Published in final edited form as:

Urol Clin North Am. 2012 November ; 39(4): 573–581. doi:10.1016/j.ucl.2012.07.012.

The Experience with Cytotoxic Chemotherapy in Metastatic Castration-Resistant Prostate Cancer

Mario A. Eisenberger, MD* and Emmanuel S. Antonarakis, MD

Department of Oncology, The Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University, Baltimore, MD, USA

Keywords

Cytotoxic chemotherapy; Metastatic castration-resistant prostate cancer; Docetaxel

THE EXPERIENCE WITH CHEMOTHERAPY IN THE PRE-TAXANE ERA

The taxane agents (docetaxel and cabazitaxel) represent the current standard chemotherapy drugs used for the treatment of advanced castration-resistant prostate cancer (CRPC).^{1–6} However, in the years preceding the Food and Drug Administration (FDA) approval of docetaxel (which occurred in 2004) and cabazitaxel (in 2010), various other chemotherapeutic drugs were being used, although none had demonstrated evidence of improved survival.⁷ Importantly, the historical data reported in the literature should be evaluated in the context of when it was published. More specifically, clinical trials conducted before the late 1980s should be evaluated separately from those reported subsequently, because of the introduction and availability of serum prostate-specific antigen (PSA) measurement in 1987. In addition, the evolving data with chemotherapy during the past 3 decades suggest that the survival of patients with metastatic castration-resistant prostate cancer (mCRPC) is substantially longer than previously described, which is probably also a reflection of lead-time effect caused by PSA-detecting treatment failure earlier in the disease process. Therefore, patients in contemporary chemotherapy trials have lesser tumor burden. In addition, the incidence and severity of critical clinical parameters associated with poor prognosis (such as anemia, renal dysfunction, symptoms, and impaired functional status) are much less frequent in contemporary series, which, in part, explains the differences in clinical outcomes since PSA was introduced. A historical perspective of chemotherapy development in the pre-docetaxel era is outlined later in this article.

There is modest single-agent activity with the alkylating drug, cyclophosphamide, with reported responses in only about 10% to 20% of patients based on the older literature. In more recent reports, cyclophosphamide given in standard oral doses or high intravenous doses with hematopoietic growth factors support has been reported to have a higher order of activity.^{8–10} Doxorubicin, 5-fluorouracil, and cisplatin, agents all of which have demonstrable antitumor activity in other various tumor types, have shown only modest single-agent benefits in patients with mCRPC.⁷ None of these agents are used with any frequency in the current era.

Estramustine phosphate is a nitrogen mustard derivative of estradiol, which has demonstrated limited single-agent activity in advanced prostate cancer.⁷ This drug has been shown to exert its cytotoxic activity through microtubule inhibition¹¹ and binding to nuclear matrix,¹² which provided the rationale for testing this compound in combination with other agents targeting the microtubule, such as vinblastine, paclitaxel, docetaxel, and vinorelbine. However, in a prospective randomized study conducted in patients with castration-resistant disease, estramustine phosphate given at an oral dosage of 560 mg/d was not shown to be superior to placebo in terms of palliative effects or survival.^{7,13} In addition, venous thromboembolic disease was a significant toxicity with this agent. It is considered that estramustine has only marginal activity in mCRPC, and because of its unfavorable therapeutic index (safety/efficacy) compared with more modern chemotherapeutics, its use in mCRPC has virtually been abandoned.

The treatment with the best response in the pre-taxane era is mitoxantrone. Mitoxantrone is a semisynthetic anthracenedione derivative that has shown modest subjective benefits with otherwise minimal evidence of objective antitumor activity or survival improvement.³ A prospective randomized comparison of mitoxantrone plus prednisone with prednisone alone resulted in significant improvements of various quality-of-life issues including bone pain response.⁴ However, survival was not significantly different between the treatment arms. This study provided the justification for the FDA approval of the combination of mitoxantrone and prednisone for the symptomatic treatment of patients with metastatic prostate cancer in 1997. In current practice, mitoxantrone is rarely used, although it can sometimes be a reasonable agent used in thirdline chemotherapy and beyond, if other life-prolonging chemotherapy drugs have already been exhausted.

TAXANES IN MCRPC

Both paclitaxel (extracted from the bark of the Pacific yew tree, *Taxus brevifolia*) and docetaxel (from the leaves of the European yew tree) disrupt microtubule function that is required for chromosome segregation at mitosis, thereby promoting apoptosis in eukaryotic cells.^{14,15} Nonetheless, the exact mechanism by which these drugs act against prostate cancer cells is not entirely clear. Prostate cancers tend to have low growth fractions, as compared with many normal cells and most other cancers; yet prostate cancer cells remain sensitive to taxane drugs. One possibility is that microtubule function may be needed for other critical cell processes, such as nuclearcytoplasmic shuttling of critical regulatory proteins essential for prostate cancer cell viability,¹⁶ including translocation of the androgen receptor from the cytoplasm into the nucleus.

DOCETAXEL

Although paclitaxel and docetaxel showed promising activity against prostate cancer in early clinical trials, only docetaxel has been subjected to large-scale trials testing effects on survival in patients with mCRPC. Docetaxel, given intravenously every 3 weeks (75 mg/m²) to men with prostate cancer in an initial small trial (n = 35), was associated with a 46% serum PSA response rate.¹⁷ In a series of clinical trials featuring intravenous weekly docetaxel (35–40 mg/m²), serum PSA response rates ranged from 41% to 64%.^{18–22} The addition of estramustine (see earlier discussion) to docetaxel appeared to produce significant benefits in early studies, both for serum PSA responses (45%–74%) and for measurable disease responses (11%–57%).^{23–27}

These initial promising studies conducted in the late 1990s eventually resulted in the design and execution of 2 definitive randomized phase 3 studies, known as TAX-327 and SWOG-9916. The TAX-327 study (considered the pivotal trial for FDA approval of docetaxel in prostate cancer) included 3 treatment arms: docetaxel, 75 mg/m², every 3 weeks

plus prednisone, 10 mg/d; weekly docetaxel, 30 mg/m², (5 of 6 weeks) plus prednisone; and mitoxantrone, 12 mg/m², every 3 weeks plus prednisone.⁴ A total of 1006 patients were randomized into the 3 arms. The docetaxel every-3-weeks regimen resulted in significantly superior survival and higher PSA and pain response rates compared with the mitoxantrone arm. The overall survival was 18.9 versus 16.5 months; the hazard ratio (HR) for risk of death was 0.76 (confidence interval [CI], 0.62–0.92) (Fig. 1). The weekly docetaxel regimen showed a trend toward survival benefit compared with mitoxantrone, but this did not reach statistical significance.²⁸ A significantly greater proportion of patients who were treated with the 3-weekly docetaxel regimen experienced a reduction in pain (35% vs 22%, $P = .01$), a greater than or equal to 50% reduction in PSA (45% vs 32%, $P < .001$), and an improvement in quality of life (22% vs 13%, $P = .009$) compared with patients who received mitoxantrone, which itself had previously shown a quality-of-life improvement. Grade 3/4 toxicity was infrequent, other than neutropenia (32%), but the incidence of febrile neutropenia during the entire course of chemotherapy was 3% or less.

The second study, SWOG-9916, evaluated the combination of docetaxel plus estramustine versus mitoxantrone plus prednisone. The median overall survival was superior in the group receiving the docetaxel regimen: 17.5 versus 15.6 months, HR 0.80 (CI, 0.67–0.90).⁵ The patient characteristics in this trial were similar to those of the TAX-327 study, as were the survival outcomes. The incorporation of estramustine in the docetaxel regimen, however, was characterized by increased gastrointestinal and vascular toxicities (mostly thromboembolic complications).⁵ Because of the high rate of venous thromboses with estramustine, prophylactic low-dose warfarin and aspirin were added to that arm, although did not reduce the incidence of thromboembolism. Similarly, 20% and 15%, respectively, of patients in the docetaxel-estramustine arm had grade 3/4 gastrointestinal and cardiovascular toxicities. Although comparisons between the docetaxel arms across these 2 seminal trials may not be entirely appropriate because of differences in treatment schedules, patient populations, and docetaxel dosing (60 mg/m² in SWOG-9916 and 75 mg/m² in TAX-327), it may be concluded that estramustine is unlikely to add significantly to the activity of single-agent docetaxel. Consequently, estramustine is not currently used in this disease.

Based on these 2 pivotal studies, docetaxel was approved by the FDA in 2004 as the first life-prolonging chemotherapy for use as front-line treatment of mCRPC. TAX-327 was designed to include 10 cycles of docetaxel at 3-week intervals, although there were no preexisting data to justify this approach. Therefore, in clinical practice, it is reasonable to administer docetaxel for a total of up to 10 doses. However, another commonly used approach has been to treat patients with a shorter number of chemotherapy cycles (usually between 5 and 7) until stabilization of disease is observed and then to hold treatment until subsequent progression (PSA progression, clinical progression, or both). This approach provides a rationale for docetaxel retreatment before moving to second-line chemotherapeutic options. Indeed, this pattern of chemotherapy administration can be viewed as intermittent docetaxel treatment. Preliminary published reports with intermittent chemotherapy indicate that this approach is feasible and has potential advantages in terms of extending disease control without increased toxicity.^{29–31}

CROSSOVER FROM MITOXANTRONE TO DOCETAXEL OR VICE VERSA

The TAX-327 study did not include a crossover design allowing crossover from mitoxantrone to docetaxel and vice versa. As reported, treatment with docetaxel on the TAX-327 trial benefited all patient subgroups (pain vs no pain, ECOG performance status of 0/1 vs 2, and most other prognostic groups). Because the toxicity picture of mitoxantrone was more favorable than that of docetaxel, one consideration was whether patients could be treated initially with mitoxantrone, derive a reasonable quality-of-life benefit (delay of

symptoms and pain), and then be treated with docetaxel at the time of subsequent progression. To investigate this issue, Berthold and colleagues³² reported retrospective data addressing the experience with crossover treatments from mitoxantrone to docetaxel and vice versa. In that analysis, 232 crossover patients were investigated, and the median survival after crossover was 10 months and did not depend on direction of crossover. Data on PSA response were available for 96 patients: PSA response (≥ 50% reduction) occurred in 15% men receiving mitoxantrone after docetaxel and 28% of men receiving docetaxel after mitoxantrone. Median PSA progression-free survival was 3.4 months for mitoxantrone after docetaxel and 5.9 months for docetaxel after mitoxantrone. In that analysis, response to first-line chemotherapy did not predict outcome of second-line treatment. While retrospective, these data indicate that the response to second-line docetaxel (after mitoxantrone) is substantially lower than reported in the first-line setting, and although survival after crossover was similar, this only included a small number of selected patients who were considered candidates for second-line treatment. In summary, the totality of the available evidence strongly supports the use of docetaxel as the first-line treatment of choice for patients with mCRPC.

PROGNOSTIC FACTORS AND OUTCOME OF PATIENTS WITH MCRPC TREATED WITH DOCETAXEL

Armstrong and colleagues³³ evaluated TAX-327 for several prognostic covariates of interest. Among those factors evaluated with univariate analysis were age; performance status; pain at baseline; baseline levels of hemoglobin, alkaline phosphatase, and PSA; presence of visceral and/or liver metastases; pretreatment PSA doubling time; type of progression (measurable, nonmeasurable, bone scan, and PSA-only progression); number of metastatic sites; Gleason score; presence of multiple bony metastases; and prior estramustine or second-line hormonal therapy. Ten independent prognostic factors (other than treatment group) were identified to be prognostic for survival in multivariate analysis: (1) presence of liver metastases (HR, 1.66; $P = .02$); (2) number of metastatic sites (HR, 1.63 if ≥ 2 sites; $P < .01$); (3) clinically significant pain (HR, 1.48; $P < .01$); (4) Karnofsky performance status (HR, 1.39 if ≥ 70 ; $P = .02$); (5) type of progression (HR, 1.37 for measurable disease progression and 1.29 for bone scan progression; $P = .01$ and $.02$, respectively); (6) pretreatment PSA doubling time (HR, 1.19 if < 55 days; $P = .07$); (7) PSA level (HR, 1.17 per log rise; $P < .01$); (8) tumor grade (HR, 1.18 for high grade; $P = .07$); (9) alkaline phosphatase (HR, 1.27 per log rise; $P < .01$); and (10) hemoglobin (HR, 1.11 per unit decline; $P = .01$) (Table 1). An additional novel independent factor in this analysis was the mode of disease progression at baseline (ie, before trial enrollment), wherein men who had progression by bone scan and measurable soft tissue disease had a 1.28- and 1.40-fold increased risk of death, respectively, compared with men without these modes of progression, such as PSA-only progression ($P = .01$ and $< .01$, respectively). A survival nomogram was developed to assist in the definition of the prognosis of patients based on clinical criteria, and this is outlined in Fig. 2.

DOCETAXEL-BASED COMBINATIONS

Based on encouraging initial reports of uncontrolled studies, various therapeutic modalities have been developed in combination with docetaxel in phase 3 trials. GVAX, a vaccine composed of prostate cancer cell lines modified to secrete granulocyte macrophage colony-stimulating factor (GM-CSF), underwent a phase 3 trial in combination with docetaxel in patients with symptomatic mCRPC. This trial, known as VITAL-2, was interrupted early because of an unexpected higher death rate in the GVAX arm. Another trial, VITAL-1, compared GVAX against docetaxel in patients with asymptomatic CRPC and found no overall survival difference either.³⁴

DN-101 is a high-dose formulation of calcitriol, an activated vitamin D analogue that has antiproliferative effects against prostate cancer cells in vitro. The combination of docetaxel plus calcitriol was evaluated in a randomized phase 2 trial that suggested an improvement in overall survival, with a significant improvement in greater than or equal to 50% PSA reduction compared with docetaxel monotherapy. However, the results of a phase 3 trial (ASCENT-2) conducted in 953 men with progressive CRPC found a significantly shorter overall survival for the combination of docetaxel plus calcitriol compared with docetaxel plus prednisone (17.8 vs 20.2 months).³⁵ The reasons for the shorter survival were unclear but could relate to the use of the weekly schedule of docetaxel in the control arm (which was not as effective as the every-3-week schedule in the pivotal TAX-327 study).

Other compounds that have been studied in combination with docetaxel in phase 3 trials include the anti-VEGF antibody bevacizumab, aflibercept (VEGF trap), the Bcl-2 inhibitor oblimersen, the endothelin antagonists atrasentan and zibotentan, and the immunomodulatory drug lenalidomide. Unfortunately, none of these docetaxel-based combinations have been able to demonstrate improved overall survival over the use of docetaxel alone. In some cases (eg, with docetaxel plus bevacizumab), the combination treatment significantly improved progression-free survival over docetaxel alone, but this did not translate into an overall survival benefit. Currently, there are 2 phase 3 docetaxel combination studies with results pending. These studies are investigating combinations of docetaxel with Src inhibitors (dasatinib) and the anti-apoptotic chaperone molecule custirsens.

In conclusion, although docetaxel remains the gold-standard first-line chemotherapy for mCRPC, no significant additional benefit has been realized with several docetaxel combination strategies. Although at this time the authors cannot recommend the combination of docetaxel with other targeted therapies in the context of standard clinical care, their knowledge of the biologic mechanisms involved in the progression of mCRPC has reached a level at which the discovery of more effective targeted combination approaches will probably further improve outcomes in the future.

CABAZITAXEL

Cabazitaxel is a second-generation taxane that exhibited cytotoxic activity against a broad range of cancer cell lines and tumor models with greater potency than docetaxel in multidrug-resistant tumor cells. An additional characteristic of cabazitaxel is its ability to penetrate the blood-brain barrier in vivo, which is not achievable with other taxanes.^{36,37}

A phase 1 trial using this agent determined that cabazitaxel had linear pharmacokinetics similar to docetaxel and highlighted the favorable safety profile of cabazitaxel compared with docetaxel. The principal dose-limiting toxicity of cabazitaxel was neutropenia; other observed side-effects (including nausea, vomiting, diarrhea, and fatigue) were generally mild-to-moderate.³⁶ Twelve of the 24 patients evaluable for clinical response in the phase 1 study had stable disease for more than 4 months, and there were 2 partial responses observed in men with mCRPC, both of which had a reduction in measurable disease and significant declines in PSA levels.

The phase 3 (TROPIC) trial was a randomized, open-label, multinational trial conducted to assess whether cabazitaxel plus prednisone improved overall survival compared with mitoxantrone plus prednisone in men with mCRPC who had progressed either during or after docetaxel chemotherapy.³⁶ Patients aged more than or equal to 18 years with mCRPC progression despite docetaxel treatment were all given prednisone, 10 mg/d, and also randomized to receive either intravenous cabazitaxel, 25 mg/m², or mitoxantrone, 12 mg/m², every 3 weeks for 10 cycles. A total of 755 patients were included in the study (cabazitaxel; n = 378 and mitoxantrone; n = 377). The median follow-up for both treatment

groups was 12.8 months. Treatment groups were balanced with regard to demographics and baseline disease characteristics. All patients had to have evidence of disease progression with first-line docetaxel treatment. Approximately 70% of patients had progressed within 3 months of completing docetaxel treatment; almost one-third of patients had progressed while they were receiving docetaxel.

The study met its primary endpoint, demonstrating significantly improved median overall survival in patients receiving cabazitaxel (15.1 months; 95% CI, 14.1–16.3 months) compared with those who received mitoxantrone (12.7 months; 95% CI, 11.6–13.7 months). The HR for death was 0.70 (95% CI, 0.59–0.83; $P<.0001$). In addition to the survival benefit, cabazitaxel roughly doubled median progression-free survival compared with mitoxantrone (cabazitaxel 2.8 months vs mitoxantrone 1.4 months; $P<.0001$). Moreover, cabazitaxel treatment significantly improved objective response rate (RECIST criteria) more than 2-fold compared with mitoxantrone ($P<.001$). The PSA response rate (> 50% decline) was significantly higher in the cabazitaxel group compared with the mitoxantrone group, and patients receiving cabazitaxel also had a significantly longer median time-to-PSA-progression.³⁶

Patients in the cabazitaxel and mitoxantrone groups received a median of 6 and 4 cycles of treatment, respectively. The most common adverse events experienced by patients were hematologic toxicities. There was a greater incidence of hematologic events with grade greater than or equal to 3 severity in patients who received cabazitaxel. For example, 81.7% and 7.5% of patients in the cabazitaxel group experienced grade greater than or equal to 3 neutropenia and febrile neutropenia, respectively, compared with 58% and 1.3% of patients in the mitoxantrone group. Cabazitaxel treatment also increased the incidence of nonhematologic toxicities, including diarrhea (46.6% vs 10.5% for mitoxantrone; grade 3 diarrhea [6.2% vs 0.3%]) and asthenia (20.5% vs 4.6% for mitoxantrone; grade 3 asthenia [12.4% vs 2.4%]). In addition, 5% of men on the cabazitaxel arm died from causes other than disease progression within 30 days of receiving cabazitaxel. This compares with a 1% drug-related death rate in the mitoxantrone group. The most common cause of death in patients who were treated with cabazitaxel was neutropenia, including its clinical consequences such as septicemia. However, no further deaths due to neutropenic complications occurred in the cabazitaxel group after the Independent Data Monitoring Committee communication to the TROPIC investigators about the need to strictly adhere to the study protocol regarding dose delays and modifications and managing neutropenia with GM-CSF according to American Society for Clinical Oncology guidelines.

Based on the results of the TROPIC trial, cabazitaxel was approved by the FDA in June 2010 and by the European Medicines Agency in 2011 for use in combination with prednisone for the treatment of docetaxel-pretreated mCRPC. Cabazitaxel is currently being evaluated as a first-line treatment of mCRPC in 2 separate clinical trials. The first study (designated as FIRSTANA) is a standard multiinstitutional, multinational phase 3 comparison between cabazitaxel (in 2 doses: 25 mg/m² and 20 mg/m²) and standard every-3-weeks docetaxel (75 mg/m²) in men with chemotherapy-naïve mCRPC. The second study, TAXYNERGY, is a national multicenter randomized phase 2 trial to evaluate the benefit of an early switch from first-line docetaxel/prednisone to cabazitaxel/prednisone (or the opposite sequence) in men with chemotherapy-untreated mCRPC. The latter trial aims to assess PSA response after 12 weeks on study and to use this information to maintain treatment with the current taxane (if PSA reductions exceed 30%) or to switch to the alternative taxane (if PSA declines of less than 30% are observed by 12 weeks). This trial also aims to explore circulating tumor cell-based molecular markers and mechanisms of taxane resistance in men with mCRPC who have not received prior chemotherapy. Finally, in the second-line (post-docetaxel) setting, cabazitaxel is also currently being prospectively

evaluated at 2 different doses (25 mg/m² vs 20 mg/m²) in a multinational randomized trial (PROSELICA).

SUMMARY

In the vast majority of patients with mCRPC, docetaxel chemotherapy (at a dose of 75 mg/m² given intravenously every 3 weeks) remains the strong standard-of-care for first-line treatment, whereas historical drugs such as mitoxantrone and others are seldom used in the modern era. In men who have progressed during or after docetaxel-based therapy, strong evidence supports the use of cabazitaxel (at a dose of 25 mg/m² given intravenously every 3 weeks) in patients with adequate performance status and a reasonable life expectancy. The emergence of additional novel therapies for the management of mCRPC (such as sipuleucel-T, abiraterone, enzalutamide, and radium-223) is likely to complicate the therapeutic decision process, although these new drugs are certainly a welcome addition to the therapeutic arsenal for this disease. Considerations of patient performance status, comorbidities, disease characteristics, and patient preferences should guide these treatment decisions.

REFERENCES

1. Kantoff PW, Halabi S, Conaway M, et al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the Cancer and Leukemia Group B 9182 study. *J Clin Oncol*. 1999; 17:2506–2513. [PubMed: 10561316]
2. Ernst DS, Tannock IF, Winquist EW, et al. Randomized, double-blind, controlled trial of mitoxantrone/ prednisone and clodronate versus mitoxantrone/ prednisone and placebo in patients with hormonerefractory prostate cancer and pain. *J Clin Oncol*. 2003; 21:3335–3342. [PubMed: 12947070]
3. Tannock IF, Osoba D, Stockler MR, et al. Chemotherapy with mitoxantrone plus prednisone or pred-nisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. *J Clin Oncol*. 1996; 14:175–184.
4. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004; 351:1502–1512. [PubMed: 15470213]
5. Petrylak DP, Tangen CM, Hussain MH, et al. Doce-taxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med*. 2004; 351:1513–1520. [PubMed: 15470214]
6. Kantoff P. Recent progress in management of advanced prostate cancer. *Oncology*. 2005; 19:631–636. [PubMed: 15945343]
7. Eisenberger MA. Chemotherapy for prostate carcinoma. *NCI Monogr*. 1988; 7:151–163. [PubMed: 3050534]
8. Von Roemeling R, Fisher HA, Horton J. Daily oral cyclophosphamide is effective in hormoneasdlbrefractory prostate cancer: a phase-I/II pilot study [abstracts 665]. *Proc Am Soc Clin Oncol*. 1992; 11:213.
9. Smith D, Vogelzang N, Goldberg H, et al. High-dose cyclophosphamide with granulocyte-macrophage colony stimulating factor in hormone refractory prostate cancer [abstracts 666]. *Proc Am Soc Clin Oncol*. 1992; 11:213.
10. Abell F, Wilkes J, Divers L, et al. Oral cyclophosphamide for hormone-refractory prostate cancer [abstracts 646]. *Proc Am Soc Clin Oncol*. 1995; 14:213.
11. Hudes G, Einhorn L, Ross E, et al. Vinblastine versus vinblastine plus oral estramustine phosphate for patients with hormone-refractory cancer: a Hoosier Oncology Group and Fox Chase Network Phase III trial. *J Clin Oncol*. 1999; 17:3160–3166. [PubMed: 10506613]
12. Hartley AS, Kruse E. Nuclear protein matrix as a target for estramustine-induced cell death. *Prostate*. 1986; 9:387–395. [PubMed: 3786258]

13. Iversen P, Rasmussen F. Estramustine phosphate versus placebo in hormone-refractory prostate cancer. Danish prostate cancer group study 9002 [abstracts 41]. *Proc Am Urol Assoc.* 1995; 153:239A.
14. Horwitz SB. Taxol (paclitaxel): mechanisms of action. *Ann Oncol.* 1994; 5(Suppl 6):S3–S6. [PubMed: 7865431]
15. Jordan MA, Wilson L. Microtubules as a target for anticancer drugs. *Nat Rev Cancer.* 2004; 4:253–265. [PubMed: 15057285]
16. Mabbjeesh NJ, Escuin D, LaVallee TM, et al. 2ME2 inhibits tumor growth and angiogenesis by disrupting microtubules and dysregulating HIF. *Cancer Cell.* 2003; 3:363–375. [PubMed: 12726862]
17. Picus J, Schultz M. Docetaxel (Taxotere) as monotherapy in the treatment of hormone-refractory prostate cancer: preliminary results. *Semin Oncol.* 1999; 26(Suppl 17):14–18. [PubMed: 10604263]
18. Beer TM, Pierce WC, Lowe BA, et al. Phase II study of weekly docetaxel in symptomatic androgenindependent prostate cancer. *Ann Oncol.* 2001; 12:1273–1279. [PubMed: 11697840]
19. Beer TM, Berry W, Wersinger EM, et al. Weekly docetaxel in elderly patients with prostate cancer: efficacy and toxicity in patients at least 70 years of age compared with patients younger than 70 years. *Clin Prostate Cancer.* 2003; 2:167–172. [PubMed: 15040860]
20. Berry W, Dakhil S, Gregurich MA, et al. Phase II trial of single-agent weekly docetaxel in hormonerefractory, symptomatic, metastatic carcinoma of the prostate. *Semin Oncol.* 2001; 28(Suppl 15):8–15. [PubMed: 11685723]
21. Ferrero JM, Foa C, Thezenas S, et al. A weekly schedule of docetaxel for metastatic hormone-refractory prostate cancer. *Oncology.* 2004; 66:281–287. [PubMed: 15218295]
22. Gravis G, Bladou F, Salem N, et al. Weekly administration of docetaxel for symptomatic metastatic hormonerefractory prostate carcinoma. *Cancer.* 2003; 98:1627–1634. [PubMed: 14534878]
23. Savarese D, Taplin ME, Halabi S, et al. A phase II study of docetaxel (Taxotere), estramustine, and low-dose hydrocortisone in men with hormonerefractory prostate cancer: preliminary results of cancer and leukemia group B Trial 9780. *Semin Oncol.* 1999; 26(Suppl 17):39–44. [PubMed: 10604268]
24. Petrylak DP, Macarthur RB, O'Connor J, et al. Phase I trial of docetaxel with estramustine in androgen-independent prostate cancer. *J Clin Oncol.* 1999; 17:958–967. [PubMed: 10071290]
25. Oudard S, Banu E, Beuzeboc P, et al. Multicenter randomized phase II study of two schedules of do-cetaxel, estramustine, and prednisone versus mitoxantrone plus prednisone in patients with metastatic hormone-refractory prostate cancer. *J Clin Oncol.* 2005; 23:3343–3351. [PubMed: 15738542]
26. Kreis W, Budman DR, Fetten J, et al. Phase I trial of the combination of daily estramustine phosphate and intermittent docetaxel in patients with metastatic hormone refractory prostate carcinoma. *Ann Oncol.* 1999; 10:33–38. [PubMed: 10076719]
27. Sinibaldi VJ, Carducci MA, Moore-Cooper S, et al. Phase II evaluation of docetaxel plus one-day oral estramustine phosphate in the treatment of patients with androgen independent prostate carcinoma. *Cancer.* 2002; 94:1457–1465. [PubMed: 11920502]
28. Berthold DR, Pond GR, Soban F, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. *J Clin Oncol.* 2008; 26:242–245. [PubMed: 18182665]
29. Beer TM, Garzotto M, Henner WD, et al. Intermittent chemotherapy in metastatic androgen-independent prostate cancer. *Br J Cancer.* 2003; 89:968–970. [PubMed: 12966410]
30. Meulenbeld HJ, Hamberg P, de Wit R. Chemotherapy in patients with castration-resistant prostate cancer. *Eur J Cancer.* 2009; 45:161–171. [PubMed: 19775615]
31. De Wit R. Chemotherapy in hormone-refractory prostate cancer. *BJU Int.* 2008; 101:11–15. [PubMed: 18307687]
32. Berthold DR, Pond GR, de Wit R, et al. Survival and PSA response of patients in the TAX 327 study who crossed over to receive doctaxel after mitoxantrone or vice versa. *Ann Oncol.* 2008; 19:1749–1753. [PubMed: 18487550]

33. Armstrong AJ, Garrett-Mayer ES, Yang YC, et al. A contemporary prognostic nomogram for men with hormone-refractory metastatic prostate cancer: a TAX327 study analysis. *Clin Cancer Res.* 2007; 13:6396–6403. [PubMed: 17975152]
34. Small, E.; Demkow, T.; Gerritsen, WR., et al. Genitourinary Cancers Symposium 2009. Orlando FL: American society of clinical oncology; 2009. A phase III trial of GVAX immunotherapy for prostate cancer in combination with docetaxel versus docetaxel plus prednisone in symptomatic, castration-resistant prostate cancer (CRPC).
35. Beer TM, Ryan CW, Venner PM, et al. ASCENT Investigators. Intermittent chemotherapy in patients with metastatic androgen-independent prostate cancer: results from ASCENT, a double-blinded, randomized comparison of high-dose calcitriol plus docetaxel with placebo plus docetaxel. *Cancer.* 2008; 112:326–330. [PubMed: 17960793]
36. De Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet.* 2010; 376:1147–1154. [PubMed: 20888992]
37. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol.* 2006; 24:3187–3205. [PubMed: 16682719]

KEY POINTS

- Docetaxel was the first chemotherapy agent to improve survival in men with metastatic castration-resistant prostate cancer (mCRPC) and is the chemotherapy drug of choice for the initial treatment of symptomatic mCRPC.
- Cabazitaxel is the second chemotherapy drug to demonstrate improved survival and is the current standard for patients with mCRPC who have progressed during or after receiving docetaxel-containing chemotherapy regimens.
- Mitoxantrone is a reasonable second- or third-line chemotherapy agent and has been shown to reduce bone pain and improve quality of life, without a demonstrable survival benefit.
- Several clinical trials are currently comparing docetaxel and cabazitaxel as first-line therapies for men with chemotherapy-naïve mCRPC, but cabazitaxel is not currently recommended as first-line treatment outside of a clinical trial.

Fig. 1. Updated TAX-327 survival figures. A comparison of docetaxel plus prednisone (weekly vs 3-weekly) versus mitoxantrone plus prednisone. (*Data from Berthold DR, Pond GR, de Wit R, et al. Survival and PSA response of patients in the TAX 327 study who crossed over to receive docetaxel after mi-toxantrone or vice versa. Ann Oncol 2008;19:1749–53.*)

Fig. 2.

Nomogram for survival of patients in TAX-327 study. Nomogram for survival of patients with progressive CRPC, including data derived from 686 patients and 518 mortality events. Note: a present pain intensity of greater than or equal to 2 and an analgesic score of greater than or equal to 10 defined in the original protocol indicate the presence of significant pain. Instructions for physician: locate the liver metastasis axis. Draw a straight line upward to the point axis to determine how many points toward survival the patient receives for the presence or absence of liver metastases. Repeat this process for each predictor variable and sum the points for each predictor. Locate this sum on the total points axis. Draw a straight line downward from the total points axis to identify the predicted median survival and the predicted 1-year, 2-year, and 5-year overall survival probabilities. Instructions to patient: "Mr. X, if we had 100 men exactly like you, we would expect <<nomogram prediction × 100>> to be alive in 1, 2, and 5 y, respectively, and we expect 50 of those to be alive after <<median survival prediction>> months." (From Armstrong AJ, Garrett-Mayer ES, Yang YC, et al. A contemporary prognostic nomogram for men with hormone-refractory metastatic prostate cancer: a TAX327 study analysis. Clin Cancer Res 2007;13:6396–403.)

Table 1

Prognostic variables of patients treated with first-line docetaxel chemotherapy on TAX-327 trial

Variable	HR (95% CI)	P Value
Chemotherapy type (vs every-3-wk docetaxel)		
Weekly docetaxel	1.12 (0.90–1.39)	0.320
Mitoxantrone	1.43 (1.16–1.77)	0.001
Liver metastases	1.66 (1.09–2.54)	0.019
Number of metastatic sites (>3 vs ≤3)	1.63 (1.23–2.15)	0.001
Pain at baseline	1.48 (1.23–1.79)	0.001
Karnofsky performance status (≤70 vs ≥80)	1.39 (1.06–1.82)	0.016
Progression type		
Measurable disease	1.37 (1.10–1.70)	0.005
Bone scan progression	1.29 (1.06–1.57)	0.010
Baseline PSA doubling time (<55 vs ≥55 d)	1.19 (0.99–1.42)	0.066
Baseline (log) PSA (for every unit rise in [log] PSA in ng/dL)	1.17 (1.10–1.25)	0.001
Tumor grade (Gleason ≥8 vs Gleason ≤7)	1.18 (0.99–1.42)	0.069
Alkaline phosphatase, log scale (per [log] unit rise, IU/L)	1.27 (1.15–1.39)	0.001
Hemoglobin (per unit decline, g/dL)	1.11 (1.03–1.19)	0.004

NOTE: $n = 635$ with 518 failures, excluding missing values for pain, performance status, and tumor grade at baseline. Concordance index = 0.69.

Data from Armstrong AJ, Garrett-Mayer ES, Yang YC, et al. A contemporary prognostic nomogram for men with hormone-refractory metastatic prostate cancer: a TAX327 study analysis. Clin Cancer Res 2007;13:6396–403.