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Safety of cabazitaxel in senior adults with metastatic castration-resistant prostate cancer: Results of the European compassionate-use programme

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Abstract ***Background:*** Cabazitaxel/prednisone has been shown to prolong survival versus mitoxantrone/prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) that has progressed during or after docetaxel. Subsequently, compassionate-use programmes (CUPs) and expanded-access programmes (EAPs) were established worldwide, allowing access to cabazitaxel before its commercial availability. Preliminary results of the European CUP/EAP, focusing on the elderly population (aged $\geqslant$70 years), are reported.
Patients and methods: Enrolled patients with progressive mCRPC received cabazitaxel (25 mg/m^2) plus 10 mg oral prednisone/prednisolone every 3 weeks until disease progression, death, unacceptable toxicity or physician/patient decision. Safety was analysed by age group (<70, 70–74 and $\geqslant$75 years). The influence of selected variables on grade $\geqslant$3 neutropenia and/or neutropenic complications was analysed in multivariate analysis.
Results: 746 men were enrolled (<70 years, $n = 421$; 70–74, $n = 180$, $\geqslant$75 years, $n = 145$). Number of cabazitaxel cycles, dose reductions for any cause, dose delays possibly related to

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cabazitaxel adverse events, and tolerability were similar in the three age groups. Prophylactic granulocyte colony-stimulating factor (G-CSF) use was more common in men aged ⩾70 years. In multivariate analysis, age ⩾75 years, treatment cycle 1, and neutrophil count <4000/mm^3 before cabazitaxel injection were associated with increased risk of developing grade ⩾3 neutropenia and/or neutropenic complications. Prophylactic use of G-CSF at a given cycle significantly reduced this risk by 30% (odds ratio 0.70, $p = 0.04$).

Conclusion: The results suggest that cabazitaxel has a manageable safety profile in everyday clinical practice. Prophylactic use of G-CSF, especially at cycle 1 and in men aged ⩾75 years, is important and improves tolerability in senior adults treated with cabazitaxel.

1. Introduction

The past 4 years have seen significant advances in the management of metastatic castration-resistant prostate cancer (mCRPC), with five novel therapies (abiraterone, cabazitaxel, enzalutamide, radium-223, and sipuleucel-T) demonstrating a survival benefit in phase III clinical trials [1–5].

Taxanes have an important role in this broad armamentarium. Their anti-tumour activity has been shown to promote assembly and stabilisation of microtubules, blocking tumour cell division [6], and inhibiting tumour cell trafficking, including nuclear translocation of the androgen receptor, a key driver of prostate cancer growth [7,8]. In 2004, the results of two pivotal phase III studies (TAX 327 and SWOG 99-16) demonstrated, for the first time, a significant improvement in overall survival (OS) with docetaxel/prednisone and docetaxel/estramustine compared with mitoxantrone/prednisone [9–11]. Moreover, 19% of patients treated in TAX 327 and receiving docetaxel every 3 weeks (q3w) survived for at least 3 years, versus only 14% with mitoxantrone [11]. Based on these results, docetaxel plus prednisone became the standard of care for mCRPC, recommended by many international guidelines [12–17].

Cabazitaxel is a next generation taxane, selected for clinical development based on its ability to overcome docetaxel resistance and its ability to cross the blood–brain barrier in preclinical animal models [18–20]. In the phase III TROPIC trial, median survival was 15.1 months (95% confidence interval [CI] 14.1–16.3) with cabazitaxel/prednisone, and 12.7 months (95% CI 11.6–13.7) with mitoxantrone/prednisone [1]. Updated results showed a long-term survival benefit, with almost twice as many patients alive at 2 years with cabazitaxel compared with the active control arm mitoxantrone (15.9% versus 8.2%; odds ratio [OR] 2.11; 95% CI 1.33–3.33) [21].

Cabazitaxel is now considered an effective treatment option for mCRPC for patients progressing during or after docetaxel [12,13,15,16]. In TROPIC, however, cabazitaxel was associated with some clinically important adverse events (AEs)—mainly an increased risk of grade ⩾3 febrile neutropenia (cabazitaxel 8% versus mitoxantrone 1%) and grade ⩾3 diarrhoea (cabazitaxel 6% versus mitoxantrone <1%) [1]. Overall, 5% of patients in the cabazitaxel group and 2% of those in the mitoxantrone group died within 30 days of the last infusion—the most frequent cause of death in the cabazitaxel group was neutropenia and its clinical consequences. This toxicity might have, at least in part, been because patients were heavily pretreated and had very advanced disease, prophylactic G-CSF at the first cabazitaxel cycle was not allowed (it was only allowed at first occurrence of either neutropenia lasting ⩾7 days or neutropenia complicated by fever or infection) and because in this worldwide study, some centres lacked expertise in pro-active management of AEs [22]. The crucial role of adequate patient care was highlighted by a post hoc analysis limited to French TROPIC centres (90 patients in total) where proactive management of side-effects was required [23]. In this sub-study, the discontinuation rate due to AEs with cabazitaxel was lower than in the global TROPIC population (11% versus 18%) and there was no death due to toxicity, resulting in a greater OS benefit versus mitoxantrone (18.0 months versus 14.3 months).

The TROPIC results led to the establishment of compassionate-use programmes (CUPs) and early-access programmes (EAPs) in 30 countries worldwide, allowing access to the drug before its commercial availability. An awareness programme for physicians and nurses on the pro-active management of AEs related to cabazitaxel was implemented in each centre. Results from the German CUP and the Italian EAP have already been published [24,25]. Compared to TROPIC, there was a consistently lower rate of febrile neutropenia (Germany 1.8%; Italy 5% versus 8% in TROPIC) and grade ⩾3 diarrhoea (Germany 0.9%; Italy 2.8% versus 6% in TROPIC) [1,24,25], demonstrating the benefits of pro-active measures to reduce the incidence and severity of cabazitaxel-related AEs. In this paper, we report the preliminary safety results of the European CUPs/EAPs. In the interest of patients, the safety analysis focuses particularly on the senior adult patients (aged 70–74 and ⩾75 years) as this population is at increased risk of chemotherapy-induced AEs due to associated comorbidities [26].

2. Materials and methods

The European CUP/EAP allowed patients with mCRPC that had progressed during or after docetaxel to access cabazitaxel before its commercial availability and aimed to further document the safety profile of cabazitaxel. In agreement with national regulations, no efficacy data were collected.

Men with mCRPC with documented disease progression during or after a docetaxel-containing regimen and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 were eligible. Additional inclusion criteria were signed informed consent; life expectancy of $\geqslant 3$ months; surgical or ongoing medical castration (testosterone serum levels <50 ng/dl); and adequate bone marrow, liver and renal function (neutrophils >1500/mm^3; haemoglobin >10 g/dl; platelets > 100×10^9/l; bilirubin <1 × upper limit of normal [ULN]; aspartate transaminase <1.5 × ULN; alanine aminotransferase <1.5 × ULN; creatinine <1.5 × ULN, or creatinine clearance >60 ml/min if creatinine 1.0–1.5 × ULN).

Ineligibility criteria included prior radiotherapy to $\geqslant 40\%$ of bone marrow; prior radionuclide therapy with samarium-153 or P-32 within 8 weeks of enrolment or with strontium-89 or radium-223 within 12 weeks of enrolment; and prior surgery, radiation or chemotherapy within 4 weeks of enrolment. Patients were ineligible if they had active grade $\geqslant 2$ peripheral neuropathy or grade $\geqslant 2$ stomatitis; active infection requiring systemic antibiotic or anti-fungal medication; second primary cancer in the previous 5 years (except superficial non-melanoma skin cancer); and known brain or leptomeningeal involvement. Patients with hypersensitivity to docetaxel, polysorbate-80-containing drugs, prednisone or prednisolone, or an uncontrolled severe illness or medical condition (including uncontrolled cardiac arrhythmias, angina pectoris, hypertension, diabetes mellitus or a history of congestive heart failure or myocardial infarction) within the last 6 months were also excluded. A 1-week washout period was required for potent inducers of cytochrome P450 3A4/5.

2.1. Treatment modalities and follow-up

Cabazitaxel (25 mg/m^2 q3w) was provided free of charge and administered as a 1-h intravenous infusion, in combination with oral prednisone/prednisolone (10 mg daily). Patients were treated until disease progression, death, unacceptable toxicity, physician's or patient's decision to stop treatment, or commercial availability of cabazitaxel.

Patients were followed during treatment and for 30 days after last cabazitaxel administration. Most recent haematology (neutrophils, platelets, haemoglobin) before each cabazitaxel injection was collected in the case report form. Prophylactic and therapeutic use of G-CSF according to the American Society of Clinical Oncology (ASCO) and European Organisation for Research and Treatment of Cancer (EORTC) guidelines was recommended, including from cycle 1 [14,27] and an awareness programme for physicians and nurses on the pro-active management of AEs related to cabazitaxel was implemented.

2.2. Statistical analysis

Statistical analyses were mainly descriptive. The influence of selected variables (age [<70 versus 70–74 versus $\geqslant 75$], treatment cycle [1 versus >1], median time since diagnosis, presence or absence of visceral metastases, median number of prior docetaxel cycles [$\geqslant 10$ versus <10], ECOG performance status, G-CSF prophylactic use at a given cycle and neutrophil count [<4000 versus $\geqslant 4000$/mm^3] before cabazitaxel injection) on the occurrence of grade $\geqslant 3$ neutropenia and/or neutropenic complications was analysed using a Generalised Estimating Equations (GEE) model which adjusts for the clustering of treatment cycles within a patient [28]. This model offers the ability to reassess the risk of grade $\geqslant 3$ neutropenia and/or neutropenic complications before each chemotherapy cycle. Variables with a p value $\leqslant 0.25$ were kept in the final model. A multivariate logistic GEE analysis with backward selection procedure was then applied based on GICu criterion.

3. Results

3.1. Population characteristics

Up to 31 August 2011, 746 patients from 20 European countries were enrolled in the CUP/EAP. At baseline, 421 were aged <70 years, 180 were aged 70–74 years and 145 were aged $\geqslant 75$ years. Disease characteristics of the age groups, listed in Table 1, were similar in the three age groups, with expected differences in time since first diagnosis and diagnosis of metastatic disease. Around 90% had an ECOG performance status of 0–1.

The types of progression prior to cabazitaxel initiation are listed in Table 1. Approximately two-thirds of patients demonstrated clinical or radiological progression and one-third of patients demonstrated biochemical progression only. Metastases were mainly located in the bone (92%), lymph nodes (regional 32%, distant 30%) and visceral/soft tissues (28%). Overall, 16% of patients progressed during docetaxel therapy and 84% after discontinuation of docetaxel (within a median of 4.2 months).

3.2. Cabazitaxel exposure in patients having completed treatment or withdrawing from the study for any reason

Cabazitaxel exposure was analysed in 426 patients who ended treatment (Table 2). Reasons for ending of

Table 1
Characteristics of patients <70, 70–74 and ⩾75 years at baseline.

	<70 years ($n = 421$)	70–74 years ($n = 180$)	⩾75 years ($n = 145$)	Total ($n = 746$)
Mean age (years) [SD]	62.5 [5.2]	71.9 [1.5]	77.8 [2.6]	67.7 [7.5]
ECOG performance status (%)				
0	40.4	40.6	31.3	38.7
1	50.4	48.3	55.6	50.9
2	9.3	11.1	13.2	10.5
Androgen deprivation (%)				
Medical	89.3	87.2	87.6	88.5
Surgical	10.7	12.8	12.4	11.5
Median time since diagnosis of PCa (months) [Q1–Q3]	50.6 [30.5–74.7]	73.8 [46.6–110.2]	82.2 [46.5–121.3]	58.5 [36.9–93.2]
Median time since diagnosis of mCRPC (months) [Q1–Q3]	20.6 [12.8–33.7]	21.0 [13.9–39.5]	22.8 [15.2–38.1]	21.0 [13.5–36.4]
Median time from last docetaxel dose[a] (months) [Q1–Q3]	4.9 [2.4–10.2]	5.6 [2.5–10.9]	6.5 [2.3–10.9]	5.3 [2.4–10.6]
Time to progression since last docetaxel dose[a]				
During last docetaxel therapy (%)	18.5	11.8	16.0	16.4
<6 months since last docetaxel dose (%)	51.1	54.5	44.4	50.6
⩾6 months since last docetaxel dose (%)	30.5	33.7	39.6	33.0
Median time from last docetaxel dose[a] to first cabazitaxel dose (months) [Q1–Q3]	5.2 [2.7–10.4]	6.0 [2.8–11.7]	6.7 [2.6–11.4]	5.6 [2.7–10.8]
Metastatic sites (%)				
Bone	91.9	94.4	87.6	91.7
Regional lymph nodes	32.1	29.4	32.9	31.6
Distant lymph nodes	27.8	35.0	30.6	30.1
Visceral	24.9	23.4	28.9	25.3
Type of progression prior to cabazitaxel initiation (%)				
Bone scan	39.7	45.0	34.5	39.9
Clinical progression (worsening of symptoms or cancer pain)	34.2	24.4	24.8	30.0
PSA progression only	30.2	29.4	33.1	30.6
Measurable lesions	20.9	30.6	26.9	24.4
Median number of cycles during last docetaxel line [Q1–Q3]	9.0 [6.0–10.0]	8.0 [6.0–10.0]	8.0 [6.0–12.0]	8.0 [6.0–10.0]
Cumulative doses of previous docetaxel treatment (mg/m^2)				
Mean [SD]	748.2 [438.5]	684.3 [502.9]	789.7 [610.1]	740.7 [492.7]
Median [Q1–Q3]	675.0 [450.0–900.0]	600.0 [450.0–805.0]	600.0 [450.0–840.0]	600.0 [450.0–840.0]
Previous docetaxel dose >900 mg/m^2 (%)	26.2	21.1	24.3	24.6

ECOG = Eastern Cooperative Oncology Group; mCRPC = metastatic castration-resistant prostate cancer; PCa = prostate cancer; PSA = prostate-specific antigen; SD = standard deviation.
[a] The last docetaxel dose was defined as the date of the last intravenous administration of docetaxel.

Table 2
Cabazitaxel exposure in patients having completed therapy or withdrawing from the study for any reason.

	<70 years ($n = 238$)	70–74 years ($n = 100$)	⩾75 years ($n = 88$)	Total ($n = 426$)
Median number of cabazitaxel cycles [range]	4.0 [1–16]	4.0 [1–12]	4.0 [1–11]	4.0 [1–16]
Dose delay for AEs possibly related to cabazitaxel (%)	14.3	13.0	5.7	12.2
Dose reduction for any cause (%)	18.5	16.0	15.9	17.4
Median relative dose intensity (%)	98.9	98.9	99.1	98.9

AEs = adverse events.

therapy were disease progression (38.4%), adverse event (26.1%), cabazitaxel becoming commercially available (18.6%), investigator decision (8.5%) or other reason (8.6%), Patients who were switched to commercially available drug continued to be treated until disease progression or significant toxicity but subsequent cycles were no longer collected in the case report form. A median of four cycles (range 1–16) of cabazitaxel was administered within a median duration of 12 weeks. At the time of analysis (31st August 2011), 36% of patients aged <70 years, 35% of patients aged 70–74 years and 29% of patients aged ⩾75 years had received six cycles

Table 3
Most common treatment emergent adverse events (classified by decreased order of all grade toxicities in men aged ⩾75 years).

Toxicity	<70 years ($n = 421$)		70–74 years ($n = 180$)		⩾75 years ($n = 145$)		Total ($n = 746$)	
	All grades	Grade ⩾3	All grades	Grade ⩾3	All grades	Grade ⩾3	All grades	Grade ⩾3
Haematological (%)								
Neutropenia	17.8	15.0	19.4	16.7	26.2	23.4	19.8	17.0
Anaemia	20.9	5.0	22.8	4.4	22.1	4.1	21.6	4.7
Leukopenia	9.5	6.2	11.7	8.3	12.4	9.7	10.6	7.4
Febrile neutropenia	5.5	5.2	5.6	5.6	5.5	5.5	5.5	5.4
Thrombocytopenia	5.0	1.4	3.9	0.6	4.8	0.7	4.7	1.1
Neutropenic sepsis	1.0	1.0	1.7	1.7	1.4	1.4	1.3	1.3
Non-haematological (%)								
Diarrhoea	34.9	3.3	32.2	1.7	36.6	2.8	34.6	2.8
Fatigue	24.5	4.0	27.8	3.3	24.1	5.5	25.2	4.2
Asthenia	13.5	1.4	20.0	4.4	22.8	5.5	16.9	2.9
Nausea	25.4	0	16.7	0.6	19.3	3.4	22.1	0.8
Decreased appetite	12.1	0.5	15.6	1.7	15.2	0.7	13.5	0.8
Vomiting	16.6	1.0	15.6	1.1	10.3	2.1	15.1	1.2
Constipation	13.5	0	12.2	0.6	11.7	0	12.9	0.1
Urinary tract infection	7.8	1.7	5.0	1.1	9.7	2.8	7.5	1.7
Dysgeusia	5.5	0	3.3	0	7.6	0.7	5.8	0.1
Haematuria	6.2	0.5	11.1	2.8	6.9	1.4	7.5	1.2
Back pain	8.8	1.4	5.6	0	6.9	0	7.6	0.8
Peripheral oedema	1.0	0	3.3	0	5.5	0	2.9	0
Bone pain	9.5	1.2	5.0	0.6	4.1	1.4	7.4	1.1
Dyspnoea	4.3	0.7	7.2	1.1	4.1	1.4	5.0	0.9
Alopecia	3.8	0	2.2	0	3.4	0.7	3.4	0.1
Peripheral neuropathy	5.2	0	3.9	0	2.8	0.7	4.4	0.1
Nail disorders[a]	1.0	0	1.1	0	2.1	0	1.2	0

[a] Includes nail changes, nail decolouration, nail dystrophy, onychoclasis, onycholysis, onychomadesis.

Table 4
G-CSF use during therapy.

	<70 years ($n = 421$)	70–74 years ($n = 180$)	⩾75 years ($n = 145$)	Total ($n = 746$)
G-CSF use at cycle 1 (%)	47.0	57.2	60.0	52.0
Primary prophylaxis	39.2	46.1	50.3	43.0
Therapeutic use	5.5	6.1	6.9	5.9
Primary prophylaxis and therapeutic use	2.4	5.0	2.8	3.1
G-CSF use at any cycle during the trial (%)	58.0	67.8	65.5	61.8
Primary prophylaxis	52.3	58.9	58.6	55.1
Therapeutic use	7.8	9.4	10.3	8.7
Primary prophylaxis and therapeutic use	5.2	7.2	6.2	5.9

G-CSF = granulocyte colony-stimulating factor.

or more. The median relative dose intensity was 99% in all groups. The percentage of patients experiencing dose delays for treatment-emergent AEs (TEAEs) possibly related to cabazitaxel (<70 years, 14.3%; 70–74 years, 13.0%, ⩾75 years, 5.7%) and dose reductions for any cause (<70 years, 18%; 70–74 years, 16.0%; ⩾75 years, 15.9%) did not increase with age.

3.3. Safety overview

The overall incidence of TEAEs was similar between the three groups (<70 years, 88%; 70–74 years 90.5%, ⩾75 years, 88.3%). Grade ⩾3 toxicities, related or not to cabazitaxel, occurred in 47% of men aged <70 years, 50% of men aged 70–74 years and 56.6% of men aged ⩾75 years. Treatment discontinuations due to TEAEs occurred in 13.3% of men aged <70 years, 17.2% of men aged 70–74 years and 21.4% of men aged ⩾75 years. Eight patients aged <70 years (1.9%) and eight patients aged ⩾70 years (2.5%) experienced TEAEs possibly related to cabazitaxel that led to death. In seven cases (three aged <70 years, one aged 70–74 years and three aged ⩾75 years) death was related to neutropenia or its complications (febrile neutropenia, neutropenic infection or sepsis), which occurred mainly at cycle 1 ($n = 6$) in patients who did not receive G-CSF prophylaxis ($n = 5$). In six other cases (four aged <70 years and two aged ⩾75 years), death was consecu-

Table 5
Predictive factors for grade ⩾3 neutropenia, febrile neutropenia or neutropenic sepsis.

Predictive factor	OR (95% CI)[b]	*p* Value
Univariate analysis		
Age (70–74 versus <70 years)[a]	1.12 (0.75–1.67)	0.578
Age (⩾75 versus <70 years)[a]	1.65 (1.11–2.45)	0.014
Cycle 1 versus cycle >1[a]	6.12 (4.73–7.92)	<0.0001
Prior docetaxel cycles (⩾10 versus <10)[a]	0.76 (0.55–1.06)	0.107
ECOG performance status (1 versus 0)	0.84 (0.60–1.19)	0.331
ECOG performance status (2 versus 0)	0.68 (0.36–1.29)	0.234
G-CSF prophylaxis at a given cycle[a]	0.63 (0.45–0.88)	0.007
Time since initial diagnosis (⩾59.6 versus <59.6 months)	0.96 (0.69–1.34)	0.818
Neutrophils at previous cycle (<4.0 versus ⩾4.0 giga/l)[a]	2.19 (1.61–2.98)	<0.0001
Visceral metastatic site(s) (at least one)	0.91 (0.61–1.35)	0.643
Multivariate analysis		
Age (70–74 versus <70 years)	1.08 (0.70–1.64)	0.733
Age (⩾75 versus <70 years)	1.66 (1.09–2.52)	0.018
Cycle 1 versus cycle >1	5.16 (3.92–6.79)	<0.0001
Prior docetaxel cycles (⩾10 versus <10)	0.77 (0.54–1.09)	0.140
G-CSF prophylaxis at given cycle	0.70 (0.49–0.99)	0.042
Neutrophils at previous cycle (<4.0 versus ⩾4.0 giga/l)	1.73 (1.25–2.39)	0.0008

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; G-CSF = granulocyte colony-stimulating factor; GEE = generalised estimating equation; OR = odds ratio.
[a] Variables retained after initial univariate process (*p* value ⩽0.25).
[b] Univariate ORs were estimated via a simple logistic GEE regression. Multivariate ORs were estimated via a multivariate logistic regression using data from patients with available data for all parameters ($n = 732$).

tive to infections—half of these occurred at cycle 1, there was no concomitant neutropenia, and in five of the six cases the patient received prophylactic G-CSF.

3.4. Most common TEAEs

The most common haematological and non-haematological TEAEs are listed in Table 3. Overall, any grade diarrhoea (35%), fatigue (25%), nausea (22%), anaemia (22%) and neutropenia (20%) were the most common TEAEs. Grade ⩾3 toxicities were mainly haematological (neutropenia 17%, leukopenia 7%, febrile neutropenia 5% and anaemia 5%). Main non-haematological grade ⩾3 toxicities were fatigue (4.2%), asthenia (2.9%) and diarrhoea (2.8%). Grade ⩾3 peripheral neuropathy, alopecia and nail disorders were uncommon (0.1%). No major difference between age groups was observed, but prophylactic use of G-CSF was more common in patients aged ⩾70 years than in younger patients (Table 4).

3.5. Analysis of predictive factors for grade ⩾3 neutropenia and neutropenic complications

In univariate analysis, predictors of grade ⩾3 neutropenia and/or neutropenic complications (febrile neutropenia and neutropenic sepsis) were advanced age (⩾75 years), first cabazitaxel cycle, no G-CSF prophylaxis at a given cycle, neutrophil count <4000/mm^3 before cabazitaxel injection and less than 10 prior cycles of docetaxel (Table 5).

Except for the number of prior docetaxel cycles, a multivariate analysis with backward selection procedure confirmed the predictive value of these factors (Table 5). First cabazitaxel cycle was associated with a five-times increased risk of grade ⩾3 neutropenia and/or neutropenic complications (OR 5.16, $p < 0.0001$), followed by neutrophil count <4000/mm^3 (OR 1.73, $p = 0.0008$) and age ⩾75 years (OR 1.66, $p = 0.018$). Even in the presence of these factors, prophylaxis with G-CSF at a given cycle significantly reduced the risk of grade ⩾3 neutropenia and/or neutropenic complications by 30% (OR 0.70, $p = 0.04$).

4. Discussion

Results and analysis of this large European CUP/EAP, which included 746 older patients with mCRPC progressing during or after docetaxel, suggest that cabazitaxel has a manageable safety profile. In this population of rather fit elderly men (only 10.5% had an ECOG performance status of 2), dose intensity, dose delays for AEs possibly related to cabazitaxel and dose reductions for any cause, in men aged 70–74 years and ⩾75 years, were similar to those in younger patients. Diarrhoea, the most common non-haematological AE reported with cabazitaxel, was usually mild in severity, with grade ⩾3 occurring in only 2% of patients.

Chemotherapy-associated neutropenia is a particular concern in the elderly [29]. The EORTC has published guidelines for the management of neutropenia, including an algorithm based on evaluation of predisposing factors, to determine if prophylactic G-CSF should be offered to the individual patient [27]. Evaluation of the need for G-CSF should be repeated at each treatment

Table 6
Rates of key adverse events in the TROPIC trial and the European compassionate-use programmes (CUP)/expanded-access programmes (EAP).

Toxicity	TROPIC [1]				European CUP/EAP	
	Mitoxantrone ($n = 371$)		Cabazitaxel ($n = 371$)		Cabazitaxel ($n = 746$)	
	All grades	Grade ⩾3	All grades	Grade ⩾3	All grades	Grade ⩾3
Haematological (%)						
Neutropenia	88	58	94	82	19.8	17.0
Anaemia	81	5	97	11	21.6	4.7
Leukopenia	92	42	96	68	10.6	7.4
Febrile neutropenia	–	1	–	8	5.5	5.4
Thrombocytopenia	43	2	47	4	4.7	1.1
Non-haematological (%)						
Diarrhoea	11	<1	47	6	34.6	2.8
Fatigue	27	3	37	5	25.2	4.2
Asthenia	12	2	20	5	16.9	2.9
Nausea	23	<1	34	2	22.1	0.8
Vomiting	10	0	23	2	15.1	1.2
Constipation	15	1	20	1	12.9	0.1
Haematuria	4	2	17	2	7.5	1.2
Urinary tract infection	3	1	7	1	7.5	1.7
Bone pain	5	2	5	1	7.4	1.1
Back pain	12	3	16	4	7.6	0.8
Dyspnoea	5	1	12	1	5.0	0.9
Peripheral neuropathy	–	1	–	1	4.4	0.1
Alopecia	4.9	0	10	0	3.4	0.1
Nail and nail-bed conditions	4	0	3.5	0	1.2	0

cycle. Similar recommendations have been issued by the National Comprehensive Cancer Network (NCCN) and ASCO [13,14]. Accordingly, prophylactic G-CSF use was more common in patients aged ⩾70 years in the European CUP/EAP. In such conditions, haematological tolerability of cabazitaxel appeared similar to younger counterparts.

We conducted a multivariate analysis to identify clinical variables associated with an increased risk of grade ⩾3 neutropenia and/or neutropenic complications, according to a cycle-based prediction model developed by Dranitsaris and colleagues that enables reassessment of the risk at each additional chemotherapy cycle [28]. Data have shown that the risk of neutropenic complications is higher at chemotherapy initiation, and decreases with subsequent cycles [30]. In agreement with the literature [27], we observed that advanced age (⩾75 years) was an independent predictor of grade ⩾3 neutropenia and/or neutropenic complications. The finding that first cabazitaxel cycle is associated with a fivefold higher risk of developing grade ⩾3 neutropenia and/or neutropenic complications, especially when there is a neutrophil count <4000/mm^3 before cabazitaxel injection, is a strong rationale for using prophylactic G-CSF in older patients with advanced mCRPC. This is in agreement with a pilot analysis of predictive factors for neutropenia in the Italian EAP, which found that the use of prophylactic G-CSF reduced the risk of grade 3 neutropenia sevenfold [31].

The results of this interim analysis extend the knowledge of the safety profile reported in TROPIC to a setting that is more reflective of everyday clinical practice, especially for senior adults [1]. Table 6 lists the rates of key haematological and non-haematological AEs in the TROPIC trial and, from this preliminary European CUP/EAP analysis. This table is provided for information only, since both studies cannot be compared for several reasons: (1) It is possible that the patients included in the TROPIC trial and CUP/EAP had a different disease burden, (2) TROPIC was conducted in 26 countries in Europe, North America, Latin America, India, Asia and South Africa, and it appears that some centres were not sufficiently experienced in monitoring and managing the toxicities of chemotherapy. (3) Haematology was monitored on a weekly basis in TROPIC while it was collected before each injection in the European CUP/EAP in order to reflect real-life practice (4) Prophylactic G-CSF at the first cabazitaxel cycle was not allowed in TROPIC (it was allowed at physicians' discretion after first occurrence of either neutropenia lasting 7 days or more or neutropenia complicated by fever or infection) [1] while in the European CUP/EAP, prophylactic G-CSF was allowed from the first cycle, as per ASCO and EORTC guidelines [14–27]. The lower rate of AEs in this large European cohort may also be partly attributed to the physician and nurse awareness programme for proactive management of AEs related to cabazitaxel which was systematically implemented in all CUP/EAP centres. It has been shown that the optimal oncological care of older men with prostate cancer, including effective prevention, early reporting, and management of the disease and

treatment-related side-effects, can prolong survival, improve quality of life, and reduce depressive symptoms and treatment discontinuations [32,33]. The TROPIC centres in France incorporated a number of pro-active measures—analysis of outcomes of the 90 patients enrolled in these centres evidenced a lower discontinuation rate due to AEs compared with the overall TROPIC population and no death associated with therapy, possibly contributing to a greater survival benefit [23]. The importance of proactive AE management was also confirmed by results of the German CUP, which included patients with more advanced and heavily pretreated disease than in the TROPIC trial [24]. Grade $\geqslant 3$ haematological toxicity and febrile neutropenia were observed in only 21% and 2% of patients in the German CUP, respectively. Patients had been intensively counselled about symptoms necessitating early readmission to hospital, and informed about the probability of diarrhoea and the initial management measures to be implemented at home. However, there is still room for improvement in order to further decrease the 2.1% death rate, mainly due to infections and/or neutropenic complications, reported in this CUP/EAP. Administration of chemotherapy in well-trained centres, adequate patient selection, guidance and information are all important measures which should help to achieve this goal [34].

Accumulating evidence from CUPs/EAPs indicate that real-world toxicity of cabazitaxel is less than that experienced in the TROPIC trial and is manageable with appropriate prophylactic and supportive care measures, even in older patients. The importance of such measures should not be underestimated, especially in older men heavily pretreated for advanced prostate cancer who may be vulnerable to treatment complications or side-effects.

5. Conclusion

The preliminary results of this large European CUP/EAP show that the AE profile is manageable in routine practice in both younger (<70 years) and elderly patients (70–74 years and $\geqslant$75 years) with mCRPC. Prophylactic G-CSF use was more common in older men, as normally recommended by international guidelines—in such conditions, haematological tolerability of cabazitaxel appears similar to younger counterparts. In multivariate analysis, age $\geqslant$ 75 years, treatment cycle 1 and a neutrophil count <4000/mm^3 before cabazitaxel injection were associated with an increased risk of developing grade $\geqslant 3$ neutropenia and/or neutropenic complications. In the presence of these factors, G-CSF significantly reduced this risk by 30%. These results underline the importance of adequate proactive management of AEs, including G-CSF prophylaxis, and patient follow up, to improve the tolerability of cabazitaxel in the real-world setting. These supportive care measures should ultimately contribute to improved patient outcomes.

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