NEW ALTERNATIVES FOR THE MANAGEMENT OF PATIENTS WITH HORMONE-REFRACTORY PROSTATE CANCER

Joel B. Nelson, MD,* Philip W. Kantoff, MD,1 A. Oliver Sartor, MD,‡ and Daniel P. Petrylak, MD§

ABSTRACT

Nearly all men receiving androgen deprivation therapy for metastatic prostate cancer will ultimately manifest evidence of disease progression, thus requiring a re-evaluation of treatment strategy. Treatment alternatives for men with hormone-refractory prostate cancer (HRPC) have been limited to palliative care in the absence of a survival advantage associated with chemotherapy. In 2004, docetaxel-based chemotherapeutic regimens, now the standard for HRPC, were shown to confer a significant survival advantage in 2 large, randomized, controlled phase III trials. Bone-targeted therapies, specifically endothelin-A receptor antagonists (eg, atrasentan), bone-targeted radiopharmaceuticals, and bisphosphonates (eg, zoledronic acid), directly address the bone-stromal interactions underlying painful bone metastases. Atrasentan potentially reduces the incidence of and delays time to the onset of bone pain, may delay time to disease progression, and may improve the quality of life in patients with HRPC. Zoledronic acid was shown, in a phase III trial, to decrease the incidence of skeletal-related events and prolong the time to a first skeletal-related event in men with HRPC. Bone-targeted radiopharmaceuticals have been shown in phase III trials to decrease bone pain and decrease opioid utilization in patients with bony metastatic disease. Clinical trials are in progress to identify novel agents, in addition to optimize the combination of chemotherapeutic, bone-targeted agents and immunologic approaches. A wide variety of novel approaches, including immunologic therapies, are being tested. (Adv Stud Med. 2006;6(4C):S300-S312)

HORMONE-REFRACTORY PROSTATE CANCER: A CLINICAL DEFINITION

Hormone-refractory prostate cancer (HRPC), also referred to as androgen-independent prostate cancer (AIPC) or postcastration progressive prostate cancer, is typically characterized by successive rises in prostate-specific antigen (PSA) levels within the setting of serum estrate testosterone levels (<50 ng/mL). The European Association of Urology Guidelines define HRPC biochemical progression as 3 consecutive rises in PSA levels, 2 weeks apart, resulting in two 50% increases over nadir or baseline (whichever is higher); antiandrogen withdrawal for at least 4 weeks; and progression of osseous or soft-tissue lesions. Clinically, radiographic evidence of progression in the absence of PSA progression is rare and can be characteristic of unusual histologic conditions, such as small-cell cancer. By this definition, even small increases in PSA (ie, successive elevations as low as 0.1 ng/mL) are sufficient to consider the patient for the category of hormone-refractory disease.

As the nature of the disease changes in the era of chemotherapy and bone-targeted therapies, the term HRPC is being redefined to encompass patients with...
metastatic and nonmetastatic disease, in addition to patients with and without symptomatic disease. Although the level of testosterone required to declare a patient castrate remains open to debate, it is important to realize that some patients will respond to secondary hormonal manipulation (ie, antiandrogen withdrawal, antiandrogen administration, ketoconazole, estrogens, and corticosteroids), despite having failed initial hormonal therapy.1

In the recently issued position statement of the Society of Urologic Oncology, a multidisciplinary panel recognized 3 broad categories of tumors based on hormone sensitivity: hormone-naïve/hormone-sensitive tumors that respond to initial hormonal manipulation; androgen-independent/hormone-sensitive tumors that may respond to secondary or tertiary hormonal manipulation; and androgen-independent/hormone-insensitive tumors that have failed to respond (or progress) after secondary hormonal manipulation in a castrate setting.2

Clinically, tumors may also be classified based on hormonal status (castrate vs noncastrate levels of testosterone), extent and location of radiographically detectable disease, and the presence or absence of symptoms. Therefore, patients may have biochemical disease recurrence only, clinically evident local (nonmetastatic) or distant (metastatic) disease progression, or both.2 Increasingly, more men are seen with biochemical evidence of HRPC (ie, rising PSA alone) without radiographic evidence of disease and without any symptoms. Even in HRPC, despite low or undetectable testosterone levels, the androgen receptor pathway retains its ability to signal and thereby comprises a potential target for drug therapy. Therefore, clinicians must adapt therapy to an individual patient’s clinical status in light of the heterogeneous nature and shifting definitions of HRPC. In general, the broadest definition of HRPC includes all patients who experience PSA and/or clinical disease progression in the context of castrate levels of testosterone.2 Overall, the prognosis for patients with HRPC is improving, in part because of the advent of novel therapeutic approaches and earlier institution of therapies. However, given that HRPC is now diagnosed earlier than in the past, a component of the improvement is likely because of lead-time biases.

CHEMOTHERAPY IN THE MANAGEMENT OF HORMONE-REFRACTORY DISEASE

Traditionally, the management of HRPC was directed toward palliating symptoms with secondary and tertiary hormonal therapy, focal external beam radiation to symptomatic lesions, and systemic radio-pharmaceuticals. Until recently, many urologists and oncologists viewed chemotherapy as toxic and ineffective for HRPC because no single or combination approach had demonstrated a survival benefit. In the 1990s, results from 2 trials showed that mitoxantrone-based regimens conferred a palliative benefit, although no overall survival advantage, and slightly delayed time to treatment failure for men with HRPC. However, in 2004, the publication of results from 2 large, prospective, randomized, controlled phase III studies using docetaxel-based regimens set a new standard for chemotherapeutic treatment for patients with HRPC.4,5 Studies by Petrylak et al and Tannock et al indicated that a docetaxel-based regimen reduced the risk of death by 20% to 24%, and increased the median survival time by 1.9 to 2.4 months.6,7 These improvements in survival are similar to the results of patients with metastatic prostate cancer treated with chemotherapy for lung or breast cancer.7 To date, docetaxel-based treatment is the only chemotherapeutic approach to demonstrate a survival advantage in phase III trials of patients with HRPC.

**DOCETAXEL/PREDNISONE**

In a pivotal phase III trial (TAX 327), Tannock et al compared 2 schedules of docetaxel plus daily prednisone versus standard chemotherapy with mitoxantrone plus prednisone.6 Patients with HRPC (n = 1006) were randomized to 1 of 3 groups: docetaxel 75 mg/m² every 3 weeks for 10 cycles (group 1); docetaxel 30 mg/m² weekly for 5 cycles (group 2); or mitoxantrone 12 mg/m² every 3 weeks for 10 cycles (group 3). Prednisone (5 mg daily) was added to each regimen.7 The primary endpoint was overall survival. The study had a 90% power to detect a hazard ratio of 0.75 for death. Secondary endpoints were pain, PSA levels, and quality of life (QOL).8

Patients were recruited from centers in 24 countries and all had progressive disease, defined as increasing serum levels of PSA from 3 consecutive measurements obtained at least 1 week apart, or findings on physical examination or imaging studies. Importantly, the characteristics of this mostly elderly patient population reflected those typically seen in oncology practices. Approximately 25% of patients received 2 or more prior hormonal regimens, with more
than 80% of patients with metastases to bone. Overall, almost 50% of treated patients had substantial pain. Pain was defined by a score of 2 or more on the Present Pain Intensity scale (range 0–5, with higher scores indicating greater pain) or an analgesic score of at least 10. A standard dose of a narcotic analgesic (eg, 10 mg morphine) was assigned a score of 4; a standard dose of a nonnarcotic analgesic was assigned a score of 1.

Even in this advanced-stage population, the results showed clear superiority of docetaxel/prednisone every 3 weeks versus mitoxantrone/prednisone in lengthening median survival time by approximately 2.5 months (18.9 months vs 16.4 months, respectively; \( P = .009 \); Figure 1). In addition, the study showed a 24% reduction in the risk of death in patients treated with docetaxel/prednisone every 3 weeks. Notably, the survival advantage of docetaxel every 3 weeks was maintained regardless of patient age, Karnofsky performance score, and presence or absence of pain. By contrast, no significant survival benefit was observed between docetaxel/prednisone given once weekly versus mitoxantrone/prednisone given every 3 weeks (17.4 months vs 16.5 months; \( P = \text{NS} \)). Table 1 summarizes the major findings of TAX 327.

In secondary endpoints, significantly more men in the docetaxel-treated arms had at least a 50% decline in PSA (\( P < .001 \)). Additionally, more men had met the criteria for a predefined reduction in pain (\( P < .01 \) and \( P < .08 \)) versus the mitoxantrone-treated arm. QOL was evaluated in 815 patients using the Functional Assessment of Cancer Therapy-Prostate questionnaire. A significantly higher percentage of patients in the docetaxel groups (22%, docetaxel every 3 weeks [\( P = .009 \)]; 23%, docetaxel weekly [\( P = .005 \)]) reported improvement in QOL compared with the mitoxantrone group (13%). The greatest improvements in QOL occurred in prostate-specific domains (ie, weight loss, appetite, pain, physical comfort, bowel function, and genitourinary function).

Safety. Although adverse events were more common in the docetaxel groups, they were not life threatening (eg, sensory neuropathy). Serious adverse events

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy schedule</strong></td>
<td>Docetaxel 75 mg/m² every 3 weeks for 10 cycles + prednisone 5 mg daily</td>
<td>Docetaxel 30 mg/m² weekly for 5 cycles + prednisone 5 mg daily</td>
</tr>
<tr>
<td><strong>Median survival</strong></td>
<td>18.9 months (( P = .009 ) vs group 3)</td>
<td>17.3 months (( P = .3 ) vs group 3)</td>
</tr>
<tr>
<td><strong>Pain response rate</strong></td>
<td>35% (( P &lt; .01 ) vs group 3)</td>
<td>31% (( P &lt; .07 ) vs group 3)</td>
</tr>
<tr>
<td><strong>Prostate-specific antigen response rate</strong></td>
<td>45% (( P &lt; .001 ) vs group 3)</td>
<td>48% (( P &lt; .001 ) vs group 3)</td>
</tr>
</tbody>
</table>

occurred among 26% of patients in the group receiving docetaxel every 3 weeks and 29% in the group receiving weekly docetaxel compared with 20% in the group receiving mitoxantrone. Although grade 3 or 4 neutropenia was most common in the group receiving docetaxel every 3 weeks, febrile neutropenia was rare (3%), as was treatment-related death (0.3%).

**DOCETAXEL/ESTRAMUSTINE**

In the phase III Southwest Oncology Group (SWOG) Intergroup Protocol 9916 study, Petrylak et al randomized 770 patients with progressive HRPC to receive estramustine (280 mg, 3 times daily, on days 1 through 5) plus docetaxel (60 mg/m² every 3 weeks) plus dexamethasone (60 mg in 3 divided doses before docetaxel) versus standard chemotherapy with mitoxantrone (12 mg/m² every 3 weeks) plus prednisone (5 mg twice daily). Progressive disease was defined according to recommended criteria as: a bidimensionally measurable lesion assessed within 28 days before study registration; progression of disease that could be evaluated but not measured (eg, by bone scanning) as assessed within 42 days before registration; or an increase in serum PSA level over the baseline level in at least 2 consecutive samples, obtained at least 7 days apart.

Treatment continued until disease progression, unacceptable adverse events occurred, or until a maximum of 12 cycles of docetaxel and estramustine or 144 mg/m² mitoxantrone had been administered. The primary endpoint of the study was overall survival. The study had an 80% statistical power to detect a 33% improvement in median survival. Secondary endpoints included progression-free survival, objective response rates, and post-treatment declines of at least 50% in serum PSA.

Study results showed a 20% reduction in mortality in the docetaxel/estramustine group compared with the mitoxantrone/prednisone group (95% confidence interval, 3%–33%). Median overall survival time was approximately 2 months longer in the docetaxel/estramustine group (17.5 months) than in the mitoxantrone/prednisone group (15.6 months; P = .02 by the log rank test; Figure 2). Additionally, median time to disease progression was significantly superior in the

---

**Figure 2. Kaplan-Meier Estimates of Overall Survival Among Men with Androgen-Independent Prostate Cancer Treated with Mitoxantrone and Prednisone or Docetaxel and Estramustine**

![Graph showing Kaplan-Meier estimates of overall survival among men with androgen-independent prostate cancer treated with mitoxantrone and prednisone or docetaxel and estramustine.]

---

**Figure 3. Kaplan-Meier Estimates of Progression-Free Survival Among Men with Androgen-Independent Prostate Cancer Treated with Mitoxantrone and Prednisone or Docetaxel and Estramustine**

![Graph showing Kaplan-Meier estimates of progression-free survival among men with androgen-independent prostate cancer treated with mitoxantrone and prednisone or docetaxel and estramustine.]

---
docetaxel/estramustine group versus the mitoxantrone/prednisone group (6.3 months vs 3.2 months, respectively; P < .001; Figure 3). PSA declines of at least 50% occurred in 50% of docetaxel/estramustine-treated patients compared with 27% of mitoxantrone/prednisone-treated patients (P < .001). The proportion of patients with a partial response in measurable disease (17% vs 11%) did not differ significantly between the 2 groups. Table 2 summarizes the major findings of this study.

Safety. Although docetaxel/estramustine therapy was generally well tolerated, a higher incidence of grade 3/4 toxicity, particularly cardiovascular events and neutropenia, was reported in the docetaxel/estramustine arm of the study. No difference in deaths caused by toxicity or study discontinuation was observed between the 2 arms.

The SWOG 9916 study team concluded that although treatment with estramustine and docetaxel moderately prolongs survival, it is at the cost of an increased rate of adverse events. Physicians and patients must weigh both the benefits and risks when considering the use of docetaxel and estramustine as first-line therapy for men with metastatic HRPC.

Based on the results from TAX 327, the US Food and Drug Administration (FDA) approved docetaxel/prednisone for the treatment of AIPC. Because the experimental combination of estramustine and docetaxel also demonstrated a survival benefit, one must question whether estramustine should be included in the treatment of HRPC. Despite the known toxicities of estramustine, improved time to progression and the proportion of patients with a PSA decline of 50% or more can be demonstrated when it is combined with paclitaxel, vinblastine, or epothilone-B compared with these agents administered alone. Although underpowered, when compared with the respective single agent alone, significant survival differences were seen when estramustine was combined with vinblastine or paclitaxel. Direct comparisons of the results of SWOG 9916 and TAX 327 to answer the question of estramustine administration cannot be made because of different post-treatment crossover patterns, in addition to minor differences in study entry criteria. The only valid method to evaluate the contribution of estramustine is with adequately powered randomized trials comparing estramustine combined with docetaxel to docetaxel alone. The toxicities of estramustine and the small postulated improvement in survival make it unlikely that such a trial will ever be implemented. Given toxicity considerations, both SWOG and the Cancer and Leukemia Group B (CALGB) use docetaxel/prednisone as the standard treatment arm for phase III studies.

**Investigational Docetaxel-Based Combination Regimens: A to Z**

Phase II trials of docetaxel in combination with various agents, including atrasentan, bevacizumab, calcitriol, thalidomide, and zoledronic acid, have been completed. The impact of these combination regimens on survival and PSA response awaits confirmation in appropriately designed, large-scale, randomized phase III trials. The investigational goal is to identify multiagent chemotherapeutic regimens with a docetaxel backbone that further extend the survival benefits of docetaxel, while avoiding redundant toxicities.

**Docetaxel Plus Atrasentan**

Atrasentan, a selective endothelin receptor antagonist, is a novel agent that, in part, targets tumor-stromal

---

**Table 2. Summary of Results of SWOG 9916: Docetaxel/Estramustine Versus Mitoxantrone/Prednisone**

<table>
<thead>
<tr>
<th>Experimental Arm (21-Day Cycle)</th>
<th>Control Arm (21-Day Cycle)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy schedule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel 60 mg/m² every 21 days + estramustine 280 mg, TID, days 1–5</td>
<td>Mitoxantrone 12 mg/m², every 21 days + prednisone 5 mg BID</td>
<td></td>
</tr>
<tr>
<td>Median survival</td>
<td>18 months</td>
<td>16 months</td>
</tr>
<tr>
<td>Time to progression</td>
<td>6 months</td>
<td>3 months</td>
</tr>
<tr>
<td>Prostate-specific antigen response</td>
<td>50%</td>
<td>27%</td>
</tr>
<tr>
<td>Partial response rate</td>
<td>17%</td>
<td>11%</td>
</tr>
</tbody>
</table>

interactions, and is discussed in more detail later in this article. In a planned phase III SWOG study (SO421) of docetaxel plus placebo versus docetaxel plus atrasentan \((n = 706)\), patients with HRPC will be randomized to receive docetaxel 75 mg/m\(^2\) every 3 weeks plus placebo or docetaxel 75 mg/m\(^2\) every 3 weeks plus atrasentan 10 mg. The trial is designed to detect a 30% increase in median survival with 85% power, and the primary and secondary endpoints are being finalized.

**DOCETAXEL PLUS BEVACIZUMAB**

Bevacizumab is a monoclonal antibody that exerts its effects by binding to the vascular endothelial growth factor (VEGF). In 2004, bevacizumab became the first antiangiogenesis agent to receive US FDA approval based on data in patients with metastatic colorectal cancer. In HRPC xenograft models, this agent appears to slow the growth of prostate cancer, an effect that is enhanced with the addition of chemotherapy. Plasma and urine levels of VEGF are prognostic in men with HRPC. Plasma VEGF levels are significantly elevated in patients with metastatic prostate cancer versus localized prostate cancer \((P = .003)\) and are inversely correlated with survival time \((P = .002)\). Additionally, patients with a baseline urine VEGF of 28 pg/mL or less had an average survival time of 17 months, whereas those with a level above 28 pg/mL had a survival time of 10 months \((P = .024)\).

On the basis of these data, Picus et al investigated the use of bevacizumab in combination with docetaxel/estramustine in 79 patients with HRPC enrolled in the phase II CALGB 90006 trial. Patients received estramustine 280-mg thrice-daily dosing on days 1 to 5, docetaxel 70 mg/m\(^2\) on day 2, and bevacizumab 15 mg/kg over 30 minutes on day 2. Dexamethasone 8-mg twice-daily dosing was administered on days 1 to 3, and warfarin 2 mg daily was encouraged but not required to reduce estramustine-associated thromboembolic complications. Results showed a post-therapy PSA decline of greater than 50% in 59% of study participants. The DN101/docetaxel-treated patients had a lower rate of significant adverse events compared with docetaxel-treated patients alone. The reduction in significant adverse events was primarily because of lower rates of thrombotic and gastrointestinal events in the combination arm. Based on these study results, a phase III study of weekly docetaxel combined with DN101 is being compared with administration of docetaxel/prednisone every 3 weeks.

**DOCETAXEL PLUS CALCITRIOL**

Calcitriol, a biologically active form of vitamin D, has been found to inhibit angiogenesis and induce apoptosis in vitro and in vivo. A phase II study found that the regimen of calcitriol 0.5 µg/kg on day 1, followed by docetaxel 32 mg/m\(^2\) on day 2, and repeated weekly for 6 of 8 weeks, was associated with a median survival advantage of 19.5 months and a PSA reduction rate of greater than 75% for 59% of study participants. To evaluate whether a high-dose preparation of calcitriol, DN101, combined with weekly docetaxel had a superior PSA decline rate when compared with weekly docetaxel alone, randomized phase II trials enrolled 250 patients. Although the PSA decline rates at 6 months were not significantly different between the DN101/docetaxel (58%) and docetaxel arms (49%), an adjusted survival analysis demonstrated an improved survival with DN101/docetaxel. The DN101/docetaxel-treated patients had a lower rate of significant adverse events compared with docetaxel-treated patients alone. The reduction in significant adverse events was primarily because of lower rates of thrombotic and gastrointestinal events in the combination arm. Based on these study results, a phase III study of weekly docetaxel combined with DN101 is being compared with administration of docetaxel/prednisone every 3 weeks.

**DOCETAXEL PLUS THALIDOMIDE**

Thalidomide, another angiogenesis inhibitor, has also shown promise in combination with docetaxel. In a randomized phase II trial, 75 chemotherapy-naïve patients with metastatic HRPC were randomized to receive docetaxel monotherapy or docetaxel in combination with thalidomide (200 mg daily). Fifty-three percent of patients treated with the combination regimen showed a post-therapy PSA decline of greater than 50% in 58 of 72 patients (81%), a median time to objective disease progression of 9.7 months, and an overall median survival time of 21 months.

A randomized, double-blind, placebo-controlled phase III trial of more than 1000 patients (CALGB 9040) is under way, comparing docetaxel/prednisone with and without bevacizumab in patients with HRPC. The primary endpoint of the study will be overall survival, with the secondary endpoints of PSA, relative risk, and progression-free survival. The study is designed to show a median survival time improvement from 19 to 24 months, with a 2-sided alpha of 0.05. Patients will be stratified based on a validated nomogram.
a survival difference, further follow-up demonstrated a significant difference in median survival time (25.9 vs 14.7 months; \( P = .04 \)) in favor of the docetaxel/thalidomide regimen.23

**DOCETAXEL PLUS ZOLEDRONIC ACID**

Zoledronic acid is a potent intravenous bisphosphonate with proven utility in the management of skeletal complications of HRPC. It has been reported that the bisphosphonates may have a synergistic antitumoral effect when combined with taxanes.

In a recent study, 54 patients with HRPC received zoledronic acid along with a docetaxel/estramustine treatment regimen.24 Every 2 weeks, patients received docetaxel 45 mg/m2 and estramustine 140 mg (administered orally every 8 hours for 9 doses). Zoledronic acid 4 mg was administered every 28 days. All patients had received at least 2 previous regimens of hormonal therapy, and 43% had also undergone estramustine therapy. Of the 54 patients in the study, 27 (50%) had only bone metastases, and 17 (31%) had disease in the prostate. At the end of the study, 45% (22/49) of assessable patients had a PSA response, defined as a decrease of more than 50% from baseline with no objective progression; 38% (9/24) with measurable disease had a response to therapy (1 complete, 8 partial); and 37% (14/38) of the patients who had been using analgesics had discontinued use. Overall survival time was 13.3 months. Results of this study indicate that docetaxel/estramustine plus zoledronic acid is a well-tolerated regimen that results in symptomatic improvement in a significant proportion of patients with HRPC.24 Whether this combination warrants further study is debatable.

Osteonecrosis of the jaw has been reported in patients receiving treatment regimens including bisphosphonates. A dental examination should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (eg, chemotherapy, corticosteroids, or poor oral hygiene) and these patients should avoid invasive dental procedures during treatment, if possible. It is also recommended that the bisphosphonate dose be adjusted based on the patient’s baseline creatinine clearance.

**DOCETAXEL PLUS RADIOPHARMACEUTICALS**

A variety of studies have suggested potential synergy between taxanes and radiation, thus examination of docetaxel and radiopharmaceuticals represents a reasonable clinical approach. Docetaxel has been used in combination with the radiopharmaceutical samarium-153 EDTMP (ethylene diamine tetramethylene phosphonate) in small European trials that have been published to date only in abstract form.25 These data indicate that combinations of these agents may be used safely. Efficacy data are limited. Additional studies are now ongoing in several centers in the United States and these trials should begin to mature in the next year.

**TIMING AND SEQUENCING OF CHEMOTHERAPY**

For patients who have failed androgen deprivation therapy, the optimal time to initiate chemotherapy remains unresolved. In the absence of data, a stepwise approach, in which potentially toxic chemotherapy is deferred until symptoms progress, seems reasonable. Secondary or tertiary hormonal manipulation is appropriate for asymptomatic patients with slowly progressive disease. Chemotherapy should be reserved for patients with a rapidly rising PSA and/or metastatic disease. Patients generally prefer a stepwise approach that starts with the least toxic agent and progresses to more toxic agents as their therapeutic options narrow or their symptoms increase.

In the recently issued position statement of the Society of Urologic Oncology, a multidisciplinary panel outlined a logical progression of treatment choices and determined that management strategies must consider individual patient status.2 Because of the heterogeneous nature of the disease process, treatment options must be based on the nature and degree of the patient’s cancer.2 Using this approach, chemotherapy may be an option for patients with symptomatic disease or asymptomatic disease with bone metastases.2 However, what steps to take after chemotherapy treatment with a taxane fails remains a major question for physicians and patients. There are no drugs approved by the US FDA in this setting, and only 1 large, randomized clinical trial is currently addressing the issue. In that trial, a novel oral platinum (satraplatin) plus prednisone is being compared with prednisone alone. This trial has completed its accrual of more than 900 patients. Endpoints include time to progression and overall survival. Results are anticipated in the next year.

Clinical trials are needed to assess the value of chemotherapy earlier in the disease course, before or after radical prostatectomy or radiation, in hormone-
naïve patients with a rising PSA, particularly those with a rapid doubling time or other adverse prognostic features.

**SELECTIVE ENDOTHELIN RECEPTOR ANTAGONISTS: POTENTIAL OPTIONS FOR THE TREATMENT OF BONY METASTATIC PROSTATE CANCER**

Because docetaxel-based chemotherapeutic regimens have been shown to confer a small but significant survival advantage in 2 large phase III trials, subsequent research efforts have focused on identifying novel agents. Agents targeting signaling pathways that are potentially important in HRPC growth represent an area of particular focus. Recent research has generated significant interest in compounds termed selective endothelin-A (ET_A) receptor antagonists. These compounds were originally investigated for hypertension and congestive heart failure because of endothelin's role in vasoconstriction. Research showed that prostate cancer cells secrete endothelin; therefore, compounds that block this excess secretion may play a role in the metastases of prostate cancer in bones and elsewhere.26 These agents may offer another treatment alternative for patients who choose not to undergo chemotherapy, in addition to those patients with concomitant medical conditions that do not permit the use of cytotoxic agents or for taxane-resistant populations.

Some of the more important advances in this area have been the bone-targeting strategies. One such target is endothelin-1 (ET-1), a potent vasoconstrictor that modulates cell growth and proliferation, inhibits apoptosis, and stimulates osteoblast activity by selectively binding to the ET_A receptor.27 The bony metastases in prostate cancer are primarily osteoblastic in nature, rather than osteolytic, and are mediated in part by ET-1 stimulation of growth factor and cell signaling pathways (Figure 4).27,28 Therefore, an ET_A receptor antagonist would inhibit the deleteriously prolific effects of ET-1 on the osteoblasts that contribute to the painful bone metastatic lesions of prostate cancer. Atrasentan, a novel agent that targets tumor-stromal interactions, is an ET_A receptor antagonist that is being evaluated for use in patients with bony metastatic HRPC to delay tumor progression in bone.

A normal ejaculatory protein, ET-1 concentrations are highest in seminal fluid, reaching levels almost 500 times greater than those found in plasma (Figure 5).29,30 Of the 2 endothelin receptors found in the normal prostate, endothelin-B (ET_B) predominates in epithelium, whereas underlying stromal cells express ET_A.31 In prostate cancer, ET_B expression is lost, whereas ET_A expression increases with the stage of prostate cancer.31-33 As with serum PSA, studies confirm that levels of ET-1 are higher in some men with metastatic prostate cancer.30-33 Finally, the pain associated with the bony metastatic lesions of advanced prostate cancer may be induced by ET-1.34

Bone pain is often associated with advanced prostate cancer and is the cause of significant morbidity. As a mediator of pain, ET-1, acting through the ET_A receptor, has a direct effect on nerves and as a potentiator of other noxious stimuli.35 The endothelin axis, including ET-1 and the endothelin receptors, promotes a variety of other tumorigenic cellular events, including proliferation, apoptosis inhibition, abnormal osteogenesis, and altered nociceptive stim-

---

Figure 4. Endothelin-1 Activity in Bone Remodeling

The proliferative effects of ET-1 on osteoblasts are enhanced by 1,25-dihydroxyvitamin D₃, enhancing ET_A receptor expression and by a direct stimulatory effect. Parathyroid hormone (PTH) inhibits Ca²⁺-dependent signaling and downregulates ET-receptor expression; ET_A receptor antagonists block the effects of ET-1 on osteoblasts. Conversely, osteoclastic function is inhibited by ET-1 as resorptive activity and osteoclast motility are dose-dependently reduced in the presence of ET-1. A host of factors that are abundantly found in bone, such as transforming growth factor-β (TGF-β), interleukin-1B (IL-1B), and bone morphogenetic protein-7 (BMP7), are potent inducers of ET-1 expression. ET = endothelin.

Atrasentan effectively targets this pathway to several of these phenomena. In the phase III clinical setting, atrasentan has been shown to suppress the markers of biochemical and clinical prostate cancer progression in bone.

Blockade of the endothelin axis (ETA/ET-1 receptor binding) is an intriguing therapeutic approach because it may disrupt osteoblastic metastasis, modulate cancer-induced bone pain, and inhibit tumor progression. Atrasentan, the first agent in its class to enter late-phase clinical trials for prostate cancer, is orally bioavailable. It is a potent competitive inhibitor of ET1 binding, with an 1800-fold superior selectivity for ETA compared with ETB.

**PHASE II TRIALS**

Two large, randomized, double-blind, multicenter phase II trials assessed atrasentan in men with HRPC. In the initial 12-week study (M96-500), Carducci et al randomized 131 men with metastatic HRPC to 1 of 3 groups to receive placebo, atrasentan 2.5 mg, or atrasentan 10 mg. Study participants had pain severe enough to require opioid analgesics. There were no statistically significant differences in response rates for the primary endpoint (pain relief at week 12). However, a trend toward improvement in pain without increased analgesic consumption was noted in the atrasentan 10-mg group.

In the second phase II study (M96-594), Carducci et al randomized 288 asymptomatic patients with metastatic HRPC to 1 of 3 groups to receive placebo, atrasentan 2.5 mg, or atrasentan 10 mg. All groups had metastatic disease as indicated by elevated serum markers of PSA, alkaline phosphatase, acid phosphatase, and lactate dehydrogenase (LDH). The primary endpoint was time to disease progression, and results from the intention-to-treat (ITT) analysis showed that median time to disease progression was 183 days in the atrasentan 10-mg group compared with 137 days for the placebo-treated group ($P = .13$). In the evaluable subset of 244 patients, there was a significant ($P = .021$) delay in disease progression from 129 days (placebo group) to 196 days (atrasentan 10-mg group).

These phase II trials also studied bone deposition and bone resorption markers based on preclinical data connecting ETA to osteoblastic activity. Although LDH and acid phosphatase, markers of overall disease burden, continued to increase from baseline in the placebo group, both markers were attenuated in the atrasentan treatment groups in the ITT and evaluable populations compared with placebo. These phase II findings provided the first indication that atrasentan may be most active in men with bony metastatic HRPC and provided the impetus for phase III trials. The phase II trials suggested that atrasentan showed a beneficial effect and that further studies were needed.

**Figure 5. Increased Concentration of Plasma Immunoreactive ET-1 in Prostate Cancer**

**PHASE III TRIALS**

With the phase II data indicating a significant delay in disease progression in the evaluable subset, 2 phase III trials were designed. One of these studies (M00-211) was designed to duplicate the time to disease progression phase II trial (M96-594); however, with only 2 treatment arms, a placebo and an atrasentan 10-mg arm. In addition, the M00-211 trial required bone scans and axial imaging every 3 months. In this phase III study, Carducci et al randomized 809 men with asymptomatic metastatic HRPC to receive atrasentan 10 mg (n = 408) or placebo (n = 401).41

The primary endpoint, time to disease progression defined as clinical events, pain, or progression on bone scan, did not meet clinical significance.41 Nonetheless, atrasentan showed significantly smaller increases in other clinical parameters, including bone alkaline phosphatase, total alkaline phosphatase, and PSA.41 In a subset of 671 patients identified before the study was unblinded (n = 329, placebo; n = 342, atrasentan), atrasentan significantly delayed time to disease progression and time to bone alkaline phosphatase progression.41 In 681 patients with at least 3 on-treatment bone alkaline phosphatase values, atrasentan 10 mg extended bone alkaline phosphatase doubling time 4-fold longer compared with placebo. A bone alkaline phosphatase doubling time of less than 12 months is a marker of rapid disease progression and shortened survival.42

Another phase III trial of atrasentan (M00-244) in men with nonmetastatic HRPC is in progress to evaluate time to disease progression as defined by the appearance of first metastasis. These patients are earlier in the disease continuum and have no clinical or radiographic evidence of metastatic disease. Accrual was completed in May 2003 with 942 men enrolled.35

Another recent study found that ETA antagonists improved blood flow into tumors.37 These results suggest that ETA antagonists may potentiate the effects of radiation and chemotherapy, modalities that depend on well-oxygenated blood flow for efficacy.

**RECOMMENDATIONS FOR PHARMACOLOGIC MANAGEMENT OF BONE PAIN IN HRPC**

Traditional modalities, including radiation and radioisotopes, will continue to play an important role in alleviating pain from single and widespread osseous lesions. Although effective, chemotherapy does not directly address the underlying mechanisms responsible for the bone pain and skeletal complications associated with metastatic disease. Bone-targeted agents, such as atrasentan and zoledronic acid, may also play a role.

Zoledronic acid, a potent intravenous bisphosphonate, has shown promise in the management of skeletal-related events in patients with prostate cancer with bone metastases. However, no evidence to date suggests that these agents decrease pain. Results from a phase III double-blind, placebo-controlled, randomized trial established that zoledronic acid (4 mg) decreased the incidence of and prolonged the time to a first skeletal-related event in men with metastatic HRPC.43 Skeletal-related events were defined as pathologic bone fractures (vertebral or nonvertebral), spinal cord compression, bone surgery, radiation therapy to bone, or change of antineoplastic therapy to treat bone pain.43 In this trial, zoledronic acid did not appear to significantly decrease pain compared with placebo; however, patients in the trial had increasing pain compared with the baseline.43 Nonetheless, although patients in the zoledronic acid group and the placebo group experienced pain, those treated with zoledronic acid had less of an increase in pain than placebo-treated patients.44

Combination bone-targeted therapy with atrasentan and zoledronic acid is intriguing because the agents may interact synergistically to help restore bone homeostasis in men with metastatic HRPC. Because metastasis disrupts the balance between osteoblast-mediated bone formation and osteoclast-mediated bone resorption, it has been postulated that the dual combination of an osteoclast inhibitor (zoledronic acid) with an osteoblast inhibitor (atrasentan) may further reduce skeletal complications and bone pain in men with HRPC.27 A phase I/II clinical trial is completed but results are not compelling.35

**APC8015**

APC8015 is an autologous CD54-positive dendritic cell vaccine loaded with a recombinant granulocyte macrophage colony-stimulating factor and a prostatic acid phosphatase fusion protein. In a phase III randomized, placebo-controlled trial of 127 men with asymptomatic AIPC, patients received APC8015 or placebo. The primary endpoint was time to disease progression. Secondary endpoints included time to onset of disease-related pain and overall survival. Although treatment with APC8015 did not result in a statistically significant delay in time to disease pro-
gression, it did result in a statistically significant ($P = .01$) survival advantage of 4.5 months in an ITT analysis of patients with AIPC. In a subset analysis, treatment with APC8015 resulted in a 6-month survival advantage ($P = .047$) in patients with a Gleason score of 7 or less, forming the basis for an ongoing phase III trial. The combination of APC8015 with bevacizumab is also being evaluated in a phase II trial in men with hormone-sensitive prostate cancer.

**GVAX Vaccine**

GVAX (Cell Genesys, San Francisco, CA) promotes granulocyte macrophage colony-stimulating factor secretion through genetic modification of allogeneic prostate cancer cell lines. In a small phase II trial of men with metastatic HRPC ($n = 34$), Simons et al found that GVAX immunization was well tolerated. In a larger phase II trial ($n = 80$), Small et al found that GVAX immunization stabilized or decreased levels of a biomarker of osteoclast activity in the majority of patients with metastatic disease.

Two phase III trials are in progress with symptomatic and asymptomatic men with metastatic prostate cancer, regardless of Gleason score: one to evaluate GVAX in combination with docetaxel/prednisone, and the second to evaluate whether GVAX plus chemotherapy is more effective than chemotherapy alone.

**Collaboration in the Management of Patients with Prostate Cancer**

As the value of adjuvant and neoadjuvant therapies for prostate cancer becomes realized, greater partnership will be needed among the members of a patient’s cancer care team, including the urologist, the medical oncologist, and the radiation oncologist. Optimal patient management will require these specialists to collaborate in a multidisciplinary team approach throughout all stages of the disease and all phases of care. For example, a collaborative relationship between the urologist and the medical oncologist is important for the early recognition and management of ureteral complications, such as urinary obstruction, urinary retention, chronic irritative voiding symptoms, and persistent hematuria, in addition to painful bony metastases, while the patient is undergoing cytotoxic chemotherapy. The management of painful bony metastatic HRPC typically requires further collaboration with a radiation oncologist.

As the management of prostate cancer evolves, the integration of medical therapies, such as chemotherapy, bone-targeted therapies, and other targeted therapies, earlier in the disease course will become the driving force involving not only urologists but also medical oncologists in the management of prostate cancer from its onset.

**Conclusions**

With continued aging of the general population, an increased number of men are being diagnosed with prostate cancer in the United States and throughout the world. Given the morbidity and mortality associated with advanced disease, continued development of therapeutic alternatives is a top priority for physicians and patients alike. Today, more treatment options exist for men with HRPC than ever before. The establishment of docetaxel-based chemotherapy as therapy associated with survival benefit has been a critical step in the management of these patients. Bone-targeted therapies, such as atrasentan, bisphosphonates, and radiopharmaceuticals, may inhibit the bone-stromal interactions that underlie the metastatic process.

The biologic activity of atrasentan is evident in clinical trials showing a delay in time to disease progression versus placebo, especially in patients with bone metastatic disease, in addition to a trend toward improving the pain that compromises QOL for men with metastatic disease. Aggressive new treatment alternatives, including chemotherapy and bone-targeted therapy, need to be tested in randomized trials to determine whether further improvements in the quantity of life and QOL can be achieved for men with HRPC. Further research is warranted to identify novel agents and optimize the use of existing agents in combination regimens that focus on lengthening and improving QOL for men with HRPC.

**References**


2. Chang SS, Benson MC, Campbell SC, et al. Society of Urologic Oncology Position Statement: redefining the man-
38. Carducci MA, Vogelzang NJ, Dalili D, et al. A placebo (PBO) controlled phase II dose-ranging evaluation of an endothelin receptor antagonist for men with hormone refracto-


