Advanced prostate cancer: the future

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The demonstration of a survival benefit with docetaxel for the treatment of metastatic hormone refractory prostate cancer (HRPC) is an important step forward in advancing treatment options for advanced prostate cancer. While docetaxel-based therapy has demonstrated improvement in symptomatic and quality-of-life endpoints, certainly there is a pressing need for improvement in outcomes. A number of novel agents are in basic and clinical development for advanced prostate cancer, some of which are specific to mechanisms that may be important in the development and spread of prostate cancer. Novel approaches including novel cytotoxics, immunotherapy, PSMA targeted monoclonal antibodies are among the broad categories that will be discussed in this brief review

Key Words: prostate cancer, immunotherapy, angiogenesis, novel therapies, vaccines

Introduction

The 2-3 month survival benefits reported in the TAX327 and SWOG 9916 trials were the first demonstrated improvements in overall survival with a cytotoxic agent and confirmed that docetaxel-based chemotherapy is the new standard of care with which to compare novel agents.[1,2] Currently, over 200 novel therapies are being tested in patients with advanced prostate cancer, both in combination and as single agents. Given the molecular complexity of the prostate cancer cell pathways and our overall current lack of understanding of the driving forces behind prostate cancer development and progression, the inhibition of multiple pathways may be required to produce sustained and clinically meaningful responses. The major pathways that are under therapeutic investigation in prostate cancer are those involved in growth and survival, chemotherapy and hormonal therapy resistance, angiogenesis, immune surveillance and escape, and in stem cell renewal. The following sections will provide an overview of some of these

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TABLE 1. **Overview of rational target exploration in prostate cancer**

Target pathways	**Examples of agents in development**
Receptor tyrosine kinase inhibitors	Imatinib, gefitinib, lapatinib, others
Proteasome inhibitors	Bortezomib
Endothelin-1 inhibitors*	Atrasentan
mTOR inhibitors	CCI-779, RAD001
Anti-angiogenic agents	Thalidomide, bevacizumab
Differentiation therapy	Vitamin D analogs, HDAC and methylation inhibitors
Anti-apoptosis	Oblimersen sodium
Immunomodulatory agents*	Vaccines, thalidomide, anti-CTLA4 combinations, revlimid, actimid
Monoclonal antibodies to surface antigens	MLN 2704, MDX 070, radioisotope conjugates
Novel cytotoxics*	Epothilones, satraplatin, abraxane

*Discussed in this article

pathways as they pertain to prostate cancer specifically as rational targets and the approaches that are currently being developed to block these pathways Table 1. Novel cytotoxic agents will be discussed first.

Novel cytotoxic agents

While a full discussion of novel cytotoxic agents is beyond the scope of this discussion, epothilone analogs, abraxane, and satraplatin will be discussed briefly. The epothilones are a class of microtubule targeting cytotoxic agents in development for second line and relapsed HRPC, and are derived from the myxobacterium *Sorangium cellulosum*.[3] In preclinical models they have demonstrated a wide range of clinical activity, including taxane resistant models. While sharing a common mechanism of action with the taxanes, they are not apparently susceptible to P-glycoprotein induced drug efflux.[3] One such agent, Epothilone-B analogue BMS-247550 (Ixabepilone®, Ingenta, Cambridge MA) has been studied in a phase II trial of men with HRPC.[4] Initial results demonstrated a 34% PSA response and 30% objective response, with a progression free survival of 8 months, comparable those seen with docetaxel based therapy. Use of these drugs may be limited by dose limiting neurotoxicity similar to that seen with the taxanes.[4,5] The use of BMS 247550 in taxane-resistant HRPC is under investigation.[6,7]

Other novel formulations of taxanes, such as the nanoparticle albumin-bound paclitaxel formulation Abraxane® (Abraxis Oncology, Los Angeles CA) remains untested in prostate cancer but of emerging interest. Abraxane is the first biologically interactive nanoparticle composition exploiting the albumin receptor-mediated (gp60/caveolin-1) pathway, achieving high intratumor concentrations of the active ingredient paclitaxel.[8] Abraxane may exploit SPARC (Secreted Protein Acidic Rich in Cysteine, or Osteonectin) and Caveolin-1 to deliver drug preferentially to tumors. Both SPARC and Caveolin-1 are over-expressed in prostate cancer and are associated with poor prognosis.[9]

The oral platinum drug Satraplatin (SpectrumPharm, Irvine CA), is under investigation as second line chemotherapy for HRPC. While this does not likely represent any mechanistic advance in management, the tolerability, ease of administration, and preliminary efficacy may make this compound suitable for those patients who have progressed on therapy. An underpowered phase II trial of Satraplatin given orally for 5 days at 100 mg/m2 in combination with prednisone showed non-significantly improved overall survival and time-to-progression compared to prednisone alone in HRPC, and a larger phase III trial, the SPARC trial (Satraplatin in Refractory Cancer) has been initiated for relapsed patients.[10]

Endothelin-1 and its receptor as a therapeutic target

While the endothelin receptor may seem an unlikely target in prostate cancer given its predominantly vascular role, ET-A receptors are over-expressed in prostate cancer and higher plasma endothelin levels have been shown to correlate with tumor stage, grade, and metastases.[11-13] Endothelin-1 is a

potent vasoconstrictor and one such antagonist (bosentan) has been developed for the treatment of pulmonary hypertension; however, the endothelin family (ET-1, 2 and 3) has also been shown to have multiple effects on cellular physiology and paracrine signaling in prostate cancer. Endothelin-1 is known to influence cell growth via the MAPK pathway and is co-mitogenic with additional growth factors such as IGF-I and II and it has been shown to regulate apoptosis, perhaps through its interactions with bcl-2 and PI3K/akt pathways.[11-13] ET-1 also has been shown to regulate angiogenic and osteoblast activity and is likely involved in the paracrine signals between osteoblasts and prostate cancer cells that regulate the development of painful bony metastases in prostate cancer.[12-15] Thus, the endothelin axis is a rational target for the interference of prostate cancer and bone stromal interactions.[12-15]

Atrasentan (Xinlay®, Abbott Labs, Abbott Park IL) has been developed as highly selective ET-A receptor antagonist and is the most clinically developed agent of this class in prostate cancer.[16] In dose-ranging trials of this agent, the 10 mg dose was found to prolong time-to-progression in the fully evaluable subset of men with metastatic HRPC by 67 days when compared to placebo (196 versus 129 days, respectively, p=0.021).[14,17] Adverse events with atrasentan were mild and related to vasomotor reactions, including headache, rhinitis, flushing, and peripheral edema. Favorable effects were seen in markers of bone deposition and resorption, which led to its further clinical development.

In the phase III trial, 809 patients with metastatic HRPC were randomized to placebo or 10 mg of oral atrasentan, with the primary clinical endpoint being time to progression (TTP). Although TTP was not found to be statistically significantly different from placebo in the intent-to-treat analysis, several secondary endpoints indicated clinical activity, including improvements in quality-of-life scores, pain scores, and reductions in the rise of laboratory markers including alkaline phosphatase and PSA.[14] A robust meta-analysis of pooled phase II and III data of similarly treated patients with similar baseline characteristics increased the power of the original planned analyses and demonstrated a significant increase in time-to-progression (p=0.013), a 19% reduction in risk of disease progression. The median pain-free duration was also found to be prolonged in this meta-analysis by 100 days, and patients taking atrasentan remained pain-free for a longer period of time (224 versus 127 days in the placebo arm).[14]

These results clearly point to biologic activity of the endothelin axis in modulating osteoblastic metastases, but underscore the difficulty in studying bony lesions and measuring bony progressive disease. Abbott has filed for FDA approval for atrasentan based on these results, and a large phase III trial of atrasentan in asymptomatic men with a rising PSA after local therapy is ongoing.[14] Another ET-A receptor antagonist, ZD4054 (Astra Zeneca, Waltham MA), is earlier in clinical phase II development at this time.[13]

Immunotherapy

Entraining the host immune system to reject its own developing tumor has been a long-sought after goal of cancer therapy since the original theories of immune surveillance were proposed by Paul Ehrlich, Sir MacFarlane Burnet and Lewis Thomas.[18,19] Active immunotherapy with vaccination against tumor antigens has been pursued in many different cancer models with a variety of techniques, including dendritic cell based therapies, novel adjuvants such as BCG, GM-CSF, or viral carriers, single antigen or whole cell vaccines, and genetically modified tumors.[20] More recently, as our knowledge of danger signals and the link between the innate, adaptive, and regulatory immune response increases, combination therapies using co-stimulatory molecules, CTLA4 blockade, toll-like receptor agonism, and intracellular viral or bacterial mediators have been developed.[20-23]

In prostate cancer, several vaccine strategies have moved forward into rational clinical development. These include the Provenge® autologous PAP (prostate acid phosphatase) loaded dendritic cell vaccine, the GVAX® allogeneic recombinant whole cell vaccine, the Prostvac®-VF recombinant vaccinia-fowlpox PSA vaccine, and the BLP25 MUC1 liposomal vaccine.[24-27] Provenge® and GVAX® are currently in phase III trials of men with HRPC and will be discussed briefly.

Provenge (Dendreon, Seattle WA) is a vaccine derived from CD54+ dendritic cells, the major antigen presenting cells, which are pheresed from individuals and processed with the recombinant fusion protein PAP (prostate acid phosphatase) and GM-CSF. PAP was chosen based on its prostate cell membrane localization and the success of preclinical models using it to generate prostate-specific immune responses and autoimmune prostatitis.[24] In a phase II study of 31 patients receiving every 3 month infusions and a final 24 month boost, 3 patients experienced a PSA decline >50%.[24] This led to a large randomized phase III trial against placebo in 127

asymptomatic men with metastatic HRPC (PAP positive). At the most recent 3 year update, a statistically significant improvement in survival was seen regardless of original Gleason sum despite earlier reports of survival benefits being limited to an unplanned subgroup of men with tumor Gleason sums <=7.[28] While preparation and production of large scale quantities of individually tailored vaccine may be difficult, this vaccine was well-tolerated with minimal infusion-related fever and rigors being the predominant adverse event. Immunologic correlates are forthcoming but were initially reported to be more robust in those with more well-differentiated tumors, suggesting that those at highest risk may not obtain as great of benefit.[29] A larger confirmatory phase III trial is underway in men with metastatic HRPC who have a Gleason score <=7, and the FDA has designated fast-track status to this vaccine.

Prostate GVAX® (Cell Genesys, San Francisco CA) is based on the demonstration of improved immune mediated tumor rejection in melanoma mouse models when an irradiated tumor vaccine expressed the cytokine GM-CSF as compared to other transduced cytokine adjuvants.[30] Given that GM-CSF likely facilitates the maturation and activation of dendritic cells, further work extrapolated these findings in mouse models of prostate cancer with results showing prolonged survival and tumor regression.[31] In a phase I study, autologously derived vaccines were generated and expanded in 8 of 11 patients and T-cell responses were generated in 7 of these 8 following every 21 day vaccination until supply depletion.[32] No clinical responses were observed, and the inherent lack of feasibility of this approach led to the pursuit of allogeneic vaccine strategies using similar technologies. A phase II study of prostate carcinoma cell lines (PC-3 and LnCaP) virally transduced to secrete GM-CSF and lethally irradiated, was conducted in 34 patients with metastatic HRPC.[33] At the highest doses of vaccine (300 million cells), trends toward improved time-to-progression were seen without any observed dose limiting toxicities or autoimmune phenomena. Median survival in this trial was 26 months, historically very favorable. A further evaluation of 80 patients with metastatic HRPC treated at higher doses demonstrated one partial PSA response and improvement in markers of bone turnover, with survival analysis still ongoing.[25] A phase III trial of GVAX® versus docetaxel in men with minimally symptomatic men with metastatic HRPC is currently open for enrollment.

Monoclonal antibodies and targeted cytotoxic agents

Several compounds in early clinical development in prostate cancer include those that use monoclonal antibody technology and tumor-associated antigen specificity to target prostate cancer cells or enhance drug delivery to prostate cancer cells. Phase II testing is underway for several of these agents, including antibodies to PSMA (Prostate surface membrane antigen), MUC-1, and CTLA-4 (cytotoxic lymphocyte-associated antigen-4). Passive immunotherapy with monoclonal antibodies may lead to cell death through a variety of mechanisms, such as antibody-dependent cellular cytotoxicity, complement fixation, and T and B cell idiotype networks. Given the cell surface expression of prostate specific membrane antigen (PSMA) and the over-expression of this antigen on prostate cancer cells, PSMA represents a potential target for these monoclonal antibodies and in fact is currently in clinical use for imaging purposes (Prostascint® scan).[34]

Conjugates to anti-PSMA antibodies in clinical development include the cytotoxin maytansinoid (DM1) and the radioisotopes lutetium-177 and yttrium-90. The anti-PSMA humanized murine monoclonal antibody J591 is one such antibody in development and has shown clinical and biochemical responses in phase I trials in advanced prostate cancer using both radioconjugated and unconjugated approaches.[35,36] In particular, a conjugate of J591 to yttrium-90 was administered to 29 patients with HRPC and showed a maximum tolerated dose of 17.5 mCi/m2, additionally demonstrating selective targeting to metastatic sites and prolonged PSA (>8 months) and measurable disease responses in two patients.[36] MLN 2704 is also derived from J591 and utilizes a conjugated microtubule destabilizing agent maytansinoid (DM1) as a form of targeted cytotoxicity.[37] MLN 2704 is currently in phase I-II studies given as monthly injections for HRPC. Finally, an antibody to MUC-1, a mucin protein on the cell surface of prostate cancer cells that may be important in regulating cell survival, has undergone phase I trials in combination with paclitaxel, another microtubule-targeted agent.[38] Its tolerability and feasibility with demonstrated targeting of bone lesions has also led to the initiation of a phase II study.

While perhaps best suited for discussion in the vaccine section, antibodies to CTLA-4 are also in clinical development in conjunction with vaccination. CTLA-4 is a co-stimulating molecule for B7 that is involved in attenuating activated T-cell responses.

The inhibition of this molecule may enhance T-cell activation, and when used in combination with prostate specific vaccination, may enhance the immunogenicity and autoimmunity induced by vaccination.[39] CTLA-4 blockade in conjunction with GM-CSF is being assessed in early phase I trials, and further dose escalation trials with vaccination strategies are in development with the goal of targeted immunotherapy without the autoimmunity seen in other clinical models such as melanoma.[40,41]

Conclusions

The development of emerging therapies for prostate cancer has required a continual reassessment of the rational targets and the molecular biology underlying prostate cancer development, progression, and therapeutic resistance. As prostate cancer is a heterogeneous disease with widely varying PSA doubling times, survival rates, Gleason scores, and hormone and chemosensitivity, a key to the design of trials of these novel agents is to adequately define the patient population in advance that is most likely to benefit from target inhibition, and that those patients at greatest risk for progression be considered first for targeted therapies. Given the cytostatic nature of many biologic agents, novel trial designs that take into account endpoints such as prolonged stable disease, time to progression, and tissue pharmacodynamic responses are important to fully understand their clinical benefit. It is essential that urologists and both radiation and medical oncologists continue to develop multi-disciplinary collaboration in advancing high priority clinical trials. □

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