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Novel targeted therapeutics for metastatic castration-resistant prostate cancer

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Abstract

Virtually all patients that succumb to prostate cancer die of metastatic castration-resistant disease. Although docetaxel is the standard of care for these patients and is associated with a modest prolongation of survival, there is an urgent need for novel treatment strategies for metastatic prostate cancer. In the last several years, great strides have been made in our understanding of the biological and molecular mechanisms driving prostate cancer growth and progression, and this has resulted in widespread clinical testing of numerous new targeted therapies. This review discusses some of the key therapeutic agents that have emerged for the treatment of metastatic castration-resistant prostate cancer in the last 5 years, with an emphasis on both molecular targets and clinical trial design. These agents include mammalian target of rapamycin (mTOR) pathway inhibitors, anti-angiogenic drugs, epidermal growth factor receptor (EGFR) inhibitors, insulin-like growth factor (IGF) pathway inhibitors, apoptosis-inducing drugs, endothelin receptor antagonists, receptor activator of nuclear factor κB (RANK) ligand inhibitors, vitamin D analogues, cytochrome P17 enzyme inhibitors, androgen receptor modulators, epigenetic therapies, vaccine therapies, and cytotoxic T lymphocyte-associated antigen (CTLA)-4 blocking agents.

Keywords

Metastatic castration-resistant prostate; cancer; Targeted therapies; Immune therapies; Molecular targets; Clinical trials; Drug development

1. Introduction

Prostate cancer is the most common malignancy in men worldwide. In the United States, there were an estimated 186,300 new diagnoses of prostate cancer and 28,700 prostate cancer deaths in 2008, representing 25% of new cancer cases and 10% of male cancer deaths

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Conflict of interest

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[1]. This makes prostate cancer the second leading cause of cancer death in men. While the disease can potentially be cured when localized, metastatic prostate cancer remains incurable.

Treatment of localized prostate cancer is usually centered around surgery and/or radiation therapy. However, even after definitive local therapy, approximately 30–50% of patients will have a local or distant recurrence [2,3]. Patients with metastatic prostate cancer have a median survival of 3–7 years, and most men die of it [2]. Treatment for metastatic disease involves surgical castration or hormonal manipulation using gonadotropin-releasing hormone (GnRH) agonists, antiandrogens, or both. Although the majority of these patients initially respond to androgen deprivation therapy, all eventually progress to a state of castration-resistant prostate cancer (CRPC). Treatment options for these men are limited. Secondary hormonal manipulations, such as ketoconazole, are often used but these produce short-lived responses and do not improve survival [4]. Other acceptable approaches in these men include watchful waiting until the development of symptoms, or the initiation of cytotoxic chemotherapy. In this regard, the chemotherapeutic agent docetaxel has been shown to improve overall survival in patients with CRPC, but only by a median of 2.9 months (median survival 19.2 months versus 16.3 months using mitoxantrone, $P = .004$) [5,6]. Novel therapies for this patient population are urgently needed.

Since the approval of docetaxel by the Food and Drug Administration (FDA) in 2004, no new anti-cancer therapies have entered the market for the treatment of metastatic CRPC. On the other hand, the number of agents for CRPC in various stages of clinical development is higher than ever before. This has been made possible due to our accelerated understanding of the biological and molecular mechanisms underpinning prostate cancer growth and spread, which has fueled an expansion in research on new therapeutic approaches. This review will highlight novel targeted therapies that have emerged for CRPC in the last 5 years, focusing on the mechanism of action and developmental status of some key clinical compounds that have reached phase II and III clinical trials (Table 1). Advances in chemotherapeutic drugs, hormonal agents, and bisphosphonates will not be discussed herein.

2. Targeted treatments

Although a prostate cancer stem cell has yet to be conclusively demonstrated, prostate cancer clearly progresses from an androgen-dependent tumor (with features similar to the luminal differentiated glands of the prostate) to a castration-resistant tumor that has features of adult stem cells, including anti-apoptotic mechanisms, chemotherapy resistance, and reliance on nonhormonal signaling pathways [7]. Candidate prostate cancer progression pathways under investigation include epidermal growth factor receptor (EGFR) signaling, vascular endothelial growth factor (VEGF) receptor-mediated pathways, phosphatidylinositol 3-kinase (PI3K)/Akt signaling, the insulin-like growth factor (IGF) axis, Hedgehog signaling, mitogen-activated protein (MAP) kinase signaling, the endothelin axis, and others. Given the molecular complexity of these pathways in the prostate cancer cell and the potential redundancy of individual pathways in the process of cancer progression, the simultaneous inhibition of multiple pathways remains a common strategy to induce sustained and clinically meaningful responses in metastatic CRPC.

The major biologic processes under therapeutic investigation in CRPC involve growth and survival, nutrition, apoptosis, chemotherapy and hormone therapy resistance, extra-gonadal androgen production, modulation of the androgen receptor, angiogenesis, the bone interface, epigenetic regulation, immune surveillance and escape, and stem cell renewal. This article provides an overview of these pathways as they pertain to prostate cancer rational targets and the approaches that are currently being developed for therapeutic purposes (Table 1).

2.1. PI3K/Akt/mTOR pathway

In advanced prostate cancer, loss of the tumor suppressor gene PTEN occurs in more than 50% of metastatic lesions and in approximately 20% of locally advanced lesions [8,9]. Loss of PTEN correlates with high Gleason score and stage, chemotherapy resistance, and other features of advanced prostate cancers [8]. PTEN is a negative regulator of the phosphatidylinositol 3-kinase (PI3K)/Akt survival pathway, and advanced prostate cancers frequently have elevated levels of phosphorylated (activated) Akt [10]. The Akt pathway is involved in signal transduction from multiple cell surface receptors, including the insulin receptor, epidermal growth factor receptor, insulin-like growth factor receptor, platelet-derived growth factor receptor, and interleukin-6 receptor, and it is likely to function as a cellular sensor for nutrient and growth signals [11]. In addition to promoting cell survival through the inhibition of apoptosis, the Akt pathway regulates cell growth, proliferation, and angiogenesis through the mTOR (mammalian target of rapamycin) pathway and the facilitated translation of signals such as c-Myc, cyclin D, and vascular endothelial growth factor [10]. Restoration of functional PTEN activity or inhibition of mTOR activity can block the growth of PTEN−/− prostate cancer xenografts in mice and restore chemotherapy (and possibly hormonal) sensitivity [12,13].

Rapamycin is a natural compound derived from soil samples containing the bacterium *Streptomyces hygroscopicus*, and has been used as a potent immunosuppressive agent in solid organ transplantation. Its antiproliferative properties and anti-tumor activity in cell lines also led to its clinical development in cardiology as a means of preventing stent restenosis and in oncology, in which a wide variety of tumors were found to exhibit sensitivity to this agent and its analogue, temsirolimus [14–16]. Temsirolimus has now been approved for the treatment of metastatic renal cell carcinoma [17]. Toxicities with rapamycin and its analogues are predictable and are not dose-related; they include maculopapular rash, hypertriglyceridemia, hyperglycemia, allergic reactions, pedal edema, mucositis, and thrombocytopenia [14,17–19].

Although mTOR inhibitors probably have little single-agent activity in advanced CRPC [20], the combination of these agents with docetaxel is an attractive option given their ability to reverse chemotherapy resistance in prostate cancer cell lines [21]. In addition, these agents induce apoptosis when they are given in combination with chemotherapy in patients who have demonstrable activation of the Akt pathway as a result of PTEN mutation/loss or other genetic alterations [22]. To this end, the mTOR inhibitor, everolimus, is currently being evaluated in combination with docetaxel for the first-line treatment of metastatic CRPC in a phase I/II clinical trial [23]. Everolimus is already approved for the treatment of advanced renal cell carcinoma [24]. A new mTOR inhibitor, deforolimus (AP23573), is also

being investigated in the phase II setting as single-agent therapy for men with advanced taxanerefractory CRPC.

2.2. Angiogenesis targets

Tumor angiogenesis is likely to be an important biologic component of prostate cancer metastasis, and elevated levels of the potent angiogenic molecule, vascular endothelial growth factor (VEGF), have been shown to correlate with advanced clinical stage and survival [25,26]. In a retrospective study of archived serum samples, VEGF levels were independently associated with survival from prostate cancer [27]. Similarly, antibodies to VEGF have slowed prostate xenograft growth rates, especially in combination with chemotherapy [28,29].

These findings led to the phase II CALGB 90006 trial, which added bevacizumab to docetaxel and estramustine in men with metastatic CRPC. Among 79 treated patients in this study, a fall in PSA of 50% or more was seen in 65% of men, median time to progression was 9.7 months, and overall median survival was 21 months [30]. Other phase II trials combining docetaxel and bevacizumab have also shown promising results [31,32]. These favorable trials have led to the design of a phase III randomized study (CALGB 90401) evaluating docetaxel 75 mg/m^2 every 3 weeks and prednisone 10 mg daily plus either bevacizumab 15 mg/kg or placebo given every 3 weeks. The primary endpoint of this trial is overall survival, and accrual of 1020 patients with metastatic CRPC has been completed. The initial results of this pivotal trial are awaited.

Thalidomide was originally developed in the 1960s for treatment of morning sickness and subsequently linked to teratogenic effects resulting in phocomelia and dysmelia. Whereas the exact mechanism of teratogenesis is unproven, the metabolites of thalidomide have been shown to inhibit angiogenesis through multiple potential mechanisms, including inhibition of pro-angiogenic signals such as VEGF, basic fibroblast growth factor (bFGF), interleukin-6, and tumor necrosis factor-α [33,34]. Preclinical studies suggest that thalidomide also has T-cell co-stimulatory activity and immunomodulatory properties. Phase I/II studies using high doses of thalidomide as a single agent have yielded low PSA response rates in the order of 20% [33,35]. However, in a randomized phase II trial of weekly docetaxel and low-dose thalidomide versus docetaxel alone, PSA responses, time to disease progression, and overall survival were greater in the combination arm [36]. Although this trial was underpowered to detect a difference from the standard arm, the clinical activity and manageable toxicity of this agent have led to the development of more potent thalidomide analogues for combination therapy, and these are currently undergoing clinical evaluation. Finally, a recent report of a phase II trial using a three-drug combination of docetaxel, thalidomide and bevacizumab showed PSA responses in approximately 80% of patients; however neurotoxicity was significant with this combination [37].

Toxicities with thalidomide include deep venous thrombosis, sedation, neuropathy, constipation, and fatigue. Newer thalidomide analogues with immunomodulatory features have been developed that lack the neurotoxicity of thalidomide but retain many of the T-cell modulatory effects, anti-angiogenic properties, and even direct pro-apoptotic functions [34]. Lenalidomide and CC-4047 are second-generation compounds with much more potent

tumor necrosis factor-α inhibition than the parent compound, and clinical testing with these agents has begun. For example, several phase I and II studies have revealed PSA responses and partial radiological responses with lenalidomide, both when used alone and when combined with ketoconazole or docetaxel [38–40]. However, phase III trials using thalidomide or lenalidomide in CRPC have not yet been conducted.

There has been a recent interest in the evaluation of tyrosine kinase inhibitors (TKIs), agents which block angiogenic growth factor targets such as the VEGF and PDGF receptors. The drug sorafenib is an oral inhibitor of RAF kinase, VEGFR, and PDGFR, which has been approved for use in metastatic renal cell carcinoma and hepatocellular carcinoma [41,42]. In phase II studies using sorafenib in men with metastatic CRPC, this agent was shown to prevent radiological progression and cause regression of bone metastases in some patients, but without affecting PSA levels [43,44]. The agent sunitinib and a novel multi-kinase inhibitor, vatalinib, are currently being tested in phase II studies in combination with docetaxel for chemotherapy-naïve CRPC; radiological responses rather than PSA responses have been chosen as primary endpoints in these trials. Finally, single-agent sunitinib is being evaluated in a phase III study of patients with docetaxel-refractory disease.

An alternative anti-angiogenic strategy is the use of VEGF decoy receptors (VEGF-Trap) to saturate circulating VEGF and prevent it from binding to its natural transmembrane receptor. One such agent is aflibercept (AVE0005), a novel recombinant decoy fusion protein of VEGFR and the Fc fragment of IgG1 [45]. In a phase I/II study of intravenous aflibercept combined with docetaxel in 54 heavily-pretreated patients with advanced solid tumors, the optimal dose of aflibercept was determined to be 6 mg/kg given every 3 weeks [46]. Toxicities from this combination regimen included neutropenia, hypertension, proteinuria, epistaxis, and dysphonia. Five patients (9%) achieved partial radiological responses, and 32 (59%) had stable disease. A multicenter, randomized, placebo-controlled phase III study of docetaxel with or without aflibercept in men with chemotherapy-naïve metastatic CRPC is now accruing patients.

A final approach to angiogenesis inhibition involves the use of tumor-vascular disrupting agents, drugs that primarily act against established tumor blood vessels by disrupting vascular endothelial cells and causing a range of subsequent antivascular effects [47]. The prototype in this class of agents is 5,6-dimethylxanthenoine-4-acetic acid (DMXAA). Motivated by experiments showing that DMXAA functioned synergistically with docetaxel in human prostate cancer xenografts [48], a multicenter randomized phase II trial of docetaxel plus or minus DMXAA (1200 mg/m^2 intravenously every 3 weeks) was conducted for men with metastatic CRPC in the first-line setting. In that study of 71 patients, PSA responses (>30% PSA reduction) at 3 months were 47% and 63% in the docetaxel-alone and docetaxel-DMXAA arms, respectively, and radiological response rates were 9% and 23% in the monotherapy-arm and the combination-arm, respectively [49]. Adverse events with DMXAA-docetaxel included neutropenia/febrile neutropenia, cardiac toxicities (supraventricular tachycardia, myocardial ischemia), gastrointestinal effects, and infectious complications.

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