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Lack of Cumulative Toxicity Associated With Cabazitaxel Use in Prostate Cancer

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Abstract: Cabazitaxel provided a survival advantage compared with mitoxantrone in patients with castration-resistant prostate cancer refractory to docetaxel. Grade 3 to 4 (G3–4) neutropenia and febrile neutropenia were relatively frequent in the registrative XRP6258 Plus Prednisone Compared to Mitoxantrone Plus Prednisone in Hormone Refractory Metastatic Prostate Cancer (TROPIC) trial, but their incidence was lower in the Expanded Access Program (EAP). Although cumulative doses of docetaxel are associated with neuropathy, the effect of cumulative doses of cabazitaxel is unknown. In this retrospective review of prospectively collected data, the authors assessed “per cycle” incidence and predictors of toxicity in the Italian cohort of the EAP, with a focus on the effect of cumulative doses of cabazitaxel.

The study population consisted of 218 Italian patients enrolled in the cabazitaxel EAP. The influence of selected variables on the most relevant adverse events identified was assessed using a Generalized Estimating Equations model at univariate and multivariate analysis.

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“Per cycle” incidence of G 3 to 4 neutropenia was 8.7%, whereas febrile neutropenia was reported in 0.9% of cycles. All events of febrile neutropenia occurred during the first 3 cycles. Multivariate logistic regression analysis showed that higher prior dose of cabazitaxel was associated with decreased odds of having G3 to 4 neutropenia (OR = 0.90; 95% CI: 0.86–0.93; $P < 0.01$), febrile neutropenia (OR = 0.52; 95% CI: 0.34–0.81; $P < 0.01$) and G3 to 4 anemia (OR = 0.93; 95% CI: 0.86–1; $P = 0.07$). Patients with a body surface area $>2\text{ m}^2$ presented increased odds of having G 3 to 4 neutropenia (OR = 0.93; 95% CI: 0.86–1; $P = 0.07$), but decreased odds of having G3 to 4 anemia.

Among the toxicities assessed, the authors did not identify any that appeared to be associated with a higher number of cabazitaxel cycles delivered. Prior cumulative dose was associated with reduced G3 to 4 neutropenia and anemia. The apparent protective effect associated with higher doses of cabazitaxel is likely to be affected by early dose reduction and early toxicity-related treatment discontinuation. Because this analysis is limited by its retrospective design, prospective trials are required to assess the optimal duration of cabazitaxel treatment.

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Abbreviations: CRPC = castration-resistant prostate cancer, EAP = Expanded Access Program, G-CSF = granulocyte colony-stimulating factor, GEE = Generalized Estimating Equations, IR = interquartile range.

BACKGROUND

Several agents provide a survival advantage and symptom palliation in patients with docetaxel-refractory, metastatic castration-resistant prostate cancer (CRPC).^{1,2} These agents include cabazitaxel, enzalutamide, abiraterone, and radium 223.^{1,2} Presently, the treatment choice is influenced by several factors, including physician's and patient's preference, drug availability, reimbursement policies, performance status, organ function, as well as expected toxicity profile, but comparative efficacy data are lacking. Similarly to other taxane agents, cabazitaxel is frequently associated with bone marrow toxicity. In the XRP6258 Plus Prednisone Compared to Mitoxantrone Plus Prednisone in Hormone Refractory Metastatic Prostate Cancer (TROPIC) trial,³ grade (G) 3–4 neutropenia and febrile neutropenia were reported in 82% and 8% of patients treated with cabazitaxel, respectively, whereas these adverse events were respectively reported in 33.9% and 5% of the Italian patients enrolled in the Expanded Access Program (EAP).⁴ Conversely, G3 to 4 neuropathy was a rare event both in the TROPIC and in the EAP study.^{3–5} To further analyze the safety profile of cabazitaxel, we retrospectively reviewed prospectively collected data about the most common toxicities reported in the Italian cohort of the EAP. “Per cycle,” rather than “per patient” incidence was computed, and an explorative analysis

was performed to investigate potential predictors of toxicity. In view of the risk of cumulative toxicity (neuropathy) associated with docetaxel,⁶ the effect of prior cumulative dose of cabazitaxel was investigated in a multivariable model along with other potential predictive factors.

METHODS

Study Population and Treatment

The study population consisted of 218 Italian patients included in the cabazitaxel Expanded Access Protocol, a prospective, open-label, single-arm clinical trial in mCRPC patients progressing after or during a docetaxel-based regimen (EudraCT number: 2010-021128-92). Patients were enrolled between January 2011 and February 2012. Eligibility, study treatment, and characteristics of the patients have already been published.⁴ At the time of the data analysis, 216 patients had either completed or discontinued study treatment.

Data Retrieval

The study database was accessed on 5th July 2013. The following data of each individual patient were extracted: age, weight, height, ECOG (Eastern Cooperative Oncology Group) performance status, previous cumulative dose of docetaxel received, duration of metastatic disease, presence of visceral metastases, reason for treatment discontinuation. The following data of each individual cycle administered were extracted: neutrophils, platelets, and hemoglobin levels at the time of cabazitaxel administration, prophylactic use of G-CSF (granulocyte colony-stimulating factor), total dose of cabazitaxel administered. The following toxicities associated with each chemotherapy cycle were extracted: neutropenia G3 to 4, anemia G3 to 4, thrombocytopenia G3 to 4, febrile neutropenia, fatigue/asthenia G2, fatigue/asthenia G3 to 4, vomiting G2, vomiting G3 to 4, diarrhea G2, diarrhea G3 to 4 (Table 1).

Statistical Analysis

Body surface area was computed using the Mosteller formula ($\text{height (cm)} \times \text{weight (kg)} / 3600$)^{1/2}. Body mass index was computed by dividing weight (kg) by height² (m²). Incidence per cycle of adverse events was computed by dividing the total per cycle number of events by the number of cycles. A univariable and multivariable analysis was performed to explore predictors of selected toxicities. A Generalized Estimating Equations (GEE) model was employed to adjust for the clustering of treatment cycles within a patient. After

TABLE 1. Toxicities Associated With Each Chemotherapy Cycle that Were Extracted

Neutropenia G3–4
Anemia G3–4
Thrombocytopenia G3–4
Febrile neutropenia
Fatigue/asthenia G2
Fatigue/asthenia G3–4
Vomiting G2
Vomiting G3–4
Diarrhea G2
Diarrhea G3–4

initial GEE univariate analysis, only variables with a *P* value <0.25 were used in the multivariate analysis. Adverse events were included in the univariate and multivariate analysis if they presented an incidence per cycle of ~1% or more. Multivariate logistic regression analysis was performed using a backward selection procedure. Variables with a *p* value <0.1 were considered statistically significant in the multivariate analysis and reported. All results are to be considered hypothesis generating and require independent validation. All analyses were performed using SPSS 22.0.

RESULTS

Treatment

At the time of the analysis, 1494 cycles had been administered to 218 patients included in the entire cohort, whereas a total of 553 cycles had been administered to 61 patients with a body surface area >2 sqm. Patients were administered a median of 6.0 (interquartile range: IR, 4–10) cycles. The median dose delivered was 24.00 mg/sqm (IR: 22.3–24.7). Each patient received a median cumulative dose of 149.9 mg/sqm (IR: 92.8–232.2). Sixty-four patients (29.6%) received at least 10 cycles (Table 2). Primary G-CSF prophylaxis was administered in 87 patients (39.9%), whereas G-CSF secondary prophylaxis was administered in 76 patients (34.8%). Therapy was delayed in 274 cycles, which was because of cabazitaxel toxicity only in 65 (23.7%) of these. Dose was reduced 52 times (Table 2), and in 45 cases dose reduction was because of cabazitaxel adverse events. In the safety population, the main reason for treatment discontinuation was disease progression (43.1%), followed by adverse event (24.5%) and physician's decision (18.5%). Of note, in the subgroup of 64 patients receiving at least 10 cycles, 51.6% discontinued cabazitaxel because of investigator's decision, and only 1 patient (1.6%) discontinued for toxicity (Table 3).

TABLE 2. Patients Requiring First Dose Reduction and Receiving Cabazitaxel Treatment

Cycle n°	Patients Requiring First Dose Reduction		Patients Receiving Cabazitaxel	
	n	%	n	%
1	–		218	100
2	15	28.8	199	91.2
3	6	11.5	182	83.4
4	8	15.3	169	77.5
5	8	15.3	151	69.2
6	12	23.0	127	58.2
7			102	46.7
8	1	1.9	88	40.3
9	1	1.9	80	36.6
10			64	29.3
11			38	17.4
12			29	13.3
13			22	10.0
14	1	1.9	13	5.9
15			7	3.2
16			4	1.8
17			1	0.4

TABLE 3. Reasons for Treatment Discontinuation in the Whole Population (N=218) and in Patients Who Received ≥10 Cycles (n=64)

Reason for Treatment Discontinuation	Whole Population (N=218) n (%)	Patients ≥10 Cycles (N=64) n (%)
Disease progression	93 (42.6)	17 (26.5)
Death	0 (0)	0 (0)
Adverse event	53 (24.3)	1 (1.5)
Physician/investigator's decision	40 (18.3)	33 (51.5)
Other	30 (13.7)	13 (20.3)
Missing	2 (0.91)	0 (0)

Safety

Overall incidence of toxicity per cycle is detailed in Table 4. Main G3 to 4 hematologic toxicities were neutropenia and anemia. The “per cycle” incidence rate of G3 to 4 neutropenia was 8.7%, whereas febrile neutropenia occurred only in 0.9% of all cycles and it was an early event, occurring during the first 3 cycles only (Figure 1). Main non hematologic toxicities were G2 asthenia/fatigue and G2 diarrhea, occurring in 3.7% and 0.8% of cycles, whereas G3 to 4 asthenia/fatigue and G3 to 4 diarrhea occurred in 1.8% and 0.4% of cycles. Four adverse events had a per cycle incidence >1% and were selected for univariate (Tables 5 and 6) and multivariate (Table 7) analysis GEE logistic regression analysis. Febrile neutropenia was also assessed because of its clinical relevance. Multivariate logistic regression analysis showed a significant reduction of the odds of having G3 to 4 neutropenia (−10%), febrile neutropenia (−48%) and anemia (−7%), per 10 mg/m² increase of total prior dose of cabazitaxel. A body surface area >2 m² was associated with increased odds of having G3 to 4 neutropenia (OR: 2.58; 95% CI=1.50–4.43; P<0.01), but decreased odds of having G3 to 4 anemia (OR: 0.10; 95% CI=0.02–0.52; P<0.01). Age as a continuous variable was not associated to an increased rate of any of the adverse events analyzed. Of note, higher previous dose of docetaxel appeared to be associated with a slightly, but statistically significant decreased odds of having G 3–4 anemia (OR: 0.859; 95% CI= 0.73–1.00; P=0.06), G3 to 4 neutropenia (OR: 0.95; 95% CI=0.91–0.99; P=0.03), and G2 and G3 to 4 fatigue/

TABLE 4. Overall Incidence of Toxicity per Cycle (n=1494)

Toxicity	Incidence per Cycle, n (%)
Grade 3–4 neutropenia	125 (8.3)
Grade 3–4 anemia	19 (1.2)
Febrile neutropenia	13 (0.87)
Grade 2 fatigue/asthenia	56 (3.7)
Grade 3–4 fatigue/asthenia	27 (1.8)
Grade 2 vomiting	4 (0.27)
Grade 3–4 vomiting	2 (0.13)
Grade 2 diarrhea	11 (0.7)
Grade 3–4 diarrhea	6 (0.40)
Grade 3–4 thrombocytopenia	3 (0.20)

asthenia (OR: 0.90; 95% CI=0.84–0.96; P<0.01). Twelve patients died within 30 days since last cabazitaxel treatment for causes judged to be unrelated to cabazitaxel by the local investigators. Three patients died as a result of treatment-emergent adverse events possibly related to cabazitaxel treatment. Of these 3 patients, 1 patient died after 1 cycle because of respiratory and renal failure, 1 patient died after 2 cycles because of respiratory failure and the third patient died after 3 cycles because of pancytopenia and hepatic failure.

DISCUSSION

In a cohort of 746 patients enrolled throughout Europe in the cabazitaxel EAP, G3 to 4 neutropenia, febrile neutropenia and G3 to 4 diarrhea occurred in 17%, 5.4% and 2.8% of patients, respectively.⁵ The discrepancy of these results with those obtained in the TROPIC trial has been explained by study differences in patient characteristics, frequency of *hematologic assessment*, as well as proactive management of adverse events of cabazitaxel.⁵ Dose reductions were also more frequent in the EAP compared with the TROPIC trial (17.4% versus 12%) and may also have affected the safety profile.^{4,5} Furthermore, in the EAP versus the TROPIC trial, 1% versus 2% of patients died as a result of neutropenia, respectively. In our study cohort, only 3 deaths (≈1.3%) possibly related to cabazitaxel treatment were reported, whereas 12 patients died within 30 days since the last cabazitaxel dose for reasons, which were definitely judged to be unrelated to cabazitaxel by the local investigator. Treatment delay, which was reported in 274 cycles, was because of cabazitaxel toxicity approximately only in one-fourth of cases and to “other causes” in 180 cases. This finding may be related to the influence of logistic reasons (eg, waiting list) or patient’s compliance as a common cause of treatment delay. Dose reduction, which was reported in 52 cases, was mainly because of cabazitaxel adverse events. Ongoing phase III trials are assessing whether lower doses of cabazitaxel are equally effective and better tolerated than higher doses.⁷ In the analysis of our study cohort, the dose of 25 versus 20 mg/m² was associated with increased risk of G3 to 4 neutropenia (OR=1.8; CI=1.0–3.55; P=0.049) in the multivariable model, but this result is likely to be confounded by patients who received the 25 mg/m² dose and then permanently interrupted treatment for toxicity. Differently from the results obtained in other series,^{5,8} we have not found the use of G-CSF to be associated with decreased incidence of G3 to 4 neutropenia, possibly because frailer patients are both more likely to experience G 3–4 neutropenia and to receive G-CSF prophylaxis. Similarly to the results obtained in the work by Heidenreich et al,⁸ we found that prior cumulative dose of docetaxel was associated with lower odds of G3 to 4 neutropenia. Reintroduction of docetaxel was reported to be a feasible option in selected patients, although docetaxel rechallenge is not supported by randomized-controlled trials.^{9,10} A favorable association of prior cumulative dose of docetaxel with G3 to 4 anemia and G 2–4 asthenia/fatigue was also reported, along with an overall low “per cycle incidence” of febrile neutropenia and G3 to 4 diarrhea and neutropenia. These toxicities do not recur throughout the course of the treatment in most of the cases. Higher prior cumulative dose of cabazitaxel was associated with lower risk of G3 to 4 neutropenia and febrile neutropenia, and the majority of G3 to 4 events of bone marrow toxicity occurred during the first 5 cycles. Heidenreich et al⁵ compared toxicities associated with first versus subsequent doses and reported higher odds of severe neutropenia at the first cycle versus

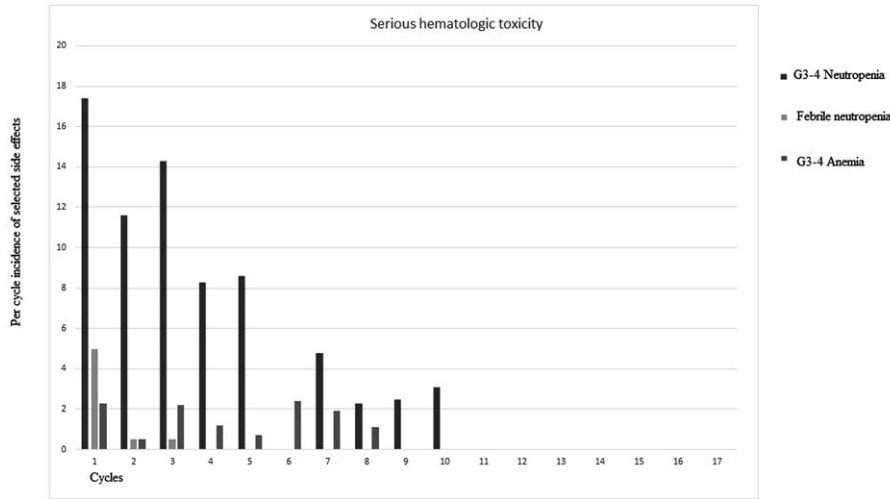


FIGURE 1. Per cycle incidence rate of G3 to 4 hematologic events expressed as a percentage.

subsequent cycles. This result is consistent with existing data.¹¹ In our work, we found no evidence of cumulative toxicity for any of the adverse events considered in a multivariable model assessing their association with prior cumulative dose of cabazitaxel. In this regard, it is noteworthy that of the 64 patients receiving at least 10 cycles, only 1 (1.5%) had to interrupt treatment because of toxicity and approximately 50% (33 patients, 51.6%) suspended treatment because of investigator’s decision. Although continuation of docetaxel after 10 cycles does not appear to yield any benefit,¹² the optimal duration of cabazitaxel treatment in nonprogressive patients is unknown.

No studies have been specifically conducted to assess the additional benefit associated with continuation of cabazitaxel treatment beyond 10 cycles. Nevertheless, the risk of rapidly

progressive disease following cabazitaxel interruption must be carefully considered and discussed with the patient, especially in those with high disease burden who may experience clinical deterioration and be unable to resume systemic therapy.¹³ We also reported that patients with a body surface area greater than 2 m² showed an OR of 2.58 for G3 to 4 neutropenia, but an OR of 0.1 for G3 to 4 anemia. We are unable to provide an explanation for this finding at the present time.

Our analysis has a number of limitations, including its retrospective nature, the arbitrary selection of the variables included in the multivariable model, the lack of sample size calculation, as well as the lack of assessment of peripheral neuropathy, which is a clinically relevant adverse event in patients receiving chemotherapy after first-line docetaxel^{6,14}.

TABLE 5. Odds Ratio and 95% Confidence Intervals From Univariate Analysis for Grade 3 to 4 Neutropenia, Febrile Neutropenia, and Grade 3 to 4 Anemia

Variable	Grade 3–4 Neutropenia			Febrile Neutropenia			Grade 3–4 Anaemia		
	Odds Ratio	95% CI	P	Odds Ratio	95% CI	P	Odds Ratio	95% CI	P
Age (y)	1.00	0.97–1.03	0.65	1.03	0.94–1.12	0.457	0.93	0.89–0.98	0.01
ECOG PS (1–2 versus 0)	0.97	0.55–1.69	0.91	0.87	0.22–3.34	0.83	4.18	1.22–14.32	0.02
Prior docetaxel treatment (per 100 mg/m ²)	0.95	0.91–0.99	0.02	0.96	0.84–1.1	0.57	1.12	0.99–1.27	0.05
Duration of metastatic disease (mo)	1.00	0.91–1.01	0.48	1.00	0.99–1.02	0.51	0.97	0.94–1.03	0.09
Visceral metastasis (yes versus no)	0.86	0.49–1.52	0.62	0.92	0.24–3.40	0.91	1.70	0.51–6.16	0.35
Neutrophils (10 ⁹ /L)	1.01	0.95–1.08	0.61	0.94	0.78–1.12	0.51	1.03	0.97–1.08	0.24
Platelets (10 ⁹ /L)	0.98	0.95–1.00	0.14	1.01	0.98–1.04	0.41	1.00	0.93–1.07	0.98
Hb (g/dL)	0.99	0.96–1.02	0.74	1.02	1.00–1.04	0.08	0.68	0.58–0.81	0.01
Prophylactic use of G-CSF (yes versus no)	1.38	0.80–2.30	0.24	0.79	0.21–2.99	0.73	0.89	0.26–3.00	0.44
Dose of cabazitaxel used (per 5 mg/m ²)	1.41	0.82–2.41	0.20	2.60	0.29–23.00	0.39	1.05	0.44–2.5	0.9
Prior dose of cabazitaxel (per 10 mg/m ²)	0.90	0.86–0.93	0.01	0.52	0.34–0.81	0.01	0.92	0.85–0.99	0.02
BSA > versus <2 m ²	2.00	1.13–3.42	0.01	1.30	0.37–4.70	0.65	0.14	0.1–0.86	0.03
BMI	1.02	0.96–1.07	0.45	0.97	0.86–1.10	0.70	1.06	0.93–1.20	0.34

Odds ratio is computed per unit increase in continuous variables unless otherwise specified. Variables with a P value <0.25 were included in the multivariate analysis and are in bold.

BMI = body mass index, BSA = body surface area, CI = confidence interval, ECOG PS = Eastern Cooperative Oncology Group performance status, Hb = hemoglobin.

TABLE 6. Odds Ratio and 95% Confidence Intervals From the Univariate Analysis for Grade 2 Fatigue/Asthenia and Grade 3–4 Fatigue/Asthenia

Variable	Grade 2 Fatigue/Asthenia			Grade 3–4 Fatigue/Asthenia		
	Odds Ratio	95% CI	P	Odds ratio	95% CI	P
Age (y)	0.98	0.94–1.02	0.36	0.98	0.94–1.03	0.51
ECOG PS (1–2 versus 0)	3.09	1.36–7.01	0.01	1.57	0.59–4.19	0.36
Prior docetaxel treatment (per 100 mg/m ²)	0.91	0.86–0.97	0.01	0.90	0.84–0.96	0.01
Duration of metastatic disease (mo)	1.00	0.97–1.02	0.98	1.00	0.99–1.02	0.37
Visceral metastasis (yes versus no)	1.10	0.51–2.70	0.68	0.40	0.17–1.20	0.11
Neutrophils (10 ⁹ /L)	0.98	0.89–1.08	0.78	0.89	0.73–1.10	0.29
Platelets (10 ⁹ /L)	1.02	0.99–1.06	0.11	1.01	0.97–1.05	0.46
Hb (g/dL)	0.90	0.75–1.08	0.28	0.90	0.69–1.16	0.42
Prophylactic use of G-CSF (yes versus no)	0.51	0.22–1.18	0.11	0.87	0.32–2.30	0.28
Dose of cabazitaxel used (per 5 mg/m ²)	0.72	0.42–1.20	0.21	1.70	0.53–5.60	0.36
Prior dose of cabazitaxel (per 10 mg/m ²)	1.00	0.97–1.03	0.70	0.96	0.90–1.02	0.26
BSA > versus ≤ 2 m ²	1.80	0.78–4.20	0.16	0.62	0.20–1.80	0.39
BMI	1.09	0.95–1.26	0.19	0.99	0.86–1.14	0.93

Odds ratio is computed per unit increase in continuous variables unless otherwise specified. Variables with a P value <0.25 were included in the multivariate analysis and are in bold.

BMI = body mass index, BSA = body surface area, CI = confidence interval, ECOG PS = Eastern Cooperative Oncology Group performance status, Hb = haemoglobin.

Furthermore, the number of patients receiving >10 cycles was small and no patient received more than 17 cycles. In this regard, it must be noted that a report of 4 patients with CRPC cancer treated with >15 cycles of cabazitaxel found that peripheral neuropathy was the only clinically significant toxicity associated with cumulative doses.¹⁵ There is no established clinical variable predictive of cabazitaxel efficacy in the postdocetaxel setting, although preliminary evidence by our work group suggest that cabazitaxel could be more effective

than novel hormonal agents in a number of clinical settings, which include patients with brain metastases,¹⁶ high Gleason score at diagnosis,¹⁷ and primary refractoriness to docetaxel.¹⁸ Similarly to other antineoplastic agents (eg, sunitinib¹⁹), cabazitaxel may also be more effective in patients showing greater treatment-related toxicity. A recent post-hoc analysis of the TROPIC trial suggested that treatment outcomes, in terms of Overall Survival, Progression Free Survival, and Prostate Specific Antigen response, were improved in patients

TABLE 7. Odds Ratios and 95% Confidence Intervals for the Variables Retained in the Model for Multivariate Analysis

Variable	Variables Retained in The Model at Multivariate Analysis Using GEE and Backward Selection			
		Odds Ratio	95% CI	P
Grade 3–4 neutropenia	Prior docetaxel treatment (per 100 mg/m ²)	0.95	0.91–0.99	0.03
	Dose of cabazitaxel used (per 5 mg/m ²)	1.88	1.00–3.55	0.05
	Prior dose of cabazitaxel (per 10 mg/m ²)	0.90	0.86–0.93	<0.01
	BSA > versus ≤ 2 m ²	2.58	1.50–4.43	<0.01
Febrile neutropenia	Prior dose of cabazitaxel (per 10 mg/m ²)	0.52	0.34–0.81	<0.01
	ECOG PS (1–2 versus 0)	3.49	1.03–11.83	0.04
Grade 3–4 anemia	Prior docetaxel treatment (per 100 mg/m ²)	0.85	0.73–1.00	0.06
	Hb (g/dL)	0.63	0.49–0.81	<0.01
	Prior dose of cabazitaxel (per 10 mg/m ²)	0.93	0.86–1.00	0.07
	BSA > versus ≤ 2 m ²	0.10	0.02–0.52	<0.01
Grade 2 fatigue/asthenia	ECOG PS (1–2 versus 0)	3.59	1.55–8.31	<0.01
	Prior docetaxel treatment (per 100 mg/m ²)	0.90	0.84–0.96	<0.01
Grade 3–4 fatigue/asthenia	Prior docetaxel treatment (per 100 mg/m ²)	0.90	0.84–0.96	<0.01

Odds ratio is computed per unit increase in continuous variables unless otherwise specified.

BMI = body mass index, BSA = body surface area, CI = confidence interval, ECOG PS = Eastern Cooperative Oncology Group performance status, Hb = hemoglobin.

developing G3 to 4 neutropenia.²⁰ Our analysis confirms that the safety profile of cabazitaxel compares favorably with that of docetaxel, which was associated with G3 to 4 diarrhea, nail changes, and peripheral neuropathy in approximately 30% of the patients.²¹ Among the toxicities assessed, we did not identify any that appeared to be dependent on the cumulative dose of cabazitaxel priorly administered. As this finding is likely to be influenced by early dose reduction and early toxicity-related treatment discontinuation, it must be confirmed by prospective larger trials in patients with metastatic castration resistant prostate cancer.

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