Optimal management of patients receiving cabazitaxel-based chemotherapy

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Abstract

The emergence of chemotherapy as a survival-improving treatment for metastatic castration-resistant prostate cancer has focused attention on the need for effective prevention and management of side effects. The most recent chemotherapeutic agent in this setting is cabazitaxel, licensed for use when the disease progresses on or after docetaxel-based treatment. Experience with cabazitaxel shows that, as with docetaxel, its side effects are largely predictable and manageable using methods that are already well-known to oncology teams. Patient education, clear instructions for when and how patients should seek advice, and properly implemented local policies on side effect management are essential to optimal patient care.

Introduction

There are currently three licensed treatments that offer a survival benefit for men with metastatic castration-resistant prostate cancer (mCRPC): (1) first-line chemotherapy with docetaxel; (2) second-line chemotherapy with cabazitaxel; and (3) the hormonal agent abiraterone.[1-3] There are also various other promising agents on the horizon. As discussed previously in this supplement on page S11),[4] rational sequencing of these agents is likely to play a pivotal role in ensuring optimal care for each individual patient. Another key factor is proactive management of side effects.

When the first of these treatments (docetaxel-based chemotherapy) was introduced, the likelihood of cytotoxic side effects was a potential hurdle. In part, the perceived barrier to chemotherapy reflected the advanced age of the patient population—the median age of men at prostate cancer diagnosis is 67 years.[5] It also stemmed from lack of experience; before the TAX327 trial,[1] chemotherapy had not been used in prostate cancer outside of the setting of symptom relief. However, the TAX327 investigators and subsequent guideline authors advised that the survival benefit offered by docetaxel was worthwhile, and that the side effects could be managed through a combination of prophylaxis (where indicated), patient monitoring and appropriate intervention.[1,6,7] Furthermore, guidelines from the International Society of Geriatric Oncology (SIOG) state that advanced age is not a barrier to chemotherapy for mCRPC for individuals who are healthy (controlled comorbidities, independence in daily living and good nutritional status) or following effective interventions for any reversible impairments.[8]

Docetaxel is now the standard of care for men with mCRPC.[6,7] Moreover, since June 2011, multidisciplinary teams in Canada have had access to second-line chemotherapy, namely cabazitaxel, with the potential to improve overall survival once the disease has progressed during or after docetaxel. Once again, careful management of side effects is essential to ensure that eligible patients have access to the survival benefit offered by this treatment.

The TROPIC trial showed that the common side effects of cabazitaxel, notably neutropenic complications, diarrhea and fatigue/asthenia (Table 1, Table 2), are typical of cytotoxic agents, hence their management is familiar to experienced oncology professionals.[2] Of note, however, the adverse events associated with chemotherapy generally occur several hours or days after the administration of treatment, so detailed patient education/counselling on symptom recognition, self-care and when/how to seek professional advice is a key component of effective side effect management.

This article looks at the common side effects of cabazitaxel, and how they can be optimally managed. We also present case studies of patients who have been treated with cabazitaxel in Canada, showing how it is used in the context of ongoing management of mCRPC.

Table 1. Common adverse events in the TROPIC trial (restricted to those with ≥5% incidence at grade ≥3 in the cabazitaxel arm)[2]

Adverse events experienced by patients*	Cabazitaxel (n=371)		Mitoxantrone (n=371)	
	Any grade, %	Grade ≥3, %	Any grade, %	Grade ≥3, %
Febrile neutropenia	-	8	-	1
Diarrhea	47	6	11	<1
Fatigue	37	5	27	3
Asthenia	20	5	12	2

*Excludes hematological events detected by laboratory tests, but not described clinically.

Infusion-site reactions/extravasation

Incidence

Infusion-site reactions (any grade) and extravasation (any grade) were rare in the TROPIC trial, being reported in one patient each in the cabazitaxel arm.[10]

Management

Because cabazitaxel is neither a vesicant nor an irritant, it may be administered via either a central or peripheral line. However, in general, there is a reduced risk of extravasation when chemotherapy is given centrally rather than peripherally.[11] Because extravasation and infusion-site reactions are rare with the agent, there are no specific recommendations for their prevention and management in cabazitaxel recipients.

Neutropenic complications

Incidence

As described earlier in this supplement (Saad F, Asselah J, pg. S5),[12] febrile neutropenia was more frequent with cabazitaxel (8%) than with mitoxantrone (1%) in the TROPIC trial, and neutropenic complications were the most frequent cause of death in the cabazitaxel arm (2% of recipients).[2] However, neutropenia-related deaths ceased once the investigators were reminded to follow the trial protocol to minimize the risk of febrile neutropenia, and only two treatment-related deaths (one each in the cabazitaxel and mitoxantrone arms) were recorded in the North American trial population.[13] It was noted, in a commentary accompanying the TROPIC report, that differences between investigators in the management of febrile neutropenia might have explained the pattern of treatment-related mortality seen in the trial.[14]

Management

Patients receiving cabazitaxel may be considered for prophylactic antibiotics or granulocyte colony-stimulating factor (G-CSF), based on institutional guidelines, or those from the American Society of Clinical Oncology (ASCO).[15,16] The latter suggest that a high risk of neutropenic complications is indicated by age >65 years, extensive prior radiotherapy, poor nutrition, previous febrile neutropenia, poor performance status and serious comorbidities. Local guidelines are often more conservative; for example, some centres in Canada base the use of prophylactic G-CSF mainly on previous experience of febrile neutropenia (e.g., with docetaxel).

The manufacturer of cabazitaxel recommends weekly complete blood counts during the first treatment cycle, then before each subsequent cycle thereafter.[15] If grade ≥3 neutropenia persists for more than a week, or if the patient develops febrile neutropenia, cabazitaxel treatment should be delayed until the neutrophil count exceeds 1500 cells/mm^3, and any symptoms of febrile neutropenia resolve, and the dose should be reduced from 25 mg/m^2 to 20 mg/m^2.

To ensure early detection and appropriate treatment of febrile neutropenia, all oncology services that offer myelosuppressive treatments should have clear local protocols for patient education (both verbal and written) and rapid assessment and intervention, with specific provision for days/times outside of normal clinic hours. Patients must be made aware of the need to monitor their temperature and to seek advice immediately, via clearly specified local contact arrangements, if they have a reading of 38°C or higher and/or develop flu-like symptoms. It is important to stress

Table 2. Grading of diarrhea and fatigue[9]

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	Increase of <4 stools per day over baseline	Increase of 4-6 stools per day over baseline	Increase of ≥7 stools per day, incontinence, hospitalization indicated	Life-threatening consequences, urgent intervention indicated
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest, limiting to instrumental activities of daily living	Fatigue not relieved by rest, limiting to self-care activities of daily living	Not categorized

that patients should not wait to see if their symptoms resolve before making contact. Assessment needs to be conducted by professionals who are aware of the risk of febrile neutropenia in chemotherapy recipients. Where febrile neutropenia is suspected, patients should receive antibiotics (intravenously or orally, depending on risk assessment), according to local agreements (e.g., ceftazidime 1 g 8-hourly or piperacillin 3.375 g 6-hourly), and this treatment should be initiated without awaiting the results of bacterial culture.[17] Note that diarrhea in the presence of febrile neutropenia warrants particularly urgent management.

Diarrhea

Incidence

In all, 47% of cabazitaxel recipients in the TROPIC trial reported diarrhea. Grade ≥3 diarrhea was less common; it was seen in 6% of cabazitaxel recipients.[2] However, even mild diarrhea can reduce patients' quality of life (e.g., through restriction of normal activities), and its effective management is central to the care of patients receiving a wide range of different cytotoxic treatments.[18]

Management

The management of chemotherapy-induced diarrhea depends on patient education, prompt intervention and accurate assessment. Patients need to be made aware that they may experience diarrhea following their cabazitaxel dose. In addition to advice on dietary manipulation (e.g., adequate fluid intake, avoidance of spicy, fatty or high-fibre foods), patients should be given a prescription for anti-diarrheal medication (e.g., the absorbent agent loperamide), and advised to have the treatment ready for use as soon as they experience loose stools.[18]

Patients should also contact their chemotherapy team so that their diarrhea can be graded. Patients with severe diarrhea may be advised to phone for advice immediately, even if outside of normal clinic hours; where the symptoms are less severe, the phone call can be made during the next clinic session. The patient should be given clear information on what constitutes severe diarrhea, and who to call for advice. Depending on the assessment, the patient may need over-the-phone advice or a face-to-face consultation—in some cases as soon as possible. Occasionally, the patient may need to be admitted to hospital for treatment (e.g., for grade ≥3 diarrhea plus fever), which may indicate febrile neutropenia (to be managed as per local protocols), or for intractable symptoms, which may indicate an infection such as *Clostridium difficile* (again, to be managed as per local protocols).[18]

Where grade ≥3 diarrhea persists despite appropriate management, the next cycle of cabazitaxel should be delayed until the symptoms have improved, and the cabazitaxel dose should be reduced from 25 mg/m^2 to 20 mg/m^2.[15]

Fatigue/asthenia

Incidence

Fatigue, along with weakness and lack of energy, is commonly reported by patients undergoing chemotherapy, and can be a distressing side effect, with negative implications for quality of life.[19] However, its pathophysiology is poorly understood. In the TROPIC trial, fatigue was reported in 37% of cabazitaxel recipients and asthenia in 20% (compared with 27% and 12%, respectively, in the mitoxantrone arm). At grade ≥3, both side effects had a 5% incidence in the cabazitaxel arm, versus 3% (fatigue) and 2% (asthenia) with mitoxantrone.[2]

Management

The experience of fatigue and/or asthenia can be a source of alarm to patients who have previously been fit and active. To allay such fears, it is useful to explain, before treatment starts, that many chemotherapy regimens can cause feelings of tiredness and weakness.[18] Patients should be monitored for such symptoms before every treatment, and some may find it helpful to record their fatigue levels in a symptom diary.[19] Specific advice should be given on planning, prioritizing, delegating and postponing activities, although patients may also benefit from moderate physical exercise. Other nonpharmacological approaches include nutritional intervention to address changes in diet, and sleep therapy to combat insomnia or hypersomnia. In some patients, symptoms of fatigue or asthenia may be a sign of comorbidity (e.g., thyroid disorder or depression), which can be managed as appropriate.[19]

Conclusion

Experience to date with cabazitaxel in the treatment of patients with mCRPC that has progressed during or after docetaxel has shown that it benefits survival, and has a predictable, manageable side effect profile.[2] The side effects of greatest note are neutropenic events, diarrhea and fatigue/asthenia. Their management is familiar to oncology teams, and relies on careful patient education, preventive strategies where appropriate, patient monitoring where indicated, and vigilant intervention and/or dose modification as required.

With clear and properly implemented local policies on side effect management, it is hoped that many men in Canada will be able to reap the benefits of second-line chemotherapy for mCRPC.

Competing interests: Dr. Catherine Sperlich has participated in advisory boards for Amgen, Janssen and Sanofi, and has received speaker honoraria from Amgen, Janssen, Novartis and Sanofi. Fred Saad has served as a consultant and has been involved in research with Amgen, Astellas, Janssen, Novartis and Sanofi.

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Box. 1. Patient A: docetaxel (8 cycles), cabazitaxel (10 cycles), then abiraterone (5 months) (Fred Saad, personal report)

Patient A, currently aged 58 years, was diagnosed with prostate cancer (Gleason score 8) in 1999, at the age of 45 years. He underwent radical prostatectomy, radiotherapy and several years of hormonal therapy until 2009, when his disease was deemed to be castration resistant, and he developed pain and deterioration in his quality of life. Docetaxel-based chemotherapy was initiated in October 2009, and was stopped after cycle 8, on disease progression. The patient also received zoledronic acid between October 2009 and September 2010, which was halted because of a rise in creatinine.

He developed significant pain in the lumbar spine, for which palliative radiotherapy was delivered in June 2010. A bone scan in July 2010 showed an increase in lesions. In August 2010, Patient A was randomized to receive either MDV3100 or placebo as part of the AFFIRM clinical trial. No response was noted, and it was later determined that the patient had been in the placebo arm of the study. In December 2010, there was evidence of prostate-specific antigen (PSA) progression. In February 2011, the patient was administered palliative pelvic radiotherapy to address his pain.

He experienced a significant increase in pain from April 2011. As soon as cabazitaxel-based chemotherapy became available, it was initiated (June 2011; baseline PSA 40 µg/L). No prophylactic antibiotics or G-CSF were administered. The patient experienced a significant improvement in pain and overall well-being immediately after the first cycle. He went on to receive 10 cycles of cabazitaxel (finishing in December 2011), with no dose delays or dose reductions, and his PSA reached a nadir of 4 µg/L at cycle 5. The patient was delighted with the treatment, and with the reduction in pain and fatigue. As with the first line of chemotherapy, he had no adverse events.

A slow rise in his PSA was detected at cycle 8, but there was no evidence of radiographic or symptomatic progression. However, the disease went on to progress biochemically as well as radiologically, and he began to develop pain 2 months after stopping cabazitaxel. Abiraterone was started in February 2012. After 2 months of therapy, there was reduction in PSA and pain, but abiraterone was stopped after 5 months because of significant disease progression and deterioration of performance status.

At the time of writing (October 2012), Patient A is alive and living at home, but his performance status has declined significantly and he is about to be transferred to the palliative care unit. He has survived for over 3 years with mCRPC.

The management of Patient A is an example of the sequential approach to treating mCRPC (i.e., the benefits of multiple therapies used in turn. I believe that this strategy led to additive improvements in the patient's survival).

Rational sequential use of the increasing number of agents available for mCRPC can be achieved in a cost-effective manner, and in some cases may lead to excellent results. The remaining challenge is how to decide the order in which to use the agents, and knowing when to stop each treatment, with the aim of maximizing each patient's opportunity of accessing as many potentially effective interventions as possible.

Box 2. Patient B: docetaxel (9 cycles), abiraterone (8 months) then cabazitaxel (10 cycles) (Fred Saad, personal report)

Patient B was diagnosed with prostate cancer (Gleason score 3+4) in 1995. He underwent radical prostatectomy and pelvic lymphadenectomy, and was found to have stage T3 disease with metastases to two pelvic lymph nodes. Hormonal therapy was started immediately after surgery.

Asymptomatic mCRPC (with bone metastases) was diagnosed in 2007, and the patient was enrolled into a phase III trial of immunotherapy (CG1940 and CG8711) versus docetaxel plus prednisone.[20] He was randomized to the docetaxel arm, and received 9 cycles, finishing in December 2007. He remained clinically stable for a year, but his PSA began to rise significantly towards the end of 2008, and disease progression was detected on bone scan. Patient B received zoledronic acid from November 2008 until November 2011, when he developed mild osteonecrosis of the jaw following a tooth extraction.

In March 2009, Patient B commenced abiraterone as part of the COU-AA-301 trial of abiraterone versus placebo [Asselah J, Sperlich C, pg. S11].[3,4] He responded well to the treatment—his PSA at the commencement of the trial was 88 µg/L, and reached a nadir of 13 µg/L in January 2010. Abiraterone was halted in November 2010 after the detection of significant disease progression, and the patient received a single dose of palliative radiotherapy to address pain in his left hip.

The patient had temporary relief of pain, but then his disease progressed biochemically, radiologically and symptomatically. In light of this progression, cabazitaxel was commenced in January 2012 (baseline PSA 90 µg/L). Ten cycles were delivered without prophylactic antibiotics or G-CSF. He responded well to this third line of treatment for mCRPC, and continues to respond. At his tenth cycle, his PSA was 14 µg/L, and a month later, it had fallen further to 12 µg/L. He tolerated the treatment well, other than experiencing mild diarrhea during the first 2 cycles, which resolved without medical intervention. Indeed, he felt well enough throughout his chemotherapy to drive himself to the hospital for all of his cabazitaxel infusions—a round trip of 3 hours every 3 weeks.

At the time of writing (October 2012), Patient B is 75 years old and has lived with mCRPC for over 5 years. He still enjoys an active life (he is involved in the renovation of his house), and has no pain.

This case demonstrates the ongoing benefits of active treatment for mCRPC, and shows that an older patient may well be able to tolerate and respond well to cabazitaxel, even in the third-line setting.

Box 3. Patient C: docetaxel (8+8 cycles), cabazitaxel (5+10 cycles), then abiraterone (ongoing) (Catherine Sperlich, personal report)

Patient C was 57 years old when he was initially diagnosed with metastatic prostate cancer in 2002. He was treated with hormonal therapy for about 5 years before he went on to develop mCRPC.

In September 2007, with a PSA level of 146 µg/L and evidence of bone progression, he commenced docetaxel-based chemotherapy, plus zoledronic acid. In May 2008, after 8 cycles of docetaxel, his PSA had dropped to 49 µg/L. Docetaxel was halted, but was recommenced in September 2009 when the patient had symptomatic bone lesions and a PSA of 520 µg/L. He received a further 8 cycles. By cycle 4, there was a response in terms of both pain and PSA, but the disease progressed thereafter, reaching a PSA of 869 µg/L, and the patient was enrolled into a trial of radiotherapy with/without ipilimumab in 2010. This treatment was complicated by hepatitis, but the patient eventually showed an improvement in his performance status. Palliative radiotherapy was administered in late 2010, while he was still on the trial protocol and had evidence of bone progression, pain and a PSA of 3490 µg/L. A few weeks later he still showed signs of bone progression, but his PSA had fallen to 2701 µg/L.

He came off the trial in March 2011, and embarked on cabazitaxel-based chemotherapy. At this time he had a PSA of 2882 µg/L and a low hemoglobin count of 87 g/L. A blood smear also showed multiple dacryocytes, indicating that metastatic disease had infiltrated the bone marrow. At cycle 1, the patient was receiving regular blood transfusions, and treatment with epoetin alfa, as well as narcotic analgesia. However, with further cycles of cabazitaxel, the requirement for transfusions and narcotic analgesia reduced, as did the patient's PSA (nadir 914 µg/L in January 2012).

His performance status improved after the first cycle of cabazitaxel. His second cycle was delayed by a week because of an upper respiratory tract infection not requiring antibiotics, and treatment was halted temporarily after cycle 5 (June 2011; PSA 1395 µg/L) when the patient developed a fever of unknown origin. This fever was treated in hospital, with intravenous antibiotics. However, at no time was there any evidence of neutropenia. In July 2011, during his break from cabazitaxel, the patient's PSA rose to 2031 µg/L, and there was a decline in his performance status.

Cabazitaxel was restarted (i.e., cycle 6) in August 2011. After 3 further cycles, the patient showed improved performance status and a reduction in pain, PSA and markers of bone progression. In view of the patient's good response, a decision was made to continue cabazitaxel beyond 10 cycles. At cycle 13 he still showed reduction in PSA (914 µg/L) and no pain. However, at cycle 14, there was a rise in PSA (933 µg/L). Cabazitaxel was stopped when the patient developed pain and a further rise in PSA (997 µg/L) before the 15th cycle, which was administered in February 2012. Throughout his cabazitaxel treatment, Patient C had no documented neutropenia or febrile neutropenia, and did not receive G-CSF prophylaxis.

In March 2012, 12 months after the commencement of cabazitaxel, the patient was switched to treatment with abiraterone. This treatment is still ongoing and is well-tolerated. The patient has again been able to reduce his narcotic usage and has increased his activity level. His PSA level in June 2012 was 261.4 µg/L, and he is transfusion independent.

This case study shows that cabazitaxel chemotherapy is a viable option even for heavily pre-treated patients with evidence of lowered bone marrow reserve as a result of prior radiotherapy or prior chemotherapy. It is notable that Patient C experienced no neutropenic adverse events, even in the absence of G-CSF prophylaxis.

Although the TROPIC trial of cabazitaxel treatment was based on 10 treatment cycles,[2] it was decided to continue beyond this number, based on his response to the agent and the absence of additional toxicity. Treatment was stopped only when the patient showed clinical signs and symptoms of progression as well as PSA progression.

Continued access to new therapies, administered in a timely fashion, has extended this patient's survival above the expected median for mCRPC. He remains alive and well, despite having been diagnosed with mCRPC 5 years ago.

Box 4. Patient D: docetaxel (7+10+2 cycles), cabazitaxel (10 cycles), then abiraterone (6 months) (Catherine Sperlich, personal report)

Patient D was 56 years old when he was first diagnosed with metastatic prostate cancer, and his disease became castration resistant 2 years later in 2004. After a trial with ketoconazole, to which he did not respond, he commenced docetaxel-based chemotherapy. His PSA fell from 67 μg/L to 38 μg/L after 7 cycles, but the treatment was halted because of fatigue and Cushingoid symptoms. A month later (April 2005), the patient started vincristine and oral cyclophosphamide. He received 4 cycles, and his PSA fell to 28 μg/L. After a subsequent rise in PSA, to 32 μg/L, the patient was given 2 cycles of mitoxantrone. Because of a persistently rising PSA, Patient D restarted docetaxel in August 2005. He received 10 cycles, finishing in February 2006. He reported fatigue that did not interfere with daily living, and his PSA fell to 52 μg/L, after an initial rise. In April 2006, his ongoing goserelin was stopped because of persistent fatigue.

Throughout the rest of 2006, his disease was stable, both clinically and radiologically, but his PSA rose to 181 μg/L in January 2007, and imaging showed worsening of his disease in bone and lymph nodes. Docetaxel was restarted, and after 2 cycles his PSA rose to 309 μg/L. At this point, it was found that the patient no longer had castrate levels of testosterone, so docetaxel was interrupted, and goserelin was resumed, achieving a PSA reduction to 240 μg/L. From May 2007 to September 2009, the patient received daily oral cyclophosphamide plus dexamethasone, during which time his PSA reached a nadir of 2.3 μg/L and he was able to stop all narcotic treatment. Cyclophosphamide plus dexamethasone was administered again between March and September 2010, and was stopped because of a rising PSA.

A rapid rise in PSA was noted between December 2010 (56 μg/L) and January 2011 (86 μg/L), and a 10-cycle course of cabazitaxel was started in February 2011, without any primary prophylaxis for neutropenia. The increase in PSA continued initially, reaching 161 μg/L at cycle 4, but fell to 100 μg/L before cycle 7. There was a short break in the treatment course before cycle 7, as a result of a statutory holiday.

Although he had some side effects, Patient D felt generally well throughout his cabazitaxel treatment. He developed febrile neutropenia at cycle 7, requiring hospital admission for 3 days for intravenous antibiotic treatment and blood transfusion. Thereafter, he received G-CSF for 7 days following each cycle of cabazitaxel, and developed no further neutropenic complications. He occasionally had leg edema, which required no intervention. Hematuria was detected after cycle 9, but no pathology was identified, and it was noted that the patient had also been taking naproxen and warfarin. The problem resolved without intervention. Anemia (hemoglobin 86 g/L) after cycle 3 necessitated blood transfusions in June, July and September. Mild hepatic enzymitis (aspartate aminotransferase, 125 U/L; alkaline phosphatase, 287 U/L) was detected after cycle 6 and resolved without intervention. The patient also reported slight fatigue during his cabazitaxel course, particularly when he was anemic and during the mild hepatitis. No therapy was required, other than the transfusions. Overall, the patient reported a feeling of well-being, and declined to stop cabazitaxel even in the face of rising PSA.

The final (10th) cycle of cabazitaxel was delivered in September 2011. At this time the patient's PSA was 97.6 μg/L, and he started abiraterone the following month, without any additional imaging. His PSA rose over the next months, reaching 550 μg/L in April 2012, and he developed shortness of breath, fatigue and leg edema, and required further blood transfusions. Abiraterone was stopped and degarelix was prescribed in place of goserelin. Cyclophosphamide plus dexamethasone was restarted in July 2012. At the latest follow-up, his PSA had decreased to 272 μg/L and he reported that he was feeling better.

This case shows that a heavily pre-treated patient who has received multiple courses of docetaxel can respond to cabazitaxel. Also, although he lacked a sustained PSA response to cabazitaxel, the patient reported an increase in well-being and did not want to stop therapy. He had many side effects that could be attributed to either the disease or therapy, but these were easily managed and had very little clinical consequence. The episode of febrile neutropenia was short-lived, and the proper protocol was applied. The episode happened after cycle 6, so secondary prophylaxis was required for only the final 4 cycles.