Targeted Therapy in the Treatment of Castration-Resistant Prostate Cancer

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In this review, we focus on the testosterone/androgen receptor pathway that is being targeted with potent new agents; we also discuss other important alternative biologic pathways that have given rise to new therapeutics that may attenuate prostate cancer growth, survival, and propagation.

Introduction

Approximately 2.5 million men in the United States are living with prostate cancer. Although survival has increased significantly in the past decade, more than 28,000 men die of metastatic castration-resistant prostate cancer (mCRPC) each year.[1] Androgen deprivation in the form of castration, either medical or surgical, remains the backbone of prostate cancer treatment. Nevertheless, most prostate cancers eventually become resistant to traditional medical or surgical castration and require additional therapeutic interventions. Historically, secondary systemic treatments have included first-generation anti-androgens, adrenal steroid synthesis inhibition with ketoconazole, estrogenic agents, and docetaxel (Taxotere) chemotherapy. However, a clearer understanding of mechanisms of resistance to castration have led to the development of next-generation androgen synthesis inhibitors; androgen receptor (AR) signaling inhibitors; and agents targeting other dysregulated signaling pathways that promote prostate cancer cell proliferation, invasion, and survival. Many of these agents have contributed to improved survival in men with mCRPC, and the median survival for these patients is now approaching 3 years.[2] This review will first discuss novel androgen synthesis inhibitors and AR signaling inhibitors, then focus on other targeted agents in development for the treatment of mCRPC.

Next-Generation Androgen Synthesis Inhibitors and AR Signaling Inhibitors

The role of testosterone in the pathogenesis of prostate cancer has been well established since it was first described by Drs. Huggins and Hodges in 1941.[3] In essence, androgen deprivation therapy (ADT) was one of the first molecular-targeted therapies in oncology. Few other cancers have therapies with such uniformly high initial response rates. Unfortunately, prostate cancer progression usually occurs despite initial castration, and mechanisms of resistance to castration have historically been thought to be independent of the AR signaling axis. However, overexpression of AR; androgen synthesis by prostate cancer cells; alterations in expression of coactivators and corepressors of AR signaling; and constitutively active, ligand-independent AR splice variants have all been implicated as potential mechanisms of castration resistance.[4-7] Two novel agents that address such resistance mechanisms have earned approval by the US Food and Drug Administration (FDA) in the last 2 years.

Abiraterone acetate (Zytiga) is a potent selective inhibitor of CYP17-hydroxylase and C17,20-lyase, enzymes necessary for the synthesis of androgens from steroid precursors.[8] A phase I study in men with mCRPC demonstrated that treatment with abiraterone was well tolerated and led to reductions in dehydroepiandrosterone sulfate (DHEA-S) and testosterone to near undetectable levels, resulting in significant decreases in prostate-specific antigen (PSA) levels, even in some patients who had received prior ketoconazole.[9] The COU-AA-301 phase III trial involved a 2:1 randomization of men with mCRPC who had previously received docetaxel chemotherapy to abiraterone 1,000 mg/day with prednisone 5 mg bid (n = 797), or placebo with prednisone 5 mg bid (n = 398). Abiraterone significantly prolonged overall survival (OS) compared with placebo (median, 14.8 vs 10.9 months; hazard ratio [HR] = 0.65 [95% confidence interval (CI), 0.54–0.77]; P < .001). Improvements in all secondary endpoints, including progression-free survival (PFS), response rates, and pain response, favored abiraterone acetate.[10] This trial was followed by the COU-AA-302
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The PI3K Signaling Pathway

The phosphatidylinositol 3-kinase (PI3K) family of enzymes is responsible for transducing a host of
intracellular signals that facilitate cell survival and inhibit apoptosis. Activation of the PI3K/Akt signaling pathway leads to upregulation of mammalian target of rapamycin (mTOR) and nuclear factor kappa B (NF-κB), thus inhibiting the p53 tumor suppressor and promoting cell growth and survival. Multiple germline mutations within the PI3K pathway have been implicated in the pathogenesis of malignancies. The tumor suppressor phosphatase and tensin homologue (PTEN) is a critical negative regulator of the PI3K pathway.[20,21] Loss of PTEN is the most prevalent genomic abnormality in both localized and metastatic prostate cancers, causing dysregulated PI3K signaling and contributing to the development of castration resistance.[22-24] This provides a rationale for evaluating agents targeting various components within the PI3K pathway.

Inhibitors of mTOR, including rapamycin analogues, have been studied in prostate cancer cell lines and xenografts, and demonstrate dose-dependent inhibition of mTOR and decreased phosphorylation of S6-kinase, the downstream target of mTOR. Inhibition of mTOR leads to modest reductions in prostate cancer growth and volume in mouse xenografts[25,26]; however, it failed to impact tumor proliferation or apoptosis in men with prostate cancer.[27] A phase II clinical trial evaluating the mTOR complex 1 (mTORC1) inhibitor everolimus (Afinitor) with bicalutamide in men with CRPC demonstrated minimal activity[28]; nonetheless, several trials evaluating everolimus in various combinations and settings are ongoing in prostate cancer. The lack of efficacy of mTOR inhibition may be due to interference with negative feedback, leading to activation of Akt and the mitogen-activated protein (MAP) kinase pathway.[29]

Carver et al performed a series of experiments to better illustrate the relationship between the PI3K and AR signaling pathways in prostate cancer. BEZ235, a dual inhibitor of PI3K and mTORC1/2, was studied in PTEN-deficient prostate cancer xenografts. Treatment with BEZ235 decreased cell proliferation within the tumors but did not reduce tumor volume. Although AR levels were low in the PTEN-deficient mice, they could be partially restored upon treatment with BEZ235 or everolimus, as these interventions led to upregulation of human epidermal growth factor receptor 3 (HER3) and subsequent promotion of AR activity. Conversely, AR inhibition of PTEN-deficient xenografts with castration plus enzalutamide resulted in no changes in tumor volume, proliferation, or histology. Instead, Akt was upregulated, implying that AR signaling serves as negative feedback for the Akt pathway. Combining BEZ235 and enzalutamide in PTEN-deficient prostate cancer models led to profound tumor regression and apoptosis, indicating that PI3K (and/or mTORC1/2) and AR are critical cotargets in a PTEN-deficient prostate cancer model.[30] Understanding this relationship provides a rational basis for clinical trial design that combines PI3K pathway inhibitors with potent AR antagonists in prostate cancer. Numerous PI3K pathway inhibitors that target PI3K, Akt, and mTORC1/2 are being developed. Selected trials utilizing PI3K pathway inhibitors in prostate cancer are summarized in Table 1.

DNA Damage Repair Pathways

Repair of ongoing damage to cellular DNA is critical for cell survival. Poly (adenosine diphosphate [ADP]-ribose) polymerases (PARPs) are enzymes that play a major role in repairing single-stranded DNA breaks via base excision. Single-stranded DNA breaks accumulate in the absence of PARP activity, and this can lead to double-stranded DNA breaks. The tumor suppressor proteins BRCA1 and BRCA2 are necessary components of the double-stranded DNA repair pathway. Germline mutations in BRCA1 or BRCA2 cripple the double-stranded DNA repair machinery, making affected individuals susceptible to breast, ovarian, and prostate cancers.[31,32] Cancers that carry BRCA1/2 mutations or other defects within the DNA damage repair pathways may be particularly sensitive to PARP inhibition. Although BRCA mutations are rare in prostate cancer, other abnormalities in DNA damage repair have been observed.
Gene fusions that involve the ETS family of transcription factor genes (ERG, ETV1, ETV4, ETV5) are present in 40% to 60% of prostate cancers; the most common of these is a fusion of ERG and the androgen-regulated transmembrane protease, serine 2 gene (TMPRSS2).[33] The resultant androgen-stimulated overexpression of ERG has been associated with accelerated carcinogenesis in mouse prostates in the setting of PTEN loss[34]; however, its role in disease progression remains unclear. DNA-dependent protein kinase is the large catalytic subunit of PI3/4-kinase and is necessary for repair of DNA strand breaks, specifically nonhomologous end-joining. Both PARP1 as well as DNA-dependent protein kinase interact with ERG and are necessary for ERG-mediated transcription in prostate cancer cells. Furthermore, PARP1 inhibition with olaparib prevents ERG-induced invasion and metastasis in prostate cancer cell lines positive for the ETS fusion gene.[35]

In the phase I study of olaparib in patients with advanced solid tumor malignancies, a patient with mCRPC who was a BRCA2 mutation carrier experienced a prolonged clinical response with a greater than 50% reduction in PSA level and resolution of bone metastases.[36] Veliparib, a PARP1/2 inhibitor, was tested along with temozolomide (Temodar) in a phase II study that involved 26 patients with mCRPC. Two patients exhibited significant declines in PSA levels; one patient had a 37% reduction in his PSA level, and the second patient had a 96% reduction in PSA level, as well as a 40% reduction in measurable tumor size.[37] There are ongoing efforts to combine PARP inhibitors with radiation and abiraterone in prostate cancer (NCT01576172).

**Stress-Response Pathways**

Oncologic therapies designed to kill cancer cells often trigger a stress response in the cancer cell, leading to activation of pro-survival pathways, and often conferring therapeutic resistance. Heat shock proteins (HSPs) serve as molecular chaperones that help cells cope with stress and that participate in cell signaling pathways and transcription regulation. HSP27 is a molecular chaperone, highly expressed in CRPC cells, that protects against apoptosis. Castration leads to increased expression of HSP27 in prostate cancer cells. HSP27 blocks castration-mediated apoptosis and fosters castration resistance. In prostate cancer, HSP27 may also displace HSP90 from the AR complex and facilitate shuttling of AR into the nucleus to act as a transcription factor.[38] Inhibition of HSP27 with small interfering RNA (siRNA) or antisense oligonucleotides (ASOs) decreases prostate cancer cell proliferation, and increases caspase-3 activity and apoptosis, thereby increasing sensitivity to taxane chemotherapy.[39-41]

OGX-427 is a modified ASO that is complimentary to HSP27, blocks its expression, and enhances sensitivity to anticancer drugs. Treatment with OGX-427 induces apoptosis and promotes survival in several human cancer cell lines.[39-41] A phase I study assessed the dosing and safety of OGX-427, both alone and in combination with docetaxel, in patients with advanced solid tumors, including 27 with mCRPC. Single-agent treatment with OGX-427 was well tolerated at its maximum dose level (1,000 mg IV weekly on a 21-day schedule, after 3 loading doses), either alone or combined with docetaxel. Of the seven patients with CRPC and measurable disease who received OGX-427 plus docetaxel, two had confirmed partial responses and one had stable disease. A reduction in PSA level of ≥ 30% was observed in 3 of 16 patients who received OGX-427 alone and in 5 of 9 patients who received OGX-427 plus docetaxel. Additionally, correlative analysis of circulating tumor cell (CTC) counts demonstrated that of the 41 patients with pretreatment CTC levels > 5 per 7.5 mL, 37% observed a reduction in CTCs to ≤ 5 per 7.5 mL.[42] A phase II trial randomly assigned 32 patients with mCRPC and no prior chemotherapy to treatment with OGX-427 and prednisone or prednisone alone. A reduction in PSA level of ≥ 50% was seen in 41% of patients in the OGX-427 arm and in 20% of patients in the prednisone-alone arm. In patients with measurable disease, a partial response was observed in 3 of 8 patients in the OGX-427 arm but in none of the 9 patients in the prednisone arm. Reductions in CTC levels and in PFS at 12 weeks both favored OGX-427. The study is now fully accrued, and mature data are pending.[43]

Secretory clusterin is a cytoprotective small HSP chaperone that inhibits protein aggregation in response to cellular stress. Clusterin inhibits BAX, blocking stress-induced activation of the Bcl-2-mediated apoptotic pathway, and it prevents release of cytochrome C from the mitochondria. Overexpression of clusterin also leads to increased phosphorylation of Akt, promoting nuclear transactivation of NF-κB and cell survival. Increased expression of clusterin in cancer cells is associated with resistance to cytotoxic drug-induced cell death, including androgen deprivation–induced apoptosis in prostate cancer cells. Targeting secretory clusterin is not possible with traditional agents and has only been feasible with the use of siRNA/ASO-mediated inhibition.[44,45]
Custirsen (OGX-011) is a potent second-generation ASO inhibitor of the translation initiation site of human exon II clusterin, which suppresses expression of clusterin in vitro and in vivo. Treatment with custirsen significantly reduces secretory clusterin levels, enhancing the efficacy of chemotherapy, radiation, and ADT, and increasing apoptosis in several xenograft models, including models of prostate, breast, lung, kidney, and bladder cancers.[46,47] A phase I study investigated custirsen in patients with localized prostate cancer, using a presurgical escalating dose level trial design to allow for evaluation of tumor tissue clusterin expression after treatment with custirsen. Patients received a single 6.3-mg dose of buserelin acetate (2-month depot formulation), as well as flutamide, 250 mg tid for 28 days. Custirsen was administered as an IV infusion on days 1, 3, and 5, and then weekly (on days 8, 15, 22, and 29). Patients underwent prostatectomy within 1 week of their last dose of custirsen. Twenty-five patients were enrolled in custirsen 40-, 80-, 160-, 320-, 480-, and 640-mg dose cohorts. No dose-limiting toxicities were observed. The most common side effects included fever, fatigue, rigors, and myelosuppression. Treatment with custirsen was associated with a statistically significant dose-dependent decrease in clusterin messenger RNA (mRNA) and protein expression. Decreased clusterin mRNA and protein expression in the tissue correlated with increased tumor apoptosis.[48] A second phase I study evaluating custirsen administered on days 1, 3, and 5, and then weekly in combination with docetaxel demonstrated that custirsen could be safely administered at a full (640-mg) dose along with docetaxel without dose-limiting toxicities.[49] An 82-person randomized phase II trial compared docetaxel and prednisone with custirsen (arm A) vs docetaxel and prednisone without custirsen (arm B) in men with mCRPC who had not received prior chemotherapy. The primary endpoint was the proportion of patients with a ≥ 50% reduction in PSA level; the results showed no appreciable difference between arms A and B (58% vs 54%, respectively). The median PFS and OS were 7.3 months (95% CI, 5.3–8.8) and 23.8 months (95% CI, 6.2 to NR), respectively, in arm A; and 6.1 months (95% CI, 3.7–8.6) and 16.9 months (95% CI, 12.8–25.8), respectively, in arm B. Although there was no significant improvement in PFS, a multivariate analysis revealed a statistically significant improvement in OS.[50] Based on the survival benefit seen in phase II, the SYNERGY phase III trial has completed accrual, randomly assigning men with mCRPC to treatment with docetaxel and prednisone either with or without custirsen, with OS as the primary endpoint (NCT01188187). Additionally, the AFFINITY randomized phase III trial is currently evaluating cabazitaxel (Jevtana) and prednisone with or without custirsen as second-line chemotherapy in men with mCRPC (NCT01578655).

**Invasion Pathways**

Tissue invasion and metastasis are inherent characteristics of cancers. MET is a proto-oncogene that encodes a receptor tyrosine kinase responsible for promoting cell motility and growth.[51,52] MET activation by its ligand, hepatocyte growth factor (HGF), triggers signaling via the Ras-Raf-ERK/mitogen-activated protein kinase (MAPK) pathway, as well as the PI3K/Akt pathway, resulting in transcription of growth-, proliferation-, and survival-promoting genes. Studies in epithelial cell lines have demonstrated that activation of MET leads to cell dissociation and subsequent invasion of a collagen matrix, which correlates with the invasive and metastatic potential of the cell.[53,54]

Cabozantinib (XL184) is a potent inhibitor of MET and vascular endothelial growth factor receptor 2 (VEGFR2), and has demonstrated activity in cells that overexpress wild-type MET, as well as in cells with activating mutations. Treatment with cabozantinib leads to decreased tumor and endothelial cell proliferation, as well as increased apoptosis, in xenograft models. Moreover, cabozantinib did not increase metastatic tumor burden, a phenomenon that has been seen with other VEGF-signaling inhibitors.[55] Cabozantinib demonstrated an acceptable safety profile in a phase I study in patients with advanced solid malignancies.[56] A phase II trial evaluated cabozantinib in men with mCRPC. Investigators used a randomized discontinuation adaptive design in which patients received cabozantinib 100 mg daily for 12 weeks, at which time those with stable disease were randomly assigned to either continued cabozantinib or placebo. Randomization was suspended after enrollment of 122 patients, due to high response rates and symptomatic improvement during the lead-in phase of the trial; a total of 171 patients with prostate cancer were enrolled. Of the 154 patients who had disease evaluable by RECIST criteria, 9 patients had confirmed partial responses, 127 had stable disease, and 18 had disease progression. After observation of significant bone scan changes, a post-hoc analysis was performed. Of the 116 patients with bone metastases and at least one follow-up bone scan, 68% had improvement and 12% had complete resolution of all skeletal
metastases on bone scan. Improvement in markers of bone turnover, as well as pain improvement, was seen in responding patients; however, PSA levels did not correlate with bone or soft-tissue responses.[57] Given the impressive early activity, the COMET-1 phase III double-blind placebo-controlled trial is currently evaluating OS for cabozantinib vs prednisone in men with mCRPC whose disease had progressed on prior docetaxel and either abiraterone or enzalutamide (NCT01605227).

**Antiangiogenesis**

Neovascularization, the development and growth of new blood vessels, is critical for malignant cell proliferation, invasion, and metastasis.[58] Activation of endothelial cells via release of angiogenic peptides, most notably VEGF, leads to new vessel formation. The VEGFR complex includes several ligands (VEGF-A, -B, -C, -D, and -E, and placental growth factor) and their associated receptors (VEGFR1/FLT1, VEGFR2/KDR, VEGFR3/FLT4, and neuropilin-1 and -2).[59] VEGF-A expression by cancer cells is critical for angiogenesis and tumor growth.[60] VEGFR activation leads to endothelial cell proliferation and migration, changes in the extracellular matrix, increased vascular dilation and permeability, and inhibition of endothelial cell apoptosis (which promotes survival of newly formed blood vessels).[59] In prostate cancer, ADT leads to decreased VEGF mRNA and protein expression, as well as to a corresponding reduction in new blood vessel formation.[61]

Inhibition of angiogenesis has played a crucial role in the treatment of several cancers. Multiple antiangiogenic drugs have been developed and are in use in different tumor types, including monoclonal antibodies and tyrosine kinase inhibitors. Bevacizumab (Avastin), a humanized monoclonal antibody targeting VEGF, was first approved in 2004 for use along with chemotherapy in metastatic colon cancer; it is also currently approved for use in metastatic non–small-cell lung cancer, ovarian cancer, glioblastoma, and renal cell carcinoma.

**TABLE 2**

Randomized Phase III Prostate Cancer Trials With Antiangiogenic Agents

Antiangiogenic properties of the chemotherapeutic drug docetaxel induce VEGF overexpression in docetaxel-treated cancer cells; however, the addition of bevacizumab overcomes this resistance mechanism.[62] A phase II trial evaluating bevacizumab in men with mCRPC and progression after docetaxel chemotherapy suggested activity based on PSA responses.[63] Unfortunately, the phase III trial of docetaxel and prednisone with bevacizumab or placebo in men with mCRPC showed no difference in OS between the bevacizumab and placebo arms (median, 22.6 vs 21.5 months; HR = 0.91 [95% CI, 0.78–1.05]; \( P = .181 \)).[64] Trials evaluating several other antiangiogenic agents, including sunitinib (Sutent), afiblercept (Zaltrap), and lenalidomide (Revlimid), in mCRPC have also failed to demonstrate significant clinical benefit (Table 2).[65-67]

Despite the negative results from previous trials with antiangiogenic agents, there are still other promising antiangiogenic agents in development for the treatment of mCRPC. Tasquinimod is a second-generation, orally active quinolone-3-carboxamide analogue that demonstrates antiangiogenic and antineoplastic properties. Potential mechanisms of action include binding to S100A9, which can regulate cell-cycle progression and differentiation, as well as upregulate expression of thrombospondin-1, an inhibitor of angiogenesis. In both castration-sensitive and castration-resistant xenograft prostate cancer models, treatment with tasquinimod reduced tumor volume and new blood vessel formation and enhanced antitumor activity when combined with ADT and docetaxel.[68] The phase I trial in men with CRPC demonstrated that tasquinimod (MTD, 0.5 mg daily) was safe and well tolerated, with anemia, nausea, fatigue, myalgia, and pain among the most common toxicities.[69] A randomized, double-blind, placebo-controlled phase II trial was performed in men with minimally symptomatic CRPC. Two hundred one men were randomly assigned in a 2:1 fashion to receive either tasquinimod 0.25 mg/day escalating to 1.0 mg/day over 4 weeks (n = 134) or placebo (n = 67). There was a statistically significant difference in 6-month PFS (the primary endpoint) between tasquinimod (69%) and placebo (37%). In addition, a significant improvement in median PFS was seen in the tasquinimod arm (7.6 months vs 3.3 months; \( P = .0042 \)).[70] A phase III
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trial comparing tasquinimod vs placebo in chemotherapy-naive men with minimally symptomatic mCRPC has completed accrual; results are pending.

Discussion

Treatment paradigms for men with mCRPC have changed dramatically in the last 3 years due to regulatory approval of agents like abiraterone and enzalutamide, as well as other agents not discussed in this review, such as sipuleucel-T (Provenge), cabazitaxel (Jevtana), denosumab (Xgeva), and radium-223 (Xofigo). Identifying predictive biomarkers and selecting sensitive patient populations present unique challenges for future drug development. Ascertainment of resistance mechanisms will lead to informed therapeutic decision making. Some of these resistance mechanisms may have been addressed by the molecular pathways, targets, and therapeutic agents discussed in this review, although many distinct mechanisms remain undiscovered, leaving room for progress. Individualizing treatment with knowledge of these biologic mechanisms will lead to more effective therapeutic sequencing and rational drug combinations. These efforts necessitate ongoing translational research, including tissue acquisition from tumor metastases and molecular characterization of circulating tumor cells.

Despite refining the use of novel AR signaling inhibitors, therapeutic resistance naturally occurs, and it remains unlikely that cures will be seen with current treatment strategies. It is also possible that the prostate cancer cells that emerge resistant to these potent new hormonal agents will be dependent upon alternative signaling pathways, and could potentially exhibit extraordinarily aggressive behavior. For this reason, efforts must continue not only to bolster the discovery process for new biologic targets through personalized cancer medicine initiatives, but also to optimize development of next-generation targeted therapies.

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