New Directions in the Treatment of Castration-Resistant Prostate Cancer

INTRODUCTION

Prostate cancer is the second leading cause of cancer death in men, with an estimated 218,890 new cases of prostate cancer and 27,050 deaths per year in the United States. Approximately 72% of men diagnosed with prostate cancer will survive 10 years; 53% will survive 15 years. Many patients with localized disease have an excellent long-term survival and high cure rates with standard approaches. However, patients with high-risk, locally advanced, and metastatic disease have a poor prognosis. Hormonal therapy is considered the first-line treatment for these patients.

Approximately 80% to 90% of men with recurrent or disseminated prostate cancer following local therapy will respond to androgen deprivation therapy (ADT). However, the initial favorable response of improvement in pain, shrinkage of soft tissue metastases, and decrease in prostate-specific antigen (PSA) has a median duration of only 12 to 20 months. Progression during ADT is followed by the emergence of a castration-resistant phenotype (also referred to as hormone-refractory or castration-refractory prostate cancer [CRPC]). After development of metastatic hormone-refractory disease, prostate cancer is incurable, with a median survival of 9 to 12 months.

The prognosis of CRPC is associated with performance status, presence of bone pain, extent of disease on bone scan, and serum alkaline phosphatase levels. Bone metastases develop in 90% of men with CRPC, often resulting in significant morbidity that includes pain, pathologic fractures, spinal cord compression, and bone marrow failure. Paraneoplastic effects are also common, including anemia, weight loss, fatigue, hypercoagulability, and increased susceptibility to infection. Thus, CRPC presents a spectrum of disease ranging from nonmetastatic and asymptomatic disease with rising PSA levels despite ADT to metastases and significant debilitation due to cancer symptoms.
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Learning Objectives At the completion of this educational activity, participants should be able to:
• Describe the current standard of care for the treatment of CRPC/HRPC
• Review recent efficacy and safety data on the use of newer cytotoxic agents for CRPC/HRPC
• Describe the results of recent studies evaluating novel targeted agents for the treatment of CRPC/HRPC

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Jeanne Held-Warmkessel
MSN, RN, AOCN®, ACNS-BC
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Publisher
Senior Production Manager
Copy Editor
Circulation Department
Business Manager
Executive Administrator
Phil Pawelko
Robyn Jacobs
Bjarne Hansen
phil@greenhillhc.com
circulation@greenhillhc.com
blanche.marchitto@greenhillhc.com
Andrea Boylston

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Most prostate cancer cells are hormone dependent and therefore have normal expression of androgen receptors. These receptors bind to dihydrotestosterone, and the complex migrates to the nucleus and binds to the androgen response element, resulting in cell growth. ADT mediates prostate cancer by inducing death of androgen-sensitive cells via apoptosis. Androgen-resistant clones can survive in most patients and eventually predominate and contribute to hormonal failure.⁸

Some tumor cells proliferate despite castrate levels of testosterone, and tumors that grow despite initial surgical or chemical castration are considered hormone-sensitive, androgen-independent tumors. Hormone-independent prostate cancer may respond to additional hormonal maneuvers, but subsequent progression leads to hormone-refractory, androgen-independent cells unresponsive to further hormonal manipulation.⁹⁻¹¹

When prostate cancer progresses following ADT, few treatment options are available, with only one, docetaxel, being shown to prolong life.³ The survival advantage of docetaxel is modest, and the limitations of standard ADT and cytotoxic chemotherapy have compelled the search for targeted therapies that circumvent the various mechanisms of resistance to therapy.

Mechanisms of Androgen Receptor Activation and ADT Resistance in CRPC

CRPC utilizes several sources of ligands. ADT does not completely eliminate serum androgens, and serum levels of adrenal androgens such as dehydroepiandrosterone (DHEA) and androstenedione are unaffected. Intraprostatic androgen concentration is reduced by only ~75%, sufficient to activate the androgen receptor (AR).¹²⁻¹³ Although this level of androgen reduction is sufficient to arrest the progression in untreated prostate cancer, cellular alterations occur that sensitize the AR pathway, induce resistance, and foster growth.³ Also, overexpression of AR is common in CRPC, and compared with localized disease, CRPC has a higher expression of AR.³

Initial favorable response of improvement in pain, shrinkage of soft tissue metastases, and decrease in prostate-specific antigen has a median duration of only 12 to 20 months.

The HER2 receptor tyrosine kinase is progressively overexpressed in more advanced CRPC.¹⁴ In addition to HER2, increased signaling by a number of other growth factor receptors (eg, epidermal growth factor receptor [EGFR], insulin-like growth factor 1 receptor [IGF-1R], and interleukin-6 receptor [IL-6R]) can enhance AR signaling, induce downstream activation of critical growth and survival pathways, and facilitate castration resistance.¹⁵

As prostate cancer progresses, prostate cancer cells evolve and develop mechanisms to survive in an androgen-depleted environment. Reactivation of the AR and AR-responsive pathways is one adaptive mechanism.¹⁶ Prostate cancer cells also develop the ability to use very low levels of androgen to grow, with DNA amplification increasing AR expression that results in a receptor capable of activation with low levels of ligand.¹⁷ Mutations in the AR allow its activation by nonandrogenic steroid molecules and antiandrogens.¹⁸ Signal transduction processes are implicated in the activation of downstream AR signaling and include the EGFR family, the IGF-1R, and the phosphoinositide 3-kinase (PI3K) pathway.¹⁹

A central mechanism in the development of CRPC is the induction of a bypass pathway independent of the AR that can overcome apoptosis induced by androgen depletion. By bypassing the AR completely, prostate cancer cells survive independent of ligand-mediated or nonligand-mediated AR activation.¹⁹ Prostate cancer stem cells are rare, undifferentiated cells that do not express the AR, are not dependent on androgens for survival, and contribute to the maintenance of the tumor because they are unaffected by ADT.²⁰

Therapeutic Options in CRPC: Cytotoxic Chemotherapy

First-Line Chemotherapy

Three drugs have been approved by the U.S. Food and Drug Administration (FDA) as first-line chemotherapy in CRPC. Estramustine disrupts microtubule-associated proteins in vitro and was approved in 1981 for the palliative treatment of metastatic and/or progressive carcinoma of the prostate.²¹ Although this agent has not demonstrated an impact on survival, some studies indicate a synergistic activity with docetaxel.²¹ Mitoxantrone is a type II topoisomerase inhibitor that disrupts DNA synthesis and DNA repair; it was approved (in combination with corticosteroids) for CRPC in 1996 based on demonstrated efficacy in relieving pain and improving quality of life compared with prednisone alone. No trial of mitoxantrone has demonstrated an impact on overall survival (OS).²¹ Docetaxel is a semisynthetic analog of paclitaxel that disrupts the microtubular network in cells that are essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules. Microtubule bundles without normal function are produced, and mitosis is inhibited.⁵ Docetaxel was approved in 2004 by the FDA (in combination with prednisone) as treatment for CRPC based on phase III clinical trial results (TAX 327) that found a survival advantage over mitoxantrone (18.9 months vs 16.5 months) and significant
improvement in pain reduction and PSA response.\textsuperscript{22} A parallel trial (SWOG 9916) confirmed these results by finding superior OS among patients given docetaxel and estramustine compared with mitoxantrone and prednisone (17.5 months vs 15.6 months), as well as significant increases in PSA response rates and objective tumor response among the docetaxel-treated patients.\textsuperscript{23}

Despite these survival differences, docetaxel is not a cure for CRPC, and the mortality rate among patients in both trials was 100%. The modest survival advantage seen with docetaxel therapy has spurred a search for other agents to further improve survival, either alone or as combination therapy, and a number of agents are currently being evaluated in phase III trials as first-line treatment of CRPC.

\textbf{Second-Line Chemotherapy}

Patients whose tumors progress through first-line chemotherapy have limited treatment options available to them, and progress toward the identification, evaluation, and approval of candidate agents has been sluggish. Several drugs, either as monotherapy or combination therapy, have been evaluated; with the exception of satraplatin trials, all trials have been phase II, with most patients pretreated with docetaxel. Overall, second-line chemotherapies have provided only modest results in progression-free survival (PFS).\textsuperscript{24}

\textbf{Antimicrotubule-Based Compounds}

The epothilones belong to a new class of cytotoxic agents being researched for the treatment of CRPC.

\textbf{Platinum-Based Compounds}

Four phase II trials involving paclitaxel found a measurable response and median duration of response of 60% to 100% and 45 to 65 months, respectively.\textsuperscript{34} A phase III clinical trial comparing satraplatin and prednisone to prednisone showed an 18% PSA response and a median survival of 13.4 months.\textsuperscript{31} Two studies involving vinorelbine have been reported; one study found the average duration of PSA response and time to PSA progression to be 7 months each,\textsuperscript{32} while the other found a median PFS and OS of 5.1 months and 9.7 months, respectively.\textsuperscript{33}

\textbf{Anthracenedione/Anthracycline-Based Chemotherapy}

A combination of epirubicin, estramustine, and celecoxib was given to CRPC patients in a phase II trial. Median survival duration was 441 days.\textsuperscript{37} Cyclophosphamide was administered to patients in whom docetaxel therapy failed; 44.4% achieved a PSA response, and median OS was 24 months. The authors suggested that the demonstration of low toxicity and efficacy makes cyclophosphamide a prime candidate for second-line therapy in combination with other agents.\textsuperscript{38}

\textbf{Other Cytotoxic Agents as Single or Combination Therapy}

An evaluation of docetaxel and oxaliplatin was presented, with 50% of patients showing a PSA response and 4 out of 6 showing a reduction in soft-tissue disease.\textsuperscript{39} A study evaluating docetaxel with carboplatin showed an 18% PSA response, a median time to progression of 4.3 months, and OS of 12.4 months.\textsuperscript{40} A study was performed to assess the efficacy of the carboplatin-etoposide combination following docetaxel failure; 23% of patients achieved a PSA response, median PFS was 2.1 months, and the median OS was 19 months. Pain response was achieved in 53%.\textsuperscript{41}

\textbf{Therapeutic Options in CRPC: Targeted Therapy}

CRPC remains dependent on a functional AR, AR-mediated processes, and the availability of intraprostatic intra-cellular androgens despite low serum androgen levels during ADT. Conventional AR-targeted therapy, including gonadotropin-releasing hormone (GnRH) agonists and antiandrogens, is inadequate in shutting down...
AR signaling. Advances in the understanding of the molecular mechanisms underlying CRPC have translated into the development of a variety of targeted treatment approaches. Some of the targets of these therapies include androgen-independent progression, androgen receptor signaling, immune tolerance, factors affecting cell proliferation and survival, and mediators of metastases.

**Antiandrogens**

MDV3100 is a potent, novel androgen antagonist that inhibits AR function by blocking nuclear translocation of AR and DNA binding. Interim results of an ongoing trial showed a 49% PSA response rate (≥50% decline from baseline) at 12 weeks. In another recent trial, 55% of chemotherapy-naive patients and 42% who had received previous chemotherapy experienced a ≥50% decrease in PSA from baseline to week 12, and 85% of patients whose circulating tumor cell counts at baseline were favorable retained favorable counts. Of 83 patients with bone metastases at baseline, 27 had stable disease at week 12. RD162, another diarylthiohydantoin compound similar to MDV3100, is undergoing preclinical testing. BMS-641988 is a novel antiandrogen with 20-fold greater affinity for AR than bicalutamide, a first-generation antiandrogen, and is in the early stage of development. Mifepristone is a potent AR antagonist that functions by competing with androgen, preventing AR coactivator binding, and by enhancing binding of AR corepressors. One trial showed very limited activity in CRPC.

**Androgen Receptor Signaling**

**Inhibition of the Steroid Synthesis Pathway**

Ketoconazole is an azole antifungal agent that weakly inhibits several cytochrome P450 enzymes involved in adrenal steroid synthesis and has been used to treat CRPC. to 35% of patients who progress on antiandrogens have a short-lived PSA response to ketoconazole and on progression have a significant rise in plasma adrenal androgens.

**Ketoconazole** is an azole antifungal agent that weakly inhibits several cytochrome P450 enzymes involved in adrenal steroid synthesis and has been used to treat CRPC.

Ablation of Intracellular AR Signaling

OGX-011 exerts an antitumor action through inhibition of clusterin. Clusterin is a chaperone protein that is overexpressed in prostate cancer, and OGX-011 causes the inhibition of clusterin mRNA translation. A Phase II trial of OGX-011 with mitoxantrone or docetaxel in CRPC patients with previous docetaxel progression found that among the mitoxantrone/OGX-011 patients, 27% had a PSA decline ≥50% from baseline and a median OS of 11.4 months. Among OGX-011/docetaxel patients, 40% had a >50% PSA decline from baseline and a median OS of 14.7 months. A Phase III trial randomizing patients to first-line docetaxel with or without OGX-011 found the median OS to be 16.9 months for the docetaxel group and 27.5 months for the docetaxel–OGX-011 group.

**Vitamin D Receptor**

Calcitriol (1,25-dihydroxycholecalciferol), the principal active metabolite of vitamin D, modulates growth factor signaling, induces apoptosis through downregulation of the antiapoptotic protein Bcl-2, and is antiangiogenic. Data indicated robust antineoplastic activity in preclinical models of prostate cancer, and although a study of patients receiving docetaxel and either oral calcitriol or placebo did not find a survival advantage with the addition of calcitriol, another trial
with a combination of calcitriol, carboplatin, and dexamethasone found a PSA response in 38.2% of patients and a median OS of 97.7 weeks.30

Signaling in CRPC

PTEN and PI3K Signaling

The PI3K pathway regulates many key cellular processes, and the PI3K/AKT/mTOR pathway regulates the malignant progression of prostate cancer and appears to be critical in the development of CRPC. In vitro data suggest that overexpression and activation of AKT can trigger prostate cancer androgen escape via altered sensitivity and activation of AR.60 PI3K inhibitors have exhibited high selectivity and growth inhibition in vitro and in vivo, and several of these inhibitors have progressed in clinical trials61; their likely optimal use is in combination with inhibitors of other survival signaling pathways such as EGFR/MEK/MAPK.62

IGF-1R Signaling

IGF-1R expression changes as prostate cells progress from a normal to a malignant phenotype, and IGF-1R is implicated in resistance to therapy.63 Targeting of IGF-1R signaling in preclinical research lead to suppressed growth and induced apoptosis of prostate cancer cells,64 and an IGF-1R targeting monoclonal antibody is now being evaluated for the treatment of CRPC.65

ErbB Receptors

Several studies suggest that crosstalk between the activated ErbB receptor kinase axis and the AR receptor signaling pathway helps promote the growth and survival of both hormone-sensitive and CRPC. However, phase II trials with small molecule kinase inhibitors (gefitinib, erlotinib, lapatinib), monoclonal antibodies (trastuzumab, pertuzumab), and tyrosine kinase receptor inhibitors (sunitinib) have shown disappointing results.36,66

Vascular Endothelial Growth Factor and Receptor

Bevacizumab is a monoclonal antibody that targets vascular endothelial growth factor-A (VEGF-A) to cause potent inhibition of VEGFR signaling and angiogenesis.42 A phase II trial of bevacizumab and docetaxel-estramus-tine found a PSA decline in 81% of patients, a median time to progression for objective disease or PSA of 9 months, and an OS of 21 months.62

HDAC (histone deacetylase) inhibitors directly inhibit the transcription of approximately half of AR target genes in CRPC models in which AR is overexpressed and present at high levels.

Immunotherapy (Vaccine)

Sipuleucel-T is a dendritic cell-based vaccine designed to stimulate T-cell immunity against prostatic acid phosphatase (PAP), which is overexpressed in the malignant prostate epithelium relative to nonprostatic tissues.42 A phase III trial in CRPC reported a significant median survival advantage of 4.1 months for patients treated with sipuleucel-T versus placebo (25.8 vs 21.7 months). Additional survival benefits were revealed in longer follow-up. A total of 34% of sipuleucel-T patients and 11% of placebo patients were alive at 36 months (P=.005).66 GVAX uses whole cells as an antigen source to provoke an immune response to multiple antigens. Two phase III studies were started, but both were halted due to concerns over toxicity and failure to achieve study objective.42 Ipilimumab is a fully humanized monoclonal antibody against CTLA-4. A recent clinical trial found a ≥50% PSA decline in 21% of patients but a high rate of grade 3 toxicity.69

Interference With Gene Transcription

HDAC (histone deacetylase) inhibitors directly inhibit the transcription of approximately half of AR target genes in CRPC models in which AR is overexpressed and present at high levels.

Metabolic Interference

Pemtrexed is an antimetabolite compound that inhibits three enzymes utilized by cancer cells in purine and pyrimidine synthesis: thymidylate synthase, dihydrofolate reductase, and glycaminide ribonucleotide formyltransferase.21 A 2006 study found a 19% PSA response and a 38% rate of stable disease, with duration of stable disease ranging from 12 to 21 weeks.70

Future Directions

New agents will need to demonstrate a survival benefit for approval as second-line therapy in CRPC. Advances in the understanding of the mechanisms that contribute to the causation and maintenance of CRPC are leading to rationally designed therapies that selectively target androgen metabolism and the AR. Minimizing the adverse effects of therapy while diminishing androgen-mediated activity at the tissue level through inhibition of testicular, adrenal, and tumoral androgen production holds promise for improving the survival outcomes in patients with CRPC.71

Although several promising approaches fell short of expectations in recent phase III trials (GVAX, satraplatin, DN-101), expectations for other agents such as abiraterone, zibotentan, and sipuleucel-T remain high. Abiraterone may be the most promising drug on the horizon and the furthest along in development. MDV311 may also play an important role in the treatment of CRPC, possibly in combi-
nation with abiraterone, where the differing mechanisms of action of these two agents would provide a complementary effect. An obvious next step that is already occurring is combining docetaxel, the current standard of care for CRPC, with targeted therapies such as azacitidine.

In addition to the categories of targeted therapies discussed above, several novel approaches with a strong theoretical basis of efficacy in CRPC are under development. One of these involves a genomic strategy for identifying and targeting the variable response to secondary hormonal manipulations through individualized therapy based on the molecular features of each patient’s tumor. Such an approach has the potential to help individualize and improve patient care in CRPC. An exciting drug in preclinical evaluation is VN-124-1, which combines the advantages of CYP17A1 inhibition, AR antagonism, and reduced AR protein synthesis. In vitro models have demonstrated potent AR antagonism in binding assays and inhibition of CYP17A1 enzymatic activity, while in vivo xenograft models showed reduced tumor burden.

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Castration-Resistant Prostate Cancer


Introduction

Prostate cancer is the leading cause of cancer in men in the United States and accounts for nearly 30,000 deaths from cancer each year.\(^1\) Localized prostate cancer is often successfully treated with radiation or surgery, leading to long-term survival in many patients. However, patients diagnosed with locally advanced or metastatic prostate cancer have less optimistic outcomes, often suffering morbidity and mortality from the disease. These patients are initially treated with androgen deprivation therapy (ADT), with excellent response rates. However, the majority of patients develop progressive disease despite castrate concentrations of testosterone.\(^2\) Following progression on ADT, patients are often labeled hormone refractory or castration resistant, and options for therapy are limited. Docetaxel/prednisone remains the only therapy shown to improve overall survival and is considered the standard of care for castration-resistant prostate cancer (CRPC).\(^3^,4\) For patients who progress or do not tolerate docetaxel/prednisone, there is no standard second-line therapy.

Current research for CRPC includes new cytotoxic, hormonal, and targeted therapies. New cytotoxic therapies include an oral platinum compound (satraplatin) and two agents in a new class of nontaxane tubulin polymerizing chemotherapy agents called epothilones (ixabepilone, patupilone). These agents are in varying phases of development, and all have shown prostate-specific antigen (PSA) responses,\(^5^,6\) but a recent phase III trial of satraplatin failed to show an overall survival benefit compared with placebo.\(^7\) These agents may offer additional cytotoxic treatment options for CRPC patients. However, research of less toxic hormonal and targeted therapies offer promising new mechanisms of action for these patients with incurable CRPC.

Research of less toxic hormonal and targeted therapies offer promising new mechanisms of action for these patients with incurable CRPC.

Hormonal Therapies

Following progression on ADT, patients were classified as hormone refractory. However, it is now understood that androgen receptor (AR) signaling remains significant in some patients despite castrate levels of testosterone. Nongonadal sources of androgen synthesis, including adrenal and tumor-derived, have been identified.\(^8^,9\) Studies evaluating AR expression and testosterone concentrations have found elevated levels of each in castration-resistant tumors compared with untreated or castration-sensitive tumors.\(^10\) Tumors that no longer respond to ADT may evolve the ability (through AR mutation, amplification, or AR modulation) to progress from exposure to low levels of adrenal hormones or tumor hormone synthesis.\(^9\) Therefore, further hormonal manipulation may play a significant role in treatment of CRPC.

Currently, additional hormonal manipulations to block adrenal production of androgens may be utilized after progression on first-line hormonal therapies. CYP17 is a key enzyme in the production of androgens by the adrenal glands and tumor tissue. Ketoconazole is a nonspecific CYP17 inhibitor that blocks adrenal androgen. However, it has limited response rates and substantial toxicities, with up to 30% of patients stopping therapy because of intolerance due to liver toxicity and gynecomastia.\(^8^,9\) Abiraterone acetate (AA) is a new oral selective, irreversible CYP17 inhibitor that has shown activity in chemotherapy-naive CRPC patients as well as in patients who have progressed after docetaxel-based therapy and ketoconazole therapy.\(^8^,9\) Attard and colleagues\(^11\) conducted a phase I/II trial in castrate, chemotherapy-naive CRPC patients. A PSA decline of ≥50% was seen in 67% of patients, and 19% of patients had ≥90% decrease in PSA. Partial responses by Response Evaluation Criteria in Solid Tumors (RECIST) were seen in 37.5% of the phase II patients.\(^11\) Abstracts from the 2009 American Society of Clinical Oncology (ASCO) Annual Meeting reported PSA declines of ≥50% in 43% to 51% of patients previously treated with docetaxel-based therapies and in almost 90% of patients who had not received docetaxel or ketoconazole.\(^12^,14\) However, due to its mechanism of action, there is an increase in levels of adrenocorticotropic hormone (ACTH) leading to elevated concentrations of corticosterone and deoxycorticosterone. Although this prevents adrenocortical insufficiency as seen with ketoconazole therapy, sec-
ondary mineralocorticoid excess may occur causing fluid retention, hypertension, and hypokalemia. This is counteracted by the addition of low-dose glucocorticoids, which decrease ACTH, or with the mineralocorticoid receptor antagonist eplerenone.\(^9\)\(^11\) AR is currently being evaluated in combination with prednisone in a phase III trial in CRPC patients who have received docetaxel-based chemotherapy and is one of the most promising drugs in development for the treatment of CRPC.

First-generation antiandrogens, including bicalutamide and flutamide, are commonly used in addition to luteinizing hormone-releasing hormone agonists (goserelin, leuprolide) in the treatment of castration-sensitive prostate cancer. However, these agents have shown agonist activity in cells that overexpress AR, as is commonly seen in CRPC.\(^15\) This potential for agonist activity is demonstrated by a PSA response seen after antiandrogen withdrawal in patients with CRPC receiving first-generation antiandrogens. The development of second-generation antiandrogens that maintain antagonism despite high levels of AR expression may provide new noncytotoxic options for patients with CRPC. MDV3100 and RD162 are second-generation antiandrogens developed with this mechanism. Both agents bind more potently to the AR than bicalutamide and, unlike bicalutamide, inhibit nuclear translocation of the AR and its subsequent binding to DNA.\(^15\)

In preclinical studies, these agents have maintained AR antagonism in the setting of increased AR expression in castration-resistant models.\(^15\) MDV3100 has moved into clinical evaluation; initial results from a phase I/II study of 30 patients with CRPC who had progressed on first-line antiandrogens, including 12 patients in whom taxane-based therapy failed, showed 43% of patients with a \(\geq50\)% decrease in PSA.\(^15\) Results presented at ASCO 2009 showed \(\geq50\)% decrease in PSA in 60% of patients who were chemotherapynaive and in 51% of patients who previously received chemotherapy.\(^16\) A phase III trial is currently enrolling patients with docetaxel-refractory CRPC to evaluate MDV3100.

Bevacizumab, sunitinib, and erlotinib, agents that are experiencing significant use in many other malignancies, are now being studied in prostate cancer.\(^15\)

### Targeted Therapies

Several targeted therapies are making their way into prostate cancer research. As mentioned in the primary article, bevacizumab, sunitinib, and erlotinib, agents that are experiencing significant use in many other malignancies, are now being studied in prostate cancer. Two agents with novel mechanisms of action being evaluated and not currently FDA approved include custirsen (OGX-011) and atrasentan.

Clustering is an antiapoptotic protein found to be overexpressed in many cancers, including breast, lung, prostate, and colorectal, and is induced by cellular stress. In prostate cancer, increased clustering expression has been found to correlate with increased Gleason score. Clustering expression is induced by castration therapy in patients with CRPC; overexpression is associated with resistance to hormonal therapy, radiation, and chemotherapy. Custis is an antisense oligonucleotide that targets the clustering translation initiation site, which leads to enhanced activity of hormones, radiation, and chemotherapy.\(^17\) Results from a randomized phase II study of docetaxel/prednisone with or without weekly custis was presented at ASCO 2009. After a median follow-up of 32 months, no difference was seen in the primary end point of \(\geq50\)% decrease in PSA. However, a 7-month difference was seen in overall survival (23.8 vs 16.9 months). Custis was well tolerated with more rigors/chills and fever documented.\(^18\)

Atrasentan is a potent oral selective antagonist of endothelin-A receptor. Endothelin-1 is a factor secreted by normal prostate tissue, with increased secretion seen in prostate cancer. Endothelin-1 has been found to inhibit chemotherapy-induced apoptosis. It is thought to be involved in osteoblastic bone remodeling and development of bone metastases frequently seen in metastatic prostate cancer.\(^19\)\(^20\) Endothelin-1 causes decreased rates of apoptosis in prostate cancer cell lines exposed to docetaxel. Preclinical models have shown reduction in tumor growth rates with endothelin-A blockade by atrasentan compared with docetaxel alone.\(^19\) Phase III trials of single-agent atrasentan have not shown significant benefit in CRPC patients despite reductions in PSA and bone alkaline phosphatase, a marker of bone remodeling.\(^20\) Due to preclinical data suggesting additive effects with docetaxel, atrasentan is being added to standard docetaxel therapy. A phase I/II study of atrasentan with docetaxel in first-line therapy for CRPC showed a PSA response in 23%, with a median overall survival of 17.6 months.\(^19\) Atrasentan is currently being studied in a phase III trial with docetaxel/prednisone in CRPC.

### Conclusion

CRPC is the second leading cause of cancer-related death in men in the United States. After progression on hormonal therapy, the current standard of care offers minimal survival benefits of approximately 2 months. Newer cytotoxic agents have demonstrated efficacy but are plagued by toxicities (eg, myelosuppression) similar to those of classic cytotoxic agents. Perhaps the future of CRPC treatment will see less toxic hormonal
and targeted therapies with novel mechanisms of action and improved outcomes.

References


PHARMACIST PERSPECTIVE
Introduction

Hormone-refractory prostate cancer (HRPC) is a term used to describe prostate cancer that is no longer responsive to treatment with hormonal manipulation. As researchers learn more about how the androgen receptor (AR) functions in prostate cancer and the process and development of loss of disease control by androgen deprivation therapy (ADT), the term castrate-resistant prostate cancer (CRPC) has become more common.

The prostate is dependent on testosterone to maintain its normal functions. Testosterone binds to the ARs in the prostate cells and is responsible for transcription of genes. Prostate cancer cells are equally dependent on testosterone and the same AR. Advanced prostate cancer is treated with gonadotropin-releasing hormone (GnRH) agonists or antagonists with or without an antiandrogen. These drugs produce castrate levels of testosterone resulting in tumor regression due to inactivation of ARs. This evolution is termed CRPC. Patients may demonstrate progression to CRPC with a rising prostate-specific antigen (PSA) in the presence of a castrate level of testosterone (<20 ng/dL), called castrate-biochemical recurrence (C-BCR), or with metastatic lesions. Localized prostate cancer recurrence or pelvic recurrence may be managed with local therapy such as radiation therapy. Metastatic disease with a rapidly rising PSA has a significant impact on the patient’s quality of life (QOL), especially the development of bone metastases. Bone metastases may produce pain and, dependent on location and extent, may be severe enough to result in fractures or spinal cord compression (SCC). Local treatment using radiation therapy is often used to manage SCC or a single bone metastasis. Systemic treatment options may include additional hormonal therapy or the initiation of chemotherapy if hormonal therapy options have been exhausted or are not appropriate due to disease severity or progression. Hormonal options may include the addition of an antiandrogen in patients who have not previously received one, antiandrogen withdrawal, a trial of a different antiandrogen agent, or second-line chemotherapy if hormonal therapy has failed (liver, kidney). Nurses caring for patients receiving docetaxel must be prepared to manage these potential side effects and treatment-related complications.

For patients starting chemotherapy, nursing care begins with an assessment of the patient’s understanding of the treatment and its goals, obtaining nursing, prior therapies, medical and surgical and allergy history, and completing a physical assessment. Patient education using both oral instructions and written information are provided. The nurse discusses the risk of a hypersensitivity reaction (HSR) from drug administration and ensures that the patient understands the need to immediately report any signs and symptoms of a HSR to the nurse. In addition, the nurse ensures that dexamethasone premedications have been prescribed. This is usually administered for 3 days, starting the day before the infusion. Only intravenous (IV) bags and tubing free of PVC (DEHP) such as bags made of polypropylene and tubing lined with polyethylene are used. During

Hormone-refractory prostate cancer (HRPC) is a term used to describe prostate cancer that is no longer responsive to treatment with hormonal manipulation.

Docetaxel Plus Prednisone

Docetaxel is the only chemotherapy agent to demonstrate improved survival rates and QOL. Docetaxel-related side effects reported in these studies included sepsis, bone marrow depression (neutropenia, febrile neutropenia, anemia, thrombocytopenia), metabolic changes, fatigue, nausea, vomiting, diarrhea, neuropathy, cardiotoxicity, peripheral edema, dyspnea, mouth sores, altered taste, nail changes, and alopecia. Deaths occurred in both studies and were related to infection and sepsis, gastrointestinal bleeding, and major organ failure (liver, kidney). Nurses caring for patients receiving docetaxel must be prepared to manage these potential side effects and treatment-related complications.
### Table. Selected Side Effects, Patient Education, and Brief Nursing Implications

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Patient Education</th>
<th>Brief Nursing Implications</th>
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<tbody>
<tr>
<td>Myelosuppression</td>
<td>Self-care to manage fatigue. How to avoid injury to self to reduce risk of bleeding. How to reduce the risk of acquiring a communicable infection such as a cold or the flu. How to perform good hand hygiene. Importance of good personal hygiene, including coughing and deep breathing. Signs and symptoms of infection. Signs and symptoms to report to the nurse or physician.</td>
<td>Monitor CBC and platelet count. Administer prescribed filgrastim or pegfilgrastim. Obtain blood and other cultures in febrile patients and patients with signs and symptoms of infection. Administer prescribed antibiotics. Monitor patient for evidence of infection.</td>
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<tr>
<td>Peripheral edema</td>
<td>To keep legs elevated when sitting and to reduce salt consumption. To take all prescribed doses of dexamethasone. To report weight gain, leg swelling, or trouble breathing.</td>
<td>Prior to each dose of docetaxel, assess for peripheral edema, weight gain, and changes in breath sounds. Administer dexamethasone premedication.</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>To avoid use of over-the-counter drugs such as acetaminophen and to avoid alcohol consumption, which require hepatic metabolism. To report darkening of urine, light-colored stool, or yellowness of skin or eye sclera. To have family/friends monitor for alterations in mental status and report any changes to nurse or physician.</td>
<td>Prior to each dose of docetaxel, review results of liver function tests. Doses are held when bilirubin or transaminases are elevated.</td>
</tr>
<tr>
<td>Cardiac toxicity</td>
<td>To report signs and symptoms such as chest pain, shortness of breath, weight gain, leg swelling, dizziness, lightheadedness, palpitations, irregular heart beat, and use of pillow at night to elevate head of bed.</td>
<td>Monitor lifetime cumulative dose of cardiotoxic chemotherapy. Monitor for signs and symptoms of cardiac toxicity at baseline and prior to each dose. Be aware of results of baseline cardiac ejection fraction. Discuss with physician frequency of echocardiograms or MUGA scans.</td>
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<tr>
<td>Nausea, vomiting, diarrhea</td>
<td>Use of antiemetics and antidiarrheals to manage symptoms. To report nausea, vomiting, or diarrhea not controlled by medications. To report reduced fluid consumption, reduced urine output, or dizziness or lightheadedness. Diet modifications such as use of soft foods and removing acids from diet.</td>
<td>Premedicate with antiemetics prior to chemotherapy administration. Be sure patient has prescription for antiemetic medication and antidiarrheal medication.</td>
</tr>
<tr>
<td>Mucositis</td>
<td>How to mix saline solution for oral care; perform oral care and frequency of oral care. Diet modifications such as use of soft foods and removing acids from diet.</td>
<td>Assess oral cavity for mouth sores. Discuss need for topical analgesics with physician to reduce pain not managed with routine oral care.</td>
</tr>
<tr>
<td>Alopecia</td>
<td>To use gentle shampoo and take care when washing and performing hair care. Use of head coverings to keep head warm and protect skin from sun exposure.</td>
<td>Hair thinning and loss are expected. Assess for alopecia and affect of hair loss on self-esteem.</td>
</tr>
<tr>
<td>Change in urine color</td>
<td>Urine will be green for 1-2 days after treatment with mitoxantrone.</td>
<td>Urine color change is related to blue color of mitoxantrone.</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
<td>To report any signs and symptoms of a reaction to the nurse immediately. Signs and symptoms of a HSR such as trouble breathing, chest pain, itching, or rash.</td>
<td>Administer premedications prior to drug administration. For ixabepilone, premedications include diphenhydramine and a H2 antagonist such as ranitidine. For docetaxel, premedication includes dexamethasone. Monitor patient for signs and symptoms of a reaction such as hypotension, wheezing, bronchospasm, or flushing. Monitor vital signs prior to infusion and periodically during infusion. Stop infusion with development of signs and symptoms and take immediate action to manage the HSR including calling the physician and checking the pulse oximetry to see if oxygen therapy is needed. The IV catheter or central line is aspirated to remove drug, flushed with saline and saline infusion started. Be prepared to administer medications such as dexamethasone, ranitidine, and diphenhydramine to manage the reaction.</td>
</tr>
<tr>
<td>Dry skin, rash</td>
<td>Keep skin moisturized. To report rash to nurse or physician.</td>
<td>Rash is common in patients receiving docetaxel. Assess patient for rash prior to treatment.</td>
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</tbody>
</table>
drug administration, the nurse stays at the bedside/chairsde for the first 15 minutes of drug delivery and monitors the patient for signs and symptoms of a HSR such as chest pain, shortness of breath, rash, or flushing. Vital signs are monitored prior to starting the infusion and periodically (usually every 15 minutes) during the infusion for hypotension. In the event of a reaction, the infusion is stopped, the prescriber is notified, the IV catheter is aspirated to remove any residual drug and then flushed with saline, a saline IV is started, and emergency medications such as diphenhydramine, ranitidine, dexamethasone, and epinephrine are administered. The patient and family are provided emotional support during the event. In addition, the nurse uses caution to avoid accidental drug extravasation as docetaxel is classified as a vesicant. Additional nursing implications associated with every 3 week treatment with docetaxel may be found in the Table.

### Mitoxantrone

Mitoxantrone is often used as second-line chemotherapy after docetaxel-resistant disease develops. Side effects include bone marrow depression, febrile neutropenia, fatigue, nausea, vomiting, constipation, and hematotoxicity. As a known vesicant that with extravasation may cause tissue necrosis, the nurse uses vesicant precautions while administering this agent. As an anthrancenedione, mitoxantrone is cardiotoxic with a lifetime cumulative dose of 180 mg/m² in patients without prior anthracycline therapy. The nurse assesses the patient for any known cardiac history and assesses and monitors the patient prior to each treatment for the development of cardiac signs and symptoms. The results of the echocardiogram or multigated radionuclide acquisition (MUGA) scan used to determine the patient’s ejection fraction are reviewed to be sure it is normal prior to starting potentially cardiotoxic therapy.

Additional nursing implications and patient education are discussed in the Table.

### Physical therapy and occupational therapy

Additional nursing implications and patient education are discussed in the Table.

### Epothilones

A promising group of agents in the treatment of CRPC is the epothilones. These agents stabilize the microtubule assembly in a manner similar to taxanes. Several studies have examined ixabepilone, an epothilone, as a single agent in the first- and second-line setting after prior chemotherapy such as docetaxel and in combination with other agents in the first-line setting. Side effects associated with ixabepilone in these studies included bone marrow depression, flu-like symptoms, infection, fatigue, gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhea, constipation), mucositis, hepatotoxicity, hypotension, electrolyte changes, HSRs, and prolonged prothrombin time (PT). Patients taking warfarin should have their PT/INR monitored closely and be instructared to report any bleeding. As with other agents capable of causing a HSR, premedications are required to reduce the risk of a reaction, and the nurse monitors the patient for any signs and symptoms during drug administration. Neuropathy is common with ixabepilone and includes both sensory and motor neuropathy and neuropathic pain, with sensory neuropathy being the most prevalent.

Sensory neuropathy affects the hands and feet and progresses from distal to proximal. Patients receiving ixabepilone may experience numbness, tingling, or dysesthesias. Patients at risk for peripheral neuropathy (PN) require baseline and ongoing assessments prior to each treatment with a neurotoxic agent. At baseline, the nurse should ask the patient about any risk factors for PN such as diabetes or alcohol consumption. The patient should be asked about numbness or tingling in his fingers or toes, about loss of balance or falling, and other neurologic signs and symptoms. Ask the patient to pick up small objects off a flat surface and to open and close buttons sewn on a piece of cloth or clothing. The patient should be observed walking to assess for altered gait. Prior to subsequent treatments, ask the patient about any new signs and symptoms that developed since the prior treatment. These screening tests should be repeated prior to each dose of a potentially neurotoxic drug. Patient education is crucial for patient safety and should include information such as the need to wear shoes at all times to avoid foot injury, to use care with hot water and sharp objects in order to avoid injury, and to remove throw rugs, which can cause tripping and falling. Physical therapy and occupational therapy consults may be useful in helping patients adapt safely to any changes, as many patients with CRPC are elderly. Treatment interruptions and dose reductions or delays may be needed dependent on the severity of neurotoxicity.

### Summary

Due to the incidence of prostate cancer, there are many patients on ADT who are at risk for the development of CRPC. Nursing care includes assessment, patient education, drug administration, and monitoring of patients for the development of side effects and toxicities. Patients have several treatment options, and with ongoing research and new drug development, the potential exists for future treatment options. Eligible patients should be encouraged to consider a clinical trial, which will assist in this endeavor.
References


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