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Treatment of Castration-Resistant Prostate Cancer: Updates on Therapeutics Targeting the Androgen Receptor Signaling Pathway

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Abstract

Androgens play a critical role in the progression of castration-resistant prostate cancer through androgen receptor (AR)-regulated signaling pathways. Progress has been made in the development of potent agents des1gne to suppress androgen function by blocking the AR, inhibiting the synthesis of androgens, or targetmg downstream AR signaling pathways. This review summarizes the development of novel therapies based on current insights into AR signaling pathways in castration-resistant prostate cancer.

Keywords

androgen receptor; castration-resistant prostate cancer; MDV3100; abiraterone

INTRODUCTION

Prostate cancer is the most common noncutaneous malignancy and the second leading cause of cancer deaths among men in the United States. The American Cancer Society estimates that approximately 192,280 men will be diagnosed with prostate cancer and about 27,360 will die of the disease in 2009.[1] This represents one third of all newly diagnosed cancers in and 10% of cancer deaths in the United States. Because of prostate-specific antigen (PSA)-based screening for prostate cancer, most patients are diagnosed localized disease. For a majority of these patients, radical prostatectomy and radiotherapy appear to provide equivalent long-term survival and cure[2]. However, a subset of men present with metastatic disease, and 20% to 30% of patients diagnosed with localized prostate cancer will eventually develop metastatic disease.

In 1941, Huggins and Hodges[3] first demonstrated that prostate cancer was influenced by androgens. Currently, therapies used to suppress the function of androgens, including androgen ablation through surgical or chemical castration, inhibition of androgen synthesis, and the use of androgen receptor antagonists (ARAs) are the mainstays of initial therapy for

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patients with metastatic prostate cancer.[4] However, the median duration of response is usually only 12 to 18 months, and the majority of patients will eventually progress despite castrate levels of testosterone, a condition described as castration-resistant prostate cancer (CRPC). Second-line hormonal approaches include ARA withdrawal, sequential use of ARAs, suppression of adrenal androgen production, and use of estrogenic compounds.[5,6] Responses to second-line hormonal therapy are usually limited, with 10% to 60% of patients experiencing a greater than 50% PSA decline and a median response duration of 2.5 to 11 months.[5] Docetaxel in combination with prednisone, the current standard chemotherapy regimen for metastatic CRPC, increases overall survival by approximately 3 months over mitoxantrone and prednisone[7–9] No standard second-line chemotherapy has been shown to increase survival after progression with docetaxel chemotherapy. Therapies with greater clinical benefit are urgently needed for progressive CRPC. This review summarizes current developments in therapies that focus on the androgen receptor (AR) signaling pathway in CRPC.

CRITICAL ROLE OF ANDROGENS IN CRPC

The AR, a member of the nuclear receptor superfamily, functions as a ligand-dependent transcription factor and plays an important role in the development and progression of prostate cancer.[10] When bound to a ligand, AR dissociates from heat shock proteins (HSP) and related chaperones, leading to homodimerization, nuclear transportation, binding to the AR element on the promoter of androgen-responsive genes, increased AR target gene transcription, and regulation of cell proliferation, differentiation, and survival.[11] It is now well recognized that both AR and its downstream signaling pathways remain activated and are critical for disease progression in prostate cancer patients with castrate levels of testosterone. Possible mechanisms of castrate resistance in patients with advanced prostate cancer include[12–15] (1) the presence of hypersensitive AR phenotypes caused by AR amplification, over-expression, or mutation, which allows for continued activation of AR with castrate levels of testosterone; (2) the presence of constitutively active AR caused by to aberrant expression of coactivators/corepressors of AR or changes in the downstream signaling pathway; (3) activation of AR by nonandrogen ligands; and (4) adrenal and intratumoral synthesis of androgens caused by changes in the expression of enzymes in steroidogenesis. AR gene amplification and over-expression have been observed in the development of CRPC.[16–18] In addition, mutated AR can be activated by nonandrogens such as progesterone, estradiol, cortisol, ARAs, or neuropeptide.[19–22] It has been shown that levels of testosterone and dihydrotestosterone remain elevated in CRPC tissues with castrate levels of serum testosterone.[17,23–25] On the basis of the current understanding of the critical role of the AR signaling pathway in prostate cancer, the term CRPC has replaced hormone-refractory prostate cance and androgen-independent prostate cancer to descnbe the clinical state at which prostate cancer progresses despite castrate levels of testosterone.

NOVEL ANDROGEN RECEPTOR ANTAGONISTS

ARAs block AR activation by competing for binding sites for androgens, thus promoting apoptosis and inhibiting prostate cancer cell growth. Classic ARAs include the nonsteroidal agents bicalutamide, nilutamide, and flutamide, as well as cyproterone acetate, a steroidal

ARA used in Europe. These agents have been used as initial treatment in combination with luteinizing hormone-releasing hormone agonists (combined androgen ablation) or upon disease progression after medical or surgical castration. ARAs have only modest activity in CRPC. Even when treated with high-dose bicalutamide, only approximately 20% of patients achieve greater than 50% PSA decline, and response is usually short-lived, averaging 4 to 6 months. This may be in part because of the weak agonist effect of the current ARAs[17] and may possibly explain ARA withdrawal responses.

An understanding of the structural basis of development of resistance to bicalutamide in prostate cancer has led to the design and development of more potent small molecule ARAsY.[11,26] MDV3100 was designed to overcome resistance to bicalutamide in prostate cancer cells with AR overexpression.[27] MDV3100 inhibits AR function by blocking nuclear translocation of AR and has no agonist activity when AR is over-expressed. MDV3100 has shown clinical benefit in CRPC patients who were chemotherapy nai:ve or who had received prior docetaxel-based chemotherapy. In a recent study,[28] 62% of chemotherapy-naive patients (40/65) had a greater than 50% PSA decline; 36% of patients with measurable disease had partial response; and 44% had stable disease by Response Evaluation Criteria In Solid Tumors (RECIST). Among patients who had received prior docetaxel treatment, 51 % (38/75) had a greater than 50% PSA decline, and 14% had partial response by RECIST. On the basis of efficacy and adverse event profile (significant fatigue with > 360 mg/day and dose-limiting toxicities of rash and seizure at 600 mg/day), MDV3100 160 mg/day is the recommended dose in an upcoming phase III study in postchemotherapy CRPC patients. In this trial, 1170 patients will be randomized 2:1 to receive MDV3100 160 mg/day versus placebo, with overall survival as the primary endpoint.

NOVEL SPECIFIC CYTOCHROME P450, SUBFAMILY XVII (CYP17) INHIBITORS

CYP17 is a key enzyme in the synthesis of androgens and estrogens in the adrenal glands and tumor tissues.[29] Ketoconazole is a synthetic antifungal agent with a similar structure to imidazole. It inhibits CYP17 nonspecifically, and at high doses (400 mg 3 times/day) it decreases the production of testosterone, leading to gynecomastia and loss of libido. High-dose ketoconazole in combination with replacement hydrocortisone has been used to treat CRPC. In multiple phase II trials, ketoconazole led to a greater than 50% PSA decline in 47% to 63% of CRPC patients, with a median duration of response of 3.5 to 6.3 months.[3031] Cancer and Leukemia Group B (CALGB) 9583 was a phase III trial that compared ARA withdrawal (antiandrogen withdrawal [AAWD]) and AAWD plus ketoconazole 400 mg 3 times a day in patients who had rising PSA while receiving ARA therapy.[30] Patients who received the combination of AAWD plus ketoconazole had a significantly higher rate of PSA decline greater than 50% compared with patients who received AAWD alone (27% vs. 11 %) and a significantly greater rate of objective response (20% vs. 2%). The median duration of response for the combination of AAWD and ketoconazole was 8.6 months, but there was no difference in overall survival compared with AAWD alone. The relatively low response rate in this trial compared with other trials was likely caused by some patients' use of proton pump inhibitors, which are known to reduce absorption of ketoconazole. High-

dose ketoconazole is associated with moderate toxicities. Patients receiving ketoconazole had more grade 3 and 4 toxicities than patients receiving AAWD alone (21 % vs. 7%). The most common adverse events with ketoconazole were neurologic toxicity (4%) and fatigue (3%). Grade 3 or 4 hepatic toxicities were seen in 2% of patients in both arms. Response to ketoconazole was associated with decreased androgen levels after treatment. Disease progression followed elevated androgen production because of loss of CYP17 inhibition.

Maximum androgen suppression with more selective, potent, and irreversible CYP17 inhibitors has been the focus of recent clinical research. Results with the CYP17 inhibitor abiraterone are the most mature and promising. In preclinical studies, abiraterone decreased the weight of androgen-dependent organs, including the prostate, seminal vesicles, and testes, but had minimal effect on other organs.[32] Abiraterone has been tested in multiple phase I and II clinical trials in patients with prostate cancer. A phase I clinical trial evaluated patients with chemotherapy-naive CRPC treated with continuous daily doses of abiraterone acetate escalating from 250 mg to 2000 mg.[33] Toxicities were mainly caused by production of excess mineralocorticosteroid and were controlled with the mineralocorticosteroid receptor antagonist eplerenone. No treatment-related grade 3 or 4 toxicities occurred, and clinical responses were reported at all dose levels. The study revealed that abiraterone durably suppresses serum androgens and estrogens, resulting in antitumor activity. Twelve of 21 (57%) patients had a greater than 50% PSA decline, and 5 of 8 (62%) patients with measurable disease had a partial response by RECIST. Suppression of upstream steroid synthesis by the addition of dexamethasone 0.5 mg/day resulted in successful salvage in 4 of 15 patients who had progressed on abiraterone acetate alone, suggesting that nonandrogenic steroids may activate the AR signaling pathway, leading to resistance to single-agent abiraterone. On the basis of the observation that upstream steroid levels plateaued at daily doses greater than 700 mg, abiraterone 1000 mg/day was the recommended dose for the phase II study.

Several phase II studies of abiraterone in combination with low-dose steroids (prednisone 5 mg twice/day) have been conducted in CRPC patients with and without prior docetaxel or ketoconazole therapies. In a phase II study of abiraterone in 44 patients with CRPC, 51 % of patients had a greater than 50% PSA decline, despite the fact that 66% of patients had received prior docetaxel and 56% had received prior ketoconazole therapy.[34] Other updated phase II trial results with abiraterone have also been reported. Of 33 patients with chemotherapy-naive CRPC and no prior ketoconazole therapy, Ryan et al[35] reported that 85% achieved a greater than 50% PSA decline, and PSA response was sustained for greater than 12 weeks in 78% of patients. Of 45 CRPC patients who had received prior docetaxel therapy, Reid et al[36] reported that 51 % had a greater than 50% PSA decline. Among patients with measurable disease, 17% achieved partial response, and 66% had stable disease by RECIST.[36] Danila et al[37] showed that abiraterone had a higher response rate in docetaxel-treated CRPC patient if they had received no prior ketoconazole therapy. In patients without prior ketoconazole therapy, PSA decline greater than 50% and time to PSA progression were 53% and 198 days, respectively; in patients who had received prior ketoconazole therapy, PSA decline greater than 50% and time to PSA progression were 33% and 99 days, respectively. These results demonstrate that abiraterone has significant antitumor activity in docetaxel-resistant CRPC.

A randomized placebo-controlled phase III study of abiraterone in CRPC patients with prior docetaxel therapy has randomized 1180 patients 2:1 to receive abiraterone plus prednisone 10 mg/day versus placebo plus prednisone 10 mg/day, with overall survival as the primary endpoint. A second randomized phase III trial of abiraterone in chemotherapy-naive CRPC patients is ongoing.[38] Patients are randomized 1:1 to abiraterone 1000 mg/day plus prednisone 10 mg/day versus placebo and prednisone 10 mg/day, with overall survival as the primary endpoint.

TARGETING THE DOWNSTREAM AR SIGNALING PATHWAY

Current research is focused not only on developing more potent ARAs and inhibitors of androgen synthesis but also at blocking the activation of AR signaling by targeting other components of the AR signaling pathway. The most studied downstream AR signaling pathway components include HSP-90, histone deacetylases (HDACs), and the mammalian target of rapamycin (mTOR).

HSP-90 is a ubiquitously expressed chaperone protein involved in maintaining the conformation, stability, activity, and cellular localization of several key oncogenic client proteins, including ERBB2, C-RAF, CDK4, AKT/PKB, mutant p53, HIF-1-α, survivin, telomerase hTERT, and steroid hormone receptors.[39] In prostate cancer, HSP-90 inhibition causes AR degradation.[40] Three HSP-90 inhibitors, the benzoquinone ansamycin antibiotic 17 -Allylamino-17-demethoxygeldanamycin (17-AAG) and its more potent and water-soluble analogs alvespimycin (17-dimethylaminoethylamino-17 -demethoxygeldanamycin; 17-DMAG) and IPI-504 (retaspimycin hydrochloride) have been tested in clinical trials in patients with CRPC. Despite positive results from phase I clinical trials, phase II trials of 17-AAG and IPI-504 as single agents in CRPC had minimal effect on PSA or tumor burden.[41,42] Results of a phase I trial of 17-DMAG administered intravenously weekly to 25 patients with advanced solid tumors showed two partial responses, one in a patient with CRPC who was still on study at 27 months.[43]

Deacetylation of histones by HDACs inactivates tumor suppressor genes, leading to neoplastic transformation. Inhibition of these enzymes might restore normal growth control. HDACs are considered among the most promising targets for new cancer therapeutics such as vorinostat, which has been approved for cutaneous T-cell lymphoma. HDAC inhibitors can sensitize prostate cancer cells to agents that produce DNA double-strand breaks.[44] Phase I clinical trials of HDAC inhibitors such as MGCD0103, CHR-3996, and MS-275 have been conducted in solid tumors, including prostate cancer.[45,46] A phase I/II randomized trial of LBH589 (panobinostat) combined with bicalutamide in men with CRPC is ongoing.[45]

PI3K/Akt/mTOR signaling is up-regulated in 30% to 50% of prostate cancers, with loss of PTEN (tensin homolog deleted on chromosome 10) as the most common cause.[47] Increased activity of the PI3K/Akt/mTOR signaling pathway has been demonstrated to differentiate benign from malignant prostatic epithelium and is associated with increasing tumor stage, grade, and risk of biochemical recurrence.[48–50] The Akt/mTOR pathway can activate AR in the absence of androgen.[51] Combined treatment with an ARA and mTOR inhibitor has a synergistic effect on prostate cancer cells.[52] Many agents that target the PI3K/Akt/mTOR

signaling pathway have been investigated for prostate cancer therapy. Among these, mTOR inhibitors such as rapamycin and its analogs RAD-001 (everolimus), CCI-779 (temsirolimus), and AP23573 (deforolimus) have shown the most promise in treating solid tumors, including prostate cancer. Multiple phase I/II trials of mTOR inhibitors in prostate cancer are ongoing.[53]

CONCLUSIONS

Promising results from phase II trials of MDV3100 and abiraterone confirm the critical role of androgens and the AR signaling pathway in CRPC and the clinical benefit of potent androgen suppression even in the postchemotherapy setting. Ongoing phase III clinical trials with these agents will provide important data on survival of patients with CRPC. The combination of these agents with docetaxel-based chemotherapy and, perhaps, immunotherapy also warrants investigation. Furthermore, the AR signaling pathway could be activated by mechanisms independent of androgens in CRPC. New agents targeting downstream components of the AR signaling pathway such as HSP-90, HDAC, and mTOR are under active investigation. These novel targeted therapies may one day overcome tumor resistance by completely blocking ligand-related activation of the AR signaling pathway.

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