



Michael Mahany. *Grazing Dall Ram on Mt. Margaret*. Photograph. Denali National Park, Alaska.

*Several approaches are now available to palliate patients with androgen-independent prostate cancer.*

## Management of Androgen-Independent Prostate Cancer

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**Background:** Although androgen withdrawal can control prostate cancer for long periods in many patients, controversy exists regarding management when the tumor becomes androgen independent. Several options are now available.

**Methods:** A review of the pertinent literature of the last 20 years was conducted to provide guidance in defining and managing hormone-refractory prostate cancer.

**Results:** Stage D prostate cancer can be subclassified to correlate tumor biology with disease stage. Secondary hormone manipulations may induce responses in patients after failure of initial androgen suppression, and chemotherapy with docetaxel has prolonged survival in patients with androgen-independent prostate cancer (AIPC). The weight of evidence supports the maintenance of castrate levels of testosterone in metastatic AIPC. Bisphosphonates decrease skeletal complications.

**Conclusions:** Secondary hormone therapy, chemotherapy, and bisphosphonate therapy may provide benefits for selected patients. Correlation of disease stage with biologic characteristics of the tumor and host facilitates proper choices of interventions. Docetaxel-based chemotherapy regimens should be considered for first-line treatment of patients with progressive metastatic AIPC.

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Abbreviations used in this paper: PSA = prostate-specific antigen, TTP = time to progression, LHRH = luteinizing hormone-releasing hormone, AIPC = androgen-independent prostate cancer, HRPC = hormone-refractory prostate cancer.

### Introduction

Prostate cancer is the most common cancer of men in the United States. In 2004, an estimated 230,110 cases will be diagnosed and 29,900 men will die of prostate cancer.<sup>1</sup> The majority of patients who are diagnosed with localized prostate cancer are treated for cure with either radiation or surgery. Patients in whom treatment with curative intent is unsuccessful and those who present with metastasis are candidates for androgen suppression. The median duration of time to progression (TTP) while on this "primary" hormone therapy is 14 to 30 months.<sup>2</sup>

The majority of men who are deprived of androgens, either by means of luteinizing hormone-releasing hormone (LHRH) agonists or bilateral orchiectomy, ultimately progress to an androgen-independent phase where the initial androgen deprivation regimen no longer controls the tumor.<sup>3</sup> As a result, treatment strategies are needed for men with androgen-independent prostate cancer (AIPC). A minority of men who have progressive disease after initial androgen deprivation respond to additional hormonal treatments. Prostate cancer that no longer responds to any hormonal treatment is referred to as hormone-refractory prostate cancer (HRPC). Older estimates of median survival for patients with HRPC range from 7 to 12 months,<sup>4</sup> but more recent studies report a median survival of 16 months.<sup>5,6</sup> This improvement may be the result of better treatments or may be explained by stage migration and prostate-specific antigen (PSA)-induced lead-time bias. Historically, cytotoxic chemotherapy for prostate cancer induced low response rates, with an average objective response rate of 8.7%.<sup>7</sup> Prior to the use of taxanes, no survival benefit supporting the use of chemotherapy was demonstrated. More recent studies of chemotherapy in patients with HRPC report benefits including reduced pain, improved quality of life, and decreased need for narcotics.<sup>8</sup>

## Description of Stage D Prostate Cancer

The most recent *American Joint Commission on Cancer Staging Manual*<sup>9</sup> describes distant metastasis (M) as being present (M1) or absent (M0), with a subcategorization of M1(a) as nonregional lymph node(s), M1(b) as bone(s), and M1(c) as other sites with or without bone disease. This categorization, even with histologic grading, is inadequate for logical treatment planning and estimation of prognosis. Thus, many investigators and clinicians continue to use the older term “stage D” to represent metastatic prostate cancer instead of the AJCC “M1.”

To provide optimal care to patients with advanced prostate cancer, several conditions are important: the sites of metastasis (if known), response to prior and current treatments, serum testosterone levels, and serum PSA levels. A separate category of PSA-alone failure of local

prostate cancer therapy, where a rising PSA is the only evidence of progression, is required. Crawford and Blumenstein<sup>10</sup> proposed a system to subcategorize stage D, including an attempt to differentiate patients who are hormone-therapy sensitive from those who are hormone-therapy insensitive (Table 1). Although this attempt is a step in the right direction, the classification is not widely used. The term *androgen-independent prostate cancer* (AIPC) implies a potential for patients to respond to a secondary hormonal measure, while the term *hormone-resistant prostate cancer* (HRPC) includes patients who do not respond to various hormone treatments or who have progressed following these treatments and would not be expected to respond to another. In the Crawford “D” classification, both would be included in the “D3” category, with D3S and D3I indicating hormonally sensitive and hormonally resistant cases, respectively.

Prostate cancers are biologically heterogeneous at the time of detection, and HRPC also represents a disease state with diverse biology and varying degrees of response to therapy.<sup>11</sup> HRPC in the clinical setting may manifest with differing symptoms and findings such as rising PSA, progression of bone scan findings, new or enlarging soft tissue masses, skeletal pain, weight loss, or urine obstruction. In order to properly assess these patients, the prior therapies and mode of tumor progression are taken into account.<sup>12</sup> Criteria for defining D3 disease continue to evolve. Scher et al<sup>13</sup> reviewed 19 published trials of patients whose disease progressed on hormone therapy. Eligibility criteria and the criteria used for defining hormone-refractory disease were reviewed. The definitions used for refractory disease ranged from none, to progression, to unsuccessful second medical or surgical castration. Furthermore, the potential contribution of the antiandrogen withdrawal syndrome on outcomes was only minimally recognized.

In an attempt to standardize eligibility criteria and end points in prostate cancer clinical trials, Dawson<sup>14</sup> surveyed 35 established investigators of HRPC to foster more uniformity regarding study eligibility and response criteria. The results of a 125-item questionnaire established a general consensus for clinical trial entry. Based on survey responses, criteria for entry into clinical trials include progression based on increasing PSA level (noted by 94% of investigators), an increase in measurable tumor (91%), and/or presence of new bone lesions on bone scan (83%).<sup>14</sup> We used the classification outlined in Table 1 to describe stage D disease in patients with prostate cancer.

## Treatments for Androgen-Independent Prostate Cancer

The choice between using chemotherapy or a secondary hormonal therapy when androgen withdrawal has failed is based on judgment; few comparative studies are avail-

**Table 1. — Proposed Classification of Stage D Prostate Cancer**

D1	Pelvic lymph nodes
D1.5	Rising PSA after failed local therapy
D2	Metastatic disease in bone and/or other organs
D2.5	Rising PSA after nadir level
D3	Hormone-refractory prostate cancer
D3S	Hormonally sensitive
D3I	Hormonally insensitive
From Crawford ED, Blumenstein BA. Proposed substages for metastatic prostate cancer. <i>Urology</i> . 1997;50:1027-1028. Reprinted with permission from Elsevier.	

**Table 2. — Proposed Treatment Considerations for Stage D Prostate Cancer**

Stage	Treatment Considerations
D1	<ul style="list-style-type: none"> <li>• Adjuvant hormonal therapy</li> <li>• Chemotherapy clinical trial</li> </ul>
D1.5	<ul style="list-style-type: none"> <li>• Observation for slowly rising PSA</li> <li>• Androgen ablation for patients with rapidly rising PSA</li> </ul>
D2	<ul style="list-style-type: none"> <li>• Androgen ablation</li> </ul>
D2.5	<ul style="list-style-type: none"> <li>• Secondary hormonal treatments for asymptomatic patients</li> <li>• Secondary hormonal manipulation or docetaxel-based chemotherapy regimen for symptomatic patients</li> </ul>
D3	<ul style="list-style-type: none"> <li>• Docetaxel-based chemotherapy regimen as first-line treatment</li> </ul>
D3S	<ul style="list-style-type: none"> <li>• Same recommendations as D2.5</li> </ul>
D3I	<ul style="list-style-type: none"> <li>• Same recommendation as D3</li> </ul>

able.<sup>3</sup> Disease progression from primary hormone therapy is often associated with an asymptomatic increase in PSA. Many physicians and patients decide to change treatment at the time of PSA progression regardless of whether symptoms accompany the rise in PSA, although it is not clear that such an intervention prolongs survival. The median survival of patients with metastatic AIPC is approximately 1 year.<sup>15</sup> Since secondary hormone therapies are palliative in nature and have not been associated with survival benefit, the choice of treatment should consider the associated toxic side effects.

Although no consensus guidelines are available to indicate when to use secondary hormonal therapies, a reasonable approach was recently outlined.<sup>16</sup> Initially, at the time of development of AIPC documented by PSA progression, secondary hormonal therapies can be prescribed in asymptomatic or minimally symptomatic patients (Table 2). Chemotherapy would follow when secondary hormonal treatments fail. Some patients with AIPC have rapidly progressive disease that warrants a preference for cytotoxic treatment before attempting another hormone manipulation.

### Secondary Hormone Therapies

**Antiandrogen Withdrawal:** The antiandrogen withdrawal syndrome has been recognized since 1993 when Kelly and Scher<sup>17</sup> observed PSA responses in men receiving combined androgen blockade when flutamide was discontinued at the time of progressive disease. Patients who are being treated with androgen deprivation in combination with an antiandrogen at the time of progression can be monitored for the antiandrogen withdrawal syndrome. After antiandrogens have been stopped, further therapeutic interventions to consider include second-line antiandrogens, adrenal androgen inhibition, and compounds with estrogenic properties.

**Antiandrogens:** Antiandrogens are classified as either steroidal or nonsteroidal. Bicalutamide is a nonsteroidal

antiandrogen with an observed dose-response effect on PSA in AIPC. Reports of patients who have been treated with higher doses of bicalutamide (150 to 200 mg) have noted that 20% to 40% have achieved more than 50% declines in PSA.<sup>18-20</sup> The majority of responses occurred in patients who had already received flutamide earlier in their treatment history. Megestrol acetate (MA) is a steroidal antiandrogen with progestational effects. Dawson et al<sup>21</sup> randomized men to receive low-dose MA (160 mg/day) or high-dose MA (640 mg/day) and reported PSA decreases of only 8% or 13% and no survival difference. Side effects included fluid retention and thrombophlebitis.

**Corticosteroids and Ketoconazole:** Testosterone is converted into a more potent compound dihydrotestosterone (DHT) in the cytoplasm of prostatic cells by the enzyme 5-alpha reductase. In addition to testosterone, DHT may derive from adrenal androgens.<sup>22</sup> Studies suggest as much as 40% of DHT is derived from adrenal precursors.<sup>23</sup> Thus, drugs that inhibit adrenal steroidogenesis or performance of bilateral adrenalectomy can induce a clinical response. Corticosteroids inhibit secretion of adrenocorticotrophic hormone (ACTH) through a negative feedback loop, thereby decreasing androgen production in the adrenal glands. Prednisone, dexamethasone, and hydrocortisone have all been studied.<sup>24-26</sup> Inhibitors of adrenal steroidogenesis include aminoglutethimide, ketoconazole, and corticosteroids. Aminoglutethimide plus hydrocortisone provided a partial response rate of 9% but with accompanying fatigue, nausea, skin rash, orthostatic hypotension, and ataxia.<sup>27</sup> Studies using ketoconazole (400 mg t.i.d.) in combination with replacement hydrocortisone have reported a broad range of response rates ranging from 15% to 63%.<sup>27-30</sup> Toxicities include nausea, diarrhea, fatigue, and skin changes that require stopping the drug. A phase II study that used a smaller dose of ketoconazole (200 mg t.i.d.) achieved a response rate of 55% but with fewer side effects.<sup>31</sup>

**Compounds With Estrogenic Properties:** The use of estrogenic compounds in AIPC continues to be studied. An additional mechanism of action beyond the suppression of the pituitary-gonadal axis may be involved. A potential mechanism may represent a direct cytotoxic effect through apoptosis.<sup>32</sup> PSA response rates of 26%<sup>33</sup> and 43%<sup>34</sup> have been reported with a daily dose of 1 mg of diethylstilbestrol (DES). PSA response rates of 32%<sup>33</sup> and 66%<sup>35</sup> using a higher dose of DES (3 mg) have also been reported.

Some patients with AIPC are interested in herbal preparations. PC SPES is an herbal preparation with estrogenic activities that has undergone clinical trial. The effects of PC SPES in patients with AIPC include PSA responses ranging from 52%<sup>36</sup> to 81%,<sup>37</sup> toxicities of thrombotic complications, and breast swelling. Although PC SPES is no longer available, a discussion of some of its estrogenic properties is relevant. Both preclinical and clinical studies of PC SPES have demonstrated estrogenic and antitumor effects.<sup>38,39</sup> PC SPES is a combination of

active substances such as skullcap, saw palmetto, and pseudoginseng.<sup>40</sup> DiPaola et al<sup>39</sup> studied PC SPES with high-performance liquid chromatography and were unable to identify DES, estrone, or estradiol. A recent phase II study comparing PC SPES (3 capsules per day) and DES (3 mg per day) was closed prematurely after PC SPES was withdrawn from the market.<sup>41</sup> Both DES and ethinyl estradiol were detected in some lots of PC SPES. This illustrates the importance of identifying the compounds responsible for clinical activity in a preparation, as well as ensuring reproducible purity for substances used as therapy in humans.

### ***Maintenance of Castrate Levels of Testosterone***

The initial therapeutic intervention for metastatic prostate cancer is to induce castrate levels of testosterone. The majority of men are treated either by testicular androgen suppression using LHRH analogs or by bilateral orchiectomy. The Leuprolide Study Group investigated the use of a depot formulation of leuprolide (7.5 mg every 4 weeks) in 53 patients.<sup>42</sup> Prior to initiation of LHRH analog, 53 patients had a mean serum testosterone level of 370.6 ng/dL (ranging from 111 to 893 ng/dL). After administration of LHRH analog, the mean serum testosterone levels peaked 4 days after administration at 552.7 ng/dL and then decreased to a castrate range that was defined in the study as less than 50 ng/dL. The mean serum testosterone levels decreased to 33.8 ng/dL by week 3 and ultimately to 17.0 ng/dL by week 4. The levels remained at less than 15 ng/dL through week 24. The study emphasized that castrate levels of testosterone occurred in all patients at some time during the study, which monitored patients for 24 weeks of continuous treatment with the LHRH analog. Of the 53 patients, 51 (96%) were observed to have castrate levels of testosterone within 30 days after the initial depot injection.<sup>42</sup> Since hormonal manipulation is not curative, most patients will at some time develop progressive disease. This is usually first manifested by a rise in serum PSA, at which point the disease is considered to be AIPC. It is important to distinguish between AIPC and HRPC. In patients who have AIPC, additional hormone therapies can still slow the progression of disease. However, for those with HRPC, further hormone manipulations provide no benefit.

Once HRPC has developed, the necessity of maintaining castrate levels of serum testosterone may be questioned. Most data support the maintenance of castrate testosterone levels in the androgen-independent patient. Fowler and Whitmore<sup>43</sup> reviewed 52 patients with metastatic HRPC. They received testosterone on protocols for different purposes, including stimulation of tumor prior to subsequent chemotherapy and prior to adrenalectomy. Of 52 patients, 45 (87%) had an unfavorable subjective response such as exacerbation of pain symptoms, and 24 (53%) of the 45 patients had unfavorable objective responses such as increased measurable disease or increased prostate-specific acid phosphatase (PAP).<sup>43</sup>

Retrospective analyses of trials by the Eastern Cooperative Oncology Group (ECOG) and the Southwest Oncology Group (SWOG) have been performed. Taylor et al<sup>44</sup> examined data from three databases for differences in survival between men who continued testicular suppression (either medical or surgical) who began investigational therapy and those with intact testes who had ceased medical testicular androgen suppression as they began their new treatment. Data from patients enrolled on ECOG trials with hormone-refractory disease were examined. Of the 341 patients, 287 patients had continued hormonal ablation and 54 patients did not. Patients who had continued maintenance of castrate levels of testosterone had a longer median survival of 2 months. Hussain et al<sup>4</sup> examined data on 205 patients with HRPC enrolled on SWOG protocols. A total of 172 continued on hormonal ablation and 33 patients did not. There was no difference in median survival between patients who had maintained castrate levels of testosterone and those who did not.

The available data are inconclusive to determine whether castrate levels of serum testosterone are necessary in HRPC patients. A prospective randomized trial would be required, but such a trial has not been performed. However, a recent consensus panel recommended that continuation of an LHRH analog be required for patients enrolling in clinical trials in HRPC.<sup>14</sup> Stopping the LHRH analog would complicate the translation of the results of clinical trials to a treated patient since treatment conditions may differ.

## **Chemotherapy in Hormone-Refractory Prostate Cancer**

### ***Evaluation of Response***

The dominant site of metastases in men with prostate cancer is bone. There is often no other measurable disease. As a result, response parameters for prostate cancer differ from those for other cancers where sites of metastases are measured serially over time and followed to assess response, stable disease, or progression. Therefore, success in the treatment of HRPC has been assessed by the ability of the intervention to decrease pain, improve quality of life, and potentially prolong survival. Published clinical trials on HRPC do not routinely use the standard definition of response such as complete or partial response, stable disease, and progressive disease.<sup>14</sup> Since PSA is an easily measured value and often correlates to the status of disease, it is also commonly measured to assess response to treatment. Kelly et al<sup>45</sup> reported data that supports using a decline of more than 50% as an end point indicating benefit for patients who have HRPC. In a series of 110 patients with HRPC treated with several different regimens, patients who had a decline in PSA of more than 50% had improved survival compared with patients who had a decline in PSA of less than 50%.

In 1999, Bubley et al<sup>46</sup> published the recommendations from the Prostate-Specific Antigen Working Group for assessing response. The Consensus Panel adopted a set of response criteria based on PSA level changes that are now widely used. These criteria propose reporting traditional objective responses in patients with measurable soft tissue disease, as well as defining responders as patients who have a decline in PSA of at least 50% if confirmed by a second PSA value measured 4 weeks or more later in the absence of clinical or radiographic disease progression. The criteria to define progressive disease include progression of measurable lesions, the appearance of at least one new lesion on bone scan, or an increase in PSA of at least 25% and an increase of the absolute value of PSA by at least 5 ng/mL.<sup>46</sup> Use of these criteria will assist in assessing new therapies in phase II trials. The outcomes of survival and quality of life remain end points of phase III trials.

### **Available Drugs for Hormone-Refractory Prostate Cancer**

Justification for the use of chemotherapy regimens in patients with HRPC was based on the observation that treatment with cytotoxic agents could improve quality of life and palliate symptoms. Many cytotoxic compounds have been tested on patients who have failed hormonal therapy including anthracyclines/anthracenediones (doxorubicin and mitoxantrone), alkylating agents (cyclophosphamide), platinum (cisplatin and carboplatin), vinca alkaloids (vinorelbine and vinblastine), topoisomerase II inhibitors (etoposide), and the taxanes (paclitaxel and docetaxel).

Until recently, the benefits of chemotherapy focused on the end points of symptom relief and quality of life. Phase I and II studies showed that the addition of mitoxantrone to corticosteroids provided better palliation of symptoms compared with corticosteroids alone.<sup>8,15</sup> Tannock et al<sup>8</sup> randomized patients with HRPC to receive either mitoxantrone at 12 mg/m<sup>2</sup> and prednisone at 10 mg or prednisone alone at 10 mg. Men treated with the combination had 29% pain relief compared to 12% pain relief if they received prednisone alone ( $P=.01$ ). The duration of pain relief was longer in patients treated with the mitoxantrone combination (48 weeks) than in those treated with the corticosteroid alone (18 weeks). This difference was significant ( $P<.0001$ ), but survival in both arms was equivalent.

In a Cancer and Leukemia Group B study, Kantoff et al<sup>15</sup> compared mitoxantrone at 14 mg/m<sup>2</sup> every 3 weeks plus hydrocortisone at 40 mg daily vs hydrocortisone alone at 40 mg daily. PSA declines of more than 50% occurred in 38% of patients treated with mitoxantrone plus hydrocortisone vs 22% in those treated with hydrocortisone alone ( $P=.008$ ). Palliation of pain symptoms was observed in more patients who received the mitoxantrone combination, but no differences in survival were observed.

Single-agent oral cyclophosphamide has shown anti-tumor activity in HRPC, with reported response rates of approximately 30%.<sup>47,48</sup> One study of 23 patients reported a response rate of 70% by PSA criteria using the combination of cyclophosphamide, tegafur/uracil (UFT), and dexamethasone.<sup>49</sup> Other combinations such as etoposide, methotrexate, and 5-fluorouracil have yielded response rates ranging from 7% to 35%, but these used a variety of response criteria such as evaluation of acid phosphatase rather than PSA.<sup>50,51</sup>

Estramustine is an estradiol derivative linked to a nitrogen mustard.<sup>52</sup> It can be given intravenously or orally. The intravenous preparation is associated with superficial phlebitis, hepatotoxicity, and perineal discomfort. The oral preparation is associated with nausea and vomiting, fluid retention, deep venous thrombosis, and myelosuppression. Estramustine binds to microtubule-associated proteins in the nuclear matrix and inhibits microtubule assembly and disassembly.<sup>53,54</sup> Single-agent estramustine induced minor PSA declines in 14% to 25% of patients treated, and some of the reported responses included palliation of symptoms without significant declines in PSA.<sup>55</sup> The use of estramustine in combination with other agents that target microtubules such as etoposide, vinblastine, paclitaxel, and docetaxel improved response rates.<sup>56-62</sup>

Single-agent vinblastine had a response rate of 17% with no improvement in survival.<sup>63</sup> In a phase III trial comparing vinblastine to vinblastine with estramustine, a decline in PSA of more than 50% was observed in 5% of patients in the vinblastine only arm compared to 35% of patients in the vinblastine plus estramustine arm. There was a statistically significant lengthening in the TTP in the combination arm. Survival difference was not significant between the two treatment arms.<sup>64</sup> A later report of this study showed that the TTP was longer in the combination arm (3.7 months vs 2.2 months, respectively) and the overall survival was also longer in the combination arm (12.5 months vs 9.4 months, respectively).<sup>65</sup>

### **Taxanes**

Taxane-based regimens appear to be a promising step in the evolution of treatment for prostate cancer. The integration of taxanes into treatment regimens targets microtubules, and taxanes preferentially bind to  $\beta$  tubulin.<sup>66,67</sup> In vitro data show that docetaxel appears to have a higher affinity for tubulin than paclitaxel has.<sup>68</sup> Dosing regimens and the choice of which agents to combine with taxanes are under investigation, and a consensus has not yet been established. Newer taxane-based regimens minimize toxicity and document PSA responses of approximately 50% of patients treated. Table 3 summarizes the results of selected studies that incorporated taxane-based regimens in prostate cancer.<sup>61,69-75</sup>

Docetaxel has been successfully paired with both estramustine and calcitriol (1,25-dihydroxycholecalciferol). For the first time, an increase in median survival has

been reported in phase II studies enrolling AIPC patients for treatment with chemotherapy. Anthracycline-based treatment of AIPC is associated with a median survival of 12 to 13 months. Two randomized studies — TAX327 and SWOG S9916 — report the first phase III randomized data available for survival comparisons.

TAX327 randomized patients to one of three arms: (1) docetaxel 75 mg/m<sup>2</sup> every 3 weeks plus prednisone 5 mg twice daily, (2) docetaxel 30 mg/m<sup>2</sup> every week for 5 out of 6 weeks plus prednisone 5 mg twice daily, or (3) mitoxantrone 12 mg/m<sup>2</sup> every 3 weeks plus prednisone 5 mg twice daily. In TAX327 the two arms using doc-

etaxel had median survivals of 18.9 months (arm 1) and 17.4 months (arm 2). Arm 3 reported a median survival of 16.5 months. When the docetaxel arms were compared to the mitoxantrone group (arm 3), only the group of men treated with docetaxel 75 mg/m<sup>2</sup> had a survival rate that was significantly higher ( $P=.009$ ), while the group treated with the lower weekly dose of docetaxel 30 mg/m<sup>2</sup> did not have a significantly different survival compared to the mitoxantrone arm.<sup>76</sup>

The S9916 trial randomized patients to docetaxel 60 mg/m<sup>2</sup> every 3 weeks plus estramustine 280 mg orally 3 times a day for 5 days or to mitoxantrone 12 mg/m<sup>2</sup> every

**Table 3. — Selected Published Taxane-based Regimens Used in Prostate Cancer**

Investigators	Taxane	Additional Agents	Regimen	Response Rate*	Toxicity**
Berry et al <sup>69</sup>	Docetaxel		- 36 mg/m <sup>2</sup> per wk × 6 - Three 8-wk cycles	41% (24/59)	Asthenia 10% Diarrhea 10% Anemia 7% Neuropathy 5%
Sitka Copur et al <sup>70</sup>	Docetaxel	Estramustine	- 35 mg/m <sup>2</sup> day 2 weeks 1 and 2 - 420 mg p.o. × 4 doses, then 280 mg p.o. × 5 doses days 1-3 wk 1-2 - 3-wk cycle	77% (23/30)	Nausea 33% Fatigue 26% Diarrhea 26% Edema 23%
Urakami et al <sup>71</sup>	Paclitaxel	Estramustine Carboplatin	- 100 mg/m <sup>2</sup> per wk - 10 mg/kg daily divided t.i.d. - AUC 6 on day 1 - 4-wk cycle	100% (32/32)	Anemia 60% Leukopenia 38% Thrombocytopenia 28% Neuropathy 13%
Hudes et al <sup>61</sup>	Paclitaxel	Estramustine	- 120 mg/m <sup>2</sup> days 1-4 - 600 mg/m <sup>2</sup> per day - 3-wk cycle	53% (17/32)	Nausea 33% Fluid retention 33% Fatigue 24%
Smith et al <sup>72</sup>	Paclitaxel	Estramustine Etoposide	- 135 mg/m <sup>2</sup> day 2 - 280 mg p.o. t.i.d. - 100 mg p.o. q.d. - 3-wk cycle	65% (26/40)	Neutropenia 25% Anemia 23% Deep venous thrombosis 8% Thrombocytopenia 4%
Savarese et al <sup>73</sup>	Docetaxel	Estramustine	- 70 mg/m <sup>2</sup> day 2 - 10 mg/kg per day divided t.i.d.	68% (30/44)	Neutropenia 56% Lymphopenia 56% Malaise/fatigue 24% Infection 24%
Kelly et al <sup>74</sup>	Paclitaxel	Estramustine Carboplatin	- 100 mg/m <sup>2</sup> per wk - 10 mg/kg per day divided t.i.d. for 5 days - AUC 6 wk 1 - 4-wk cycle	67% (36/54)	Hypophosphatemia 42% Hyperglycemia 38% Thrombosis 25% Leukopenia 22%
Beer et al <sup>75</sup>	Docetaxel	Calcitriol	- 36 mg/m <sup>2</sup> day 2 per wk for 6 out of 8 wks - 0.5 µg/kg day 1 per wk	81% (30/37)	Leukopenia 41% Neutropenia 24% Hyperglycemia 24% Peptic ulcer 11%
Tannock et al <sup>76</sup>	Docetaxel	Prednisone	- 75 mg/m <sup>2</sup> every 3 wks (or 30 mg/m <sup>2</sup> 5 of 6 wks) - 5 mg twice daily	45% of 332 (or 48% of 330)	Fatigue 53% (or 49%) Nausea 42% (or 41%) Diarrhea 32% (or 34%) Neuropathy 30% (or 24%)
Petrylak et al <sup>77</sup>	Docetaxel	Estramustine Dexamethasone	- 60 mg/m <sup>2</sup> per body-surface area day 2 - 280 mg 3 times daily days 1-5 - 60 mg in 3 divided doses - 3-wk cycle	50% (155/309)	Nausea 66% Hematologic 65% Cardiovascular events 48% Infection 45%

\* Response rate was defined as a ≥50% decrease in PSA from baseline.  
\*\* Toxicities were selected as the four most common grade 3-4 toxicities reported or the most common reported as available.

3 weeks plus prednisone 5 mg twice daily. The primary end points were TTP and survival. The median survival of men in the docetaxel/estramustine arm was 17.5 months compared with 15.6 months for men in the mitoxantrone/prednisone ( $P=.02$ ). TTP was 6.3 months in the docetaxel/estramustine arm compared with 3.2 months ( $P<.001$ ) in the mitoxantrone/prednisone arm.<sup>77</sup>

The results of both of these trials justify the preference for docetaxel-based regimens over other cytotoxic agents as first-line treatment of men with metastatic AIPC. It is important to note that only the higher doses of docetaxel given every 3 weeks were associated with a statistically significant improvement in survival over mitoxantrone.

Studies that combine compounds including angiogenesis inhibitors, endothelin axis blockers, small molecules, and antisense targets with docetaxel are underway at several institutions. Figg et al<sup>78</sup> conducted a randomized phase

II trial comparing weekly docetaxel vs docetaxel and thalidomide 200 mg/day revealed a PSA response of 53% in the combination arm vs 35% for single-agent docetaxel. Deep venous thrombosis was a significant toxicity in the thalidomide arm, but this toxicity was eliminated after low-molecular-weight heparin was added to the regimen. The authors concluded that combining a cytotoxic chemotherapeutic with an angiogenesis inhibitor is a promising area of investigation for prostate cancer management.

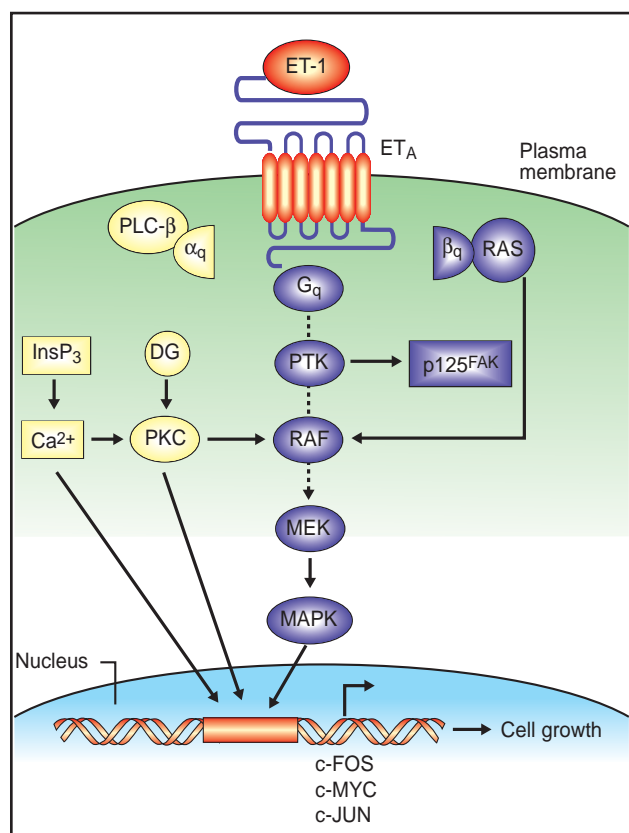
These and other combinations from single institutions that report high response rates need to be studied in larger phase II or III trials before they can be recommended as standard chemotherapy options for HRPC. However, the high response rates are encouraging.

### Newer Therapies

In vitro studies support trials of calcitriol, the activated form of vitamin D, paired with docetaxel in the treatment of prostate cancer. Calcitriol inhibits proliferation and increases taxane-induced cytotoxicity in human prostate cancer cell lines.<sup>79,80</sup> Daily dosing of calcitriol can cause hypercalcemia and hypercalciuria. Appropriate monitoring allows higher once-weekly dosing of calcitriol with minimization of adverse side effects.

Beer et al<sup>75</sup> published the results of a phase II trial on the use of calcitriol 0.5 mg/kg given orally on day 1 and docetaxel 36 mg/m<sup>2</sup> on day 2, repeated weekly for 6 weeks followed by a 2-week break. Of 37 patients, 30 (81%) had a PSA response. The 1-year survival rate was 89%, median survival was 19.5 months, and median TTP was 11.4 months. Using Response Evaluation Criteria in Solid Tumors (RECIST) guidelines,<sup>81</sup> 15 patients (41%) had measurable disease, 8 of whom had a partial response. The median progression-free survival was 11.4 months and the median survival by Kaplan-Meier estimate was 19.5 months. Deep venous thrombosis was reported as a toxicity. This small study suggests possible benefit from concurrent calcitriol in a taxane-based regimen.

Newer therapeutic strategies in cancer management continue to emphasize molecular mechanisms. The recent identification of the endothelin family of proteins has been related to the biology of prostate cancer.<sup>82</sup> The Figure summarizes the endothelin-induced signal-transduction pathway.<sup>83</sup> Endothelins are paracrine/autocrine factors with many functions such as modulation of vasomotor tone, nociception, hormone production, and cell proliferation.<sup>84</sup> The effects usually involve the binding of endothelin-A (ET<sub>A</sub>) receptor with endothelin-1 (ET-1). In prostate cancer, ET-1 concentration and expression the ET<sub>A</sub> receptor are increased.<sup>85</sup> Atrasentan is a potent and selective ET<sub>A</sub> receptor antagonist that blocks or reverses the biologic effects of ET-1.<sup>86</sup> Carducci et al<sup>87</sup> performed a randomized, placebo-controlled phase II trial in which median TTP was longer in patients treated with atrasentan compared to patients treated with placebo. Toxicity was generally mild to moderate and included headache, peripheral edema, and rhinitis.



Endothelin-induced signal-transduction pathways. Binding of ET-1 (or ET2) to the ET<sub>A</sub> receptor in the plasma membrane triggers signal-transduction pathways through G<sub>q</sub>, a pertussis toxin-insensitive G protein that is coupled to the ET<sub>A</sub> intracellular domain. Activation of phospholipase C (PLC), protein tyrosine kinases (PTKs, such as FAK), and RAS ultimately results in activation of the RAF/MEK/MAPK pathway. Mobilization of intracellular calcium (Ca<sup>2+</sup>), activation of protein kinase C (PKC) and activated MAPK induce nuclear transcription of protooncogenes (such as c-FOS, c-MYC, and c-JUN), leading to cell growth and mitogenesis. Further analysis of the signaling pathway showed that ET-1 stimulated phosphatidylinositol 3-kinase (PIK3)-mediated AKT activation (not shown). DG = diacylglycerol, InsP<sub>3</sub> = inositol 1,4,5-triphosphate, MAPK = mitogen-activated protein kinase, MEK = MAPK kinase, p125<sup>FAK</sup> = focal adhesion kinase. From Nelson J, Bagnato A, Battistone B, et al. The endothelin axis: emerging role in cancer. *Nature*. 2003;3:110-116. Reprinted with permission by Nature Publishing Group. <http://www.nature.com>.

## Supportive Care

Patients with metastatic prostate cancer are primarily treated with androgen suppression. Long-term androgen suppression results in osteoporosis with fractures.<sup>88</sup> Once patients become hormone-resistant, androgen suppression is usually continued. Both pamidronate and zoledronic acid have been shown to prevent bone loss in these patients.<sup>89,90</sup>

Zoledronic acid was recently approved for the treatment of bone metastasis in patients who have AIPC. The use of bisphosphonates results in less pain and fewer skeletal events in patients with bone metastases from breast cancer and multiple myeloma.<sup>91-94</sup> Bone metastases from these tumors are primarily osteolytic in contrast to the primarily osteoblastic bone metastases in prostate cancer. However, bone resorption is increased in men with skeletal metastases from prostate cancer.

Bone metastases can cause appreciable morbidity in patients with AIPC. Saad et al<sup>95</sup> investigated the effect of zoledronic acid on blocking bone destruction and skeletal complications in patients with prostate cancer and bone metastases. In a double-blind study, patients with HRPC and bone metastases were treated with either 4 mg of zoledronic acid (214 patients) or 8 mg of zoledronic acid (211 patients) or placebo (208 patients) every 3 weeks for 15 months. Skeletal-related events occurred more frequently in patients who received placebo than in those who received either dosage of zoledronic acid. Pain and analgesic scores were higher for patients taking placebo than those taking zoledronic acid. No differences in disease progression, performance status, or quality-of-life scores were noted. Zoledronic acid at 4 mg given as a 15-minute infusion was well tolerated, but the 8-mg dose was associated with renal function deterioration. The authors concluded that zoledronic acid at 4 mg reduced skeletal events in prostate cancer with metastasis.<sup>95</sup> We recommend zoledronic acid in patients with prostate cancer who have positive bone scans and whose disease has progressed after the use of primary androgen ablation.

## Conclusions

Since therapeutic strategies are different for patients with hormone-dependent and hormone-refractory disease, staging criteria for advanced and recurrent prostate cancer should reflect the biology of disease. The stratification proposed by Crawford and Blumenstein<sup>10</sup> can assist in identifying cohorts of patients with similar disease biology. Although this classification is not widely used, it is an important attempt to correlate biology of disease to stage.

For patients who progress after initial androgen ablation, the following treatments should be considered: for D2.5 disease, secondary hormonal treatments in asymptomatic patients or immediate initiation of docetaxel-based

chemotherapy; for D3 disease, a docetaxel-based chemotherapy regimen as first-line treatment. Clinicians who manage patients and investigators who design clinical trials should use the same criteria to classify HRPC. Dawson<sup>14</sup> established criteria to classify patients with stage D3 prostate cancer, and these criteria are in current use for patients with HRPC who are entering clinical trials. Recent clinical trials addressing HRPC are designed to require maintenance of castrate levels of serum testosterone since data are available to support exacerbation of HRPC with androgen re-exposure.

Assessing PSA levels is a reliable approach to follow men treated with HRPC when other objective measures, eg, disease progression, resolution of bone scan findings, and direct tumor measurement, are not available. Quality of life and changes in analgesic requirements may also be used in the absence of other objective response parameters. Utilizing bisphosphonates can decrease skeletal related events in men with HRPC and bone metastases.

The use of chemotherapy in HRPC continues to increase. Improved survival has been noted with the use of docetaxel chemotherapy. We recommend using docetaxel either alone or in combination with another investigational agent in patients who require chemotherapy after hormonal treatments fail. A variety of other agents (eg, estramustine, calcitriol, and atrasentan) are currently being studied to optimize the efficacy of docetaxel. Clinical trial data are available to support further investigation into potential targets associated with the endothelin axis.

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