Practical guide to the use of chemotherapy in castration resistant prostate cancer

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Introduction: Chemotherapy, once thought to be toxic and ineffective in men with castration resistant prostate cancer (CRPC), has a significant impact on survival and quality-of-life in these patients. This article summarizes recent studies performed with two Food and Drug Administration (FDA) approved agents which have improved survival in men with CRPC, docetaxel and cabazitaxel.

Materials and methods: The literature on cytotoxic chemotherapy for castration resistant prostate cancer was reviewed. The individual efficacy, mechanisms of chemotherapeutic action, and appropriate disease states of administration were identified. Recent clinical trial results of chemotherapy combined with targeted agents was also reviewed.

Results: Front line cytotoxic therapy consists of docetaxel combined with prednisone. In two randomized trials, docetaxel based therapy demonstrated a 20%-24% improvement in survival over the palliative standard of care, mitoxantrone combined with prednisone. Eight randomized trials combining docetaxel/prednisone with other antiangiogenic, bone targeted, vaccine or metabolic therapies failed to demonstrate an improvement in survival over docetaxel alone. Cabazitaxel, an analogue of docetaxel which has activity in taxane resistant cell lines, is approved by the FDA, for use in CRPC patients who have previous exposure to docetaxel.

Conclusions: Docetaxel combined with prednisone remains the standard of care as first line cytotoxic therapy for CRPC. Cabazitaxel is an effective second line cytotoxic agent that improves survival; studies are underway comparing cabazitaxel to docetaxel as first line chemotherapy. Given its lack of survival benefit, as well as the emergence of new treatments for prostate cancer, mitoxantrone has a diminished role in the treatment of CRPC.

Key Words: castration resistant prostate cancer, docetaxel, cabazitaxel, chemotherapy

Introduction

It is estimated that more than 29000 men will die from metastatic prostate cancer in 2014, making it the second leading cause of male cancer death. The initial treatment for metastatic disease is surgical or medical castration; reduction in testosterone to levels of less than 50 ng/dL can rapidly and dramatically result in prostate tumor regression. Clinical response to androgen blockade is manifested by a relief in pain from boney metastases, improvement in neurologic symptoms from spinal cord compression, and a decline in serum prostate-specific antigen (PSA). Despite initial clinical and symptomatic improvement, nearly all men will progress to castration resistant prostate cancer (CRPC). This state of disease is defined as progression of face of castrate testosterone levels, historically have a dismal prognosis with median survival times of 9-12 months. In addition, the morbidity associated with CRPC is significant as metastases to bone can lead to spinal cord compression, fractures, pain, cachexia, anemia, and ultimately death.

In the 1990s, the management of CRPC was limited to palliation of symptoms, due to a lack of effective
treatments. Historically, chemotherapy for advanced prostate cancer was viewed as toxic and ineffective. Two reviews of single agent cytotoxic therapy in men with CRPC demonstrated that objective responses to chemotherapy were 6.5% to 8.7%, with no improvement in survival.\(^3,4\) The combination of mitoxantrone-prednisone was approved by the Food and Drug Administration (FDA) based on palliation of bone pain; three randomized trials also demonstrated modest improvements in time to progression when mitoxantrone combined with corticosteroids was compared to corticosteroids alone.\(^5,7\) Until 2004, CRPC was considered a chemotherapy resistant disease with no randomized study demonstrating a survival of chemotherapy.

**Docetaxel for CRPC**

A semisynthetic taxane derived from the needles of *Taxus baccata*, docetaxel. Docetaxel reversibly stabilizes microtubules and prevents depolymerization.\(^8\) Apoptosis results from accumulation of microtubules, as well as through phosphorylation of an oncoprotein, Bcl-2.\(^9\) Both in vitro and in vivo studies found docetaxel to be effective against a wide range of human cancer cell lines, including the prostate cancer cell lines DU 145, PC-3 and LNCaP.\(^10,11\) Phase I and II trials of docetaxel administered as a single agent or in combination with estramustine phosphate demonstrated PSA decline rates of > 50% in 36%-69% of treated patients, objective response rates of 17%-38% and median survivals of 20-23 months.\(^12,15\) Two phase III trials compared docetaxel-based combination regimens with standard mitoxantrone/prednisone in men with progressive CRPC, Figure 1 and Table 1.

**TABLE 1. Docetaxel based phase III trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment regimen</th>
<th>Objective measurable response rate (%)</th>
<th>PSA response rate (%)</th>
<th>% with palliative response</th>
<th>Time to progression (months)</th>
<th>Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG 9916</td>
<td>Docetaxel/estramustine</td>
<td>17</td>
<td>50</td>
<td>17*</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Mitoxantrone/prednisone</td>
<td>10</td>
<td>27</td>
<td>11</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>TAX 327</td>
<td>Docetaxel (q 3 wks)/prednisone</td>
<td>12*</td>
<td>45</td>
<td>35</td>
<td>7.9*</td>
<td>18.9</td>
</tr>
<tr>
<td></td>
<td>Docetaxel (q wk)/prednisone</td>
<td>8*</td>
<td>48</td>
<td>31</td>
<td>8.2*</td>
<td>17.4</td>
</tr>
<tr>
<td></td>
<td>Mitoxantrone/prednisone</td>
<td>7*</td>
<td>32</td>
<td>22</td>
<td>7.8*</td>
<td>16.5</td>
</tr>
</tbody>
</table>

*did not reach statistical significance

![Figure 1. Study designs of SWOG 99-16 and TAX 327.](image-url)
objective response rates were observed in the three treatment arms. Docetaxel therapy was associated with superior palliation of bone pain (33% and 31% in the docetaxel every 3 weeks and weekly regimens as compared to 21% in the mitoxantrone group). Quality-of-life, in general, when using the FACT-P instrument was significantly better in the docetaxel groups as compared to the mitoxantrone group.

Neutropenia was more frequent in the Q3 week docetaxel group (32% compared to 21.7% in the mitoxantrone group). Grade 3 and 4 neutropenia occurred in 3% of patients in the docetaxel Q3 week group, with 2.7% experiencing febrile neutropenia. Neuropathy and alopecia were also more frequent in the docetaxel arms; however the patterns of toxicity were not significantly different between the docetaxel and mitoxantrone groups.

SWOG lead an intergroup study comparing docetaxel/estramustine to mitoxantrone/prednisone. Men randomized to the experimental arm received estramustine at 280 mg PO tid on days 1-5, docetaxel at 60 mg/m² IV on day 2 every 21 days, and dexamethasone 60 mg PO in 3 divided doses prior to docetaxel. In contrast to TAX 327, patients did not receive prednisone. Men randomized to the control mitoxantrone arm received mitoxantrone at the same dosage and schedule as in TAX 327. Dose escalation to docetaxel 70 mg/m² or mitoxantrone 14 mg/m² was permitted for those patients who did not experience grade 3 or 4 toxicity in the first cycle of therapy. Docetaxel combined with estramustine improved median survival (17.5 months compared to 15.6 months, p = 0.01), progression-free survival (6.3 months compared to 3.2 months, p < 0.001). A greater percentage of patients demonstrated a > 50% PSA decline (50% as compared with 27%, p < 0.0001) with docetaxel/estramustine than mitoxantrone/prednisone. A trend towards an improved rate of objective responses in measurable soft tissue disease was noted in favor of Q 3 week docetaxel (17% versus 11%, p = 0.030). In addition, palliation of bone pain was not found to be statistically different in the two arms. Overall, the relative risk of death was reduced by 20% with docetaxel and estramustine as compared to mitoxantrone and prednisone (HR for death, 0.80; 95% CI: 0.67-0.97).

Grade 3 and 4 toxicities was reported at higher rates in the docetaxel prednisone arm compared to mitoxantrone/prednisone. The incidence of grade 3 or 4 cardiovascular (15% versus 7%, p = 0.001), neurological (7% versus 2%, p = 0.001), neutropenic fever (5% versus 2%, p < 0.001), gastrointestinal (20% versus 5%, p < 0.001), and metabolic disturbances (6% versus 1%, p < 0.001) were increased in the experimental arm. However, there was not a higher rate of discontinuation from the study and there was no increase in toxic deaths in the docetaxel/estramustine arm. Prophylactic anticoagulation with Coumadin and aspirin was added to the experimental arm approximately half way through the trial. A post-hoc analysis of toxicity revealed that anticoagulation decreased the rate of cardiac ischemia but not the rate of thrombosis. However, the evaluation of the use of anticoagulation is limited as the trial was not designed to detect a difference in vascular events for patients using anticoagulation as compared to those who did not receive Coumadin and aspirin.

Docetaxel based investigational therapies

A number of novel agents have been investigated for combination with docetaxel in an attempt to improve survival and response in patients with CRPC. The results with docetaxel-based combination therapy have been disappointing. Although serum VEGF levels correlate inversely with survival, antiangiogenesis agents (bevacizumab, aflibercept, lenalidomide,) combined with docetaxel/prednisone have not been a therapeutic advance. Combinations of bone targeted agent such as atrasentan, dasatinib, and ZD4054 with docetaxel have also had disappointing results. Vitamin D (calcitriol, DN-101 combined with weekly docetaxel also demonstrates no survival advantage over docetaxel/prednisone. Reasons for the failure of combination therapy include marginal activity of the agents that were combined with docetaxel, as well as dose reduction of docetaxel due to overlapping toxicities.

Cabazitaxel

Granted fast track designation in November of 2009, cabazitaxel combined with prednisone was approved by the FDA in June 2010 for the treatment of men who had previously received a docetaxel-based regimen for CRPC. Cabazitaxel is the third cytotoxic agent to be approved by the FDA for castration resistant disease, and the second to demonstrate a survival benefit over mitoxantrone combined with prednisone.

Mechanism of action

Similar in structure and antitumor mechanism to paclitaxel and docetaxel, cabazitaxel is a novel second-generation, semisynthetic taxane that induces cell
death by microtubule stabilization through inhibition of disassembly. Cabazitaxel binds the N-terminal amino acids of the beta-tubulin subunit, and promotes stabilization of microtubules and the mitotic spindle. In addition to activity against paclitaxel and docetaxel sensitive human cervical, breast, and leukemia and prostate cancer cell lines, cabazitaxel demonstrates activity in taxane resistant cell lines. The explanation for this pattern of activity stems from cabazitaxel’s effect on the efflux pump of p-glycoprotein, known to be responsible for the multidrug resistance phenotype. Expressed in a variety of human tumors including prostate cancer, p-glycoprotein is responsible for the adenosine-5′-triphosphate (ATP) dependent extrusion of natural product chemotherapeutic agents such as doxorubicin, vinca alkaloids, as well as paclitaxel and docetaxel. The extra methyl groups found on cabazitaxel are more effective against the ATP dependent efflux pump of p-glycoprotein than similarly placed hydrol groups on docetaxel and paclitaxel. This phenomenon may also be responsible for the disproportional increase CNS accumulation of cabazitaxel with increasing plasma concentrations, demonstrated in rodent models; p-glycoprotein is known to be expressed in the capillary endothelium of the brain and may be responsible for the blood-brain barrier.

Phase I study of cabazitaxel

Mita et al conducted a phase 1 study in 25 patients with chemotherapy refractory solid tumors. Cabazitaxel was administered at four dose levels (10, 15, 20, and 25 mg/m²) as an intravenous (IV) infusion every 3 weeks. Of the eight CRPC patients entered on the trial, two, previously treated with mitoxantrone and docetaxel, demonstrated partial responses in soft tissue lesions to 15 mg/m² and 25 mg/m², of cabazitaxel, respectively. Both also manifested > 50% declines in PSA. A third prostate cancer patient demonstrated a minor response. Neutropenia was the major dose limiting toxicity observed, with two patients demonstrating prolonged grade 4 neutropenia at 25 mg/m², and another demonstrating febrile neutropenia at the same dose level. In contrast to patients treated with docetaxel, fluid retention was not observed with cabazitaxel treatment. The commonest non-hematologic toxicities observed were diarrhea (52%), nausea (40%), and vomiting (16%). The authors concluded that 20 mg/m² of cabazitaxel administered every 3 weeks as the recommended phase II dose. It is to be noted that prophylactic granulocyte colony stimulating factor (GCSF) was not administered.

Phase III studies of cabazitaxel in docetaxel pretreated CRPC patients

The activity of cabazitaxel demonstrated against taxane resistant cell lines, as well as the responses observed in phase I lead investigators to study cabazitaxel in men with castration resistant prostate cancer previously treated with docetaxel. The TROPIC trial randomized 755 men to either cabazitaxel 25 mg/m² Q 3 weeks or mitoxantrone 12 mg/m² Q 3 weeks. Prednisone 5 mg PO BID was administered in both arms. All patients were required to have progressive disease as evidenced by RECIST criteria or two consecutive rising PSAs at least 1 week apart in patients with non-measurable disease. The median age of patients entered in the metastatic study was 68. A median dosage of 529.2 mg/m² and 576.6 mg/m² of docetaxel were administered in the cabazitaxel and mitoxantrone/prednisone arms, respectively. Two or more cytotoxic regimens were previously administered to 29% and 31% of the patients entered on the mitoxantrone and cabazitaxel arms, respectively. Nearly half of the patients entered in the trial had symptomatic bone pain, with 25% of patients demonstrating visceral metastases.

After a median follow up of 12.5 months, a 3.1 month improvement in median survival was noted in favor of cabazitaxel treatment, with a hazard ratio of 0.7. At a median follow up of 25.5 months, 15.9% of the cabazitaxel patients survived > 2 years compared to 8.2% of patients treated with mitoxantrone. A subgroup analysis demonstrated that the survival benefit of cabazitaxel over mitoxantrone was maintained in patients who discontinued docetaxel for disease progression compared to those who stopped docetaxel due to toxicity, completion of 10 cycles of treatment, or for other reasons. Although patient selection may play a role, the median survival from the time of the first docetaxel dose in the cabazitaxel group was 29 months (95% CI 27-31) versus 25 months (95% CI 23-28) in the mitoxantrone group. PSA declines of > 50% and objective response rates were superior (39.2% and 14.4%) in the cabazitaxel arm when compared to the mitoxantrone arm (17.8% and 4.4%). The palliation rates using the PPI, were similar in both arms.

Neutropenia was the most commonly encountered toxicity, with grade 3 or higher events occurring in 82% of patients treated with cabazitaxel. Febrile neutropenia was observed in 8% of patients. The prevalence of cabazitaxel induced neutropenia increases with age, and was observed at a 6.6% higher rate in patients over the age of 65. Grade 3 diarrhea was observed in 6% of patients on the cabazitaxel arm compared to < 1% of patients on

As with neutropenia, diarrhea was more frequently observed in patients over the age of 75. Diarrhea also was observed at a 8.6% higher rate in patients who had a prior history of radiation therapy. A higher rate of death due to adverse events was noted in patients treated on the cabazitaxel/prednisone arm when compared to mitoxantrone/prednisone. Of the 18 patients on the cabazitaxel arm who died of adverse events, 7 patients died of neutropenic sepsis, in contrast to 1 patient on the mitoxantrone arm. It is to be noted that prophylactic colony stimulating factors were not administered during the first cycle of therapy, which could possibly reduce the risk of neutropenic death. This pattern of toxicity has lead the FDA to recommend administration of prophylactic growth factors in patients treated with cabazitaxel who are older than 65, have had extensive prior radiation, poor nutrition, previous febrile neutropenia, poor performance status or other serious comorbidities. In a report of a global early access program performed in Italy, CRPC patients treated with six cycles of cabazitaxel experienced neutropenia (33.9%), leukopenia (15.6%), anemia (6%), and asthenia. Table 2 shows common toxicities of docetaxel and cabazitaxel and their management.

Two relevant questions regarding sequencing of cabazitaxel and dosage are being answered by randomized clinical trials. Given cabazitaxel’s efficacy in docetaxel pretreated patients, it would be logical to evaluate cabazitaxel as front line chemotherapy in men with castration resistant prostate cancer. An international randomized trial of docetaxel combined with prednisone versus cabazitaxel (20 mg/m² or 25 mg/m²)/prednisone is underway, clinicaltrials.gov NCT01308567. To further define the optional dose, a second study is randomizing patients to either 20 mg/m² or 25 mg/m² of cabazitaxel, clinicaltrials.gov NCT01308580.

### Table 2: Common toxicities of docetaxel and cabazitaxel and their management

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/schedule</th>
<th>Toxicity</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>75 mg/m² Q 3 weeks</td>
<td>Neutropenia</td>
<td>Per ASCO guidelines, risk of febrile neutropenia &lt;20%, use Colony Stimulating Factors (GCSF, GmCSF) based on age, medical condition, history, disease characteristics. Monitor CBC at least weekly</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Baseline neutrophil count less than 1500 cells/µL, a history of severe hypersensitivity reactions to docetaxel or polysorbate 80, severe hepatic dysfunction (bilirubin &gt;Upper limit of normal (ULN), SGOT and/or SGPT &gt;1.5XULN) concomitant with alkaline phosphatase &gt;2.5XULN</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>25 mg/m² Q 3 weeks</td>
<td>Neutropenia</td>
<td>GCSF prophylaxis recommended for age &gt; 65, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation, poor nutritional status, other comorbidities. Monitor CBC at least weekly</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Baseline neutrophil count less than 1500 cells/µL, a history of severe hypersensitivity reactions to docetaxel or polysorbate 80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diarrhea</td>
<td>Hydration, treat with antidiarrheals (loperamide). If ≥ grade 3, dosage should be modified</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Corticosteroids, antihistamines, H2 antagonists</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypersensitivity reactions</td>
<td>No standard treatment</td>
</tr>
</tbody>
</table>

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Sequencing of treatments

With the recent approvals of abiraterone,\textsuperscript{30} radium 223,\textsuperscript{31} sipuleucel T\textsuperscript{32} in the pre-docetaxel space, given the relative lack of toxicity of the aforementioned treatments, chemotherapy potentially could be administered later in the course of disease. It is unclear whether administration of any of these agents before either docetaxel or cabazitaxel affects efficacy and toxicity of these cytotoxic agents. Retrospective studies have been performed in small, select groups of patients and are difficult to apply to individual treatment decisions. For example, the preclinical observation that docetaxel may actually have cross resistance with hormonal agents due to docetaxel inhibition of androgen receptor translocation theoretically could make taxanes less effective after administration of abiraterone or enzalutamide.\textsuperscript{33,34} Pond et al found that patients previously treated with ketoconazole/hydrocortisone in a randomized trial of docetaxel+/- AT-101, a novel bcl-2 inhibitor, trended towards bursting overall survival, objective response rates, and PSA declines compared to those patients who had not received prior ketoconazole/hydrocortisone.\textsuperscript{35} In a retrospective evaluation of 35 patients who received docetaxel after abiraterone treatment, the median survival was 12.5 months, significantly lower than what was observed in TAX 327. Patients refractory to abiraterone were also refractory to docetaxel. In a small subgroup of patients treated with cabazitaxel after abiraterone alone, abiraterone followed by enzalutamide, or in enzalutamide alone, 16/41(39\%) of patients demonstrated a > 50\% PSA decline, with a median survival of 15.8 months.\textsuperscript{36} Clearly, prospective randomized trials are needed, utilizing biomarkers, to determine the optimal sequence of these agents for both survival and toxicity.

Conclusions

Both docetaxel and cabazitaxel have antitumor activity in chemotherapy naïve and chemotherapy pre-treated patients, respectively. Combination therapy with docetaxel has not resulted in increased survival. Although randomized trials are currently underway to define which of these two agents should be administered as front line therapy, the optimal sequences of these agents with newer agents such as abiraterone, enzalutamide and radium 223 have yet to be defined.

Disclosure

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References


