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Cabazitaxel for metastatic castration-resistant prostate cancer: safety data from the Spanish expanded access program

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Abstract

Background: Based on the TROPIC study results, cabazitaxel was approved for the management of metastatic castration-resistant prostate cancer (mCRPC) progressing on or after docetaxel.

Methods: This multi-centre program provided early access to cabazitaxel to patients with mCRPC before its commercialization. Safety data from 153 Spanish patients receiving cabazitaxel 25 mg/m^2 i.v. Q3W, plus oral prednisone/prednisolone 10 mg daily, are reported.

Results: Median age of patients was 70 years (26.8% ≥ 75 years), 94.1 and 26.8% had bone and visceral metastasis, respectively. Most had an Eastern Cooperative Oncology Group ≤ 1 (88.9%) and had received a median of 8.0 cycles of last docetaxel treatment. The median of cabazitaxel cycles and cumulative dose were 6.0 (Interquartile range [IQR]: 4.0; 8.0) and 148.9 (IQR: 98.2; 201.4) mg/m^2, respectively. Adverse events (AEs) possibly related to cabazitaxel occurred in 143 (93.5%) patients. The most frequent grade ≥ 3 AEs were neutropenia (n = 25, 16.3%) and asthenia (n = 17, 11.1%). Febrile neutropenia and grade ≥ 3 diarrhea occurred in 5.2% of the patients each. There were five (3.3%) possibly treatment-related deaths, mainly infection-related. G-CSFs were used in 114 (74.5%) patients, generally as prophylaxis (n = 107; 69.9%). Grade ≥ 3 peripheral neuropathy and nail disorders were uncommon.

Conclusions: Cabazitaxel administration, in a real-world setting, is tolerated by Spanish patients with mCRPC, and the AEs are manageable.

Keywords: cabazitaxel, compassionate use studies, docetaxel, prostatic neoplasms, safety

1. Introduction

Docetaxel-based chemotherapy is the standard first-line therapy for metastatic castration-resistant prostate cancer (mCRPC); however, it is not curative and after initial response many patients progress. Until recently, second-line chemotherapy for mCRPC patients was an unmet clinical need for a rapidly progressing and debilitating disease, although results from the TROPIC study with cabazitaxel, a next generation taxane designed to overcome drug resistance to docetaxel, prompted its approval as second-line chemotherapy for mCRPC.

Cabazitaxel is a tubulin-binding taxane that promotes the microtubules stabilization leading to mitotic block and apoptosis of tumor cells [1], but also interferes with androgen receptor (AR)-signaling pathway, thus preventing AR nuclear translocation as suggested in recent studies [2,3]. Cabazitaxel demonstrated to provide a survival benefit over mitoxantrone in the randomized, Phase III TROPIC study in 755 mCRPC patients progressing from a docetaxel-containing regimen [4]. The median overall survival was in favor of cabazitaxel arm (15.1 months) versus the mitoxantrone arm (12.7 months) (Hazard ratio [HR]: 0.70, 95% CI 0.59 − 0.83, $p < 0.0001$), resulting in a 30% reduction in the risk of death. The PFS was also in favor of cabazitaxel arm with 2.8 versus 1.4 months (HR: 0.74, 95% CI 0.64 − 0.86, $p < 0.0001$). Nevertheless, in the TROPIC study significant hematological adverse events (AEs) (neutropenia, febrile neutropenia and neutropenic complications) were commonly reported in the cabazitaxel group, often during cycle 1. Also nonhematological AEs such as diarrhea, fatigue, asthenia and back pain were frequent. Although toxicities typical of the taxane class (neutropenia and its consequences, diarrhea) are usually predictable and manageable, a need to raise awareness of those risks and their management amongst clinicians was stated. The proactive management of AEs relative to cabazitaxel by the appropriate secondary prophylaxis with G--CSF, as per American Society of Clinical Oncology (ASCO) guidelines and EORTC guidelines, should be promoted as well to reduce the risk of neutropenic complications [5,6].

Because of the survival benefit observed from the TROPIC study, there was a significant interest and augmented demand for access to cabazitaxel until it was commercially available. Therefore, this international, single-arm, multi-centre, open-label study (NCT01254279) provided early access to cabazitaxel for use in patients with baseline and clinical characteristics similar to the patients evaluated in the TROPIC study, with the objective of further evaluate the cabazitaxel safety profile in the real-life setting and across different geographical areas. The results from an interim analysis, performed on December 2012, of the expanded access program (EAP) in Spain are described in this article.

2. Patients and methods

2.1 Eligibility criteria

Patients with mCRPC who had progressed during or after treatment with a docetaxel-containing regimen for mCRPC were enrolled at selected sites in Spain. Other eligibility criteria included: age ≥ 18 years; an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2; previous or ongoing surgical (orchiectomy) or medical castration; life expectancy of ≥ 3 months; and adequate bone marrow, liver and renal function. Exclusion criteria were the same as those of the TROPIC study [4].

The study was performed after approval by an Independent Ethics Committee of each site and in accordance with the Declaration of Helsinki, Good Clinical Practices, and local ethical and legal requirements. Signed informed consent was obtained from all patients before study entry.

2.2 Treatment plan and study assessments

Eligible patients received cabazitaxel 25 mg/m^2 intravenously over 1 h every 3 weeks, in combination with oral prednisone or prednisolone 10 mg daily until disease progression, death, unacceptable toxicity or because of the investigator's decision. Patient recruitment was stopped once cabazitaxel was commercially available.

Safety assessments (hematology and biochemistry) were performed before each cycle. Patients were evaluated for AEs during therapy and until 30 days after the last study drug dose. AEs were graded using the National Cancer Institute common toxicity criteria (NCI-CTCAE) version 4.0 [7], and summarized using the Medical Dictionary for Regulatory Activities (MedDRA) version 15.0 terminology [8].

When necessary, a treatment delay due to toxicity of up to 2 weeks or one dose reduction (to 20 mg/m^2 for cabazitaxel) per patient was permitted. Proactive management of AEs relative to cabazitaxel, primarily neutropenia and related disorders, was recommended in line with the ASCO guidelines [5]. Primary prophylaxis with G-CSF was considered in patients with high-risk features (including but not limited to age > 65 years, poor-performance status or prior febrile neutropenia episodes) according to ASCO guidelines starting from first cycle of treatment. Secondary prophylaxis with G-CSF was also recommended in case of neutropenic complication in earlier cycle of chemotherapy without primary prophylaxis.

2.3 Statistical considerations

The primary end point was to document the overall safety of cabazitaxel in mCRPC patients who had progressed during or after treatment with a docetaxel-containing regimen. A descriptive safety analysis, including number of cycles, cumulative dose received, reason for end of treatment, AEs and serious adverse events, was performed on the safety population (all enrolled patients receiving at least part of one dose of cabazitaxel).

Additionally, the cabazitaxel efficacy (prostate-specific antigen [PSA] response and biochemical progression free survival) was analyzed in a cohort of patients participating in the Spanish arm of the EAP. For this efficacy subanalysis, the patients were selected from the sites with higher recruitment rate and no formal selection was used.

3. Results

3.1 Patients and eligibility

From March 2011 to August 2011, 153 patients enrolled into the study at 25 sites in Spain and whose first treatment was taken before or on May 30 2012 were included in the interim analysis. Their characteristics are summarized in Table 1. Median age was 70 (interquartile range [IQR]: 65 − 75) years; 26.8% were aged 75 years or more; 94.1% (n = 144) had bone metastasis and 26.8% had visceral (n = 41) metastasis.

Table 1. Patient baseline characteristics.

	No. of patients	%
Total no. of patients	153	
Age (years)		
Median (IQR)	70.0 (65 − 75)	
Range		
< 65	36	23.5
65 − 75	76	49.7
≥ 75	41	26.8
ECOG PS		
0	47	30.7
1	89	58.2
2	17	11.1
*Extent of disease**		
Bone metastases	144	94.1
Visceral metastases	41	26.8
Liver	20	13.1
Lungs	14	9.2
Mediastinum, pleura, skin, muscle/soft tissue	15	9.8
Other	28	18.3
Regional lymph nodes	40	26.1
Distant lymph nodes	35	22.9
No. of metastatic sites		
1	67	43.8
≥ 2	86	56.2
*Type of progression**		
Clinical progression overall	47	30.7
Increased PSA overall	122	79.7
Bone scan overall	74	48.4
Measurable lesions overall	38	24.8

Data are number of patients (%) or median (IQR).
*Each patient may have more than one location or more than one type of progression.
ECOG PS: Eastern Cooperative Oncology Group performance status;
IQR: Interquartile range; PSA: Prostate-specific antigen.

Patients had previously received a median of 8.0 (IQR: 6.0; 10.0) cycles of last docetaxel. Docetaxel was received as firstline treatment in 72 patients. Disease progression occurred at a median time of 6.5 months (IQR: 2.5; 12.1) from last docetaxel dose with 59.5% (n = 91) patients experiencing disease progression ≥ 3 months from last docetaxel dose. The proportion of patients receiving first cabazitaxel dose within or after 6 months of last docetaxel dose was similar (Table 2).

Table 2. Previous treatment with docetaxel-containing regimen.

	No. of patients	%
Total no. of patients	153	
No. of previous docetaxel lines		
Median (IQR)	1.0 (1.0 − 2.0)	
No. cycles of last docetaxel administration		
Median (IQR)	8.0 (6.0 − 10.0)	
*Cumulative dose of docetaxel (mg/m^2)**		
Median (IQR)	560.0 (420.0 − 675.0)	
*Distribution of docetaxel cumulative dose (mg/m^2)**		
< 225	9	6.0
225 − 450	29	19.5
451 − 675	69	46.3
676 − 900	24	16.1
< 900	18	12.1
Disease progression relative to docetaxel administration‡		
During treatment	16	10.5
< 3 months from last dose	45	29.6
≥ 3 months from last dose	91	59.5
Time from last docetaxel dose to disease progression (months)§		
Median (IQR)	6.5 (2.5; 12.1)	
Time elapsed from last docetaxel dose to first cabazitaxel dose‡		
within 6 months since last docetaxel dose	72	47.4
> 6 months since last docetaxel dose	80	52.6

* 4 missing.
‡ 1 missing.
§ For pats who progressed after last docetaxel dose.
IQR: Interquartile range.

3.2 Treatment exposure

Patients received a median number of 6.0 (IQR: 4.0; 8.0) cycles of cabazitaxel and a median cumulative dose of 148.9 (IQR: 98.2; 201.4) mg/m^2 (Table 3). A hundred of patients (65.4%) completed 6 cycles and 27 (17.6%) patients received up to 10 cycles of treatment with one patient receiving 17 cycles.

At the cut-off date of the data interim analysis (May, 2012), 21 patients were still under treatment in the EAP in Spain, and cabazitaxel treatment was ended in 132 patients. Cabazitaxel dose reduction was necessary in 25 cycles in 24 patients of the 132 patients who ended treatment (18.2%) due to non-hematological (7.6% patients), hematological (4.5% patients) or both (3.8% patients) cabazitaxelrelated AEs. A total of 77 cycles were delayed in 54 patients (40.9%), due to non-hematological AEs (11.4% patients), hematological AEs (6.1% patients) or both toxicities (2.3% patients) and in 29 patients (22%) for non drug-related reasons (i.e., administrative issues, holidays, patient's request or investigator's decision). The median relative dose intensity was equivalent to 99.7% (IQR: 97.9; 100.3) of the predicted dose intensity.

Main reasons for discontinuation were disease progression (n = 64; 48.5%), AEs (n = 36; 27.3%), investigator's decision (n = 24, 18.2%), patient's decision (n = 5; 3.8%), treatment completed (n = 1; 0.8%), bad tolerance (n = 1; 0.8%) or lost to follow-up (n = 1; 0.8%). The Investigator decided to discontinue treatment in 15 (11.4%) patients because the best clinical benefit was achieved or because they have completed 10 cycles of cabazitaxel treatment.

Table 3. Cabazitaxel treatment received.

	No. of patients	No. of cycles
Total no. of patients*	132	
Actual dose intensity (mg/m^2/week)		
Median (IQR)	7.9 (7.3 − 8.3)	
Relative dose intensity (%)		
Median (IQR)	99.7 (97.9 − 100.3)	
No. of treatment cycles		
Median (IQR)	6.0 (4.0 − 8.0)	
In patients who received G-CSF for at least once	97	
Median (IQR)	7.0 (4.0 − 8.0)	
In patients never receiving G-CSF	35	
Median (IQR)	6.0 (4.0 − 8.0)	
Treatment delays		
Treatment delays due to any cause	54 (40.9)	77
Due to AE not related to cabazitaxel	10 (7.6)	10
Due to AE related to cabazitaxel	24 (18.2)	31
Hematological AE related to cabazitaxel	8 (6.1)	8
Non-hematological AE related to cabazitaxel	15 (11.4)	19
Both 3	(2.3)	4
Due to other causes	29 (22.0)	36
Dose reductions		
Dose reductions due to any cause	24 (18.2)	25
Due to AE not related to cabazitaxel	2 (1.5)	2
Due to AE related to cabazitaxel	20 (15.2)	21
Hematological AE related to cabazitaxel	6 (4.5)	6
Non-hematological AE related to cabazitaxel	10 (7.6)	10
Both	5 (3.8)	5
Due to other causes	2 (1.5)	2

Data are number of cycles or median (IQR).
*Patients who ended cabazitaxel treatment at the interim analysis cut-off date.
AE: Adverse event; IQR: Interquartile range.

3.3 Safety

All 153 patients were included in the safety analysis as they received at least one dose of treatment. One hundred and forty three patients (93.5%) reported possibly treatment related AEs. Possible related AEs observed in > 20% of patients were mainly general disorders (asthenia [62.7%]), gastrointestinal (GI) (diarrhea [45.8%], nausea [22.2%] and decreased appetite [22.2%]) or hematological (anemia [37.9%] and neutropenia [22.2%]).

Grade ≥ 3 AEs were recorded in 66 patients (43.1%). The most common clinically significant grade ≥ 3 AEs were neutropenia (25 [16.3%] patients) and asthenia (17 [11.1%] patients) (Table 4). Grade ≥ 3 febrile neutropenia and diarrhea occurred in 8 (5.2%) patients each. Although direct comparisons are not feasible, the percentage of patients reporting hematological grade 3 − 4 AEs differ from those in the TROPIC study (Figure 1) possibly due to prophylactic use of G-CSF. Grade ≥ 3 peripheral neuropathy (1 [0.7%]) were uncommon. No grade ≥ 3 nail disorders were reported.

Table 4. Patients with at least one treatment-related TEAE.

	Total (n = 153)	
	All grades	Grade 3/4
Any class	143 (93.5)	66 (43.1)
Hematological		
Anemia	58 (37.9)	9 (5.9)
Neutropenia	34 (22.2)	25 (16.3)
Febrile neutropenia	8 (5.2)	8 (5.2)
Leucopenia	19 (12.4)	10 (6.5)
Thrombocytopenia	9 (5.9)	3 (2.0)
Lymphopenia	4 (2.6)	2 (1.3)
Non-Hematological		
Asthenia	96 (62.7)	17 (11.1)
Diarrhea	70 (45.8)	8 (5.2)
Nausea	34 (22.2)	2 (1.3)
Decreased appetite	34 (22.2)	4 (2.6)
Vomiting	24 (15.7)	-
Constipation	21 (13.7)	-
Mucosal inflammation	16 (10.5)	-
Peripheral neuropathy	11 (7.2)	1 (0.7)
Fatigue	7 (4.6)	2 (1.3)
Blood alkaline phosphatase increased	4 (2.6)	3 (2.0)
Neutrophil count decreased	4 (2.6)	3 (2.0)
White blood cell count decreased	3 (2.0)	2 (1.3)
Urinary tract infection	3 (2.0)	2 (1.3)

Data are number of patients (%). TEAEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0)
and summarized with the Medical Dictionary for Regulatory Activities terminology (version 15.0). Events listed are those occurring at grade 3 or higher severity
in ≥ 1% of patients and/or at all grades in ≥ 10% of patients.
TEAES: Treatment emergent adverse events.

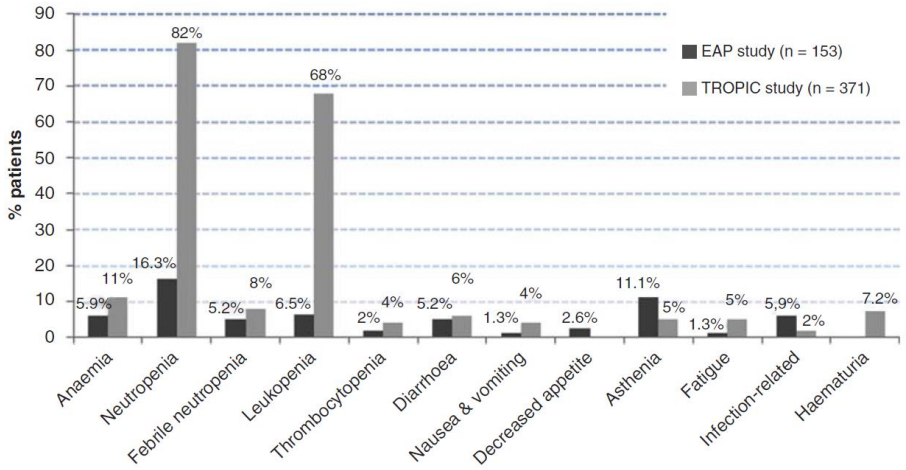

Figure 1. Grade $ 3 treatment emergent adverse events (TEAEs) reported in $ 2% of patients in the Spanish EAP and in the TROPIC study.
EAP: Expanded access program.

Cabazitaxel treatment was discontinued in 36 (27.3%) patients due to AEs. Most common AEs leading to discontinuation were grade 3/4 infection-related disorders (n = 9; 5.9%), grade 3/4 general disorders and administration site conditions (n = 5; 3.3%) and grade 3/4 GI disorders mainly diarrhea (n = 4, 2.6%).

There were five (3.3%) possibly treatment-related deaths, mainly infection-related: urinary tract infection (n = 1), neutropenic infection (n = 1), peritonitis (n = 1), septic shock (n = 1) and febrile neutropenia (n = 1). Four out of the five patients were aged ≥ 70 years. All had received ≤ 2 cycles of treatment (drug exposure: 1 day [n = 2]; 22 days [n = 2] and 30 days [n = 1]).

G-CSF were used in 114 (74.5%) patients mostly as preventive treatment (n = 107; 69.9%), with 101 patients receiving G-CSF at cycle 1. Of 101 patients, 88 received G-CSF as primary prophylaxis at first cycle (Table 5).

Table 5. Prevention of neutropenia with G-CSF in high-risk patients.

	All pats (n = 153)	≤ 65 years (n = 44)	> 65 years (n = 109)	ECOG PS > 2 (n = 17)
	n (%)	n (%)	n (%)	n (%)
Prophylactic G-CSF use at cycle 1				
No. of patients	88	18	70	9
Febrile neutropenia	2 (2.3)	-	2 (2.9)	-
Neutropenia grade 3 − 4	11 (12.5)	2 (11.1)	9 (12.9)	2 (22.2)
Neutropenia grade 3 − 4 for > 7 days	4 (4.5)	2 (11.1)	2 (2.9)	1 (11.1)
Decreased neutropenic count	2 (2.3)	-	2 (2.9)	1 (11.1)
Neutropenic infection	1 (1.1)	-	1 (1.4)	-
Neutropenic colitis	1 (1.1)	-	1 (1.4)	-
No G-CSF use at cycle 1				
No. of patients	52	20	32	7
Febrile neutropenia	2 (3.8)	-	2 (6.3)	-
Neutropenia grade 3 − 4	4 (7.7)	2 (10.0)	2 (6.3)	-
Neutropenia grade 3 − 4 for > 7 days	1 (1.9)	1 (5.0)	-	-
Decreased neutropenic count	-	-	-	-
Neutropenic infection	-	-	-	-
Neutropenic colitis	-	-	-	-

ECOG PS: Eastern Cooperative Oncology Group performance status.

3.4 Efficacy subanalysis: PSA response

Additionally, the PSA response and biochemical progression free survival after cabazitaxel treatment was analyzed outside the EAP protocol in a cohort of 65 patients from 6 sites participating in the Spanish arm of the EAP. Median baseline PSA was 864 ng/ml. A PSA response to cabazitaxel (PSA reduction of > 50%) was achieved in 47.7% (31 out of 65) patients. Median progression-free survival was 4.4 months (range: 2.7 − 6.1) [9].

4. Discussion

The results from our study further evaluate the cabazitaxel safety profile in mCRPC patients from Spain participating in the EAP program. These results are particularly relevant as they provide safety and efficacy data in a real-life setting, which does not differ from that observed in the TROPIC study.

Data from the Spanish EAP suggest a good safety profile of cabazitaxel, with asthenia, myelosuppression (i.e., anemia, neutropenia) and GI symptoms (diarrhea, nausea and decreased appetite) as common toxicities (> 20% of patients), which is consistent with the results reported in the TROPIC study. Besides, cabazitaxel treatment was well tolerated, with < 30% of patients discontinuing treatment due to AEs. A majority of patients completed 6 cycles of cabazitaxel treatment and almost 20% received up to 10 cycles of treatment. In addition, most patients received the full dose of study treatment (median relative dose intensity was almost 100% of the predicted dose intensity).

The exposure to treatment and the sources for AE collection in the Spanish EAP (single-arm, compassionate-use) and the TROPIC (randomized, Phase III) studies are not comparable, thus a direct comparison is not possible. However, despite having a patient population that mirrored that of the TROPIC study, cabazitaxel seems to be better tolerated in our study than in the TROPIC study possibly due to preventive toxicity management. The percentage of patients reporting hematological grade ≥ 3 AEs, namely grade ≥ 3 neutropenia and febrile neutropenia, was considerably reduced in the EAP in Spain (16.3 and 5.2% patients, respectively) compared to the TROPIC study (82 and 8% patients, respectively). A more frequent follow-up for neutropenia was made in the TROPIC (weekly) than in the EAP (every 3 weeks) study, which might partly explain the difference in the number of neutropenia cases. The percentage of infection-related AEs was slightly higher in our study (5.9 vs 2% in the TROPIC study), but even if we include these infection-related AEs within the group of neutropenic complications the hematological safety profile of cabazitaxel continues to be better in the EAP in Spain (27.4 vs 92% in the TROPIC study). In addition, no cases of grade ≥ 3 peripheral neuropathy or arthralgia/back pain were reported here and the rate of grade ≥ 3 diarrhea was slightly lower than that reported in the TROPIC study. Grade ≥ 3 asthenia/fatigue (12.4%), which is commonly reported with cytotoxic chemotherapy [10], did not differ from that of the TROPIC study [4].

The key safety data for cabazitaxel in mCRPC were derived from the TROPIC study; however, the results observed in our real-world Spanish population demonstrate that cabazitaxel toxicities are usually predictable and manageable in clinical practice. The main characteristics of the study population in the EAP study compared to the TROPIC study, with a higher proportion of patients aged > 75 years (26.8 vs 18%, respectively) and with more advanced disease (94 vs 80% with bone metastasis, respectively), cannot explain the differences in the safety profiles. The proactive management of certain clinical factors, which predispose to increased complications from prolonged neutropenia, such as age > 65 years or poor performance status (ECOG ≥ 2), probably have played a role for minimization of hematological AEs. Investigators participating in our study had extensive experience in administering taxanes and were instructed in the use of appropriate prophylaxis with G-CSF to reduce the risk of neutropenic complications from the first cycle of treatment [5]. In line with this, Di Lorenzo et al. suggested a marked decrease in the relative risk of grade ≥ 3 neutropenia/febrile neutropenia per cycle per patient (by approximately seven times) with cabazitaxel if prophylaxis with PEG-filgrastim was used [11]. Investigators were also required to strictly follow the information provided by the Sponsor for cabazitaxel dose reduction, interruption or delay. Educational local programs might be promoted in clinical practice, which include the use of the appropriate cabazitaxel dose modifications recommended by the Sponsor as required, the use of preventive strategies to avoid cabazitaxel AEs, and careful patient education on symptom recognition, self-care and clear instructions for seeking advice for an effective management of AEs [12].

The safety results from the EAP in other countries indicate that cabazitaxel has an acceptable tolerability in the routine clinical practice setting across the globe [11,13-19]. Preliminary safety results of the European EAP program has shown that prophylactic use of G-CSF, especially at cycle 1 improves tolerability in patients aged ≥ 75 years treated with cabazitaxel. In our study, the number of patients aged

≥ 75 years (n = 41) was too low to be analyzed. In addition, data on the impact of cabazitaxel treatment in patient's quality of life has been collected within the EAP in several countries like UK or Canada, and preliminary results are promising [13,17]. Final results from the whole international EAP program are awaited with interest.

On the other hand, our study population was representative of the 'unselected' population of mCRPC patients attended in daily clinical practice which usually have poor prognostic factors: aged > 75 years; presenting bone or visceral metastasis (including liver metastasis in 13%); with two or more metastatic sites involved; with bone-scan progression or measurable disease progression [20,21]. Pre-treatment with docetaxel, that is, cumulative dose and median number of cycles of, received by the patients in our study was equivalent to that of the TROPIC study. Bearing in mind that this study was not designed to evaluate efficacy, the PSA response of cabazitaxel in a cohort of 65 patients demonstrated a similar efficacy of cabazitaxel to that observed in the TROPIC study (median progression-free survival 4.4 vs 2.8 months, respectively). Actually, in 11.4% of patients the treatment was discontinued because the best clinical benefit was achieved or because they have completed 10 cycles of cabazitaxel treatment. A recent analysis by Bahl et al. of the survival rates in the TROPIC study showed longer survival rates (≥ 2 vs < 2 years) in patients receiving higher number of cabazitaxel cycles (median of 10 cycles vs median 6 cycles, respectively) [22].

5. Conclusions

In conclusion, the treatment of mCRPC with cabazitaxel is safe and tolerable with manageable AEs in the routine clinical practice, especially in a real-life Spanish population with poor prognostic factors (aged > 70; with visceral metastasis). Proactive management of AEs, especially in > 65 years and ECOG ≥ 2 patients is important and likely has a role for minimization of hematological AEs.

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Declaration of interest

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