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Article

Intravenous therapies for castration-resistant prostate cancer: Toxicities and adverse events☆

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Abstract

Prostate cancer (CaP) continues to be a significant burden on men's health. While significant advances have been made in the diagnosis and treatment of localized disease, androgen deprivation therapy remains the treatment of choice for advanced and metastatic disease. However, once a man progresses on androgen deprivation, therapies targeting castration-resistant CaP have been extremely limited until quite recently. Urologic oncologists who wish to play an active role in the treatment of men with CaP from diagnosis through end-of-life care should be familiar with administration of and toxicities associated with chemotherapeutic agents. This review is directed at urologists and urologic oncologists and will discuss many of the FDA-approved intravenous agents currently available for castration-resistant CaP with a specific focus on the side-effects associated with these regimens. Published by Elsevier Inc.

Keywords: Prostate cancer; Castration-resistant prostate cancer (CRPC); Chemotherapy; Toxicity; Mitoxantrone; Docetaxel; Cabazitaxel; Zoledronic acid

1. Introduction

Prostate cancer (CaP) continues to be a significant burden on men's health. Globally, more than 900,000 new cases of CaP are diagnosed and over 250,000 deaths are expected annually from the disease [1]. Among men in developed nations, CaP has the highest incidence and third highest mortality rate of any malignancy [1]. Within the United States, CaP affects more men than any other non-cutaneous malignancy with an estimated 217,730 new cases and 32,050 deaths in 2010 alone [2].

While androgen deprivation therapy (ADT) effectively reduces PSA and shrinks tumors in the vast majority of men with metastatic CaP, the duration of its effects are finite. Published series have found progression-free survival on ADT to be 14–20 months [3,4]. Therefore, nearly all men who ultimately die of CaP will have failed ADT and progressed to castration-resistant prostate cancer (CRPC) [5,6].

Treating these men with cytotoxic chemotherapy can be challenging because of their advanced age, medical comorbidities, and limited bone marrow reserves [7]. Prior to 2004, systemic therapies for CRPC were quite limited, with mitoxantrone being the only agent demonstrating clinical benefit in phase III studies. The development of taxane-based chemotherapy revolutionized the treatment of CRPC, improving both the quality and duration of many men's lives [8,9]. However, these therapies have unique and serious toxicities that urologic oncologists must consider before, during, and after treatment (Table 1). This review will focus on FDA-approved, intravenously administered therapeutics used in the management of CRPC.

2. Mitoxantrone

Until 2004, mitoxantrone was the only chemotherapy agent approved by the US FDA for treatment of CPRC. In two randomized phase III trials, mitoxantrone, given in combination with prednisone or hydrocortisone, was shown to provide pain relief for men with symptomatic CRPC [7,10]. Based on the results of the 1996 Canadian prospective, randomized trial of 161 men with symptomatic CRPC, the main toxicities associated with treatment were hematologic in nature and included WHO grade 3 or 4 neutropenia seen in 45% of 520 evaluable treatment cycles and throm-

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Table 1
Toxicities of systemic therapies for prostate cancer

Therapy	Indication	Mechanism of action	Significant toxicities
Mitoxantrone	Palliation of CRPC. No survival advantage, but may be considered for third line chemotherapy. Diminishing role given rapidly changing landscape of drugs with activity in prostate cancer	Inhibits topoisomerase II; interferes with RNA; crosslinks and breaks DNA	Neutropenia Cardiac toxicity (cumulative dose >140 mg/m^2)
Docetaxel	First-line chemotherapy for CRPC	Stabilizes microtubules inhibiting mitosis	Neutropenia Hypersensitivity reaction Peripheral neuropathy Fluid retention
Cabazitaxel	Second-line chemotherapy for CRPC after progression on docetaxel	Binds microtubules preventing mitosis	Neutropenia Neutropenic fever Diarrhea
Zoledronic acid	CRPC with bony metastases	Inhibits osteoclast activity reducing bone resorption	Fatigue Anemia Myalgia Fever Lower extremity edema Electrolyte abnormalities Osteonecrosis of the jaw

bocytopenia seen in 4.8% of 520 evaluable treatment cycles [7]. Neutropenia (absolute neutrophil count $<1.0 \times 10^9$/L) with fever was rare, occurring in only 9 of 796 treatment cycles, or 1.1%, and no deaths were associated with this complication [7].

In the pivotal trials of mitoxantrone, the subjects who received mitoxantrone and prednisone were more likely to experience grade 3 or 4 toxicities than those in the corticosteroid-only arm [7,10]. Cardiac toxicity, a well known consequence of mitoxantrone therapy, is more likely to occur at a cumulative dose >140 mg/m^2, and must be monitored for carefully, as reductions in left ventricular ejection fraction are often asymptomatic [7,10]. Unfortunately, mitoxantrone did not demonstrate a survival advantage in either of these pivotal studies, so the US FDA approved it in 1996 as a palliative measure only. It did, however, provide a useful benchmark to which future regimens could be compared.

As more agents with activity against CRPC become available, mitoxantrone is likely to be used much less frequently and only then in patient populations that have already failed more active and better tolerated therapies. Additionally, emerging data has shown that mitoxantrone therapy may increase the risk of secondary malignancies, specifically leukemia, further minimizing its role in contemporary CaP management [11,12].

3. Docetaxel

The advent of docetaxel-based regimens was a significant step forward in the treatment of CRPC; docetaxel not only palliated symptoms and improved quality of life, but also reduced PSA and prolonged survival [13,14]. The landmark TAX 327 trial compared two different dosing regimens of docetaxel (75 mg/m^2 i.v. every 3 weeks vs. 30 mg/m^2 i.v. given weekly) to mitoxantrone (12 mg/m^2 i.v. every 3 weeks) in men with advanced CRPC; patients in all three arms received prednisone (5 mg by mouth twice daily) [13]. Docetaxel (75 mg/m^2) given every 3 weeks was found to be superior to mitoxantrone in terms of PSA response rate (45% vs. 32%, $P < 0.001$), overall survival (OS) (median 18.9 months vs. 16.5 months, $P = 0.009$), and quality of life measures. Weekly docetaxel did not prolong overall survival when compared to mitoxantrone (median OS 17.4 months vs. 16.5 months, $P = 0.36$), but led to a significantly better PSA response rate (48% vs. 32%, $P < 0.001$).

Although docetaxel given every 3 weeks provided a statistically significant overall survival benefit, the 2.4 month median survival advantage associated with this agent appears modest. However, it must be noted that docetaxel was compared against mitoxantrone, an agent with known activity against CRPC; moreover, cross-over between study arms was allowed, and many patients progressing on mitoxantrone received docetaxel, potentially obscuring a larger survival benefit. Furthermore, docetaxel provided superior palliation and quality of life compared to mitoxantrone. This pivotal trial led to the FDA approval of docetaxel 75 mg/m^2 i.v. every 21 days plus prednisone 5 mg by mouth twice daily for 10 cycles for CRPC.

A variety of adverse events were noted on this study in all three arms. Serious adverse events (AEs) were more common among the group of subjects receiving docetaxel every 3 weeks (26%) and weekly (29%) than among the mitoxantrone cohort (20%) [13]. While reasonably well tolerated, among subjects receiving docetaxel every 3 weeks, 24% had their infusions delayed, 12% required dose reductions, and 11% required discontinuation of the agent due to an AE. Treatment related deaths were rare, with 1/332 subjects (0.3%) in the every 3-week docetaxel arm and 1/330 subjects (0.3%) in the weekly docetaxel arm

dying due to causes ascribed to the chemotherapy. The frequency of AEs was similar in both docetaxel regimes.

The overall incidence of grade 3 and 4 neutropenia was low (32%) and febrile neutropenia was rare (3%) in the every 3 week docetaxel arm. As expected, cardiac events were more commonly seen in the mitoxantrone group, but the majority of other toxicities were more frequently encountered in patients receiving docetaxel. The most common treatment related adverse events of any grade seen in patients receiving docetaxel every 3 weeks included alopecia (65%), fatigue (53%), neutropenia (32%), peripheral neuropathy (30%), nail/skin changes (30%), stomatitis (20%), fluid retention 19%), dyspnea (15%), and excessive tearing (10%) [13]. Docetaxel hypersensitivity reaction, a rare but serious AE associated with this agent, was not reported in this trial.

Docetaxel hypersensitivity reaction can range from a mild reaction to a life threatening one. These reactions were observed mostly in early studies with this agent and led to routine premedication with corticosteroids in later studies, virtually eliminating this complication. A variety of premedication regimens have been used; 8 mg of dexamethasone given 12, 3, and 1 hour before infusion is a popular schedule.

Neutropenia, defined as an absolute neutrophil count (ANC) $<$ 1500 cells/ul, was more commonly seen with 3-weekly docetaxel. Nearly one-third of TAX 327 subjects in this arm experienced grade 3–4 neutropenia (an ANC $<$ 1000 cells/ul), compared with only 2% of subjects in the weekly docetaxel arm [13]. Close monitoring of the WBC count in patients receiving chemotherapy is mandatory; if the ANC is $<$1500 cells/ul at the start of a cycle, treatment should be postponed until adequate recovery of counts. Grade 3–4 anemia occurred in 5% of both docetaxel arms while grade 3–4 thrombocytopenia occurred in only 1% of the docetaxel every 3-week arm.

Febrile neutropenia is a life threatening AE that is defined by a temperature $>$ 38.3 °C or 38.0 °C sustained for more than an hour in a patient with an ANC $<$ 500 cells/ul (or an ANC $<$ 1000 cells/ul with a predicted decrease to $<$500 cells/ul). This complication was observed in approximately 3% of patients receiving docetaxel every 3 weeks in the TAX327 study. Presenting symptoms can be subtle in the elderly and those receiving steroids; these patients may present with no fever or with low grade temperatures, with accompanying symptoms such as confusion, hypotension, hypothermia, and malaise. Since most men with advanced CaP are elderly, and all men receiving docetaxel receive steroids daily as well as for premedication, oncologists must be vigilant for this complication when using docetaxel for CRPC.

Approximately 30% to 50% of patients with febrile neutropenia have a documented or occult infection [15]. The most common pathogens identified are endogenous gastrointestinal or skin flora [15]. Although a major source of mortality associated with chemotherapy early on, the use of empiric broad-spectrum antibiotics at presentation is now the norm and has significantly improved the outcome associated with neutropenic fevers. The selection of empiric antibiotics is driven by patient factors and the clinical presentation. For uncomplicated febrile neutropenia, third generation cephalosporins with antipseuodomonal coverage (such as ceftazidime or cefipime) or a carbapenem are appropriate [15]. Further management should be guided by response to initial therapy, results from laboratory and imaging studies, and the patient's clinical course. Empiric gram-positive coverage does not seem to improve outcomes, but may be used in selected circumstances [15]. The routine use of granulocyte-colony stimulating factor (G-CSF) is not recommended.

Once a patient has recovered from febrile neutropenia, decisions regarding further chemotherapy must take into account several factors, such as the magnitude of anticipated benefit from continued therapy, severity of the febrile neutropenic illness, likelihood of repeated episodes of febrile neutropenia, etc. If it is determined that the risk–benefit ratio favors further treatment with docetaxel, the use of prophylactic G-CSF and a reduction in the dose of docetaxel should be considered. This approach should also be considered in men who had grade 4 neutropenia or a prolonged duration ($>$1 week) of neutropenia without a febrile episode. In patients at high risk of morbidity from neutropenia (elderly, immunocompromised, etc.), or those not tolerating the 3-weekly docetaxel regimen, using the weekly docetaxel dosing regimen is worthy of consideration as it has a lower incidence of neutropenia, although it has not been approved by the FDA for the treatment of CRPC.

Fluid retention is another notable side effect of docetaxel and is often seen with higher cumulative doses of the agent. Fluid retention can manifest as peripheral edema, pleural effusions, or ascites. The exact mechanism underlying this phenomenon is unclear, but it is hypothesized that capillary leak may be a contributing factor. Glucocorticoid premedication minimizes the incidence and severity of fluid retention. In patients with clinically significant or symptomatic fluid retention, diuretics and/or drug holidays are usually helpful.

Epiphora, or excessive tearing, is another relatively common and often distressing side effect of docetaxel and also appears to occur more frequently with higher cumulative doses of the agent. It was reported in 10% of men treated with docetaxel every 3 weeks but is more common with the weekly regimen (21%). Epiphora often presents after several cycles of docetaxel and is thought to be due to nasolacrimal duct stenosis. Supportive management and topical steroids in conjunction with discontinuation of docetaxel usually provides relief, and surgical correction is only rarely needed.

Sensory neuropathy, which occurred in 30% of subjects treated with docetaxel every 3 weeks, 24% of subjects treated weekly, and in 7% of subjects treated with mitoxantrone (P $<$0.0015 for both docetaxel arms when com-

pared against mitoxantrone), can severely impact a patient's quality of life [13]. Given the irreversible nature of this docetaxel side-effect, patients should be counseled about this AE prior to beginning therapy and closely monitored for its development throughout treatment.

A second docetaxel-based regimen, which administered docetaxel 60 mg/m^2 every 21 days and extramustine 280 mg three times daily on days 1–5, was also found to be superior to mitoxantrone 12 mg/m^2 plus prednisone 5mg by mouth twice daily in terms of median OS (17.5 months vs. 15.6 months, $P = 0.02$), PFS (6.3 months vs. 3.2 months, $P < 0.001$), and PSA response rate (50% vs. 27%, $P < 0.001$) [14]. However, the group given docetaxel and estramustine had significantly higher rates of grade 3–4 neutropenic fever (5% vs. 2%, $P = 0.01$), cardiovascular events (15% vs. 7%, $P = 0.001$), nausea and vomiting (20% vs. 5%, $P < 0.001$), metabolic abnormalities (6% vs. 1%, $P < 0.001$), and neurologic events (7% vs. 2%, $P = 0.001$) [14]. Additionally, 8 treatment related deaths occurred in the docetaxel and estramustine arm vs. 4 deaths in the mitoxantrone and prednisone arm [14]. Taken together, the toxicity profile of docetaxel and extramustine is unfavorable compared with that of docetaxel plus prednisone; this regimen is infrequently used in men with CRPC.

4. Cabazitaxel

Most patients receiving docetaxel either discontinue therapy due to toxicity or eventually develop progressive disease. Until recently, there were no standard or effective second-line treatments for CRPC patients who had progressed on docetaxel. Cabazitaxel, which is also a member of the taxane family, showed potent preclinical anti-tumor activity in CRPC cell lines [16]. Unlike other taxanes currently in clinical use, cabazitaxel appears to have relatively low affinity for P-glycoprotein, which may explain its activity in docetaxel and paclitaxel resistant preclinical models. Phase I and II trials found that 20–25 mg/m^2 was the optimal dose for cabazitaxel and that neutropenia was the primary dose limiting AE [17,18].

In a recently reported phase III trial (TROPIC), 755 men with metastatic CRPC who had progressed on docetaxel were randomized to receive either mitoxantrone 12 mg/m^2 i.v. every 3 weeks plus prednisone or cabazitaxel 25 mg/m^2 i.v. every 3 weeks plus prednisone. Patients randomized to receive cabazitaxel had significant improvements in OS (median 15.1 months vs. 12.7 months, $P < 0.0001$) as well as progression-free survival (PFS) (median 2.8 months vs. 1.4 months, $P < 0.0001$) [19]. Cabazitaxel is the first agent with demonstrated activity in post-docetaxel CRPC patients and was recently approved for clinical use in this setting by the US FDA.

The adverse event profile associated with this drug was similar to that seen with other taxanes. The most frequently reported grade 3–4 AEs in patients receiving cabazitaxel included neutropenia (82%) and diarrhea (6%). Eight percent of subjects in the cabazitaxel arm experienced neutropenic fever. Peripheral neuropathy of any grade was reported in 14% of subjects but grade 3 events were rare (1%). Cabazitaxel was discontinued because of an AE in 18% of study subjects and a total of 5% of subjects receiving cabazitaxel died within 30 days of their last dose of the drug.

The high incidence of neutropenia associated with cabazitaxel in the TROPIC trial is cause for some concern and may limit its use, particularly with the recent regulatory approval of other agents (such as abiraterone) with better safety profiles [20,21]. It has been hypothesized that the high degree of neutropenia seen with cabazitaxel may reflect poor bone marrow reserves in participants, all of whom had received prior docetaxel chemotherapy, with most also presenting with widespread disease and the potential for occult marrow infiltration. Given this AE profile, patients receiving cabazitaxel therapy should be carefully selected and closely monitored with particular attention to WBC counts [19]. Despite these challenges, cabazitaxel is currently the only approved agent for men with metastatic CRPC who have progressed on docetaxel and is a reasonable choice for second-line chemotherapy.

5. Zoledronic acid

Skeletal metastases are a hallmark of advanced CaP, occurring in more than 80% of men [22]. Advanced age and ADT exposure are additional risk factors for skeletal-related events (SRE), including fracture, pain, and disability. Complications from SREs are significant causes of morbidity in men with CRPC [23]. A prospective, randomized trial comparing the use of the bisphosphonate zoledronic acid to placebo in men with CRPC and bony metastases found that the zoledronic acid arm had fewer SREs and a longer median time to first SRE [24]. Survival was not affected.

Toxicities from zoledronic acid that were seen in at least 5% of subjects included fatigue, anemia, myalgia, fever, and lower extremity edema [24]. Grade 3–4 hypocalcemia and anemia occurred more commonly in the active treatment arm than with placebo. Similarly, grade 3 (but not grade 4) serum creatinine elevations were seen more commonly with zoledronic acid compared to placebo. These creatinine elevations were felt to be related to bisphosphonate dose and the rapidity of infusion [24]. Osteonecrosis of the jaw (ONJ) is a rare but serious side effect of bisphosphonate use that typically occurs in patients with poor dentition. All patients should undergo a dental evaluation and any necessary interventions should be performed prior to initiating zoledronic acid therapy.

6. Conclusion

The therapeutic armamentarium available to treat men with advanced CaP has grown significantly over the past

decade. Cytotoxic chemotherapy, from first-line docetaxel, to second-line cabazitaxel, to palliative mitoxantrone, and zoledronic acid for the prevention of SREs, offer considerable palliative as well as survival benefits to men with CRPC. However, each of these agents is associated with potentially debilitating or life-threatening toxicities that must be monitored and managed appropriately. By understanding these toxicities, urologic oncologists can continue to provide optimal care to patients with CaP across the entire spectrum of their disease.

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