Current Standard and Investigational Approaches to the Management of Hormone-Refractory Prostate Cancer

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Prostate cancer is a common cause of death in men and remains incurable in the metastatic setting. In 2004, 2 landmark trials using docetaxel-based chemotherapy, TAX 327 and SWOG 99-16, showed a survival benefit for the first time in metastatic, hormone-refractory prostate cancer. Current research suggests that several distinct mechanisms of androgen-refractory disease may converge in patients with disease progression on androgen deprivation therapy. These findings have identified several potential targets for therapeutic intervention. Current standard and investigational treatment options for this disease are discussed, including chemotherapy and rapidly evolving therapies in phase II/III trials involving antiangiogenic therapies, signal transduction inhibitors, immunomodulatory agents, and nuclear receptor targets. In light of a growing array of treatment options and an increasingly chronic natural history, this review supports a multidisciplinary care approach to these patients, including medical oncologists, urologists, and radiation oncologists, to optimize survival and quality of life.
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As of 2006, prostate cancer remains the third most common cause of cancer death in men, after lung and colorectal cancer.[1] Despite its effectiveness over the past 60 years, androgen ablative therapies are unable to cure this disease in the vast majority of patients with gross metastatic disease. For the majority of patients, disease progression will occur despite ongoing

systemic androgen deprivation, resulting in a stage commonly referred to as hormone-refractory prostate cancer (HRPC). In 2004, 2 landmark trials, TAX 327 and Southwest Oncology Group (SWOG) 99-16, showed for the first time a survival benefit in men with metastatic HRPC. Specifically, docetaxel-based chemotherapy demonstrated a median improvement in survival of 2.5 months as compared with mitoxantrone and prednisone in metastatic HRPC.[2,3] Ongoing studies are investigating the role of docetaxel plus prednisone in earlier-stage prostate cancer, and combinations with novel agents are building off this platform. New advances in the management of advanced prostate cancer, focusing on the distinct mechanisms of androgen-refractory disease and other potential targets, may further lengthen survival of patients with this chronic disease.

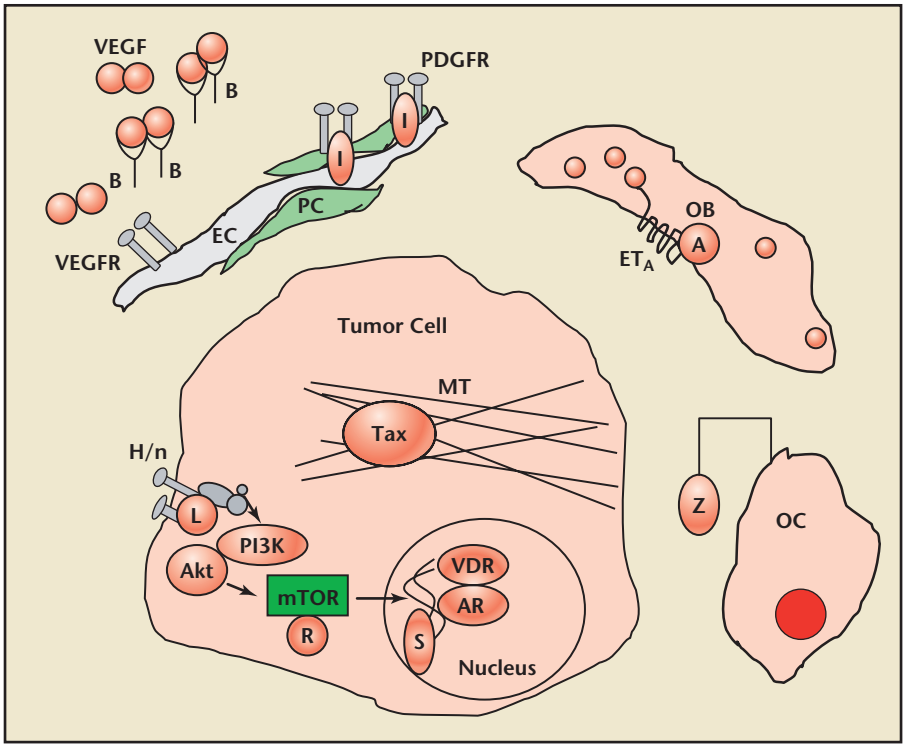
This review will focus on the current standard and investigational treatment options for patients with metastatic HRPC, loosely defined as biochemical, objective, or evaluable disease in the face of castrate levels of serum testosterone (< 50 ng/dL).[4] Neoadjuvant, adjuvant, and therapies for those patients with rising prostate-specific antigen (PSA) levels alone will not be discussed. Figure 1 provides an overview of the many current drugs being investigated and their corresponding cellular targets used to battle prostate cancer. This article will summarize important trials using cytotoxic therapy in HRPC to help battle this common disease and then focus on rapidly evolving therapies in phase II/III trials, including antiangiogenic therapies, signal transduction inhibitors, immunomodulatory agents, and nuclear receptor targets.

Natural History of HRPC

Being able to predict which patients will develop metastasis and death with rising PSA levels after treatment with androgen ablation is essential for deciding therapeutic interventions and gauging prognosis. Over the last decades, several prognostic factors have been identified to stratify patients for clinical trials.[5] Through the Cancer and Leukemia Group B (CALGB) cooperative study group, Halabi and colleagues[6] performed a pooled analysis combining data from 6 trials and more than 1100 patients with HRPC accrued from 1991 to 2001 and created a prognostic model for risk stratification of metastatic HRPC patients. The observed median survival durations (in months) were 7.5 (95% confidence interval [CI] 6.2-10.9), 13.4 (95% CI 9.7-26.3), 18.9 (95% CI 16.2-26.3), and 27.2 (95% CI 21.9-42.8) for the first, second, third, and fourth risk groups, respectively. The factors involved in this model can be broadly divided into clinical variables that reflect the condition of the host (eg, performance status, anemia, fatigue), the tumor burden (eg, sites of metastatic disease, PSA level, alkaline

Docetaxel-based chemotherapy demonstrated a median improvement in survival of 2.5 months as compared with mitoxantrone and prednisone in metastatic HRPC.

Figure 1. *An overview of selected cellular targets associated with prostate cancer and their inhibitors. VEGF, vascular endothelial growth factor; B, levacizumab; VEGFR, VEGF receptor; PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; I, imatinib mesylate; EC, endothelial cell; PC, pericyte; ET_A, endothelin A receptor; A, atrasentan; OB, osteoblast; Z, zoledronic acid; OC, osteoclast; H/n, HER2/neu; L, lapatinib; mTOR, mammalian target of rapamycin; R, rapamycin analogues; MT, microtubules; Tax, docetaxel; S, satraplatin; VDR, vitamin D receptor; AR, androgen receptor.*



phosphatase level), or the biologic aggressiveness of the cancer itself (eg, lactate dehydrogenase [LDH] levels, Gleason sum).

One relatively new factor that may also reflect the biologic aggressiveness of HRPC is the velocity of PSA increase, otherwise referred to as *PSA doubling time*. Although frequently studied in large population cohorts and registry studies in men with recurrent, hormone-naïve prostate cancer, PSA doubling time has only recently been evaluated in the hormone refractory setting. Retrospective evaluations have revealed that a slow PSA doubling time of more than 10 months is associated with an indolent clinical course, with a median cancer-specific survival of 89.1 months (95% CI 69.0-109.2 months).[7] For these patients, a more conservative management plan, involving secondary hormonal strategies such as the addition of an antiandrogen (eg, bicalutamide or flutamide) or an inhibitor of steroidal hormones (eg, ketoconazole or aminoglutethimide) may be indicated. More recently, Smith and coworkers[8] analyzed 201 patients from an aborted randomized trial of zoledronic acid that included men with a rising PSA level despite androgen deprivation therapy, as well as no radiographic evidence of bone metastasis. After 2 years of follow-up, 33% of patients developed bone metastasis. Both baseline PSA values (> 10 ng/mL) and increased PSA velocity independently predicted overall survival and metastasis-free survival. For patients with more rapidly progressive disease, a more aggressive approach with the additional use of investigational strategies, including chemotherapy for asymptomatic metastases, is recommended.

First-Line Chemotherapy

The indications for chemotherapy are clinical or radiographic progression in the face of castrate levels of testosterone, with evidence of metastatic disease. Men with PSA progression alone without evidence of metastatic disease, despite being hormone refractory, have been a difficult group to study, and chemotherapy in this heterogeneous population remains experimental. Chemotherapy has evolved over time since the 1960s, with 3 agents currently approved by the US Food and Drug Administration for use: estramustine (1981), mitoxantrone (1996), and docetaxel (2004). The combination of mitoxantrone/prednisone showed promise in initial trials with palliative benefits, yet no overall survival benefit was found when the regimen was compared with oral prednisone alone.[9,10] Docetaxel emerged as a promising agent because of its ability to stabilize tubulin and prevent dissociation of the mitotic spindle. Docetaxel also has the potential ability to counter the prosurvival effects of BCL-2, which has been found to be overexpressed in androgen-resistant prostate cancer.[11] Promising phase II trials led to 2 major, large, phase III, randomized, multicenter, controlled trials in patients with HRPC: TAX 327 and SWOG 99-16.[1,2] Patient characteristics and response rates for both trials are summarized in Table 1.

For patients with more rapidly progressive disease, a more aggressive approach with the additional use of investigational strategies, including chemotherapy for asymptomatic metastases, is recommended.

The TAX 327 trial involved 1006 men with HRPC. All patients received 5 mg of prednisone and were randomized to 12 mg/m^2 of mitoxantrone every 3 weeks, 75 mg/m^2 of docetaxel every 3 weeks, or 30 mg/m^2 of docetaxel weekly for 5 of every 6 weeks. Patients were stratified by their performance status and the presence of pain, and the treatment duration for the study was 30 weeks of therapy (10 cycles of chemotherapy every 3 weeks of 25 total doses of weekly chemotherapy). The primary

Table 1
Comparison of SWOG 99-16 and TAX 327 Data

Trial	SWOG 99-16	SWOG 99-16	TAX 327	TAX 327	TAX 327
Regimen	D+E+D	M+P	D3P	D1P	MP
Median age (y)	70	70	68	69	68
Visceral disease (n)	18	19	22	24	22
Median PSA score (ng/mL)	84	90	114	108	123
Median survival (mo)	17.5	15.6	18.9	17.4	16.5
≥ 50% decline in serum PSA level (%)	50	27	45	48	32

SWOG, Southwest Oncology Group; D+E+D, docetaxel, estramustine, and dexamethasone; M+P, mitoxantrone and prednisone; D3P, every-3-week docetaxel and prednisone; D1P, weekly docetaxel and prednisone; MP, mitoxantrone and prednisone; PSA, prostate-specific antigen.
Data from Tannock IF et al and Petrylak DP et al.[2,3]

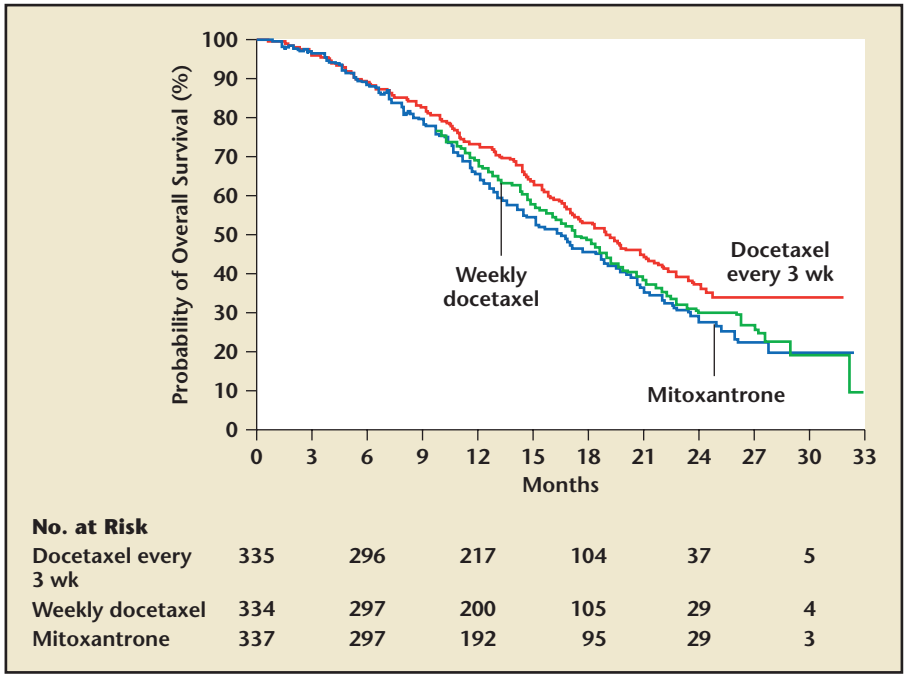


Figure 2. *Kaplan-Meier overall survival curve from TAX 327. Data From Tannock IF et al,[2] with permission. Copyright © 2004 Massachusetts Medical Society. All rights reserved.*

endpoint was overall survival, with secondary endpoints including pain, PSA levels, and quality of life. An adapted Kaplan-Meier curve for overall survival from the study is shown in Figure 2. Median overall survival in TAX 327 was improved by 2.4 months in the every-3-week docetaxel arm versus the every-3-week mitoxantrone arm (18.9 vs 16.5 months, hazard ratio 0.76, $P = .009$); however, the weekly docetaxel arm (median overall survival of 17.4 months) did not reach statistical significance compared with mitoxantrone. The every-3-week regimen also showed statistically significant improvements in pain control, quality of life, and PSA level. No notable differences between toxicities were noted between the every-3-week docetaxel arm and the mitoxantrone-treated arm.

The study was unfortunately not intended for a direct comparison of the docetaxel dosing schedules. Weekly docetaxel dosing surprisingly had slightly higher PSA response rates yet did not reach a statistically significant survival benefit compared with mitoxantrone, illustrating that the modest surrogate activity of PSA declines after cytotoxic therapy for overall survival. Hematologic toxicity, neuropathy, alopecia, and peripheral edema were more common in the every-3-week arm. Although a similar percentage of patients came off study for progressive disease in the docetaxel arms (every-3-week vs weekly), a higher percentage of patients discontinued weekly treatment for either adverse drug reaction or other reason (29% vs 16%), suggesting that chronic tolerance of the weekly regimen may have been a factor.

SWOG 99-16 consisted of 674 patients with HRPC randomized to mitoxantrone 12 mg/m^2 on day 1 and prednisone 5 mg twice daily versus 280 mg of estramustine 3 times daily on days 1 through 5 with docetaxel 60 mg/m^2 on day 2. Both were given on a 21-day cycle, and dose escalation to docetaxel 70 mg/m^2 or mitoxantrone to mg/m^2 was allowed on cycle 2 if no grade 3/4 toxicities were detected in the first cycle. Primary endpoint was overall survival, with secondary endpoints including progression-free survival, objective response rate, and rate of PSA decline. Median overall survival was improved in patients treated with combination docetaxel/estramustine over the mitoxantrone/prednisone regimen (17.5 vs 15.6 months; $P = .01$). PSA decline and time to progression were also improved, yet no benefit was seen in objective tumor response or pain relief. The combination of docetaxel and estramustine led to increases in cardiovascular, gastrointestinal, and thromboembolic toxicity, despite the use of low-dose anticoagulant prophylaxis (2 mg warfarin and 325 mg aspirin). These rates may be attributable to the estrogenic properties of estramustine, leading to an approximately 7% to 15% incidence of thromboembolic disorders.[12] Although cross-trial comparisons are difficult because of eligibility and baseline differences in patient populations, estramustine seems to provide little if any added benefit other than a greater rate of PSA declines, and thus the regimen used in TAX 327 with docetaxel and prednisone has been the preferred regimen of oncologists in clinical practice.

It is essential to compare key differences between the patients studied and results in these 2 trials before extrapolating the data to clinical practice. Lower PSA values at baseline were found in SWOG 99-16. These patients had also received less treatment before the study, had less pain and fewer visceral metastases, and improved baseline performance status as compared with those in TAX 327. The docetaxel dosing was different in these trials, being dose-reduced in the presence of estramustine. In TAX 327, patients were treated up to 10 cycles

or 30 weeks of therapy, whereas in SWOG 99-16 patients were treated until disease progression, adverse events, or 12 cycles of docetaxel or 144 mg/m^2 of mitoxantrone. Continuous corticosteroid treatment can reduce serum PSA levels by at least 50% in a significant portion of patients with HRPC.[13] The doses of steroids were very different in each arm of the trials, making it difficult to separate the added benefit of steroids versus docetaxel alone. The every-3-week regimen of docetaxel used in TAX 327 has become the most common regimen used by oncologists in clinical practice, owing to the increased side effects and no added survival benefit of the docetaxel/estramustine combination.

Zoledronic Acid for Metastatic HRPC

Bone metastases occur in up to 90% of patients with HRPC. These metastases can lead to significant morbidity, including severe pain, fractures, and spinal cord compression. Bisphosphonates, which inhibit bone loss associated with both treatment and age, can potentially affect the progression of osseous metastases. Many trials have looked at the effect of bisphosphonates on bone protection in solid tumors. Initial trials with first- and second-generation bisphosphonates (clodronate and pamidronate) have shown no significant effect on prevention of skeletal-related events.[14,15] Zoledronic acid is a third-generation bisphosphonate that was studied in a large, phase III, double-blind, placebo-controlled study comparing it with placebo in delaying skeletal-related events in HRPC.[16] The study included 643 patients with both symptomatic and asymptomatic bony metastases. All patients received calcium and vitamin D. Results showed that a greater number of placebo-treated patients had skeletal-related events than those who received 4 mg of zoledronic acid (44.2% vs 33.2%; $P = .021$). The time to first skeletal-related event was 321 days for patients who received placebo, versus 420+ days for those who received 4 mg of zoledronic acid ($P = .011$). No difference was seen in time to disease progression, quality of life measures, or survival. A higher incidence of fatigue, anemia, myalgia, fever, lower limb edema, and weight loss was seen with zoledronic acid compared with placebo. A follow-up study of 24 months using a similar dose of zoledronic acid confirmed its long-term efficacy in delaying skeletal-related events in patients with HRPC.[17] On the basis of these data, use of zoledronic acid has become a standard approach in patients with osseous metastatic HRPC to prevent primary or secondary skeletal complications.

Second-Line Strategies After Chemotherapy

In the past, palliative care options for patients who have failed frontline chemotherapy have included best supportive care, radiation to symptomatic bony metastasis, or radiopharmaceuticals. With median survival of approximately 12 months after chemotherapy in both TAX 327 and SWOG 99-16 and with no approved second-line agents, many patients are appropriate for second- or third-line investigational trials. Second-line chemotherapy has not been extensively studied, but in general has a short median progression-free survival of just a few months. Lin and colleagues[18] recently determined the PSA response rates of taxane-resistant (TR) HRPC patients treated with either mitoxantrone/prednisone or ixabepilone (epothilone B analogue with activity against TR cell lines) to be approximately 15%, with a median survival of 1 year. Retreatment with docetaxel and mitoxantrone and prednisone has been studied with similar modest results.[19]

Another potential option includes retreatment with docetaxel or intermittent schedules of chemotherapy including docetaxel. As part of the Androgen-Independent Prostate Cancer Study of Calcitriol Enhancing Taxotere (ASCENT), Beer and colleagues[20] looked at stopping treatment in patients who were responders and showed a median duration of first chemotherapy holiday as 16 weeks, with 50% of patients responding after retreatment, 35% with stable disease after retreatment, and 15% progressing after retreatment. The select subsets of patients were initially chemotherapy naïve and included those who initially responded to docetaxel-based therapy. Response was based on PSA reduction or elevation. Future studies are needed to confirm the value of intermittent chemotherapy. Because of the lack of an approved agent in second-line disease, more trials are needed looking at novel cytotoxic agents in this disease.

Satraplatin is a new third-generation oral platinum analogue with activity in platinum-resistant tumor models and in prostate cancer. A randomized, multicenter, phase III trial evaluated satraplatin and prednisone versus prednisone alone in HRPC.[21] The sponsoring company closed the trial early after 50 patients, thus not meeting the phase III objectives. Post hoc analysis showed a trend toward prolonged progression-free survival and PSA response rate in the combined therapy arm versus the prednisone-only arm. Recently, the double-blind, randomized, placebo-controlled SPARC (Satraplatin and Prednisone Against Refractory Cancer) phase III trial reached its progression-free survival endpoint, showing a 40% reduction ($P < .00001$) in the

satraplatin and prednisone arm compared with prednisone and placebo.[22] Overall survival data are expected later this year. It remains to be seen whether progression-free survival is a valid endpoint for approval of this agent, and more trials are needed to confirm the results. Data presented at the American Society of Clinical Oncology (ASCO) 2006 annual meeting have also indicated that the combination of docetaxel and satraplatin has activity in prostate cancer in both in vivo and in vitro mouse models.[23]

Novel Agents

A better understanding of the mechanisms responsible for prostate cancer growth and metastatic spread has allowed for the development of a wide array of new therapies. Many of these therapies show promise in combination with proven chemotherapy and as single agents alone. The rest of this review will focus on selected agents targeting pathways involving angiogenesis, cell growth and survival, immune modulation, and nuclear receptor targeted agents. A summary of several key ongoing clinical trials of novel agents is included in Table 2.

Antiangiogenic Strategies

As with many solid tumors, angiogenesis may play a functional role in prostate cancer growth and progression. Microvessel density in clinically localized prostate cancer is an independent prognostic for progression and survival.[24,25] Moreover, through the CALGB we demonstrated that the plasma level of vascular endothelial growth factor (VEGF), a potent angiogenic growth factor, is an independent prognostic factor in men with metastatic HRPC.[26] Antiangiogenic agents using monoclonal antibodies to VEGF, such as bevacizumab (Avastin®; Genentech, San Francisco, CA), have been studied in prostate cancer. Although single-agent studies have failed to demonstrate significant results, a phase II trial conducted by the CALGB added bevacizumab to docetaxel and estramustine in men with HRPC; 79% of patients had a greater than 50% decline in PSA level, median time to progression of 9.7 months, and overall median survival of 21 months.[27] On the basis of these promising results, a randomized, double-blind, placebo-controlled, phase III trial has been designed comparing docetaxel 75 mg/m^2 every 3 weeks with prednisone 10 mg orally daily with either bevacizumab 15 mg/kg IV or placebo every 3 weeks (CALGB 90401). The primary endpoint for this trial is overall survival, and secondary endpoints include progression-free survival, PSA reduction, and grade 3+ toxicities. This trial opened in April 2005 and is actively accruing.

Thalidomide has also been shown to inhibit angiogenesis through multiple potential mechanisms, including inhibition of proangiogenic signals such as VEGF, as well as immunomodulatory effects by affecting T-cell costimulatory activity.[28] This

Table 2
Selected Ongoing Clinical Trials of Novel Agents in Development for the Treatment of HRPC

Agent	Type of Therapy	Phase	Overview of Trial
Satraplatin	Cytotoxic	III	SPARC Trial: prednisone ± satraplatin in HRPC
Bevacizumab	Anti-angiogenic	III	CALGB 90401: docetaxel/prednisone ± bevacizumab in HRPC
Sorafenib (BAY 43-9006)	Tyrosine kinase inhibitor	II	NCI-04-C-0262: sorafenib in HRPC
Everolimus (RAD 001)	mTOR inhibitor	II	Single-arm study of RAD 001 in patients with HRPC (Novartis)
Lapatinib (GW 572016)	Dual EGFR kinase inhibitor	II	Oral once-daily lapatinib in patients with HRPC (GlaxoSmithKline)
Atrasentan	ET-A receptor antagonist	III	SWOG 04-21: Docetaxel and atrasentan vs docetaxel and placebo for patients with HRPC
Sipuleucel-T (Provenge®)	Vaccine	III	D9902B: sipuleucel-T vs placebo in HRPC
Prostate GVAX®	Vaccine	III	VITAL 1: GVAX® vs docetaxel/prednisone in asymptomatic HRPC VITAL 2: docetaxel/GVAX® vs docetaxel/prednisone in symptomatic HRPC
DN-101	Vitamin D receptor	III	ASCENT 2: docetaxel/prednisone ± DN-101 in HRPC

HRPC, hormone-refractory prostate cancer; SPARC, Satraplatin and Prednisone Against Refractory Cancer; CALGB, Cancer and Leukemia Group B; mTOR, mammalian target of rapamycin; ET-A, endothelin A; EGFR, epidermal growth factor receptor; VITAL, Vaccine ImmunoTherapy with Allogeneic Prostate Cancer Cell Lines; ASCENT, Androgen-Independent Prostate Cancer Study of Calcitriol Enhancing Taxotere.

agent was studied in a phase II randomized study in combination with docetaxel in hormone-refractory disease and demonstrated an impressive 53% PSA decline (> 50% decrease in PSA) and improved time to progression and overall survival.[29] The study was underpowered, and toxicities of this combination therapy included high rates of thrombosis, sedation, and neuropathy.

More recently, multitargeted tyrosine kinase inhibitors (TKIs) that inhibit angiogenic growth factor receptors such as VEGF have been studied in prostate cancer. In addition to VEGF, another potential angiogenic growth factor target inhibited by several TKIs is platelet-derived growth factor (PDGF). Prostate cancer cells have been shown to express high levels of PDGF receptor (PDGFR), which in turn enhances the phosphoinositide 3 kinase/Akt pathway leading to prostate cancer progression.[30] Sorafenib (Nexavar®; Bayer Pharmaceuticals Corporation, West Haven, CT) is an oral agent with proven inhibition of Raf kinase, VEGF receptors, and PDGFR.[31] Sorafenib was approved for advanced renal cell carcinoma on the basis of data from an abstract presented at ASCO 2005, with improved progression-free survival and overall survival.[32] A study at ASCO 2006 focused on 22 patients with HRPC treated with sorafenib until progression of disease.[33] Of the 19 patients who progressed, 10 progressed with PSA rise only and 2 patients with PSA progression were found to have dramatic resolution of bony disease. Vatalanib (PTK787/ZK 222584) is another multitargeted TKI, inhibiting VEGF receptors 1-3 and PDGFR at nanomolar concentrations.[34] We performed a small, phase I study to describe the effect of food on absorption and evaluate preliminary efficacy in metastatic HRPC patients. Overall, 1 of 19 patients demonstrated a greater than 50% reduction from baseline in serum PSA level and duration of response of 12 months; 2 other patients demonstrated a greater than 40% reduction in PSA, with duration of 4 and 5 months, respectively.[35] The modest results of these and other TKI studies suggest that PSA response may not represent the most sensitive endpoint to evaluate novel agents. A surrogate marker more robust than PSA and less dependent on androgen receptor activity is necessary in analyzing response to novel agents.

Cell Survival and Growth Pathways

Loss of the tumor suppressor PTEN (phosphatase and tensin homologue deleted on chromosome 10) has been found in advanced prostate cancer, leading to phosphoinositide 3 kinase/Akt activation, which leads to increased activity of a downstream kinase mTOR (mammalian target of rapamycin).[36] Multiple mTOR inhibitors exist, including temsirolimus, everolimus, and rapamycin. Phase I data using RAD 001 (everolimus) have shown successful target inhibition in solid tumors, and phase II trials are ongoing.[37] Studies have also shown that this agent may have benefit with chemotherapy due to its ability to induce apoptosis as combination-based therapy.[37] Once phase II trials evolve, the use of this agent with combination docetaxel could show promise. A recent phase I/II study reported in abstract form at ASCO 2006 looked at the combination of RAD 001 with gefitinib (selective inhibitor of the tyrosine kinase domain of the epidermal growth factor receptor [EGFR]) in metastatic prostate cancer and glioblastoma multiforme, showing 5 of 29 patients with no progression at 12 weeks.[38]

Another potential target involved in cellular growth includes the human epidermal growth factor receptor 2 (HER2)/neu (ErbB-2) tyrosine kinase. HER2 expression has been shown to increase androgen receptor activation, leading to growth of prostate cells.[39] Phase II studies involving gefitinib and trastuzumab (a monoclonal antibody that acts on HER2/neu-erb2 receptor) both showed poor efficacy in HRPC.[40,41] However, studies have shown successful inhibition of PSA expression and androgen receptor recruitment with the use of a dual EGFR/HER2 kinase inhibitor, GW572016 (lapatinib).[42] This disruption of the androgen receptor could potentially stop the growth of tumor cells. Phase II trials of lapatinib in HRPC are ongoing.

Another potential target focuses on the bone microenvironment. HRPC has been shown to have high levels of endothelin, which correlates with aggressive disease.[43] Atrasentan (a highly selective endothelin A receptor antagonist) has been studied in a phase III, randomized, placebo-controlled trial.[44] No statistically significant difference was seen in the primary endpoint (time to progression); however, secondary endpoints (eg, quality-of-life scores, pain scores, rise of laboratory markers including alkaline phosphatase, and PSA level) were all improved in the atrasentan arm. Several issues have limited approval of this agent, including trial design, difficulty in defining progression in the bone-only population, the risk of cardiovascular events, and the small overall primary and secondary benefits seen despite an unplanned meta-analysis of all phase II and III trials of this agent; these issues illustrate

A surrogate marker more robust than PSA and less dependent on androgen receptor activity is necessary in analyzing response to novel agents.

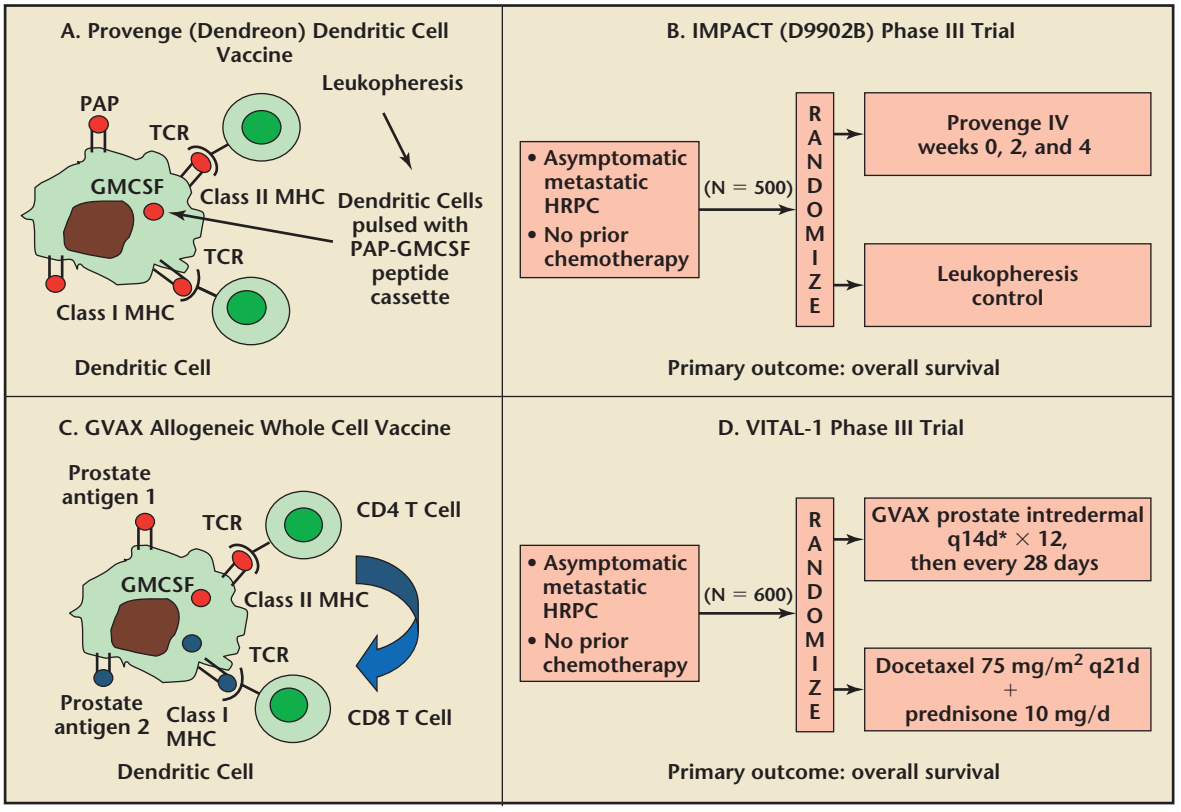
the difficulty in studying this population. The combination of this agent with docetaxel versus docetaxel and placebo is being evaluated in SWOG 04-21. This drug may have proven benefit in the subset of bone-only metastatic disease.

Immunotherapy

Induction of the immune system against normal and cancerous prostate tissue has been proven by vaccination with prostate-specific proteins/peptides including PSA, prostatic acid phosphatase (PAP), and prostate-specific membrane antigen (PSMA).[45] Two types of immunotherapy that are promising are dendritic cell (autologous)-based immunotherapy and whole-cell (allogenic)-based immunotherapy. Figure 3 provides a brief overview of how each of these vaccines is prepared and its mechanism of action, as well as the corresponding ongoing clinical trials using these agents. The goals of both of these therapies involve activating T cells to attack the tumor. Most of the current vaccine-based therapeutic approaches use granulocyte-macrophage colony-stimulating factor (GM-CSF), which has been shown to improve antigen presentation and activation of T cells, and have progressed up to phase III trials.

Sipuleucel-T (Provenge®; Dendreon, Seattle, WA) is an example of dendritic cell-based therapy. Leukophoresed dendritic cells are collected from patients and are shipped to a central location, where they are fused with a proprietary combination of factors including GM-CSF and PAP antigen. These cells are then matured and activated in vitro and finally shipped back to the treating facility, where the vaccine is immediately injected subcutaneously into the patient. Trials to

Figure 3. *Immunotherapy in HRPC. A: Autologous dendritic cell preparation is administered intravenously in a proprietary formulation using PAP as the target antigen and fused to GM-CSF as a cytokine adjuvant, and is known as sipeuleucel-T. B: D9902B (IMPACT) is a phase III trial designed to demonstrate improved overall survival with sipeuleucel-T in asymptomatic or minimally symptomatic men with HRPC. C: Allogeneic prostate cancer whole cell-irradiated vaccine (GVAX®) uses numerous antigens for presentation on dendritic cells, with GMCSF transfection to enhance bystander immunity and antigen presentation. D: VITAL 1 is a phase III trial in asymptomatic men with HRPC designed to demonstrate an overall survival advantage with prostate GVAX as compared with standard docetaxel and prednisone. GM-CSF, granulocyte-macrophage colony-stimulating factor; HRPC, hormone-refractory prostate cancer; IV, intravenous; MHC, major histocompatibility complex; PAP, prostatic acid phosphatase; TCR, T cell receptor.*



date have included 3 sequential injections, 2 weeks apart. A phase III, placebo-controlled trial studied 127 patients with asymptomatic HRPC and showed a trend to increased time to progression (not statistically significant); yet there was a statistically significant improvement in overall survival in the vaccine-treated group compared with placebo (25.9 vs. 21.4 months).[46] The vaccine was well tolerated, with the most common side effects including grade 1 rigors, pyrexia, tremor, and feeling cold. Although the trial was not powered to show survival benefit, the initial results show promise, and confirmatory trials are ongoing. A phase III trial (Study D9902B), which is accruing patients, is evaluating Provenge versus placebo in PAP-expressing patients with disease-related pain and disease progression, with the primary endpoint of time to disease progression.

Prostate GVAX® vaccine (Cell Genesys, Inc., San Francisco, CA) is immunotherapy using inactivated allogenic prostate carcinoma cell lines (PC-3 and LNCaP), which are modified genetically through adenoviral transfer to secrete GM-CSF. The advantage is that the vaccine can be used off the shelf in multiple patients, and multiple tumor antigens can be targeted. Two phase II trials have demonstrated activity, with 1 trial showing an overall survival of 26 months and another trial showing improvement of osteoclast activity in a majority of patients and an expected overall survival of more than 24.4 months.[47] Because these were uncontrolled trials in an asymptomatic population with a relatively high expected survival, the true benefit of this approach remains unclear. The vaccines were well tolerated, with common side effects including injection site reactions, fatigue, malaise, myalgias, and arthralgias without any dose-limiting toxicities. Two ongoing phase III trials will further test the response to vaccines versus standard chemotherapy. The Vaccine ImmunoTherapy with Allogeneic Prostate Cancer Cell Lines (VITAL) 1 trial will accrue 600 men with asymptomatic HRPC with no prior chemotherapy, randomized to GVAX or docetaxel/prednisone, with the primary endpoint being overall survival. VITAL 2 will also study 600 men but will involve symptomatic HRPC patients randomized to docetaxel with or without GVAX. Prednisone will be omitted from the GVAX-containing regimen to prevent blunting of the immune response to the vaccine.

Two ongoing phase III trials will further test the response to vaccines versus standard chemotherapy.

Nuclear Receptor Target Agents

Multiple epidemiologic studies have shown an increased risk of prostate cancer with relative vitamin D deficiency.[48] Studies have also shown that vitamin D receptors are expressed in prostate cancer cells and that prostate cancer cells are deficient in converting 25-hydroxyvitamin D to 1,25-hydroxyvitamin D, which is an active differentiating agent in prostate cancer.[49] In vitro studies have shown that calcitriol (1,25-dihydroxycholecalciferol) may be able to inhibit growth and allow for differentiation of prostate cancer cells.[50] This finding has led to the development of calcitriol and related products as a potential targeted therapy. DN-101 is a proprietary oral formulation of 1,25-dihydroxycholecalciferol that is able to provide supraphysiologic doses of vitamin D without side effects such as hypercalcemia. Preclinical studies have shown that DN-101 has an added effect when combined with chemotherapy. This combination was recently studied in a randomized, phase III, multi-institutional study of 250 men with progressive HRPC treated with weekly docetaxel with or without DN-101 (ASCENT 1).[51] The primary endpoint was PSA response rate. There was a trend toward improved PSA response rate in the combined group, but it was not statistically significant. The study was underpowered to detect survival differences, yet the estimated median survival was nonsignificantly prolonged, from 16.4 months (placebo) to 23.5 months (DN-101) in the unadjusted analysis. An ongoing phase III trial (ASCENT 2) will randomize patients to docetaxel/prednisone with and without DN-101 and have power to detect survival benefit as the primary endpoint. Other endpoints will include skeletal-related events and reduction of blood clots.

Conclusions

The management of men with HRPC is clearly changing at a faster rate than ever before. Increased knowledge regarding the prognosis, natural history, and underlying biology of HRPC, coupled with new evidence of clinical benefit associated with systemic chemotherapy and renewed interest in drug development for this patient population, has changed and will continue to change our management algorithms. Further research is essential in defining the molecular biology of prostate cancer development, progression, and therapeutic resistance, including the identification of putative prostate cancer stem cells and the mechanisms for achieving hormone-refractory states. Docetaxel-based chemotherapy is the first US Food and Drug Administration–approved

cytotoxic agent in this setting that has been shown to prolong survival. Strategies to build on this new front-line strategy are essential, as is the development of second- and third-line options after docetaxel failure. We are entering an exciting time in this field. A number of promising phase III clinical trials using molecular targets and immunotherapy as single agents or in combination are accruing well and may lead to improvements in our ability to modify the natural history of this disease. Given the complexity of prostate cancer progression and the number of likely mutations or epigenetic alterations that occur during progression, combination therapy is likely to be the next frontier of clinical trials in the disease. Medical oncologists, urologists, and radiation oncologists will need to continue to collaborate toward patient accrual and trial design to transform metastatic prostate cancer into a more chronic and symptom-free disease. ■

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Main Points

- New advances in the management of hormone-refractory prostate cancer (HRPC), focusing on the distinct mechanisms of androgen-refractory disease and other potential targets, may further lengthen survival of patients with this chronic disease.
- The indications for chemotherapy are clinical or radiographic progression in the face of castrate levels of testosterone, with evidence of metastatic disease. Docetaxel has emerged as a promising agent because of its ability to stabilize tubulin and prevent dissociation of the mitotic spindle.
- The every-3-week regimen of docetaxel used in the TAX 327 study has become the most common regimen used by oncologists in clinical practice, owing to the increased side effects and lack of added survival benefit of the docetaxel/estramustine combination.
- Bone metastases occur in up to 90% of HRPC patients and can lead to significant morbidity, including severe pain, fractures, and spinal cord compression. Treatment with zoledronic acid has become a standard approach in patients with osseous metastatic HRPC to prevent primary or secondary skeletal complications.
- As with many solid tumors, angiogenesis may play a functional role in prostate cancer growth and progression. Recently studied antiangiogenic agents include bevacizumab, thalidomide, and the tyrosine kinase inhibitors sorafenib and vatalanib.
- Recently studied agents affecting cell survival and growth pathways include temsirolimus, everolimus, rapamycin, gefitinib, trastuzumab, and atrasentan. Everolimus may have benefit with chemotherapy due to its ability to induce apoptosis as combination-based therapy. Phase II studies involving gefitinib and trastuzumab showed poor efficacy in HRPC.
- Two types of immunotherapy that are promising are dendritic cell (autologous)-based immunotherapy (eg, sipuleucel-T) and whole-cell (allogenic)-based immunotherapy (eg, the GVAX® vaccine). The goals of both of these therapies involve activating T cells to attack the tumor.
- In vitro studies have shown that calcitriol (1,25-dihydroxycholecalciferol) may be able to inhibit growth and allow for differentiation of prostate cancer cells. This finding has led to the development of calcitriol and related products as a potential targeted therapy.

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