

Cabazitaxel shows a consistently greater survival benefit compared to mitoxantrone in patients with mCRPC

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Aim. This sub analysis of TROPIC study evaluates overall survival (OS) under cabazitaxel in patients who had no initial response to docetaxel (D) and discontinued D for disease progression and those who initially responded to D but experienced disease progression < 3 months since last D dose. These patients are believed unlikely to benefit from D re-treatment and need new treatment options such as cabazitaxel.

Methods. Of the 755 patients with metastatic castration-resistant prostate cancer (mCRPC) enrolled in TROPIC study, 362 (47.9%) had no initial response to D and discontinued it for disease progression, 155 (20.5%) had an initial response to D therapy according to investigator judgment but progressed < 3 months since last D dose and 238 (31.5%) did not belong to these two subgroups. All patients were randomized to receive cabazitaxel 25 mg/m² or mitoxantrone 12 mg/m² both every 3 weeks and prednisone 10 mg per os daily.

Results. Median OS with cabazitaxel was consistently longer than with mitoxantrone in all subgroups. The highest survival benefit versus mitoxantrone was observed for patients who initially responded to D and then progressed < 3 months since last D dose (median OS 15.7 versus 11.6 months, Hazard ratio (HR) 0.52 [95% CI 0.35–0.76]). Median PFS was also significantly improved in the latter subgroup compared to mitoxantrone (2.6 versus 1.4 months, HR 0.66 [0.48–0.91]).

Conclusion. Cabazitaxel plus prednisone consistently shows a greater survival benefit compared to mitoxantrone plus prednisone whatever the subgroup considered, including responders to first-line D who progressed < 3 months since last D and pts without initial response to D who discontinued it for disease progression.

Kabazytaksel konsekwentnie wykazuje poprawę czasu przeżycia w porównaniu z mitoksantronem u chorych z opornym na kastrację, przerzutowym rakiem gruczołu krokowego (*metastatic castration-resistant prostate cancer, mCRPC*)

Cel. Niniejsza analiza — wtórna do badania TROPIC — ma na celu ocenę czasu przeżycia całkowitego (*overall survival, OS*) po zastosowaniu kabazytakselu w podgrupach chorych, u których od początku nie uzyskano odpowiedzi na docetaksel (D) i odstawiono docetaksel D z powodu progresji choroby, oraz u chorych, u których uzyskano początkowo odpowiedź na D, lecz u których wystąpiła progresja nowotworu w czasie < 3 miesiące od ostatniej dawki D. U takich pacjentów uzyskanie korzyści z ponownego leczenia D jest mało prawdopodobne, dlatego też potrzebują oni nowych opcji terapeutycznych, takich jak kabazytaksel.

Metody. Z 755 chorych z przerzutami raka gruczołu krokowego opornego na kastrację (*metastatic castration-resistant prostate cancer, mCRPC*), włączonych do badania TROPIC, u 362 (47,9%) nie zaobserwowano początkowej odpowiedzi na D i przerwano jego podawanie. U 155 (20,5%) — w ocenie badacza — obserwowano początkowo odpowiedź na leczenie D, lecz wystąpiła progresja w czasie < 3 miesiące od ostatniej dawki D, a 238 (31,5%) nie należało do żadnej z tych podgrup. Wszystkich pacjentów zrandomizowano do grup otrzymujących kabazytaksel w dawce

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25 mg/m² lub mitoksantron w dawce 12 mg/m² podawanych dożylnie co 3 tygodnie oraz prednizon, przyjmowany doustnie w dawce 10 mg/dzień.

Wyniki. W każdej z podgrup mediana czasu przeżycia całkowitego (OS) dla chorych otrzymujących kabazytaksel była zawsze większa niż w grupie otrzymującej mitoksantron. Największą korzyść wydłużenia czasu przeżycia całkowitego w porównaniu z grupą otrzymującą mitoksantron obserwowano w podgrupie chorych, u których początkowo zaobserwowano odpowiedź na D, a następnie progresję w czasie < 3 miesiące od ostatniej dawki D {mediana 15,7 miesiąca w porównaniu z 11,6 miesiąca, współczynnik ryzyka HR (*hazard ratio*) 0,52; 95% przedział ufności CI (*confidence interval*) [0,35–0,76]}. Mediana czasu przeżycia wolnego od progresji była także znacząco lepsza w tej podgrupie w porównaniu z grupą otrzymującą mitoksantron (2,6 miesiąca w porównaniu z 1,4 miesiąca, HR 0,66 (0,48–0,91)).

Wniosek. Kabazytaksel w skojarzeniu z prednizonem wykazuje konsekwentnie korzystniejsze działanie na czas przeżycia w porównaniu z leczeniem mitoksantronem w skojarzeniu z prednizonem w każdej z podgrup, w szczególności u chorych, u których zaobserwowano odpowiedź na D zastosowany w pierwszej linii i u których doszło do progresji w czasie < 3 miesiące od ostatniej dawki D, a także u chorych bez początkowej odpowiedzi na D, którzy przerwali jego przyjmowanie w celu kontroli progresji choroby.

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Słowa kluczowe: rak gruczołu krokowego, oporny na kastrację, chemioterapia, oporność na docetaxel, kabazytaksel

Introduction

All patients with metastatic castration-resistant prostate cancer (mCRPC) eventually progress during or following first-line docetaxel therapy and until recently, second-line treatment approaches have been limited. Within the last three years, novel therapies able to prolong survival in the post-docetaxel setting have emerged, including the novel semi-synthetic taxane cabazitaxel [1–5]. The challenge for physicians is now to integrate this broad armamentarium rationally in daily practice and appropriately tailor therapy to optimize treatment outcomes and benefits of each individual patient. Prostate cancer is a heterogeneous disease [6–8] and optimal treatment of mCRPC will involve better classification of the disease based on the androgen-sensitivity status and underlying molecular mechanisms of progression [9].

Taxanes have an important place in mCRPC management. By stabilizing microtubule spindle, they inhibit cell division and also contribute to inhibit ligand-dependent and ligand-independent AR nuclear translocation which is mediated by microtubules [10]. Cabazitaxel is a next generation taxane selected for clinical development based on its ability to overcome taxane resistance *in vitro* and *in vivo* and its activity in docetaxel-sensitive and docetaxel-resistant cell lines and tumor models [11]. In addition, unlike docetaxel and paclitaxel, cabazitaxel has demonstrated the ability to cross the blood-brain barrier *in vivo* [11]. Results of the randomized, multinational, phase III TROPIC trial (NCT00417079) comparing cabazitaxel with mitoxantrone in patients with mCRPC progressing during or after a docetaxel-containing regimen have been reported [1]. A total of 755 patients were randomized to cabazitaxel (25 mg/m²; n = 378) plus prednisone (10 mg/day), or mitoxantrone

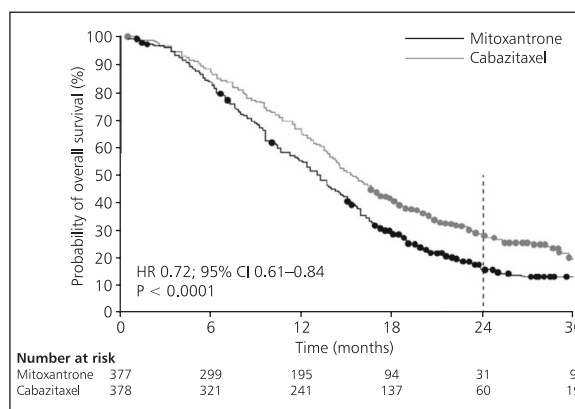


Figure 1. Cabazitaxel significantly improves overall survival compared to mitoxantrone in 755 mCRPC patients progressing during or after docetaxel — Updated results [12]. HR — hazard ratio; CI — confidence interval

(12 mg/m²; n = 377) plus prednisone, every three weeks. Cabazitaxel significantly improved median overall survival (OS) compared to mitoxantrone (15.1 versus 12.7 months, hazard ratio [HR] 0.70; p < 0.0001), representing a 30% reduction in the relative risk of death. Updated results of TROPIC (figure 1) confirm the long-term survival benefit of cabazitaxel, with almost twice as many patients alive at 2 years compared to the active control arm mitoxantrone (odds ratio [OR] 2.11; 95% CI 1.33–3.33) [12]. This survival benefit was associated with a significant improvement in progression-free survival (PFS), a composite end-point defined as time from randomization to either PSA progression, or tumor progression, or pain progression, or death (2.8 versus 1.4 months, HR 0.74; p < 0.0001) [1]. Cabazitaxel also significantly improved the objective response rate evaluated according to RECIST cri-

teria (14.4% versus 4.4%; $p=0.0005$) and the PSA response rate (39.2% versus 17.8%; $p = 0.0002$) [1].

We examined the survival benefit observed in TROPIC trial with cabazitaxel according to prior response to docetaxel (D) treatment, in order to determine which patients have the greatest benefit of the drug.

Methods

Details of eligibility and exclusion criteria are provided in the primary publication [1]. In brief, men with mCRPC were eligible if they had documented disease progression during or after completion of docetaxel treatment. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, no prior mitoxantrone therapy and no radiotherapy $\geq 40\%$ of the bone marrow. Patients with measurable disease were required to have documented disease progression by Response Evaluation Criteria in Solid Tumors (RECIST). Patients with non-measurable disease were required to have rising serum prostate-specific antigen (PSA) or the appearance of at least one new demonstrable radiographic lesion. Patients were stratified for disease measurability (measurable vs non-measurable) and ECOG performance status (0–1 versus 2). Physical examination and radiologic investigations, including computed tomography and bone scanning, were performed at baseline, along with blood tests, including serum PSA. Pain was assessed with the McGill- present pain intensity (PPI) scale and analgesic use was derived from consumption normalized to morphine equivalents.

Treatment was continued for a maximum of ten cycles. Patients were followed up until the cutoff date for analysis or until death (whichever occurred first). Prophylactic granulocyte colony-stimulating factor was not allowed during the first cycle, but was allowed at physicians' discretion after first occurrence of either neutropenia lasting 7 days or more or neutropenia complicated by fever or infection.

In this post-hoc analysis of TROPIC trial, subgroups of interest were defined as follows:

1. Patients without initial response to D who discontinued D for disease progression, according to physician judgment ($n = 362$).
2. Patients who responded first to D and then progressed < 3 months after the last D dose ($n = 155$). Response to D was defined by a PSA decrease during D therapy without signs of radiological or clinical progression.
3. Patients who did not satisfy criteria of subgroups (1) and (2) ($n = 238$). This corresponds to patients with stable disease during D therapy who progressed after the last D dose, irrespective of the time ($n = 131$) and patients who responded first to D and then progressed ≥ 3 months after the last D dose ($n = 107$).

Overall survival was analyzed using the Kaplan-Meier method, and comparisons between treatment arms were performed using the log-rank test; Hazard Ratios (HRs) and

95% confidence intervals (CIs) were calculated with a Cox proportional hazards model (for both primary and secondary analyses). Overall survival data were censored at the last date the patient was known to be alive or at the analysis cutoff date, whichever was earliest.

Results

Clinical characteristics of the 755 mCRPC patients enrolled in TROPIC are provided according to prior D response in table I. In patients who initially responded to D and progressed < 3 months since last D dose, the percentage of patients with only one line of prior D was slightly higher (75%) compared to the other groups. Other clinical characteristics were well balanced between subgroups.

Cabazitaxel improved OS compared to mitoxantrone, irrespective of the subgroup (table II). Nevertheless, the highest survival benefit was observed for patients who initially responded to D and then progressed < 3 months since last D dose with a median OS 15.7 in cabazitaxel group versus 11.6 months in mitoxantrone group (HR 0.52, 95% CI [0.35–0.76]) (figure 2). Median PFS was also significantly improved in the subgroup compared to mitoxantrone (2.6 versus 1.4 months, HR 0.66 [0.48–0.91]).

The safety profile of cabazitaxel in TROPIC study has been reported previously [1]. In the TROPIC trial, the percentage of patients who discontinued treatment due to adverse events (AEs) was 18% in the cabazitaxel group compared to 8% in the mitoxantrone group [1]. Grade ≥ 3 AEs in both treatment arms were primarily hematologic, with neutropenia (82% vs 58%), leucopenia (68% vs 42%), and febrile neutropenia (8% vs 1%) being higher with cabazitaxel compared to mitoxantrone (table III). The most common grade ≥ 3 nonhematologic AEs with cabazitaxel compared to mitoxantrone were diarrhea (6% vs $< 1\%$), fatigue (5% vs 3%) and asthenia (5% vs 2%). The rate of mortality within 30 days of last drug infusion was 5% in the cabazitaxel arm, compared with 2% in the mitoxantrone arm.

Discussion

This sub analysis of TROPIC study confirms that median OS with cabazitaxel is consistently greater than with mitoxantrone whatever the subgroup considered regarding response to docetaxel. The highest survival benefit versus mitoxantrone was observed for patients who initially responded to D and then progressed < 3 months since last D dose (HR 0.52, 95% CI [0.35–0.76]). Median PFS was also significantly improved in the subgroup compared to mitoxantrone (2.6 versus 1.4 months, HR 0.66 [0.48–0.91]). Patients who had no initial response to D and discontinued it for disease progression also showed a significant benefit with cabazitaxel compared to mitoxantrone (HR 0.74, 95% CI [0.58–0.94]). These data support the efficacy of cabazitaxel in patients with either acquired or primary resistance to D. These results further confirm subgroup analyses of TROPIC

Table I. Clinical characteristics of patients according to prior response to D

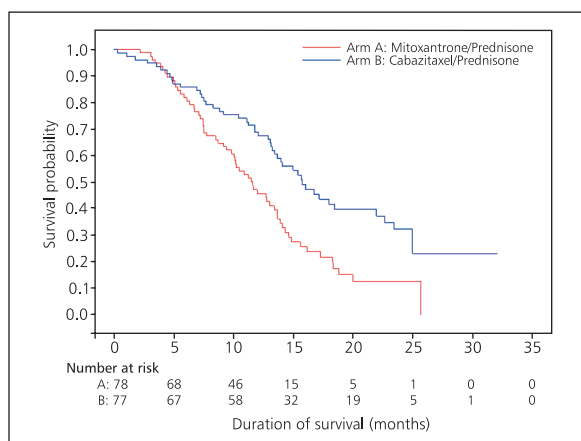
	Overall population		No initial D response and progression during D		Initial D response and progression < 3 mo after last D dose		Remaining patients	
	MP (n = 377)	CBZP (n = 378)	MP (n = 183)	CBZP (n = 179)	MP (n = 78)	CBZP (n = 77)	MP (n = 183)	CBZP (n = 179)
Median age (years)	67.0	68.0	67.0	67.0	65.5	67.0	67.0	69.0
ECOG Performance Status 0–1	91.2%	92.6%	88.5%	91.1%	92.3%	93.5%	94.8%	94.3%
Tumor location								
Bone	87%	80.2%	85.8%	76.5%	93.6%	88.3%	84.5%	80.3%
Lymph nodes	44.8%	45%	49.7%	44.7%	37.2%	40.3%	42.2%	48.4%
Visceral	24.9%	24.9%	29%	24%	20.5%	22.1%	21.6%	27.9%
Baseline PSA (ng/ml) — median	127.5	143.9	172.1	144.1	122.0	192.8	91.0	119.0
Measurable disease	54.1%	53.2%	58.5%	54.7%	47.4%	49.4%	51.7%	53.3%
Pain at baseline	44.6%	46%	45.9%	49.2%	47.4%	44.2%	40.5%	42.6%
N prior chemotherapy regimen								
1 regimen	71.1%	68.8%	70.5%	67%	76.9%	74%	68.1%	68%
2 regimens	21%	24.9%	21.9%	27.4%	17.9%	16.9%	21.6%	26.2%
3 or more regimens	8%	6.3%	7.7%	5.6%	5.1%	9.1%	10.3%	5.7%

D — docetaxel; MP — mitoxantrone plus prednisone; CBZP — cabazitaxel plus prednisone

Table II. Overall survival with cabazitaxel and mitoxantrone according to prior response to D

Patients	MP		CBZP		CBZP vs MP
	Number dead/N (%)	Median OS [95% CI]	Number dead/N (%)	Median OS [95% CI]	Hazard Ratio [95% CI]
Whole TROPIC population (ITT)	279/377 (74%)	12.7 [11.6–13.7]	234/378 (61.9%)	15.1 [14.1–16.3]	0.70 [0.59–0.83]
Patients with no initial response to D who discontinued D for disease progression (subgroup [1])	149/183 (81.4%)	10.3 [9.0–12.7]	124/179 (69.3%)	13.6 [11.3–14.5]	0.74 [0.58–0.94]
Patients with initial response to D and who progressed < 3 months after the last D dose (subgroup [2])	60/78 (76.9%)	11.6 [9.8–13.7]	47/77 (61.0%)	15.7 [13.4–21.9]	0.52 [0.35–0.76]
Remaining patients (excluding [1] + [2])	70/116 (60.3%)	16.4 [15.1–19.3]	63/122 (51.6%)	18.0 [15.3–28.7]	0.74 [0.52–1.05]

D — docetaxel; MP — mitoxantrone plus prednisone; CBZP — cabazitaxel plus prednisone; OS — overall survival; CI — confidence interval

**Figure 2.** Cabazitaxel significantly improves overall survival compared to mitoxantrone in 155 mCRPC patients with initial response to prior D and progression < 3 mo since last D dose

already published showing a consistent OS benefit with cabazitaxel compared to mitoxantrone [1, 12].

The fact that cabazitaxel is effective in patients with primary resistance to D is important because therapeutic options may be limited for such patients. Muckerji et al reported in a cohort of 44 men with CRPC treated with D followed by abiraterone at the Royal Marsden Hospital, that none of the 7 patients who were D refractory had a subsequent PSA, radiological or clinical response with abiraterone [13]. Similarly, patients developing acquired resistance to D also represent an unmet need. Hence, in patients with initial good response to D who progressed in less than 3 months after having stopped therapy, D rechallenge seems associated with marginal PSA and clinical responses and more importantly no OS benefit has been demonstrated with such a treatment option [14, 15]. The efficacy of abiraterone in such a population has not been documented.

Table III. Adverse Events in the TROPIC Trial [2]

Selected Adverse Events, ^a n (%)	MP (n = 371)		CBZP (n = 371)	
	All grades	Grade ≥ 3	All Grades	Grade ≥ 3
Hematologic				
Neutropenia	325 (88%)	215 (58%)	347 (94%)	303 (82%)
Leukopenia	343 (92%)	157 (42%)	355 (96%)	253 (68%)
Anemia	302 (81%)	18 (5%)	361 (97%)	39 (11%)
Febrile neutropenia	–	5 (1%)	–	28 (8%)
Nonhematologic				
Diarrhea	39 (11%)	1 (< 1%)	173 (47%)	23 (6%)
Fatigue	102 (27%)	11 (3%)	136 (37%)	18 (5%)
Asthenia	46 (12%)	9 (2%)	76 (20%)	17 (5%)
Back pain	45 (12%)	11 (3%)	60 (16%)	14 (4%)
Nausea	85 (23%)	1 (< 1%)	127 (34%)	7 (2%)
Vomiting	38 (10%)	0	84 (23%)	7 (2%)
Hematuria	14 (4%)	2 (1%)	62 (17%)	7 (2%)
Abdominal pain	13 (4%)	0	43 (12%)	7 (2%)

^aSorted by decreasing frequency of grade ≥ 3 events in the CBZP arm. CBZP — cabazitaxel + prednisone; MP — mitoxantrone + prednisone

Several mechanisms have been involved in resistance to D. The first one is an overexpression of membrane-bound efflux proteins resulting in decreased cellular drug accumulation: indeed some men with CRPC exhibit an overexpression of the ATP-binding cassette transporter P-glycoprotein (P-gp) [16, 17]. Another possible mechanism is the aberrant expression of tubulin isotypes, in particular beta-III tubulin or microtubule-regulating proteins [18]: expression of beta-III tubulin is increased by androgen deprivation in prostate cancer patients and appears to be associated with progression to castration resistance [19]. Overexpression of beta-III tubulin has been shown to be an independent predictor of OS in men with mCRPC treated with D, and in vitro manipulations of beta-III tubulin can reverse resistance to D [20]. Changes in actin regulation can also mediate resistance to tubulin-binding agents [19]. Defects in apoptotic pathways may also be associated in resistance to D: during treatment with D, prostate cancer cells can activate antistress and antiapoptotic mechanisms (eg, Bcl-2, survivin, clusterin) that promote survival [21–23]. Hypoxia may also confer resistance to chemotherapy but may also select for tumor cells with a more malignant phenotype [25].

Lastly, it is important to consider that most fatal adverse events possibly related to cabazitaxel in TROPIC trial occurred at the beginning of the recruitment phase and were attributed to lack of proactive management of adverse events (mainly neutropenia and diarrhea) [26]. The importance of adequate patient care to optimize treatment benefits was highlighted by a sub-analysis of TROPIC limited to French centers [27]. Proactive management of adverse events was associated with a lower rate of discontinuation due to adverse events with cabazitaxel than in the global

study population (11% versus 18%) and there was no toxic death, resulting in a greater OS benefit versus mitoxantrone (+3.7 versus +2.4 months). A large compassionate use programme which included an awareness programme on proactive management of adverse events confirmed that toxicity of cabazitaxel was manageable in real life practice, including in older patients (≥ 70 year-old) with a much lower incidence of grade ≥ 3 toxicities and discontinuation for adverse events than in TROPIC trial [28, 29]. Of note, it also confirmed that cabazitaxel was associated with a particularly low rate of grade ≥ 3 neuropathy and nail disorders (< 1% for both) which are particularly bothersome for the patients.

Conclusion

This sub analysis of TROPIC study, cabazitaxel plus prednisone consistently shows a greater survival benefit compared to mitoxantrone plus prednisone whatever the subgroup considered, including patients without initial response to D who discontinued it for disease progression. Patients responding to first-line D who progressed < 3 months since last D showed an excellent benefit with cabazitaxel.

Conflict of interest: none declared

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II Konkurs na projekty naukowe w zakresie badań podstawowych w onkologii

Polskie Towarzystwo Onkologiczne ogłasza II Konkurs na projekty naukowe w zakresie badań podstawowych w onkologii, podejmowanych w celu zdobycia nowej wiedzy o patogenezie i leczeniu chorób nowotworowych.

Środki finansowe na realizację II Konkursu przekazała na rzecz PTO firma Roche. Polskie Towarzystwo Onkologiczne powołało Komisję, złożoną z przedstawicieli polskich towarzystw naukowych działających w dziedzinie onkologii, w celu przeprowadzenia oceny zgłoszonych projektów i przyznania grantów.

Szczegółowe informacje znajdują się na stronie PTO: www.pto.med.pl w zakładce: „Granty i nagrody PTO”.

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