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Retrospective analysis of the efficacy and safety of cabazitaxel treatment in castration-resistant prostate cancer after docetaxel failure

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ABSTRACT

Introduction. Cabazitaxel has been approved by the FDA and EMEA for the treatment of metastatic castration-resistant prostate cancer (mCRPC) after failure of docetaxel-based chemotherapy. Between June 2011 and November 2013 cabazitaxel was reimbursed for Polish mCRPC patients as a non-standard chemotherapy. The study objective was a retrospective analysis of the efficacy and safety data of mCRPC patients treated with cabazitaxel in this period.

Material and methods. Collection of retrospective data on 48 consecutive mCRPC patients treated with cabazitaxel after docetaxel failure. Data on baseline characteristics, cancer history, and the efficacy and safety of cabazitaxel treatment were collected. Progression-free survival (PFS) (radiological/clinical/biochemical) and overall survival (OS) were estimated by the Kaplan-Meier method. Objective response rate and clinical benefit were also assessed.

Results. Forty-eight patients were included. Median PFS was 4.2 (95% CI 3.4–5.1) months, and median OS was 15.1 (95% CI 12.7–17.4) months. OS since docetaxel initiation in patients treated with cabazitaxel as second-line chemotherapy (n = 47) was 28.7 (95% CI 25.3–32.1) months. OS rates at 1, 2, and 3 years after first cabazitaxel cycle were 65%, 25%, and 15%, respectively. In total, 289 cycles of cabazitaxel were administered (mean six per patient). There were 41 patients evaluable for biochemical response, 19/41 (46%) of whom had a PSA decrease of at least 50% from baseline, including 3/41 who had an initial PSA flare followed by a decrease of at least 50% from baseline. Adverse events comprised predominantly haematological (26 patients) and gastrointestinal (14 patients) toxicities. Ten SAEs were reported, including one death due to acute renal failure.

Conclusions. Treatment of mCRPC patients with cabazitaxel after docetaxel failure is an important therapeutic option with acceptable toxicity with respect to clinical stabilisation and possibly increased survival.

Key words: castration-resistant prostate cancer, cabazitaxel, prostate-specific antigen, chemotherapy, cytotoxic agent, progression-free survival, overall survival, time to treatment failure

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Introduction

Prostate cancer is the most commonly diagnosed cancer in men; it is the third most common cause of cancer deaths in men after lung cancer and colorectal cancer in Europe [1].

Treatment of advanced/metastatic prostate cancer is palliative, and the main form of systemic therapy is endocrine therapy based on androgen ablation (surgical or pharmacological castration). Endocrine treatment in advanced symptomatic prostate cancer patients allows achievement of rapid clinical response (decrease in the severity of bone pain, tumour burden reduction), and a biochemical response (decreased level of prostate-specific antigen (PSA)). However, at some point in time (median 18–24 months), cancer becomes resistant to castration in all patients (castration-resistant prostate cancer, CRPC) [2].

Until 2010 chemotherapy with docetaxel (75 mg/m² every 21 days IV) in combination with prednisone was the only therapy significantly improving overall survival (OS) in metastatic CRPC (mCRPC) patients. Two prospective randomised phase III studies (TAX327 and SWOG 9916), which enrolled approximately 2000 men [3–5], demonstrated a significant superiority of docetaxel compared to mitoxantrone in mCRPC patients. Docetaxel in combination with prednisone given every 21 days reduced the relative risk of death by 24% compared with the combination of mitoxantrone plus prednisone (HR 0.76 [95% CI, 0.62–0.92]), while reducing the severity of pain and positively affecting the patients' quality of life.

Cabazitaxel is a novel generation taxane, which was designed *de novo* to overcome resistance to docetaxel. It has been shown that cabazitaxel is comparable to docetaxel in terms of efficacy in tumour cells sensitive to docetaxel, but in docetaxel-resistant cell lines and tumours it demonstrates 10-times higher anticancer activity [6]. It was further shown that cabazitaxel, contrary to paclitaxel and docetaxel, crosses the blood-brain barrier *in vivo*, and therefore may exhibit anticancer activity in patients with brain or lepto-meningeal metastases. The efficacy of cabazitaxel in the treatment of mCRPC was demonstrated in a phase III study, TROPIC, which enrolled 755 men who had progressed during or after treatment with docetaxel. Patients were randomly assigned in a 1:1 ratio to the experimental arm (cabazitaxel 25 mg/m² IV every three weeks + prednisone 10 mg/day) or the control arm (mitoxantrone 12 mg/m² IV every three weeks + prednisone 10 mg/day). In both arms, up to 10 courses of chemotherapy could be administered [7]. The study met its primary endpoint, achieving a significant improvement in overall survival in patients treated with cabazitaxel compared to mitoxantrone (15.1 months vs. 12.7 months, respectively), which translated into

a significant reduction in the relative risk of death by 30% (HR 0.70; 95% CI, 0.59–0.83). Median progression-free survival (PFS), which was a composite endpoint defined as time from randomisation to disease progression (biochemical, radiological, or clinical progression) or death, was 2.8 months in the cabazitaxel group vs. 1.4 months in the mitoxantrone group (HR 0.74; 95% CI, 0.64–0.86). Biochemical and radiological responses were also significantly more frequent with cabazitaxel compared to mitoxantrone. The updated TROPIC study data confirmed continuous improvement of OS: the two-year survival rate was 15.9% in the cabazitaxel arm and 8.2% in the mitoxantrone arm [8]. Based on the TROPIC study, cabazitaxel has been approved by the FDA and EMEA for the treatment of mCRPC patients after failure of docetaxel-based chemotherapy. It was subsequently shown in a phase II prospective, randomised trial that cabazitaxel retains its activity in patients who have progressed on novel androgen receptor-targeting agents [9].

In the period from June 2011 to November 2013 cabazitaxel was reimbursed for Polish mCRPC patients as a non-standard chemotherapy. The aim of this multicentre, retrospective, observational study was to analyse data on the efficacy and safety of treatment with cabazitaxel in the population of Polish patients with mCRPC after docetaxel failure.

Material and methods

Data on the efficacy and safety of cabazitaxel was collected for patients who received at least one course of chemotherapy (with cabazitaxel followed docetaxel) as part of a non-standard chemotherapy reimbursement procedure in the period from 1 June 2011 to 31 August 2013.

Statistical analyses were descriptive [10, 11]. The primary end-point was progression-free survival (defined as time to PSA and/or radiological progression and/or clinical progression and/or death). Secondary end-points included PSA response rate (defined by a PSA decrease of at least 50% from baseline after three cycles), number of patients with PSA flare during the first 12 weeks of therapy, clinical benefit as per physician judgment (based on performance status, pain, and analgesic consumption), OS, safety (incidence of adverse events and serious adverse events), and usage of G-CSF.

Sample size

It was planned to collect data on approximately 50 patients. This number was based on the estimated number of patients treated with cabazitaxel in the period 2011–2013 within the framework of non-standard chemotherapy reimbursement procedure in Poland.

The study was approved by the Ethics Committee at the Cancer Centre — Maria Skłodowska-Curie Memorial in Warsaw.

Data collected

The data were collected on the basis of a review of medical source records of mCRPC patients treated with cabazitaxel. The information covering at least 12 months from the start of cabazitaxel treatment was analysed for each patient included in the study. The study design reflected the management of these patients in a real-life setting. Collected retrospective data were related to the primary histopathological data on prostate cancer, information about prior curative treatment and palliative care (surgery, radiotherapy, hormone therapy, chemotherapy), changes in the PSA levels in the course of the disease, and the use of cabazitaxel in patients with castration-refractory prostate cancer — see details below.

The following data were collected at initiation of cabazitaxel therapy: age, the presence of metastases, their location (bone, lymph nodes, visceral), and disease burden (massive spread, defined as the presence of visceral metastases and/or ≥ 4 bone metastases, including at least one outside the pelvis and the spine); progression type (biochemical/clinical/radiological); the presence of measurable disease (according to the standard criteria used at a given site or as defined by RECIST); the presence of symptoms; performance status (according to ECOG); changes in PSA value; and other laboratory parameters. In the case of pain, information on the analgesics used was additionally collected (trade name of the drug, number of applications per day, and/or daily dose).

Moreover, for the period of cabazitaxel treatment, the following data were also collected: all adverse events (AEs) and serious adverse events (SAEs), grade 3–4 adverse events by WHO regarding hormone therapy and chemotherapy with cabazitaxel during follow-up; date of last visit during follow-up; disease progression: yes or no; type and date of progression; date of the last dose of the drug; and the patient's condition during the last visit in the follow-up period: survival, death (date), cause of death.

Results

From the seven Polish cancer centres participating in the study, 48 patients with metastatic castration-resistant prostate cancer treated with cabazitaxel after failure of docetaxel treatment were identified.

Disease history of patients enrolled in the registry is provided in Table 1. The majority of patients were

Table 1. Disease history of patients included in the study

	Number of patients (n = 48)
Histopathological diagnosis	
Adenocarcinoma	45
N/A	3
Histological grade in the Gleason scale (2–10)	
< 7	13
7	11
8	11
9	9
N/A	4
Clinical stage at diagnosis	
T2, M0	9
T3–T4, M0	6
M1	16
N/A	17
Prior treatment with curative intent	
Radical prostatectomy	9
External beam radiation therapy	20
Brachytherapy	1

diagnosed with primarily metastatic disease with a high Gleason score (≥ 8).

In most cases, first-line endocrine therapy was pharmacological castration — only one patient underwent orchiectomy (2%). Half of the evaluated patients underwent secondary hormonal manipulations as part (mainly with the use of maximum androgen blockade (flutamide, bicalutamide); seven men (15% of the group) were treated with abiraterone acetate. In 47 of 48 patients first-line chemotherapy was based on docetaxel; one patient received mitoxantrone as first-line chemotherapy. Less than half of the analysed patients (17 of 48; 35%) received second-line chemotherapy (mostly docetaxel or mitoxantrone) before cabazitaxel initiation.

Treatment with cabazitaxel was preceded by a re-assessment of disease severity, the number and location of metastases, performance status, disease progression diagnosis method, PSA levels, and the use of analgesics. Cabazitaxel initiation was associated with clinical progression in 35% and radiological progression in 29%. A significant percentage of patients (25 out of 48-men) met the criteria for diagnosis of massively advanced metastatic disease (the category “Many metastases”). ECOG performance status score was mainly 2 or higher (n = 30). Detailed data are provided in Table 2. In total, the study group reported 289 cycles of cabazitaxel treatment (an average of six cycles of chemotherapy per patient), and 16 out of 48 men (33%) included in the analysis received the planned number of chemotherapy cycles. In 230 cycles (80%) the typical dose of cabazitaxel (25 mg/m²) was used, in 40 cycles (14%) the dose

was reduced to 20 mg/m², and there was even a greater reduction of cabazitaxel dose in a total of 19 cycles. The dose reduction in eight patients was associated with adverse events (a total of 19 cycles of chemotherapy, representing 7% of the administered courses). Chemotherapy was delayed in 46 cycles of treatment, of which only 20 (7% of all) were delayed due to toxicity. Delays for any other reason, including unavailability of the drug, occurred in 26/289 (9%) cycles. Prednisone was administered in 253/289 (88%) cycles. Table 3 shows the parameters related to cabazitaxel dosage. The most commonly used concomitant medications were bisphosphonates (34/48) and denosumab (2/48) — 85% of patients had bone metastases. The G-CSF support was used in 19/48 patients. Opioid analgesics were administered daily in 9/48 (19%), and non-opioid drugs in 6/48 (13%) of patients.

The reasons for discontinuing cabazitaxel therapy are presented in Table 4. In most cases, chemotherapy was discontinued after administration of a pre-planned number of cycles, or due to biochemical progression — 33% and 35% of cases, respectively. The next most common cause of treatment cessation was performance status deterioration (21%). In two cases, the treatment was not completed due to the patient’s death. Finally, cancer progression was seen in 41 of 48 (85%) men included in the analysis. The most common forms of progression were biochemical progression (increase in PSA levels above the defined value) — 17/48 (35%) and clinical progression

(worsening of performance status and an increase in pain severity) — 6/48 (13%). Serious skeletal-related events (SRE) were reported in seven patients (15%).

PSA response was evaluable in 41 patients as per prostate cancer working group recommendations (i.e. at least three cycles of cabazitaxel). Of these 41 patients, 19 (46%) had a PSA decrease of at least 50%, including three who had an initial PSA flare followed by PSA drop below 50% of baseline. Median PFS was 4.2 months (95% CI: 3.4–5.1), and median OS was 12.8 months (95% CI: 9.7–15.9). Detailed data on the primary endpoint (progression-free survival) and OS are presented in Table 5. One-year survival rate in the study group was 65%, and two-year and three-year survival rates were 25% and 15%, respectively. A graphical representation of PFS and OS analysis using the Kaplan-Meier method is presented in Figure 1 and 2.

Table 2. Patient characteristics at initiation of cabazitaxel therapy

	n = 48
Age, years — median (range)	65 (45–80)
Metastases — location	
Bones	41
Lymph nodes	15
Visceral organs	7
Numerous metastases	25
Missing data	4
Progression	
Biochemical	44
Clinical	17
Radiological	14
— in scintigraphy	12
Opioid analgesics daily	9
Non-opioid analgesics daily	6
ECOG	
0–1	14
2	24
> 2	6
N/A	5
PSA [ng/ml] (mean, median)	326; 186

Table 3. Course of cabazitaxel therapy

	Number of patients/number of cycles
Number of cycles administered	289
Mean (± SD); range	6.0 (3.4); 1–18
Median	5.0
1–6	31
7–10	14
> 10	3
Number of patients who received the planned number of cycles (4–13 cycles)	25
N patients (%) with dose reduction	8/48 (16.7%)
N cycles/total number of cycles with a reduced dose	19/289 (7%)
N cycles delayed/total number of cycles (%)	46/289 (16%)
Due to toxicity	20 (7%)
For other reasons (usually unavailability of the drug)	26 (9%)
Prednisone (number of cycles)	253/289 (88%)

Table 4. Reasons for termination of cabazitaxel chemotherapy¹

	Number of patients (n = 48)
Treatment completion, planned number of chemotherapy courses	16
Biochemical progression	17
Clinical progression	6
Radiological progression	1
Worsening of performance status	10
Toxicity (WHO grade 3–4 adverse events)	5
Other (e.g. death)	3 (2)

¹There could be more than one cause in a single patient

Table 5. Cabazitaxel therapy efficacy assessment — progression-free survival (since cabazitaxel initiation until progression for whatever reason) and overall survival

Progression-free survival (PFS) and overall survival (OS) in months for cabazitaxel-treated patients			
PFS	Number of patients	Median	95% CI
Confirmed	44	4.2	3.4–5.1
Generalised ¹	48	4.1	3.3–5.1
OS	Number of patients	Median	95% CI
With known date	14	12.8	9.7–15.9
Confirmed ²	19	10.5	7.9–13.1
Generalised ¹	48	15.1	12.7–17.4

¹In both generalisations — the date of the last contact with the patient was used

²In case of the lack of the death date — the date of the last contact with the patient was used

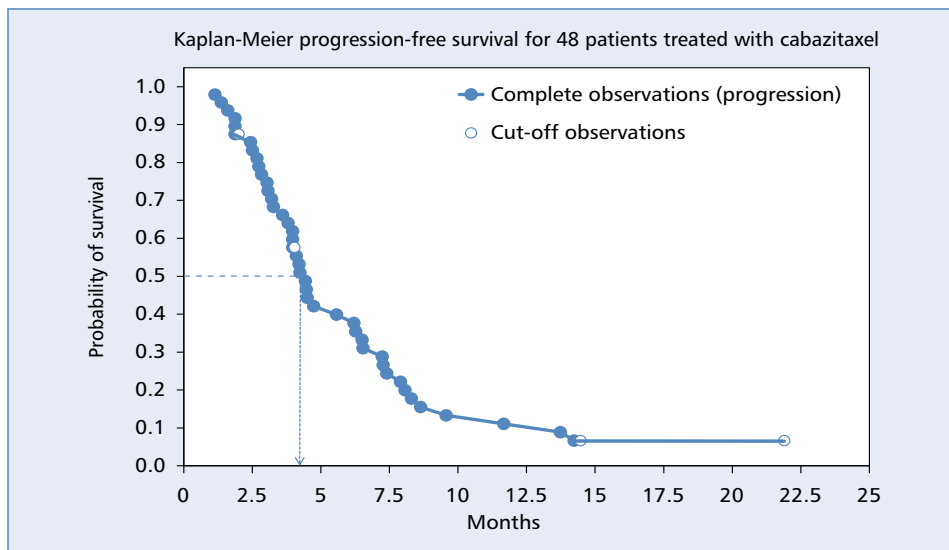


Figure 1. Kaplan-Meier analysis of progression-free survival (PFS) in cabazitaxel-treated patients

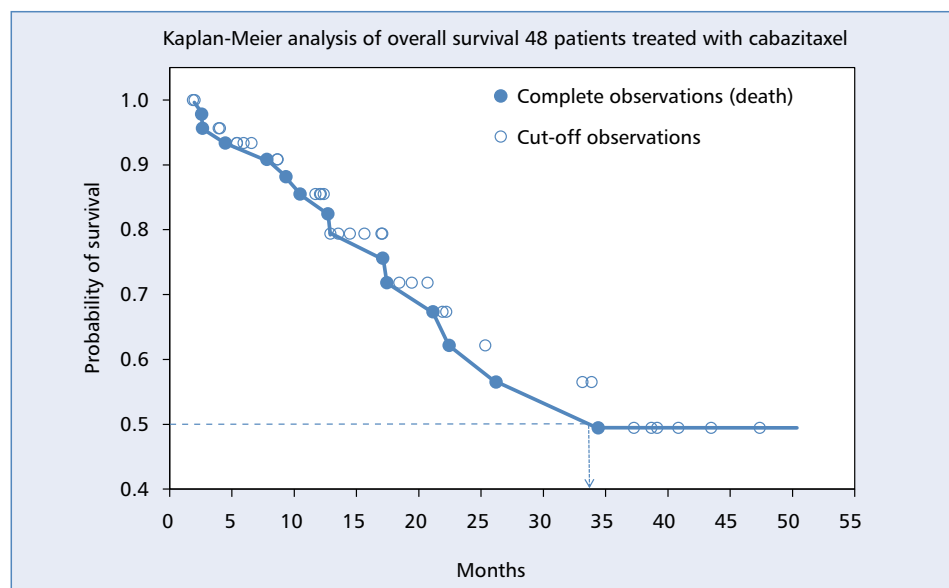


Figure 2. Kaplan-Meier analysis of overall survival in patients treated with cabazitaxel (n = 48)

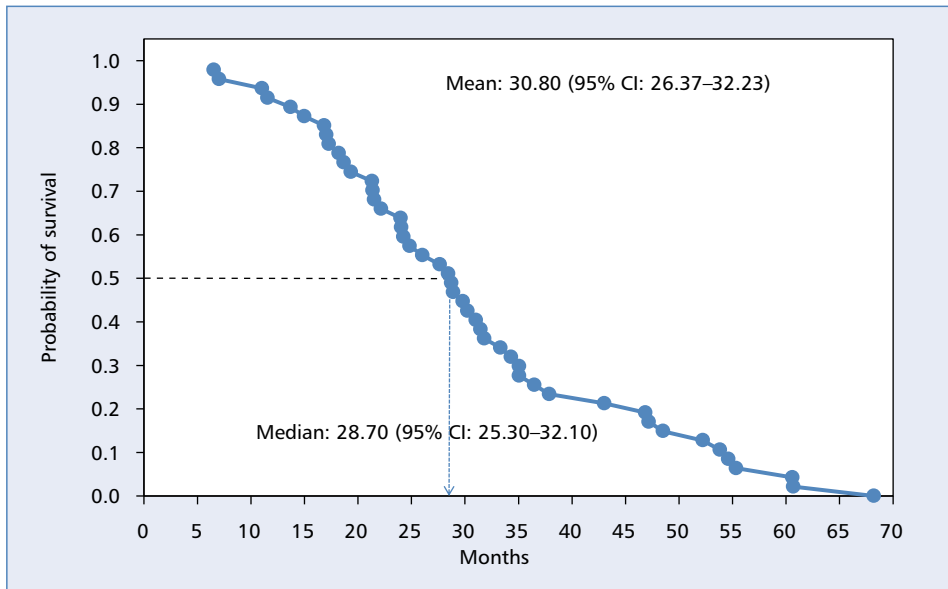


Figure 3. Kaplan-Meier analysis of overall survival since docetaxel initiation in patients treated with cabazitaxel as second-line chemotherapy (n = 47)

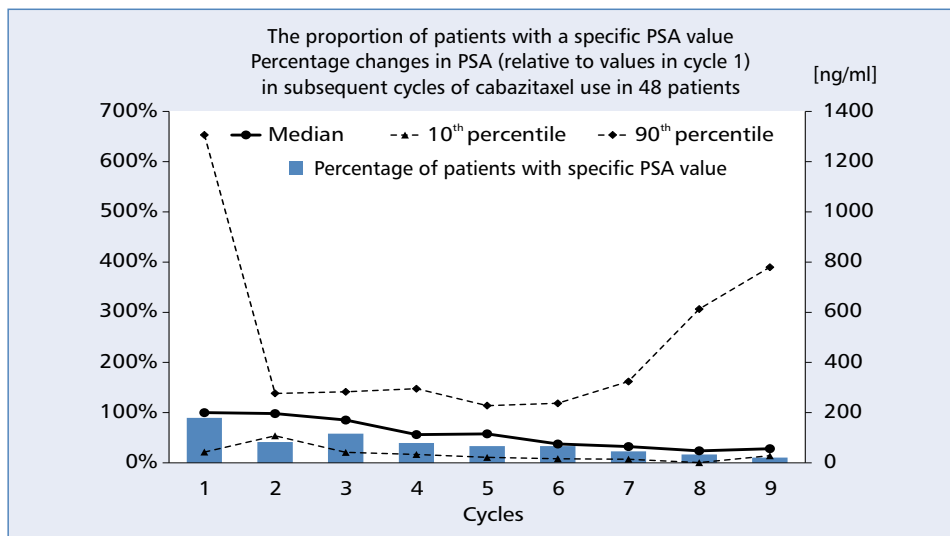


Figure 4. Percentage changes in PSA levels from baseline in the consecutive cycles of cabazitaxel therapy

The overall survival estimate since docetaxel initiation is presented in Figure 3. The OS median was 28.70 (95% CI: 25.30–32.10) months.

In order to reliably assess OS in cabazitaxel-treated patients, data on next-line systemic therapy was collected (after the end of cabazitaxel therapy). Forty-seven patients (the date of docetaxel initiation in one patient was unavailable) were administered a treatment sequence of docetaxel-cabazitaxel after failure of endocrine therapy. Nine patients (19%) in this study population received abiraterone acetate after progression on cabazitaxel. One of them received cabazitaxel rechallenge (six cycles until biochemical progression; previously 10 cycles) after

discontinuation of abiraterone. No data on response to abiraterone was collected.

Serum PSA level variations observed during cabazitaxel treatment, their range, and dynamics are presented in Figure 4.

Clinical benefit from cabazitaxel, defined as objective responses or disease stabilisation, was verified after each cycle of chemotherapy (Table 6). Furthermore, clinical response (improvement in performance status and/or decrease in the severity of pain and/or reduction of the need for analgesics) was seen after administration of 53 out of 289 cycles of cabazitaxel treatment. Four of nine patients administered with narcotic analgesics and 4/6 patients

Table 6. Clinical effects of cabazitaxel therapy

	Number of cycles (n = 289)
Clinical benefit during cabazitaxel therapy — evaluation after each cycle	
Improvement in ECOG performance status ¹	21
Pain severity reduction	24
Reduction of the need for analgesics ²	53
Stable condition	174 (60%)
No response	22 (7%)
N/A	59 (20%)

¹ECOG performance status improved in 4 patients with ECOG 3, in 5 patients with ECOG 2, and in 1 patient with ECOG 1 prior to cabazitaxel

²4/9 and 4/6 patients, respectively, had their need for narcotic and non-narcotic daily analgesics at cabazitaxel initiation reduced

taking non-narcotic analgesics at initiation of cabazitaxel therapy responded with reduction of the need for analgesics.

In the analysis of investigator-reported adverse events (AE) associated with cabazitaxel, there was a prevalence of haematological complications with anaemia (10 cases [20.8%], including three cases [6.3%] in grade 3 of severity according to the WHO), neutropaenia (nine cases, representing 18.8% of the group, including two cases [4.2%] in grade 3, and two cases in grade 4), and thrombocytopenia (10.4%), mainly in grade 1 and 2. Gastrointestinal adverse events (nine cases of diarrhoea [18.8%], and two cases [4.2%] each of vomiting and abdominal pain) were the second most common AEs; however, their severity did not exceed WHO grade 2. Symptoms of polyneuropathy (only sensory) was observed only in two patients (4.2%), and their severity did not exceed grade 2. The following corrective actions were taken: extending the interval between cycles (14 patients, 29 cycles), dose reduction (8 patients, 19 cycles), discontinuation of treatment (8 patients). Detailed data on adverse events are presented in Table 7.

Ten serious adverse events (SAEs) related to cabazitaxel were reported, including one fatal event due to acute renal failure eight months from the start of cabazitaxel therapy (nine cycles). The others were: anaemia (three times in the same patient), febrile neutropaenia (1), febrile neutropaenia with diarrhoea and haematuria (1), secondary neutropaenia (1), diarrhoea with abdominal pain and vomiting (1), myocardial infarction (1), unstable coronary disease (1).

Discussion

Data from seven national cancer centres, derived from 48 patients with mCRPC receiving cabazitaxel, allowed a retrospective evaluation of the efficacy and safety of this drug in routine clinical practice.

Table 7. Safety assessment of cabazitaxel therapy — adverse events reported

Adverse event	Number of cases (n = 50)*	3° (n = 12)	4° (n = 5)
Haematological			
Anaemia	10	3	–
Neutropenia	8	2	2
Thrombocytopenia	4	1	–
Leucopaenia	2	1	1
Febrile neutropaenia	2	1	–
Gastrointestinal tract			
Diarrhoea	10	–	–
Vomiting	2	–	–
Abdominal pain	2	–	–
Enteritis	1	1	–
Urinary tract system			
Acute renal failure	1	–	1
Urinary incontinence	1	1	–
Urinary tract infection	1	–	–
Cardiovascular system			
Myocardial infarction	1	–	1
Unstable coronary artery disease	1	1	–
Other			
Paresthesia	2	1	–
Dehydration	1	–	–
Secondary neutropaenia	1	–	–

*44 adverse events occurred during cabazitaxel therapy

On the basis of the performed analyses, it was shown that in the vast majority of patients, cabazitaxel was used in accordance with the Summary of Product Characteristics (in combination with prednisone), and more than half of the patients received treatment with the planned intensity. Dose reductions or delays in the administration of the planned courses of chemotherapy were caused by both toxicity and problems with drug availability. The vast majority of patients did not receive primary prevention of febrile neutropaenia. In the period covered by the retrospective analysis, the majority of patients experienced disease progression. Median overall survival and progression-free survival in the analysed population were characterised by similar values as in the pivotal study [12].

The use of cabazitaxel was associated with the occurrence of adverse events of all grades; however, their frequency was comparable to the pivotal study, and the incidence of serious adverse events was relatively low compared to the pivotal study.

Cabazitaxel, in addition to docetaxel, is one of two cytotoxic drugs that significantly improve the prognosis in

patients with castration-resistant prostate cancer. This drug, in addition to two hormonal drugs (abiraterone acetate and enzalutamide), is a systemic treatment option for patients with mCRPC after failure of docetaxel therapy. It is an especially active drug in patients who have progressed during or after docetaxel [12, 13], and it retains its activity in patients progressing after novel AR-targeted agents [9]. Unlike cabazitaxel, both abiraterone acetate and enzalutamide can be used, in accordance with their approved indications, in mCRPC patients who still do not require docetaxel. Thus, the value of cabazitaxel, as a drug with proven therapeutic effect in patients after failure of docetaxel-based chemotherapy, who have already failed new-generation endocrine therapy. Its estimated important data were recently presented at the Congress of the American Society of Clinical Oncology — ASCO 2016. A phase III study comparing two doses of cabazitaxel (25 mg/m² and 20 mg/m²) in the treatment of mCRPC patients after failure of docetaxel therapy demonstrated comparable efficacy of the two doses, with a clear reduction of toxicity in patients receiving the lower dose. Also, taking into account the beneficial effect of cabazitaxel on the quality of life of mCRPC patients, which was shown, among others, in an expanded access study conducted in the UK [14], this drug can certainly be considered a valuable therapeutic option in clinical practice. A randomised trial of cabazitaxel was also recently presented at the European Society of Medical Oncology (ESMO) Annual Meeting showed a significantly greater activity than abiraterone or enzalutamide in mCRPC patients with high-risk features (liver metastases, time to castration less than one year with first androgen deprivation therapy, high LDH — Kim Chi ESMO 2018) [15].

Conclusions

In this cohort of patients cabazitaxel showed it can be an good therapeutic option for patients with metastatic castration-resistant prostate cancer after docetaxel failure and is an important therapeutic option with acceptable toxicity with respect to clinical stabilisation and possibly increased survival.

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Conflict of interest

All authors received honoraria from Sanofi related to the study conduct.

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JZ — scientific advisor, presenter, speaker (Janssen); travel grants (Janssen).

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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