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Biweekly Cabazitaxel Is a Safe Treatment Option for Metastatic Castration-resistant Prostate Cancer (mCRPC) Patients After Docetaxel – A Final Analysis of the Prosty II Trial

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Abstract. *Background/Aim: Our phase III trial showed that biweekly docetaxel (D) is better tolerated than triweekly D in metastatic castration-resistant prostate cancer (mCRPC). The safety of biweekly cabazitaxel (CBZ) post-docetaxel was studied in mCRPC. Patients and Methods: Altogether, 60 patients received CBZ 16 mg/m^2 i.v. on day 1 and day 14 of a 4-week cycle. The mean serum PSA levels were 305 ng/ml, and the mean age 67 years. The primary endpoint was safety according to CTCAEv4.0. Results: A total of 255 4-week cycles of CBZ were administered. The most common grade 3/4 adverse events were neutropenia (16.7%), pain (13.3%), fatigue (10.0%), anemia (5.0%) and non-neutropenic infection (10.0%). PSA responses occurred in 10 patients (16.7%). Clinical benefit rate was 38.3% and median survival 10 months. Conclusion: Biweekly CBZ is a well-tolerated treatment resulting in meaningful benefits for heavily pretreated mCRPC patients.*

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Androgen deprivation is a standard noncurative treatment for advanced prostate cancer (APC). Although symptoms are reduced in approximately 70-80% of patients, APC invariably transforms into a castration-resistant disease after a median time of two to three years (1-3). Several treatment options have shown a survival benefit in patients with metastatic castration-resistant prostate cancer, including docetaxel plus prednisone (4) or docetaxel plus estramustine (5), cabazitaxel (CBZ) plus prednisone (6), abiraterone plus prednisone (7, 8), sipuleucel-T (9), enzalutamide, apalutamide, darolutamide (3, 10, 11), and radium-223 (12). Aside from docetaxel and CBZ, other chemotherapy agents have only a modest activity against APC (3, 13-15).

The first two randomized trials, published in 2004, showed docetaxel to be superior to mitoxantrone plus prednisone, yielding a survival gain of approximately 2-3 months (4, 5). In both of these studies, the TAX-327 study and Southwest Oncology Group (SWOG) 9916 trial, docetaxel every three weeks alone or combined with estramustine was associated with more adverse events compared with mitoxantrone plus prednisone. These adverse events (AEs) included neutropenic fever, fatigue, diarrhea, nail changes, sensory neuropathy, and alopecia (4, 5). Based on these studies, docetaxel administered every three weeks intravenously in combination with oral prednisone has been considered standard first-line chemotherapy for metastatic castration-resistant prostate cancer (mCRPC). In addition, docetaxel in hormone-sensitive APC has been shown to

increase survival by more than one year in large randomized trials (16, 17).

In our Prosty 1 trial, we showed that biweekly administration of docetaxel might be better tolerated than 3-weekly docetaxel in elderly prostate cancer patients, and might lead to patients continuing treatment for longer. The biweekly dose of 50 mg/m^2 docetaxel was both better tolerated and gave better progression-free and overall survival than the 75 mg/m^2 dose every three weeks (18).

The phase III randomized TROPIC trial included 755 patients with mCRPC whose disease progressed during or after docetaxel-containing treatment (6). Patients were randomized to receive CBZ 25 mg/m^2 every 3 weeks + prednisone/ prednisolone (CBZP) for 10 cycles (n=378) or mitoxantrone 12 mg/m^2 every 3 weeks + prednisone/ prednisolone (MP) for 10 cycles (n=377). Primary prophylaxis with granulocyte colony stimulating factor was not allowed at cycle 1. The primary endpoint was overall survival; the secondary endpoints were progression-free survival, response rate and safety. The population in the TROPIC study was heavily pretreated: 60% had received radiotherapy, potentially decreasing the bone marrow reserve, and patients had received a median of 7 cycles of docetaxel prior to entry into the study. The median number of cycles delivered was 6 in the CBZP arm *versus* 4 in the MP arm. The median overall survival, 15.1 months, was longer in the CBZP arm compared to the MP arm, 12.7 months (HR=0.70, 95%CI=0.59-0.83, p<0.0001), and resulted in a 30% reduction in the risk of death. The progression-free survival was also longer in the CBZP arm, 2.8 months *versus* 1.4 months in the MP arm (HR=0.74, 95%CI=0.64-0.86, p<0.0001). AEs of grade ≥3 occurred in 57.4% of patients in the CBZ group and 39.4% of patients in the mitoxantrone group, and serious AEs occurred in 39.1% and 20.8% of patients, respectively. The most frequently occurring grade ≥3 AEs in the CBZ group were neutropenia (81.7% at nadir), febrile neutropenia (7.5%), diarrhea (6.2%), fatigue (4.9%), asthenia (4.6%), back pain (3.8%), leukopenia (3.8%), and anemia (3.5%). Eighteen deaths due to adverse events occurred during the trial in the CBZP arm *vs*. 7 in the MP arm, mainly due to neutropenic complications, often during cycle 1. Later, in the FIRSTANA trial, CBZ at two dose levels was compared with 3-weekly docetaxel as a first-line chemotherapy in mCRPC. The lower dose of CBZ was better tolerated, and both CBZP groups had similar survival as the group receiving docetaxel every three weeks (19).

The aim of this study was to explore a new, biweekly schedule of CBZ in metastatic castration-resistant prostate cancer patients after docetaxel treatment. Our hypothesis that a biweekly dosing regimen might be better tolerated than the every-three-weeks dosing regimen was based on our previous study, which showed that the biweekly administration of docetaxel as a 1st-line treatment of mCRPC was better tolerated than docetaxel administered every three weeks. Additionally, the efficacy of biweekly docetaxel was better than that of docetaxel every three weeks, and biweekly dosing presented a significant overall survival benefit (18). As the occurrence of neutropenia in the TROPIC trial was high, our aim was to reduce the incidence of severe adverse events by administrating a lower dose of CBZ more frequently, while maintaining the same dose intensity as in the every-three-weeks dosing schedule.

Patients and Methods

Patients. The enrolled patients were required to have histologically/ cytologically confirmed prostate cancer that had progressed during or after docetaxel treatment. Prior surgical castration or treatment with a luteinizing hormone-releasing hormone analog was mandatory for inclusion in the study. Other main inclusion criteria were World Health Organization (WHO) performance status 0 to 2; presence of distant metastases; and PSA >10 ng/ml with a value that had increased in at least 2 consecutive measurements performed ≥2 weeks apart. Exclusion criteria included a history of other cancer types and any medical condition that precluded the administration of chemotherapy. Patients with impaired liver function [serum bilirubin >1.5×N (times the normal upper limit), alanine or aspartate aminotransferase >3.0×N, alkaline phosphatase >5.0× N except in the presence of bone disease and in the absence of liver disorder] were not eligible, nor were those who had impaired renal function (serum creatinine >1.5×N), a blood neutrophil count <1.5×10^9/ml, platelet count <100×10^9/ml, or hemoglobin <110 g/l.

Primary and secondary endpoints. The primary endpoint was safety. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTC-AE v 4.0) (20). Secondary end points were time to treatment failure, response, survival and quality of life. The time to treatment failure was counted from the start of treatment to the end of treatment, including disease progression, adverse events, patient refusal or death.

Objective responses [complete response (CR) and partial response (PR)] for measurable disease were assessed by investigators according to RECIST version 1.1 (21), while those for non-measurable disease were assessed by PCWG2. Confirmation of objective responses was performed by repeat tumor imaging [computed tomography (CT) scans, magnetic resonance imaging (MRI)] or evaluation of non-measurable disease at 6 weeks (at least 4 weeks for PSA) after the first documentation of response.

PSA response: A PSA decline of ≥50% was confirmed by a second PSA value at least four weeks later. The duration of the PSA response was measured from the first to the last assessment at which the above criteria were satisfied.

PSA progression: PSA progression was defined as an increase in PSA by 25% above the baseline level (at least 2 ng/ml) in patients who had not achieved a >50% decrease in PSA or an increase of 25% above the nadir value (at least 2 ng/ml) in patients who had achieved a prior >50% decrease in PSA. A confirmatory PSA was taken at least 3 weeks later. During the first twelve weeks of therapy, PSA rises were misleading. A rising PSA during the first 12 weeks of treatment, without clinical and/or radiological signs of progression, was not considered disease progression (22).

Overall survival was calculated from the start of treatment to death.

Quality of life assessment was performed using the Finnish translation of "Functional Assessment of Cancer Therapy-Prostate"

Table I. *Demographic characteristics*.

WHO performance status; 0/1/2 (%)	18/40/2 (30.0/66.7/3.3)
Baseline PSA (ng/ml); mean (SD)	305.0 (471.2)
Time from the diagnosis of prostate cancer (months); mean (SD)	84.7 (61.7)
Type of disease at diagnosis; Local/Metastatic (%)	30/30 (50.0/50.0)

(FACT–P) questionnaire, version 4 (23). Pain was evaluated according to VAS (Visual Analog Scale).

Ethics. The study protocol was approved by the institutional review committees and was registered at ClinicalTrials.gov (identifier NCT01558219). All study participants provided written informed consent.

Medication. Jevtana® (CBZ) 16 mg/m^2 *i.v.* in 1 h on cycle day 1 was given every second week with prednisone/prednisolone 10 mg PO daily. Intravenous premedication included antihistamine (dexchlorpheniramine 5 mg or diphenhydramine 25 mg or equivalent), corticosteroid (dexamethasone 8 mg or equivalent), and H2 antagonist (ranitidine or equivalent) to be given ½ hour prior to the treatment. Antiemetic prophylaxis (oral or intravenous) was recommended as needed.

Statistical analysis. The sample size was based on the following: a power of 80% is reached with 60 patients if testing against the 82% observed neutropenia in the TROPIC trial, using the assumption that 67% grade 3/4 neutropenia will be observed with a new treatment regimen [*i.e.*, a 15% reduction from what was seen in the TROPIC trial by de Bono *et al*. (6)]. The primary interest in this study was safety. The incidence of grade 3/4 neutropenia was the primary parameter. A 95% confidence interval was calculated for the incidence and was tested against the historical control. With this sample size, the width of the 95% confidence interval is approximately ±10%. The incidence of other safety findings was also reported. The toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTC-AE v 4.0) and summarized using MedDRA terminology. Kaplan–Meier curve was used to analyse survival. A *p*-value less than 0.05 was considered significant.

Results

The baseline patient characteristics are shown in Table I. The mean age of the patients was 67 years (range=50-79 years). The time from prostate cancer diagnosis to the start of cabazitaxel treatment was 85 months, and the mean baseline PSA was 305 ng/ml (range=3.7-2,425 ng/ml).

A total of 253 cycles (one cycle was two biweekly doses) of cabazitaxel were administered. The median number of cycles was 4. Nine patients (15%) received less than 3 cycles, 19 patients (32%) received at least 3 cycles, and 3 patients (5%) received 12 cycles. No prophylactic G-CSF was used. All adverse events are summarized in Table II. The most common grade 3/4 adverse events were neutropenia 10/60 (16.7%), pain 8/60 (13.3%), fatigue 6/60 (10.0%), anemia 3/60 (5.0%), non-neutropenic infection 6/10 (10.0%), leucopenia 2/60 (3.3%), neutropenic infection 1/60 (1.7%), mucositis 1/60 (1.7%), elevated ALP 1/60 (1.7%) and limb edema 1/60 (1.7%). In addition, one grade 4 pulmonary embolism and one intracerebral hemorrhage occurred. In one patient, a cancer-related bone fracture (grade 4 AE) occurred during the second CBZ cycle. During the treatment exposure period, reported AEs were as follows: grade 1 AEs in 3 pts (5.0%), grade 2 AEs in 28 pts (46.7%), grade 3 AEs in 24 pts (40.0%) and grade 4 AEs in 5 pts (8.3%).

Of the patients who were followed up, most (39 out of 60, 65%) discontinued the treatment due to progressive disease. Additional causes for stopping treatment were adverse events (N=17, 28.3%) and other reasons (N=2. 3.3%), or death (N=1, 1.7%). PSA responses occurred in 10 patients (16.7%), and overall response as PR was recorded in 3 patients (5.0%) and as stable disease (SD) in 20 patients (33.3%, leading to a clinical benefit ratio of 38.3% (Table III). The median overall survival was 10 months (Figure 1), and 33% of patients were alive at the end of the study.

The occurrence of grade 3/4 neutropenia was significantly lower than the predefined 82% at nadir in the TROPIC trial. The observed rate of grade 3/4 neutropenia in our study was 16.7% (exact 95% confidence interval of 8.3% to 28.5%, $p<0.0001$ compared to 82% rate).

Discussion

At present, there is an appeal for physicians to treat elderly mCRPC patients with new androgen receptor (AR) pathway-targeted agents, such as abiraterone acetate (AA) and enzalutamide, that have been proven to prolong overall survival (OS), and are orally delivered and well tolerated. However, because prostate cancer is a heterogeneous disease, all patients will not respond to AR-targeted agents (3). Indeed, some cancers present a primary resistance to these agents, and others will develop an acquired resistance over time. Moreover, retrospective studies involving a small number of patients suggest that once a patient's disease progresses after treatment with an AR-targeted agent, this patient will not respond to another AR-targeted agent. This assumption was shown to be true in a recent study of patients with post-docetaxel mCRPC treated with either abiraterone or enzalutamide (6, 10). In the randomized trial, patients treated with cabazitaxel had significantly longer survival than those

Table II. *Adverse events in all 60 patients treated with biweekly cabazitaxel.*

Grade	0	1	2	3	4
Alopecia, n (%)	49 (81.7)	7 (11.7)	4 (6.7)	0	0
Diarrhea, n (%)	37 (61.7)	16 (26.7)	7 (11.7)	0	0
Fatigue, n (%)	14 (23.3)	22 (36.7)	18 (30.0)	5 (8.3)	1 (1.7)
Infection with nANC*	49 (81.7)	0	5 (8.3)	6(10.0)	0
Nail loss, n (%)	55 (91.7)	4 (6.7)	1 (1.7)	0	0
Nausea, n (%)	39 (65.0)	11 (18.3)	10 (16.7)	0	0
Vomiting, n (%)	48 (80.0)	10 (16.7)	2 (3.3)	0	0
Weight loss, n (%)	50 (83.3)	8 (13.3)	2 (3.3)	0	0
ALAT, n (%)	53 (83.3)	6 (10.0)	1 (1.7)	0	0
ASAT, n (%)	41 (68.3)	15 (25.0)	4 6.7)	0	0
ALP, n (%)	30 (50.0)	22 (36.7)	6 (10.0)	2 (3.3)	0
Allergic reaction	56 (93.3)	2 (3,3)	2 (3.3)	0	0
Anaphylaxis	60 (100)	0	0	0	0
Bilirubin	58 (96.7)	1 (1.7)	1 (1.7)	0	0
Creatinine	32 (53.3)	24 (40)	4 (6.7)	0	0
Febr. neutropenia	60 (100)	0	0	0	0
Fever	53 (88.3)	6 (10.0)	1 (1.7)	0	0
Hemoglobin	1 (1.7)	41 (75.0)	15 (25.0)	3 (5.0)	0
Neutropenic inf.	57 (95.0)	0	2 (3.3)	1 (1.7)	0
Leukocytes	42 (70.0)	6 (10.0)	10 (16.7)	2 (3.3)	0
Neutrophils	39 (65)	4 (6.7)	7 (11.7)	8 (13.3)	2 (3.3)
Platelets	45 (75.0)	14 (23.3)	1 (1.7)	0	0

nANC: Normal absolute neutrophil count; ALAT: alanine aminotrasferase; ASAT: asparate animotrasnferasel; ALP: alkaline phosphatase.

treated with either AR-targeted agent (24). Finally, the place of first-line androgen deprivation therapy (ADT) for advanced prostate cancer is now strongly challenged. The results of the CHAARTED trial showed that the addition of 6 cycles of docetaxel to ADT in patients with hormone-sensitive metastatic prostate cancer is associated with a survival benefit of more than one year *versus* ADT alone (17).

Older age is not an absolute contraindication to chemotherapy. Many elderly patients tolerate chemotherapy just as well as younger patients. Docetaxel-based regimens are the standard of care because they provide a survival advantage, while reducing pain and improving health-related quality of life (HR-QoL). In the TAX-327 trial, the survival benefit of 3-weekly docetaxel plus prednisone compared with mitoxantrone plus prednisone was consistent among age groups (25). In men aged 75 years and older, the 3-weekly schedule resulted in more dose reductions than the weekly schedule (22% *versus* 8%, p=0.007), but tolerability was otherwise comparable (25). In a prospective survey involving 333 mCRPC patients at least 70 years old, a taxane-based regimen was associated with significantly improved OS, progression-free survival (PFS), and clinical benefit (based on pain and analgesic consumption) than a non-taxane regimen, even in frail patients (26, 27).

Cabazitaxel is a new taxane developed to overcome docetaxel resistance and to penetrate the blood-brain barrier (28). In nonresistant tumors, cabazitaxel shows a similar activity as docetaxel. In 168 patients in the phase 3 FIRSTANA trial, CBZ failed to demonstrate superiority in OS when compared to docetaxel 75 mg/m^2 as first-line treatment in metastatic prostate cancer, possibly because patients were docetaxel naïve and less than 1% had received prior abiraterone or enzalutamide (19). CBZ and docetaxel had different toxicity profiles: docetaxel was associated with

Table III. *Final response evaluation.*

PSA response	
PR	10 (16.7%)
SD	22 (36.7%)
PD	18 (30.0%)
NA	10 (16.7%)
Target and non-target lesion evaluation	
CR	-
PR	3 (5.0%)
SD	20 (33.3%)
PD	32 (53.3%)
NA	5 (8.3%)

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease.

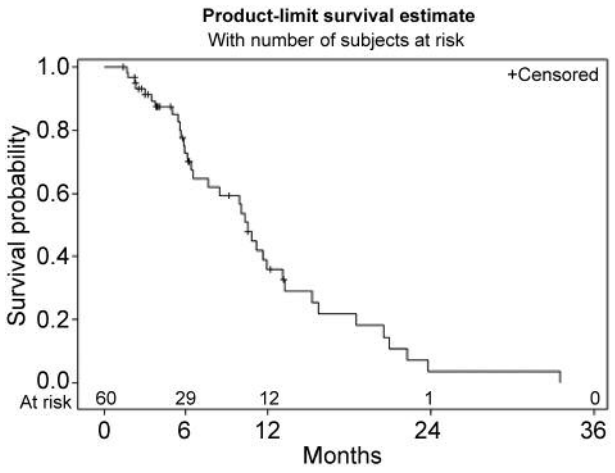

Figure 1. *Kaplan–Meier curve of the survival of all patients.*

more peripheral neuropathy, peripheral edema, alopecia, and nail disorders (19). In the TROPIC trial, cabazitaxel plus prednisone significantly prolonged OS *versus* mitoxantrone plus prednisone in mCRPC patients progressing during or after docetaxel therapy (5). It has also been shown that cabazitaxel retains its antitumor activity in patients progressing on AA or enzalutamide, with a higher efficacy than docetaxel (27). However, cabazitaxel is associated with a high incidence of grade ≥3 neutropenia, although a large European compassionate-use program has clearly shown that this hematological toxicity was manageable even in patients 75 years and older (26, 29). Prophylactic management of adverse events, including an increased use of granulocyte-colony stimulating factor (G-CSF), could significantly improve the risk of febrile neutropenia and/or neutropenic complications in elderly patients (26, 27, 30).

It was shown in our Prosty 1 trial, a phase III trial involving 344 patients, that a biweekly administration of docetaxel plus prednisone for mCRPC is better tolerated than a three-weekly administration (18). Therefore, the efficacy of 2-weekly docetaxel was better than that of 3-weekly docetaxel with a longer time to progression (TTP) and a significant OS benefit.

The purpose of the present study was to evaluate whether the safety profile of cabazitaxel may further be improved with biweekly administration. Patients with mCRPC who were previously treated with docetaxel received cabazitaxel 16 mg/m^2 every 2 weeks until disease progression or unacceptable toxicity. G-CSF was not given systematically. Our results showed that biweekly dosing was much better tolerated than the 3-weekly dosing regime in the TROPIC trial (6) and PROSELICA trial (31). In both studies, G-CSF was not allowed during cycle 1, and neutropenia was determined by hematology tests performed at nadir (Days 8 and 15). Even with the lower cabazitaxel dose of 20 mg/m^2 in PROSELICA, 42% of patients experienced grade 3 or greater neutropenia. In addition, in the FIRSTANA trial, with the lower 20 mg/m^2 dose, the grade 3 or 4 treatment-emergent AE rate was 46.0%. In this Prosty II trial, only 16.7% of patients had grade 3 or greater neutropenia, and 65% of patients did not have any neutropenia during the biweekly dosing of cabazitaxel. Thus, the primary endpoint of our trial was achieved. In addition, the survival of these heavily pretreated patients with advanced disease was quite long in our trial, and in the same range as in the FIRSTANA and PROSELICA trials. According to our results, biweekly cabazitaxel is a safe and well-tolerated option even after docetaxel for mCRPC.

Conflicts of Interest

Antti Jekunen, Katariina Klintrup, Vesa Kataja, Tapio Utriainen, Kalevi Pulkkanen, Anna-Liisa Kautio and Teppo Huttunen: no conflicts of interest. Pirkko-Liisa Kellokumpu-Lehtinen: Travel expenses from Sanofi, hornoraria for lecturing from BMS. Timo Marttila: Travel expenses from Sanofi, honoraria for lecturing from Jansen and Astellas. Markku J. Leskinen: Travel expenses from Sanofi and Astellas, honoraria for lecturing from Amgen, honoraria for expert testimony from Ipsen. Marjaana Luukkaa: Scientific congress costs from Astellas, Merck and Sanofi, honoraria for lecturing from BMS.

Authors' Contributions

Conception and design: Pirkko-Liisa Kellokumpu-Lehtinen, Timo Marttila, Marjaana Luukkaa, Petteri Hervonen, Anna-Liisa Kautio, Tapio Utriainen, Vesa Kataja. Administrative support: Pirkko-Liisa Kellokumpu-Lehtinen. Provision of study materials or patients: Pirkko-Liisa Kellokumpu-Lehtinen, Timo Marttila, Antti Jekunen, Petteri Hervonen, Katariina Klintrup, Vesa Kataja, Tapio Utriainen, Marjaana Luukkaa, Markku Leskinen, Kalevi Pulkkanen, Anna-Liisa Kautio. Collection and assembly of data: All Authors. Data analysis, interpretation and final approval of manuscript: Pirkko-Liisa Kellokumpu-Lehtinen and Teppo Huttunen drafted the first manuscript and all Authors approved the final manuscript. Financial and funding support: Sanofi and the Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital.

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