Achieving Treatment Goals for Hormone-Refractory Prostate Cancer with Chemotherapy

WILLIAM BERRY, a MARIO EISENBERGER b

aCancer Centers of North Carolina, Cary, North Carolina, USA; bThe Johns Hopkins University, Baltimore, Maryland, USA

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LEARNING OBJECTIVES
After completing this course, the reader will be able to:
1. Describe the efficacy and toxicity results of two phase III trials that evaluated a docetaxel-based regimen for the treatment of HRPC.
2. Discuss the utility of PSA as a survival marker in HRPC trials.
3. List agents under investigation for the second-line treatment of HRPC.

Abstract
The belief that hormone-refractory prostate cancer (HRPC) is a chemotherapy-resistant disease has been effectively refuted by the results of two recent randomized phase III trials. The TAX327 trial compared weekly docetaxel, every-3-weeks (Q3W) docetaxel, and Q3W mitoxantrone plus prednisone in 1,006 patients with HRPC, and results demonstrated that survival was significantly longer with a docetaxel-based regimen than with mitoxantrone. That trial demonstrated that only Q3W docetaxel was significantly superior to mitoxantrone with respect to overall survival. Quality of life was also superior in the docetaxel groups. In the Southwest Oncology Group (SWOG) 9916 trial, 674 men with progressive HRPC were randomized to 3-week cycles of docetaxel plus estramustine or mitoxantrone plus prednisone. Overall and disease-free survival times were significantly longer in the docetaxel arm. Collectively, the results of these trials demonstrate that survival can be significantly improved with chemotherapy in patients with HRPC to an extent that is comparable with the survival benefits seen in other cancers considered sensitive to chemotherapy such as breast cancer. Among various research tasks in HRPC is the definition of potential surrogate end points for survival, which will facilitate the conduct of pivotal trials. Prostate-specific antigen (PSA) response rate and changes in PSA constructs (i.e., PSA doubling time and PSA velocity) are promising potential surrogate end points for future trials and are being actively evaluated at the present time. Until there is clear demonstration of a surrogate role for these alternative end points, survival remains the appropriate end point for phase III trials in HRPC. There is a need for safe and effective second- and third-line regimens for patients progressing after docetaxel, and these patients should enter clinical trials designed for this population. Mitoxantrone, vinorelbine, the platinum analogue satraplatin, and epothilone are among compounds that require careful testing in this setting. The addition of targeted therapies, such as the endothelin receptor antagonist, atrasentan, and angiogenesis inhibitors,
such as thalidomide and bevacizumab, to docetaxel-based therapy is being evaluated. High-dose calcitriol may also be an effective addition to docetaxel. The extensive effort devoted to the evaluation of chemotherapy and other systemic modalities of treatment of HRPC is likely to yield additional clinical benefit for patients, making HRPC a more manageable, less lethal, and less debilitating disease. The Oncologist 2005;10(suppl 3):30–39

**INTRODUCTION**

Evolving data with chemotherapy in hormone-refractory prostate cancer (HRPC) over the past several years suggest that this modality of treatment is likely to become an important component in the overall treatment of prostate cancer. Until recently, the role of chemotherapy was limited to palliation, based on the results of randomized clinical trials that found a modest improvement in symptoms associated with mitoxantrone-based (Novantrone®; Serono, Inc., Rockland, MA, http://www.seronousa.com) therapy [1, 2]. However, results of recent clinical trials have renewed the enthusiasm for developing effective treatments for this disease [3, 4]. Based on compelling results from two randomized, controlled clinical trials, docetaxel (Taxotere®; Aventis Pharmaceuticals Inc., Bridgewater, NJ, http://www.aventispharma-us.com) can now be considered the standard of care for the treatment of men with HRPC. These trials and the ongoing efforts to address other unmet clinical needs for men with HRPC are the focus of this review.

**FIRST-LINE DOCETAXEL FOR HRPC**

The results of two recently reported phase III randomized trials clearly demonstrate that docetaxel is the chemotherapy treatment of choice for men with metastatic HRPC [3, 4]. The TAX327 trial compared two different schedules of docetaxel plus prednisone (Deltasone®; Pfizer Pharmaceuticals, New York, http://www.pfizer.com) with mitoxantrone plus prednisone, whereas the Southwest Oncology Group (SWOG) 9916 trial compared docetaxel plus estramustine (Emcyt®; Pfizer Pharmaceuticals) with mitoxantrone plus prednisone (Fig. 1 and Fig. 2).

**TAX327**

TAX327 was a randomized phase III trial comparing survival in men with progressive HRPC treated with docetaxel or mitoxantrone, both in combination with prednisone [3]. Two schedules of docetaxel were compared with the standard every-3-week (Q3W) mitoxantrone regimen (12 mg/m² Q3W). One group was randomized to receive docetaxel (30 mg/m²), given every week for 5 consecutive weeks of a 6-week cycle. Another group received docetaxel (75 mg/m²) Q3W. The two docetaxel regimens were designed to provide the same dose intensity over a 6-week time period. Patients in all three groups received prednisone (5 mg) twice a day; patients in the docetaxel groups also received premedication with dexamethasone (Decadron®; Merck & Co., Inc., Whitehouse Station, NJ, http://www.merck.com) before each dose. The primary end point was overall survival; prostate-specific antigen (PSA) response, pain response, objective tumor response, and quality of life (QoL) were secondary end points. QoL was evaluated using the validated Functional Assessment of Cancer-Prostate (FACT-P) tool.

A total of 1,006 patients was enrolled in this international trial, and baseline characteristics were well balanced among patients in all three arms. Stratification factors included baseline pain level, Karnofsky performance status score, and presence of extrapelvic disease.

**Figure 1.** Design of the TAX327 randomized phase III trial in men with HRPC. Abbreviations: AS, analgesic score; bid, twice a day; HRPC, hormone-refractory prostate cancer; KPS, Karnofsky performance status score; PPI, Present Pain Intensity score; Q3W, every 3 weeks.

**Figure 2.** Design of the Southwest Oncology Group 9916 trial.
the three treatment groups. At a median follow-up of nearly 21 months, 50% (166/335) of the patients in the Q3W docetaxel group, 57% (190/334) in the weekly docetaxel group, and 60% (201/337) in the mitoxantrone group had died. There was a significantly longer survival time with Q3W docetaxel than with mitoxantrone (hazard ratio [HR], 0.76; \( p = 0.0009 \)), but not with weekly docetaxel relative to mitoxantrone (Table 1). When data from the docetaxel arms were combined (as designed in the protocol) and compared with mitoxantrone, there was a significantly lower risk for death (HR, 0.83; \( p = 0.04 \)) associated with docetaxel.

Significant improvements were also demonstrated with docetaxel in several of the secondary end points (Table 1). The PSA response rate was significantly higher with each docetaxel regimen relative to mitoxantrone. A pain response was defined as a two-point reduction in the Present Pain Intensity (PPI) score without an increase in analgesic score, or as a 50% or greater reduction in the analgesic score without an increase in PPI, maintained for at least 3 weeks. Nearly half (45%) of the patients had pain at baseline, and a pain response was significantly more frequent in the Q3W docetaxel arm than in the mitoxantrone arm for these patients. Finally, significant improvements in QoL were also reported in the docetaxel arms. Improvement in QoL was defined as at least a 16-point improvement from baseline in the FACT-P score on two measurements obtained at least 3 weeks apart, and data were collected from only those sites for which a native language FACT-P tool was available (\( n = 815 \)). Nearly one quarter of the patients in each docetaxel arm had a significant improvement in QoL, whereas only 13% of the patients in the mitoxantrone arm achieved this end point (\( p = 0.009 \) and \( p = 0.005 \), respectively).

Adverse events were generally more common in the docetaxel arms, although the highest rate of completion of all cycles of therapy (46%) was in the Q3W docetaxel arm. Grade 3–4 neutropenia occurred in 32% of patients treated with Q3W docetaxel (\( p \leq 0.05 \) for comparison with mitoxantrone), 22% of patients treated with mitoxantrone (\( p \leq 0.0015 \) for comparison with weekly docetaxel), and 1.5% of patients treated with weekly docetaxel. Febrile neutropenia, however, was not seen with weekly docetaxel and was rare in the Q3W docetaxel arm (3% with Q3W docetaxel and 2% with mitoxantrone). The rate of impaired left ventricular ejection fraction (LVEF) was significantly higher in the mitoxantrone arm than in the other treatment arms (22%, vs. 10% with Q3W docetaxel and 8% with weekly docetaxel; \( p \leq 0.0015 \) for each comparison). Adverse events that led to treatment discontinuation included fatigue, musculoskeletal or nail changes, sensory neuropathy, and infection in the docetaxel group and cardiac dysfunction in the mitoxantrone group.

**SWOG 9916**

The SWOG 9916 trial was conducted to determine if the combination of docetaxel plus estramustine could produce a survival benefit relative to mitoxantrone plus prednisone in patients with progressive HRPC [4]. A total of 674 patients with pathologically confirmed adenocarcinoma of the prostate and progressive metastatic disease despite androgen ablative therapy and cessation of antiandrogen treatment was enrolled. Disease progression was determined by the presence of increasing levels of serum PSA, computed tomography changes, or a positive bone scan; 18% of the patients had a rising PSA level as the only manifestation

<table>
<thead>
<tr>
<th>Table 1. Efficacy outcomes from the TAX327 trial</th>
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<tr>
<td><strong>Q3W Docetaxel (n = 335)</strong></td>
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<tr>
<td>-----------------------------------------------</td>
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<tr>
<td><strong>Median survival (months)</strong></td>
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<tr>
<td>( p = 0.009 )</td>
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<tr>
<td><strong>Secondary end points</strong></td>
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<tr>
<td>≥50% decline in serum PSA</td>
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<tr>
<td>( p &lt; 0.001 )</td>
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<tr>
<td>Pain response rate</td>
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<tr>
<td>( p = 0.01 )</td>
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<tr>
<td>Tumor response rate</td>
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<td>( p = 0.11 )</td>
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<tr>
<td>Quality of life response rate</td>
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<td>( p = 0.009 )</td>
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All \( p \) values are for comparison with mitoxantrone.

Abbreviations: PSA, prostate-specific antigen; Q3W, every 3 weeks.
of progressive disease. Patients randomized to docetaxel received docetaxel (60 mg/m²), estramustine (280 mg given orally three times a day for 5 days), and premedication with dexamethasone (20 mg orally three times a day beginning the day prior to docetaxel), with cycles repeated Q3W. Patients randomized to mitoxantrone plus prednisone received mitoxantrone (12 mg/m²) Q3W with continuous prednisone at a dose of 5 mg twice a day. The doses of docetaxel and mitoxantrone were escalated to 70 mg/m² and 14 mg/m², respectively, for patients who did not experience grade 3–4 toxicity in the first cycle of therapy. Prophylactic anticoagulation with daily warfarin (Coumadin®; Bristol-Myers Squibb, New York, http://www.bms.com) (2 mg) and aspirin (325 mg) was initiated halfway through the trial for patients receiving docetaxel plus estramustine based on the release of data demonstrating a significant reduction in estramustine-related coagulopathies with such therapy.

At a median follow-up of 32 months, 64% (217/338) of the patients randomized to docetaxel and 70% (235/336) of the patients randomized to mitoxantrone had died. Both overall survival and disease-free survival were significantly longer with docetaxel plus estramustine than with mitoxantrone plus prednisone (Table 2). The relative risk for death was 20% lower with docetaxel-based therapy (HR, 0.80; 95% confidence interval [CI], 0.67–0.97). Significantly more patients treated with docetaxel plus estramustine had a PSA response as well. Pain relief was similar in both groups.

Toxicities were significantly higher in the docetaxel–estramustine group. Sixteen percent of patients in the docetaxel–estramustine group and 10% in the mitoxantrone–prednisone group discontinued treatment as a result of adverse events. Rates of grade 3–4 neutropenia did not differ between groups, but the incidence of severe and life-threatening febrile neutropenia was higher with docetaxel plus estramustine (5% vs. 2%; p = .01). Gastrointestinal, neurologic, metabolic, and cardiovascular events were also significantly more common with docetaxel plus estramus-

tine. The protocol was amended about halfway through its accrual to include prophylactic use of warfarin and aspirin; however, this did not appear to reduce the initial incidence of severe thromboembolic complications.

**DISCUSSION OF RANDOMIZED TRIALS**

**EVALUATING DOCETAXEL**

The phase III trials evaluating docetaxel in HRPC support the superior efficacy of docetaxel over mitoxantrone for the treatment of men with progressive HRPC. Importantly, findings of the TAX327 and SWOG 9916 trials demonstrate that survival can be improved with chemotherapy in patients with HRPC at a magnitude comparable with that observed with cytotoxic therapy in other chemotherapy-sensitive cancers such as breast cancer.

Subsequent to the publication of the SWOG 9916 and TAX327 trial results, Oudard and colleagues [5] published the results of a randomized phase II trial that compared docetaxel, estramustine, and prednisone (DEP) with mitoxantrone plus prednisone (MP) in 130 men with progressive HRPC. Patients were randomized to one of two DEP regimens: docetaxel was given either as 70 mg/m² on day 2 of each 3-week cycle or as 35 mg/m² on days 2 and 9 of each 3-week cycle. Estramustine (280 mg three times a day) was given on days 1–5 and 8–12, and premedication with prednisolone (Orapred®; BioMarin Pharmaceutical Inc., Novato, CA, http://www.biomarinpharm.com) (300 mg) and continuous warfarin (2 mg) were given in both DEP groups. Mitoxantrone was administered at 12 mg/m² Q3W, and all three groups received prednisone at a dose of 10 mg daily. PSA response was the primary end point. Significantly more patients treated with DEP achieved a PSA response relative to mitoxantrone (67% and 63%, respectively, vs. 18% with mitoxantrone; p < .0001). The median time to PSA progression was five times longer with DEP than with MP (p = .000001). Overall survival was numerically longer with DEP, but these differences did not reach

**Table 2. Efficacy outcomes from Southwest Oncology Group 9916 trial**

<table>
<thead>
<tr>
<th></th>
<th>Docetaxel plus estramustine (n = 338)</th>
<th>Mitoxantrone plus prednisone (n = 336)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival (mos)</td>
<td>17.5</td>
<td>15.6</td>
<td>.02</td>
</tr>
<tr>
<td>Secondary end points</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to progression (mos)</td>
<td>6.3</td>
<td>3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥50% decline in serum PSA</td>
<td>50%</td>
<td>27%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Objective tumor response rate</td>
<td>17%</td>
<td>11%</td>
<td>.30</td>
</tr>
</tbody>
</table>

Abbreviation: PSA, prostate-specific antigen.
statistical significance (18.6 and 18.4 months, respectively, vs. 13.4 months with mitoxantrone; \( p = .3 \)).

Oudard and colleagues [6] conducted a meta-analysis using the data from all three trials to determine if the schedule of docetaxel treatment affected survival. They assessed overall survival at 12, 18, 24, 30, and 36 months and evaluated the impact of weekly and Q3W therapy on overall survival. Using combined data from 1,807 patients, they found that overall survival was significantly greater with docetaxel at all time points evaluated. The relative risk for death ranged from 8%–21% lower. As in TAX327, the difference in survival was significant for the comparison of Q3W docetaxel with MP but not for weekly docetaxel compared with MP. Second, the utility of estramustine and its associated toxicity is another important consideration. Because the HRs for death and the secondary end points (PSA response, pain response, and QoL response) were similar in the TAX327 and SWOG 9916 trials, yet the docetaxel–prednisone regimen appeared to be better tolerated, it is reasonable to conclude at this time that treatment with docetaxel plus prednisone alone is the appropriate choice for the first-line treatment of HRPC. The regimen approved for use in HRPC in the U.S. and Europe is docetaxel plus prednisone administered Q3W.

**Utility of PSA as a Survival Marker**

Despite the clear improvement in the survival endpoint observed with chemotherapy in the TAX327 and SWOG 9916 trials, potential surrogate end points for survival need to be identified to facilitate the conduct of pivotal trials in HRPC. PSA response rate and changes in PSA constructs (i.e., PSA doubling time and PSA velocity) are promising potential surrogate end points. There has long been interest in using PSA response rate both as a guide to the selection of promising phase II regimens and as a surrogate end point for survival in HRPC clinical trials. Recent data, however, suggest that this approach may not be optimal. Note that in the TAX327 trial, for example, both docetaxel arms had a similar rate of PSA response (Table 1), but only the Q3W arm produced a significantly longer survival relative to MP. The PSA response rate was highest in the weekly docetaxel arm, but overall survival was not ultimately longer. In a formal analysis of these data designed to assess the efficacy of PSA as a surrogate for overall survival, the TAX327 investigators reported that, in fact, PSA response only partially explained the survival benefits observed in the trial; they cautioned against the use of PSA response as the primary end point for future phase III trials [7]. The same conclusion was drawn in a report describing the results of a meta-analysis of nine contemporary clinical trials of docetaxel-based therapy for HRPC (\( n = 1,330 \)) [8]. Half of the patients achieved a PSA response, but the correlations with survival data were weak in the overall group, the Q3W group, and the weekly group.

PSA constructs, including both PSA doubling time and PSA velocity are also promising surrogate markers [9, 10]. PSA doubling time is an effective surrogate in earlier stages of prostate cancer, and it has been suggested that a PSA doubling time \( \leq 70 \) days predicts a significantly shorter survival than does a PSA doubling time \( > 70 \) days in men with HRPC [10]. Similarly, PSA velocity during the first 3 months of chemotherapy was reported to be an independent prognostic factor for mortality, regardless of treatment, based on the SWOG 9916 trial [9]. These intriguing findings need further confirmation before being incorporated as end points in clinical trials. Until there is clear demonstration of a surrogate role for these alternative end points, survival remains the appropriate end point for phase III trials in HRPC.

**Second-Line Chemotherapy**

Despite a survival benefit with docetaxel-based chemotherapy, patients with HRPC eventually progress and require subsequent treatment. For example, Beekman and colleagues [11] evaluated subsequent treatments for 108 patients treated with first-line microtubule-targeting agents for HRPC and found that 83% and 40%, respectively, ultimately received second- and third-line chemotherapy. These data demonstrate the need for additional, effective treatment options for men with HRPC. Patients requiring second- or third-line treatments should enter clinical trials designed for this population. Several compounds are being evaluated in this setting.

**Mitoxantrone**

A logical second-line approach is to sequence mitoxantrone-based therapy after docetaxel. Retrospective analyses, however, suggest that the response rate and duration of response associated with second-line mitoxantrone are low [12, 13]. Michels and colleagues identified 83 patients in British Columbia who had received either docetaxel then mitoxantrone (D\( \rightarrow \)M) or mitoxantrone then docetaxel (M\( \rightarrow \)D) as first- and second-line therapy for HRPC. The PSA response rate was significantly higher with second-line docetaxel than with second-line mitoxantrone (44% vs. 15%; \( p = .012 \)), but overall survival did not differ between groups. Approximately half (46%) of the patients receiving second-line mitoxantrone required a dose reduction, delay, or discontinuation because of toxicity. Oh and colleagues conducted a similar retrospective, single-institution study and reported similar results. A total of 68 patients had been treated with a taxane first
followed by mitoxantrone or mitoxantrone first followed by a taxane. Responses to first-line mitoxantrone were seen in 12% of patients and to second-line mitoxantrone in 6%. Responses to first-line taxane therapy were seen in 69% of patients and to second-line taxane therapy in 61%. Hence, the response to the taxane was higher than that to mitoxantrone regardless of whether it was used as first- or second-line therapy ($p < .0001$). Only two patients (6%) treated with second-line mitoxantrone achieved a partial response, and the median progression-free survival time was 6.1 weeks. Most patients (50%) had disease stabilization with second-line mitoxantrone. Taken together, these analyses suggest that docetaxel remains active even when its use is delayed but that second-line mitoxantrone has limited efficacy for the treatment of progression after docetaxel.

Docetaxel
In patients who had not demonstrated evidence of disease progression on docetaxel, rechallenge with lower dose, weekly docetaxel as second-line therapy was evaluated in a small trial [14]. Results of that study, which enrolled 25 patients with PSA progression after first-line docetaxel, showed that docetaxel (35 mg/m²) given weekly for 3 consecutive weeks of a 4-week cycle is generally well tolerated and potentially effective. The majority of patients (72%) achieved a PSA response that lasted 5.8 months on average.

For patients with evidence of progression after first-line mitoxantrone, the results of ongoing phase II trials support that it is safe and active in this setting [15, 16]. When given weekly for 3 of every 4 weeks, 9 of 20 patients had a >50% reduction in PSA that lasted more than a month [16]. The median time to progression was 5 months, and median survival time was 13 months. Toxicity was generally mild with the weekly schedule. The conventional schedule (75 mg/m² Q3W) produced PSA reductions >50% in 85% (17/20) of patients and a pain response in 60% [15]. However, because docetaxel has supplanted mitoxantrone as the standard of care for the initial treatment of patients with HRPC, these data may have relevance for only a small, select group of patients.

Vinorelbine
The semisynthetic vinca alkaloid vinorelbine (Navelbine®, GlaxoSmithKline, Philadelphia, http://www.gsk.com) is well tolerated by elderly patients with non-small cell lung cancer, which led to interest in its use in HRPC. Phase II trials demonstrate that vinorelbine produces PSA responses and improvements in pain and performance status scores in this setting. i.v. vinorelbine (plus hydrocortisone, with or without aminoglutethimide [Cytadren®; Novartis Pharmaceuticals Corporation, East Hanover, NJ, http://www.pharma.us.novartis.com]) was compared with second-line hormone therapy (hydrocortisone with or without aminoglutethimide) in a randomized phase III trial in patients with progressive HRPC [17]. A regimen of continuous hydrocortisone (40 mg/day) with vinorelbine (30 mg/m²) on days 1 and 8 of a 3-week cycle resulted in a longer progression-free survival time relative to the comparator (3.7 vs. 2.8 months; $p = .055$). Multivariate analysis revealed that the risk for progression was 29% lower with the addition of vinorelbine to the regimen ($p = .005$). The median survival times were similar in the two groups, although more patients in the control arm crossed over to chemotherapy at disease progression. Vinorelbine was well tolerated. Nonhematologic toxicities were rare, and the rate of grade 4 neutropenia was 6.5%. Vinorelbine may be particularly well suited for elderly patients and for those with contraindications to mitoxantrone or docetaxel. An oral formulation has been studied in a small trial (n = 18) involving HRPC patients 70 years of age and older [18]. The preliminary data support that oral vinorelbine is safe and moderately active in these patients. It is unlikely that vinorelbine will be shown to be superior to docetaxel in the first-line setting, making it a potential alternative second-line treatment. Initial therapy with weekly docetaxel was compared with weekly i.v. vinorelbine in a phase II trial (n = 40) [19]. Docetaxel produced a significantly superior response rate (67% vs. 18%; $p = .02$), and the relative risk for progression was double with vinorelbine (HR, 2.05).

Satraplatin
Satraplatin (GPC Biotech, Martinsried/Munich, Germany, http://www.gpc-biotech.com), an oral platinum compound with in vitro efficacy against taxane-resistant cell lines, is also currently under investigation as a second-line chemotherapy option for men with HRPC [20]. Initially, a randomized, open-label, phase III trial was undertaken to compare satraplatin (100 mg/m² daily for 5 days) plus prednisone (10 mg twice a day) with prednisone alone as first-line therapy for patients with HRPC [21]. However, the trial was terminated early by its original sponsor for commercial reasons, with only 50 of the anticipated 380 patients enrolled and randomized. The treated patients were followed until disease progression or death, and ad hoc data analyses support that the satraplatin–prednisone combination has antitumor activity. The progression-free survival time was significantly longer with satraplatin (5.2 months vs. 2.5 months; $p = .023$), and more patients in the satraplatin arm achieved a PSA response (33% vs. 9%, respectively; $p = .046$) [20, 21]. Nonhematologic toxicities were generally mild with satraplatin. Grade 3 nausea and vomiting were reported by 7% of
patients; however, nearly all patients receiving satraplatin also received antiemetics (96%, or 26/27). One third of the patients had grade 3 thrombocytopenia, and 15% had grade 3–4 neutropenia in the satraplatin arm. An international, randomized, double-blind phase III clinical trial, the Satraplatin and Prednisone Against Refractory Cancer (SPARC) trial, is currently under way to evaluate satraplatin plus prednisone as second-line chemotherapy for HRPC [20]. The SPARC trial will compare time to progression and progression-free survival in patients with HRPC who are randomized to receive either satraplatin plus prednisone or placebo plus prednisone after failure of one prior chemotherapy regimen. Data from that trial will be analyzed after 637 disease progression events occur.

**Ixabepilone**

Ixabepilone (Bristol-Myers Squibb) is an epothilone B analogue with a mechanism of action similar to that of the taxanes. Epothilones are microtubulin-stabilizing agents, but their macrolide structure makes them chemically distinct from the taxanes [22]. Indeed, in vitro studies demonstrate activity in taxane-resistant models [23]. First-line, single-agent ixabepilone produced a 39% PSA response rate in men with HRPC [22]. First-line treatment with the combination of ixabepilone plus estramustine was compared with ixabepilone alone in another phase II trial, although that trial was designed to rapidly assess the safety and efficacy of each regimen rather than to directly compare outcomes between groups [23]. Ixabepilone (35 mg/m²) was given i.v. Q3W (on day 2 if concomitant with estramustine), and estramustine was dosed at 280 mg three times a day on days 1–5. Prophylactic warfarin was administered in the ixabepilone–estramustine arm. A total of 92 patients was treated. Both regimens demonstrated clinical antitumor activity, producing PSA declines and regressions of measurable disease. A PSA response was documented for 69% of the patients in the combination arm and for 48% of the patients in the ixabepilone arm. Peripheral neuropathy and neutropenia were the most common side effects and, not unexpectedly, toxicity was greater in the arm that included estramustine. Ongoing trials are evaluating ixabepilone as second-line chemotherapy in HRPC as well as in chemotherapy-naïve patients.

**Chemotherapy Combined with Targeted Agents**


Endothelin-1 (ET-1) is implicated in the progression of prostate cancer as well as in the development of the painful osteoblastic bone lesions that characterize metastatic disease. ET-1 mediates these effects through the ET₄R, which is overexpressed in advanced prostate cancer [24]. In addition, levels of ET-1 rise incrementally as prostate cancer advances, with the highest levels found in men with HRPC [25]. Interference with the ET-1/ET₄R pathway with the use of the ET₄R antagonist atrasentan significantly delayed clinical progression in men with asymptomatic HRPC in a randomized, placebo-controlled phase II trial [26]. A meta-analysis of data from 1,002 patients treated with atrasentan (10 mg/day orally) or placebo in phase II and phase III clinical trials revealed that atrasentan therapy resulted in significantly longer time to progression, time to onset of bone pain, and time to biochemical progression relative to placebo [27]. Atrasentan has been combined with docetaxel in a phase I/II study. Determination of the maximum-tolerated dose (MTD) and pharmacokinetic profile were primary aims of the trial because both agents are substrates for cytochrome P3A4 [28]. Docetaxel dose escalation was begun at 60 mg/m², and atrasentan (10 mg/day) was started on day 3 of the first cycle. Initial results (≤ 15) suggest that there are no significant pharmacokinetic interactions and that the combination is generally well tolerated up to a docetaxel dose of 75 mg/m². Completion of the trial is necessary to determine the MTD. Additional trials of the combination are in development or under way, such as the SWOG S0421 trial, a randomized, placebo-controlled phase III trial designed to compare docetaxel, prednisone, and atrasentan with docetaxel plus prednisone alone in men with advanced HRPC.

Angiogenesis appears to be important to the growth and spread of prostate cancer [29]. Microvessel density, a measure of tumor angiogenesis, is significantly greater in tumors from men with metastatic prostate cancer than in tumors from those with localized disease [30]. Similarly, plasma levels of vascular endothelial growth factor (VEGF) increase incrementally and significantly from healthy men, to men with localized prostate cancer, then to those with metastatic disease [31]. Moreover, the plasma VEGF level at diagnosis predicts clinical and biochemical
Thalidomide is a putative angiogenesis inhibitor. It inhibits angiogenesis and reduces VEGF levels in preclinical models, although a reduction in VEGF levels was not seen in a phase II clinical trial in men with HRPC [29]. In that trial, the combination of thalidomide and docetaxel was compared with docetaxel alone in 75 men with chemotherapy-naïve, progressive HRPC [29]. Patients were randomized 2:1 to treatment with docetaxel (30 mg/m²) given for 3 consecutive weeks of a 4-week cycle, with or without thalidomide (200 mg/day). The trial design sought to determine whether the combination could produce a response rate sufficient to warrant further evaluation. With a median follow-up of 26.4 months, 53% of patients in the combination arm and 37% in the docetaxel-only arm achieved a PSA response. The median progression-free survival time was 5.9 months with the combination, versus 3.7 months with single-agent therapy. These results met the predetermined statistical criteria for the demonstration of sufficient clinical benefit. Of note, thromboembolic events were reported in 12 of the first 43 patients treated with combination therapy; the addition of prophylactic low-molecular-weight heparin (LMWH) prevented this adverse event in the remainder of the patients randomized to this arm (n = 7). It may, therefore, be prudent to monitor closely for thromboembolic events and initiate prophylaxis as needed when thalidomide is combined with chemotherapy in other disease settings.

Bevacizumab, a humanized monoclonal antibody that targets VEGF, is also under investigation in combination with docetaxel. Initial results from the Cancer and Leukemia Group B (CALGB) 90006 trial, a single-arm phase II trial, demonstrate encouraging activity for a combination of bevacizumab, docetaxel, and estramustine in chemotherapy-naïve men with progressive HRPC [33, 34]. PSA progression occurred in 29 of 75 treated patients, for a PSA response rate of 77% [33]. The median time to PSA progression was 10.3 months. Prophylactic warfarin was encouraged, but not required, in that trial; no major bleeds were reported, although there was one death from mesenteric venous thrombosis, two nonlethal cases of pulmonary embolism, and two reports of deep venous thrombosis. The National Cancer Institute is currently conducting a phase II study of a four-drug combination consisting of docetaxel, prednisone, thalidomide, and bevacizumab (with LMWH prophylaxis) in men with chemotherapy-naïve progressive HRPC [35], and the CALGB is coordinating a phase III, double-blinded, placebo-controlled trial of docetaxel plus prednisone with or without bevacizumab [36].

DN-101 is a novel formulation of high-dose calcitriol designed for investigation as anticancer therapy [37]. High-dose calcitriol has both antiproliferative and proapoptotic effects in prostate cancer and enhances the efficacy of chemotherapy in several preclinical models. A phase II trial of high-dose oral calcitriol with docetaxel in HRPC revealed high response rates [38]. In that trial, 37 men with metastatic HRPC were treated with calcitriol (0.5 μg/kg) on day 1 followed by docetaxel (36 mg/m²) on day 2, repeated weekly for 6 weeks of an 8-week cycle. Most patients (30/37, or 81%) achieved a PSA response, and 22% had a >75% reduction in serum PSA level. The median time to progression and overall survival time were 11.4 months and 19.5 months, respectively. Tolerability was generally similar to that with single-agent, weekly docetaxel.

These initial results formed the basis for the Androgen-independent prostate cancer Study of Calcitriol Enhancing Taxotere® (ASCENT) trial, a randomized, double-blinded, placebo-controlled trial evaluating the combination of docetaxel with the proprietary high-dose calcitriol formulation DN-101 [37]. A total of 250 patients with chemotherapy-naïve HRPC has been randomized to treatment with docetaxel (36 mg/m²) for 3 consecutive weeks of a 4-week cycle with DN-101 (45 μg/day) or placebo. The primary objective of the study, PSA response rate at 6 months, was better with the addition of DN-101, but did not meet statistical significance (63% vs. 52%; p = .073). However, median survival, a secondary end point, was significantly longer with DN-101 (23.5 months estimated with docetaxel plus DN-101 vs. 16.4 months observed with docetaxel plus placebo; multivariate HR, 0.67; p = .035). Treatment was well tolerated; the incidences and types of adverse events were similar in the two groups. With the weekly docetaxel regimen, the incidence of grade 3–4 hematologic events was relatively low for both the docetaxel–DN-101 and docetaxel–placebo groups (10% and 8%, respectively, for neutropenia, and 4% and 6%, respectively, for anemia). A larger phase III trial is planned to further investigate these results.

**Conclusions**

The benefits of docetaxel-based chemotherapy in HRPC are now firmly established. Two randomized, controlled phase III clinical trials have shown that docetaxel-based therapy improves survival for men with progressive HRPC. The combination of Q3W docetaxel (75 mg/m²) and daily oral prednisone (5 mg twice daily) used in the TAX327 study is the new standard of care for progressive HRPC and should be the comparator in future phase III trials. Survival is the most appropriate end point for pivotal phase III trials in HRPC until alternative surrogate end points are fully elucidated.
Many patients with HRPC will require second- and even third-line treatment upon progression. With several promising agents on the horizon, more data are needed to formalize treatment recommendations in these settings, and the standard of care for these patients should be enrollment into a clinical trial. It is becoming apparent that the future management of patients with HRPC will involve building on the success of docetaxel, perhaps using a sequence of chemotherapy and targeted therapies that together reduce the risk for death, prevent or improve disease-related symptoms, and improve QoL for men with this debilitating disease.

**Disclosure of Potential Conflicts of Interest**

Dr. Berry has been a member of the Speakers’ Bureau for sanofi-aventis.

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