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Emerging Therapies in Castrate-Resistant Prostate Cancer

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Abstract

Prostate cancer is the most common cancer in men in the United States, and despite screening and early treatment, more than 27,000 men are predicted to die of the disease this year, almost all of whom will die of castrate-resistant, metastatic cancers that have progressed despite androgen deprivation therapy, also known as hormonal therapy. In recent years, an increased understanding of molecular mechanisms of prostate cancer progression and castration resistance has led to improved treatment strategies. This review focuses on emerging therapies for the treatment of castrate-resistant prostate cancer, with an emphasis on the importance of the drug targets as well as the state of current clinical trials, including those utilizing hormonal therapies, biological agents, and immunotherapy that are underway or have recently been completed.

Keywords

Prostate cancer; Castration-resistant

Introduction

Prostate cancer is the most common cancer in men in the United States [1]. Despite early identification of this disease through screening, 50,000 men were estimated to recur despite local treatments last year, and 27,000 men were estimated to die of the disease [1]. Prostate cancer may be subdivided into three general categories: 1) hormone therapy-naive, in which androgen deprivation therapy (ADT) has not yet been given and serumlevels of testosterone are not castrate; 2) hormone therapy-responsive, in which patients are responding to ADT and serum levels of testosterone are castrate; and 3) castration-resistant, in which patients are progressing despite ADT in the setting of low serum levels of testosterone. Castrate-resistance has replaced “androgen independence” to describe prostate cancers that have progressed despite ADT due to recent work demonstrating that the androgen receptor (AR) is still active in castrate-resistant prostate cancer (CRPC) cells, and that adequate levels of androgens to activate AR persist in prostate cancer cells despite low levels of serum testosterone [2, 3].

A wealth of information demonstrates that patients who have developed resistance to one form of hormonal therapy may respond to additional hormonal manipulations [4]. Due to the widespread use of ADT at earlier phases of the disease, such as for prostate-specific antigen (PSA)-only recurrences, many patients now develop castrate-resistant tumors in the absence

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of metastatic disease. In addition, in many cases patients with castration-resistant metastatic prostate cancer have few symptoms and are interested in postponing treatment with chemotherapy for as long as possible. Due to the preponderance of current clinical trials testing agents in CRPC, patients with CRPC now have many investigational options.

Standard Treatment Options for Castrate-Resistant Prostate Cancer

Until recently, castrate-resistant metastatic prostate cancers were considered unresponsive to cytotoxic chemotherapy [5]. In the 1990s, mitoxantrone, an anthracycline, was tested in combination with prednisone and was shown to cause tumor regression, reduce PSA levels, and provide palliative benefit in patients with CPRC [6, 7]. However, mitoxantrone failed to improve overall survival [6, 7].

It was not until 2004 that two groups showed that docetaxel, either given with prednisone or in combination with estramustine, improved overall survival versus mitoxantrone and prednisone, which at that time was the standard of care treatment for patients with CRPC [8, 9]. The TAX327 study, in which docetaxel was combined with prednisone, was associated with a more favorable side effect profile than SWOG 9916, in which docetaxel was combined with estramustine; in TAX327, treatment with docetaxel every 3 weeks led to improved objective and PSA response rates, improved pain control, and improved quality of life versus mitoxantrone and prednisone [9]. Currently, no standard therapy exists for postdocetaxel CRPC patients, but mitoxantrone and prednisone are commonly used despite modest activity [10]. The modest 2-month increase in overall survival with docetaxel and lack of effective treatments after docetaxel underscores the continued need for improved treatments in patients with CRPC.

Emerging Therapies for Castrate-Resistant Prostate Cancer (Fig. 1 highlights the pathways modulated by many of the agents discussed below)

Hormonal Therapies

Lyase Inhibitors

Abiraterone acetate: Abiraterone acetate is an orally active acetate salt of the steroidal compound abiraterone. As a lyase inhibitor, abiraterone acetate irreversibly inhibits the activity of the steroid enzyme CYP17A, also known as 17alpha-hydroxylase/17,20 lyase, involved in androgen biosynthesis in the adrenal gland and possibly within prostate tumors, themselves [11]. CYP17 is a key enzyme in the androgen-biosynthesis pathway, catalyzing conversion of progesterone and pregnenolone into weaker androgens, namely 17-hydroxypregnenolone and then to dehydroepiandrostenedione (DHEA) [11] Fig. 1.

Recently, Attard et al. [12•] published results of their phase I/II study of abiraterone acetate in 54 patients with metastatic CRPC who had not received prior chemotherapy. A dose of 1000 mg per day was used in the phase II expansion, which consisted of 42 patients. Abiraterone acetate was safe, and the most common adverse events were symptoms of mineralacorticoid excess, including hypokalemia, hypertension, and fluid overload. Of these patients, 66% had≥50% declines in PSA values, and partial radiographic responses by RECIST (Response Evaluation Criteria In Solid Tumors) were seen in 37.5% of patients. The median time to PSA progression for phase II patients was 225 days. This is similar to the 231 day median time to PSA progression with docetaxel in TAX327 [9]. Of note, the addition of corticosteroids reversed disease progression in one third of patients; this highlights the compensatory upstream endocrine mechanisms of resistance to this therapy, which may be modulated by corticosteroid supplementation.

Abiraterone acetate has also been tested in the postdocetaxel setting in multiple clinical trials. PSA response rates (≥ 50% declines) ranged from 43% to 51%, and objective tumor responses were also seen [13–15]. Of note, the phase II trial by Danila et al. [13] showed a lower PSA response rate with abiraterone acetate in patients who had received prior ketocaonazole, which also acts to inhibit adrenal steroidogenesis; thus, these patients were excluded from the recently completed randomized phase III study (Cougar 301) of abiraterone acetate and prednisone versus placebo and prednisone, whose primary end point was overall survival. Results from this phase III trial should be forthcoming in the next 1 to 2 years. An additional randomized phase III study (Cougar 302) of abiraterone acetate and prednisone versus placebo and prednisone in patients with CRPC who have not received prior chemotherapy, whose primary end point is overall survival, recently opened and is predicted to close in mid-2010.

Antiandrogens—MDV3100 is a selective androgen receptor antagonist shown to be effective in slowing growth and inducing death of castrate-and bicalutamide-resistant prostate cancer cells [16•]. MDV3100 is more potent than bicalutamide, does not have androgen agonist activity, and has three complimentary actions on cancer cells: blocking testosterone binding to AR, impeding AR movement to the nucleus (nuclear translocation), and inhibiting AR binding to DNA; the latter two mechanisms are unique to MDV3100 versus other antiandrogens [16•] (Fig. 1).

Scher et al. [17] recently presented the findings of a phase I, first-in-man trial of MDV3100 in patients with CRPC, which included both chemotherapy-naïve and previously chemotherapy-treated patients. The therapy was well tolerated, but seizures were seen in three patients (2%). Of the chemotherapy-naïve patients, 62% had≥50% declines in their PSA levels, and 36% had partial radiographic responses by RECIST. Of the patients who had been treated with chemotherapy previously, 51% achieved ≥ 50% PSA declines, and the partial radiographic response rate was 12%. The median time to PSA and radiographic progression for chemotherapy-naïve patients had not been reached, whereas it was 186 days for PSA progression and 201 days for radiographic progression in patients who had received prior chemotherapy. These results with MDV3100 compare favorably to front-line treatment with docetaxel or with mitoxantrone and prednisone used after docetaxel, in which the PSA response rate was 20% and the median duration of therapy was only 2.3 months [9, 10]. AFFIRM, a multinational phase III randomized trial of MDV3100 versus placebo in patients with castrate-resistant, metastatic prostate cancer who have received prior docetaxel therapy, opened this fall, and its primary end point is overall survival.

Biological Agents

Histone Deacetylase Inhibitors—Histone deacetylases (HDACs) remove acetyl groups from lysine residues on histones, alpha-tubulin, HSP90, and other proteins, which leads to changes in gene expression or protein function [18] (Fig. 1). Vorinostat, a hydroxamic acid HDAC inhibitor, is currently the only US Food and Drug Administration (FDA)-approved HDAC inhibitor and is used in the treatment of cutaneous T-cell lymphoma [19]. There are multiple mechanisms of action of HDAC inhibitors, including interference with cell proliferation and tumor angiogenesis and induction of differentiation and apoptosis [18]. In addition to the multiplicity of actions listed above, HDAC inhibitor treatment of prostate cancer cells has been shown to cause degradation or decreased production of AR protein, highlighting the worthiness of testing this class of agents in prostate cancer [20–22].

However, the clinical experience with HDAC inhibitors has been variable. A single agent phase II study of vorinostat in patients with CRPC, who had received prior chemotherapy, was complicated by excess toxicity leading to early discontinuation of therapy, which

limited the ability to assess antitumor activity [23, 24]. These results, along with results from a phase II clinical trial of depsipeptide in CRPC patients, which showed minimal clinical activity, suggest that combinations of HDAC inhibitors with other therapies may be more promising [25]. Currently, there are ongoing trials assessing the effects of other HDAC inhibitors, including LBH589 in combination with docetaxel. A phase I/II dose-finding trial showed that combination therapy with docetaxel and LBH589 was feasible, although neutropenia was a common finding in this study [26].

PI3 kinase/mTOR Pathway Inhibitors—Phosphatidylinositol 3 (PI3) kinase is an enzyme that catalyzes the conversion of phosphatidylinositol to phosphatidylinositol 3-phosphate, the first committed step in a critical signal transduction pathway regulating cell growth, proliferation, apoptosis, and angiogenesis [27] (Fig. 1). Functional loss of the tumor suppressor phosphatase and tensin homologue (PTEN), which is a negative regulator of this pathway, is a common event in prostate cancer and may lead to transformation of normal prostatic epithelial cells [28, 29]. The PI3 kinase/Akt pathway regulates and operates upstream of the mammalian target of rapamycin (mTOR) pathway, which has emerged as a drugable pathway [30].

Rapamycin, an inhibitor of mTOR, is derived from soil containing *Streptomyces hygroscopicus* and has been used as an immunosuppressive agent in organ transplant patients for years. This compound, and the related temsirolimus and everolimus, which are approved for the treatment of renal cell carcinoma, has been shown to have antitumor activity [31]. However, a phase II trial with the mTOR inhibitor rapamycin did not show strong single-agent activity in CRPC [32]. In addition, a phase I/II clinical trial in CRPC with the mTOR inhibitor RAD-001 and docetaxel closed early due to lack of efficacy [33]. Given the redundancy of the PI3 kinase/Akt pathway, treatment with a PI3 kinase inhibitor may be more effective. Indeed, a recent phase I trial showed that the pan-PI3 kinase inhibitor, GDC-0941, is generally well tolerated with potential signs of antitumor activity [34].

Poly (ADP-ribose) Polymerase Inhibitors—Poly (ADP-ribose) polymerase (PARP) is an enzyme involved in the regulation of DNA damage repair [35] (Fig. 1). PARP inhibition leads to unrepaired single-strand breaks, which are normally repaired by the homologous recombination double-stranded DNA repair pathway, whose key components include the BRCA1 and BRCA2 proteins that are commonly mutated in cancer [35, 36•]. PARP inhibitors work by disabling the base-excision repair mechanism in cells with mutant BRCA1 or BRAC2 proteins with defects in homologous recombination; these cells, as opposed to those harboring wild-type BRCA1 or BRCA2, are unable to repair DNA and consequently die, a paradigm known as synthetic lethality [35]. PARP inhibitors are selective, and normal cells without these DNA damage repair defects are spared from the effects of PARP inhibitors, which makes this class of drugs an attractive therapeutic target [37, 38]. Preliminary results from a randomized phase II trial of the PARP inhibitor BSI-201 or placebo plus gemcitabine/carboplatin in patients with breast cancer demonstrated a significant improvement in clinical benefit rate, progression-free survival, and overall survival [39]. These results also demonstrated the tolerability and safety of PARP inhibitors with chemotherapy. Fong et al. [36•] published their experience with the PARP inhibitor olaparib in a phase I clinical trial in cancers associated with the BRCA1 or BRCA2 mutations, which included several prostate cancer patients. Olaparib was well tolerated, and antitumor activity was demonstrated. Further studies with olaparib or ABT-888, another PARP inhibitor, are planned or are ongoing in CRPC.

Immunotherapy

Vaccine-Based Approaches

PROSTVAC: The vaccine PROSTVAC (Prostate-Specific Antigen Expressing Vaccinia Virus Vaccine) consists of recombinant vaccinia virus-encoding transgenes for PSA and multiple T-cell costimulatory molecules (TRICOM) [40] (Fig. 1). Vaccination infects antigen-presenting cells (APCs) that interact with T cells, which is designed to stimulate the host immune system to mount targeted immune responses against tumor cells expressing PSA. A phase I trial of PROSTVAC administered subcutaneously in a heterologous prime-boost regimen in CRPC patients showed safety and PSA stabilization in 40% of men [40]. However, a randomized, double-blind phase II trial of PROSTVAC versus empty vector in men with CRPC did not achieve its primary end point of prolonging progression-free survival [41]. Later, updated results presented at the American Society of Clinical Oncology this year did show an 8.5-month improvement in median overall survival. As this trial was not powered to detect an overall survival difference, these findings remain unclear, particularly in the absence of improved progression-free survival [42]. Currently, a randomized phase III trial using docetaxel with or without PROSTVAC as first-line therapy is being planned [43].

Sipuleucel-T (Provenge): Sipuleucel-T is an autologous vaccine that is designed to activate one's immune system against one's own prostate cancer cells (Fig. 1). Pheresed patient APC cells are processed with recombinant prostatic acid phosphatase antigen, a prostate cancer antigen, and granulocyte-macrophage colony-stimulating factor prior to re-infusion in patients. Phase I and II trials showed that sipuleucel-T was tolerated well with fever being the most common adverse event [44]. However, a randomized phase II/III trial with sipuleucel-T versus placebo failed to achieve the primary end point of improved time to progression [45]. An unplanned analysis of overall survival, which is subject to the bias of differences in post–sipuleucel-T treatments between the two groups, did show an improvement in overall survival for those who had received sipuleucel-T [45]. Another randomized phase II/III trial in men with asymptomatic CRPC did not achieve its primary end point of improved time to progression, and this trial failed to show improved overall survival. An unplanned pooled analysis of these two phase II/III trials demonstrated a 4.3-month improvement in median overall survival that was statistically significant (P=0.01). However, an FDA panel rejected the request for approval of sipuleucel-T in 2007.

The phase III randomized, placebo-controlled IMPACT trial powered to assess the impact of sipuleucel-T on extending overall survival was recently completed. The results, which were presented this year, showed a median survival benefit of 4.1 months (25.8 months versus 21.7 months) with sipuleucel-T versus placebo-treated metastatic CRPC patients [46]. The FDA is expected to rule on this trial result in 2010. If approved, sipuleucel-T would be the first new agent for the treatment of prostate cancer since approval docetaxel of in 2004.

Immune-Regulating Agents

Anti-CTLA4 monocloncal antibodies (Ipilimumab): CTLA-4 is a costimulatory molecule expressed on the surface of T-lymphocytes and plays a role as a negative regulator of T-cell activation, leading to attenuation of T-cell responses against tumor cells [47] Fig. 1. CTLA4 blockade by CTLA4 monoclonal antibodies works by enhancing T-cell responses, alleviating restraints on T-cell activity to promote immune-mediated tumor regression [47]. A randomized phase II trial evaluated ipilimumab alone or in combination with a single dose of docetaxel in CRPC [48]. The PSA response rate was similar between both arms, and radiological responses were not seen [48]. A single-agent phase I/II study of ipilimumab in men with CRPC was recently completed [49, 50]. Common adverse events associated with ipilimumab included fatigue, rash, pruritus, nausea, diarrhea, constipation, and weight loss.

Rare immune-based toxicities included adrenal insufficiency, hepatitis, endocrinopathy, and autoimmune colitis [43, 49]. The addition of radiotherapy, which was designed to stimulate immune responses, to ipilimumab, led to PSA declines≥50% in 10 of 45 patients [50].

Conclusions

Prostate cancer is the second leading cause of cancer death in men in the United States, and nearly all of these deaths will occur due to CRPC. For men with castrate-resistant metastatic prostate cancer, docetaxel remains the only FDA-approved treatment with a proven survival benefit [8, 9]. While this underscores the unmet needs in these patients, the current state of basic and translational prostate cancer research informs the many promising new therapies reviewed herein. Although many of the aforementioned agents appear promising, large, randomized phase III trials will be necessary prior to concluding that any of these therapies improve outcomes for patients with CRPC. In the future, we hope that the biggest challenge, to both oncologists and patients, will be deciding which active therapy against metastatic CRPC to use and in what order.

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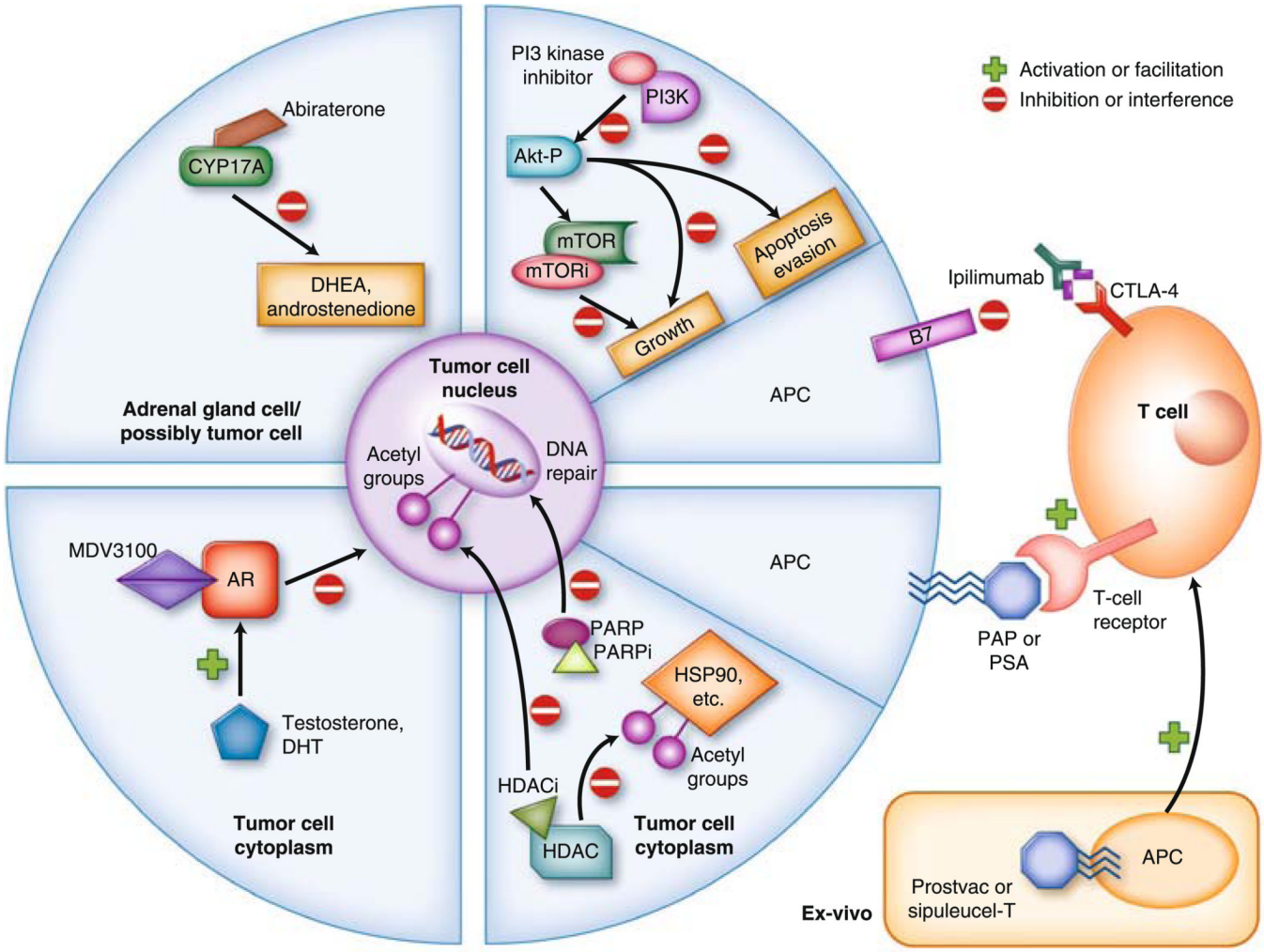

Fig. 1.

Mechanism of action of emerging therapies in prostate cancer. *Red circle with white bar* indicates inhibition or interference. *Green plus sign* indicates activation or facilitation. APC —antigen-presenting cell; AR—androgen receptor; CTLA—cytotoxic T-lymphocyte antigen 4; CYP17A—17alpha-hydroxylase/17,20 lyase; DHEA—dehydroepiandrostenedione; DHT— dihydrotestosterone; HDAC—histone deacetylases; HSP90—heat shock protein 90; mTOR—mammalian target of rapamycin; PAP—prostatic acid phosphatase; PARP—poly (ADP-ribose) polymerase; PI3 kinase—Phosphoinositide 3-kinase; PSA—prostatespecific antigen