REVIEW

New treatment options for castrate-resistant prostate cancer: a urology perspective

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Introduction: *Castrate-resistant prostate cancer (CRPC) is the most clinically advanced form of prostate cancer. Prior to 2004, treatment options for patients with CRPC were limited to palliative care with mitoxantrone. However, two phase III trials in 2004 showed improved survival with docetaxel compared with mitoxantrone in patients with metastatic CRPC. Docetaxel remains the current standard chemotherapy for CRPC.*
Materials and methods: *A literature review was conducted to ascertain agents recently approved or in development for CRPC as well as several treatment algorithms being developed in this patient population.*
Results: *Recently, the US Food and Drug Administration (FDA) approved chemotherapy agents including cabazitaxel, a novel taxane, for the treatment of patients with metastatic CRPC who were previously treated with docetaxel-based chemotherapy. The immunotherapy sipuleucel-T and the androgen biosynthesis inhibitor, abiraterone, have also just been approved. A number of other novel agents are in clinical development for the management of CRPC.*
Conclusions: *Options for the management of CRPC are rapidly expanding. Based on improved survival with docetaxel in patients with CRPC, chemotherapy is being investigated for use earlier in the prostate cancer disease spectrum. Studies are actively evaluating chemotherapy in the neoadjuvant and adjuvant settings for patients with high risk, localized prostate cancer. A multidisciplinary approach towards patients with difficult-to-manage prostate cancer in which urologists familiarize themselves with these newer systemic agents and refer appropriate patients to oncologists may be beneficial.*

Key Words: prostate cancer, metastatic, castration-resistant prostate cancer

Introduction

Prostate cancer is the most commonly diagnosed solid tumor in men in the United States (US), accounting for an estimated 28% of all new cancers diagnosed in US men in 2011 and, the second leading cause of cancer deaths in US men.[1] The majority of prostate cancers in the US (80%) are diagnosed as localized disease,[1] which may be treated with local curative intent, such as surgery or radiation therapy or, in selected cases, active surveillance.[2,3] Prostate cancer progresses from clinically localized disease to a clinical state characterized by rising prostate-specific antigen (PSA) levels; this may indicate local recurrence or, more commonly, the development of metastatic disease.[2,4] The standard treatment for patients with non-localized or metastatic prostate cancer is androgen ablation therapy in order to achieve castrate levels of testosterone.[2] Androgen ablation also has a role in the management of patients with intermediate or high risk localized prostate cancer treated by external beam radiation therapy.[5] However, despite castrate levels of serum testosterone, many patients eventually develop castrate-resistant disease characterized by progression.[2,4,6] This advanced disease state is now termed castrate-resistant prostate cancer

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(CRPC) or metastatic (m)CRPC.[4] The earlier term, "hormone refractory prostate cancer," is typically a misnomer since it has long been recognized that these advanced tumors continue to respond to additional hormonal manipulations even though, based on a serum testosterone level of < 50 ng/dL, patients are "castrate".[7] This has been further exemplified with the findings that indicate increased production of intratumoral androgens in patients with castrate-resistant disease, and also significant clinical benefit for patients with CRPC treated with new inhibitors of androgen biosynthesis.[7-9]

Prostate cancer is thought to progress despite androgen suppression through other mechanisms in addition to the increased intratumoral production of androgens.[10] Upregulation of androgen receptor mRNA is a common mechanism of castrate resistance in prostate cancer.[10] A small proportion of castrate-resistant disease is attributed to mutations in the androgen receptor gene, including mutations in the ligand-binding domain that may allow ligands other than testosterone to bind to the androgen receptor and act as agonists.[10] Increase in the number of copies of the androgen receptor gene, which can increase the levels of androgen receptor, also accounts for a small proportion of castrate-resistant disease.[10] Active androgen receptor signaling in the presence of increased kinase signaling or altered coactivator/corepressor balance, as well as alternative signaling pathways that bypass androgen receptor signaling, are other mechanisms that may mediate the development of castrate resistance in prostate cancer.[10]

Although treatment options for patients with CRPC are limited, docetaxel was approved by the US Food and Drug Administration (FDA) for first-line treatment of mCRPC.[11] More recently, cabazitaxel, another taxane, was approved for the treatment of patients with mCRPC who had progressed during or after previous treatment with a docetaxel-containing regimen.[12] A number of additional agents are under investigation for the treatment of CRPC. In addition, trials are investigating the use of chemotherapy in combination with surgery or radiotherapy for the treatment of prostate cancer, including earlier stage prostate cancer. It is important for urologists to have an understanding of the chemotherapy agents and other novel strategies currently in use or being investigated for the treatment of prostate cancer. Besides helping urologists explain to patients the types of chemotherapeutic procedures they may expect to receive, this knowledge allows urologists to make informed decisions regarding when to refer a particular patient to an oncologist. We reviewed the recent literature in this area to provide a comprehensive review of the topic of CRPC.

Multidisciplinary management of patients with CRPC

Patients with prostate cancer are managed by a number of different healthcare providers including urologists, radiation oncologists, and medical oncologists. With increasing chemotherapeutic and other options that have an impact on overall survival for patients with prostate cancer, urologists may refer patients to medical oncologists for a discussion of their treatment options.[13] Patients should be referred to medical oncologists before their disease has progressed to the point where they are no longer candidates for chemotherapy. The National Comprehensive Cancer Network (NCCN) guidelines recommend early referral to a medical oncologist for patients with advanced prostate cancer, but chemotherapy is not recommended for patients without mCRPC outside of a clinical trial setting.[14]

Patients with localized prostate cancer who, based on PSA, Gleason score, and T stage, are identified as high risk, are administered neoadjuvant or adjuvant therapy with chemotherapy; however, the clinical benefit of this approach in terms of PSA reductions, progression-free survival, disease-free survival, or overall survival has not been established. There are several randomized studies that are currently evaluating the role of neo-adjuvant and adjuvant chemotherapy.[15-17] Neoadjuvant chemotherapy has been associated with PSA response in patients with high risk, localized prostate cancer.[13] In addition, other clinical trials that combine radiation therapy with neoadjuvant chemo-hormonal therapy are being initiated, such as those combining docetaxel in the radiation therapy regimen.[18] Consultation with medical or radiation oncology for inclusion in clinical trials that employ chemotherapy earlier in the treatment process (i.e., before the patient experiences significant or symptomatic clinical progression) should be considered. These are discussed further in this article.

The responsibility of moving up chemotherapy to earlier in the spectrum of prostate cancer in men with high risk features (such as locally advanced disease), as well as deciding upon the appropriate therapy for an individual patient at any particular time, may be helped by a clinic approach that is multidisciplinary.[3] Our data supports that the multidisciplinary approach can improve the outcome of patients with high risk prostate cancer.[3] At the Jefferson Kimmel Cancer Center, prostate cancer patients have access to a multidisciplinary clinic where a team of urologists, radiation oncologists, medical oncologists, and other specialists work to coordinate care with patients and their referring physicians with the aim of providing individualized treatment for each patient.[3] In a recent report on the clinic's 15 year experience

with prostate cancer, the probability of overall survival at 5 years for patients in the center's cohort initially diagnosed with AJCC stage III (T3N0M0) disease was 0.90, which exceeds the probability of overall survival at 5 years for similar patients in the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) cohort (0.78).[3]

Recent advances in chemotherapy for the treatment of CRPC

Prior to 2004, chemotherapy for CRPC was limited to palliative care with mitoxantrone.[19,20] Mitoxantrone, in combination with corticosteroids, is indicated as initial chemotherapy for pain related to CRPC.[21] In 2004, reports from two phase III trials demonstrated improved survival with docetaxel compared with mitoxantrone in patients with mCRPC, Table 1.[22,23] In TAX 327, median survival was 18.9 months with docetaxel administered every 3 weeks plus prednisone (n = 335, 20.8 months median follow up) versus 16.5 months with mitoxantrone plus prednisone (n = 337, 20.7 months median follow up; p = 0.009).[22] Significantly more patients taking docetaxel every 3 weeks showed a reduction in pain when compared with patients taking mitoxantrone (35% versus 22%; p = 0.01), ≥ 50% reduction in PSA (45% versus 32%; p < 0.001), and improvement in quality of life (22% versus 13%; p = 0.009).[22] A greater percentage

TABLE 1. **Recent phase III clinical trials for the treatment of castrate-resistant prostate cancer (CRPC)**

Drug name	Class	Patients	Median overall survival	Reference
Docetaxel	Chemotherapy	CRPC	**TAX 327** 18.9 months with docetaxel every 3 weeks + prednisone versus 16.5 months with mitoxantrone + prednisone (HR = 0.76; p = 0.009) **SWOG 9916** 17.5 months with docetaxel + estramustine versus 15.6 months with mitoxantrone + prednisone (HR = 0.80; p = 0.02)	Tannock et al[22] Petrylak et al[23]
Cabazitaxel	Chemotherapy	CRPC progressing after docetaxel-containing regimens	**TROPIC** 15.1 months cabazitaxel + prednisone versus 12.7 months mitoxantrone + prednisone (HR = 0.70; p < 0.0001)	de Bono et al[25]
Satraplatin	Chemotherapy	CRPC progressing after 1 previous chemotherapy regimen	**SPARC** 61.3 weeks with satraplatin + prednisone verss 61.4 weeks with placebo + prednisone (HR = 0.98; p = 0.80)	Sternberg et al[45]
Sipuleucel-T	Immunotherapy	Asymptomatic or minimally symptomatic CRPC	**IMPACT** 25.8 months with sipuleucel-T versus 21.7 months with placebo (HR = 0.78; p = 0.03)	Kantoff et al[26]
Abiraterone acetate	CYP17-inhibitor	CRPC progressing after docetaxel-based regimens	**COU-AA-301** 14.8 months with abiraterone acetate + prednisone versus 10.9 months with placebo + prednisone (HR = 0.65; p < 0.001)	de Bono et al[9]

HR = hazard ratio

of patients experienced grade 3 or 4 neutropenia with docetaxel compared with mitoxantrone (32% versus 22%, $p \leq 0.05$), but there was no significant difference in the rates of febrile neutropenia (3% with docetaxel versus 2% with mitoxantrone); most other adverse events (AEs) were more common with docetaxel.[22] The survival benefit with docetaxel was confirmed with a March 2007 extended survival analysis of patients who were alive in August 2003 (median survival 19.2 months versus 16.3 months with mitoxantrone; $p = 0.004$).[24] Docetaxel plus prednisone was approved in 2004 by the FDA for the treatment of patients with mCRPC.[11]

Another trial, SWOG 9916 (n = 770), compared docetaxel plus estramustine versus mitoxantrone plus prednisone in patients with mCRPC.[23] At 32 months of median follow up, median overall survival was 17.5 months with docetaxel plus estramustine versus 15.6 months with mitoxantrone plus prednisone ($p = 0.02$); median progression-free survival was 6.3 months with docetaxel versus 3.2 months with mitoxantrone ($p < 0.001$).[23] The rates of grade 3 or higher neutropenia were not significantly different between the treatment arms (16.1% docetaxel versus 12.5% mitoxantrone, $p = 0.22$), but the rate of grade 3 or 4 neutropenic fevers was higher with docetaxel (5% versus 2% with mitoxantrone, $p = 0.01$).[23]

New and emerging treatment options for mCRPC

Dozens of agents are currently under clinical study for the treatment of patients with mCRPC. In addition to newer cytoxic chemotherapeutic agents, immunotherapies, and agents that interfere with various components of the androgen signaling pathways, other novel agents are at the earliest stages of clinical study. We review the agents that are newly approved as well as agents that are more advanced from a clinical trials perspective.

Cabazitaxel

Combined with prednisone, cabazitaxel is a recently approved taxane for the treatment of patients diagnosed with mCRPC and treated previously with a docetaxel-based regimen.[12] In the randomized, open-label, phase III TROPIC trial (n = 755), cabazitaxel plus prednisone was associated with a significant improvement in median overall survival compared with mitoxantrone plus prednisone (15.1 months versus 12.7 months; $p < 0.0001$) in patients with mCRPC who progressed following docetaxel-based regimens, Table 1.[25] The cabazitaxel regimen was associated with a 30% relative reduction in risk of death compared to the mitoxantrone regimen.[25] There was also a significant benefit in progression-free survival with cabazitaxel (2.8 months versus 1.4 months; $p < 0.0001$) and significantly more patients in the cabazitaxel group had ≥ 50% reduction in both PSA (39.2% versus 17.8%; $p = 0.0002$) and tumor response (14.4% versus 4.4%; $p = 0.0005$) according to Response Evaluation Criteria in Solid Tumors (RECIST).[25] Hematologic AEs were the most common AEs associated with cabazitaxel: the rates (all-grade) of neutropenia, leukopenia, and anemia were > 90% (grade ≥ 3: 82%; 68%; and 11%, respectively).[25] The most common grade ≥ 3 non-hematologic AEs with cabazitaxel were diarrhea (6%), fatigue (5%), asthenia (5%), and back pain (4%).[25]

Sipuleucel-T

Sipuleucel-T is a therapeutic cancer vaccine that uses a patient's own immune cells to stimulate an immune response against prostate cancer cells.[26] It is indicated for the treatment of patients with mCRPC with either minimal or no symptoms and was approved by the FDA in 2010.[27] Two phase III trials investigated sipuleucel-T in patients with asymptomatic mCRPC.[28,29] The first trial (n = 127) showed a significant improvement in median overall survival with sipuleucel-T compared with placebo (25.9 months versus 21.4 months; $p = 0.010$). In the second trial (n = 98), the difference in median survival with sipuleucel-T compared with placebo was not statistically significant (19.0 months versus 15.7 months; $p = 0.331$).[28,29] A third phase III trial, a double-blind, randomized IMPACT trial, was conducted in patients with asymptomatic mCRPC (n = 512) to confirm whether there is a survival benefit with sipuleucel-T compared with placebo.[26] There was a significant 22% reduction in the risk of death with sipuleucel-T versus placebo (HR = 0.78; $p = 0.03$), and median overall survival was 25.8 with sipuleucel-T versus 21.7 months with placebo, Table 1.[26] Sipuleucel-T was associated with AEs including chills, fever, fatigue, nausea, headache, and tremor within the first 1 to 2 days after infusion; most were grade 1 or 2.[26,28,29]

Abiraterone acetate

Abiraterone acetate is an oral, small-molecule inhibitor of CYP17, an enzyme required for androgen synthesis.[30] Although abiraterone acetate blocks androgen synthesis in the testes, adrenal glands, and prostate, it does not cause adrenal insufficiency.[30] Abiraterone acetate is associated with AEs related to secondary mineralocorticoid excess, including hypokalemia, hypertension, and fluid retention.[31] These AEs can be managed with low dose prednisone (5 mg BID per FDA label) or eplerenone, a mineralocorticoid antagonist.[31] The phase III COU-AA-301 trial (n = 797 abiraterone acetate, n = 398 placebo)

showed a significant improvement in overall survival, the primary endpoint, with abiraterone acetate plus prednisone compared with placebo plus prednisone (median 14.8 months versus 10.9 months; 12.8 months median follow up) in patients with mCRPC who progressed following docetaxel-based therapy, Table 1.[9] In multivariate analysis adjusting for stratification factors, the significance of the reduction in the risk of death with abiraterone acetate was robust (HR = 0.66; $p < 0.001$).[9] A consistent effect on overall survival was observed in all subgroups. There was also a significant improvement in time to PSA progression (10.2 months with abiraterone acetate versus 6.6 months with placebo; HR = 0.58; $p < 0.001$), radiographic progression-free survival (5.6 months versus 3.6 months; HR = 0.67; $p < 0.001$), and total PSA response rate (38.0% versus 10.1%; $p < 0.001$).[9] Mineralocorticoid-related AEs were more frequent with abiraterone acetate than with placebo (fluid retention: 31% versus 22%; hypokalemia: 17% versus 8%), but few were grade 3 or 4 (fluid retention: 2% versus 1% [grade 3], < 1% versus 0% [grade 4]; hypokalemia: 3% versus 1% [grade 3], < 1% versus 0% [grade 4]).[9] The incidence of cardiac disorders was 13% with abiraterone acetate and 11% with placebo, and the incidence of liver function test abnormalities was 10% with abiraterone acetate and 8% with placebo.[9]

In early 2011, abiraterone acetate was FDA-approved for use in men with CRPC who had failed chemotherapy with docetaxel. Another phase III trial (COU-AA-302) is being conducted in men diagnosed with mCRPC prior to receiving docetaxel.[32]

Denosumab

Denosumab is a RANK-ligand (RANKL) inhibitor indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumors, and is also approved for female osteoporosis. While it was not specifically developed for primary therapy of CRPC, denosumab is currently being studied for its ability to reduce bony metastasis in patients with CRPC.[33]

MDV3100

MDV3100 is a novel androgen receptor antagonist with increased binding affinity for the androgen receptor and no agonist effects compared with previous androgen receptor antagonists.[34] MDV3100 slows growth and induces cell death in bicalutamide-resistant tumors via three complementary mechanisms: androgen receptor antagonism, inhibition of nuclear translocation of the androgen receptor complex, and inhibition of DNA binding by the androgen receptor.[35] MDV3100 is an oral agent that does not require the coadministration of prednisone. In a phase I/II study in patients with CRPC (n = 140), the rate of PSA reduction > 50% with MDV3100 at 12 weeks was 57% for chemotherapy-naïve patients and 36% for chemotherapy-treated patients ($p = 0.02$).[34] Radiological results showed a tumor response with MDV3100 for soft tissue (22% partial response; 49% stable disease) and bone (56% stable disease) metastases.[34] The most common grade 3 or 4 AE was fatigue, which was reported for 11% of patients taking MDV3100 doses of 30 mg/day to 600 mg/day.[34] The most common grade ≤ 2 AEs were nausea, constipation, diarrhea, and anorexia.[34] In addition, two patients experienced seizures with MDV3100 doses of 360 mg/day and 600 mg/day, but it is not clear whether the seizures were related to MDV3100, since the patients were undergoing other treatments and had other medical problems that may have contributed to the seizures.[34] Based on these results, the dose chosen for further study was 240 mg/day.[34] MDV3100 is currently being evaluated in phase III clinical trials in chemotherapy-naïve patients with mCRPC[36] and in patients with CRPC who were previously treated with docetaxel-containing chemotherapy regimens, Table 2.[37]

Orteronel (TAK-700)

Orteronel (TAK-700) is a selective, oral, non-steroidal androgen synthesis inhibitor that binds to and inhibits the enzyme 17,20-lyase 1 in the testes and in the adrenal glands. Several phase III trials, including one in patients with chemotherapy-naïve mCRPC, are underway.[38]

Endothelin-A receptor antagonists

Endothelin (ET)-A receptor antagonists block the activation of the ET-A receptor by ET-1, which promotes prostate tumor growth, invasion, metastases, and angiogenesis.[39] Zibotentan (ZD4054) is an oral ET-A receptor antagonist currently being investigated for the treatment of patients with CRPC.[39] In the final analysis of a phase II trial in patients with CRPC and bone metastases, and either mild or no pain symptoms (n = 312), zibotentan was associated with nonsignificant improvement in overall survival compared with placebo; median overall survival was 23.5 months with zibotentan 10 mg (HR = 0.83; $p = 0.254$) and 23.9 months with zibotentan 15 mg (HR = 0.76; $p = 0.103$) compared with 19.9 months with placebo.[39] There was no significant difference in PSA response or in tumor response rate by RECIST with either dose of zibotentan compared with placebo.[39] The most common AEs associated with zibotentan treatment were peripheral edema, headache, and nasal congestion.[39] Two phase

TABLE 2. **Ongoing phase III clinical trials of novel agents for the treatment of castrate-resistant prostate cancer**

Drug name	Class	Patients	Trial	Reference
Atrasentan	Endothelin-A receptor antagonist	Advanced CRPC and bone metastases	SWOG-S0421	44
Custirsen	Clusterin inhibitor	CRPC	SYNERGY	50
Custirsen	Clusterin inhibitor	mCRPC with pain and progression following docetaxel-containing regimens	SATURN	51
Ipilimumab	Anti-CTLA-4 monoclonal antibody	Asymptomatic or minimally symptomatic chemotherapy-naïve mCRPC	CA184-095	47
Ipilimumab	Anti-CTLA-4 Monoclonal antibody	mCRPC previously treated with docetaxel	CA184-043	48
MDV3100	Androgen receptor antagonist	Chemotherapy-naïve mCRPC	PREVAIL	36
MDV3100	Androgen receptor antagonist	CRPC previously treated with docetaxel-containing regimens	AFFIRM	37
Orteronel (TAK-700)	Androgen biosynthesis inhibitor	mCRPC, chemotherapy-naïve	Millenium Pharmaceuticals trial	69
Orteronel (TAK-700)	Androgen biosynthesis inhibitor	mCRPC with progression during or following docetaxel-containing regimens	Millenium Pharmaceuticals trial	70
Zibotentan	Endothelin-A receptor antagonist	CRPC and bone metastases	ENTHUSE M1	40
Zibotentan	Endothelin-A receptor antagonist	mCRPC	ENTHUSE M1C	41

III trials investigating zibotentan in patients with mCRPC are currently underway: a study of zibotentan in patients with mCRPC and bone metastases,[40] and a study of zibotentan in combination with docetaxel in patients with mCRPC.[41] It was announced in September 2010 that zibotentan did not show a benefit in overall survival in the first study; publication of the full study results is expected sometime in 2011.[42] A third phase III trial investigating zibotentan in patients with non-metastatic CRPC was terminated.[43] Atrasentan, another oral ET-A receptor antagonist, is currently being investigated in combination with docetaxel and prednisone in a phase III trial for the treatment of patients with advanced CRPC and bone metastases (SWOG-S0421), Table 2.[44]

Satraplatin

Satraplatin, an investigational, oral platinum chemotherapy agent, was investigated in the phase III SPARC trial for the treatment of CRPC in patients who had progressed following one previous chemotherapy regimen (n = 635, satraplatin plus prednisone; n = 315, placebo plus prednisone); progression-free survival; and overall survival were coprimary endpoints.[45] Although median progression-free survival was significantly longer with satraplatin versus placebo (11.1 weeks versus 9.7 weeks, HR=0.67; $p < 0.001$), there was no significant difference in median overall survival (61.3 weeks with satraplatin versus 61.4 weeks with placebo; HR=0.98; $p = 0.80$), Table 1.[45] Hematologic toxicities including neutropenia, leukopenia, thrombocytopenia, and anemia were the most common AEs (all-grade and grade 3/4) with satraplatin, and were significantly more common with satraplatin than with placebo.[45]

Ipilimumab

Modulation of so-called "immune checkpoint inhibitors" represents a novel approach to the immunotherapy of prostate cancer. Ipilimumab is a fully human monoclonal antibody that binds to CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4). The absence

or presence of CTLA-4 in T cells can augment or suppress the immune system's T-cell response. CTLA-4 activation is a negative or inhibitory signal to T cells, and truncates T-cell responses important in tumor immunotherapy. This antibody blocks the activity of CTLA-4, enhancing active immune tumor response. In early 2011, ipilimumab was approved for the treatment of patients with metastatic melanoma and has been used in men diagnosed with prostate cancer.[46] Ipilimumab is in phase III clinical trials for a variety of chemotherapy-naïve and castration-resistant prostate cancer (mCRPC) eligibilities, Table 2.[47,48]

Custirsen

Custirsen (OGX-011) is an antisense inhibitor of clusterin, a cytoprotective protein that plays a role in cell survival.[49] The expression of clusterin has been associated with CRPC.[49] A phase II study in patients with mCRPC showed a PSA reduction ≥ 50% in 58% of patients taking custirsen in combination with docetaxel and prednisone when compared with 54% in patients taking docetaxel and prednisone alone.[49] Median progression-free survival was 7.3 months with custirsen versus 6.1 months with docetaxel plus prednisone alone, and median overall survival was 23.8 months with custirsen versus 16.9 months with docetaxel plus prednisone alone.[49] Custirsen is being investigated in combination with docetaxel and prednisone in phase III trials as first-line treatment[50] and as second-line treatment[51] after prior docetaxel-based chemotherapy, Table 2.

Current status of chemotherapy in combination with radiation or surgery for the treatment of prostate cancer

The results of TAX 327 and SWOG 9916 showing improved survival with docetaxel-based chemotherapy in patients with CRPC have led to increased investigation of chemotherapy earlier in the prostate cancer disease spectrum.[13] Chemotherapy is being investigated in both the neoadjuvant and adjuvant settings for patients with high risk localized prostate cancer.[13,52] There is a group of high risk prostate cancer patients that can be identified for treatment failure after radiation therapy. In an analysis of 500 patients treated with radiation therapy alone for clinically localized prostate cancer, Pisansky et al noted that clinical tumor stage, Gleason score, and pre-treatment PSA level were all independently associated with clinical or biochemical recurrence.[53] Separating patients into low, intermediate, and high risk groups based on these factors, recurrence-free probabilities at 5 years' post-radiation therapy were 92%, 67%, and 24%, respectively.[53] Others have noted similar results. Horwitz et al reviewed a series of 470 patients with clinically localized prostate cancer who were treated with radiation therapy and found that T stage ≥ T3, pre-treatment PSA > 20 ng/mL, and Gleason score ≥ 7 were adverse prognostic factors for biochemical recurrence.[54] In a cohort of 456 consecutive patients treated with conformal radiation therapy, independent prognostic factors by multivariate analysis included pre-treatment PSA, clinical T stage, and Gleason score.[5] The 5 year, biochemically free-of-failure (bNED) rate for patients with pre-treatment PSA ≥ 20 ng/mL was only 28%, as opposed to a 5 year bNED rate of 61% for the entire group.[5]

Two phase II trials have shown PSA reductions with neoadjuvant docetaxel in patients with locally advanced or high risk localized prostate cancer prior to radical prostatectomy, Table 3.[55,56] In addition, a study of paclitaxel, estramustine, and carboplatin (TEC) in patients with locally advanced prostate cancer, local relapse following either radiation therapy or radical prostatectomy, or metastatic prostate cancer showed PSA reductions of ≥ 50% in 67% of patients.[57] A multicenter, phase II trial of neoadjuvant TEC plus androgen deprivation prior to radiation therapy in patients with high risk localized prostate cancer showed median PSA progression-free survival of 12.1 months, Table 3.[58] CALGB 90203 is a phase III study being conducted to compare radical prostatectomy alone to neoadjuvant estramustine plus docetaxel prior to radical prostatectomy in approximately 700 patients with high risk, clinically localized prostate cancer.[59] The trial is currently recruiting patients, Table 3.[15]

Initial pilot studies have demonstrated the feasibility and tolerability of adjuvant therapy with paclitaxel plus estramustine; paclitaxel plus androgen deprivation; or docetaxel alone in patients with high risk prostate cancer following radical prostatectomy.[60-62] TAX 3501, a phase III 2X2 trial designed to compare androgen ablation with or without docetaxel following radical prostatectomy or as salvage treatment, was closed due to poor accrual; a similar trial with a 1:1 randomization design, TAX 3503, is currently ongoing, Table 3.[52] In TAX 3503, patients with increasing PSA levels following radical prostatectomy are randomized to androgen-deprivation therapy alone or to androgen-deprivation therapy plus docetaxel.[16] SWOG 9921, a phase III trial designed to compare androgen ablation with or without mitoxantrone following radical prostatectomy, was closed to further accrual, and mitoxantrone administration was suspended after the development of three cases of acute myelogenous leukemia in the mitoxantrone arm, Table 3.[63] RTOG 99-02 was a phase III trial designed to compare adjuvant chemotherapy

TABLE 3 **Completed and ongoing phase II or III clinical trials of chemotherapy for the treatment of high risk localized prostate cancer**

Drug/regimen	Setting	Phase	Trial	Results/status	Reference
Docetaxel	Neoadjuvant	II	Dreicer et al	24% of patients with PSA reduction ≥ 50%	55
Docetaxel	Neoadjuvant	II	Febbo et al	58% of patients with PSA reduction ≥ 50%	56
Paclitaxel, estramustine, and carboplatin + androgen deprivation	Neoadjuvant	II	Kelly et al	12.1 months median progression-free survival	58
Estramustine + docetaxel	Neoadjuvant	III	CALGB 90203	Currently recruiting patients	56
Docetaxel + prednisone	Adjuvant	III	TAX 3501	Closed due to poor accrual	52
Docetaxel + prednisone	Adjuvant	III	TAX 3503	Currently recruiting patients	16
Mitoxantrone	Adjuvant	III	SWOG 9921	Closed after 3 cases of acute myelogenous leukemia	63
Paclitaxel, estramustine + ectoposide	Adjuvant	III	RTOG 99-02	Closed due to excess thromboembolic toxicity	64
Docetaxel + prednisone	Adjuvant	III	RTOG 0521	Ongoing, but not recruiting patients	65
Docetaxel + androgen ablation	Adjuvant	III	VA Cooperative study #553	Currently recruiting patients	17
Docetaxel, brachytherapy, + androgen deprivation	Adjuvant	II	Dibiase et al	76.2% median 5 year disease-free survival 70.4% median 7 year disease-free survival 83.3% median 5 year overall survival 80.1% median 7-year overall survival	67
Docetaxel + prednisone	Adjuvant	II	UTHSC-045-0015-377	Currently recruiting patients	68

with paclitaxel, estramustine, and etoposide following androgen suppression and radiotherapy to androgen suppression plus radiotherapy alone in patients with high risk non-metastatic prostate cancer, Table 3.[64] The trial was stopped due to excess thromboembolic toxicity, and an initial toxicity analysis showed more grade ≥ 3 AEs (71% versus 37%) and significantly more grade ≥ 3 hematologic ($p < 0.0001$) and gastrointestinal toxicity ($p = 0.017$) in the chemotherapy arm than in the arm receiving only androgen suppression plus radiotherapy.[64] A successor trial (RTOG 0521) investigating androgen suppression and radiation therapy versus androgen suppression and radiation therapy followed by chemotherapy with docetaxel and prednisone for high risk localized prostate cancer is currently ongoing, Table 3.[65] In addition, a phase III trial of adjuvant docetaxel and prednisone following radical prostatectomy completed accrual and is in follow up, Table 3.[17]

In two recent reports, a multi-modality approach combining chemotherapy with androgen-deprivation therapy and radiation was investigated for the treatment of patients with high risk prostate cancer.[66,67] A prospective trial with a median follow up of 75.3 months demonstrated the feasibility of weekly paclitaxel, radiation, and androgen deprivation in patients with

high risk prostate cancer with or without prior radical prostatectomy.[66] The 5 year and 7 year overall survival rates were 83% and 67%, respectively.[66] The most common grade 3 toxicities were diarrhea, urinary urgency/incontinence, tenesmus, and leukopenia.[66] Similarly, a prospective phase II study with a median follow up of 5.6 years showed promising results with external beam radiation therapy, permanent prostate brachytherapy boost, 2 years of androgen deprivation, and three cycles of adjuvant docetaxel in patients with high risk prostate cancer.[67] The 5 year and 7 year rates of disease-free survival, the primary endpoint, were 76.2% and 70.4%, Table 3.[67] The 5 year and 7 year rates of overall survival were 83.3% and 80.1%, Table 3.[67] Grade 3 and 4 hematologic toxicities during chemotherapy were reported in 19% and 2.4% of patients, respectively.[67] Another adjuvant trial, a phase II trial investigating docetaxel plus radiotherapy and prednisone following surgery for prostate cancer, is currently underway, Table 3.[68]

Summary

With recent clinical trial results underscoring a growing role for chemotherapy and other systemic therapies in the treatment of patients with CRPC, as well as the approval of CRPC-targeting agents, potential survival advantages for patients are significant. Agents approved in the last year include cabazitaxel, sipuleucel-T and abiraterone. Those currently in clinical development, such as novel antiandrogens, ET-A receptor antagonists, novel immunomodulatory agents, and others may yet provide additional treatment options for patients with CRPC. Patients with prostate cancer can potentially benefit from a multidisciplinary approach in which urologists, radiation oncologists and medical oncologists coordinate care for men with high risk prostate cancer.

Docetaxel and paclitaxel based chemotherapy, either alone or in combination with other treatment modalities, is being investigated as neoadjuvant and adjuvant therapy for patients with high risk localized prostate cancer. The role for chemotherapy earlier in the spectrum of disease for prostate cancer remains an area of active interest. Urologists should remain informed about these newer agents and how to best apply newly approved agents to men with CRPC.

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