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REVIEW

Castration-Refractory Prostate Cancer: New Drugs in the Pipeline

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ABSTRACT

The standard treatment for patients with castration-refractory prostate cancer (CRPC) is the combination docetaxel-prednisone, if the patient can support chemotherapy. Several new treatments have been tested in chemotherapy-naïve or docetaxel-pretreated patients with CRPC. Some of these treatments have shown activity in first-line and second-line treatment. In this review, an update is given of new treatment studies performed in patients with CRPC.

Keywords: castration-refractory prostate cancer; docetaxel; cabazitaxel; abiraterone acetate; angiogenesis modulators; vaccines

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INTRODUCTION

Every year, around 540,000 men develop prostate cancer and around 205,000 men die from prostate cancer worldwide.[1] Prostate cancer is a hormone-sensitive cancer that is influenced by testosterone, the male sex hormone. Testosterone is produced from cholesterol and is the main androgen end product of the testis, but can also be derived from androgens secreted by the adrenal gland and other tissues including prostate tissue. Testosterone is metabolized by prostate tissue to dihydrotestosterone, which is the principal ligand for the androgen receptor (AR). After transfer from the cytoplasm to the nucleus, the ligand-receptor complex activates different pathways involved in cell cycle progression and cell division.[2]

In patients with metastatic prostate cancer and in need of treatment (symptoms; a fast increasing prostate specific antigen [PSA] level) standard first-line treatment is castration. Castration can be by bilateral orchiectomy or biochemical castration with luteinizing hormone-releasing hormone (LHRH) agonists or antagonist. These treatments have a beneficial effect in around 80% to 90% of patients with metastatic prostate cancer. After a median of 22 months,[3] the disease

becomes refractory to castration and castration-refractory prostate cancer (CRPC) develops. This can be due to changes in the regulation of the AR because of increased sensitivity for androgens by overexpression of nuclear coactivators or AR amplification. Other mechanisms that have been implicated are the loss of the phosphatase and tensin homolog (PTEN) gene with activation of the phosphatidylinositol 3-kinase-Akt pathway leading to the release of BCL-2, resulting in cell survival.[2]

Patients with CRPC can be treated with the addition of antiandrogens to castration, which results in a response in 33% of patients. In case of progression, antiandrogen withdrawal induces a response in 5% to 20% of patients. Other possible treatments are the addition of steroids, estrogen or ketoconazole to castration.[3] More recently, many patients with CRPC are treated with docetaxel chemotherapy in combination with prednisone that has been proven to prolong survival with a median survival time of 18 months.[3] However, most patients with CRPC will die of their cancer and new treatments are necessary. New drugs that are being tested in CRPC are discussed in this review.

CHEMOTHERAPEUTIC AGENTS

The role of chemotherapy in patients with CRPC was first demonstrated by Tannock et al., who showed that the combination of mitoxantrone with prednisone improved the quality of life compared to prednisone alone.[4] Also, the combination of docetaxel-prednisone was able to improve median survival.[3] Thereafter, several groups have studied different chemotherapeutic agents in this patient population. Several studies looked at the activity of chemotherapy after first-line docetaxel. However, second-line chemotherapy showed only limited activity.

Chemotherapeutic agents include mitoxantrone in combination with prednisone gives a PSA response (≥50% decrease) in 15% of docetaxel-pretreated patients with a median PSA progression-free survival of 3.4 months.[5]

The combination of two older drugs, carboplatin, and etoposide was tested in 40 docetaxel-pretreated patients with CRPC. A PSA response was seen in 23% of patients with a median progression-free survival of 2.1 months and a median overall survival of 19 months.[6]

Satraplatin, an oral platinum analogue, was tested as second-line treatment in docetaxel-pretreated patients with CRPC. In a randomized phase 3 trial, there was a risk reduction of disease progression or death by 33% compared to placebo; however, the primary endpoint defined as improved overall survival was not reached.[7]

In a phase 2 study, the activity of second-line pemetrexed, an intravenous folate antimetabolite, was evaluated in 49 patients with CRPC. A PSA response was observed in only 8% and in patients with measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) criteria,[8] 8% demonstrated a partial response.[9]

Epothilones represent a new class of chemotherapeutics that stabilize microtubules but have a distinct mechanism of action compared with taxanes and a low susceptibility to drug resistance. Preclinical studies show that epothilones have an activity in taxane-resistant CRPC cell lines,[10] and patupilone,[11] ixabepilone,[12,13] and sagopilone[14] have demonstrated clinical activity and tolerability in phase 2 CRPC trials.[10]

Patupilone (epothilone B) was tested in 45 patients with CRPC of whom 55% had been treated previously with taxanes. Patupilone was generally well tolerated with diarrhea, fatigue, and neuropathy as the most serious side effects. In all, 13% of patients had a PSA response; no

objective response was reported and the median survival was 13.4 months.[11]

Ixabepilone, a semisynthetic derivative of epothilone B was compared with mitoxantrone as a second-line treatment after docetaxel in a randomized phase 2 study. The PSA response was 17% and 20% for ixabepilone and mitoxantrone, respectively, with a similar median survival (10.4 vs. 9.8 months, respectively).[12]

Ixabepilone was combined with mitoxantrone plus prednisone in a phase 1 trial in patients with docetaxel-refractory CRPC. The dose-limiting toxicities were grade 3 diarrhea, prolonged grade 4 neutropenia, and grade 5 neutropenic infection.[13] The recommended phase 2 dose was ixabepilone 35 mg/m² plus mitoxantrone 12 mg/m² every 21 days and continuous prednisone 5 mg twice per day in combination with pegfilgrastim 6 mg subcutaneously. In patients treated with this schedule, 43% experienced a PSA response.[12]

Paclitaxel poliglumex, a macromolecular polymer-drug conjugate of paclitaxel, was combined with transdermal estradiol in 21 patients with CRPC and pretreated with docetaxel. There was no PSA response or other evidence of activity.[15]

Cabazitaxel is a novel taxane compound that is active in cell lines refractory to taxanes. It acts by binding to and stabilizing tubulin and the combination of cabazitaxel plus prednisone was compared with mitoxantrone plus prednisone in the TROPIC (Treatment of Hormone-Refractory Metastatic Prostate Cancer Previously Treated With a Taxotere-Containing Regimen) trial as second-line treatment in patients with CRPC failing on docetaxel treatment. Cabazitaxel and prednisone/prednisolone significantly reduced the risk of death by 30% (hazard ratio [HR] 0.70; 95% CI: 0.59, 0.83; $P<0.0001$) with a clinically meaningful improvement in the median overall survival of 15.1 months in the cabazitaxel combination arm versus 12.7 months in the mitoxantrone combination arm. Patients who received the combination treatment with cabazitaxel also experienced a significant increase in median progression-free survival (2.8 months vs. 1.4 months. HR 0.74; 95% CI: 0.64, 0.86; $P<0.0001$). The most frequent grade 3/4 hematological adverse events with cabazitaxel included neutropenia (81.7%), febrile neutropenia (7.5%), and infections (10.2%); the most frequent grade 3/4 nonhematological adverse events were nausea (1.9%), vomiting (1.9%), and diarrhea (6.2%). Deaths due to adverse events were 4.9% in the cabazitaxel arm (predominantly due to neutropenia and its complications) versus 1.9% in the mitoxantrone arm.[16]

HORMONAL MANIPULATIONS

Androgen Production

After a surgical or biochemical castration, a small amount of androgens are still produced. One source is the adrenal gland and its androgen production can be suppressed by adrenalectomy, steroids interfering with the negative feedback loop of the hypothalamus-pituitary-adrenal gland axis, or by inhibiting steroid production by imidazole derivatives such as ketoconazole or aromatase inhibitors as aminogluthethimide.[3]

Abiraterone Acetate

The production of testosterone can be completely blocked by abiraterone acetate. This orally administered drug is a prodrug of 17-(3-pyridyl)androsta-5,16-dien-3-ol, abiraterone that inhibits the 17-hydroxylase/C17,20-

lyase complex (CYP17), an essential enzyme complex in the production of testosterone from cholesterol.[17]

During phase 1 studies, the most prevalent side effects were mild arterial hypertension, hypokalemia and edema. They were easily controlled by potassium supplements, eplerenone, a selective mineralocorticosteroid antagonist, antihypertensive drugs and low-dose corticosteroids. Based on the phase 1 studies, low-dose steroids are combined with abiraterone acetate to suppress the pituitary-adrenal gland axis and the related increase in adrenocorticotropic hormone and adrenal gland hormones.[18]

Several phase 2 studies in patients with CRPC were performed. In two phase 2 studies in docetaxel-pretreated patients (n=58 and n=47 patients),[19,20] the PSA response was 36% and 51% and in patients with evaluable disease according to the RECIST criteria a partial response was seen in 27% of 30 patients[20] and in 18% of 22 patients[18] in a phase 1 trial. A randomized phase 3 trial in this patient population was completed in 2009 and results are currently awaited.

In 42 chemotherapy-naive patients with CRPC, a PSA response was observed in 67% and a radiological partial response in 37.5% of 24 evaluable patients.[21] A phase 3 study has also reached completion in this group of patients and results are awaited. Abiraterone acetate is also active in patients pretreated with ketoconazole.[22]

AR Modulators

The AR can be activated despite very low testosterone levels. This activation can be due to androgens produced in tumor tissue, overexpression or amplification of the AR or mutation of the AR rendering it more sensitive to androgens or antiandrogens. The androgen receptor can also be activated by other peptide growth factors, cytokines, increased expression of coactivator proteins or decreased expression of corepressors.[23] MDV3100 (Medivation, San Francisco, CA, USA) is an AR antagonist that inhibits its nuclear translocation and blocks its binding with DNA.[23] This oral drug showed activity in patients with CRPC with a PSA response of 55% in chemotherapy-naive patients and of 36% in docetaxel-pretreated patients.[24]

ANGIOGENESIS MODULATORS

Angiogenesis is a complex process with interaction of hypoxic cells secreting ligands (eg, vascular endothelial growth factor [VEGF]) that stimulate endothelial cell proliferation by activating the VEGF receptor and modifying the structure of the microenvironment enabling vascular sprouting. In cancer, interfering with angiogenesis can result in a deprivation of the tumor of nutrition and oxygen and/or a modification of the hyperpermeability of the vasculature improving drug delivery to the tumor.[25] Several drugs have been developed that interfere with different factors in the process of angiogenesis and have been tested in patients with CRPC.

Antibodies Against Vascular Endothelial Growth Factor or VEGF Receptor

Several antibodies block the VEGF pathway by interfering with the ligand or the receptor. Two main monoclonal antibodies are being used for this: bevacizumab, directed against VEGF and by binding to VEGF inhibits its interaction with the VEGF receptor; and aflibercept, which binds to the VEGF receptor and so interferes with the binding of VEGF to the receptor.

Bevacizumab when used by intravenous administration as single agent showed no activity

in patients with CRPC with no PSA or radiological responses.[26] A combination of bevacizumab with docetaxel and estramustine gave a PSA response in 79% of 79 patients and a partial response rate of 42%,[26] while the combination of bevacizumab with docetaxel, prednisone and thalidomide proved to be too toxic in 60 evaluable patients. Although the PSA response rate was 90% and the radiological partial response rate 56% in 32 RECIST evaluable patients, severe toxicities were reported (neutropenic fever [5/60]; syncope [5/60], thrombosis [3/60], gastrointestinal perforation [2/60], grade 3 bleeding [2/60], and nephrotic syndrome [1/60]).[26]

Another study combined bevacizumab with docetaxel, prednisone, and thalidomide in 60 patients with CRPC. The PSA response was 90% and the median overall survival 28.2 months, which was higher than predicted by the Halabi nomogram. All patients developed grade 3/4 neutropenia.[27]

Aflibercept is a fusion protein of the constant part (Fc) of the human immunoglobulin IgG1 and the extracellular ligand-binding part of the VEGF receptors 1 and 2 (VEGF-trap). A phase 3 study is currently ongoing comparing docetaxel in combination with prednisone with or without aflibercept in patients with CRPC.[26]

Tyrosine Kinase Inhibitors

Tyrosine kinase acts at the intracellular part of the receptor and can block different pathways necessary for angiogenesis or cell cycle regulation. Several agents have been developed that interfere with angiogenesis by influencing the VEGF receptor.

Sorafenib is an oral multityrosine kinase inhibitor that targets the Ras/Raf kinase pathway, the VEGF receptor and the platelet-derived growth factor (PDGF) receptor. Several phase 2 studies with single agent sorafenib have been performed in patients with CRPC in first-line or second-line treatment showing a modest activity in terms of PSA and radiological response.[28-31]

Combinations with docetaxel-prednisone or mitoxantrone-prednisone after progression are underway.[26]

Sunitinib is also an orally administered multikinase inhibitor that inhibits the VEGF receptor, PDGF receptor and c-Kit in addition to other kinases which leads to significant antiangiogenesis.[32] In 36 patients with CRPC progressing after one or two lines of chemotherapy of which at least one with docetaxel, the PSA response rate was 12.1% and the radiological response in 18 evaluable patients was 11.1%.[33] However, these results could not be confirmed in another phase 2 study with chemotherapy-naive (*n*=17) and chemotherapy-pretreated (*n*=17) patients with CRPC, in which the PSA response rate was 5.8% and no objective responses were reported.[34]

Cediranib is an oral indole-ether quinazoline ATP-competitive small molecule that inhibits proliferation via inhibition of all VEGF receptors. This agent, when tested in patients with CRPC and pretreated with chemotherapy, showed a partial response rate in 11 evaluable patients of 18%.[26]

IMMUNOMODULATORY DRUGS

Immunomodulatory drugs such as thalidomide and its analogs act by immune modulation and antiangiogenic, anti-inflammatory and antiproliferative effects. Although activity has been shown in patients with prostate cancer, their exact mechanism in this disease is not fully understood. Their immunomodulatory activity has been linked to interference with different cytokines such as inhibition of interleukin (IL)-1 beta, IL-6 and tumor necrosis factor (TNF)-alpha, and

stimulation of IL-10 and augmentation of IL-2 and interferon-gamma.

Interference with angiogenesis might be by inhibition of TNF-alpha and interferon-gamma, which results in increased expression of endothelial cell integrin, a process essential for angiogenesis. In addition they block the secretion of basic fibroblast growth factor, an angiogenic factor secreted by tumor cells.[35]

Thalidomide

When thalidomide was administered as single agent in chemotherapy-naive patients (n=20)[36] or chemotherapy-pretreated patients (n=63)[37] PSA response was between 15% and 28% with no objective responses. Therefore the use of single agent thalidomide in this patient population was not continued but it was combined with different chemotherapeutic agents.

The combination of low-dose thalidomide (200 mg/day) with docetaxel (30 mg/m²/week three times every 4 weeks) was compared to docetaxel alone in 75 chemotherapy-naïve patients with CRPC in a randomized phase 2 trial. The PSA response was 53% in the combination arm versus 37% in the docetaxel alone arm. After a median follow-up of 47 months there was a survival benefit for the combination arm (29.5 vs. 14.7 months; P=0.04). There were more thromboembolic complications in the combination arm.[38] The development of a triple combination treatment with thalidomide, paclitaxel and estramustine was discontinued due to toxicity.[26]

Lenalidomide

Lenalidomide is a thalidomide analog that is 10 to 1000 times more potent than thalidomide and has a different toxicity profile with less neurotoxicity and sedative effects. It was tested in 35 patients with prostate cancer but no single agent activity has been demonstrated.[26]

The combination of docetaxel and lenalidomide was feasible in patients with CRPC and a phase 3 study is currently initiated comparing docetaxel and prednisone with or without lenalidomide.[26]

ENDOTHELIN INHIBITION

Endothelins are peptides with a paracrine/autocrine function that regulate vasomotor tonus, nociception, hormone production, and cell proliferation. These effects are mainly mediated by the interaction of endothelin 1 (ET-1) with the endothelin A (ETA) receptor.

In normal prostate tissue, ET-1 is produced by epithelial cells; in prostate cancer, the metabolism of ET-1 is disturbed leading to an increased level of ET-1 with activation of the ET-1/ETA axis and promotion of prostate cancer progression.[39]

Atrasentan is a selective oral ETA antagonist that has been tested in combination with androgen suppression in a randomized double-blind phase 3 trial in 941 patients with nonmetastatic CRPC and a biochemical disease progression. There was no difference in disease progression, while there was a benefit in PSA doubling time in favor for atrasentan (P=0.03).[40]

Atrasentan was combined with docetaxel in a phase 1-2 study in patients with metastatic CRPC. The maximum tolerated doses were 10 mg/day and 70-75 mg/m² every 3 weeks of atrasentan and docetaxel, respectively, with grade 3-4 toxicities including neutropenia and febrile neutropenia. PSA responses were observed in 23% (95% CI: 10%, 41%) of 31 patients with a median overall survival of 17.6 months (95% CI: 13.0, 23.2 months). This schedule is tested in a randomized trial.[41]

SRC INHIBITION

The Src kinase family is the largest group of non-receptor-linked protein kinases and is responsible for signal transduction during cellular differentiation, adhesion and migration. In the development of CRPC, there is an overexpression of Src kinases.[42,43]

Dasatinib is an oral inhibitor of BRC/ABL and of p60Src that was tested in 47 patients with CRPC. There were no PSA responses in this patient population but there seemed to be a beneficial effect on bone remodeling.[44] Another dual-specific inhibitor of Src and Abl protein tyrosine kinases, AZD0530, was tested in 28 patients with CRPC. There were no PSA responses observed.[45]

STRESS-RELATED REACTION MODULATORS

When a cancer cell is exposed to anticancer treatments, several stress-related mechanisms are activated with the production of stress-related proteins such as heat shock proteins (HSPs). These HSPs interact with other proteins, chaperones, enabling the cell to repair the damage with recovering of the protein homeostasis and cell survival. Some of these chaperones are involved in control of cell growth and resistance to anticancer treatments.[46]

Clusterin Inhibition

Clusterin is a chaperone protein that is involved in prostate cancer development and disease progression to CRPC, although the results of different studies are not conclusive. Clusterin expression was found to be significantly reduced in patients with untreated prostate cancer and CRPC. The regulation of clusterin seems thus an important epigenetic event in the development of prostate cancer.[47]

Custirsen (OGX-011, OncoGenex Pharmaceuticals, Bothell, WA, USA) is a 2'-methoxyethyl modified phosphorothioate antisense oligonucleotide that is complementary to clusterin mRNA. It has been tested in combination with docetaxel in 40 patients with CRPC in a phase 1 study showing that it is possible to administer doses that could give full biological effect with as main side effects myelosuppression, fatigue, hair loss, gastrointestinal effects, and dose-related chills and fever.[48] In-vitro studies showed that custirsen could reverse resistance in docetaxel-resistant cell lines.[49]

In a randomized phase 2 study in 82 chemotherapy-naive patients with CRPC, the combination of custirsen with docetaxel resulted in a PSA response in 45% of patients compared to 34% with docetaxel alone. Progression-free and overall survival were 7.3 and 23.8 months for the combination treatment and 6.1 and 16.9 months for docetaxel alone.[50]

Histone Deacetylation Inhibition

Dysregulation of histone deacetylase (HDAC) enzymes has been reported in the development of prostate cancer. HDAC1 and HDAC3 suppress the AR-mediated gene expression. HSP90 is an ATPase-driven molecular chaperone protein that influences the molecular stability, confirmation and function of oncogene tyrosine and serine-threonine kinases (eg, human epidermal growth factor receptor 2 [HER2]/neu, Akt) and steroid hormone receptors. Inhibition of HSP90 decreases the activity of these enzyme systems leading to apoptosis in vitro.[51]

Romidepsin is a HDAC inhibitor that was intravenously administered to 35 chemotherapy-naive patients with CRPC. The PSA response was

5.7% and 1/25 evaluable patients developed a partial response. Major side effects were nausea (85.7%), fatigue (80.0%), vomiting (65.7%), and anorexia (57.1%).[52]

THERAPEUTIC PROSTATE CANCER VACCINES

Several therapeutic vaccines have been tested in patients with prostate cancer. Different types of vaccines were used such as genetically modified viruses (eg, Prostvac-VF, Bavarian Nordic, Denmark), protein or peptide pulsed dendritic cells (eg, Sipuleucel-T) or genetically modified tumor cells producing cytokines (eg, GVAX).[53] The aim of these vaccines is to stimulate the patient's own immune system to induce an antitumor response. However, as therapeutic vaccines have been only tested in patients with extensive disease and multiple pretreatments, positive results are rather limited.

Prostvac-VF

Prostvac is a regimen of cancer vaccines consisting of a recombinant vaccinia vector followed by multiple booster vaccinations employing a recombinant fowlpox vector. Both vectors contain the transgenes for PSA and multiple T cell costimulatory molecules (TRICOM). The PSA-TRICOM vaccines infect antigen-presenting cells (APCs) and generate proteins that are expressed on the surface of the APCs. The interaction of these APCs with T cells initiates a targeted immune response and T cell-mediated tumor cell destruction.[54]

This strategy was tested in 125 patients with metastatic CRPC, of whom 82 received Prostvac-VF and 40 control vectors. The primary endpoint, progression-free survival was similar between the two groups. However, after a median follow-up of 3 years, the overall survival rate was 30% in the Prostvac-VF group compared to 17% in the control arm and the median survival time increased by 8.5 months (25.1 vs. 16.6 months for controls; HR 0.56; 95% CI: 0.37, 0.85; P=0.0061).[55] These results have to be confirmed in a phase 3 study.

Sipuleucel-T

Sipuleucel-T (Provenge®, Dendreon, Seattle, WA, USA) is a dendritic cell treatment in which APCs are extracted by leukaferese and exposed in vitro to a fusion protein of prostate alkaline phosphatase, and granulocyte macrophage colony-stimulating factor (GM-CSF). The cells are matured and reinfused into the patient. Sipuleucel-T stimulates the immune system to target prostate alkaline phosphatases, present in 95% of patients with prostate cancer.[53]

Combining two phase 3 trials in 225 patients with CRPC (sipuleucel-T: n=147; placebo: n=78) with similar design showed a reduction by 33% of risk of death (HR 1.50; 95% CI: 1.10, 2.05; P=0.011). The most common adverse events associated with treatment were chills, pyrexia, headache, asthenia, dyspnea, vomiting, and tremor.[56] Sipuleucel-T has been registered on April 29, 2010 for the treatment of asymptomatic or minimally symptomatic metastatic CRPC by the Food and Drug Administration.

GVAX

GVAX is a vaccine of two allogeneic prostate carcinoma cell lines modified to secrete GM-CSF that, when tested in 80 patients with CRPC resulted in a median survival time of 35 months.[57] It was compared in two large phase 3 studies with (VITAL-2) or without docetaxel (VITAL-1) to docetaxel but they were closed early because of not reaching the interim

endpoints. Furthermore the combination arm in VITAL-2 had an excess of deaths.

MONOCLONAL ANTIBODIES AGAINST OTHER TARGETS

Several groups are studying the activity of monoclonal antibodies against targets that might be important in patients with CRPC. The combination of cetuximab, a monoclonal antibody directed against the epidermal growth factor receptor, and doxorubicine resulted in a PSA response of 8.3% in 36 patients with CRPC.[58] Trastuzumab, a monocloncal antibody against HER2-neu showed no activity in patients with CRPC.[59]

CNTO-238, a monoclonal antibody against IL-6, was combined with docetaxel and induced a PSA response in 55% of 29 patients. When this monoclonal antibody was combined with mitoxantrone and compared to mitoxantrone alone in a phase 2 study, the results of the combination were inferior to mitoxantrone alone.[60]

CONCLUSION

Several new treatments are currently being tested in patients with CRPC. Some of these treatments have already shown an improvement in survival in selected patient populations. However, at the moment, the combination of docetaxel-prednisone is still considered standard treatment in patients with symptomatic CRPC and who can support chemotherapy. Also, one should await randomized phase 3 trials before changing daily clinical practice.

If these new agents are proven effective, this will change the prospective of cancer patients with increasing life expectancy and less toxic treatments. However, the sequence of administration and the most effective combinations will still have to be explored, since with the current trials a multitude of treatment possibilities will become available making the treatment of CRPC more complex and a multidisciplinary approach will be even more important.

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