Developing Treatments for Hormone-refractory Prostate Cancer

a report by
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Prostate cancer is the most commonly diagnosed non-cutaneous malignancy afflicting American males. Initial androgen deprivation achieved through either surgical or medical castration leads to symptomatic and biochemical improvement in approximately 80% of men with metastatic prostate cancer. The long-term outcome for patients with newly diagnosed metastatic prostate cancer was reviewed in a large retrospective analysis by Tangen et al.[1] Of the 794 evaluable patients followed for at least 10.5 years, 23% were alive at five years and 7% at 10 or more years.

For many years prostate cancer was considered to be inherently resistant to most conventional chemotherapeutic agents. In 2004, the results of two pivotal studies were reported, demonstrating for the first time a survival advantage for hormone-refractory prostate cancer (HRPC) patients treated with docetaxel.[2,3] Recent advances in our understanding of the molecular biology of prostate cancer and the processes that regulate prostate cancer cell growth and death have led to the rational development of targeted therapies. Unlike traditional cytotoxic chemotherapy, targeted therapies block cancer cell proliferation by interfering with specific molecules that are often mutated or over-expressed in tumors and play an important role in their growth and development. This article will provide an update of some of the promising secondary hormonal therapies, newer chemotherapeutic agents, and targeted therapies currently under study for the treatment of HRPC.

New Secondary Hormonal Therapies

After failure of initial androgen-deprivation therapy, a number of secondary hormonal treatments for metastatic prostate cancer have been utilized, including antiandrogens,[4] adrenal androgen inhibitors,[5] estrogens and progestins,[6] and glucocorticoids.[7] Although meaningful responses have been achieved with many of these agents, a survival benefit in a randomized phase III trial has not yet been demonstrated.

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Abiraterone acetate is a member of a new class of drugs that blocks the production of intratumoral androgen by irreversibly inhibiting a lyase enzyme known as CYP17. This enzyme is vital for the synthesis of dehydroepiandrosterone (DHEA) and androstenedione, the direct precursors of testosterone synthesis in humans, and its inhibition results in a decrease in downstream androgenic steroid signaling.[8] Although abiraterone shares some similarities with ketoconazole, a commonly used secondary hormonal therapy, it is a more potent and specific inhibitor of CYP17.[9]

The results of two phase II trials of abiraterone in chemotherapy-naïve and docetaxel pre-treated metastatic HRPC patients were recently reported. In the COU-AA-001 trial, 44 chemotherapy-naïve patients who had received a median of three prior hormone therapies were treated with abiraterone for at least three months.[10] Twenty-seven patients (61%) had prostate-specific antigen (PSA) declines of >50% and 11 patients (25%) had PSA declines of >90%. Twenty-one patients had measurable tumor lesions and 12 of these (57%) had partial radiological responses according to the Response Evaluation Criteria in Solid Tumors (RECIST). Patients also experienced reductions in pain intensity and analgesic use. The most commonly observed side effects were grade 1–2 hypertension, hypokalemia, and lower-extremity edema. The median time to PSA progression was 8.4 months. In the COU-AA-004 trial, abiraterone was given in combination with prednisone to 38 metastatic HRPC patients previously treated with docetaxel.[11] Seventeen patients (45%) had PSA declines of >50%. Twenty-one patients had not previously received ketonocazole and 12 (57%) had PSA declines of >50%. In 17 patients previously treated with ketoconazole, five (29%) had PSA declines of >50%. Of the 24 patients with lesions evaluable by bone scan, 16 had stable disease as defined by PSA Working Group Criteria. One of 16 patients with evaluable lymph node metastasis had a partial response and nine had stable disease. Three of six patients with evaluable visceral metastases had stable disease. There was no grade 3 or 4 hypertension or hypokalemia. Based on these preliminary results, a phase III trial whose primary end-point is improvement in overall survival is currently comparing abiraterone plus prednisone with placebo and prednisone in patients with metastatic castrate-resistant prostate cancer who have failed one or two chemotherapy regimens (one of which contained docetaxel).

New Chemotherapeutic Agents

Tubulin-targeting Agents

Drugs that target the mitotic spindles and disrupt the normal progression of mitosis have been among the most widely studied and active chemotherapeutic agents in the treatment of prostate cancer. These agents can bind to a number of tubulin-binding sites and induce the polymerization

and stabilization of microtubules, leading to cell-cycle arrest, inhibition of tumor cell proliferation, and programmed cell death.[12] Epothilones are a novel class of tubulin-targeting agents that demonstrate activity in taxane-resistant cell lines and animal models.[13] Ixabepilone was the first epothilone to be evaluated in clinical trials and the first to be approved for the treatment of metastatic breast cancer.[14] Antitumor activity was also demonstrated in phase I and II trials against metastatic prostate cancer. In a phase II trial of ixabepilone monotherapy in chemotherapy-naïve HRPC patients, a PSA response rate of 33% was reported with a median survival of 18 months.[15] In a second phase II trial of ixabepilone with or without estramustine, a PSA response rate of 48% was observed in patients receiving ixabepilone alone compared with a 69% rate in the combination arm.[16] The results of a randomized phase II trial of ixabepilone or mitoxantrone in the second-line setting following progression on a taxane have been reported.[17] A PSA decline of 17% was observed for the ixabepilone arm. A phase I–II trial of ixabepilone in combination with mitoxantrone as second-line therapy for metastatic HRPC is in progress.

XRP6258 (Sanofi-aventis) is an oral bioavailable semi-synthetic taxoid derivative that binds to and stabilizes tubulin, resulting in the inhibition of microtubule depolymerization and cell cycle arrest.[18] Unlike other taxanes, XRP 6258 is a poor substrate for the MDR P-glycoprotein efflux pump, and may therefore be useful for treating multidrug-resistant tumors. XRP 6258 has shown activity in patients with taxane-resistant metastatic breast cancer.[19] A study of an intravenous formulation of XRP6258 plus prednisone versus standard mitoxantrone and prednisone in patients with HRPC after failure of docetaxel-based chemotherapy is currently under way.

Platinum Analogs

Satraplatin was the first oral platinum analog to enter clinical trials. Its antitumor activity in pre-clinical models was similar to that of cisplatinum and carboplatin, with less cross-resistance to these platinum drugs.[20] In phase I–II trials, significant activity against a variety of solid tumors—including prostate cancer—was demonstrated. Based on preliminary results from a randomized phase III trial in which chemotherapy-naïve HRPC patients randomized to a combination of satraplatin plus prednisone had a significant improvement in progression-free survival (PFS) compared with prednisone alone,[21] a large multinational phase III trial was conducted. This trial compared satraplatin plus prednisone versus placebo plus prednisone in patients with HRPC who had progressed on first-line therapy.[22] Its primary end-point was an improvement in PFS. The median time to progression for patients who received satraplatin was 11.1 versus 9.7 weeks for the placebo arm ($p<0.001$). Satraplatin was also superior to prednisone in PSA response, pain response, and duration of pain response. However, with longer follow-up, median survival for both satraplatin and placebo was 61 weeks.[23] Due to the lack of survival data, the US Food and Drug Administration (FDA) did not recommend approval for satraplatin as a second-line treatment for HRPC.

Differentiation Therapies

The most widely studied differentiation agents in prostate cancer treatment have been the vitamin D analogs. The major active metabolite of vitamin D is calcitriol, a naturally occurring hormone that is believed to exert its main antineoplastic effects by inhibiting cellular proliferation and inducing apoptosis.[24] Early dose-escalation clinical trials of calcitriol in the treatment of prostate cancer were hampered by the development of treatment-induced hypercalcemia and hypercalciurea.[25] Subsequently, a weekly oral formulation of calcitriol, DN-101, which allowed higher concentrations of the active metabolite to be achieved without dose-limiting toxicities, was developed.[26] Following the demonstration of *in vitro* synergy when calcitriol was combined with cytotoxic drugs,[27] a series of clinical trials was initiated.

In a pilot study of weekly DN-101 with or without docetaxel in patients with metastatic HRPC, 81% of patients had a PSA decline of >50% after a median duration of therapy of 10 months.[28] There was no increased toxicity in the combination arm compared with docetaxel alone. A confirmatory double-blind, randomized, placebo-controlled phase II trial of weekly docetaxel, prednisone, and DN-101 versus weekly docetaxel and prednisone alone (the Androgen-independent Prostate Cancer Study of Calcitriol Enhancing Taxotere [ASCENT] trial) was then conducted in 250 men with HRPC.[29] The primary end-point of this study was the proportion of men who achieved a PSA response within six months of study entry. Although there was no statistically significant difference between the two arms in the proportion of patients achieving a PSA response, there was a benefit in estimated overall survival favoring the combination arm (24.5 versus 16.5 months). Based on these results, a phase III placebo-controlled trial (ASCENT II) was initiated to compare weekly docetaxel and prednisone plus DN-101 versus standard docetaxel and prednisone given every three weeks, with overall survival as the primary end-point. However, this study was closed to accrual in November 2007 after an initial review by the Data and Safety Monitoring Board, and the status of further development for DN-101 is unclear.

Antiangiogenic Therapies

The major mediator of tumor angiogenesis is vascular endothelial growth factor (VEGF), which signals mainly through VEGF receptor 2 (VEGFR-2). This receptor is over-expressed in tumor endothelial cells engaged in angiogenesis.[30] In patients with prostate cancer, high VEGF expression and increased microvessel density have been associated with angiolymphatic invasion, lymph node status, and distant metastasis.[31] Pre-clinical studies have suggested several possible mechanisms by which antiangiogenic therapies may enhance the efficacy of chemotherapy.[32–34] In an early phase II trial of an antiangiogenic and cytotoxic agent, 75 patients with metastatic HRPC were randomized to receive combined thalidomide and docetaxel or docetaxel alone.[35] Although this study was not powered to detect a statistically significant difference in survival, the median overall survival was doubled from 14.7 months in the docetaxel-alone arm to 28.9 months in the combination arm ($p=0.0407$). Treatment was well tolerated, but patients in the combination arm required low-molecular-weight heparin to reduce the risk for venous thromboembolism. Despite the impressive median overall survival achieved with thalidomide and docetaxel, a confirmatory phase II trial has not been performed to date.

Bevicizumab, a humanized monoclonal antibody that targets vascular endothelial growth factor, has significant activity in combination with chemotherapy in metastatic colorectal, lung, and breast cancer.[36–38] Although inactive as a single agent in HRPC,[39] the combination of bevacizumab, docetaxel, and estramustine showed substantial activity in a phase II co-operative group trial.[49] A PSA decline of >50% was achieved in 81% of patients with HRPC. The median time to progression (9.7 months) and median survival (21 months) was similar to that seen with previous docetaxel–etramustine-based studies. A randomized phase III study of docetaxel and prednisone with or without bevacizumab is currently being

conducted by the Cancer and Leukemia Group B (CALGB), with the primary goal of improving median survival from 19 to 24 months. Since thalidomide and bevacizumab exert their antiangiogenic effects by different mechanisms, it was postulated that combining these agents with docetaxel might provide high PSA and objective response rates in patients with advanced prostate cancer. In a phase II study, 55 patients with metastatic HRPC (most with a high Gleason score and pre-study PSA doubling time of <3 months) were treated with this combination.[41] A high durable PSA decline rate (87%) and high response rate in measurable disease (52%) was achieved, with an estimated PFS of 18.2 months. However, significant toxicities, including febrile neutropenia, syncope, gastrointestinal perforation or fistula, thrombosis and grade 3 bleeding, were observed.

VEGF-trap, or aflibercept, is a specific antagonist that binds to and inactivates circulating VEGF in the bloodstream and extravascular space. It was designed to prevent the growth of primary and metastatic tumors by reducing tumor vascularity and vascular permeability. In addition to its high binding affinity for VEGF, aflibercept also binds to insulin-like growth factors, which have been implicated in the development, maintenance, and progression of cancer.[42] A phase II multicenter randomized double-blind study comparing docetaxel with or without aflibercept in the first-line treatment of metastatic HRPC is currently being conducted. The primary efficacy end-point is overall survival.

Bone-targeting Agents

Bone metastasis occurs in up to 80% of prostate cancer patients and is largely driven by the secretion of endothelin 1 (ET-1), a vascular endothelial protein, and its receptors ETA and ETB. Activation of the ETA receptor by ET-1 facilitates several aspects of prostate cancer progression.[43] Atrasentan is a selective oral ETA receptor antagonist that significantly reduced the osteoblastic response occurring in ET-1-secreting animal models. In a phase III study, men with non-metastatic HRPC and PSA progression were randomized to receive atrasentan or placebo. There were no statistically significant differences observed in the primary end-points of time to development of metastatic disease and PFS between the two treatment arms. However, there was a trend toward improved survival in the atrasentan arm.[44] Based on these preliminary findings, a phase III trial comparing docetaxel, prednisone, and atrasentan versus docetaxel, prednisone, and placebo is currently accruing patients with the primary end-point of PFS. Further studies with other selective ET-1 antagonists (ZD4054) are ongoing.[45]

Therapeutic Prostate Cancer Vaccines

Several prostate-specific and tumor-associated antigens that serve as targets for vaccine therapy have been identified. These include cell surface proteins (PMSA, prostate stem cell antigen, and human epidermal growth factor receptor 2 [HER-2]-neu), secreted proteins (PSA and PAP), and intracellular proteins (P- and G-antigen family members).[46] There are currently four main types of prostate cancer vaccine, based on the technique used for preparation.[47] These include vaccines generated from allogeneic tumor cells (G-VAX), vaccines prepared from autologous tumor cells enriched with dendritic cells (Sipuleucel-T or Provenge), protein and peptide vaccines, and poxvirus-based vaccines (PROSTVAC). G-VAX (Cell Genesys, Inc.) is a tumor cell vaccine made from irradiated allogeneic prostate cancer cells that are genetically modified to secrete high levels of human GM-CSF to enhance the immunogenicity of the tumor cells.[48–50] A combined analysis of 114 metastatic HRPC patients treated with G-VAX in two phase II trials was reported by Small et al.[51] Median survival estimated by the Kaplan-Meier method was compared with survival predicted by a pre-treatment nomogram developed by Halabi that included the parameters of lactate dehydrogenase, PSA, alkaline phosphatase, Gleason sum, ECOG performance status, and the presence or absence of visceral metastases.[52] In the first phase II trial (G9803), the median survival for 34 patients was 26.2 months compared with 19.5 months (p=0.01) predicted by the Halabi nomogram. In the second phase II trial (G-0010), a re-engineered GVAX formulation was used to secrete higher levels of GM-CSF. The median survival in this trial was 35 months.

Based on a median survival that was longer than would be expected with chemotherapy or observation alone, two phase II trials comparing G-VAX and docetaxel were initiated. In the VITAL-1 study, patients with asymptomatic HRPC were randomized to receive initial treatment with G-VAX followed by a treatment boost every 14 days for six months or docetaxel every 21 days with prednisone for up to nine cycles. The primary end-point of this trial is overall survival. VITAL 1 recently completed accrual and a final analysis is planned for 2009. In the VITAL-2 study, symptomatic HRPC patients were randomized to receive G-VAX in combination with docetaxel or docetaxel plus prednisone every 21 days for 10 cycles.

Sipuleucel-T, or provenge vaccine (Dendrion, Inc.), is an active cellular immunotherapy that uses the patient's own antigen-presenting (dendritic) cells obtained during a standard leukopheresis procedure.[53] The harvested cells are then co-cultured *ex vivo* with a recombinant fusion protein containing human prostate acid phosphatase (PAP) and granulocyte-macrophage colony stimulating factor (GM-CSF). Activated antigen-loaded dendritic cells are then infused into the patient, where they stimulate a T-cell response (via internalization and processing of PAP antigen) to cells expressing the GM-CSF receptor.

The results of a phase III trial comparing sipuleucel-T with placebo were reported in 2006.[54] One hundred and twenty-seven men with asymptomatic metastatic HRPC were randomized to receive intravenous sipuleucel-T or placebo once every two weeks for a total of three doses. Eligible patients were either chemotherapy-naïve or previously chemotherapy-treated, and had ECOG performance status of 0 or 1, radiological evidence of metastatic disease, and castrate levels of testosterone. The primary end-point was time to progression (TTP), defined as radiological or cancer-related pain progression, but not PSA progression. The median TTP was 11.7 weeks for sipuleucel-T versus 10 weeks for placebo (p=0.052). Treatment on the vaccine arm was well-tolerated. Although the primary end-point of TTP was not achieved, the three-year overall survival was 34% in the vaccine-treated group versus 11% in the placebo group (p=0.0046). This was the first demonstration of prolongation of survival by a vaccine treatment for prostate cancer. FDA approval of sipuleucel-T is awaiting final analysis of a confirmatory phase III placebo-controlled trial with overall survival as the primary end-point.

PROSTVAC (Therion, Inc.) was the first viral vector vaccine to be tested in prostate cancer. In this type of vaccine, genes that encode tumor-associated antigens or co-stimulatory proteins are sequentially

inserted into attenuated smallpox and fowlpox viral vectors. The efficacy of the vaccine is enhanced by the addition of three co-stimulatory molecules called TRICOM to enhance T-cell stimulation and GM-CSF to help increase tumor-specific immunity.[55] These viral vectors stimulate antigen-presenting cells and induce a specific T-cell response to tumor cells expressing PSA.

Phase I and II studies have confirmed the safety and efficacy of PROSTVAC in early- and advanced-stage prostate cancer.[55,56] A randomized, double-blind phase III trial (the Paradigm study) is currently recruiting men with biochemical PSA progression and no measurable disease. The primary end-point is time to development of metastatic disease.

Conclusion

Docetaxel given every three weeks with prednisone is the current standard of care for the treatment of metastatic HRPC. A number of promising targeting agents, as well as secondary hormonal therapies and new chemotherapeutic agents, are currently under investigation in phase II and III clinical trials with the hope of further improving overall survival in this group of patients. ■

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