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REVIEW

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Clinical concepts for cabazitaxel in the management of metastatic castration-resistant prostate cancer

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Abstract

Prostate cancer is the most common malignancy in male patients. The second-generation taxanes, cabazitaxel, is a therapeutic option with an overall survival advantage for patients with metastatic castration-resistant prostate cancer. This review explores specific aspects of cabazitaxel including the duration of treatment, the efficacy of lower dose and effect on the incidence of adverse effects, and optimal sequencing of cabazitaxel. A systematic search of data baselines "PubMed, Ovid Medline, Scopus, and Embase" was carried out using the keywords "cabazitaxel" and "metastatic prostate cancer." The search was limited to clinical studies performed after October 2010 addressing duration of treatment, the efficacy of lower dose, adverse effects, the sequence of cabazitaxel in relation to other lines of therapy and use in chemotherapy naïve patients. The current evidence supports the utility and safety of cabazitaxel as either a second- or third-line agent after docetaxel, or as an alternative to docetaxel in the chemotherapy-naive setting. Extended duration of cabazitaxel beyond 10 cycles is feasible and does not appear to lead to cumulative toxicity. In conclusion, cabazitaxel can improve survival in castrate-resistant prostate cancer with an acceptable risk of toxicity. Studies confirmed the efficacy of reduced dose and utility in patients without prior chemotherapy.

KEYWORDS

cabazitaxel, chemotherapy naïve, duration of treatment, metastatic castration-resistant prostate cancer, number of cycles, reduced dose, sequence of therapy

1 | INTRODUCTION

Prostate cancer is the most common malignancy in male patients, second only to lung cancer, with an estimated 1.1 million new cases and 307 000 deaths in 2012 worldwide.[1] Prostate cancer is a progressive disease where, despite androgen deprivation therapy controlling the disease for a period of time, patients eventually become castration resistant. This is defined by serum testosterone levels <50 ng/Dl (1.7 nmol/L) with evidence of progression either biochemical (rising serum prostate-specific antigen [PSA] level) or radiological (new or progressing lesions).[2] The estimated prevalence of castration-resistant cases, usually associated with metastatic disease, is about 10% to 20% of all patients with prostate cancer.[3] The management of metastatic castrate-resistant prostate cancer (mCRPC) was mainly palliative before 2004 after which it substantially changed with the advent of docetaxel as the first agent to show an improvement in overall survival.[4] Since then, more therapeutic options with survival advantages have become available, including the second-generation taxane, cabazitaxel; the androgen-modulating agents, abiraterone acetate and enzalutamide; the cellular immunotherapy, sipuleucel-T and the radiopharmaceutical targeting bone lesions, radium 223. The availability of effective therapeutic options facilitates testing of different approaches and strategies to enhance the prognosis of patients with advanced prostate cancer. This review will explore the evolving evidence regarding the duration and dose of cabazitaxel and sequencing of therapies beyond the second line in patients with mCRPC.

2 | MATERIALS AND METHODS

A systematic search of databases "PubMed, Ovid Medline, Scopus and Embase" were carried out with addition hand on searching for relevant publications. Searching was done using the keywords ("cabazitaxel"

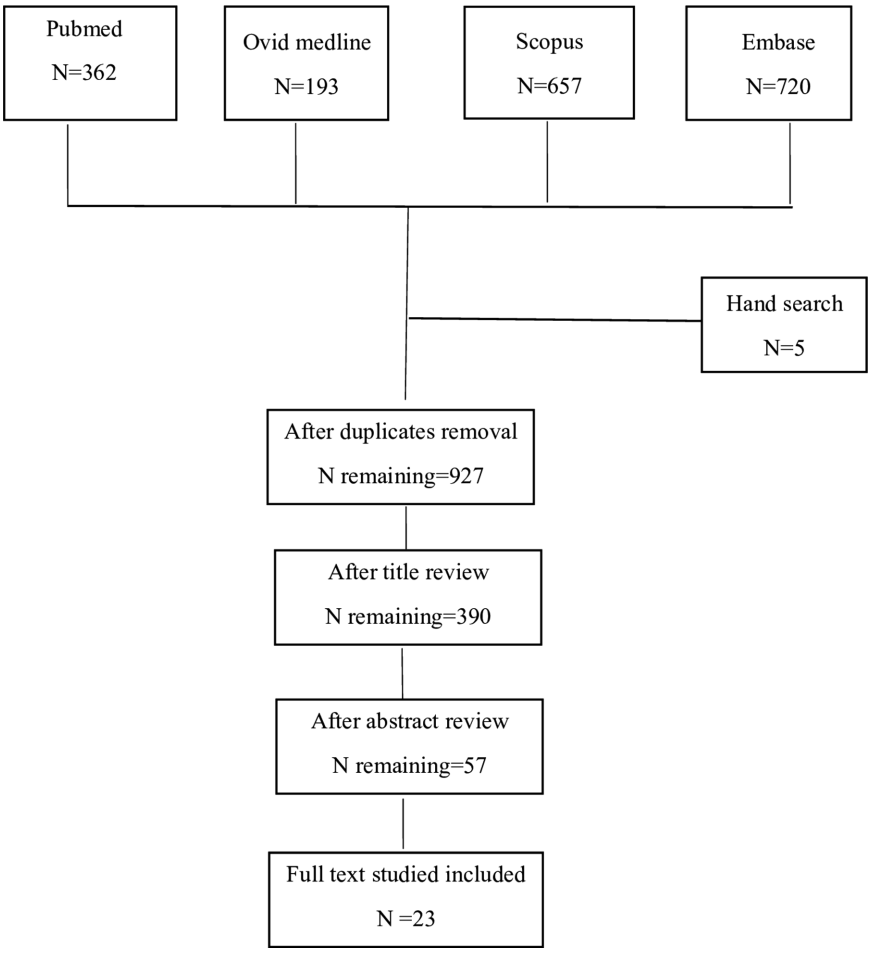

FIGURE 1 Flowchart of databases search for the literature review

and "metastatic castration-resistant prostate cancer." The search was limited to clinical studies performed after October 2010 (date of publication of TROPIC trial),[5] manuscripts in English and publications in full text were chosen. Reviewed publications included prospective and retrospective studies evaluating patients with metastatic castration-resistant cancer receiving cabazitaxel. The studies addressed advances in the role of cabazitaxel related to the duration of treatment, the efficacy of lower dose in the event of adverse effects, optimal sequencing of cabazitaxel in relation to other treatments and the use in chemotherapy naïve patients.

After removing duplicates, the titles and abstracts were screened for relevance. Remaining studies were assessed in full text to extract data, and the outcomes of the related studies were presented in the review according to the investigated intervention.

3 | RESULTS

Initial search resulted in 1937 matches. After removing duplicates and screening for relevant studies, 23 studies were selected for data extraction, including four phases III, one phase II and one phase I trials, seven prospective and eight retrospective studies (Figure 1). An overview of the efficacy and safety of cabazitaxel were performed using recently published phase III randomized controlled studies, followed by reviewing studies investigating duration, dose reduction and optimal sequencing.

3.1 | Cabazitaxel overview

Cabazitaxel, a semisynthetic second-generation taxane, acts through a tubulin stabilization mechanism leading to cell death. It has been designed to overcome the resistance encountered by first-generation taxanes mediated by multidrug resistance (MDR) proteins such as p-glycoprotein (P-gp). Cabazitaxel has higher activity against different tumor cell lines, including docetaxel-resistant variants due to a low predilection for P-gp, and more effective penetration of the blood–brain barrier.[6,7]

The approval of cabazitaxel was based on the results of phase III randomized controlled TROPIC trial showing a 30% reduction in risk of death in addition to superior progression-free survival when compared to mitoxantrone. In addition to patients who developed acquired resistance to docetaxel, analysis of data confirmed the benefits of cabazitaxel in refractory patients who never responded to docetaxel treatment (30% of patients). The major limitation is the myelosuppressive effects, especially neutropenia, which may lead to treatment delay, dose reductions and premature cessation of treatment. Less common toxicities were nonhematological with diarrhea and fatigue most frequently reported.[5] Several subsequent studies from different

TABLE 1 Studies of cabazitaxel in post-docetaxel setting

Phase III RCTs	Patients, *N*	Cycles number median (range)	OS median (range), months	PFS median (range) months	PSA response (%)	Grade ≥3 neutropenia/febrile neutropenia (%)
TROPIC Trial (5)	378	6^{3-10}	15.1 (95% CI, 14·1–016·3)	2·8 (95% CI, 2·4–3·0)	39·2	82 / 8
PROSELICA Trial (8)	602	7^{1-11}	14.5 (95% CI, 13.47–15.28)	3.5 (95% CI, 3.12–3.9)	42.9	73.3 / 9.2
AFFINITY Trial (9)	318	8^{4-10}	13·4 (12·1–14·9)			20 / 3
Prospective expanded -access studies						
Heidenreich et al. (10)	111	6^{3-10}	Mean 13.9 (0.7–35.8)	Mean 3.78 (0.7–31.4)	37.6	7.2 / 1.8
Wissing et al. (11)	49	6^{1-21}	8.7 (IQR 6.0–15.9)	2.8 (IQR 1.7–4.9)		4.1 / 4.1
Bracarda et al. (12)	218	6				33.9 / 5
Castellano et al. (13)	153	6 (IQR 4–8)		4.4 (2.7–6.6)	47.7	16.3 / 5.8
Heidenreich et al. (14)	746	4^{1-16}				17 / 5.4
Bahl et al. (15)	112	6 (IQR 3–10)				9.8 / 1.8
Parente et al. (16)	104	6 (IQR 4–10)				20.2 / 11.5

countries have now been published, confirming the efficacy and safety of cabazitaxel as second-line treatment after docetaxel. Furthermore, these newer studies had a lower incidence of neutropenia with prophylactic use of granulocyte colony-stimulating factors (Table 1).[5,8-16]

3.2 | Optimal sequencing of cabazitaxel in the treatment of mCRPC

Progression of prostate cancer after docetaxel is an inevitable fate calling for subsequent lines of therapy to prolong survival, especially in patients with good performance status. The landscape of mCRPC treatment has expanded in the last few years with the availability of novel agents that have created a new horizon for these patients. The new androgen axis inhibitors (AAI), abiraterone acetate and enzalutamide have shown a survival benefit in the pre-and post-docetaxel setting.[17–20] However, there is no agreement regarding optimal sequencing strategies as well as no consensus recommendations for patient selection.[21,22]

Use of cabazitaxel in the third-line setting after docetaxel and the novel AAI is expanding in clinical practice. The phase III Affinity Trial evaluating the addition of custirsen to cabazitaxel and prednisone has reported that 59% of patients had received abiraterone acetate or enzalutamide before cabazitaxel.[9] In the other phase III trial comparing a reduced dose versus a standard dose of cabazitaxel, prior abiraterone therapy was encountered in 25% of patients.[8] Concerns were raised previously about impaired tumor response to taxanes following AAI[23] due to shared inhibitory effects of both taxanes and AAI on AR nuclear translocation, which is vital for AR singling and transport.[24] Although tumor cells resistant to both abiraterone and enzalutamide expressed lower levels of androgen receptors (ARs) and PSA proteins secondary to cabazitaxel exposure in vitro, both AR-positive and AR-negative cells responded equally to cabazitaxel, confirming no cross-resistance between cabazitaxel and AAI.[25] Furthermore, the antitumor activity of cabazitaxel is unaffected by the presence of the AR splice variant 7 (AR-V7) in circulating tumor cells (CTC), which has previously been shown to be a marker of resistance to AAI.[26]

The optimal sequencing of these life-prolonging therapies (enzalutamide, abiraterone, docetaxel and cabazitaxel) remains unclear, with no prospective trials, specifically examining different sequential regimen.

Third-line cabazitaxel following previous AAI therapy has been evaluated in several retrospective reports of sequential therapy strategies in mCRPC (Table 2). There was a wide variation in results of cabazitaxel therapy with median OS ranging from 8.2 to 17 months (15.1 months in TROPIC), median PFS from 3.3 to 11.7 months (2.8 months in TROPIC) and 50% PSA response from 17% to 45% (39.2% in TROPIC).[25,27–35]

In some studies, the overall survival with cabazitaxel was similar for those with prior AAI compared to those without prior AAI (13 months *vs* 14 months; $P = 0.65$).[31] In addition, PSA changes in response to cabazitaxel did not differ in relation to prior second-line hormonal treatment, with changes reported in 45% of patients with prior abiraterone and 36% without ($P = 0.54$).[34] However, two retrospective analyses suggest that cabazitaxel followed by abiraterone acetate (CAB-AA) had superior overall survival (18.2 months *vs* 11.8

TABLE 2 Retrospective studies evaluating cabazitaxel in third-line setting

	Total no. of patients	Third-line cabazitaxel no. of patients	Second-line treatment no. of patients	OS median (months)	PFS Median (months)	PSA response (%)
Pezaro et al.[27]	59	41	AA[a] 32 AA + EN 5 EN[b] 4	15.8	4.6	39
Sella et al.[28]	130	24	AA 24	8.2	NA	31.5
Al-Nakouzi et al.[25]	79	79	AA 79	10.9	4.4	35
Sonpavde et al.[30]	350	36	AA 36	11.8	NA	NA
Wissing et al.[32]	132	69	AA 69	17.0	6.5	21.2
Caffo et al.[29]	260	110	AA 94 EN 16	12.0	5.0	28
Kongsted et al.[33]	94	66	AA	11.4	3.3	17
Bando et al.[35]	66	66	AA 14 EN 20 AA-EN 32	NA	10.3	26.9, 43.8
Van Soest et al.[31]	114	44	AA39 EN 3 AA + EN 2	13.0	4.8 (PSA–PFS)	34
Saad et al.[34]	60	25	AA 25	NA	4.9 (PSA–PFS)	45

[a]AA, abiraterone acetate.
[b]EN, enzalutamide.

months, respectively; Hazard Ratio (HR) = 0.13; 95% confidence interval (CI), 0.02–0.73; $P = 0.02$) and progression-free survival (8.1 months *vs* 6.5 months, respectively; $P = 0.05$) compared to abiraterone followed by third-line cabazitaxel (AA-CAB).[30,32] Furthermore, a retrospective analysis of real-world data of patients treated in the post-docetaxel setting showed that in the subset of those with high-risk features (defined by albumin, alkaline phosphatase, ECOG performance status, hemoglobin, lactate dehydrogenase, lymph node, and PSA), cabazitaxel was associated with a higher overall survival compared to those who received AAI.[36] A potential advantage of using AAI as third-line agents after cabazitaxel is higher tolerability with milder toxicities, which is especially important in frail patients with high disease burden and multiple prior lines of treatment. Taking in consideration, the result of these studies are limited by the risk of selection bias due to their retrospective design.

The frequency of adverse events with cabazitaxel in the second line versus third line was examined in retrospective series and found to be comparable, with the most common complications being hematological, including neutropenia, anemia and febrile neutropenia, followed by nonhematological, diarrhea and fatigue.[34,37] Improvement in quality of life (QoL) and pain was also equivalent in patients receiving cabazitaxel earlier compared to third-line therapy in the mCRPC.[34]

A study reporting the outcome combining abiraterone and enzalutamide followed by cabazitaxel added no benefit in comparison to single hormonal therapy before cabazitaxel, possibly due to cross-resistance between the two AAI agents. In fact, third-line cabazitaxel following one AAI demonstrated longer progression-free survival than combined AAI.[35] Treatment with cabazitaxel in the fourth line setting was assessed in a small cohort of patients, with no overall survival and progression-free survival observed, due in part to the high disease burden and worse performance status in more advanced stages of disease.[29,38] More importantly, these patients had higher mortality, with 73% of patients requiring hospitalization due to either tumor progression and cabazitaxel toxicity or both.[38]

A widespread opinion is to use a patient-centered approach to decide on a treatment course based on individual patient characteristics and tumor behavior. Generally, cabazitaxel, as second-line therapy following docetaxel is preferred in symptomatic patients with a high probability of disease progression.[36] In the third-line setting, cabazitaxel can be used safely and effectively after abiraterone or enzalutamide, taking into consideration the patient's tolerability to the adverse effects of chemotherapy.

Despite the limitations of these studies, including retrospective analysis, small sample size, nonhomogenous methodology and patients' selection bias, they provide evidence supporting the utility and safety of cabazitaxel as either a second- or third-line agent after docetaxel. Future larger prospective and randomized studies may be able to provide definitive evidence and help identify patients who have a high chance of responding to cabazitaxel beyond second-line treatment with an acceptable toxicity profile.

3.3 | Extended duration of cabazitaxel

Duration of cabazitaxel treatment depends on multiple factors, including disease response and progression, safety profile, the patient's preference and the physician discretion. Continuing cabazitaxel in case

of disease regression may be of benefit, especially in patients with a substantial risk of recurrence where stopping cabazitaxel may lead to rapid tumor regrowth. There is no consensus regarding the optimum number of cabazitaxel cycles, and no prospective studies addressing the benefit/risk ratio of administering cabazitaxel beyond 10 cycles. Furthermore, the suggested beneficial effect of extending cabazitaxel treatment on survival is questionable in the current practice. However, evidence from retrospective studies suggests that prolonged treatment with cabazitaxel may be associated with a superior outcome without the increased risk of side effects.

In the TROPIC trial, patients with mCRPC were randomized to receive either cabazitaxel or mitoxantrone.[5] The maximum number of cycles for mitoxantrone was set at 10 in this study due to the risk of cardiotoxicity and to maintain an equal exposure in both arms the maximum number of cabazitaxel cycles was also set at 10. The median number of cabazitaxel cycles received was 6 (range 3–10), with 28% of patients completing all 10 cycles. Follow-up analysis of the TROPIC trial showed a survival advantage in favor of a higher number of cycles, with 53% of patients who received all 10 cycles surviving more than 2 years.[39] In addition, disease progression was delayed in the patients in the cabazitaxel group who received higher than a median number of cycles, with no significant increase in adverse effects. Regarding the QoL, the longer duration of cabazitaxel was associated with a slightly lower rate of analgesic use.[39]

After the TROPIC results and before registration, a number of access schemes for cabazitaxel were undertaken throughout the world in which the maximum cycle number was not capped at 10.[10–16] An interesting aspect of cabazitaxel is that, unlike docetaxel, cumulative toxicity appeared to be minimal. Toxicity of cabazitaxel mainly occurs early in the treatment course, and the risk of serious hematological adverse events peaks in cycle one and regresses with the continuation of therapy. Multivariate analysis showed that cycle one is a significant predictive factor for high-grade hematological complications (OR = 5.16; 95% CI, 3.92–6.79; $P < 0.0001$).[14]

Comparable results were reported from patients enrolled in the Australian Early Access Program (EAP), with a higher incidence of adverse events occurring early in the treatment course, which reduced with subsequent cycles. Apart from fatigue, all hematological adverse effects and diarrhea peaked in the first cycle, with neutropenia and febrile neutropenia rarely occurring after cycle 10.[16]

Analysis of data from the Italian EAP showed that 64 patients (29.6%) who completed 10 or more cycles reported a lower toxicity profile compared to the entire study cohort. The rate of treatment discontinuation due to adverse effects in the whole study population was 24.5% whereas it was very low (1.6%) in the subset of patients who had received ≥10 cycles and dose reduction was rarely needed after 10 cycles. There was an inverse relationship between the cumulative dose of cabazitaxel and incidence of high-grade hematological adverse events. The odds of adverse events occurring were reduced for every 10 mg/m^2 cumulative cabazitaxel dose in several parameters; neutropenia (−10%), febrile neutropenia (−48%) and anemia (−7%). Furthermore, no serious hematologic side effects were detected after 10 cycles.[40] Overall, there was only one report raising concerns regarding the risk of progressive peripheral neuropathy with extended use of cabazitaxel.[41]

QoL is an important parameter reflecting chemotherapy effect on the lives of incurable cancer patients receiving treatment that is prolonging survival. Effects of cabazitaxel on quality of life were studied in the United Kingdom Early Access Program (UK EAP) study. The results showed a trend towards improved QoL, assessed by both EQ-5D-3L and VAS scores, with increasing cycle number. Despite pain being assessed using nonvalidated methods, the proportion of patients reporting no pain was progressively increasing with the increased number of cabazitaxel cycles (57.1% at cycle 10% *vs* 22.3% at baseline).[15] Another study analyzed QoL in 104 patients using both physical and psychological assessment, where 21.2% received more than 10 cycles. There was a detected and stable trend throughout the treatment course that did not change by the number of cycles, with no difference in pain response from baseline to the end of treatment.[16]

Despite limitations due to retrospective nature and missing information in some studies, there is considerable evidence suggesting no negative impact from the extended duration of cabazitaxel treatment in terms of toxicity and QoL. Evaluation of extending cabazitaxel duration in prospective studies is needed to provide specific recommendations for responding to patients. However, given the relative lack of cumulative toxicity, treating beyond 10 cycles is a reasonable option, especially in the patient who is experiencing continued clinical benefit.

3.4 | Starting dose and dose reduction due to toxicity

Treatment-related toxicities are the major limitation of delivering an effective dose of chemotherapy and can have a negative impact on patients outcomes.[42] In the initial phase II study of cabazitaxel in breast cancer, a 20 mg/m^2 dose was used with dose escalation to 25 mg/m^2 if there was minimal toxicity, the later achieved in 28% of patients.[7] In the phase III TROPIC trial, the standard dose was set at 25 mg/m^2, but dose reduction to 20 mg/m^2 was required in 12% of patients due to adverse effects.[5] Subsequent studies reported dose reductions in up to 17.4% of patients.[14]

In clinical practice, lower cabazitaxel dose is used in those who develop serious adverse events including grade ≥3 neutropenia, febrile neutropenia or neutropenic sepsis, grade ≥ 3 diarrhea and grade 2 peripheral neuropathy. However, upfront dose reduction may be considered in frail or elderly patients or those with infiltrated bone marrow since the risk of complications is very high.[16]

The survival outcomes of patients receiving a reduced starting dose of cabazitaxel were not confirmed until recently. The PROSELICA trial prospectively compared efficacy parameters of reduced (20 mg/m^2; C20) versus standard (25 mg/m^2; C25) doses of cabazitaxel, and results from 1200 patients showed similar overall survival, PFS, and pain response (Table 2). However, significantly higher PSA response was reported in standard dose arm compared with the reduced dose arm (42.9% *vs* 29.5%, $P < 0.001$) with longer time to PSA progression (6.8 months *vs* 5.7 months). Higher adverse events were observed in

TABLE 3 Outcome measures of reduced *vs* standard dose cabazitaxel (C20 *vs* C25)

	PROSELICA trial (post-docetaxel)[8]		FIRSTANA trial (chemotherapy-naïve)[43]	
	C20 ($n = 598$)	C25 ($n = 602$)	C20 ($n = 389$)	C25 ($n = 388$)
OS Median, months	13.4	14.5	24.5	25.2
Composite PFS Median, months	2.9	3.5	4.4	5.1
PSA response (% of patients)	29.5	42.9	60.7	68.7
Pain response (% of patients)	34.7	37.3	45.5	43.3
Neutropenia, grade ≥3 (% of patients)	41.8	73.3	37.8	70.6
Febrile neutropenia/neutropenic infection, grade ≥3 (% of patients)	2.1	9.2	1.4	5.9
Diarrhea, grade ≥3 (% of patients)	1.4	4.0	3.5	5.6
Fatigue, grade ≥3 (% of patients)	2.6	3.7	1.6	3.1
Dose reduction (% of patients)	10.2	21.7	13.6	35.8

standard dose patients, leading to higher rates of dose delays and reductions compared to the reduced dose arm. Analysis of patient subsets demonstrated superior results for reduced dose in patients with poor performance status (ECOG ≥2) and patients with the metastatic bone disease.[8]

Concordant results have been reported in the FIRSTANA trial comparing cabazitaxel, both reduced (20 mg/m^2) and standard dose (25 mg/m^2), in chemotherapy-naïve patients with mCRPC against docetaxel. No significant differences in major outcomes between all groups were found, and a lower incidence of serious adverse effects was shown with reduced dose cabazitaxel (Table 3).[43]

The conclusion of these trials was that a reduced dose of cabazitaxel of 20 mg/m^2 did not compromise patient outcomes and can be considered as an effective and safer alternative to standard dose 25 mg/m^2. This is particularly important in patients in whom intolerable toxicity may be predicted, such as those with poor performance status or advanced age.

3.5 | Chemotherapy naïve mCRPC

Higher potency and a lower rate of resistance, including P-gp positive resistant variants[44] suggest a potential role for cabazitaxel as initial chemotherapy for mCRPC to overcome the resistance developed by tumor cells against docetaxel.

The efficacy of cabazitaxel in chemotherapy naïve patients as the first line has been compared to docetaxel in the phase III FIRSTANA trial. No significant difference was found between cabazitaxel, both reduced (C20) and standard (C25) doses, and docetaxel (D75) regarding overall survival (C20: 24.5 months, C25: 25.2 months, D75: 24.3 months) and progression-free survival (C20: 4.4 months, C25: 5.1 months, D75: 5.3 months). The rate of PSA response was equivalent in all groups with a higher rate of tumor response with cabazitaxel (C25). High-grade toxicities were lower with reduced dose cabazitaxel (C20: 41.2%, C25: 60.1%, D75: 46%).[43] Unlike the TROPIC study, the number of cycles was not limited to 10. This study suggests that cabazitaxel could be reserved a preferred option for a patient with comorbidities that can be worsened by docetaxel.

Other approaches to use cabazitaxel in the first line include the early taxanes switch protocol. The phase II study, TAXYNERGY trial, tested the use of either cabazitaxel or docetaxel as first-line chemotherapy followed by crossing over the therapy in patients with a PSA response <30% early in the treatment course (within weeks 12). Of the 63 patients enrolled, 22 patients received cabazitaxel with only 3 of 22 patients (13.6%) switching to docetaxel, whereas 12 of 41 (39.3%) switched from docetaxel to cabazitaxel. The primary endpoint, which was a ≥50% PSA response rate, was achieved in 55.6% of all patients, higher than previously reported in docetaxel trials.[4] Of the 15 patients who switched early, 7 of 15 (46.7%) showed subsequent PSA response. The safety of cabazitaxel as first-line therapy (19 patients) was comparable to other studies; neutropenia 10.5%, febrile neutropenia 15.8%, diarrhea 5.3% and fatigue 15.8%. Interestingly, no hematological events were detected in the 15 patients who switched treatments, and of the noticeable nonhematological adverse effects, only peripheral neuropathy (13.3%) and fatigue (20%) was observed. Although survival analysis was not included, the early switch of first-line taxanes has shown preliminary results that should be considered for further evaluation in larger studies.[45]

Another proposed approach is to use a combination of cabazitaxel and mitoxantrone in chemotherapy naïve patients. The combination was tested in a phase I study showing considerable response with median overall survival 23.3 months and PSA response in 60% of patients. However, the use of this regimen could be limited by the cumulative myelosuppressive effects of the combination of both drugs.[46]

It is possible that future research will investigate cabazitaxel further in the front setting for mCRPC treatment to determine approaches that enhance outcomes with the lowest risk of toxicity, especially cumulative toxicity.

4 | CONCLUSION

Cabazitaxel prolongs overall survival in patients with mCRPC and is well tolerated, especially after the first cycle where the risk of febrile

neutropenia and diarrhea is at its highest. Randomized trials confirm the utility of reduced dose without compromising efficacy and should be considered especially in special risk groups such as frail patients, the elderly, and those with evidence of bone marrow impairment. Cabazitaxel has similar efficacy to docetaxel in the first-line chemotherapy setting. There are no prospective trials examining the relative utility of cabazitaxel versus novel androgen axis inhibitors, and retrospective data are inconclusive. Studies are needed to provide definite answers for the preferred optimal sequence of these life-prolonging agents. Initial studies of cabazitaxel limited the number of cycles to 10, but subsequent compassionate use programs indicate that giving more than 10 cycles is feasible and does not appear to lead to cumulative toxicity. Whether a benefit exists for treating beyond 10 cycles is unproven and warrants further investigation, although continued treatment with cabazitaxel is an option in those who experience continued clinical benefit.

CONFLICTS OF INTEREST

Loma Al-Mansouri: None.

Howard Gurney: Advisory board for Astellas, Sanofi-Aventis, Janssen.

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