The Treatment of Hormone-Refractory Prostate Cancer: Docetaxel and Beyond

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Two randomized clinical trials demonstrated a survival benefit of 20% to 24% with docetaxel-based therapy when compared with survival with mitoxantrone and prednisone after failure of androgen ablation therapy. These studies supported the approval of docetaxel-based therapy for the treatment of metastatic hormone-refractory prostate cancer by the US Food and Drug Administration in May 2005. Clinical trials in hormone-refractory prostate cancer are now focused on building on the survival improvement seen with docetaxel-based therapy. This article presents a summary of some of the more promising treatments and regimens for advanced prostate cancer.
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Androgen ablative therapy induces rapid and dramatic responses in men with metastatic prostate cancer; characteristics of this response include improvement in bone pain, regression of soft tissue metastases, and decreases in serum prostate-specific antigen (PSA) levels. In the past, none of the options available at treatment failure of androgen blockade improved survival past 10 to 12 months. Treatments such as secondary hormonal manipulations, mitoxantrone-based chemotherapy, external beam radiation therapy, or radioisotope therapy could at best achieve palliation. This paradigm changed with the

publication of 2 randomized clinical trials in 2005, which demonstrated a survival benefit of 20% to 24% with docetaxel-based therapy when compared with survival with mitoxantrone and prednisone. These studies supported the approval of docetaxel-based therapy for the treatment of metastatic hormone-refractory prostate cancer by the US Food and Drug Administration in May 2005. Clinical trials in hormone-refractory prostate cancer are now focused on building on the survival improvement seen with docetaxel-based therapy. The future is bright for the treatment of prostate cancer, with many new drugs and targets being evaluated. Activation of the immune system either through dendritic cells or novel prostate cancer vaccines provides a new approach to the treatment of metastatic disease. This article summarizes some of the more promising treatments and regimens for advanced prostate cancer.[1]

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Docetaxel-Based Therapy for Androgen-Independent Prostate Cancer: Southwest Oncology Group Study 99-16 Design

Clinical trials were designed based on synergy observed between 2 agents, estramustine and docetaxel, both of which target tubulin in human prostate cancer cell lines. Estramustine, a synthetic non-nitrogen mustard, has been demonstrated to interfere with microtubule-associated proteins. This is in contrast with its designed mechanism of action, alkylation of DNA. Docetaxel stabilizes tubulin and thus prevents dissociation of the mitotic spindle; it is also known to phosphorylate Bcl-2. Preliminary phase I and II studies treating men who have androgen-independent prostate cancer with docetaxel and estramustine demonstrated median survival times of 20 to 23 months. On the basis of these promising preliminary data, a phase III study was designed by the Southwest Oncology Group (SWOG), randomizing 770 men to receive estramustine, 280 mg orally 3 times daily on days 1 to 5, docetaxel 60 mg/m^2 IV on day 2 every 21 days, and dexamethasone 60 mg orally in 3 divided doses before docetaxel or mitoxantrone, 12 mg/m^2 IV every 21 days plus prednisone 5 mg orally twice daily. For study entry, patients were required to have progressive metastatic androgen-independent prostate cancer, demonstrated by an increasing serum PSA, progression on bone scan, or progression on computed tomography. If the patient tolerated the first cycle without grade 3 or 4 toxicities, dose escalation was permitted to 70 mg/m^2 and 14 mg/m^2 for docetaxel and mitoxantrone, respectively. The trial was powered to detect a 33% improvement in overall survival between the 2 treatment arms. To prevent vascular events, the protocol was amended in January 2001 to administer 2 mg of coumadin and 325 mg of aspirin per day in patients treated on the estramustine/docetaxel arm.

SWOG 99-16 Study Results

In an intent-to-treat analysis, patients receiving docetaxel/estramustine had a 20% reduction in the risk of death compared with patients treated with mitoxantrone and prednisone (hazard ratio 0.80; 95% confidence interval 0.67–0.97). Longer median survivals were also noted in the docetaxel/estramustine-treated compared with the mitoxantrone/prednisone-treated patients (median 17.5 vs 15.6 months, logrank $P = .020$). The median times to progression of the docetaxel/estramustine and the mitoxantrone/prednisone arm were 6 and 3 months, respectively (logrank $P < .0001$); PSA declines of 50% or more occurred in 50% and 27% of doctaxel/estramustine and mitoxantrone/prednisone patients, respectively ($P < .0001$). A trend toward improved objective responses in measurable soft tissue lesions was observed (17% docetaxel/estramustine vs 11% mitoxantrone/prednisone), but this was not statistically significant ($P = .30$). Despite the fact that the mitoxantrone arm contained continuously administered prednisone, palliation of bone pain was not significantly different between both treatment arms. Grade 3/4 gastrointestinal and cardiac toxicity and neutropenic fevers were more common in docetaxel/estramusine treated patients than in those treated with mitoxantrone/prednisone. The rates of cardiac ischemia appeared to be lower in those patients who received prophylactic anticoagulation; however, no differences in deep venous thrombosis were observed. The evaluation of the use of prophylactic anticoagulation is limited; the trial was not initially designed to detect a difference in the rates of vascular events between those estramustine/docetaxel patients receiving prophylactic anticoagulation and those who did not receive coumadin/aspirin.

TAX 327 Study Design

Single-agent docetaxel, when administered either every 3 weeks, or weekly at low doses, also demonstrated significant PSA declines and measurable soft tissue responses in men with androgen-independent prostate cancer. These observations

supported the design and implementation of TAX 327, a phase III trial comparing 2 separate schedules of single-agent docetaxel combined with prednisone to mitoxantrone and prednisone. Patients with progression of metastatic prostate cancer despite surgical or medical castration were randomized to (1) docetaxel 75 mg/m^2 every 3 weeks with 5 mg prednisone twice daily; (2) docetaxel 30 mg/m^2 weekly for 5 out of 6 weeks with 5 mg prednisone twice daily; or (3) mitoxantrone 12 mg/m^2 every 3 weeks with 5 mg prednisone twice daily. Pretreatment stratifications included pain index ≥ 2, analgesic score ≥ 10 versus pain index < 2, analgesic score < 10, and Karnofsky performance status ≤ 70 versus > 80. In contrast to SWOG 99-16, no dose escalation was planned, and treatment was limited to total of 30 weeks. The SWOG study limited the patients treated with docetaxel/estramustine to 12 cycles, and the mitoxantrone/prednisone arm to 144 mg/m^2 total dose of mitoxantrone. Patients were not permitted to have prior chemotherapy in TAX327, whereas 6% of patients treated on SWOG 99-16 had 1 prior non-taxane, non-estramustine, non-anthracycline chemotherapeutic regimen. The dose of the weekly docetaxel regimen was calculated to deliver an equivalent dose intensity to the every-3-week docetaxel regimen. The primary endpoint was overall survival, with secondary endpoints including pain response, 50% or greater PSA decline, measurable response, and quality of life.

Results of TAX 327

When compared with mitoxantrone/prednisone, an improved survival was noted for patients treated with the every-3-week docetaxel regimen, but not with the weekly regimen. The median survivals were 18.9, 17.4, and 16.9 months for every-3-week docetaxel/prednisone, weekly docetaxel/prednisone, and mitoxantrone/prednisone, respectively. The reduction in the risk of death, when compared with that with mitoxantrone and prednisone, was 24% and 9% for the every-3-week and the weekly docetaxel regimens, respectively. PSA declines of 50% or greater were noted in 45%, 48%, and 32% of patients in the every-3-week, weekly docetaxel, and mitoxantrone arms, respectively. As in SWOG 99-16, there was a nonsignificant trend toward improved objective response rate in patients treated with every-3-week docetaxel.

Palliation of bone pain was superior in both docetaxel arms when compared with mitoxantrone and prednisone.

Palliation of bone pain was superior in both docetaxel arms when compared with mitoxantrone and prednisone. The every-3-week and weekly docetaxel regimens had pain response rates of 35% and 31%, respectively. In mitoxantrone-treated patients, the pain response rate was significantly lower at 22%. One of the commonly preconceived notions about chemotherapy, worsening quality of life, is dispelled by the data from TAX 327. Quality of life response favored both docetaxel arms compared with mitoxantrone using the FACT-P instrument. Scores achieved in the every-3-week and weekly docetaxel arms were 9 to 10 points higher than that noted in the mitoxantrone arm.

Consistent with the phase II data, rates of grade 3 or 4 neutropenia were higher in the every-3-week docetaxel arm (3%), with rates of febrile neutropenia at 2.7%. In comparison, grade 3 or 4 neutropenia was noted in 0.0% and 0.9% with weekly docetaxel or mitoxantrone. These relatively low rates of neutropenia were not supported by colony-stimulating factors. The rates of study discontinuation due to adverse events were similar in all 3 treatment arms. Although lacrimation, nail bed changes, neuropathy, and alopecia appeared more frequently in docetaxel-treated patients compared with mitoxantrone treated patients, the toxicity patterns of docetaxel-treated patients were not remarkably different from mitoxantrone-treated patients.

SWOG 99-16 and TAX 327 were the first trials to demonstrate improvements in survival for men treated with chemotherapy for androgen-independent prostate cancer. There are several findings in both these studies that have implications to patient treatment and future clinical trial designs. The median survival of the standard arm, mitoxantrone/prednisone, is higher than that reported in other phase III studies. This could be attributed to a stage migration. The TAX 327 study required progressive symptomatic disease, and asymptomatic biochemical progression in the face of metastatic disease occurred in 18% to 19% of patients on SWOG 99-16. The percentage of patients who had an asymptomatic PSA increase without other evidence of progression cannot be

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determined from the data presented in the final publication of TAX 327. Crossover could also account for the increased median survival of the control arm; 35% of patients who experienced progression while taking mitoxantrone and prednisone received second-line therapy with SWOG 99-16, whereas 20% of patients failing mitoxantrone and prednisone received further chemotherapy.

One perplexing finding of TAX 327 was that the weekly regimen did not have an improved survival rate compared with mitoxantrone/prednisone. This has important implications to the design of future trials because many of the newer signal transduction agents have been combined with weekly docetaxel. The statistical design of TAX 327 did not include a direct comparison of the weekly arm to the every-3-week arm; thus, no valid comparisons can be made. Statistical variation, differences in dose and schedule, as well as unidentified biologic mechanisms may in part account for the failure of weekly docetaxel. Despite the lack of survival benefit, weekly docetaxel still demonstrated significant improvements in palliation and quality of life indices when compared with mitoxantrone/prednisone.

The role of estramustine is not defined by either TAX 327 or SWOG 99-16. Although identical control arms were used in both TAX 327 and SWOG 99-16, comparisons of the survival times obtained in the docetaxel/estramustine and docetaxel/prednisone arms cannot be validly made. This is due in part to slightly different entry criteria (previous chemotherapy vs no chemotherapy), different crossover patterns, and possible patient selection bias. Thus, only a randomized trial comparing docetaxel/estramustine with docetaxel/prednisone can properly evaluate the contribution of estramustine. The emergence of newer agents with potentially less toxicity and greater efficacy than estramustine make the concept of such a large randomized trial less attractive. Based on lower rates of toxicity, Cancer and Leukemia Group B (CALGB) and SWOG have accepted docetaxel/prednisone as the standard of care for future phase III studies, rather than docetaxel/estramustine.

The endothelin A receptor is expressed in 71% of primary prostate cancers, and is expressed at a higher rate in high-grade tumors and metastases.

Bone-Specific Targeted Therapy: Endothelin Receptor Antagonists

The endothelins are a class of peptides expressed in a variety of human tissues that control vasoconstriction, mitogenesis, nociception, and bone matrix formation. Three ligands (ET-1, -2, and -3), consisting of 21 amino acids, can be found in endothelial cells, kidney and intestine, and brain, respectively. The endothelin receptor consists of two receptors, ET_A and ET_B.[2] The endothelin receptor is expressed in a variety of human tumors, including prostate cancer. The endothelin A receptor is expressed in 71% of primary prostate cancers, and is expressed at a higher rate in high-grade tumors and metastases. Osteoblasts also robustly express the ET_A receptor. Binding of endothelin to its receptor results in cell proliferation, bone matrix synthesis, and resistance to apoptosis. Atrasentan, a specific ET-1_A inhibitor, decreases mitogenic activity, osteoblastic activity, rates of bone metastases, and angiogenesis, and blocks nociceptive effects. Atrasentan is orally bioavailable and is dosed once daily. Adverse effects include peripheral edema, rhinitis, headache, and dyspnea. Atrasentan has been evaluated in patients with hormone-refractory prostate cancer. M96-500 was a 12-week study that evaluated pain response as a primary endpoint. A total of 131 patients were entered in the study. M96-594 randomized 288 patients either to placebo, atrasentan 10 mg, or atrasentan 2.5 mg.[3] The primary endpoint of this trial was time to disease progression, with PSA progression as a secondary endpoint. There was a significant difference in time to progression and survival for the evaluable patients who received atrasentan compared with placebo. Unfortunately, these differences in survival and time to progression were not observed in the intent-to-treat analysis.[3] Bone alkaline phosphatase and PSA changed at a slower rate in those patients treated with atrasentan compared with placebo-treated patients. These results provided the justification for further studies. A recently completed randomized trial, M00-211, compared atrasentan 10 mg with placebo in 811 patients with hormone-refractory prostate cancer with asymptomatic progressive metastatic disease. The primary endpoint of the study was time to disease progression, defined as the development of 2 or more new lesions on bone scan, development of extraskeletal metastases, worsening of prostate cancer pain, or skeletal-related events. For all patients, the time to disease progression was not significantly different in the atrasentan compared with the placebo arm. However, a significant difference in time to progression was observed in favor of atrasentan for those patients with bone metastases only. Median changes in bone alkaline phosphatase, PSA, and quality-of-life parameters also favored the atrasentan-treated patients. A

significant difference in favor of atrasentan was also observed in the time to the 50% worsening of the PCS pain score. There was also a delay in time to development of bone pain in the atrasentan-treated patients. A meta-analysis of 1097 patients treated on M00-211 and M96-594 found an improved time to disease progression in favor of atrasentan-treated patients compared with that in placebo-treated patients. One of the major issues that needs to be resolved regarding atrasentan treatment is the proper duration of therapy. In a meta-analysis, more than half of patients progressed at first evaluation.[4] The separation of the curves occurs after this point. It is possible that the mechanism of action of atrasentan requires continuous administration; bone scan progression may not be the proper primer to use. Further studies are clearly needed to define response to progression in relationship to endothelin receptor inhibition.

On the basis of primary activity, as well as preclinical studies, SWOG is moving forward with a randomized phase III study comparing docetaxel 75 mg/m^2 every 3 weeks, prednisone 10 mg combined with atrasentan 10 mg every day, to docetaxel 75 mg/m^2 every 3 weeks, and prednisone 10 mg every day in men with hormone-refractory prostate cancer. The primary endpoint is progression-free survival, with secondary endpoints including overall survival, pain, quality-of-life, PSA response, and objective response. The trial is designed to accrue 706 patients over a 4-year period, and has 96% power to detect a 33% increase in progression-free survival from 6 to 8 months.

New Antimicrotubule Agents: Epothilones

Newer agents focusing on microtubules are currently in phase I and II trials. Epothilone B, a semisynthetic analogue of natural epothilones derived from *Sorangium cellulosum*, is 2 to 20 times more cytotoxic than paclitaxel in vitro and demonstrates preclinical activity in paclitaxel-resistant cell lines. Preclinical data demonstrate that epothilone B has significant cytotoxicity against the DU-145 prostate cancer cell line in vitro. The drug has completed phase I evaluation, with diarrhea and neuropathy as major dose-limiting toxicities. Epothilones are being evaluated in patients with hormone-refractory prostate cancer, both in previously untreated patients as well as in patents who have failed one prior chemotherapeutic regimen. The Southwest Oncology Group evaluated ixabepilone (BMS-247550) in 48 men with hormone-refractory prostate cancer. The estimated progression-free survival was 6 months; 33% of patients treated had at least a 50% PSA decline.[5] The most common toxicities included neutropenia and neuropathy. In a randomized phase I study at Memorial Sloan-Kettering Cancer Center, the combination of epothilone B with estramustine phosphate was compared with epothilone B alone. In 45 patients randomized to receive ixabepilone alone, 48% demonstrated a greater than 50% PSA decline, whereas 68% of the 47 patients who received ixabepilone/estramustine manifested a similar level of PSA decline. Parallel to other reports of estramustine combinations, a higher rate of vascular events was observed in the estramustine-treated patients.

Angiogenesis in Prostate Cancer

The growth of new blood vessels is essential to both the growth and metastases of solid tumors. Cancer cells must generate new blood vessels to grow to sizes of greater than 3 mm^3.[6] The process of neovascularization is regulated by a system of vascular growth factors, including vascular endothelial growth factor (VEGF), matrix metalloproteins, and integrins. Inhibition of these targets can arrest tumor growth, as well as inhibit metastatic spread. These vascular growth factors are expressed in both the tissue and serum of patients with prostate cancer. A CALGB study found that circulating levels of VEGF were increased in patients with hormone-refractory prostate cancer, and are prognostic to survival.[7] Microvessel density has been found to be increased in patients who have metastatic disease compared with those who have clinically localized cancer. Thus, the tumor vasculature appears to be a rational therapeutic target for men with prostate cancer.

Circulating levels of VEGF were increased in patients with hormone-refractory prostate cancer, and are prognostic to survival.

One of the first antiangiogenic agents to be evaluated in patients with prostate cancer was thalidomide. Thalidomide has single-agent activity in hormone-refractory prostate cancer, as demonstrated in a study by Figg and colleagues,[8] in which 14% of patients treated with thalidomide at dosages of oral 200 to 1200 mg every day manifested a 50% or greater PSA decline. Unfortunately, the reported median survival of 15.8 months was not significantly higher than that in historical controls.[8] However, thalidomide appears to sensitize epithelial cells to the effects of chemotherapeutic agents. In addition to their ability to stabilize cytoplasmic microtubules, taxanes, both in vitro and in animal model systems, are antiangiogenic. To evaluate the possible interactions

between docetaxel and thalidomide, a randomized phase II study designed by Figg and colleagues compared weekly docetaxel with the combination of docetaxel and thalidomide. Although the primary endpoint of this trial was to evaluate the increase in toxicity of adding thalidomide to docetaxel, and not to detect a survival difference, the reported median survival of 28.9 months for docetaxel combined with thalidomide is the highest median survival reported for a phase II study at that time. Further follow-up found that the survival difference was significant in favor of docetaxel combined with thalidomide (25.9 months vs 14.7 months).[9] Newer compounds in this class have significantly higher levels of antitumor activity in animals, and will be evaluated in men with androgen-independent prostate cancer.

Monoclonal antibodies directed against VEGF can inhibit angiogenesis. A randomized trial found that a monoclonal antibody to VEGF, bevacizumab, can improve survival in patients with colorectal cancer treated with irinotecan, 5-fluorouracil, and leucovorin when compared with those treated with irinotecan, 5-fluorouracil, or leucovorin alone.[10] This antiangiogenesis approach is also being evaluated in prostate cancer. Picus[11] treated 79 men with hormone-refractory prostate cancer with docetaxel 70 mg/m^2 every 3 weeks, oral estramustine 280 mg 3 times daily for 5 days, and bevacizumab 15 mg/kg on day 2. This study found a similar time to progression and survival times with docetaxel/bevacizumab in patients with hormone-refractory prostate cancer when compared with previous estramustine-docetaxel–based studies.[11]

It is clear that these preliminary results evaluating combination chemotherapy with antiangiogenesis agents in hormone-refractory prostate cancer are promising, and may represent a therapeutic avenue to improving overall survival. A randomized study comparing docetaxel/prednisone/avastin with docetaxel and prednisone is now underway in the CALGB.

Calcitriol Combined with Taxanes

Calcitriol, the biologically active form of vitamin D, inhibits proliferation of prostate cell lines.[12,13] Additionally, calcitriol increases cytotoxicity of taxanes independent of bcl-2. One difficulty in treating patients with high doses of calcitriol is the development of hypercalcemia; this complication can be avoided by administering calcitriol pulsed at a high dose weekly. A single-institution phase II study of docetaxel 36 mg/m^2 for 6 of 8 weeks combined with calcitriol in men with androgen-independent prostate cancer found a PSA decline rate of 50% in 81% of treated patients, with a median time to progression of 11.4 months. Fifty-three percent of patients with measurable disease had a partial response.[14] To further evaluate this high response rate, a randomized phase II trial, Androgen Independent Prostate Cancer Study of Calcitriol Enhancing Taxotere (ASCENT) compared pulsed high-dose calcitriol, 45 μg every day (DN101) plus weekly docetaxel 36 mg/m^2/week for 3 of 4 weeks versus docetaxel alone. Although the primary endpoint, measuring a difference in 50% PSA decline rates at 6 months (power of 85% to detect a difference from 45% to 65%) did not reach statistical significance, an adjusted survival analysis demonstrated improved survival in patients treated with the combination over weekly docetaxel. The rates of serious adverse events were significantly lower in the combination arm (27%) versus the docetaxel-only arm (47%). There were significantly fewer gastrointestinal events (9.6% vs 2.4%) and deep venous thrombosis (7.2% vs 1.5%) in those patients receiving combination therapy versus docetaxel alone. The exact mechanism of the decreased risk of deep venous thromboses is unknown but may be related to reductions in the level of tissue factor, a known procoagulant. Prospective confirmation is needed to determine whether DN101 truly reduces docetaxel-based toxicity.[15] A 900-patient phase III study, ASCENT II, will compare every-3-week docetaxel 75 mg/m^2 combined with prednisone to weekly docetaxel combined with DN101. This study is scheduled to open in 2006.

Calcitriol, the biologically active form of vitamin D, inhibits proliferation of prostate cell lines.

Sipuleucel-T

Sipuleucel-T is an autologous CD54-positive dendritic cell vaccine loaded with a recombinant granulocyte macrophage–colony-stimulating factor (GM-CSF) and a prostatic acid phosphatase fusion protein. In a phase III randomized placebo-controlled trial of 127 men with progressive asymptomatic androgen-independent prostate cancer (AIPC), patients received sipuleucel-T or placebo. The primary endpoint was time to disease progression. Secondary endpoints included time to onset of disease-related pain and overall survival. Although treatment with sipuleucel-T did not result in a statistically significant delay in time to disease progression, it did result in a statistically significant (P = .01) survival advantage of 4.5 months in

an intention-to-treat analysis of patients with AIPC. Subsequent chemotherapy with docetaxel was equally distributed in both arms. After adjusting for 20 prognostic factors, the overall treatment effect was significant at a *P* value of .002.[16] A second trial found similar results. It is clear that the traditional measures of outcome such as time to progression may not be appropriate for the evaluation of the efficacy of immune therapy. The observation of improved survival with sipuleucel-T is being confirmed in the third randomized trial in men with hormone-refractory prostate cancer. Other populations are also under study; the combination of sipuleucel-T with bevacizumab is also being evaluated in a phase II trial in men with hormone-sensitive prostate cancer.[17]

GVAX Vaccine

GVAX (Cell Genesys, South San Francisco, CA) promotes GM-CSF secretion through genetic modification of allogeneic prostate cancer cell lines LNCaP and PC-3.[18] Preliminary results in patients treated with autologous prostate cancer cells transduced with GM-CSF found this technique to be safe, and found induction of T cell responses.[18] In a small phase II trial of men with metastatic hormone-refractory prostate cancer (N = 34), Simons and colleagues found that GVAX immunization was well tolerated. In a larger phase II trial (N = 80), Small and colleagues found that GVAX immunization stabilized or decreased levels of a biomarker of osteoclast activity in the majority of patients with metastatic disease.[19] Two phase III trials are in progress in symptomatic and asymptomatic men with metastatic prostate cancer. VITAL I compares GVAX to docetaxel and prednisone in men with asymptomatic hormone-refractory prostate cancer. VITAL II will be performed in symptomatic patients, and will compare GVAX combined with docetaxel and prednisone to docetaxel.

Viral vectors can provide another delivery mechanism for antigens for vaccination.

Viral vectors can also provide another delivery mechanism for antigens for vaccination. These vectors can mimic natural infection and thus augment the immune response. The poxvirus family has been used to deliver PSA antigens as well as other immunomodulatory genes. The Eastern Cooperative Oncology group evaluated the feasibility and tolerability of a prime/boost vaccine strategy using vaccinia virus and fowlpox virus expressing human PSA in patients with biochemical progression after local therapy for prostate cancer. 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.[20] A phase I study evaluated a vaccine virus vector and the co-stimulatory molecules B7-1, ICAM-1, and LFA-3. The approach was found to be safe, and PSA stabilization was noted in 4 of 10 patients treated.[21]

In conclusion, docetaxel-based therapy is the FDA-approved standard of care for men with androgen-independent prostate cancer. New combinations are showing promising activity in this disease, and the optimal sequences and timing of treatment are undergoing evaluation. ■

References

1. Petrylak DP. Chemotherapy for androgen-independent prostate cancer. *Semin Urol Oncol.* 2002;20:31-35.
2. Nelson J, Bagnato A, Battistini B, et al. The endothelin axis: emerging role in cancer. *Nat Rev Cancer.* 2003;3:110-116.
3. Carducci MA, Padley RJ, Breul J, et al. Effect of endothelin-A receptor blockade with atrasentan on tumor progression in men with hormone-refractory prostate cancer: a randomized, phase II, placebo-controlled trial. *J Clin Oncol.* 2003; 21:679-689.
4. Vogelzang N, Nelson J, Schulman C, et al. Meta-analysis of clinical trials of atrasentan 10 mg in metastatic hormone-refractory prostate cancer. *Proc Am Soc Clin Oncol.* 2005;23:393S.
5. Hussain M, Tangen CM, Lara PN Jr, et al. Ixabepilone (epothilone B analogue BMS-247550) is active in chemotherapy-naive patients with hormone-refractory prostate cancer: a Southwest Oncology Group trial S0111. *J Clin Oncol.* 2005;

Main Points

- Docetaxel-based therapy improves survival in patients with advanced prostate cancer when androgen ablative therapy has failed.
- Patient survival with docetaxel-based therapy is improved by 20% to 24% when compared with survival with mitoxantrone and prednisone therapy.
- Preliminary results evaluating combination chemotherapy with antiangiogenesis agents in hormone-refractory prostate cancer are promising, and may represent a therapeutic avenue to improving overall survival.
- Activation of the immune system either through dendritic cells or novel prostate cancer vaccines provides a new approach to the treatment of metastatic disease.

23:8724-8729.
6. Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease. *Nat Med*. 1995; 1:27-31.
7. George DJ, Halabi S, Shepard TF, et al. Prognostic significance of plasma vascular endothelial growth factor levels in patients with hormone-refractory prostate cancer treated on Cancer and Leukemia Group B 9480. *Clin Cancer Res*. 2001;7:1932-1936.
8. Figg WD, Dahut W, Duray P, et al. A randomized phase II trial of thalidomide, an angiogenesis inhibitor, in patients with androgen-independent prostate cancer. *Clin Cancer Res*. 2001;7:1888-1893.
9. Retter AS, Ando Y, Price DK, et al. Follow-up analysis of a randomized phase II study of docetaxel (D) and thalidomide (T) in androgen-independent prostate cancer (AIPC): updated survival data and stratification by CYP2C19 mutation status. *Proc 2005 ASCO Prostate Cancer Symposium*. 2005;1:Abstract 65.
10. Hurwitz H. Bevacizumab (a monoclonal antibody to vascular endothelial growth factor) prolongs survival in first-line colorectal cancer (CRC): results of a phase III trial of bevacizumab in combination with bolus IFL (irinotecan, 5-fluorouracil, leucovorin) as first-line therapy in subjects with metastatic CRC. *Proc Am Soc Clin Oncol*. 2003;22.
11. Picus J. The use of bevacizumab (B) with docetaxel (D) and estramustine (E) in hormone refractory prostate cancer (HRPC): initial results of CALGB 90006. *Proc Am Soc Clin Oncol*. 2003; 22:393.
12. Wang YR, Wigington DP, Strugnell SA, et al. Growth inhibition of cancer cells by an active metabolite of a novel vitamin D prodrug. *Anticancer Res*. 2005;25:4333-4339.
13. Getzenberg RH, Light BW, Lapco PE, et al. Vitamin D inhibition of prostate adenocarcinoma growth and metastasis in the Dunning rat prostate model system. *Urology* 1997;50:999-1006.
14. Beer TM, Hough KM, Garzotto M, et al. Weekly high-dose calcitriol and docetaxel in advanced prostate cancer. *Semin Oncol*. 2001;28:49-55.
15. Beer TM, Ryan CW, Venner PM, et al. Interim results from ASCENT: a double-blinded randomized study of DN-101 (high-dose calcitriol) plus docetaxel vs. placebo plus docetaxel in androgen-independent prostate cancer (AIPC). *Proc Am Soc Clin Oncol*. 2005;23:382s.
16. Small EJ, Schellhammer PF, Higano CS, et al. Results of a placebo-controlled phase III trial of immunotherapy with APC8015 for patients with hormone refractory prostate cancer (HRPC). *Proc Am Soc Clin Oncol*. 2005;23:378s.
17. Beinart G, Rini BI, Weinberg V, et al. Antigen-presenting cells 8015 (Provenge) in patients with androgen-dependent, biochemically relapsed prostate cancer. *Clin Prostate Cancer*. 2005;4:55-60.
18. Simons JW, Mikhak B, Chang JF, et al. Induction of immunity to prostate cancer antigens: results of a clinical trial of vaccination with irradiated autologous prostate tumor cells engineered to secrete granulocyte-macrophage colony-stimulating factor using ex vivo gene transfer. *Cancer Res*. 1999;59:5160-5168.
19. Simons J, Higano C, Smith D, et al. Clinical and immunologic findings in a phase 2 study of a GM-CSF-secreting prostate cancer cell line vaccine in patients with metastatic hormone-refractory prostate cancer (met HPRC). *Proc Soc Am Clin Oncol*. 2005;23:170s.
20. Kaufman HL, Wang W, Manola J, et al. Phase II randomized study of vaccine treatment of advanced prostate cancer (E7897): a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2004;22:2122-2132.
21. Dipaola R, Plante M, Kaufman H, et al. A Phase I trial of Pox PSA vaccines (PROSTVAC(R)-VF) with B7-1, ICAM-1, and LFA-3 co-stimulatory molecules (TRICOMtrade mark) in patients with prostate cancer. *J Transl Med*. 2006;4:1.