Advances in Prostate Cancer Chemotherapy: A New Era Begins

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ABSTRACT Prostate cancer continues to be the most common lethal malignancy diagnosed in American men and the second leading cause of male cancer mortality. Over 60 years ago, Huggins and Hodges discovered androgen deprivation as a first-line therapy for metastatic prostate cancer, which leads to remissions typically lasting 2 to 3 years, but in most men prostate cancer ultimately progresses to an androgen-independent state resulting in death due to widespread metastases. Multiple mechanisms of androgen independence have now been documented, including amplification of the androgen receptor as well as signal transduction pathways that bypass the androgen receptor completely. In 2004, two landmark studies demonstrated a survival advantage in androgen-independent prostate cancer patients utilizing docetaxel chemotherapy, setting a new standard of care for this disease. In addition, treatments with the bisphosphonate zoledronic acid and systemic radioisotopes have also been shown to have palliative benefits in this population. Building on these advances, several new traditional chemotherapeutic agents as well as new targeted therapies are under development. (CA Cancer J Clin 2005;55:300–318.) © American Cancer Society, Inc., 2005.

INTRODUCTION

Prostate cancer continues to be the most common lethal malignancy diagnosed in American men and the second leading cause of male cancer mortality. The American Cancer Society estimates that during 2005 about 232,090 new cases of prostate cancer will be diagnosed in the United States and 30,350 men will die of metastatic disease.1 About 1 man in 5 will be diagnosed with prostate cancer during his lifetime, and 1 man in 33 will die of this disease. As the population ages, these numbers are expected to increase. Over 60 years ago, Huggins and Hodges discovered androgen deprivation as a first-line therapy for metastatic prostate cancer.2,3 Hormonal therapy leads to remissions typically lasting 2 to 3 years, but in most men metastatic prostate cancer ultimately progresses to an androgen-independent state resulting in death due to widespread metastases.4-8 Bone metastases are accompanied by an osteoblastic reaction in the bone that is unmatched by any other type of cancer (Figure 1). Autopsy studies reveal that metastases to other organs are prevalent with common sites including lymph nodes, lung, adrenal glands, and liver.

MECHANISMS OF ANDROGEN RESISTANCE

During androgen–dependent progression, prostate cancer cells depend primarily on the androgen receptor for growth and survival.9-11 When testosterone enters the cell, it is converted to its active metabolite dihydrotestosterone (DHT) by the enzyme 5α reductase. DHT then binds androgen receptors in the cytoplasm and translocates into the nucleus, binding to the androgen–response elements within the DNA and thereby activating genes involved in cell growth.9 During androgen–independent progression, prostate cancer cells develop a variety of cellular pathways to survive and flourish in the androgen depleted environment (Figure 2).9,14 The first pathway has been referred to as the hypersensitive pathway. In this pathway, more androgen receptor (AR) is produced by the cell and may be activated despite reduced levels of...
dihydrotestosterone. This increased production of 
AR is likely the result of the prostate cancer cells 
developing more copies of the AR gene (gene 
amplification) as a result of mutation or through 
selective pressure of the androgen-depleted envi-
ronment, causing the cells with fewer androgen 
receptors to die off and the clonal expansion of 
cells with more AR. It is likely that hormone 
refractory prostate cancer is not “androgen inde-
pendent” in the classic sense, but rather “castration 
independent” and that the cancer is now able to 
use very low levels of androgen to grow.

The specificity of the AR can also be broad-
ened by mutations, creating a promiscuous receptor 
that can be activated by nonandrogenic steroid 
molecules normally present in the circulation. 
To be activated, the AR must be phosphorylated 
and this phosphorylation can be accomplished by 
other nonsteroid molecules through two separate 
pathways. In one pathway, termed the outlaw 
pathway, molecules such as deregulated growth 
factors and cytokines directly phosphorylate and 
activate the AR. In the second pathway, termed the 
bypass pathway, cell survival occurs indepen-
dent of AR activation. The best example of this 
pathway is the upregulation of the molecule 
BCL-2 by androgen-independent prostate cancer 
cells which protect them from apoptosis or pro-
grammed cell death when they are exposed to 
lack of testosterone.

Other postulated mechanisms of androgen in-
dependence include the involvement of cells that 
support the growth of the cancer cells. For ex-
ample, neuroendocrine cells may secrete neu-
ropeptides that induce the growth of androgen-
independent cancer cells. Alternatively, prostate 
cancer stem cells may be present in the prostate 
tumor, supporting the growth of androgen-
independent cells as the androgen dependent cells 
regress as a result of hormone therapy.
In 1993, Yagoda and Petrylak wrote a definitive review on the use of chemotherapy in patients with hormone refractory prostate cancer.\textsuperscript{15} Earlier reviews had reported objective responses in the form of complete and partial remissions in approximately 6.5\% of patients treated with anthracyclines, alkylating agents, antimetabolites, platinum, and topoisomerase inhibitors. In their review of 26 new trials published in the years 1987 to 1991, they found an overall response rate of 8.7\% (95\% confidence interval, 6.4\% to 9.0\%).
and concluded that hormone-refractory prostate cancer was unresponsive to cytotoxic agents. They further noted that documentation of response was complicated by a lack of established criteria to judge activity in a disease in which few patients had measurable soft tissue lesions. They noted that: “Chaos will continue to reign when the efficacy of one drug is reported to be 0 to 85%...when investigators continue to include stable disease findings within a so-called objective response category, thereby intimating that significant prostate cancer cell death has occurred.”

In 1997, Raghavan and colleagues reinforced the concept that the clinical utility of cytotoxic therapy in advanced prostate cancer was undefined and that this was partially attributable to the lack of established criteria for judging response in treatment of a disease that was largely evident by bone scan only.

Before the prostate-specific antigen (PSA) era, classic response rates could only be determined in the minority of patients with measurable disease (approximately 10% to 20%). Controversy existed as to whether these patients with soft tissue disease were representative of advanced prostate cancer patients in general who only had metastases to bone. In the early 1990s, PSA assays became widely available and response to agents in clinical trials began to be measured and reported in terms of PSA response. In Phase II trials, a decline in PSA by 50% appeared to correlate with increased survival. In 1999, a consensus conference suggested that a partial response in clinical trials be defined as a minimum a PSA decline of at least 50% confirmed by a second PSA value 4 or more weeks later in the absence of clinical or radiographic evidence of disease progression during this time period. The use of the PSA endpoint, although not validated in a Phase III trial as a surrogate for response or survival, has become the standard method to screen for activity in Phase II trials.

### CHEMOTHERAPY FOR HORMONE REFRACTORY PROSTATE CANCER: THE TAXANES

Starting in the 1990s, preclinical studies demonstrated that prostate cancer cells appeared to be especially sensitive to mitotic spindle inhibitors including vinblastine, paclitaxel, and docetaxel. Several Phase II studies were initiated based on the preclinical data. The most active agent preclinically and clinically was docetaxel, either alone or in combination with estramustine. Docetaxel, a semisynthetic taxane, likely has multiple mechanisms of antineoplastic activity. Microtubule stabilization, the most widely accepted mechanism of action, involves binding of docetaxel to β-tubulin, thus promoting polymerization. In normal cellular division, microtubules act as the cytoskeleton for the mitotic spindle. Under usual conditions, microtubules undergo polymerization in the presence of microtubule-associated proteins. Once bound by taxanes, microtubules cannot be disassembled. This static polymerization disrupts the normal mitotic process, usually arresting cells in the G2M phase of the cell cycle, ultimately leading to apoptosis. Estramustine is known to bind to microtubule associated proteins and one proposed mechanism for this agent is to act in concert with the taxanes to inhibit microtubule function.

A second proposed mechanism for the cytotoxicity of docetaxel is that it can counter the prosurvival effects of BCL-2 expression. It has been demonstrated that BCL-2 overexpression protects prostate cancer cells from apoptosis after androgen withdrawal, and that increased BCL-2 expression confers both chemo- and androgen-resistance. The BCL-2 gene is part of a class of oncogenes that contributes to neoplastic progression by inhibition of apoptotic cell death. Phosphorylation of BCL-2 protein leads to loss of BCL-2 antiapoptotic function. Docetaxel induced microtubule stabilization arrests cells in the G2M phase, inducing BCL-2 phosphorylation and forcing the continued activation of the caspase cascade, leading to increased apoptosis. Other studies have reported multiple other proapoptotic effects of docetaxel, including effects on BCL-xL, induction of p53, ability to overcome multidrug resistance and antiangiogenic properties.
tory prostate cancer. The pharmacokinetics of docetaxel are linear with dose and remain independent of schedule. A variety of weekly and every 3-week schedules have been evaluated. Results of these studies are summarized in Table 1. Response rates by PSA criteria ranged from 38% to 48%. Neutropenia was the principal toxicity, occurring in up to 70% of patients treated on an every 3-week schedule. Neutropenia was less common on the weekly schedule with similar response rates. Clearance of docetaxel is primarily via hepatic metabolism with increased toxicity associated with decreased hepatic metabolism. Other notable toxicities include fluid retention, rash, and peripheral neuropathy. Premedication with steroids is used to decrease the risk of fluid retention. Response rates as high as 70% were seen in the studies that investigated the combination of estramustine and docetaxel. Side effects were significant, with neutropenia in up to 70% of patients and thrombosis in up to 10%. Fatigue and hyperglycemia were also common. Based on these studies, Phase III trials of docetaxel and the combination of docetaxel and estramustine were designed.

PHASE III STUDIES OF DOCETAXEL IN HORMONE REFRACTORY PROSTATE CANCER

Two Phase III trials of docetaxel in men with hormone refractory disease were reported in 2004. Both demonstrated a survival advantage and docetaxel has become the new standard of care for first-line treatment in this setting. Both trials randomized docetaxel versus mitoxantrone, an agent that has been shown to improve quality of life but failed to demonstrate a survival benefit. The Southwest Oncology Group (SWOG) 9916 trial, docetaxel and estramustine compared

FIGURE 3 Docetaxel Has Multiple Mechanisms of Antineoplastic Activity. Microtubule stabilization involves binding of docetaxel to β-tubulin, thus promoting polymerization. In normal cellular division, microtubules act as the cytoskeleton for the mitotic spindle. Under usual conditions, microtubules undergo polymerization in the presence of microtubule-associated proteins. Once bound by taxanes, microtubules cannot be disassembled, disrupting the cell and leading to programmed cell death (apoptosis).

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with mitoxantrone and prednisone for advanced refractory prostate cancer, accrued 770 patients, randomizing them to mitoxantrone (12 mg/m²) and prednisone (5 mg twice daily) versus docetaxel 60 mg/m² on Day 2 and estramustine 280 mg/m² 3 times daily on Days 1 to 5, each on a 21-day cycle.44 The primary endpoint was overall survival and secondary endpoints included progression-free survival, objective response rate, and rate of PSA decline. Patient stratification was to type of progression (PSA only or evaluable disease), pain, and performance status. Overall survival was significantly higher in the docetaxel/estramustine (D/E) arm when compared with the mitoxantrone/prednisone (M/P) arm (17.5 months versus 15.6 months, \( P = 0.01 \)). Also statistically significant were PSA response rate (50% for D/E versus 27% for M/P) and objective response rate in patients with measurable soft tissue disease (17% versus 11%, respectively). Neutropenia (Grades 3 to 5) was similar for both groups (D/E: 16.1%, M/P: 12.5%) but the D/E group did have higher rates of neutropenic fever, cardiovascular events, nausea and vomiting, metabolic disturbances, and neurologic events. In all, 66 patients treated with D/E had Grade 3 or above nausea and vomiting (20%) compared with 17 in the M/P group (5.1%) \( (P < 0.001) \). There were 2 episodes of Grade 3 thrombosis and 11 episodes of Grade 4 thrombosis noted in the D/E group and none in the M/P group, but this difference was not statistically significant. There were 48 cardiovascular events of Grade 3 or greater in the D/E group (14.5%) and 22 in the M/P group (6.7%) \( (P = 0.001) \). The authors’ conclusion was that docetaxel/estramustine should be considered a standard of care for men with advanced prostate cancer secondary to a 20% increase in overall survival, an increase in progression-free survival, and higher PSA and objective response rates (Figure 4A).36

The second multicenter trial, TAX 327, docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer, compared mitoxantrone 12 mg/m² every 3 weeks with prednisone 5 mg twice daily to either

| Trial                        | Docetaxel             | Combination                                      | Patients with ≥ 50% Decline in Prostate-Specific Antigen Level (%) | Patients with a Soft Tissue Response (%) | Overall Survival |
|------------------------------|-----------------------|--------------------------------------------------|-----------------------------------------------------------------|----------------------------------------|------------------|
| Picus and Schultz36 (1999)   | 75 mg/m² every 21 days | Not available                                    | 46                                                              | 24                                      | 27 months        |
| Friedland, et al.37 (1999)   | 75 mg/m² every 21 days | Not available                                    | 38                                                              | 29                                      | 67% at 15 months |
| Berry, et al.38 (2001)       | 36 mg/m² weekly for 6 of 8 weeks | Not available                                    | 41                                                              | 33 (complete response: 17)             | 9.4 months       |
| Beer, et al.39 (2001)        | 36 mg/m² weekly for 6 of 8 weeks | Not available                                    | 46                                                              | 40                                      | 39 weeks         |
| Gravis, et al.40 (2003)      | 35 mg/m² weekly for 6 of 8 weeks | Not available                                    | 48                                                              | 28 (stable disease)                    | 20 months        |
| Petrylak, et al.41 (2000)    | 70 mg/m² every 21 days | Estramustine 280 mg three times a day for 1–5     | 68                                                              | 55                                      | 77% at 1 year     |
| Sinibaldi, et al.42 (2002)   | 70 mg/m² every 21 days | Estramustine 280 mg every 6 hours × 5 doses; coumadin 2 mg daily | 45                                                              | 20                                      | 13.5 months      |
| Savarese, et al.43 (2001), CALGB 9780 | 70 mg/m² every 21 days | Estramustine 10 mg/kg/day in three daily doses for days 1–5; hydrocortisone 30 mg every morning and 10 mg every afternoon daily | 68                                                              | 50 (partial response: 38; complete response: 13) | 20 months        |
| Petrylak, et al.44 (2004), SWOG/Intergroup (Phase III) | 60 mg/m² every 21 days | Estramustine 280 mg three times a day for 1–5     | 50                                                              | 17                                      | 18 months        |
| Tannock, et al.45 (2004), TAX-327 (Phase III) | 75 mg/m² every 21 days | Prednisone 5 mg twice daily                       | 45                                                              | 12                                      | 18.9 months      |
|                             | 30 mg/m² weekly for 5 of 6 weeks | Prednisone 5 mg twice daily                       | 48                                                              | 8                                       | 17.3 months      |

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Table 1: Examples of Trials of Single-agent Docetaxel and Combined Chemotherapy Regimens for Androgen-independent Prostate Cancer

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FIGURE 4  Overall Survival Rates. (A) Southwest Oncology Group 9916 Kaplan-Meier estimates of overall survival among men with androgen-independent prostate cancer treated with mitoxantrone and prednisone or docetaxel and estramustine. (B) TAX 327 Kaplan–Meier estimates of the probability of overall survival in the patients treated with docetaxel plus prednisone in two different schedules versus mitoxantrone and prednisone. Reprinted with permission from Petrylak, et al.44
docetaxel 30 mg/m² weekly for 5 of 6 weeks or docetaxel 75 mg/m² every 3 weeks and prednisone 5 mg twice daily. In all, 1,006 patients were enrolled and were stratified by pain level or performance status. Weekly docetaxel demonstrated a trend toward improved survival but failed to reach statistical significance (median survival: 17.3 months, $P = 0.3$). The every 3-week schedule of docetaxel showed an advantage in median survival when compared with mitoxantrone (18.9 versus 16.4 months, $P = 0.009$; Figure 4B). Furthermore, the every 3-week docetaxel regimen had a significant improvement in pain control, PSA response rate, tumor response rate, and quality of life. Toxicity in the every 3-week docetaxel schedule was a 32% rate of Grade 3 to 4 neutropenia, and patients treated with this regimen suffered more adverse events than the mitoxantrone group (26% versus 20%). The weekly docetaxel group experienced an adverse event rate of 29%, which was higher than the 3-week schedule despite Phase II data suggesting similar antitumor activity with a concomitant reduction in neutropenia. Based on these data, the US Food and Drug Administration (FDA) approved the regimen of docetaxel 75 mg/m² every 3 weeks in combination with prednisone 5 mg orally twice per day for the treatment of advanced prostate cancer.

THE STATUS OF ESTRAMUSTINE IN 2005

Based on preclinical data, estramustine has been considered to be an important component of taxane-based regimens for prostate cancer. Several Phase II trials demonstrated a superior response to estramustine plus docetaxel versus docetaxel alone as measured by both PSA response and objective soft-tissue response (Table 1). Although the patient populations enrolled on SWOG 9916 and TAX 327 are not exactly the same, general comparisons can be made about the efficacy and toxicities of the regimens. Estramustine and docetaxel in SWOG 9916 had similar efficacy to docetaxel and prednisone in TAX 327. Toxicities between the trials were markedly different. The main side effects of estramustine have been well documented; nausea, vomiting, and thrombosis secondary to the high estrogen content of estramustine are common. In SWOG 9916, 20% of patients suffered Grade 3 or greater nausea and vomiting on the D/E arm. In TAX 327, there was no nausea and vomiting of Grade 3 or greater reported. Similarly, in SWOG 9916, 15% of patients suffered Grade 3 or higher cardiovascular or clotting adverse events, but there were none of these events in the patients treated with docetaxel in TAX 327. These data suggest that estramustine was the factor causing the cardiovascular and gastrointestinal toxicity and did not add significantly to the efficacy of docetaxel. Thus, it appears that the use of estramustine with docetaxel in advanced prostate cancer is not necessary and may be detrimental.

PALLIATIVE CHEMOTHERAPY

While docetaxel has become the standard first-line therapy for hormone refractory prostate cancer, mitoxantrone plus prednisone remains a useful regimen in this disease. This combination has significant palliative activity in patients experiencing pain from advanced prostate cancer. Tannock, et al. demonstrated that the percentage of patients achieving pain relief or having declines in analgesic consumption was substantially greater in those receiving mitoxantrone compared with those treated with prednisone alone. This observation was confirmed by another Phase III trial conducted by Kantoff and colleagues of the Cancer and Leukemia Group B. These studies demonstrated that approximately one-third of patients receiving mitoxantrone chemotherapy demonstrated significant pain relief for an average of 8 months. Mitoxantrone is FDA-approved and is given as 12 to 14 mg/m² intravenously every 3 weeks with 10 mg of prednisone or the equivalent hydrocortisone dose given orally daily. Currently, it is unclear how the effectiveness of mitoxantrone is affected when it is used as a second-line agent after docetaxel compared with the results seen in first-line studies.
LOCAL AND SYSTEMIC RADIATION FOR PALLIATION

Radiation therapy has long been known to provide effective palliation for patients with advanced prostate cancer. For patients with single sites of osseous pain or with limited obstructing masses or lymph nodes, external-beam radiation has been demonstrated to be very effective in controlling progressive disease. For patients with multiple sites of bone involvement and pain, systemic radioisotopes administered intravenously have significant therapeutic effects. The two most commonly used radioisotopes are strontium-89 and samarium-153. These isotopes have significant differences in physical half-life and particle energy, which result in differing side effect profiles. In a Phase III trial, Porter and colleagues demonstrated that strontium was more effective than placebo in the control of painful metastases when given as an adjunct to local radiation. 50 Although no significant differences in survival or in relief of pain at the index site were noted, intake of analgesics over time demonstrated a significant reduction in the arm treated with strontium-89 and progression of pain (as measured by sites of new pain or the requirement for radiotherapy) and quality of life showed statistically significant differences in favor of strontium-89. These data demonstrate the effectiveness of strontium. Unfortunately, strontium has a long half-life of almost 60 days in bone and can lead to decreased blood counts, especially affecting platelets. This makes strontium difficult to give in a setting where patients are also eligible for chemotherapy.

Samarium, by contrast, can be given with minimal marrow toxicity. Sartor and colleagues conducted a Phase III trial using samarium and demonstrated that a 1 mCi/kg dose was more effective than placebo in controlling pain secondary to bone metastases. 51 Mild, transient bone marrow suppression was the only adverse event associated with samarium administration. The mean nadir white blood cell (WBC) and platelet counts at 3 to 4 weeks after treatment were 3,800/μL and 127,000/μL, respectively. Counts recovered to baseline after approximately 8 weeks. No Grade 4 decreases in either platelets or white bloods cells were documented. These findings demonstrate that samarium is both safe and effective for the palliation of painful bone metastases in patients with hormone-refractory prostate cancer and suggest that it may be considered for integration with chemotherapy regimens.

The combination of radioisotopes with chemotherapy may lead to increased effectiveness when compared with either type of agent alone in the treatment of bone metastases. 52,53 NCI-3410 is a Phase III trial to compare the effectiveness of chemotherapy with or without strontium-89 in treating patients who have prostate cancer that has spread to the bone. 54 Patients receive one of two chemotherapy regimens for 6 weeks. Treatment may be repeated every 8 weeks for up to two courses. Patients are then randomly assigned to one of two groups. Patients in Group 1 receive a 24-hour continuous infusion of doxorubicin once a week for 6 weeks plus an infusion of strontium-89 at the beginning of chemotherapy. Patients in Group 2 receive doxorubicin alone. Enrollment to this trial is ongoing.

BISPHOSPHONATE THERAPY

The production of an osteoblastic metastasis in prostate cancer is the result of a complex interaction between prostate tumor cells, osteoclasts, and osteoblasts. Before the osteoblasts are activated, osteoclasts first break down the bone and initiate bone remodeling. Bisphosphonates are analogs of pyrophosphate, a normal constituent of the bone matrix. These agents bind to bone surfaces (hydroxyapatite crystals), making them less available to osteoclast resorption. Additionally, bisphosphonates inhibit recruitment of osteoclast precursors, prevent the migration of osteoclasts toward bone, and inhibit the production of prostaglandin-E2, interleukin-1, and proteolytic enzymes. In a placebo-controlled randomized clinical trial, zoledronic acid 4 mg via a 15-minute infusion every 3 weeks for 15 months reduced the incidence of skeletal-related events (SREs) in men with hormone-refractory metastatic prostate cancer. 55,56 Among 122 patients who completed a total of 24 months on study, fewer patients in the 4-mg zoledronic acid group than in the placebo group had at least one SRE
The annual incidence of SREs was 0.77 for the 4-mg zoledronic acid group versus 1.47 for the placebo group ($P = 0.005$). The median time to the first SRE was 488 days for the 4-mg zoledronic acid group versus 321 days for the placebo group ($P = 0.009$). Compared with placebo, 4 mg of zoledronic acid reduced the ongoing risk of SREs by 36% (risk ratio = 0.64, 95% CI = 0.485 to 0.845; $P = 0.002$). The investigators concluded that long-term treatment with 4 mg of zoledronic acid is safe and provides sustained clinical benefits for men with metastatic hormone-refractory prostate cancer. Based on these data, this agent has been approved for the treatment of men with bone metastases who have failed hormonal therapy. Although generally considered safe, serum creatinine must be monitored and recent evidence has linked bisphosphonate use with osteonecrosis of the mandible in a minority of patients. It may be prudent for patients started on zoledronic acid to have a dental exam before initiating therapy and patients should be regularly asked about their dental health.

**A SUGGESTED PARADIGM OF CURRENT PRACTICE GUIDELINES**

Patients with androgen-independent prostate cancer fall into three broad categories: biochemical-only disease, asymptomatic disease with positive scans, and symptomatic disease (Figure 5). The variability of the natural history of the disease in these categories raises several major questions: who should be treated, when should they be treated, and how should they be treated? A patient with a rising PSA despite hormonal therapy should undergo staging with a physical exam, bone scan, and computed tomography scan of the abdomen/pelvis. If they have biochemical-only disease, a decision must be made as to whether to treat these patients or to follow them. This first decision can be based, at least partially, on the speed at which the PSA is doubling (PSADT) as well as other factors such as patient age and overall health. Patients with slow doubling times ($\geq 8$ to 12 months) are suitable for monitoring. Bone scans can be performed every six months or on a yearly basis. Patients with rapid PSADT ($\leq 6$ to 8 months) should be considered for clinical trials.

One common presentation is the patient who is asymptomatic with a rising PSA and a positive bone scan. These patients should be considered for a clinical trial. Patients in this category are eligible to receive docetaxel; however, there are no set criteria as to when to treat these patients. Many physicians and patients choose to wait to start docetaxel until symptoms have developed. Patients with visceral disease with or without bone disease are more likely to be started on cytotoxic chemotherapy while still asymptomatic than are those with bone-only disease. The utility of starting chemotherapy in asymptomatic patients has not been proven. Few would now question that patients with symptomatic androgen-independent prostate cancer (AIPC) should be offered chemotherapy as a treatment option. Docetaxel is considered to be the first-line agent of choice. Mitoxantrone, however, has a proven palliative benefit in patients with symptoms and can be considered as a first-line agent in patients who may not tolerate docetaxel. Of note, mitoxantrone is approved for use in patients with symptomatic prostate cancer and has no proven benefit in asymptomatic patients. Because neither of these agents is curative, clinical trials for these patients should always be considered. Symptomatic patients with sites of pain secondary to bone lesions should be considered for palliative radiation therapy. Zoledronic acid is approved for use in patients with bone metastases who have failed hormonal therapy. The question of when to initiate therapy with this agent has not yet been fully answered. Symptomatic patients appear to have some benefit with improvement in pain, but the real utility may be in the prevention or delay of skeletal related events. Systemic radioisotopes have proven palliative benefit in patients with multiple sites of bone disease but should not be used prophylactically.

Patients with a known history of prostate cancer who present with back pain are best treated for impending spinal cord compression as a medical emergency until proven otherwise. Pain is the presenting symptom in 90% of spinal cord compression patients and usually precedes
FIGURE 5  A Suggested Paradigm of Current Practice Guidelines for Androgen-Independent Prostate Cancer. Patients with androgen-independent prostate cancer fall into three broad categories: biochemical-only disease (DZ), asymptomatic disease with positive scans, and symptomatic disease. If patients have biochemical only disease, a decision when to treat them can be based, at least partially, on the speed at which the PSA is doubling (PSADT) as well as other factors such as patient age and overall health. Asymptomatic patients with a rising PSA and a positive bone scan should be considered for a clinical trial. Patients in this category are eligible to receive docetaxel; however, there are no set criteria as to when to treat these patients. Patients with symptomatic androgen-independent prostate cancer (AIPC) should be offered chemotherapy as a treatment option. Docetaxel is considered to be the first-line agent of choice. Mitoxantrone has a proven palliative benefit in patients with symptoms and can be considered as a first-line agent in patients who may not tolerate docetaxel. Because neither of these agents is curative, clinical trials for these patients should always be considered. Symptomatic patients with sites of pain secondary to bone lesions should be considered for palliative local or systemic radiation therapy. Patients with potential spinal cord compression should be treated with steroids and then evaluated for therapy with radiation or surgery. Zoledronic acid is approved for use in patients with bone metastases who have failed hormonal therapy.
neurologic deficits. Patients should be treated with dexamethasone and then evaluated with magnetic resonance imaging (MRI) or computed tomography myelogram. MRI is currently the most sensitive method for evaluating spinal cord compression. Patients with metastases to the spine with or without spinal cord compression can be treated with external beam radiation, although the optimal dose for treatment has not been defined. Benefit can be demonstrated for patients even if neurologic changes have already occurred. Alternatively, patients with spinal cord compression can be treated with surgery or a combination of surgery/radiation. It is unclear whether radiation or surgery is better therapy for spinal cord compression; however, at least one randomized study demonstrated that surgery plus radiation was better than radiation alone in allowing patients to remain ambulatory and continent. It is appropriate to consult both the radiation oncologist and neurosurgeon for patients with spinal cord compression to determine the best therapy for a particular patient.

INVESTIGATIONAL AGENTS

Several novel agents are under investigation to treat AIPC. They can now be separated into broad classes, including classic cytotoxic agents, vaccines, radiolabeled monoclonal antibodies, and targeted agents. Agents reviewed in this section provide examples of many of the promising drugs in these categories.

Cytotoxic Agents

Satraplatin is a member of the platinum-based class of chemotherapy drugs that can be given orally. In a preliminary randomized trial conducted in previously untreated AIPC patients in Europe, the combination of satraplatin and prednisone had superior activity as measured by PSA decline and progression-free survival compared with prednisone alone. A current trial is designed to compare the combination of satraplatin and prednisone versus prednisone alone as second-line chemotherapy in patients with AIPC. The epothilones are a novel class of microtubule inhibitors that have shown both preclinical and clinical activity in AIPC. In chemotherapy naïve patients, the combination of estramustine and the epothilone B analog BMS-247550 (ixabepilone) resulted in a decline in PSA of greater than 50% from pretreatment values in 11 of 12 patients (92%). In a follow-up study, 92 patients were randomized to receive ixabepilone 35 mg/m² by intravenous infusion every 3 weeks with or without estramustine (EMP) 280 mg orally three times daily on Days 1 to 5. PSA declines of ≥50% from baseline were observed in 21 of 44 patients on the ixabepilone arm, and 31 of 45 patients on the ixabepilone + EMP arm. In patients with measurable disease, partial responses were observed in 8 of 25 patients on the ixabepilone arm and 11 of 23 on the combination arm. Toxicities of Grade 3 or greater included neutropenia in approximately 25% and neuropathy in approximately 10% of patients. Ixabepilone appears to be well-tolerated and have activity in patients with AIPC, with or without EMP. Several trials are underway to further investigate the activity of this class of agents, including a multi-institutional randomized Phase II trial to determine the efficacy of the epothilone B versus mitoxantrone/prednisone in patients who have progressed on taxane-based therapy.

Vaccines

Many scientists and physicians consider the development of cancer to be a failure of the immune system. The body is very good at recognizing abnormal cells and antigens but cancer cells are able to escape this immune surveillance. Several vaccines are under development and in clinical trials that attempt to increase the effectiveness of the immune system, either by increasing the immunogenicity of the tumor cells or increasing the effectiveness of the immune system effector cells themselves.

APC8015 (Provenge) is an investigational therapeutic vaccine that uses autologous antigen presenting cells (APCs) loaded with a recombinant fusion protein of prostatic acid phosphatase linked to a molecule that specifically targets a
receptor expressed on the surface of human APCs. This type of immunotherapy approach is based on helping the body develop an immune response to prostate cancer cells. Early trial results have demonstrated activity and possible increased survival in patients with androgen-independent prostate cancer. A randomized Phase III trial studying the effectiveness of APC8015 in delaying disease progression and disease-related pain in patients who have asymptomatic AIPC metastatic prostate cancer is underway.

Onyxvax-P is a cell vaccine made from a combination of three irradiated allogeneic cell lines. Each cell line expresses antigens representative of a different stage of prostate cancer (primary, lymph node metastasis, and bone metastasis). Onyxvax-P therefore contains a broad range of both known cancer-specific antigens, as well as many targets that have yet to be identified. By presenting a broad range of antigens to the immune system, the risk of the cancer becoming resistant to the therapy is reduced. Data from a Phase II trial suggests that Onyxvax-P therapy results in an increased progression-free survival in AIPC patients. A Phase III trial in patients with AIPC is under development.

Cancer patients have defective macrophage function and preclinical data demonstrate that peripheral blood monocytes and macrophages can be utilized following stimulation with GM-CSF (granulocyte macrophage–colony-stimulating factor) to induce an immune cytotoxic effect against malignant cells mediated in part through dendritic cell stimulation. Dendritic cells are antigen presenting cells that play a major role in induction of primary and secondary T-cell immune responses against cancer. In addition, GM-CSF is a significant mediator of proliferation, maturation, and migration of dendritic cells themselves. GVAX is a GM-CSF gene-modified autologous tumor vaccine in which cells from the patient’s tumor are transduced in vitro with an engineered adenovirus containing the GM-CSF gene. A Phase III trial comparing GVAX versus docetaxel and prednisone in patients with metastatic AIPC is underway.

Viral gene delivery into dendritic cells can be done using poxviruses, herpes simplex, adenovirus, retrovirus, lentivirus, and adeno-associated virus. Recombinant attenuated poxviruses (vaccinia, fowlpox, and canarypox) are notable for their ability to accept and express multiple transgenes and can be efficiently transfected into most mammalian cells without the risk of insertional mutagenesis because they do not integrate into the genome. The Eastern Cooperative Oncology Group conducted a Phase II clinical trial (E7897) to evaluate the prime/boost vaccine strategy using vaccinia virus and fowlpox virus expressing PSA in patients with biochemical progression after local therapy for prostate cancer. In all, 64 patients were randomly assigned to receive four vaccinations with fowlpox-PSA (rf-PSA), three rf-PSA vaccines followed by one vaccinia-PSA (rv-PSA) vaccine, or one rv-PSA vaccine followed by three rf-PSA vaccines. Of the eligible patients, 45.3% of men remained free of PSA progression at 19.1 months and 78.1% demonstrated clinical progression-free survival. TRICOM is a modification of poxvectors to boost their effectiveness in eliciting an immune response by including the insertion of three genes encoding molecules important for providing the second signal for T-cell activation through different but collaborative pathways: CD80 (B7.1), which interacts with CD28; CD54 (intercellular adhesion molecule-1), which interacts with the CD11a/CD18 (leukocyte function-associated antigen-1/β2-integrin) complex; and CD58 (leukocyte function-associated antigen-3), which interacts with CD2. A Phase II randomized study of vaccinia-PSA-TRICOM vaccine, Fowlpox-PSA-TRICOM vaccine, and sargramostim (GM-CSF) versus empty vector control in patients with metastatic AIPC (sponsored by Therion) is testing this strategy.

Radiolabeled Monoclonal Antibodies

Radiolabeled monoclonal antibodies can locate tumor cells by recognizing an antigen on their cell surface and either kill them directly or deliver a radioactive agent to kill them without harming normal cells. Although non–Hodgkin lymphoma is currently the only indication in which radioimmunotherapy has been proven to be effective, clinical trials are showing usefulness in other forms of lymphomas.
hematologic neoplasms, and solid tumors. Radiolabeled antibodies based on the prostate-specific membrane antigen (PSMA) have been under development for several years. PSMA is a transmembrane glycoprotein that is highly expressed by virtually all prostate cancers and is also expressed on the tumor vascular endothelium of virtually all solid carcinomas but not on normal vascular endothelium. The antibody J591 recognizes the extracellular domain of PSMA and has been studied for efficacy and toxicity conjugated to multiple different radiopharmaceuticals, including $^{90}$Ytrium, $^{131}$Iodine, and $^{177}$Lutetium. Early studies have been promising and currently the most promising agent appears to be $^{177}$Lutetium, which is being stud-
ied in a Phase II clinical trial in patients with AIPC.54,80

**Targeted Therapies**

Targeted therapy now generally refers to inhibiting specific signal-transduction molecules important in cell growth. Multiple signal transduction pathways that are important in the growth and death of cells have been identified and a review of all of the therapeutic targets is almost impossible.82-84 In addition, although in the traditional sense these are targets on the prostate cancer cells, several agents now target the endothelial cell as well as other cells in the tumor microenvironment such as the osteoblast (Figure 6).

Cytokines and growth factors that stimulate prostate cancer cells or supporting stromal cells can be inhibited using several different strategies (Figure 6). The prototypical cytokine to describe these strategies is the inhibition of vascular endothelial growth factor (VEGF). VEGF is the primary cytokine released by tumor cells to stimulate new blood growth and several different strategies are under development to block its function.85-87 VEGF binding to its receptor can be blocked with an antibody that binds to VEGF itself such as bevacizumab.86 Alternatively, an antibody can bind to the VEGF receptor itself and block function.87

The activation of VEGF receptors can also be blocked with a small molecule inhibitor. Growth factor receptors function through the activation of tyrosine kinase. Tyrosine kinases can be blocked at the level of the receptor or by interrupting its downstream signaling (Figure 6). PTK787 is an oral aminophthalazine, which acts as a tyrosine kinase inhibitor that binds to and inhibits the function of all known VEGF receptors.88 The novel biaryl urea BAY 43-9006 is an oral potent inhibitor that inhibits several receptor tyrosine kinases involved in neovascularization and tumor progression both by binding to the receptor and by inhibiting the downstream Ras/Raf signaling.89,90

The growth of new blood vessels can also be blocked by inhibiting integrin function. Tumor-related blood vessels sprout into the extracellular matrix (ECM) in a process that is dependent on the ability of the proliferating endothelial cells to interact with diverse glycoprotein components of this ECM. This interaction is mediated by the integrins αvβ3 and αvβ5, which bind to a variety of ECM molecules containing the amino acid sequence Arg-Gly-Asp (RGD) including vitronectin.91 EMD 121974 (Cilengitide) is the inner salt of a cyclized pentapeptide that is a potent and selective integrin antagonist and Vitaxin is an antibody targeting this interaction.92,93

Another cell important to prostate cancer growth in bone is the osteoblast. Endothelin -1 (ET-1), a potent vasoconstrictor, has been demonstrated to be an important mediator of osteoblast growth and function.94,95 Atrasentan is a small molecule that blocks the binding of ET-1 to the endothelin receptor A subtype (ET_A), thereby blocking the function of osteoblasts. In Phase II and III clinical trials of atrasentan, the agent appears to have activity in delaying disease progression in men with AIPC. The data of recently finished Phase III studies is maturing and one Phase III trial is currently accruing patients.

Several agents that utilize the paradigm outlined above for VEGF that directly target tumor cells themselves are in clinical trials for AIPC (Figure 6). These include inhibitors of platelet-derived growth factor receptor (PDGFR), epidermal growth factor receptor (EGFR), and insulin-like growth factor (IGF).96-102 Several intracellular cell signaling pathways have been targeted for therapeutic intervention in AIPC, including the BCL-2 family, the MAP kinase pathway, the raf proteins, and mammalian target of rapamycin (mTOR).103,104 mTOR plays a critical role in cell survival and lies downstream of PTEN/Akt and upstream of HIF-1α. PTEN is commonly lost in advanced prostate cancer and the deregulation of this pathway results in the upregulation of HIF-1α.105 HIF-1α in turn upregulates multiple pathways involved in cell survival, including genes involved in anaerobic glycolysis, cell motility, dissolution of the ECM, and production of angiogenesis factors.106 Derivatives of rapamycin have the potential to play a critical role in targeting this pathway. Several rapamycin analogs are in clinical trial in AIPC, including CCI-779 and RAD001.107
Another treatment that is actively being explored in the treatment of AIPC is the inhibition of histone deacetylase (HDAC) by the small molecule inhibitor suberoylanilide hydroxamic acid (SAHA).\textsuperscript{108} The action of HDACs on nucleosomal histones leads to tight coiling of chromatin and silencing of expression of various genes, including those implicated in the regulation of cell survival, proliferation, differentiation, and apoptosis.\textsuperscript{108-110} Although previous inhibitors of HDAC have met with limited success, aberrant HDAC activity has been implicated in a variety of cancers and development of HDAC inhibitors is a rational approach to the design of targeted therapeutics against AIPC.\textsuperscript{110}

\section*{CONCLUSION}

The traditional paradigm for prostate cancer treatment, as well as all cancer treatment, has been to target the tumor cell directly with cytotoxic single agent or combination chemotherapy. For the first time, it has been demonstrated that chemotherapy increases survival in patients with hormone refractory prostate cancer and we can now set recommendations for care utilizing currently available agents including docetaxel, mitoxantrone, and zolendronic acid (Figure 5). These current chemotherapy regimens debulk the tumor but cannot eradicate late-stage disease. The paradigm of targeting the tumor cell is now being expanding beyond classic chemotherapy not only with the identification of new chemotherapy agents and new targeted signal transduction agents, but with the recognition that cancer cells exist in complex microenvironments that offer therapeutic targets, including the immune system and the supporting stromal cells (Figure 7).\textsuperscript{111-113} The treatment of bone metastases in advanced prostate cancer provided the prototypic example of this approach in cancer therapy. Effective chemotherapy is now being combined with agents that inhibit components of the prostate cancer–bone microenvironment. Bisphosphonates inhibit osteoclast action and atrasentan inhibits osteoblast action. Vaccines are targeting the immune system and several agents can now target endothelial cell proliferation. The radioisotopes
target the entire cancer–bone microenvironment.

Cancer should be considered a multicellular “organ” involving both heterogeneous cancer cells as well as multiple normal cell types interacting with the tumor cells and, therefore, must be treated as such. Treating the tumor cell represents only one avenue for attacking the disease of advanced prostate cancer. It is imperative that we expand the therapeutic target options to include the cancer as “organ” and not just the cancer as “tumor cell.” At the level of the tumor cell, cancer has developed multiple methods centering on genetic mutation to promote self-survival and perpetuation. The pliability of cancer cells to mutate into several different phenotypes in an attempt to find one that will survive and colonize at the metastatic site is a tremendous hurdle to overcome in the pursuit of better cancer therapies. The future of cancer therapy resides in the combining of classic chemotherapy with the ability of new agents to focus on targeted signal transduction pathways and to exploit relationships of the cancer cell with the host environment.

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