New Agents for the Management of Castration-Resistant Prostate Cancer

Robert J Cersosimo

Prostate cancer is the most commonly diagnosed malignancy in American men. The American Cancer Society estimates that 241,740 men will be diagnosed with prostate cancer in 2012, accounting for 29% of newly diagnosed cancers. Approximately 28,170 men will die from this disease in 2012. At diagnosis, approximately 4% of patients have advanced disease. Using American Cancer Society figures, approximately 9670 men will be diagnosed with advanced disease annually. Androgen deprivation therapy is the most common initial treatment for men with advanced disease. First-line therapy includes luteinizing hormone-releasing hormone (LHRH) agonists, antiandrogens, and orchectomy. Most men treated with androgen deprivation therapy respond, but with time most patients develop hormone-refractory or castration-resistant prostate cancer (CRPC). A review characterizing the CRPC population revealed that 10-20% of patients develop castration-resistant disease within 5 years of follow-up. The most commonly used initial treatment for CRPC is chemotherapy with docetaxel and prednisone. In a pivotal Phase 3 randomized study of 1006 men with metastatic CRPC, the median overall survival with 3-week docetaxel plus prednisone was 19.2 months, versus 16.3 months with mitoxantrone plus prednisone (p = 0.004), an advantage of about 3 months. This docetaxel regimen has become the standard of care for men with CRPC and is endorsed by the American Society of Clinical Oncology and the National Comprehensive Cancer Network (NCCN).

Three new agents have been approved for management of CRPC: sipuleucel-T (approved in April 2010), cabazitaxel, and abiraterone acetate.

OBJECTIVE: To review the activity of 3 new agents approved for the management of advanced castration-resistant prostate cancer (CRPC): sipuleucel-T, cabazitaxel, and abiraterone acetate.

DATA SOURCES: Literature was accessed through MEDLINE (1977-June 2012) and abstracts from the American Society of Clinical Oncology (2000-2012) using the terms castration-resistant and hormone-refractory prostate cancer, sipuleucel-T, cabazitaxel, abiraterone, Provenge, Jevtana, and Zytiga. Reference citations from publications identified were also reviewed.

STUDY SELECTION AND DATA EXTRACTION: Articles identified from the data sources in English on human subjects were evaluated.

DATA SYNTHESIS: Options for patients with CRPC have been limited, with little to offer those who failed or could not tolerate docetaxel-based therapy. Three new drugs, with very different mechanisms of action, have changed that and will undoubtedly change the treatment paradigm for these patients. Each agent has demonstrated an impact on patient survival. Sipuleucel-T, the first immunotherapy approved for treatment of CRPC, improved median overall survival by 4.1 months and reduced the risk of death by 22% in a placebo-controlled trial of asymptomatic patients. Sipuleucel-T can be administered prior to docetaxel-based therapy. Cabazitaxel, a taxane chemotherapy agent, improved median overall survival by 2.4 months and reduced the risk of death by 30% in a Phase 3 trial of patients whose cancer progressed during or after docetaxel-based therapy. Abiraterone acetate, a hormonal therapy, improved median overall survival by 3.9 months and reduced the risk of death by 35% in patients with relapse during or after docetaxel-based therapy.

CONCLUSIONS: The advent of new agents for the management of advanced CRPC has increased the choices for patients whose options were limited. Additional experience will determine the optimal sequencing of these agents, their roles in combination therapy, and their activity in patients with earlier disease.

KEY WORDS: abiraterone, cabazitaxel, castration-resistant prostate cancer, hormone-refractory prostate cancer, sipuleucel-T.
taxel (June 2010), and abiraterone (April 2011). These agents are the focus of this review. A comparison of agents currently approved for treatment of patients with metastatic CRPC is presented in Table 1.\textsuperscript{3,4,7-10}

Sipuleucel-T

MECHANISM OF ACTION

Sipuleucel-T is indicated for the treatment of asymptomatic or minimally symptomatic metastatic CRPC.\textsuperscript{11} Sipuleucel-T is the first vaccine approved for treatment of malignant disease. It consists of activated autologous peripheral blood mononuclear cells, including antigen-presenting cells that have been obtained from the patient by leukapheresis at an approved apheresis center.\textsuperscript{7} After collection, these cells are sent to 1 of 3 processing centers (New Jersey, Georgia, or California) where they are activated with a recombinant human protein. This protein consists of prostatic acid phosphatase (PAP), an antigen found in prostate cancer tissue, that is linked to granulocyte-macrophage colony-stimulating factor (GM-CSF), which serves as an immune cell activator. The final composition of sipuleucel-T depends on the composition of the patient’s cells obtained during leukapheresis, but should consist of antigen-presenting cells, T cells, B cells, natural killer cells, and other cells. After activation, the product is sent to the provider for reinfusion into the patient. Leukapheresis should take place 3 days before the planned reinfusion date. Treatment with sipuleucel-T is a form of autologous cellular immunotherapy. Although the exact mechanism of action is unknown, it is designed to induce an immune response against PAP in prostate cancer cells. A Phase 2 study demonstrated that it may take 8 weeks for maximum T cell proliferation responses to develop.\textsuperscript{12}

ADMINISTRATION

Sipuleucel-T is supplied as a 250-mL suspension that contains a minimum of 50 million autologous CD54 cells activated with PAP–GM-CSF in lactated Ringer’s injection. The final product is supplied in a sealed, patient-specific infusion bag. A complete course of therapy consists of 3 doses, administered every 2 weeks. The infusion must begin prior to the expiration date and time indicated on the cell product disposition form and product label. The entire volume of the bag should be administered as an intravenous infusion over 60 minutes. The product should not be administered through a cell filter. The patient should be observed for at least 30 minutes following each infusion.\textsuperscript{11}

Patients should be pretreated with acetaminophen and an antihistamine such as diphenhydramine 30 minutes prior to the infusion. Acute infusion reactions are commonly seen after administration and may include chills, fatigue, fever, nausea, and joint aches. Should an infusion reaction occur, the infusion should be slowed or interrupted, depending on the severity of the reaction. Treatment appropriate to the severity of the reaction should be administered. In controlled clinical trials the most commonly administered therapy was acetaminophen, intravenous histamine H\textsubscript{1} and/or H\textsubscript{2} blockers, and low-dose meperidine. If the reaction required the infusion to be stopped, the patient recovered, and it was deemed safe to resume the infusion, the manufacturer recommends not resuming the in-

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Docetaxel\textsuperscript{3,4}</th>
<th>Sipuleucel-T\textsuperscript{7,8}</th>
<th>Cabazitaxel\textsuperscript{9}</th>
<th>Abiraterone\textsuperscript{10}</th>
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<tbody>
<tr>
<td>Brand name</td>
<td>Taxotere</td>
<td>Provenge</td>
<td>Jevtana</td>
<td>Zytiga</td>
</tr>
<tr>
<td>Administration</td>
<td>75 mg/m\textsuperscript{2} intravenously over 1 hour every 3 weeks plus prednisone 5 mg orally twice daily</td>
<td>3- to 4-hour leukapheresis followed by 1-hour intravenous readministration every 2 weeks for 3 doses</td>
<td>25 mg/m\textsuperscript{2} intravenously over 1 hour every 3 weeks with prednisone 10 mg orally daily</td>
<td>1000 mg orally daily plus prednisone 5 mg orally twice daily</td>
</tr>
<tr>
<td>Overall survival vs control (months)</td>
<td>19.2 vs 16.3\textsuperscript{a}</td>
<td>25.8 vs 21.7\textsuperscript{b}</td>
<td>15.1 vs 12.7\textsuperscript{a}</td>
<td>14.8 vs 10.9\textsuperscript{c}</td>
</tr>
<tr>
<td>Reduction in risk of death (%)</td>
<td>24</td>
<td>22</td>
<td>30</td>
<td>35.4</td>
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<td>Adverse effects</td>
<td>Myelosuppression</td>
<td>Chills, fever, nausea, fatigue, headache, asthenia, myalgia</td>
<td>Myelosuppression, diarrhea</td>
<td>Hypokalemia, hypertension, edema</td>
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<tr>
<td>Indication</td>
<td>With prednisone for pts. with metastatic castration-resistant prostate cancer</td>
<td>Asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing regimen</td>
<td>With prednisone for pts. with metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing regimen</td>
<td>With prednisone for pts. with metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing regimen</td>
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</table>

\textsuperscript{a}Control group received mitoxantrone 12 mg/m\textsuperscript{2} every 3 weeks plus prednisone 5 mg orally twice daily.
\textsuperscript{b}Control group received placebo.
\textsuperscript{c}Control group received prednisone 5 mg orally twice daily plus placebo.
fusion if the bag was maintained at room temperature for more than 3 hours.\textsuperscript{11} Patients who receive sipuleucel-T should have good immune systems. Since it takes a few months for the immune system to fully respond, those who receive sipuleucel-T should be patients who their physicians believe will have stable disease for several months after treatment.

**CLINICAL ACTIVITY**

Sipuleucel-T has been evaluated in 3 randomized Phase 3 trials of patients with asymptomatic metastatic CRPC (Table 2).\textsuperscript{7,8,13,14} All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 and serum testosterone levels <50 ng/dL. Patients enrolled in the first 2 trials also had to have positive staining for PAP in 25\% of tumor cells. Patients with cancer-related bone pain and visceral metastases were excluded. The first study, D9901, randomized 127 patients in a 2:1 ratio to receive 3 infusions of sipuleucel-T (n = 82) or placebo (n = 45) every 2 weeks.\textsuperscript{13} The primary end point was time to progression, which was assessed by radiographic imaging, appearance of new cancer-related pain with radiographic anatomic correlation, or other evidence consistent with progression such as pathologic fracture, nerve root compression, or spinal cord compression. Prostate-specific antigen (PSA) was not used to determine disease progression. Although the study was not powered to detect a survival difference between the 2 groups, patients were followed for up to 36 months and survival data were reported. Upon progression, patients in the control arm were offered APC8015F, a product manufactured to the same specifications as sipuleucel-T but prepared from the patient’s cells that were cryopreserved when the placebo was prepared. At the time of publication, 115 patients (90.5\%) had experienced progression and 34 subsequently received APC8015F. After progression, 55.7\% of patients receiving sipuleucel-T and 62.8\% of patients receiving placebo received some type of chemotherapy.

Median time to progression was 11.7 weeks in patients who received sipuleucel-T and 10.0 weeks in patients who received placebo (p = 0.052). An intention-to-treat analysis revealed a median overall survival of 25.9 months in the sipuleucel-T group versus 21.4 months in the placebo group (p = 0.01). The estimated survival rate at 36 months was 34\% in the sipuleucel-T group and 11\% in the placebo group (p = 0.005, based on the number of survivors at 36 months). This analysis included the placebo patients who crossed over to sipuleucel-T. Sipuleucel-T maintained a significant impact on survival after adjustments were made for clinical variables that might affect survival (p < 0.002), including PSA, lactate dehydrogenase, number of bone metastases, body weight, and localization of disease.\textsuperscript{13}

Another study, D9902, was a 2-stage double-blind, placebo-controlled Phase 3 trial. Both D9901 and D9902 were instituted at the same time.\textsuperscript{14} Enrollment in the first stage, D9902A, was stopped after accrual of 98 patients when the results of D9901 revealed no significant benefit in time to progression with sipuleucel-T. Since a benefit was noted in patients with a Gleason score of 7 or less, the trial was amended to study only patients with Gleason scores of 7 or less. The first part of the study, in which patients with all Gleason scores were included, was designated as D9902A. The second part, in which only patients with Gleason scores of 7 or less were included, was designated as D9902B and was reported separately.\textsuperscript{28}

An integrated analysis was performed of the data from D9901 and D9902A in which 225 patients were randomized to receive sipuleucel-T (n = 147) or placebo (n = 78).\textsuperscript{14} In D9902A, the median time to progression was 10.9 months with sipuleucel-T and 9.9 months with placebo (p = 0.719). Integration of the data from the 2 trials revealed median times to progression of 11.1 months with sipuleucel-T and 9.7 months with placebo (p = 0.111). Respective median overall survival with sipuleucel-T versus placebo was 19.0 versus 15.7 months (p = 0.331) in D9902A and 23.2 versus 18.9 months (p = 0.011) in the integrated analysis. At 36 months, 33\% of sipuleucel-T patients and 15\% of placebo patients were still alive.

Study D9902B, the IMPACT (Immunotherapy for Prostate Adenocarcinoma Treatment)
The study was later amended to include men with all Gleason scores and men with minimally symptomatic disease. Exclusion criteria included an ECOG performance status of 2 or greater, visceral metastases, spinal cord compression, and pathologic bone fractures. The primary end point was overall survival, with a secondary end point of time to progression. In the initial report, after 331 patient deaths, the median overall survival in the sipuleucel-T group was 25.8 months, versus 21.7 months in the placebo group (p = 0.032). A follow-up report after 349 deaths revealed no change.7 The probability of surviving 36 months was 31.7% with sipuleucel-T and 23% with placebo. Sipuleucel-T therapy was associated with a 22% relative reduction in the risk of death. There was no significant difference in median time to progression between sipuleucel-T (14.6 weeks) and placebo (14.4 weeks).

Eighty-two percent of patients in the sipuleucel-T arm and 73% in the control arm received additional treatment after sipuleucel-T or placebo, including docetaxel, which was administered to 57.2% who received sipuleucel-T and to 50.3% who received placebo. The survival curves were similar for both groups with and without docetaxel therapy, suggesting that the results seen with sipuleucel-T were not affected by the poststudy addition of docetaxel. Upon progression, patients in the control arm were offered APC8015F. Eighty-four patients in the placebo group (49.1%) received APC8015F as their first treatment after completion of the study and 109 patients in the placebo group (63.7%) received it at some point. Median survival in those who received APC8015F was 23.8 months, versus 11.6 months in those who did not receive it. These results need to be confirmed in a randomized study. However, the authors reported that the survival benefit from sipuleucel-T persisted even after the administration of APC8015F to some of the placebo group. Immune response was assessed by measurement of antibody titers against the immunizing antigen PA2024 and against PAP and by T-cell proliferation responses to PA2024 and PAP at week 6. Sipuleucel-T patients who had an antibody titer greater than 400 against PA2024 or PAP at any time after baseline had a longer survival than those whose antibody titers were less than or equal to 400 (p < 0.001 and p = 0.08, respectively). There were no differences in survival among those who had T-cell proliferation responses to PA2024 or PAP and those who did not.7

One of the unusual outcomes with sipuleucel-T therapy is the lack of objective response criteria, other than the ultimate end point of survival. There was no objective evidence of a tumor response or time to progression benefit in any of these trials. It has been suggested that vaccines work in a different manner than conventional chemotherapy, where such monitoring parameters have traditionally been used.15 Vaccines work by affecting the immune system, which takes time and may ultimately result in an impact on survival without affecting traditional outcome measures. Guidelines for the evaluation of immune therapy have been proposed.16

Hormone-Responsive Disease

The PROTECT (PROvenge Treatment and Early Cancer Treatment) trial, a double-blind controlled study, examined the activity of sipuleucel-T in patients with androgen-dependent disease.17 All patients had undergone radical prostatectomy and had a PSA increase as their only sign of recurrence. Patients received a 3-month depot injection of an LHRH agonist and, if their PSA was less than 1 ng/mL, they were randomized to receive sipuleucel-T (n = 117) or control (n = 59). Patients whose PSA was not less than 1 ng/mL were allowed a 1-month depot injection of an LHRH agonist and after that injection, if the PSA was then less than 1 ng/mL, they were eligible for randomization. The primary end point was time to biochemical failure, defined as a serum PSA of 3.0 ng/mL or more. PSA doubling time, time to distant failure, and overall survival were also assessed.

The median time to biochemical failure was 18.0 months in the sipuleucel-T group and 15.4 months in the control group (p = 0.737). Patients who received sipuleucel-T had a significantly longer PSA doubling time (155 vs 105 days; p = 0.038), a 48% increase. It was too early to report on time to distant failure or survival.17

ADVERSE EFFECTS

Sipuleucel-T was well tolerated.7 Most adverse effects were grade 1-2. Effects seen more commonly after sipuleucel-T compared to placebo were primarily infusion reactions and included chills (54.1%), fever (29.3%), fatigue (39.1%), nausea (28.1%), headache (16.0%), asthenia (10.9%), and flu-like illness (9.8%), as well as myalgia (9.8%), hypertension (7.4%), hyperhidrosis (5.3%), and groin pain (5%). Most effects resolved within 48 hours.

Cerebrovascular events were reported in 8/338 patients (2.4%) on sipuleucel-T versus 3/168 (1.8%) on placebo (p = 1.00) in the IMPACT trial.7 This contrasts with the results reported in the other Phase 3 randomized trials, which report a possible increased risk of cerebrovascular events in patients who received sipuleucel-T.14 The incidence of cerebrovascular events reported as adverse effects or causes of death was 7.5% (11/147) in the sipuleucel-T arm versus 2.6% (2/76) in the placebo arm.14 A summary of the incidence and characteristics of cerebrovascular events from 4 randomized trials revealed the following incidences of cerebrovascular events after sipuleucel-T and placebo, respectively: cerebrovascular events (including transient ischemic attack), 4.0% versus 2.9%; ischemic stroke, 2.7%
versus 2.6%; hemorrhagic stroke, 0.7% versus 0.3%; unknown stroke, 0.7% versus 0%; and transient ischemic attack, 0.8% versus 0.3%. Patients who received sipuleucel-T were at a slightly higher risk for cerebrovascular events than those who received placebo (absolute risk difference 1.1%); these differences could account for the difference in cerebrovascular events between treatment and placebo groups. There was also a higher incidence of cerebrovascular event–associated deaths with sipuleucel-T (1.4%) than placebo (0.7%). In light of the uncertainties concerning the risk of cerebrovascular events with sipuleucel-T administration, the Food and Drug Administration has required the sponsor to complete a postmarketing study to evaluate the risk of cerebrovascular events in patients who receive it.19

**COST CONSIDERATIONS**

A 3-treatment course of sipuleucel-T therapy has been priced at $31,000 per treatment, or $93,000 per course, making it one of the most expensive cancer treatments on the market.20 The Centers for Medicare and Medicaid Services began an analysis of sipuleucel-T in 2010 and reported on June 30, 2011, that it determined that the evidence was adequate to conclude that sipuleucel-T improves health outcomes for Medicare beneficiaries with asymptomatic or minimally symptomatic metastatic CRPC and that it is reasonable and necessary for that indication.21

**Cabazitaxel**

**MECHANISM OF ACTION**

Cabazitaxel is indicated for use in combination with prednisone for treatment of patients with metastatic CRPC previously treated with a docetaxel-containing regimen.22 Cabazitaxel is a member of the taxane family, which includes paclitaxel and docetaxel. Cabazitaxel binds to tubulin and promotes assembly into microtubules and inhibits disassembly, resulting in stabilization of microtubules, which interferes with mitotic and cellular interphase activity.22

**PHARMACOKINETICS**

The pharmacokinetics of cabazitaxel were evaluated in a Phase 1 trial of 25 patients with advanced cancer.39 Patients received a total of 102 courses of therapy at doses of 10–25 mg/m². A triphasic model with mean half-lives of 2.6 minutes, 1.3 hours, and 77.3 hours described elimination of cabazitaxel from the plasma. The volume of distribution at steady-state was 2034 L/m², suggesting extensive extravascular distribution, and the mean clearance was 53.5 L/h, representing 61% of hepatic blood flow. There were no significant changes in the pharmacokinetic parameters among patients who received multiple doses, implying no accumulation or autoinduction. Cabazitaxel is metabolized in the liver primarily by the CYP3A4/5 isoenzymes and to a lesser extent by the CYP2C8 enzymes.22 Although no formal drug interaction studies have been performed, the manufacturer recommends that coadministration of cabazitaxel and strong inhibitors or strong inducers of CYP3A enzymes should be avoided.22

**ADMINISTRATION**

Cabazitaxel is supplied in vials containing 60 mg/1.5 mL. It is administered intravenously as a 60-minute infusion. It should be administered through an in-line filter of 0.22-μm nominal pore size. The recommended dose is 25 mg/m² administered every 3 weeks along with prednisone 10 mg daily. Patients should be premedicated at least 30 minutes before treatment with the following intravenous medications: an antihistamine such as diphenhydramine 25 mg or equivalent, an H₂ antagonist such as ranitidine 50 mg or equivalent, and a corticosteroid such as dexamethasone 8 mg or equivalent to reduce the risk and/or severity of a hypersensitivity reaction. Subsequent doses should be reduced to 20 mg/m² if the patient experiences grade 3 or greater neutropenia that persists for more than 1 week despite administration of G-CSF, febrile neutropenia, or grade 3 or greater persistent diarrhea despite administration of appropriate medication, fluid, and electrolyte replacement.22

The NCCN states that patients receiving cabazitaxel should follow guidelines for white blood cell growth factor use, especially if the patient has been heavily pretreated.6 Supportive care should include antiemetics and symptom-directed anti diarrheal agents.

**CLINICAL ACTIVITY**

Cabazitaxel and prednisone were compared to mitoxantrone plus prednisone in the TROPIC (Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial) study, a randomized open-label trial of 755 men with metastatic CRPC.23 All patients had progressed during or after docetaxel treatment. Eligible patients had to have an ECOG performance status of 0–2; 91% of patients randomized to receive mitoxantrone and 93% of patients randomized to receive cabazitaxel had a performance status of 0–1. Visceral disease, a negative prognostic factor, was present in 25% of the patients. The median ages of patients who received mitoxantrone and cabazitaxel were 67 and 68 years, respectively. All patients received prednisone 10 mg daily and were randomized to receive intravenous mitoxantrone 12 mg/m² over 15-30 minutes (n = 377) or intravenous cabazitaxel 25 mg/m²

RJ Cersosimo
Diarrhea was more common in Abiraterone is more selective and specific than -hydroxylase/C
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A Phase 3 clinical trial comparing plus prednisone
A Phase 3 clinical trial comparing cabazitaxel versus mitoxantrone, respectively, in the TROPIC trial: neutropenia (82% vs 58%), febrile neutropenia (8% vs 1%), anemia (11% vs 5%), leukopenia (68% vs 42%), diarrhea (6% vs <1%), fatigue (5% vs 3%), and asthenia (5% vs 2%).

Median overall survival was 12.7 months in the mitoxantrone group and 15.1 months in the cabazitaxel group, a gain of 2.4 months. The hazard ratio for death in men treated with cabazitaxel versus those treated with mitoxantrone was 0.70 (95% CI 0.59 to 0.83; p < 0.0001), which corresponded to a 30% reduction in the relative risk of death. Among patients with measurable disease, the tumor response rates with mitoxantrone and cabazitaxel regimens were 4.4% and 14.4%, respectively (p = 0.0005). The respective PSA response rates for mitoxantrone and cabazitaxel regimens were 17.8% and 39.2% (p = 0.0002) and the respective pain response rates were 7.7% and 9.2% (p = 0.63). Median progression-free survival was 1.4 months with mitoxantrone and 2.8 months with cabazitaxel (p < 0.0001). In the intention-to-treat analysis there was a significantly longer median time to tumor progression (8.8 vs 5.4 months; p < 0.0001) and median time to PSA progression (6.4 vs 3.1 months; p = 0.001) in favor of cabazitaxel. This was the first study to demonstrate a significant improvement in overall survival in patients with metastatic CRPC after prior docetaxel treatment.

ADVERSE EFFECTS

The following grade 3-4 adverse effects were reported in greater than or equal to 5% of patients who received cabazitaxel versus mitoxantrone, respectively, in the TROPIC trial: neutropenia (82% vs 58%), febrile neutropenia (8% vs 1%), anemia (11% vs 5%), leukopenia (68% vs 42%), diarrhea (6% vs <1%), fatigue (5% vs 3%), and asthenia (5% vs 2%). Diarrhea was more common in patients aged 75 years or older (55.7% vs 44.5%; p < 0.1) and in patients who had undergone prior radiation therapy (50.0% vs 41.4%; p < 0.1). There were no differences in diarrhea or neutropenia in subgroups identified by race, baseline liver or renal function, performance status, or prior chemotherapy. Neutropenia was more common in patients aged 65 years or older (24.2% vs 17.6%). The incidence of neutropenia reported with cabazitaxel necessitates careful monitoring of blood counts and use of G-CSF, if needed. Primary prophylaxis with G-CSF has been suggested for patients at high risk for neutropenia (age >65 years, poor performance status, prior febrile neutropenia, extensive prior radiation therapy, poor nutritional status, and other serious comorbidities). Cabazitaxel is contraindicated in patients with a neutrophil count of less than or equal to 1500/mm³. A Phase 3 clinical trial comparing the efficacy and toxicity of cabazitaxel 20 mg/m² plus prednisone versus cabazitaxel 25 mg/m² plus prednisone (PROSELICA) is underway.

Peripheral neuropathy was reported in 14% of patients who received cabazitaxel and 3% who received mitoxantrone; however, grade 3 peripheral neuropathy was reported in only 1% of patients who received each drug. There were 18 deaths in the cabazitaxel group (5%) and 9 (2%) in the mitoxantrone group within 30 days of the last dose. Neutropenia and its clinical consequences was the most common cause of death among cabazitaxel patients (n = 7 [2%]) compared with mitoxantrone patients (n = 1 [<1%]), followed by cardiac events (n = 5 [1%] vs n = 0). The fatal cardiac events were cardiac arrest (n = 3), sudden death (1), and ventricular fibrillation (1), none of which were considered to be drug related by the investigators.

**Abiraterone Acetate**

**MECHANISM OF ACTION**

Abiraterone acetate is indicated for use in combination with prednisone for the treatment of patients with metastatic CRPC who have received prior docetaxel-containing chemotherapy. Abiraterone is a structural analogue of pregnenolone and inhibits an enzyme necessary for androgen synthesis, 17α-hydroxylase/CYP17, that is expressed in testicular, prostate, and adrenal tissue. Inhibition of CYP17 results in reduction of androgen synthesis in the testes, adrenal glands, and prostate tissue, resulting in reduced serum levels of testosterone and other androgens.

Abiraterone is more selective and specific than ketoconazole, which has also been used to treat advanced prostate cancer. Although the activity of abiraterone is primarily confined to effects on androgen production, there is a reactive increase in corticotropic secondary to a pituitary response to the partial adrenal inhibition, which can lead to increased mineralocorticoid production. This can lead to hypokalemia and hypertension, which can be reduced by concurrent prednisone administration.

**PHARMACOKINETICS**

After oral administration, peak plasma concentrations of abiraterone are reached in 1.5-4 hours (mean 2). Abiraterone is more selective and specific than ketoconazole, which has also been used to treat advanced prostate cancer. Although the activity of abiraterone is primarily confined to effects on androgen production, there is a reactive increase in corticotropic secondary to a pituitary response to the partial adrenal inhibition, which can lead to increased mineralocorticoid production. This can lead to hypokalemia and hypertension, which can be reduced by concurrent prednisone administration.
fasted state. Likewise the AUC was 5-fold higher after the low-fat meal and 10-fold higher after the high-fat meal.27

After a dose of 1000 mg the C<sub>max</sub> at steady state was 226 ng/mL and the AUC was 1173 ng•h/mL. Protein binding of abiraterone was >99% and the mean volume of distribution was 19,669 L. Abiraterone acetate is metabolized to abiraterone and exhibits a mean terminal half-life of 12 hours. After administration of 14C-abiraterone acetate, 88% of the dose was eliminated in the feces and 5% in the urine.27

**ADMINISTRATION**

Abiraterone is available as 250-mg tablets and is administered at a dose of 1000 mg daily in combination with prednisone 5 mg administered twice daily. Tablets should be taken whole and on an empty stomach, with no food for 2 hours before and 1 hour after administration. The half-life of abiraterone increased to 18 hours in patients with mild hepatic impairment and to 19 hours in those with moderate hepatic impairment. Patients with moderate hepatic dysfunction (Child-Pugh class B) should receive 250 mg daily. The drug has not been studied in patients with severe (Child-Pugh class C) hepatic impairment. If a patient develops hepatotoxicity during treatment, the dose should be withheld until recovery and reinstituted at 750 mg/day. If hepatotoxicity recurs at 500 mg/day, therapy should be discontinued.27

An early study demonstrated that administration of abiraterone alone resulted in a compensatory increase in serum luteinizing hormone levels that overcame the suppressive effect of abiraterone.31 The manufacturer recommends that LH-RH agonists be continued in patients receiving abiraterone and includes this recommendation in their patient counseling information.27 Most of the patients in the clinical trials had received prior LH-RH agonists. Although most trials did not state that LH-RH agonists were continued, most of them indicated that serum testosterone levels were maintained at 50 ng/dL or less (Table 3).10,29,32,33 which was most likely the result of continued LH-RH administration. Eligibility criteria for the study included ongoing androgen deprivation therapy and a serum testosterone level of 50 ng/dL or less.33

**CLINICAL ACTIVITY**

Clinical trials of abiraterone are summarized in Table 3.10,29,32,33 An expansion of the Phase 2 portion of a Phase 1/2 study enrolled 42 men with chemotherapy-naïve CRPC to receive abiraterone at a daily dose of 1000 mg.32 The primary end point was a 50% or greater PSA decline at any time after 12 weeks of treatment, with a secondary end point of a 30% or greater PSA decline. Measurable target lesions were identified and followed by computed tomography scans. Changes in circulating tumor cell (CTC) counts and median time to PSA progression were also followed.

A 50% or greater PSA decline was seen in 28 patients (67%), while 71% and 19% of patients experienced 30% or greater and 90% or greater declines, respectively. Measurable disease was present in 24 patients, 9 of whom (37.5%) experienced regression consistent with a partial response. Sixteen patients (66%) with measurable disease

<table>
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<th>Reference</th>
<th>Pts. (n)</th>
<th>Characteristics</th>
<th>Dosage</th>
<th>PSA Response (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Median Overall Survival (months)</th>
<th>Median Progression-Free Survival (months)</th>
<th>Median Time to PSA Progression (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danila</td>
<td>58</td>
<td>Prior docetaxel; ECOG performance status 0-2; testosterone level ≤50 ng/dL</td>
<td>1000 mg/day&lt;sup&gt;c&lt;/sup&gt;</td>
<td>36</td>
<td>NR</td>
<td>NR</td>
<td>5.5</td>
</tr>
<tr>
<td>Attard</td>
<td>42</td>
<td>Chemotherapy-naïve; ECOG performance status 0-1; testosterone level ≤50 ng/dL</td>
<td>1000 mg/day</td>
<td>67</td>
<td>NR</td>
<td>NR</td>
<td>7.4</td>
</tr>
<tr>
<td>Reid</td>
<td>47</td>
<td>Prior docetaxel; ECOG performance status 0-2; testosterone level ≤50 ng/dL</td>
<td>1000 mg/day</td>
<td>51</td>
<td>NR</td>
<td>NR</td>
<td>5.5</td>
</tr>
<tr>
<td>deBono</td>
<td>797</td>
<td>Prior docetaxel; ECOG performance status 0-2; ongoing androgen deprivation therapy; testosterone level ≤50 ng/dL</td>
<td>1000 mg/day&lt;sup&gt;d&lt;/sup&gt;</td>
<td>29</td>
<td>14.8</td>
<td>5.6</td>
<td>10.2</td>
</tr>
<tr>
<td></td>
<td>398</td>
<td>Placebo</td>
<td></td>
<td>6</td>
<td>10.9</td>
<td>3.6</td>
<td>6.6</td>
</tr>
</tbody>
</table>

ECOG = Eastern Cooperative Oncology Group; NR = not reported; PSA = prostate-specific antigen.

<sup>a</sup>PSA response: decrease of ≥50% in the PSA level from the pretreatment baseline level.

<sup>b</sup>Performance status on a scale of 0-5.

<sup>c</sup>All patients also received prednisone 5 mg orally twice daily.
demonstrated no evidence of progression at 6 months. The median time to PSA progression was 225 days. CTC counts fell from greater than or equal to 5 to less than 5 cells/7.5 mL in 10 of 17 patients, with declines of 30% or greater seen in 12 of 17 patients. Dexamethasone 0.5 mg/day was added to the regimen of patients whose disease progressed on abiraterone. Thirty patients received dexamethasone for 12 or more weeks after progression and 10 (33%) experienced a 50% or greater PSA decline, which the authors interpreted as a reversal of resistance to abiraterone.32

A small Phase 2 study administered abiraterone 1000 mg daily to 47 men with CRPC who had received prior docetaxel therapy.33 The primary end point was a 50% or greater PSA decline in 7 of the first 35 patients, at which point additional patients were enrolled. Secondary end points were a 30% or greater or 90% or greater PSA decline. PSA declines of 30% or greater, 50% or greater, and 90% or greater were seen in 68%, 51%, and 15% of the patients, respectively. Thirty patients had measurable disease, 8 of whom (27%) achieved a partial response. Median time to PSA progression was 24 weeks.

Similar results were reported in another Phase 2 study by the same group, involving 58 men with progressive metastatic CRPC who had received prior docetaxel therapy.34 The primary end point was a 50% or greater PSA decline. Additional outcomes included response among those with measurable disease, changes in performance status, time to PSA progression, and changes in CTC count. A 50% or greater PSA decline was reported in 36% of the patients, with 30% or greater declines reported in 47% and 90% or greater declines in 16%. Partial responses were seen in 4/22 patients (18%) and improvement in performance status was identified in 28%. Median time to PSA progression was 24 weeks. Twenty-nine patients had unfavorable CTC counts at baseline, 10 of whom (34%) developed favorable counts after treatment. There were no grade 4 toxicities and the only grade 3 toxicity was fatigue, which occurred in 2% of patients. The most common grade 1-2 toxicities were fatigue (32%), nausea (14%), vomiting (12%), dyspnea (10%), and peripheral edema (9%). The inclusion of prednisone for all patients resulted in much less hypokalemia (5% vs 55%), hypertension (<5% vs 17%), and fluid retention (9% vs 15%) than in the previous Phase 2 trial35 in which prednisone was not part of the regimen.

This regimen was then employed in a Phase 3 placebo-controlled trial.36 A total of 1195 patients with progressive disease, prior docetaxel therapy, and ongoing androgen deprivation therapy with a serum testosterone level of 50 ng/dL or less were randomized in a 2:1 ratio to receive prednisone 5 mg twice daily plus either abiraterone 1000 mg daily (n = 797) or placebo (n = 398). The primary end point was overall survival. Secondary end points were time to PSA progression, progression-free survival, and PSA response. The data were unblinded when an interim analysis after a median follow-up of 13 months demonstrated that the outcomes exceeded prespecified results. Median overall survival was significantly longer in the abiraterone group (14.8 vs 10.9 months; p < 0.001). Abiraterone and prednisone produced a 35.4% reduction in the risk of death compared with prednisone plus placebo. All secondary end points were also in favor of the abiraterone group, including PSA response (29% vs 6%; p < 0.001), progression-free survival (5.6 vs 3.6 months; p < 0.001), and time to PSA progression (10.2 vs 6.6 months; p < 0.001).

Abiraterone was used in chemotherapy-naive CRPC patients in 2 small studies involving a total of 77 patients.34,35 Both trials evaluated abiraterone 1000 mg daily. In the first trial, 44 patients had received a median of 3 prior hormonal therapies, 70% had bone metastases, and 21 had measurable disease.34 A 50% or greater PSA decline was reported in more than 60% of patients and the median time to PSA progression was 8.3 months. Twelve of 21 patients with measurable disease (57%) achieved a partial remission.

In the second trial, 33 patients received abiraterone plus prednisone 5 mg twice daily.35 Patients had received a median of 2 prior hormonal therapies. A 50% or greater PSA decline was reported in 79% of patients and the median time to PSA progression was 16.3 months. Nine of 13 patients with measurable disease (69%) achieved a partial remission. These studies demonstrated that abiraterone has activity in patients with CRPC despite the use of 2 or more prior hormonal therapies.

An interim analysis of the activity of abiraterone in patients with chemotherapy-naive CRPC was recently reported in a Phase 3 trial.37 Patients (n = 1088) with asymptomatic or mildly symptomatic metastatic disease were randomly assigned to receive abiraterone (1000 mg/day) plus prednisone (5 mg twice daily) or placebo plus prednisone (5 mg twice daily). The primary end points were radiographic progression-free survival (rPFS) and overall survival. After a median follow-up of 22 months there was a significant improvement in rPFS, which was 8.3 months in the placebo group and had not yet been reached in the abiraterone group (HR 0.43; 95% CI 0.35 to 0.52; p < 0.0001). Median overall survival was 27.2 months in the placebo group and had not been reached in the abiraterone group (HR 0.75; 95% CI 0.61 to 0.93; p = 0.0097). The abiraterone group had significantly better outcomes in the secondary end points of time to chemotherapy initiation (25.2 vs 16.8 months; HR 0.58; 95% CI 0.49 to 0.69; p < 0.0001) and time to PSA progression (11.1 vs 5.6 months; HR 0.49; 95% CI 0.42 to 0.57; p < 0.0001). An independent monitoring committee concluded that all end points favored the abiraterone group and recommended that the
study be unblinded and placebo patients crossed over to abiraterone treatment. This was the first randomized study to demonstrate that inhibition of extragonadal androgen synthesis can have a significant survival and rPFS advantage in chemotherapy-naïve patients and can also delay initiation of chemotherapy. This could lead the way to use of abiraterone before chemotherapy.

ADVERSE EFFECTS

Abiraterone was well tolerated in the Phase 3 trial. The most common adverse effects in the abiraterone and placebo groups, respectively, were fatigue (44% vs 43%), fluid retention and edema (31% vs 22%), back pain (30% vs 33%), nausea (30% vs 32%), arthralgia (27% vs 23%), constipation (26% vs 31%), bone pain (25% vs 28%), anemia (23% vs 26%), vomiting (21% vs 25%), and diarrhea (18% vs 14%). Most of these effects were grade 1-2. The most common grade 3-4 adverse effects in the abiraterone and placebo groups, respectively, were fatigue (9% vs 10%), anemia (7% vs 8%), back pain (7% vs 10%), and bone pain (6% vs 7%).

Adverse effects due to increased mineralocorticoid levels secondary to CYP17 blockade were more common with abiraterone. Specific effects that were significantly higher with abiraterone than placebo included fluid retention and edema (31% vs 22%; p = 0.04) and hypokalemia (17% vs 8%; p < 0.001). Coadministration with a corticosteroid reduces corticotropin influence and the incidence and severity of these reactions. Cardiac events were more common with abiraterone (13% vs 11%; p = 0.14). The most common cardiac effects with abiraterone and placebo, respectively, were tachycardia (3% vs 2%) and atrial fibrillation (2% vs 1%). The incidence of liver function abnormalities was similar between abiraterone and placebo (10% vs 8%, respectively).

A bone scan flare has been described in a small group of patients who received abiraterone for advanced CRPC. Thirty-three patients received abiraterone plus prednisone in a Phase 2 trial. PSA was evaluated at baseline and monthly and bone scans were obtained at baseline and every 3 cycles. A bone scan flare was defined as disease progression as described in a radiologist’s report after 3 months of therapy in the face of a 50% or greater PSA decline, which then improved or remained stable 3 months later. Twenty-six patients (79%) achieved a 50% or greater PSA decline, 23 of whom were evaluable for a possible bone scan flare. Twelve of 23 patients (52%) had worse bone scans from baseline at 3 months. At 6 months, 4 of these 12 patients demonstrated improvement and 7 demonstrated stability. The overall incidence of bone scan flare was 48%, seen in 11 of 23 evaluable patients. One patient had a worse scan at 6 months despite a continued PSA decline.

Recommendations/Summary

Until recently the only treatment that demonstrated improved survival in patients with CRPC was docetaxel-based therapy. Several pivotal Phase 3 studies have changed that, adding 3 new agents to the list of therapies demonstrated to improve survival in these patients. A key question is, where within the treatment scheme do these drugs belong? Sipuleucel-T is indicated for men with asymptomatic or minimally symptomatic metastatic CRPC. As indicated, this agent may be used before or after chemotherapy. However, most of the patients in the sipuleucel-T trials had not received prior docetaxel-based therapy. Since it may take some time for the immune response to develop, patients with stable disease and a life expectancy of several months would be better candidates for treatment than patients with progressive disease. Activity among patients with visceral disease, a negative prognostic factor, is unknown, as patients with visceral disease were excluded from the clinical trials. Additional exclusion factors include patients who are not able to adhere to 3 leukapheresis appointments as well as those for whom leukapheresis would be contraindicated, such as those with active infections or unstable cardiac or pulmonary conditions. Patients receiving concurrent immunosuppressive therapy should also be excluded. The NCCN classifies sipuleucel-T as a category 1 recommendation for management of asymptomatic or minimally symptomatic patients with prostate cancer with ECOG performance status 0-1. The NCCN does not recommend sipuleucel-T for patients with hepatic metastases or a life expectancy of <6 months.

Cabazitaxel and abiraterone are both indicated for the management of CRPC patients who have received prior docetaxel-based therapy. At the present time there are no data to guide selection between these 2 drugs. The optimal sequence of these agents is unknown. There are no completed clinical trials comparing abiraterone to cabazitaxel in patients with CRPC and there are no biomarkers that predict which agent might be the better first choice after docetaxel. At present cabazitaxel may have an advantage in patients with visceral disease, as 25% of patients in the TROPIC trial had visceral disease.

A major factor that may influence choice of therapy is the adverse effect potential of each drug. Administration of abiraterone before cabazitaxel may reduce toxicity that may accompany prolonged taxane use and could possibly delay emergence of taxane-resistant disease. Patients who tolerated docetaxel well might be better candidates to receive cabazitaxel next. Conversely, patients who did not tolerate docetaxel would be better candidates for abiraterone. Abiraterone has not been studied in patients with severe hepatic dysfunction and should not be used in these patients. Cabazitaxel has been associated with significant neutropenia and may not be a good choice in a patient with
a history of severe chemotherapy-associated neutropenia and should be used cautiously in the elderly. The higher incidence of cardiac deaths with cabazitaxel versus mitoxantrone suggests caution in use in patients with cardiac disease. Cabazitaxel and abiraterone have NCCN category 1 recommendations for management of metastatic castration-resistant and docetaxel-resistant prostate cancer. Additional studies should help to determine the proper sequence of these agents in patients with CRPC. Questions yet to be answered include the role of administration of abiraterone before docetaxel, the activity of cabazitaxel versus docetaxel as first-line chemotherapy in CRPC, and if there is a role for concurrent administration of abiraterone and chemotherapy. At present the NCCN recognizes that some patients with metastatic CRPC may not be candidates for docetaxel therapy. Abiraterone may be appropriate for use in these patients (category 2B recommendation).

The advent of 3 new agents has significantly increased the options available for management of patients with CRPC. Only time and experience will determine the optimum timing and sequence of all treatments available for this advanced disease.

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References

Después de la castración, la selección de nuevos agentes para el manejo de los pacientes con CRPC avanzados ha aumentado. En el presente artículo se revisaron los aspectos clínicos y farmacológicos de los nuevos agentes aprobados por la FDA para el tratamiento del cáncer de próstata resistente a la castración, con el objetivo de establecer su papel en el manejo de los pacientes.

**Fuentes de datos:**

**Selección de estudios y extracción de datos:**
Artículos en inglés y usando humanos identificados de la fuentes de datos fueron evaluados.

**Síntesis de datos:**
Las opciones para pacientes con CRPC han sido limitadas, con poco que ofrecer a los pacientes que han fallado o no toleran la terapia basada en docetaxel. Tres fármacos nuevos, con mecanismos de acción muy diferentes, han cambiado y seguirán cambiando el paradigma de tratamiento de estos pacientes. Cada agente ha demostrado un impacto en la supervivencia de los pacientes. Sipuleucel-T, la primera inmunoterapia aprobada para el tratamiento de esta enfermedad, mejoró la supervivencia mediana por 4.1 meses y redujo el riesgo de muerte por 22% en un ensayo controlado por placebo de pacientes asintomáticos y puede ser administrado antes de la terapia basada en docetaxel. Cabazitaxel, un agente quimioterapéutico taxano, mejoró la supervivencia mediana por 2.4 meses y redujo el riesgo de muerte por 30% en un ensayo de fase 3 de pacientes que habían progresado durante o después de la terapia basada en docetaxel. Acetato de abiraterone, una terapia hormonal, mejoró la supervivencia mediana por 3.9 meses y redujo el riesgo de muerte por 35% en pacientes en relapso durante o después de la terapia basada en docetaxel.

**Conclusiones:**
La llegada de estos agentes nuevos para el manejo de CRPC avanzado ha aumentado la selección para pacientes cuyas opciones eran limitadas. Experiencias adicionales determinan la secuencia óptima de estos agentes, sus roles en la terapia combinada y su actividad en pacientes con enfermedad temprana.

**Traducido por Sonia I Lugo**

**Resumen**

**Objetivo:** Evaluar las opciones probantes portando el uso de tres nuevos agentes recientemente aprobados por la agencia americana de regulación, para el tratamiento del cáncer de la próstata resistente a la castración.

**Fuentes de información:**
Una revisión de la literatura ha sido efectuada en la banca de las bases de datos de MEDLINE (1977 y los meses finales de junio de 2012) y en las bases de datos científicas presentadas al Congreso de la American Society of Clinical Oncology (2000 y 2012) en los cuales se han presentado estudios clínicos de pacientes con cáncer de la próstata.

**Selección de información y extracción de datos:**
Los artículos en inglés han sido identificados y revisados.

**Síntesis de datos:**
El uso de los nuevos agentes ha demostrado un impacto en la supervivencia de los pacientes. Sipuleucel-T, una inmunoterapia celular autóloga activa, prolongó el tiempo medio de supervivencia de 4.1 meses. Cabazitaxel, un agente quimioterapéutico taxano, prolongó el tiempo medio de supervivencia de 2.4 meses. Abiraterone, un agente hormonal, prolongó el tiempo medio de supervivencia de 3.9 meses.

**Conclusiones:**
La comercialización de nuevos agentes para el tratamiento del cáncer de la próstata resistente a la castración permite un beneficio mayor por los mecanismos de acción diferentes. Estos nuevos agentes podrían ser usados en el manejo inicial de la enfermedad o en el tratamiento de pacientes refractarios.