) were not used. The study was approved by the regional investigational review boards in Norway (2011-004178-27) and Sweden (2011/2041-31/1) and the Medical Products Agencies in each respective country (Sweden; 151:2011/95330, Norway; 12/04718-6).

The primary end-point is a comparison of treatment arms with respect to the cumulative dose of cabazitaxel that is received in relation to the planned dose at 18 weeks from the start of therapy. Secondary end-points include overall survival (OS) (time from randomisation to death from any cause) and progression-free survival (PFS) (time from randomisation to the first documentation of PSA progression, pain progression, radiological progression [RECIST1.1 or Prostate Cancer Working Group 2 (PCWG2) criteria for bone scans] or death due to any cause). PSA progression is defined as either a 25% increase (at least 2 ng/ml) from baseline in patients not achieving a prior > 50% decrease in PSA or a 50% increase in PSA (at least 2 ng/ml) above the nadir

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