Treatment of Castration-Resistant Prostate Cancer

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Clinical Considerations

Cytotoxic Chemotherapy

Palliative Management

During the past several decades, endocrine manipulations developed to inhibit hormone-dependent prostate cancer growth and differentiation have constituted the basic strategy for the systemic control of prostate cancer. Suppression of gonadal testosterone is the central principle of androgen-deprivation therapy (ADT), and this represents one of the most effective systemic palliative treatments known for solid tumors. Although it is extremely effective initially, virtually all patients eventually develop clinical evidence of treatment resistance. The outcomes with endocrine therapy have not changed significantly during the past few decades. Progression-free and overall survival figures of patients with metastatic disease with various methods of ADT have ranged from 12 to 20 months and 24 to 36 months, respectively (Leuprolide Study Group, 1984; Crawford et al., 1989; Denis et al., 1993; Eisenberger et al., 1998). Whereas somewhat longer survival times are reported in the more recent studies, this is most likely due to a “lead time” effect observed in contemporary populations of patients. The development of hormone resistance (i.e., cancer progression despite castrate levels of serum testosterone) is virtually a universal issue that affects all patients treated with ADT. Undoubtedly, further improvement in the outcome of patients with metastatic castration-resistant prostate cancer (CRPC) rests on the use of nonhormonal approaches that can effectively control the growth of the disease.

During recent years, clinical investigations testing nonhormonal approaches have shown that systemic chemotherapy improves survival and quality of life in patients with castration-resistant (i.e., hormone-refractory) disease. Advances in the understanding of the biology of prostate cancer and characterization of key molecular pathways have added an important new dimension for treatment and the opportunity to design disease-specific targeted treatment approaches. Evolving data suggest that targeted approaches may play an important role in treatment of prostate cancer that may improve the outcome of our patients.

Progress in cell and molecular biology during the past decade has also enhanced our understanding of the mechanisms involved in the progression of prostate cancer, and this may provide the opportunity for rational planning of the appropriate timing of systemic therapeutic intervention with the objective of preventing or delaying progression of disease to lethal proportions. Cancer cells demonstrating the castration-refractory phenotype can be identified during early stages of development of prostate cancer. Somatic alterations of the androgen receptor are frequently observed in patients with evidence of disease progression after androgen deprivation. It has also been demonstrated that during cancer progression, in the absence of androgens, a molecularly altered androgen receptor can still undergo ligand-dependent activation by other hormones such as estrogens and progesterational agents and non–ligand-dependent activation by growth factors and cytokines (Feldman and Feldman, 2001; Gelmann, 2002; Nelson WG et al., 2003). The observation that the androgen receptor can still be activated even after long-term gonadal ablation suggests that it continues to play an important role in prostate cancer growth and may indeed be a reasonable target for treatment in patients with androgen-independent disease.

In the presence of androgens, prostatic cancer growth is based on a cell proliferation rate that exceeds that of cell death (Isaacs et al., 1992). Androgen ablation primarily affects the cell death rate by inducing a swift apoptotic cascade. As the tumor progresses the threshold of apoptosis progressively rises to a point at which cell proliferation exceeds cell death (Berges et al., 1995). This results in the accumulation of endocrine-independent cells that eventually dominate the biologic behavior of prostate cancer in late stages.

Preclinical data suggest that the relatively low growth fraction expressed by adenocarcinoma of the prostate (compared with other common tumor types) may be a determining factor to explain the relative insensitivity to conventional cytotoxic chemotherapy. The proliferation rate of prostate cancer cells, which is directly proportional to the growth fraction, appears to increase with tumor progression especially after androgen ablation. Cell proliferation antigens, such as Ki-67 expressed by cycling cells (Cattoretti et al., 1992), may have important prognostic and therapeutic implications because most conventional cytotoxic chemotherapeutic agents available are usually more effective...
in tumors with high proliferative rates such as lymphomas, small cell lung carcinomas, and germ cell tumors of the testis.

Changes in differentiation pathways in prostate cancer have been increasingly emphasized, particularly in the form of neuroendocrine/anaplastic cells (diSant’Agnese, 1995). Evolving experience with cytotoxic chemotherapy suggests that this aggressive clinical entity may be responsive to treatment regimens frequently employed for comparable tumors at other sites with similar phenotypic characteristics, such as small cell carcinoma of the lung. There is strong evidence to support the relationship between prostate cancer growth and various peptide growth factors (Djakiew et al., 1991; Steiner, 1993; Hofer et al., 1995; Sherwood et al., 1998; Kaplan et al., 1999; Nelson WG et al., 2003). Peptide growth factors may also exert their effects through the activation of the androgen receptor. Androgens are capable of inducing stromal production of various growth factors that could replace the androgen requirements for cell growth and differentiation (Lee, 1996). In addition, cytokines released primarily by stromal cells, such as interleukin-6, may also be important in the pathogenesis of prostate cancer. Indeed, small molecule inhibitors and other modalities of treatment (e.g., monoclonal antibodies) are being actively designed to target intracellular pathways associated with the expression of various growth factors and their receptors. Such strategies have involved inhibition of receptor tyrosine kinase activity and other intracellular molecular pathways of signal transduction as well as other critical pathways of cell growth and survival.

**CLINICAL CONSIDERATIONS**

**Disease Assessment and Treatment Selection**

Conventional staging criteria, such as the TNM staging system, do not describe the extent of disease beyond a simple anatomic classification. Treatment practices result in the creation of different disease states as described by Scher and colleagues (2008). This system allows classification of patients in a more clinically applicable fashion and is increasingly being used throughout the literature. Figure 110–1 illustrates the natural history of prostate cancer relative to treatment practices and identifies the various paradigms according to the response status to different therapies. Throughout this chapter, prognostic and therapeutic considerations are largely based on the concepts proposed by this classification. A complete disease evaluation is required to estimate the outcome and to make therapeutic decisions. Critical baseline components include extent of disease, mode and site of progression (rising prostate-specific antigen [PSA] level alone, new bone metastasis, visceral and nodal metastasis), presence or absence of symptoms, and response to prior endocrine treatment. Regular monitoring with serial bone scintiscans and serum PSA levels during hormone treatment provides important information in patients demonstrating evidence of disease progression while they are receiving hormone therapy. Table 110–1 describes the postprogression survival of patients with distant metastatic disease who demonstrated progression of disease while on hormone therapy in a large prospective trial (Eisenberger et al., 1995). The data shown in this table illustrate the broad range in postprogression survival according to the mode of progression (PSA only vs. bone scintiscan progression) and according to the extent of bone metastases. This observation highlights the importance of establishing precisely the predominant mode of progression in these patients and underlines the need for serial determinations of all laboratory, clinical, and radiologic data. It also provides critical information for the interpretation of subsequent clinical trials with regard to time-dependent outcomes, such as time to disease progression and survival. Usually the first manifestation of disease progression after hormone therapy is a rising serum PSA level. In patients with metastatic disease, a rise in serum PSA level precedes evidence of advancing disease in the bone scintiscan, and during this time patients may remain relatively asymptomatic (Eisenberger et al., 1995). Routine evaluation of serum testosterone levels may provide important information for the choice of treatment. This is especially important when there are reasons to suspect treatment noncompliance.

![Figure 110–1. Prostate cancer clinical states.](https://example.com/prostate_cancer_diagram.png)

**Table 110–1.** Metastatic Castration-Resistant Prostate Cancer: Survival According to Mode of Progression

<table>
<thead>
<tr>
<th>MODE OF PROGRESSION</th>
<th>MINIMAL DISEASE, MEDIAN SURVIVAL</th>
<th>EXTENSIVE DISEASE, MEDIAN SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA only</td>
<td>40 months</td>
<td>18 months</td>
</tr>
<tr>
<td>PSA + bone scintiscan</td>
<td>23 months</td>
<td>11 months</td>
</tr>
</tbody>
</table>

or if the choice of prior treatment involved regimens known not to result in a sustained suppression of serum testosterone to castrate levels (e.g., monotherapy with nonsteroidal antiandrogens, low-dose estrogens, or 5α-reductase inhibitors).

For several years it has been postulated that discontinuation of androgen suppression in nonorchietomized patients may adversely influence the outcome of disease in terms of progression and survival (Taylor et al, 1993). Similarly, it has been shown that administration of exogenous testosterone and its derivatives may indeed produce a significant clinical flare that results in severe pain and neurologic, urologic, and coagulation complications in a small proportion of patients (Fowler and Whitmore, 1981; Manni et al, 1988).

In a retrospective analysis of 205 patients with castration-resistant disease treated with chemotherapy, various prognostic variables including orchietomy were evaluated by Hussain and associates (1994). A multivariate analysis failed to indicate a significant correlation between prior orchietomy and improved time to disease progression and survival. In these patients all medical forms of androgen deprivation were discontinued at least 4 weeks before initiation of chemotherapy and, contrary to that suggested by Taylor and colleagues (1993), this did not significantly affect outcomes. Until this issue is resolved the general consensus is to maintain all patients on luteinizing hormone–releasing hormone (LH-RH) agonists indefinitely, even during the course of chemotherapy.

Another important management aspect relates to antiandrogen withdrawal effects (Scher and Kelly, 1993; Small and Srinivas, 1995; Small et al, 2004). Discontinuation of antiandrogens (both steroidal and nonsteroidal) can result in short-term clinical responses expressed by decreases in PSA levels, symptomatic benefits, and, less frequently, objective improvements in soft tissue and bone metastasis in a small proportion of patients. Because of this, it has been recommended that in patients treated with antiandrogens in combination with other forms of androgen deprivation (e.g., LH-RH agonists) the first step should involve the discontinuation of these agents and careful observation including serial monitoring of PSA levels for a period of 4 to 8 weeks before embarking on the next therapeutic maneuver.

The next step is to determine which modality of treatment should be employed first, either administration of second-line hormonal manipulation or cytotoxic chemotherapy. There is an increasing body of data on second-line endocrine therapies suggesting that there may be a role for this approach before institution of chemotherapy (Small and Vogelzang, 1997; Small et al, 2004; Ryan 2006; Ang et al, 2009). Although initial response rates range between 20% and 60%, the median duration of such responses is short ranging, between 2 and 4 months. Agents that have been reported to produce some benefit in this setting include diethylstilbestrol (Smith et al, 1986), aminogluthethimide (Sartor and Myers, 1995), ketoconazole (Small et al, 2004), as well as corticosteroids (Storlie et al, 1995). In view of the potential higher toxicity profile associated with cytotoxic chemotherapy, a sequential hormonal approach may be a reasonable alternative for those patients with relatively limited metastatic disease who remain asymptomatic at the time of disease progression (e.g., rising serum PSA value without other clinical manifestations).

Another important consideration is the initial clinical assessment of the potential biologic behavior of these tumors.

Evolving data evaluating the role of PSA dynamics suggest that the PSA doubling time (PSADT) predicts for the rapidity of bone scintiscan progression and survival (D’Amico et al, 2005; Armstrong et al, 2007; Robinson et al, 2008). Patients with PSADTs shorter than 3 months have a particularly rapid clinical course and should be considered for more aggressive management approaches. In addition, poorly differentiated and anaplastic/neuroendocrine tumors usually have a low likelihood of significant and durable responses to androgen deprivation. The anaplastic/neuroendocrine phenotype is rare and requires special therapeutic considerations. It has been suggested that systematic biopsies of disease sites in patients with clinically aggressive disease and relatively low serum PSA levels may demonstrate evidence of a neuroendocrine component by immunostaining, which may be of prognostic and therapeutic significance (see later). The usefulness of systematic biopsies in all patients with extensive metastasis and relatively low PSA levels, however, needs to be better defined before routine clinical application.

Nonmetastatic Castration-Resistant Disease

The extraordinary stage migration that has affected all stages of prostate cancer has profoundly modified the spectrum of clinical presentation of patients with castration-resistant disease. An increasing number of patients now begin androgen deprivation at very early stages of their disease course, often at the first sign of a rising PSA, before clinical and radiologic evidence of metastasis is present. This group of patients, termed the M0 (nonmetastatic) castrate-resistant subset, is now seen in increasing proportions in the clinic. Given the changes in treatment practices with early initiation of androgen deprivation, it is conceivable that these numbers will continue to increase. At this time data on the natural history of these patients are evolving.

A number of clinical trials using second-line hormonal manipulations and noncytotoxic interventions (bone-targeted treatments) focusing on time to development of bone metastasis are providing some useful information. A report of 201 patients from a prospective clinical trial comparing the effects of the bisphosphonate zoledronate and placebo in biochemically progressing (M0), castrate-resistant disease suggests that the time to bone scintiscan positivity may be very long. At 2 years, only 33% of these patients had evidence of bone metastasis, with a median time to bone metastasis in this group of 30 months. The baseline PSA level (>10 ng/mL) and the PSA velocity independently predicted time to bone metastasis and survival (Smith et al, 2005). In a retrospective review of a similar group of patients prescribed ADT before the development of metastatic disease the median time to clinical metastasis was 9 months. The pretreatment PSA level and the PSA nadir on ADT predicted this outcome (Dotan et al, 2005). The wide difference observed with these two reports (30 months vs. 9 months for time to bone scan metastasis) underscores the heterogeneity of this group of patients and the need for careful prospective evaluation. Their outcome is dependent on various factors, among which are pre-ADT characteristics (pretreatment PSA level, PSADT, initial stage, Gleason score), as well as response to hormonal treatment. The rate of progression may be estimated by PSA constructs such as PSADT and PSA velocity.

At present there is no consensus on the most appropriate management for these patients, although the sequential endocrine approach is the most commonly employed therapeutic modality.
A trial investigating the relative efficacy of a second-line endocrine manipulation versus a docetaxel-based chemotherapy regimen in nonmetastatic disease was closed prematurely because of poor accrual. More data are needed to characterize the natural history and to define the best treatment approach of the M0 castrate subset, which represents an important evolving new paradigm.

Metastatic Castration-Resistant Disease

Patients with metastatic CRPC represent a heterogeneous group with respect to their clinical status at the time of disease progression (Fig. 110–2). Metastatic adenocarcinoma of the prostate has an overwhelming predilection to involve the bone. Although the explanation for this unique metastatic pattern has not been completely elucidated it probably reflects the combination of various biologic factors starting at the time of metastatic spread. Circulating prostatic adenocarcinoma cells are arrested in the cortical and medullary bone spaces, where they subsequently adhere to bone surfaces through specific receptors for moieties such as integrins, collagens, laminin, and other bone-derived proteins. Cell growth is subsequently promoted by various factors such as hormones, growth factors, and stromal-epithelial biologic interactions, most of which operate in the bone marrow. Expansion of tumor from the bone may cause pain, compression, or pathologic fractures, and extensive bone marrow replacement may cause impairment in hematologic function.

Clinical involvement of visceral sites is relatively uncommon even in patients with widespread castration-resistant disease. Table 110–2 illustrates the distribution of metastatic sites reported in selected chemotherapy phase 2 and phase 3 trials. These figures suggest that clinical evidence of visceral metastasis is observed in less than 10% of patients, whereas about 20% have demonstrable soft tissue nodal disease. Because the majority of tumor burden in metastatic prostate cancer is found in bone, responses to treatment (e.g., tumor shrinkage) in soft tissue sites alone (e.g., nodal or visceral sites) may not reflect a major treatment benefit because it represents only a small proportion of the overall disease burden.

Patients with metastatic CRPC may present with a range of hematologic problems caused primarily by the disease or by its treatment. Anemia is the most common hematologic abnormality, which can be explained by a variety of factors, such as anemia of chronic disease, bone marrow invasion, blood loss, and rarely secondary to a microangiopathic hemolytic anemia usually associated with a consumption coagulopathy (disseminated intravascular coagulation). A decrease in the red blood cell count of patients with advanced CRPC commonly results from a combination of factors, such as prior treatment with local irradiation of bone marrow, systemic use of radio-pharmaceuticals, long-term androgen deprivation, and systemic chemotherapy, as well as from extensive bone marrow invasion by tumor resulting in substantial decrease in bone marrow reserves. The use of erythropoietin can be effective, especially in patients with a history of long-term androgen suppression, and repeated administration may require the use of iron preparations. However, erythropoietin-stimulating agents should be used with caution, because evidence is now emerging that these agents may increase mortality in cancer patients (Bennett et al, 2008). Granulocytopenia and thrombocytopenia are most commonly a complication of extensive radiation therapy or systemic chemotherapy. Rarely, rapidly growing tumors with bone marrow involvement result in pancytopenia. Thrombocytosis is also a nonspecific manifestation associated with various neoplastic conditions, including prostate cancer. Clotting complications associated with thrombocytosis are rarely seen in patients with prostate cancer, and treatment is not usually necessary.

Among the most important urologic sequelae in patients with advanced prostate cancer is the

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**Table 110–2.**

Typical Distribution of Metastatic Sites in Patients with Castration-Resistant Prostate Cancer Entered in Clinical Trials

<table>
<thead>
<tr>
<th>STUDY</th>
<th>NO. PATIENTS</th>
<th>Bone</th>
<th>Lung</th>
<th>Liver</th>
<th>Soft Tissue–Nodal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hudes et al, 1992</td>
<td>36</td>
<td>36 (100%)</td>
<td>0 (0%)</td>
<td>2 (6%)</td>
<td>7 (19%)</td>
</tr>
<tr>
<td>Pienta et al, 1994</td>
<td>42</td>
<td>42 (100%)</td>
<td>3 (7%)</td>
<td>5 (12%)</td>
<td>13 (31%)</td>
</tr>
<tr>
<td>Sella et al, 1994</td>
<td>39</td>
<td>36 (92%)</td>
<td>3 (8%)</td>
<td>3 (8%)</td>
<td>9 (23%)</td>
</tr>
<tr>
<td>Moore et al, 1994</td>
<td>27</td>
<td>22 (81%)</td>
<td>2 (9%)</td>
<td>2 (7%)</td>
<td>10 (37%)</td>
</tr>
<tr>
<td>Eisenberger et al, 1995</td>
<td>109</td>
<td>108 (99%)</td>
<td>6 (6%)</td>
<td>4 (4%)</td>
<td>15 (14%)</td>
</tr>
<tr>
<td>Tannock et al, 2004</td>
<td>1006</td>
<td>915 (91%)</td>
<td>67 (10%)</td>
<td>57 (8%)</td>
<td>168 (25%)</td>
</tr>
<tr>
<td>Petrylak et al, 2004</td>
<td>674</td>
<td>579 (86%)</td>
<td>67 (10%)</td>
<td>57 (8%)</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 110–2.** Clinical heterogeneity of castration-resistant prostate cancer. Subpopulations according to their type of progression after androgen deprivation. PSA, prostate-specific antigen. *The percentages illustrated represent an estimation based on the distribution reported in multiple trials reviewed by the authors.
development of obstructive uropathy. This complication, related to the primary disease, can be devastating in terms of quality of life and may even have major therapeutic implications. Besides an increased incidence of infection and pain, obstructed kidneys may critically impair renal function at a point where various chemotherapeutic agents (which depend largely on renal mechanisms for their clearance) cannot be safely employed. In general, patients who are otherwise candidates for treatment with cytotoxic drugs are best first managed by relief of obstruction either with placement of internal stents or by percutaneous nephrostomies.

One of the greatest emergencies in oncology is the development of epidural spinal cord compression (Sorensen et al, 1990). Because of the frequent involvement of vertebral bodies by metastatic prostate cancer, the incidence of cord compression is of particular concern (see later).

Preclinical observations have suggested that several drugs may reduce PSA secretion without affecting tumor growth (Larocca et al, 1991; Eisenberger and Nelson, 1996; Seckin et al, 1996). Whereas these laboratory observations are likely to be clinically relevant, assays used to evaluate a separate drug effect on PSA secretion still require careful validation. A PSA consensus meeting developed by several leading investigators in the field generated initial guidelines with regard to the use of the PSA test for clinical trials in patients with CRPC (Bubley et al, 1999). These guidelines were recently updated and now also provide a consensus on the use of radiologic end points as well as clinical end points (e.g., pain) for the evaluation of men with CRPC (Scher et al, 2008). The use of serum acid phosphatase and alkaline phosphatase has not been proven beneficial. Undoubtedly, new biomarkers are needed to enhance our ability to rapidly identify active treatments for CRPC. Evolving noncytotoxic and targeted therapies may require a new set of end points and identification of drug-specific intermediate biomarkers that reflect mechanism-specific biologic activity.

Key Points: Clinical Considerations

- Evaluate the extent and aggressiveness of the disease.
- Realize that the critical issues are presence or absence of metastases, clinical versus biochemical relapse, presence of symptoms (e.g., pain), and PSA kinetics (e.g., PSA doubling time, PSA velocity).
- Consider secondary hormonal manipulations before initiation of cytotoxic chemotherapy.

**CYTOTOXIC CHEMOTHERAPY**

**Evaluation of Treatment Efficacy**

The evaluation of chemotherapy based on uncontrolled clinical trials in patients with metastatic prostate cancer is usually confounded by significant methodologic challenges. The most common metastatic site is bone (nonmeasurable disease), manifested by diffuse osteoblastic lesions that cannot be measured reliably by current methods to allow assessments of therapeutic benefit. Soft tissue or visceral metastatic sites (measurable disease) that allow serial measurements are uncommon (see Table 110–2) and represent only a small fraction of the total burden of the disease. Selection of bi-dimensionally measurable disease sites to assess therapeutic efficacy with serial “tumor measurements” has been the subject of significant criticism. Patients with soft tissue metastasis (especially visceral disease) are considered by many a subgroup with biologic and clinical features distinct from those of the usual patient with prostate cancer who presents with bone metastasis only. A number of prognostic models evaluating baseline and post-treatment characteristics have been developed (Smaletz et al, 2002; Halabi et al, 2003; Armstrong et al, 2007). Among various clinical and laboratory parameters with consistent prognostic significance are baseline functional status (performance status), presence of pain, and pretreatment hemoglobin levels (cutoffs range from 10 to 12 g/dl). Other possible parameters are the baseline PSA level, extent of bone scintiscan involvement (number of lesions or pattern/distribution of bone involvement), and presence of visceral disease. Semi-quantitative methods to evaluate PSA mRNA expression in circulating cells (using reverse transcriptase/polymerase chain reaction) and various PSA constructs (e.g., PSADT and PSA velocity) are among the post-treatment parameters most likely to be of prognostic significance (Kantoff et al, 2001; Scher et al, 2004; Armstrong et al, 2007).

Clinical Trials

Most of the chemotherapeutic agents available in oncologic practice have been employed in patients with CRPC, either as single agents or in various combinations. Examples have included cyclophosphamide, 5-fluorouracil, estramustine, vinorelbine, etoposide, cisplatin, carboplatin, doxorubicin, mitoxantrone, paclitaxel, and docetaxel (Eisenberger, 1988). With the exception of docetaxel and perhaps mitoxantrone, most other cytotoxic agents are no longer being used with frequency because they have not been associated with either symptomatic improvements or extension of survival. Evolving data with selected chemotherapy during the new millennium suggest that the survival of patients with advanced CRPC is now somewhere between 16 and 18 months (Petrylak et al, 2004; Tannock et al, 2004) as opposed to 6 to 12 months as previously described (Eisenberger, 1988).

A first step forward in the chemotherapeutic management of CRPC came with mitoxantrone. This agent, a semi-synthetic anthracycline, had previously shown modest symptomatic benefits but with minimal evidence of objective antitumor activity (Osborne et al, 1983; Rearden et al, 1995). In addition, mitoxantrone appeared to have its maximal palliative effect in combination with low-dose corticosteroids (Moore et al, 1994). In two seminal prospective randomized trials of mitoxantrone plus prednisone versus prednisone alone (Tannock et al, 1996) or mitoxantrone plus hydrocortisone versus hydrocortisone alone (Kantoff et al, 1999), the combination resulted in significant improvements of various quality of life parameters, including pain, but survival was not significantly improved in either trial. These studies provided the justification for the approval in 1997 by the U.S. Food and Drug Administration (FDA) of the combination of mitoxantrone and prednisone for symptomatic metastatic prostate cancer.

The next significant advance in the use of chemotherapy for CRPC came with docetaxel, a member of the taxane family. This agent acts by inducing apoptosis in cancer cells through TP53-independent mechanisms that are thought to be due to inhibition of microtubule depolymerization and blockade of antiapoptotic signaling. The induction of microtubule stabilization intracellularly through β-tubulin interactions causes guanosine triphosphate (GTP)-independent polymerization and cell cycle arrest at G2/M. In addition, docetaxel has been found to induce BCL2 phosphorylation in vitro, a process
that has been correlated with caspase-3 activation and loss of its normal antiapoptotic activity. Unable to inhibit the pro-apoptotic molecule BAX, phosphorylated BCL2 may also induce apoptosis through this alternate pathway. However, additional mechanisms may also be important, such as CDKN1B (formerly p27) induction and repression of BCL-XL. Data with docetaxel monotherapy previously suggested that this compound has significant activity as a single agent (Friedland et al, 1999; Picus and Schultz, 1999; Beer, 2004).

As of 2004, docetaxel has become the agent of choice for treatment of metastatic CRPC on the basis of a large phase 3 randomized trial, TAX 327 (Figs. 110–3 to 110–5 and Tables 110–3 to 110–5), which demonstrated superiority over the previous standard, mitoxantrone and prednisone (Tannock et al, 2004). TAX 327 enrolled 1006 patients with no prior chemotherapy and stable pain scores to one of three study arms (all with concomitant prednisone at 5 mg orally twice daily): mitoxantrone, 12 mg/m² intravenously every 21 days; docetaxel, 75 mg/m² intravenously every 21 days; or docetaxel, 30 mg/m² intravenously every 7 days. Patients remained on

**Table 110–3.**

<table>
<thead>
<tr>
<th></th>
<th>DOCETAXEL (THREE TIMES A WEEK)</th>
<th>DOCETAXEL (WEEKLY)</th>
<th>MITOXANTRONE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Response Rate*</td>
<td>N, evaluable</td>
<td>153</td>
<td>154</td>
</tr>
<tr>
<td>PSA response rate (%)</td>
<td>35</td>
<td>31</td>
<td>22</td>
</tr>
<tr>
<td>P value (vs. mitoxantrone)</td>
<td>.01</td>
<td>.07</td>
<td></td>
</tr>
<tr>
<td>PSA Response Rate*</td>
<td>N, evaluable</td>
<td>291</td>
<td>282</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>45</td>
<td>48</td>
<td>32</td>
</tr>
<tr>
<td>P value (vs. mitoxantrone)</td>
<td>.0005</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>Tumor Response Rate*</td>
<td>N, evaluable</td>
<td>141</td>
<td>134</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>12</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>P value (vs. mitoxantrone)</td>
<td>.10</td>
<td>.50</td>
<td></td>
</tr>
</tbody>
</table>

* Determined only for patients with pain or PSA ≥ 20 ng/mL or measurable disease at baseline, respectively.

PSA, prostate-specific antigen.
gonadal suppression (e.g., LH-RH agonists) but had all other hormonal agents discontinued. Treatment duration was 30 weeks in all study arms, or a maximum of 10 cycles in the every-3-week study arms, with more patients completing treatment in the every-3-week docetaxel group than in the mitoxantrone group, mostly because of differences in disease progression (46% vs. 25%). After a median follow-up of 20.7 months, overall survival in the every-3-week docetaxel group was 18.9 months (with a pain response rate of 35% and a PSA response of 45%), contrasted to weekly docetaxel at 17.3 months (and 31% and 48%), respectively. This translated into a 24% relative reduction in the risk of death (95% confidence interval [CI], 6% to 48%; \( P = .0005 \)) with 3-weekly docetaxel (see Fig. 110–4). Patients on the mitoxantrone arm had a median survival of 16.4 months, a pain response of 22%, and a PSA response of 32%.

Toxicity in the 3-weekly versus weekly docetaxel groups was notable for more hematologic toxicity in the every-3-week group (3% neutropenic fever vs. 0%; 32% grade-3/4 neutropenia versus 1%) (see Table 110–5) but slightly lower rates of nausea and vomiting, fatigue, nail changes, hyperlacrimation, and diarrhea. Neuropathy was slightly more common in the every-3-week group (grade 3/4 in 1.8% vs. 0.9% in the weekly treated group). Quality of life responses as measured by the FACT-P scores did not differ significantly among the docetaxel schedules but were more favorable than in the mitoxantrone group.

The Southwest Oncology Group (SWOG) 9916 study was a second large phase 3 trial (Figs. 110–6 to 110–8) (Petrylak et al, 2004) in which 770 patients with progressive CRPC were randomly assigned to oral estramustine (280 mg three times daily) plus docetaxel (60 mg/m²...
every 21 days) versus mitoxantrone (12 mg/m² every 21 days) plus prednisone. In this study, median overall survival was longer in the docetaxel-estramustine group than in the mitoxantrone-prednisone group (17.5 vs. 15.6 months, P = .02), with a corresponding hazard ratio (HR) for death of 0.80 (95% CI, 0.67 to 0.97). Because of the high rate of thromboembolic events with estramustine, prophylactic low-dose warfarin and aspirin were added to that study arm, which did not reduce the incidence of thromboembolism. Similarly, 20% and 15%, respectively, of patients in the docetaxel-estramustine arm had grade 3/4 gastrointestinal and cardiovascular toxicities. Although comparisons between the docetaxel arms across these two seminal trials may not be appropriate because of differences in schedule, patient populations, and docetaxel dosing (60 mg/m² in SWOG 9916 and 75 mg/m² in TAX 327), it may be concluded that estramustine is unlikely to add significantly to the activity of single-agent docetaxel.

Until recently, effective life-prolonging therapies for men with docetaxel-refractory prostate cancer were lacking. This changed in 2010, when the FDA approved a second chemotherapy agent, cabazitaxel, for the treatment of metastatic CRPC. Cabazitaxel (Jevtana, Sanofi-Aventis, Paris, France) is a novel tubulin-binding taxane that differs from docetaxel and paclitaxel due to its poor affinity for P-glycoprotein, the ATP-dependent drug efflux pump (Paller and Antonarakis, 2011). In preclinical studies using cancer cell lines and mouse xenograft models, cabazitaxel was shown to be active in both docetaxel-sensitive tumors as well as those with primary or acquired docetaxel resistance (Attard et al, 2006).

The first hint of cabazitaxel’s safety and efficacy in men with prostate cancer came during phase I testing, where cabazitaxel was administered by intravenous infusion every 3 weeks at escalating doses of 10 to 25 mg/m² (Mita et al, 2009). In that study, the principal dose-limiting toxicity was neutropenia. Given the lack of cross-resistance to this agent with docetaxel, and early reports of responses in men with CRPC from this phase 1 trial, a phase 3 trial was launched to evaluate efficacy.

The safety and efficacy of cabazitaxel in patients with advanced prostate cancer was definitively evaluated in a pivotal randomized phase III trial (TROPIC) conducted in 146 institutions across 26 countries, and recruited 755 men with metastatic CRPC who had progressed during/after docetaxel-based chemotherapy (de Bono et al, 2010). Of these, 377 patients were randomized to receive mitoxantrone 12 mg/m² intravenously every 3 weeks (with oral prednisone 10 mg daily), and 378 patients were assigned to receive cabazitaxel 25 mg/m² intravenously every 3 weeks (plus prednisone). This study was the basis of the FDA’s approval of cabazitaxel with prednisone for the second-line treatment of docetaxel-refractory metastatic CRPC in June 2010.

After a median follow-up of 12.8 months, overall survival in men receiving cabazitaxel was 15.1 months compared to 12.7 months in men receiving mitoxantrone (HR, 0.70; P < .0001) (de Bono et al, 2010). Compared to mitoxantrone, cabazitaxel also significantly lengthened progression-free survival (2.8 months vs. 1.4 months; P < .0001), extended time to PSA progression (6.4 months vs. 3.1 months; P = .001), increased radiographic tumor response rates (14.4% vs. 4.4%; P = .0005), and increased PSA response rates (39.2% vs. 17.8%; P = .0002). There were no differences between the two treatment arms with respect to pain responses, or time to pain progression.

In subset analyses, the survival advantage of cabazitaxel persisted regardless of whether patients had measurable disease or pain, or whether progression had occurred while receiving docetaxel or following a treatment holiday. In addition, cabazitaxel’s survival benefit was most pronounced for men with ECOG performance status 0-1 (vs. 2), and for patients with disease progression within <3 months of docetaxel initiation (vs. ≥3 months of docetaxel initiation) (de Bono et al, 2010). The last observation implies that cabazitaxel may be effective even in men with truly docetaxel-refractory disease.

The most common serious adverse events related to cabazitaxel were hematologic, including grade ≥3 neutropenia in 82% of patients (febrile neutropenia in 8%) (de Bono et al, 2010). This degree of myelosuppression begs the question of whether a lower dose of cabazitaxel (e.g., 20 mg/m²) may have been more appropriate, and a randomized trial comparing the safety and efficacy of these two doses (25 mg/m² vs. 20 mg/m²) is now being conducted. Use of growth factor support should be strongly considered, as reflected in several national guidelines (Mohler et al, 2010). Other nonhematologic toxicities included grade ≥3 diarrhea (6%) and grade ≥3 fatigue (5%). Encouragingly, although peripheral neuropathy (all grades) was observed in 14% of patients receiving cabazitaxel, only 1% developed grade 3 neuropathy.

Key Points: Cytotoxic Chemotherapy
- Docetaxel is the standard treatment for metastatic castration-resistant prostate cancer. It prolongs progression-free and overall survival, ameliorates pain, and improves quality of life.
- Toxicity of docetaxel includes myelosuppression, fatigue, edema, moderate to modest neurotoxicity, hyperlacrimation, and changes in liver function.
- No other chemotherapy regimen has shown a survival advantage in CRPC, but mitoxantrone has been approved to palliate symptoms associated with metastatic disease.
- Cabazitaxel has recently emerged as a treatment option for patients with metastatic CRPC who have experienced progressive disease during or after docetaxel treatment.

The Neuroendocrine/Anaplastic Subtype

Laboratory and clinical evidence indicates that alterations in the differentiation pathway of prostate cancer can be seen in a small proportion of patients with advanced disease, giving rise to a neuroendocrine/anaplastic transformation (di Sant’Agnes, 1995; Nelson et al, 2007). The therapeutic implications of this finding are of significance because tumors demonstrating this phenotype usually represent an inherently endocrine-resistant subtype and, in view of their different clinical and biologic properties compared with the usual adenocarcinoma of the prostate, these tumors usually require different treatment strategies.

Such tumors express a number of biologic characteristics unique to neuroendocrine tumors that can also arise from other organs, most commonly the lung. Among these are the expression of receptors to various neuroendocrine peptide growth factors, such as somatostatin, chromogranin A, and serotonin, as well as parathyroid hormone-related protein (PTHrP) and TP53 mutations. These tumors have an uncharacteristic clinical behavior (compared with the usual metastatic prostate cancer), reflected by frequent visceral involvement and rapidly growing soft tissue metastases. Patients
frequently present with subacute and often dramatic changes in their disease pattern characterized primarily by a rapidly growing soft tissue mass (frequently involving the primary site but also with retroperitoneal masses), rapid development of visceral (lung and liver) infiltration, osteolytic (as opposed to osteoblastic) bone metastasis, and a high incidence of parenchymal brain involvement (Fig. 110–9). Histologic evaluation of areas demonstrating rapid growth is strongly encouraged. This frequently culminates with demonstration of a small cell variant or a poorly differentiated neoplasm on pathology and the presence of neuroendocrine markers on immunostaining (diSant’Agnese, 1995; Nelson et al, 2007). Interestingly, patients with this tumor phenotype either stop expressing PSA in the presence of major tumor progression or even have undetectable PSA levels at the time of this transformation.

Treatment is usually similar to that of patients with other neuroendocrine tumors (e.g., small cell carcinoma of the lung) and includes combinations of cisplatin (or carboplatin) and etoposide (Frank, 1995), paclitaxel, docetaxel, and topotecan. Doxorubicin-containing combinations have been reported to be moderately effective by one group (Papandreou et al, 2002). Radiation therapy is effective and should be considered in cases with bulky disease, with brain metastasis, or when local disease control in critical areas may have a positive impact on quality of life (pain, potential pathologic fractures, and bladder outlet obstruction). A combined chemotherapy and radiation therapy approach is frequently necessary to accomplish maximal disease control. Despite high initial response rates with chemotherapy and radiation treatment, the prognosis of these patients remains poor and is dependent on various factors, including extent and location of metastases.

### Key Points: The Neuroendocrine/Anaplastic Subtype

- Rapidly growing disease with the following clinical characteristics should prompt evaluation for the neuroendocrine/anaplastic phenotype: pelvic masses, visceral involvement, osteolytic metastasis with hypercalcemia (associated with high serum PTHrP), and brain metastasis.
- PSA is most commonly undetectable (or levels are low/declining) despite evidence of rapid disease progression. Serum chromogranin A and urine serotonin metabolites may be detected.
- These tumors are invariably unresponsive to hormonal manipulations but highly sensitive to radiation therapy and platinum-etoposide combinations.

### PALLIATIVE MANAGEMENT

#### Pain and Epidural Cord Compression

As in other disseminated malignant neoplasms, palliation of symptoms and maintenance of adequate levels of quality of life represent the most important objectives in the management of advanced prostate cancer. Cancer-related pain is undoubtedly the most debilitating symptom associated with metastatic prostatic carcinoma. **Prompt recognition of the various pain syndromes associated with this disease is critical to accomplish effective control of this devastating symptom.** The most common pain syndromes and their respective therapeutic considerations are described in Table 110–6.

Focal bone pain in patients with castration-refractory disease can be well controlled by external-beam localized radiation therapy. In general, it is also recommended that painful areas
Table 110–6.
Common Pain Syndromes in Metastatic Castration-Resistant Prostate Cancer

<table>
<thead>
<tr>
<th>PAIN SYNDROME</th>
<th>INITIAL MANAGEMENT</th>
<th>OTHER THERAPEUTIC ALTERNATIVES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized bone pain</td>
<td>Pharmacologic pain management</td>
<td>Surgical stabilization of pathologic fractures or extensive bone erosions</td>
</tr>
<tr>
<td></td>
<td>Localized radiotherapy (special attention to weight-bearing areas, lytic metastasis, and extremities)</td>
<td>Epidural metastasis and cord compression should be evaluated in patients with focal back pain. Radiopharmaceuticals should be considered if local radiation therapy fails.</td>
</tr>
<tr>
<td>Diffuse bone pain</td>
<td>Pharmacologic pain management</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td></td>
<td>“Multi-spot” or widefield radiotherapy</td>
<td>Bisphosphonates</td>
</tr>
<tr>
<td></td>
<td>Radiopharmaceuticals</td>
<td>Calcitonin</td>
</tr>
<tr>
<td>Epidural metastasis and cord compression</td>
<td>High-dose corticosteroids</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Radiation therapy</td>
<td>Pharmacologic pain management</td>
</tr>
<tr>
<td></td>
<td>Surgical decompression and stabilization should be indicated in high-grade epidural blocks, extensive bone involvement, or recurrence after irradiation.</td>
<td></td>
</tr>
<tr>
<td>Plexopathies caused by direct tumor extension or prior therapy (rare)</td>
<td>Pharmacologic pain management</td>
<td>Tricyclic antidepressants (amitriptyline)</td>
</tr>
<tr>
<td>Miscellaneous neurogenic causes: postherpetic neuralgia, peripheral neuropathies</td>
<td>Radiation therapy (if not previously employed)</td>
<td>Anticonvulsants</td>
</tr>
<tr>
<td>Other uncommon pain syndromes: extensive skull metastasis with cranial nerve involvement, extensive painful liver metastasis or pelvic masses</td>
<td>Careful neurologic evaluation</td>
<td>Tricyclic antidepressants (amitriptyline)</td>
</tr>
<tr>
<td></td>
<td>Pharmacologic pain management</td>
<td>Anticonvulsants</td>
</tr>
<tr>
<td></td>
<td>Radiation therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pharmacologic pain management</td>
<td></td>
</tr>
</tbody>
</table>

shown to be abnormal on bone scintigraphy should be evaluated with plain radiographs to exclude the presence of osteolytic lesions or pathologic fractures. Such considerations become even more important when the painful areas affect extremities and weight-bearing sites.

Epidural metastasis is a fairly common and potentially devastating complication of systemic cancer. In view of the propensity for prostate cancer to metastasize to the vertebrae and paravertebral region, the incidence of epidural cord compression is particularly high in this disease. Early diagnosis and treatment of epidural metastasis is critical in preserving ambulation and bowel and bladder function and aids in the management of back pain (Grossman and Lossignol, 1990; Gabriel and Schiff, 2004). Epidural cord compressions arising from vertebral bodies account for the majority of spinal cord compression; only less frequently is it associated with soft tissue masses involving the paravertebral region. Most patients have abnormalities on bone scintiscans and abnormal findings on radiography at the time of diagnosis. However, an abnormality on neurologic examination may be the only finding in patients who have soft tissue epidural metastasis in the paravertebral region.

Spinal magnetic resonance imaging (MRI) is routinely used to exclude the possibility of significant epidural disease, and it has almost entirely replaced other methods such as computed tomographic myelography and conventional myelography. The first therapeutic intervention should include the administration of high doses of intravenous glucocorticoids. **Dexamethasone at doses ranging from 16 to 100 mg daily is most commonly employed.** Most frequently, patients are given an intravenous “loading dose” of 10 mg of dexamethasone followed by 4 to 10 mg every 6 hours; the optimal dose remains relatively undefined. On improvement of symptoms, which can be accomplished promptly with corticosteroids, the corticosteroid dose may be tapered during a 2- to 3-week period.

**Radiation therapy** is often the main modality of definitive treatment. However, recent reports suggest that surgery followed by radiation therapy may be superior to radiation therapy alone (Patchell et al, 2005). Surgery should be considered in patients who present with evidence of progressive signs and symptoms during radiation therapy, develop or present with unstable pathologic fractures, or have recurrence after radiotherapy. Clearly, the overall prognosis of the underlying disease should be taken into consideration during treatment selection. **Chemotherapy** is rarely used to treat epidural cord compressions.

**Bone-Targeted Approaches**

The pathogenesis of bone metastases in prostate cancer remains a subject of major study (Galasko, 1986). Alterations in the normal process of bone absorption and formation, which usually follows an orderly and sequential basis, appear to be a key determining factor in the development of bone metastasis associated with most malignant neoplasms (Roodman, 2004). Under normal physiologic conditions the process of bone remodeling is initiated by an increase in osteoclastic activity followed by an increase in osteoblastic differentiation and maturation, which results in the
formation of new bone and repair of the initial absorption caused by osteoblasts. Bone loss associated with prostate cancer can result from an enhanced osteoclastic activity associated with long-term androgen suppression, which in turn will cause excessive resorption of bone mineral and organic matrix. Tumor cells may also cause mineral release and matrix resorption in the areas involved by metastatic disease (Galasko, 1986). In addition, various cytokines, growth factors, tumor necrosis factors, and bone morphogenetic proteins have been shown in preclinical studies to play a major role in the induction of both osteoclastic and osteoblastic activity (Reddi and Cunningham, 1990). In prostate cancer, bone metastases are predominantly blastic, which reflects a predominance of osteoblastic activity in the process of bone remodeling (Roedman, 2004). This phenomenon may be due to specific growth factor secretion that is responsible for the induction of osteoblasts. Hypercalcemia is rare in metastatic prostate cancer. In fact, a significantly elevated serum calcium concentration is most frequently due to the neuroendocrine prostate cancer phenotype and is mediated through PTHrP, as discussed earlier (diSant’Agnese, 1995; Nelson et al, 2007).

Bisphosphonates

Bisphosphonates have become an integral part of the management of metastatic prostate cancer to the bones (Van den Wyngaert et al, 2009). These compounds reduce bone resorption by inhibiting osteoclastic activity and proliferation. Zoledronate is a potent intravenous bisphosphonate first approved for the treatment of hypercalcemia and decreased bone mineral density in postmenopausal women (Green and Rogers, 2002). In patients with progressive castration-refractory disease and bone metastases zoledronate was shown to reduce the incidence of skeletal-related events (e.g., pain, fractures) compared with placebo in a prospective randomized trial of 422 patients (Saad et al, 2004). In addition, zoledronate and pamidronate have also been shown to increase mineral bone density in patients with nonmetastatic prostate cancer receiving long-term androgen deprivation (Smith et al, 2001, 2003). At present, zoledronate is indicated for the treatment of patients with progressive prostate cancer with evidence of bone metastasis, and it is administered at a dose of 4 mg intravenously repeated at intervals of 3 to 4 weeks for several months. Side effects of this agent include fatigue, myalgias, fever, anemia, and mild elevation of the serum creatinine concentration. Hypocalcemia has been described, and concomitant use of oral calcium supplements (1500 mg/day) and vitamin D (400 units/day) is often recommended. An unusual complication of zoledronate is the development of severe jaw pain associated with osteonecrosis of the mandibular bone. The etiology of this effect is not well understood. However, it is most frequently seen in patients undergoing dental work or those with a history of poor dentition and chronic dental disease. Zoledronate should not be administered to patients with these problems. Other bisphosphonates have also been evaluated in prostate cancer, including alendronate, etidronate, ibandronate, and clodronate; however, their benefit has not been conclusively established in prospective randomized clinical trials (Berry et al, 2006; Van den Wyngaert et al, 2009).

RANKL Inhibitors

Interactions between tumor cells and the bone marrow microenvironment have been postulated as an additional important mechanism in the pathogenesis of bone metastasis. Tumor-associated cytokines have been shown to induce the expression of RANKL (the receptor activator of nuclear factor κB ligand), which binds and activates RANK, which is found in osteoclasts (Brown et al, 2001). Inhibition of the RANKL system has recently been the focus of much research and represents an evolving bone-targeted strategy. Among the approaches employed are monoclonal antibodies to RANKL and the use of recombinant osteoprotegerin (the natural decoy receptor of RANKL), both of which significantly inhibit osteoclastic function in vitro and in vivo (Schwarz and Ritchlin, 2007). Denosumab, a fully human monoclonal antibody against RANKL, has entered clinical trials in prostate and breast cancers. In a phase 2 randomized study evaluating 50 patients with metastatic prostate cancer, denosumab (180 mg subcutaneously every 4 weeks) produced a reduction in bone resorption over that of zoledronate, as indicated by a lowering of urinary N-telopeptide levels, and also resulted in less skeletal-related events (Fizzi et al, 2009). Following from these encouraging results, a pivotal multicenter phase III double-blind randomized study was conducted comparing denosumab against zoledronate for the prevention of skeletal-related events in patients with bisphosphate-naïve metastatic CRPC. In that trial of 1904 patients, compared to men receiving zoledronate (n = 951), men receiving denosumab (n = 950) had an improved time to first skeletal-related events (20.7 vs. 17.1 months; P = .008) and longer time to first-and-subsequent skeletal-related events (HR, 0.82; P = .004) (Fizzi et al, 2011). Notably, there was no difference in overall survival or progression-free survival between study arms. Based partially on the results of this study (and partially on two other large randomized studies in metastatic breast cancer and other solid metastatic tumors), the FDA approved denosumab (Xgeva, Amgen, Thousand Oaks, CA) in November 2010 for the prevention of skeletal-related events in patients with bone metastases from solid tumors. Common toxicities of denosumab include fatigue, nausea, hypophosphatemia, hypocalcemia (5% grade ≥3), and osteonecrosis of the jaw (2%), and prophylactic calcium and vitamin D supplementation is strongly encouraged. Therefore denosumab is a reasonable alternative to zoledronate for the prevention of skeletal-related events in patients with metastatic CRPC, and also has the advantage that it does not require dose adjustment or monitoring for renal impairment. The recommended dose of denosumab is 120 mg given by subcutaneous injection every 4 weeks.

Radiopharmaceuticals

The introduction of “bone-seeking” radiopharmaceuticals has provided a useful resource for the management of diffuse bone pain from widespread prostate cancer metastases (Pandit-Taskar et al, 2004). Among the most commonly used compounds are strontium-89 (89Sr) (Porter et al, 1993) and samarium-153 (153Sm) (Sartor et al, 2004). Rhenium-186 has also been used (Kucuk et al, 2000). Initial studies with 89Sr have shown palliation of bone pain in 25% to 65% of patients with castration-refractory disease and diffuse pain (Jager et al, 2000). The pharmacokinetics of 89Sr vary considerably according to the extent of bone involvement, but the half-life is generally 4 to 5 days. The retention of the isotope is significantly longer in patients with diffuse osteoblastic metastases compared with those with relatively limited bone involvement. It is important to recognize this factor because it will undoubtedly affect the degree and duration of myelotoxicity associated with this radioactive compound (its most significant side effect). The clinical experience with 153Sm suggests that this isotope is associated with a lower incidence of severe myelotoxicity, probably because of
its shorter half-life of 2 days. Encouraging results were reported by Sartor and colleagues (2004) in a phase 3 trial comparing radioactive $^{153}$Sm and nonradioactive $^{152}$Sm, indicating that a dose of $^{153}$Sm of 1 mCi/kg is both safe and effective palliation for patients with castration-refractory disease and severe bone pain. One study reported encouraging synergism with $^{89}$Sr and doxorubicin, a known and well-studied radiosensitizer (Tu et al, 2001). Randomized studies evaluating the synergism of various chemo-therapeutic agents, including taxanes, and radiopharmaceuticals are being done.

**Key Points: Palliative Management**

- Patients with back pain and a history of bone metastasis should be aggressively evaluated for epidural cord compression. The clinical syndrome often has at least one of the following signs and symptoms: back pain, focal neurologic findings (leg weakness, sensory levels), or changes in bladder or bowel control.
- Initial management of suspected cord compression includes immediate magnetic resonance imaging of the spine and high-dose intravenous corticosteroid therapy.
- Definitive therapy should include surgical decompression, radiation therapy, or both.
- Zoledronic acid and denosumab are both reasonable treatment options for the prevention of skeletal-related events in patients with castration-resistant bone metastases.

**NOVEL APPROACHES**

**Rational Target Overview**

An understanding of the basic biology involved of pathogenesis of prostate cancer provides the opportunity to identify potential targets that predict the clinical outcome of the disease. The first opportunity is the demonstration of a mutation or functional dysregulation of the target. Simply targeting overexpressed proteins has been less efficient than the specific targeting of mutations that drive the bulk of the tumor growth. The second goal is identifying target causality, indicating the importance of the target alone or in combination with other mutations in reproducing the phenotypic findings of prostate cancer. Finally, there should be evidence from preclinical models that inhibition of the target leads to tumor regression or quiescence. In prostate cancer, the androgen receptor is one potential target although there are many others. Various molecular changes in the androgen receptor have been shown to parallel disease progression in castrate patients and in some situations may provide the explanation for the responses associated with some therapeutic maneuvers (antiandrogen withdrawal syndrome, responses to secondary endocrine manipulations with compounds designed to bind to the receptor). Despite this, a precise role of the androgen receptor in the pathogenesis of disease progression remains to be better elucidated. Given the molecular complexity of the prostate cancer cell pathways and relatively poor understanding of the role of individual pathways in the process of disease-specific progression, the simultaneous inhibition of multiple pathways remains a common strategy to induce sustained and clinically meaningful responses in prostate cancer.

The major biologic processes under therapeutic investigation in prostate cancer involve growth and survival, chemotherapy and hormone therapy resistance, extragonadal androgen production, modulation of the androgen receptor, angiogenesis, the bone interface, epigenetic regulation, immune surveillance and escape, and stem cell renewal. This section provides an overview of these pathways as they pertain to prostate cancer rational targets and the approaches that are currently being developed for therapeutic purposes (Table 110–7).

**Targeted Treatments**

Although a prostate cancer stem cell has yet to be conclusively demonstrated, prostate cancer clearly progresses from an androgen-dependent tumor with features similar to the luminal

<table>
<thead>
<tr>
<th>TARGET</th>
<th>AGENT</th>
<th>PHASE</th>
<th>SUMMARY OF TRIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI3K/mTOR</td>
<td>Everolimus</td>
<td>2</td>
<td>Docetaxel + everolimus for first-line metastatic CRPC</td>
</tr>
<tr>
<td>EGFR/HER2</td>
<td>Lapatinib</td>
<td>2</td>
<td>Single-agent lapatinib for nonmetastatic CRPC</td>
</tr>
<tr>
<td>PDGFR</td>
<td>Imatinib</td>
<td>2</td>
<td>Docetaxel + imatinib for first-line metastatic CRPC</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Calcitriol</td>
<td>3</td>
<td>Docetaxel ± calcitriol for first-line metastatic CRPC</td>
</tr>
<tr>
<td>HDAC</td>
<td>Vorinostat</td>
<td>2</td>
<td>Single-agent vorinostat for second-line metastatic CRPC</td>
</tr>
<tr>
<td>Endothelin receptor</td>
<td>Atrasentan</td>
<td>3</td>
<td>Single-agent panobinostat for second-line metastatic CRPC</td>
</tr>
<tr>
<td>RANK ligand</td>
<td>Denosumab</td>
<td>3</td>
<td>Docetaxel ± atrasentan for first-line metastatic CRPC</td>
</tr>
<tr>
<td>VEGF</td>
<td>Bevacizumab</td>
<td>3</td>
<td>Docetaxel + zibotentan for first-line metastatic CRPC</td>
</tr>
<tr>
<td>VEGF receptor</td>
<td>Sorafenib</td>
<td>2</td>
<td>Denosumab vs. zoledronate for palliation in metastatic CRPC</td>
</tr>
<tr>
<td>CYP17</td>
<td>Abiraterone</td>
<td>3</td>
<td>Docetaxel ± bevacizumab for first-line metastatic CRPC</td>
</tr>
<tr>
<td>Androgen receptor</td>
<td>MDV3100</td>
<td>1/2</td>
<td>Docetaxel + sorafenib for first-line metastatic CRPC</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>Sipuleucel-T (Provenge)</td>
<td>3</td>
<td>Docetaxel + sunitinib for first-line metastatic CRPC</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>Ipilimumab</td>
<td>3</td>
<td>Single-agent vatalanib for nonmetastatic CRPC</td>
</tr>
</tbody>
</table>

**Table 110–7.**

Targeted Therapies for Castration-Resistant Prostate Cancer (CRPC): Selected Ongoing Clinical Trials
differentiated glands of the prostate to a castration-refractory tumor that has features of adult stem cells, including antiapoptotic mechanisms, chemotherapy resistance, and reliance on nonhormonal signaling pathways. Candidate pathways currently evaluated include hedgehog signaling, epidermal growth factor receptor (EGFR) signaling, phosphatidylinositol 3-kinase (PI3K)/Akt signaling, mitogen-activated protein kinase (MAPK) signaling, and others (see Table 110–7). Activation of the hedgehog developmental pathway has been demonstrated in prostate cancer metastases and in preclinical models, and inhibition of this pathway has led to antitumor effects and significant inhibition of prostatic epithelial regeneration after androgen withdrawal. Inhibitors of this pathway, such as cyclopamine analogues and other agents, are in preclinical development.

**PI3K/Akt/mTOR Pathway**

In advanced prostate cancer, loss of the tumor suppressor PTEN (phosphatase and tensin homologue deleted on chromosome 10) occurs in more than 50% of metastatic lesions and in approximately 20% of locally advanced lesions (McMenamin et al, 1999; Graff, 2002). Loss of PTEN correlates with advanced Gleason sum, stage, chemotherapy resistance, and other features of advanced prostate cancers (McMenamin et al, 1999). PTEN is a negative regulator of the PI3K/Akt survival pathway, and advanced prostate cancers frequently have elevated levels of phosphorylated (activated) Akt (Gera et al, 2004). The Akt pathway is involved in signal transduction from multiple cell surface receptors, including the insulin receptor, epidermal growth factor receptor, insulin-like growth factor receptor, platelet-derived growth factor receptor, and interleukin-6 receptor, and it is likely to function as a cellular sensor for nutrient and growth signals (Vivanco and Sawyers, 2002). In addition to promoting cell survival through the inhibition of apoptosis, the Akt pathway regulates cell growth, proliferation, and angiogenesis through the mammalian target of rapamycin (mTOR) pathway and the facilitated translation of signals such as c-MYC, cyclin D, and vascular endothelial growth factor (Gera et al, 2004). Restoration of functional PTEN activity or inhibition of mTOR activity can block the growth of PTEN+ prostate cancer xenografts and restore chemotherapy and possibly hormonal sensitivity (Neshat et al, 2001; Podsypanina et al, 2001; Grunwald et al, 2002).

Rapamycin is a natural compound derived from soil samples containing the bacterium *Streptomyces hygroscopicus*. It was initially discarded as an antifungal agent because of its immunosuppressive properties but later revived as a potent immunosuppressive agent for use in solid organ transplantation. Its antiproliferative properties and antitumor activity in cell lines led to its clinical development in cardiology as a means of preventing stent restenosis and in oncology, in which a wide variety of tumors were found to exhibit sensitivity to this agent and its analogue temsirolimus (Hidalgo and Rowinsky, 2000; Bjornsti and Houghton, 2004). Toxicities with rapamycin and its analogues have been predictable and often not dose related; they include maculopapular rash, hypertriglyceridemia, hyperglycemia, allergic reactions, pedal edema, mucositis, and thrombocytopenia (Hidalgo and Rowinsky, 2000; Atkins et al, 2004; Raymond et al, 2004). The combination of these agents with docetaxel is attractive, given their ability to induce apoptosis when they are given in combination with chemotherapy in patients who have demonstrable activation of the Akt pathway as a result of PTEN mutation or loss or other genetic alterations. For example, a new mTOR inhibitor, everolimus (RAD001), is being evaluated in combination with docetaxel as first-line treatment for metastatic CRPC in a phase 1/2 trial (Ross et al, 2008).

**EGFR and PDGFR Pathways**

The rapid development in the past several years of small molecules that inhibit tyrosine kinases has yielded encouraging results in a host of cancers. Demonstration of tumor response has usually correlated with mutation in the target tyrosine kinase, such as epidermal growth factor receptor (EGFR), BCR-ABL, and c-KIT. In these cases the target mutation has played a central role in the pathogenesis of these tumors. In prostate cancer, no such mutation has been identified, and early trials of tyrosine kinase inhibitors in prostate cancer have been disappointing.

EGFR is overexpressed in 40% to 80% of prostate cancer cells, and overexpression may be more common in African-American men with prostate cancer (Shuch et al, 2004). Furthermore, preclinical clinical data suggested a correlation of EGFR expression with Gleason sum and androgen independence (Syed, 2003). In a phase 2 study of approximately 100 patients with castrate-resistant disease evaluating the EGFR tyrosine kinase inhibitor gefitinib, minimal activity and no PSA responses were reported (Moore et al, 2002; Schroder and Wildhagen, 2004). Gefitinib resistance may be related to overactivity of the PI3K/Akt pathway in prostate cancer, and thus combinations of agents that target multiple pathways may be more beneficial (She et al, 2003). Further trials of combination EGFR or dual kinase inhibitors with chemotherapy or other novel agents are in development.

Prostate cancer cells express high levels of platelet-derived growth factor receptor (PDGFR), and this signaling pathway uses the PI3K/Akt pathway, which has been implicated in prostate cancer progression. Single-agent activity with imatinib has been disappointing; however, encouraging results in combination with weekly docetaxel have been reported. A phase 2 randomized trial of this combination compared with docetaxel alone is in progress.

Another potential target in this family of receptors is the HER2/neu tyrosine kinase, whose expression has been shown to increase androgen receptor activation leading to prostate cancer growth and survival (Gregory et al, 2005). However, phase 2 studies using the anti-HER2 monoclonal antibody trastuzumab showed minimal efficacy in CRPC, perhaps owing to a low frequency of HER2 overexpression (Ziada et al, 2004). Studies using the dual EGFR/HER2 small molecule inhibitor lapatinib for asymptomatic CRPC are now being conducted.

**Vitamin D Analogues**

Vitamin D analogues may have differentiation, antiproliferation, and chemosensitizing properties, and epidemiologic studies have shown an increased risk of prostate cancer in those with relative vitamin D deficiency. A phase 2 trial of weekly docetaxel and high-dose calcitriol demonstrated PSA responses in 30 of 37 patients (80%) and measurable responses in 8 of 15 (53%), with a median time to progression of 11.4 months and median survival of 19.4 months (Beer et al, 2005). A randomized study with a total of 250 patients (125 per study arm) comparing the combination with docetaxel alone resulted in more than 50% decline of PSA level in 63% of the patients receiving the combination treatment compared with 52% with docetaxel alone ($P = .07$). However, interestingly, the authors reported a survival difference in favor of the
combination (23.4 vs. 16.4 months; \( P = .03 \)). These results led to the design of a large phase 3 placebo-controlled trial in metastatic CRPC evaluating docetaxel chemotherapy with or without calcitriol, with power to detect a survival benefit as the primary end point. However, early reports from this trial have shown that the primary end point was not met and that mortality was increased in the calcitriol groups, leading to premature closure of the study (Novacea, Inc., 2007).

**Bone Interface**

Preclinical studies suggest that endothelin A receptors are overexpressed in prostate cancer, and higher plasma endothelin levels in patients with prostate cancer have been shown to correlate with tumor stage, grade, and metastases. Endothelin-1 is a potent vasoconstrictor, and agonists have been developed for the treatment of pulmonary hypertension. In oncology, endothelin is likely to be involved in the paracrine signals between osteoblasts and prostate cancer cells that regulate the development of bone metastases and have been shown to influence cell growth and proliferation, regulate osteoblast activity, and inhibit apoptosis. These preclinical observations suggest that this pathway may be a rational target for the interference of tumor-stromal interactions (Nelson JB et al., 2003; Carducci et al., 2002; Yin et al., 2003).

**Atrasentan** is a highly selective endothelin A receptor antagonist and has been extensively tested in prostate cancer. In preliminary phase 2 trials, a 10-mg dose of atrasentan was found to prolong time to progression compared with placebo in men with metastatic CRPC (196 vs. 129 days, respectively; \( P = .02 \)) (Carducci et al., 2003). Adverse events with atrasentan were mild and related to vasomotor reactions, including headache, rhinitis, flushing, and peripheral edema. In addition, favorable effects were seen in markers of bone deposition and resorption. However, in a placebo-controlled double-blind phase 3 trial involving 809 patients with metastatic CRPC, oral atrasentan (10 mg/day) did not reduce the risk of disease progression (\( P = .14 \)), despite evidence of biologic affects on PSA and bone alkaline phosphatase (Carducci et al., 2007). A second phase 3 trial in nonmetastatic CRPC that randomized 467 men to atrasentan and 474 to placebo also failed to improve time to metastatic progression (\( P = .29 \)) or overall survival (Nelson et al., 2008). A large cooperative group phase 3 clinical trial evaluating docetaxel plus or minus atrasentan as first-line therapy for metastatic CRPC is in progress.

A novel small molecule endothelin receptor inhibitor, zibotentan (ZD4054), has shown initial promising results. In a phase 2 trial of zibotentan versus placebo in men with metastatic CRPC, this agent did not improve time to disease progression (the primary study end point; \( P = .55 \)); however, overall survival was longer in the zibotentan group (\( P = .01 \)) (James et al., 2009). Although survival was a secondary end point, this has led to the design of several ongoing placebo-controlled phase 3 clinical trials evaluating zibotentan either alone or in combination with docetaxel in patients with metastatic CRPC.

**Angiogenesis Targets**

Tumor angiogenesis is likely to be an important biologic component of prostate cancer metastasis, and elevated levels of the potent angiogenic molecule vascular endothelial growth factor (VEGF) have been shown to correlate with advanced clinical stage and survival (Duque et al., 1999; George et al., 2002).

In a retrospective study of archived serum samples, VEGF levels were independently associated with survival from prostate cancer (George et al., 2001). Similarly, antibodies to VEGF have slowed prostate xenograft growth rates, especially in combination with chemotherapy (Fox et al., 2002; Sweeney et al., 2002). These findings led to the phase 2 CALGB 90006 trial, which added bevacizumab to docetaxel and estramustine in men with metastatic CRPC. Among 79 treated patients in this study a decline of more than 50% in PSA level was seen in 65% of men, median time to progression was 9.7 months, and overall median survival was 21 months (Picus et al., 2003). Other phase 2 trials combining docetaxel and bevacizumab have also shown promising results (Ryan et al., 2006; Di Lorenzo et al., 2008). These favorable trials have led to the design of a phase 3 randomized study (CALGB 90401) evaluating docetaxel 75 mg/m² every 3 weeks and prednisone 10 mg daily plus either bevacizumab 15 mg/kg or placebo given every 3 weeks. The primary end point of this trial is overall survival, and accrual of 1020 patients with metastatic CRPC has been completed.

Thalidomide was originally developed in the 1960s for treatment of morning sickness and subsequently linked to teratogenic effects resulting in phocomelia and dysmelia. Whereas the exact mechanism of teratogenesis is unproven, the metabolites of thalidomide have been shown to inhibit angiogenesis through multiple potential mechanisms, including inhibition of proangiogenic signals such as VEGF, basic fibroblast growth factor (bFGF), interleukin-6, and tumor necrosis factor-\( \alpha \) (Bartlett et al., 2004; Franks et al., 2004). Preclinical studies suggest that thalidomide has T-cell costimulatory activity and immunomodulatory properties as well. Phase 1/2 studies with high doses of thalidomide as a single agent have yielded low response rates on the order of 20% for PSA declines (Figg et al., 2001; Franks et al., 2004). However, in a randomized phase 2 trial of weekly docetaxel and low-dose thalidomide versus docetaxel alone, PSA responses, time to disease progression, and overall survival were greater in the combination therapy group (Dahut et al., 2004). Although this trial was underpowered to detect a difference from the standard study arm, the clinical activity and manageable toxicity of this agent have led to the development of more potent thalidomide analogues for combination therapy, and these are currently undergoing clinical evaluation. In a recent phase 2 trial using a three-drug combination of docetaxel, thalidomide, and bevacizumab, PSA responses were seen in approximately 80% of patients (Ning et al., 2008). However, neurotoxicity was a significant side effect with this regimen.

Toxicities with thalidomide include deep venous thrombosis, sedation, neuropathy, constipation, and fatigue. Newer thalidomide analogues with immunomodulatory features have been developed that lack the neurotoxicity of thalidomide but retain many of the T-cell modulatory functions, antiangiogenic properties, and even direct pro-apoptotic functions (Bartlett et al., 2004). Lenalidomide and CC-4047 are second-generation compounds with much more potent tumor necrosis factor-\( \alpha \) inhibition than the parent compound, and clinical testing with these agents has begun. For example, several phase 1 and 2 studies have revealed PSA responses and partial radiologic responses with lenalidomide, both when used alone and when combined with ketoconazole or docetaxel (Dreicer et al., 2007; Moss et al., 2007; Garcia et al., 2008). Phase 3 trials using thalidomide or lenalidomide in CRPC have not yet been conducted.

There has been a recent interest in the evaluation of tyrosine kinase inhibitors (TKIs), agents that block angiogenic growth factor targets such as the VEGF and PDGF receptors. The drug...
sorafenib is an oral inhibitor of RAF kinase, VEGFR, and PDGFR, which has been approved for use in metastatic renal cell carcinoma. In phase 2 studies using sorafenib in men with metastatic CRPC, this agent was shown to prevent radiologic progression and cause regression of bone metastases in some patients, but without affecting PSA levels (Dahut et al., 2006; Aragon-Ching et al., 2008).

To conclusively evaluate the efficacy and safety of abiraterone, a pivotal multicenter placebo-controlled blinded randomized phase III trial (COU-AA-301) was conducted in men with docetaxel-pretreated ketoconazole-naive metastatic CRPC (de Bono et al., 2011). This trial randomized men (2:1) to receive either abiraterone 1000 mg daily plus prednisone 10 mg daily (n = 797) or placebo plus prednisone (n = 398). The trial met its primary endpoint, demonstrating a median overall survival of 14.8 months in the abiraterone arm and 10.9 months in the placebo arm (HR, 0.65; P < .0001). In addition, when compared to placebo, abiraterone improved overall survival (5.6 vs. 3.6 months; P < .0001), improved time to PSA progression (10.2 vs. 6.6 months; P < .0001), and produced more PSA responses (38% vs. 10%; P < .0001). Notably, the overall survival duration seen here (14.8 months) is similar to that of cabazitaxel/prednisone (15.1 months) in this second-line population with similar baseline characteristics, while the survival of men treated with prednisone alone was slightly inferior to that of mitoxantrone/prednisone in the TROPIC trial (10.9 vs. 12.7 months). Based on the results of the COU-AA-301 trial, the FDA approved abiraterone acetate (Zytiga, Janssen Biotech, Horsham, PA) in April 2010 for the treatment of patients with metastatic CRPC who have received prior docetaxel chemotherapy. The recommended dose of abiraterone is 1000 mg daily by mouth. A second randomized phase III trial (COU-AA-302) targeting men with docetaxel- and ketoconazole-naive CRPC has completed accrual of over 1000 patients. Given the comfort level and safety of using this and other hormonal agents in prostate cancer patients prior to chemotherapy, it is very likely that abiraterone will be used clinically in both the predocetaxel and postdocetaxel settings.

**CYP17 System**

It has recently been recognized that the androgen receptor and ligand-dependent androgen receptor signaling commonly remain active and upregulated in men with castrate levels of testosterone (i.e., <50 ng/dL) (Debes and Tindall, 2004). Standard hormonal therapies inhibit gonadal androgenesis but do not affect androgen synthesis from adrenal or other extragonadal sources that may account for 5% to 10% of total androgen production. It has also been suggested that CRPC itself may produce intratumoral androgen synthesis from adrenal or other extragonadal sources that may account for 5% to 10% of total androgen production. It has also been suggested that CRPC itself may produce intratumoral androgen synthesis from adrenal or other extragonadal sources that may account for 5% to 10% of total androgen production. It has also been suggested that CRPC itself may produce intratumoral androgen synthesis from adrenal or other extragonadal sources that may account for 5% to 10% of total androgen production. It has also been suggested that CRPC itself may produce intratumoral androgen synthesis from adrenal or other extragonadal sources that may account for 5% to 10% of total androgen production. It has also been suggested that CRPC itself may produce intratumoral androgen synthesis from adrenal or other extragonadal sources that may account for 5% to 10% of total androgen production.

**Androgen Receptor Modulation**

A slightly different androgen receptor (AR)-directed approach has focused on the development of second-generation antiandrogens that have advantages over the established agents in this class (bicalutamide, nilutamide, flutamide). One such drug is MDV3100, a potent oral nonsteroidal AR antagonist (Chen et al., 2009). Importantly, MDV3100 remains a potent antagonist of the AR in the castration-resistant state, even in the setting of overexpressed or constitutively activated AR (Watson et al., 2010). In addition, unlike other antiandrogens that may also function as partial AR agonists, MDV3100 does not exhibit any measurable agonistic activity and is able to prevent AR nuclear translocation with resultant tumoricidal (not cytostatic) activity (Tran et al., 2009). Notably, recent studies have demonstrated the emergence of ligand-independent AR splice variants in CRPC, some of which may also be inhibited by MDV3100.

A pivotal placebo-controlled double-blind phase III study (AFFIRM), randomizing 1170 patients with docetaxel-pretreated ketoconazole-naive CRPC to MDV3100 160 mg daily (n = 780) or placebo (n = 390), has now completed accrual. A second randomized phase III trial (PREVAIL) investigating the same treatment arms in men with chemotherapy-naive CRPC is currently underway. One advantage of MDV3100 over agents such as abiraterone is the lack of requirement for concurrent corticosteroid administration. However, the optimal sequencing of this agent, if approved, with immunotherapies and other emerging hormonal therapies will need to be defined through future clinical trials.

A phase I/II study of oral MDV3100 in men with chemotherapy-naive (n = 65) or taxane-pretreated (n = 75) metastatic CRPC has recently been published (Scher et al., 2010). In that trial, ≥50% PSA declines were seen in 62% and 51% of chemotherapy-naive and taxane-pretreated patients, respectively; objective tumor responses were observed in 36% and 12% of men, respectively. Radiographic progression-free survival was 6.7 months in the docetaxel-pretreated patients and >17 months in chemotherapy-naive patients. Side effects of MDV3100 are generally mild and include fatigue (27%) and nausea (9%). Rare seizures (3/140 patients) have also been reported, perhaps mediated by a direct effect of AR antagonism on central nervous system GABA-A receptors.

**Epigenetic Approaches**

Histone deacetylases (HDACs) are key regulators of histone acetylation status, which is critical for AR-mediated transcriptional activation of genes implicated in the regulation of cell survival, proliferation, differentiation, and apoptosis. Vorinostat is a potent oral HDAC inhibitor that has shown antitumor activity in prostate cancer cell lines and animal models (Welsbie et al., 2009). This agent has previously been approved for the treatment of cutaneous T-cell lymphoma. However, a phase 2 study of vorinostat in the second-line treatment of men with CRPC that had progressed on docetaxel did not show significant PSA or radiologic responses and was associated with a high frequency of grade 3/4 adverse events, which included fatigue, nausea, anorexia, vomiting, diarrhea, and weight loss (Bradley et al., 2008). A novel oral HDAC inhibitor, panobinostat (LBH589), is currently in phase 1 development as an adjunct to docetaxel in first-line CRPC (Rathkopf et al., 2008).

**Immunotherapy**

Entraining the immune system to overcome tumor-induced tolerance is the goal of nearly every cancer vaccine program, and
active immunotherapy with vaccination against tumor antigens has been pursued in many different cancer models. A variety of approaches have been employed, including dendritic cell-based therapies; novel adjuvants such as bacille Calmette-Guérin (BCG), granulocyte-monocyte colony-stimulating factor (GM-CSF), and viral carriers; single-antigen or whole cell vaccines; and genetically modified tumors. More recently, combination therapies using costimulatory molecules, CTLA-4 blockade, Toll-like receptor agonism, and intracellular viral or bacterial mediators have been developed (Pardoll, 1992; Blattman et al., 2002; Mapara and Sykes, 2004; Harzstedt and Small, 2009).

In prostate cancer, several immunologic strategies have been under clinical development. The most important of these include the sipuleucel-T (Provenge) autologous prostatic acid phosphatase (PAP)-loaded dendritic cell vaccine, the GVAX allogeneic recombinant whole cell vaccine, and CTLA-4 inhibitory approaches. Less successful strategies have included the Prostvac-VF recombinant pox viral PSA vaccine and the BLP25 MUC1 liposomal vaccine, among many others. Each of these vaccines is designed to stimulate the immune system to recognize a previously tolerance-inducing tumor in a cancer-specific way (Webster et al., 2005).

Sipuleucel-T

Sipuleucel-T (Provenge) is a vaccine derived from CD54+ dendritic cells, the major antigen-presenting cells, which are apheresed from individuals and processed with the recombinant fusion protein PAP and GM-CSF. PAP was chosen on the basis of its prostate cell membrane localization and the success of preclinical models using it to generate prostate-specific immune responses and autoimmune prostatitis. Modest activity was reported in phase 2 trials in patients with CRPC. In a randomized phase 2/3 trial comparing sipuleucel-T against placebo in 127 asymptomatic men with metastatic CRPC (PAP positive), the investigators reported no significant differences in time to disease and pain progression \((P = .052)\), which corresponded to the main study end point (Small et al., 2006). Patients randomized to placebo were crossed over to receive the active vaccine at the time of progression, whereas those initially randomized to receive the active vaccine were treated at their physician’s discretion at the time of progression. This postprogression management period was not part of the study and not prospectively controlled. Whereas the study as designed was negative, a 3-year update suggested a statistically significant improvement in survival for those randomly assigned to receive the active vaccine initially \((P = .01)\). It is highly probable that survival differences were due to postvaccine treatments. Post hoc analyses also suggested that the benefits of sipuleucel-T may be limited to the subgroup of men with tumor Gleason sums of 7 or lower. Although preparation and production of large-scale quantities of individually tailored vaccine can be challenging, this vaccine was well tolerated with minimal infusion-related fevers and rigors being the predominant adverse events (Small et al., 2006).

A second phase 2/3 trial that randomized 98 men with asymptomatic CRPC to either sipuleucel-T or placebo also failed to show a statistically significant improvement in time to progression (the primary end point) but, unlike the previous study, did not demonstrate an overall survival advantage at 3 years \((P = .33)\) (Dendreon, Inc., 2005). A post-hoc pooled analyses of these two trials \((n = 225)\) did show an overall survival advantage, with median survival being 18.9 months in the placebo group and 23.2 months in the sipuleucel-T group \((HR, 1.5; P = .01)\) (Dendreon, Inc., 2005). However, because overall survival was not the primary end point in either trial, the FDA did not grant approval of this treatment.

In an effort to satisfy FDA requirements, a pivotal multicenter double-blind placebo-controlled randomized phase III trial (IMPACT) was conducted in men with asymptomatic or minimally symptomatic metastatic CRPC (Kantoff et al., 2010), leading to the FDA-approval of this agent in April 2010. In this trial, 512 patients were randomized \((2:1)\) to sipuleucel-T or placebo and the study was powered to detect an overall survival advantage. Notably, this study did not enroll men with visceral metastases or those taking narcotics for cancer pain, and most patients \((85\%)\) were chemotherapy-naïve. Impressively, median overall survival was 25.8 months in the sipuleucel-T group versus 21.7 months in the placebo group \((HR, 0.78; P = .03)\), despite \(64\%\) of patients on placebo crossing over to receive salvage sipuleucel-T. In the subset of patients with prior chemotherapy exposure, overall survival trended in favor of sipuleucel-T, but this effect was not statistically significant. Therefore, although this immunotherapy is approved for all patients with asymptomatic or minimally symptomatic CRPC, it will likely have its largest impact in the prechemotherapy setting.

Similar to previous studies with sipuleucel-T, the IMPACT study found no difference in progression-free survival or PSA/radiographic response rates between the two treatment arms. Some investigators attribute the discordance between progression-free and overall survival to a possible class effect of immunotherapy agents, relating to their mechanism of action which is distinct from cytotoxic therapies. Problematic endpoints such as progression-free survival in CRPC (which may be confounded by bone scan flare or delayed-onset effects) may perhaps be better addressed by revised guidelines using outcomes that are tailored to immunologic agents (Hoos et al., 2010).

GVAX

Prostate GVAX is based on the demonstration in mouse melanoma models of improved tumor rejection when the irradiated tumor vaccine expressed the cytokine GM-CSF compared with other cytokine adjuvants (Dranoff et al., 1993; Dranoff, 2003). This form of immunotherapy uses inactivated allogeneic prostate cancer cell lines (PC3 and LNCaP) that have been modified through adenoviral transfer to secrete GM-CSF and irradiated to prevent further cell division (Ward and McNeel, 2007). The advantage with this approach is that the vaccine can be manufactured in large quantities and that multiple tumor antigens can be targeted simultaneously. However, because of the relative weakness of individual antigens, repeated intradermal dosing is necessary.

Two uncontrolled single-arm phase 2 studies in men with asymptomatic metastatic CRPC have shown antitumor effects of prostate GVAX, one demonstrating an overall survival of 26.2 months \((n = 34)\) and the other showing an overall survival ranging from 20.0 to 29.1 months \((n = 80)\) depending on dosing regimen (Small et al., 2007; Higano et al., 2008). In both studies the proportion of patients who generated an antibody response to one or both cell lines increased with the dose of vaccine given, and no dose-limiting or autoimmune toxicities were seen. The most common adverse events in both studies were injection-site erythema, fatigue, malaise, myalgias, and arthralgias.

Based on these promising findings, two large randomized phase 3 studies of GVAX immunotherapy (VITAL-1 and VITAL-2) were designed. VITAL-1 involved 626 men with asymptomatic chemotherapy-naïve CRPC and randomized them to GVAX or docetaxel/prednisone, with the primary end point being overall survival. VITAL-2 was planned initially to enroll 600 patients with...
symptomatic metastatic CRPC, randomizing them to docetaxel/ prednisone or docetaxel/GVAX. Both trials were terminated early because of data observed at the time of interim analyses, suggesting that the survival improvements initially hypothesized were unlikely to be observed if the trials were to be continued (Higano et al, 2009). Moreover, in the VITAL-2 study, mortality was higher in patients on the experimental arm receiving docetaxel/GVAX (Small et al, 2009).

### CTLA-4 Inhibition

Due to ongoing host immunologic pressures on evolving tumors, cancers have developed mechanisms to escape immune surveillance, effectively inducing a state of immune tolerance (Drake et al, 2006). One way to inhibit immunologic evasion by tumor cells is through blockade of the immune checkpoint molecule CTLA-4 (cytotoxic T lymphocyte-associated antigen-4), thus preventing the normal attenuation of antitumor T-cell responses (Hodi, 2007). In murine prostate cancer models, CTLA-4 inhibition has been shown to potentiate T-cell effects and induce tumor rejection.

Several clinical trials using the monoclonal anti-CTLA-4 antibody, ipilimumab, have been conducted in men with metastatic CRPC. These include phase I and II studies of ipilimumab monotherapy or in combination with radiation (Small et al, 2007), as well as a phase I study combining ipilimumab with GM-CSF (Fong et al, 2009). Encouragingly, ≥50% PSA reductions have been observed in about 20% of patients, and radiologic tumor responses were seen in about 5% of men, which is particularly noteworthy given that PSA and tumor responses were rarely reported in the immunotherapy trials with sipuleucel-T or other therapeutic vaccines. Common side effects of ipilimumab include fatigue (42%), nausea (35%), pruritus (24%), constipation (21%), and rash (19%). In addition, because CTLA-4 normally serves to attenuate autoimmune, immunologic toxicities resulting from an unchecked immune response may occur. Such immune-related adverse events include colitis (8%), adrenal insufficiency (2%), hepatitis (1%), and even hypophysitis (1%) (Dillard et al, 2010). Ipiilimumab is now in placebo-controlled phase 3 testing in the postdocetaxel setting in men with CRPC following a palliative and perhaps immune-stimulatory dose of radiation to a metastatic site, with the intent to demonstrate a survival advantage over radiation alone. A second predocetaxel placebo-controlled study is also underway.

### SUGGESTED READINGS


### Key Points: Novel Approaches

- Sipuleucel-T is the first therapeutic vaccine to be FDA-approved for the treatment of any cancer and is indicated for use in men with asymptomatic or minimally symptomatic metastatic CRPC.
- Abiraterone acetate is a novel androgen biosynthesis inhibitor that has gained FDA approval for the treatment of patients with metastatic CRPC who have previously received docetaxel chemotherapy.

### CONCLUSIONS

With more drugs at our fingertips for the treatment of metastatic CRPC than ever before, and an increasing number of novel therapeutic targets being discovered every day, we are still left with several challenges and unanswered questions. First, we must determine how these approved and experimental therapies should ideally be sequenced in individual patients with CRPC. For example, should sipuleucel-T routinely be given prior to chemotherapy or abiraterone with prednisone? Should abiraterone be reserved only for docetaxel-resistant patients? How should we treat cabazitaxel-refractory patients? Second, we will need to develop strategies to optimally combine these drugs in a rational manner, taking advantage of our understanding of negative feedback loops and alternative pathway activation to overcome resistance to monotherapies. Ultimately, only prospective trials incorporating biomarker-driven hypotheses will be able to address these key clinical questions. Thus the collection of tumor specimens or correlative samples may be essential in identifying novel targets or developing enrichment strategies for future study of these agents. Third, we must design smarter trials with the goal of quickly yet reliably identifying agents that do not hold promise, while enabling those that do to move swiftly to registrational studies. For example, in the clinical development of MDV3100 and cabazitaxel, pivotal phase III trials were designed directly following the initial phase I/II studies that demonstrated significant drug activity in men with CRPC. Finally, we must select our patients more carefully based on clinical or molecular characteristics, in order to identify the subset most likely to benefit from a particular therapy. For example, in men with significant pain, perhaps sipuleucel-T is not appropriate systemic therapy given the prolonged onset of action and lack of palliative benefits; additionally, immune-based biomarkers may shed light on which men may obtain a greater degree of benefit from immunotherapies. Several active agents are currently in phase III development, and some of these therapies are also likely to further expand our therapeutic arsenal for men with metastatic CRPC in the near future.

REFERENCES
The complete reference list is available online at www.expertconsult.com.
REFERENCES


