New Options for the Management of Castration-Resistant Prostate Cancer: A Case Perspective

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Key Words

Prostate cancer, castration-resistant, hormone-refractory, chemotherapy, hormone therapy, abiraterone acetate, docetaxel, immunotherapy, sipuleucel-T, cabazitaxel

Abstract

Prostate cancer is the leading cause of cancer and second leading cause of death among men. Management of localized disease is fairly straight-forward, but treatment for locally advanced or metastatic disease is much less so. Androgen-deprivation therapy serves as the foundation of treatment for patients with locally advanced or metastatic disease. Although most patients with prostate cancer show a response to medical or surgical castration, many eventually experience a hormone-refractory, incurable state. Until recently, therapeutic options for CRPC have been limited and focused on systemic chemotherapeutic options. Unfortunately, however, this provides a minimal increase in overall survival, at the cost of significant additional toxicities. Therefore, much research has gone into developing other suitable therapies with potentially less toxicity. This article uses a case study approach to discuss new options for the treatment of castration-resistant prostate cancer. (*JNCCN* 2011;9[Suppl 3]:S13–S24)

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Educational Objectives:

Following this program, participants should be able to:

- Describe a case of castration-resistant, metastatic prostate cancer (CRPC)
- Discuss historic and recent evidence related to the treatment of CRPC.
- Describe the process for procuring, handling, and administering sipuleucel-T to a patient.
- Discuss pertinent literature support and appropriate use for cabazitaxel for CRPC.
- Design a treatment plan for a patient with CRPC, including subjective and objective monitoring parameters for efficacy and toxicity.

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Case Report

A 68-year-old man presented to an oncologist for a second opinion, with the chief complaint of rapidly rising prostate-specific antigen (PSA) levels and significant upper back and neck pain. The patient's prostate cancer history dated back to an initial diagnosis in 2007 after he complained to his primary care doctor that he had been experiencing difficulty urinating over the past 7 months. He underwent a radical laparoscopic prostatectomy in 2007 and was diagnosed with pT3b, N0 prostate adenocarcinoma with a Gleason score of 7 (3 + 4). His PSA was 0 ng/mL after surgery, and he was followed up closely by his urologist.

In early 2009, the patient's PSA increased suddenly to 15.4 ng/mL, and he started complaining of back pain. He underwent a bone scan, which showed bone metastases. The patient was referred to a local oncologist to treat the metastatic disease. He began treatment with leuprolide injections every 3 months; bicalutamide, 50 mg daily; and zoledronic acid monthly. After several months of leuprolide and bicalutamide, his PSA plateaued at 11.6 ng/mL but then sharply increased to 35 ng/mL in February 2010. Imaging showed increased bony metastases and new lymph node involvement.

The patient was then started on docetaxel, 75 mg/m^2, with prednisone every 3 weeks and continued therapy with zoledronic acid. He received 8 uncomplicated cycles of docetaxel. He experienced an initial slight drop in PSA to 31 ng/mL, but it subsequently increased again. His PSA was 67 ng/mL in July 2010, at which point he presented for a second opinion regarding treatment for progressive disease.

The patient complained of significant upper back and neck pain, and MRIs of the spine showed spinal cord compression at T10-11. Kyphoplasty was performed on July 26, 2010. At that time, the patient's ECOG performance status was 2 because he was ambulatory but could not perform any light or work-related activities. He was scheduled to return to the clinic August 11 to discuss further treatment plans.

History and Physical Examination

Medical History: The patient's medical history included hypercholesterolemia, hyperlipidemia, hypertension, and benign prostatic hyperplasia.

Surgical History: The patient's surgical history included tonsillectomy at 15 years of age and prostatectomy in 2007.

Social History: The patient's social history included tobacco use for 6 years in high school and college (he quit in 1965) and social alcohol use.

Family History: His father was diagnosed with prostate cancer at 71 years of age but died of myocardial infarction at 74 years. The patient's family history was otherwise noncontributory.

Allergies: He had no known drug allergies.

Medications: The patient was taking atorvastatin, 20 mg, by mouth at bedtime; lisinopril, 10 mg, by mouth daily; tamsulosin, 0.4 mg, by mouth at bedtime; oxycodone, 5 to 10 mg, by mouth every 4 hours as needed for pain; senna/docusate, 1 or 2 tablets, by mouth twice daily as needed for constipation; and lidocaine as a 5% patch applied to the upper back daily for 16 hours on and 8 hours off.

Review of Systems: Review of systems was negative.

Physical Examination: The patient's height was 174 cm and weight was 78 kg. Vital signs were stable, with an otherwise negative physical examination, except for some residual pain after kyphoplasty (rated 3 of 10). The pain responded well to oxycodone as needed. Laboratory values are shown in Table 1.

Patient Assessment and Plan

The patient is a 68-year-old man with metastatic castration-resistant prostate cancer (CRPC) and an ECOG performance status of 2. The patient is in otherwise good general health and presents with disease progression after 6 cycles of docetaxel chemotherapy. The patient's liver and kidney functions and latest CBC counts are within normal limits.

Treatment-related questions include:

- How would you proceed in treating this patient?
- What are the most appropriate treatment options available for him at this stage in his disease?

Castration-Resistant Prostate Cancer

Prostate cancer is the leading cause of cancer death and second leading cause of death overall among men. Experts estimate that 1 of 6 men will be diagnosed with prostate cancer and that 1 of 36 will die of this disease.[1] Management of localized disease is fairly straightforward, and definitive primary treatment with surgery and radiation is often curative for early-stage prostate cancer. Unfortunately, treatment of locally advanced or metastatic disease is more complex, with androgen-deprivation therapy serving as the foundation of treatment. Although most patients with prostate cancer show a response to medical or surgical castration, many eventually experience a hormone-refractory, incurable state.[2,3]

The terminology to describe such hormone-refractory disease has included many different terms,

Table 1 Case Patient Laboratory Values

Date	WBC (x 10^3 cells/mm^3)	Hgb (g/dL)	Plts (x 10^3/μL)	ANC (cells/mm^3)	SCr (mg/dL)	Total Bilirubin (mg/dL)	PSA (ng/mL)
2/12/2009	5.32	14.1	276		1.1	0.4	15.4
5/24/2009	4.67	13.7	264		1.2	< 0.3	12.7
8/16/2009	4.52	13.4	262		1.2	< 0.3	11.6
11/14/2009	4.78	13.2	259		1.2	< 0.3	13.4
2/18/2010	5.68	13.1	263		1.2	< 0.3	35
3/10/2010	7.23	12.6	198	4800	1.2	0.4	33
3/31/2010	9.54	12.1	212	7400	1.3	0.4	28
4/21/2010	4.56	11.2	169	3200	1.2	0.4	26
5/12/2010	5.27	11.1	174	3600	1.4	0.4	31
6/2/2010	12.63	10.7	163	7800	1.5	0.5	37
6/23/2010	6.98	10.8	194	4900	1.6	< 0.3	42
7/15/2010	6.73	10.6	204	4700	1.5	< 0.3	67
8/11/2010	5.25	11.2	233	4100	1.4	0.4	88

Abbreviations: ANC, absolute neutrophil count; Hgb, hemoglobin; Plts, platelets; PSA, prostate-specific antigen; SCr, serum creatinine; WBC, white blood count.

such as androgen-independent prostate cancer (AIPC), androgen-refractory or hormone-refractory prostate cancer, and, most recently, CRPC.[3] The Prostate Cancer Clinical Trials Working Group 2 discouraged use of the term *hormone-refractory disease* because it is now known that the hormone-refractory state is not an absolute.[3,4] Prostate cell growth is primarily regulated by androgens, and when these are ablated or withdrawn, apoptosis occurs in some of the cells while others arrest in the G1 phase of the cell cycle. Clinical progression occurs when cells that were primarily resistant to androgen ablation start to proliferate again or when cells, after some period of growth arrest, resume proliferation as a result of adaptation to the low-androgen environment.[4] Importantly, clinical progression and proliferation of androgen-independent prostate cancer cells, despite androgen deprivation, is most likely driven by an active androgen receptor signaling pathway.[4–6] Therefore, the most relevant clinical classification for this state is CRPC, because it encompasses the mechanisms for receptor activation.[3,4]

Until recently, therapeutic options for CRPC have been limited and focused on systemic chemotherapeutic options. Historically, systemic therapy for this particular setting was palliative in nature, using chemotherapy with mitoxantrone and prednisone.[7] A randomized phase III trial conducted in 1996 first defined a palliative role for mitoxantrone and prednisone over prednisone alone; however, no increase in overall survival was seen with this combination.[2,7] Later, docetaxel regimens were shown to increase survival and quality of life compared with mitoxantrone and prednisone.[8] Docetaxel regimens, both weekly and every 3 weeks, showed superior response rates compared with mitoxantrone and prednisone, and, for the first time, also showed a survival benefit.[2,8]

Based on these data, docetaxel regimens became the preferred first-line therapy for CRPC. Unfortunately, only half of the patients treated with docetaxel will show a PSA response, and the average improvement in overall survival is a disappointing 1 to 3 months, at the cost of significant additional toxicities.[9] Therefore, much research has gone into developing other suitable therapies with potentially less toxicity.

Hormone Therapies

Archaically termed hormone-refractory (now CRPC) disease can respond to other hormone manipulation therapies, such as aminoglutethimide, androgen-receptor antagonists, ketoconazole, adrenalectomy or hypophysectomy, and 5α-reductase inhibitors.[3] A study in the 1980s using aminoglutethimide suggested that the remaining androgenic drivers after surgical castration have extratesticular origins.[10] With limited therapeutic options in this setting, inhibitors of adrenal androgen synthesis, ketoconazole and aminoglutethimide, are often used as second-line hormonal treatment.[4,9] Unfortunately these medications are associated with toxicities and are not very effective.[9]

A new selective CYP17 inhibitor prodrug, abiraterone acetate, is being actively investigated for CRPC. It selectively inhibits 17α-hydroxylase and 17,20-desmolase, and has shown tolerability and efficacy in clinical trials. In clinical trials, abiraterone has shown marked decreases in serum testosterone and significant declines in PSA, as well as radiographic responses.[3,10–12] Results of a phase III clinical trial involving 1195 patients from 13 countries was presented at the October 2010 European Society for Medical Oncology (ESMO) Congress. This trial showed a 4-month longer median survival in patients with CRPC who received abiraterone plus prednisone compared with those treated with prednisone alone (14.8 vs. 10.9 months). These patients had all previously received chemotherapy, including docetaxel regimens. Abiraterone is a promising new agent for CRPC, even in heavily pretreated patients.[13] Other promising investigational therapies are shown in Table 2.

Other investigational trials using a wide variety of different agents with different mechanisms of action and targets are currently underway. Areas of research include vitamin D analogues; novel nontaxane microtubular-stabilizing agents (ixabepilone, patupilone, and sagopilone); orally available platinum salts (satraplatin and picoplatin); angiogenesis inhibitors (bevacizumab, aflibercept, thalidomide, and lenalidomide); tyrosine kinase inhibitors (ima-

Table 2 Promising Investigational Therapies for Castration-Resistant Prostate Cancer

Drug	Clinical Trial Status
Abiraterone	Phase I, II, III
Ipilumumab	Phase III
MDV-3100	Phase I, II, III
Dasatinib	Phase II, III

tinib, gefitinib, dasatinib, sunitinib, and lapatinib); endothelin receptor antagonists (atrasentan and zibotentan); and histone deacetylase inhibitors (vorinostat and phenylbutyrate) through effects on binding of heat shock protein 90 (Hsp90). Other agents under consideration include MDV 3100, a small-molecule androgen-receptor antagonist; antisense oligonucleotides such as OGX-011 (Custirsen); and receptor activator of nuclear factor-κB ligand inhibitors such as denosumab.[2,4,11,14]

Immunotherapy

One of the most promising areas of research is immunotherapy. Because prostate cancer is often considered a slow-growing tumor, vaccine treatments, which require time to activate the immune system, may be an interesting new approach to treating CRPC.[15] Immunotherapeutics may also offer a less-toxic alternative to chemotherapy for treating advanced cancer, with the possibility of a more durable response.[16] These vaccines use PSA, prostatic acid phosphatase (PAP), and prostate-specific membrane antigen to activate antigen-specific T cells to attack tumors. Some of the most promising areas for developing vaccines are antigen-loaded autologous and allogeneic whole-cell vaccines, dendritic cell vaccines, poxvirus-based vaccines, and granulocyte macrophage colony-stimulating factor (GM-CSF)-modified tumor cell vaccines.[2,16,17] Another area of study is antibody-based immunotherapies, such as CTL-associated antigen (CTLA)-4 targeted therapy. Tremelimumab and ipilimumab are humanized anti–CTLA-4 antibodies currently under investigation in many solid tumors, including prostate cancer.[16]

Immune-based therapies pose many challenges, particularly in designing clinical trials and determining end points. Biologics can require significant time (minimum 12 weeks) to promote an immune response, which can translate into an even longer period to demonstrate a clear benefit. This is in contrast to chemotherapy, for which potential benefit is often seen within weeks. Some researchers also suggest that patients involved in trials of biologic agents should continue on the study in the absence of symptomatic progression, and that researchers should exclude early progression in PSA in the absence of symptomatic progression to allow for late responses. This is also because PSA may not be a reliable measure of outcomes.

However, defining clear symptomatic progression can be difficult, and no validated gold standard exists for monitoring immune therapies. Ignoring a continually rising PSA and added risk of progression while waiting for an immune response can be difficult. Immunotherapy is also not likely to be the best option for patients with bulky or rapidly progressing disease. Finally, patients with prostate cancer typically have a preponderance of bone metastases; therefore, measuring a response using currently available imaging techniques can also be difficult.[16]

Despite these challenges, one of the many studied prostate cancer vaccines, sipuleucel-T (Provenge, Dendreon Corporation, Morris Plains, NJ), has emerged as an option for patients with CRPC. Sipuleucel-T is unique because although it is the first vaccine used to treat cancer, it does not prevent the start of disease, as do traditional vaccines.[18] Sipuleucel-T represents the first FDA approval of a novel class of agents called *autologous cellular immunotherapy*, or cancer vaccines. Because this differs dramatically from other types of currently available therapies, the next section focuses on the process of developing this personalized treatment and its mechanism of action. Furthermore, the logistical issues surrounding the preparation and administration of sipuleucel-T also greatly differ from those seen with standard chemotherapy, and this review also discusses appropriate preparation, administration, and monitoring of this therapy to minimize errors.

Sipuleucel-T

The FDA approved sipuleucel-T in early 2010 for the treatment of "asymptomatic or minimally symptomatic metastatic CRPC." Sipuleucel-T uses autologous peripheral blood mononuclear cells and antigen-presenting cells that have been primed to target PAP, an antigen expressed in most prostate cancer cells, causing an immune response.[19,20] Each dose of vaccine is individually manufactured by extracting immune cells through leukapheresis. These cells are then exposed to a minimum of 50 million autologous CD54+ cells activated with PAP–GM-CSF suspended in 250 mL of lactated Ringer's solution. The patient's personalized product is then returned and infused over 60 minutes. The approved treatment regimen consists of 3 doses given at approximately 2-week intervals. If a patient is unable to receive the regularly scheduled treatment, they must undergo an additional leukapheresis procedure.[21,22] The most common adverse events are chills, fatigue, fever, dyspnea, back pain, nausea, joint ache, and headache, most of which are mild and transient.[14,21,22] The most

serious adverse events reported were acute infusion reactions (3.5%), cerebrovascular events, and stroke (3.5% vs. 2.6% in control patients).[21,22]

Final results from 2 phase III clinical trials showed that sipuleucel-T increased median survival compared with placebo. In the phase III study of 512 patients, median overall survival was increased by 4.1 months in the treatment group. This change was statistically significant, translating into a 22.5% reduction in mortality risk. This is also the first immunotherapy product used in prostate cancer to produce a survival advantage. However, statistical significance was not reached in the primary end point of time to progression in either clinical trial.[17,19–21]

Treatment using sipuleucel-T involves many logistical concerns. First, patients and providers are required to complete an enrollment form. Second, each dose requires a leukapheresis procedure performed approximately 3 days before the infusion at a manufacturer-approved apheresis center. Unfortunately, not all centers that perform leukapheresis are approved by the manufacturer, including some NCI-designated cancer centers.

Another challenge, as with any newly approved medication, is receiving payment. Uncertain reimbursement, particularly from Medicare, has become a large issue. In daily practice, patients are undergoing screening, appropriate forms are signed, and necessary aphresis is set up, but the treatment for these patients is not being covered. Because of the affected patient population, most patients considered for sipuleucel-T therapy are Medicare beneficiaries. As a result of nonreimbursement issues, some institutions have had to make formulary decisions to suspend the use of sipuleucel-T until payment issues are resolved. Although necessary to ensure financial stability for the institutions affected, these payment issues unfortunately limit access to this treatment for a subset of patients who already have limited treatment options.

The Centers for Medicare & Medicaid Services (CMS) opened a National Coverage Analysis (NCA) to determine whether autologous cellular immunotherapy (e.g., sipuleucel-T for prostate cancer) is "reasonable and necessary."[22] Initially, concerns were raised that the analysis process would require as long as a year to complete and that, until that time, Medicare administrative contractors (MACs) would make individual decisions regarding coverage for sipuleucel-T. Unless there is a National Coverage Determination, MACs are free to make local coverage determinations. The NCA for sipuleucel-T does not restrict local MACs from covering the medication.[23,24]

CMS requested public comments on "the evidence regarding the effects of this treatment on health outcomes in patients with prostate cancer," with particular interest in clinical studies and scientific information. Public comments were taken for 30 calendar days starting June 30, 2010, when those statements were posted. A Medicare Evidence Development and Coverage Advisory Committee meeting was held November 17, 2010, and the proposed decision is due March 30, 2011 (as of publication).[22] Until CMS provides more information, however, institutions may still limit sipuleucel-T access and use because of concerns regarding unpredictable reimbursement.

To successfully receive payment for sipuleucel-T for appropriately selected patients, understanding the preparation and procedure for administration is extremely important. The vaccine cannot be infused until product release has been confirmed by the manufacturer. The product is released after safety testing for sterility is performed; however, the product is only given a 2-day incubation period to determine absence of microbial growth before release. Therefore, final 7-day incubation sterility results are not available at infusion. If results from the 7-day test are positive, the physician is notified and the manufacturer attempts to identify the microorganism.

Practitioners should be aware that the vaccine is not routinely tested for transmissible infectious diseases; caution should be taken during handling. The insulated product is shipped directly to the provider, with patient-specific labels on the outer box to verify the product. The manufacturer recommends not removing the product from the insulated container until the infusion is ready to be administered. Each infusion has an expiration date and time. After the agent is removed from the container, it is only stable for 3 hours at room temperature. It should not be returned to the shipping container.

Before the infusion is administered, the patient is premedicated with acetaminophen and an antihistamine to prevent infusion-related reactions. Then the product can be removed from the insulated container and inspected. The bag will be slightly cloudy with a cream-to-pink color, and it must be

assessed for signs of leakage. The bag should be gently mixed, re-suspended, and inspected for clumps and clots. Small clumps are normally dispersed with gentle manual mixing. If the bag is leaking or clumps remain, the product should not be administered. The final step before administering the vaccine is to verify that the patient's identifiers match the cell product disposition form and the vaccine infusion bag.

Patients need venous access, and the final product should not be filtered. For patients who develop an acute infusion reaction, the infusion rate may be decreased or stopped, depending on severity. Patients should be observed for 30 minutes after each 60-minute infusion.[25] Figure 1 presents a process summary for acquiring and administering sipuleucel-T.

Sipuleucel-T was recently added to the list of treatment options for patients with metastatic, CRPC in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer as a category 1 recommendation (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). Its use is limited to patients who are asymptomatic or minimally symptomatic with an ECOG performance status of 0-1, without visceral disease, and with a life expectancy of more than 6 months.[26]

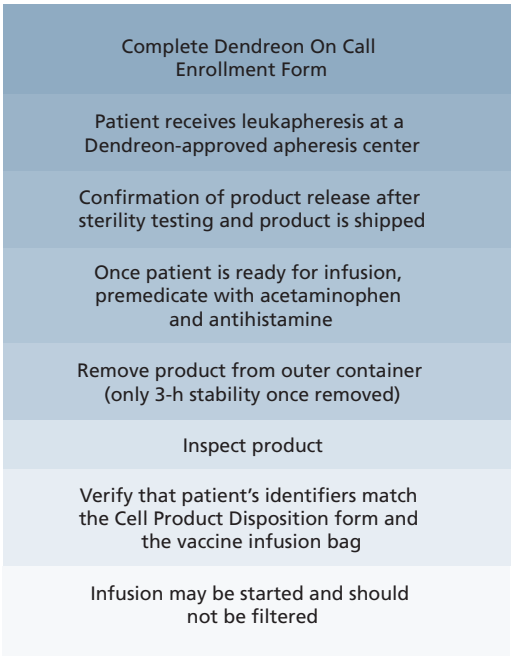

Figure 1 Summary flowchart of the process for acquiring and administering sipuleucel-T.

Other Treatment Options

Another new option, particularly for patients for whom treatment with docetaxel failed, is cabazitaxel (Jevtana, sanofi-aventis, U.S., Bridgewater, NJ). Cabazitaxel provided a significant survival benefit in second-line metastatic CRPC and was given priority review by the FDA.[27] It is currently indicated for concomitant use with prednisone in patients with CRPC who were previously treated with docetaxel, and was also added to the NCCN Guidelines for Prostate Cancer as a category 1 recommendation (available at www.NCCN.org).[26,28]

Cabazitaxel is part of the taxane class of chemotherapeutics and exerts its effects by stabilizing microtubules, thereby inhibiting their disassembly. Its approval was based on a single phase III, randomized, open-labeled, international, multicenter study involving 755 men (the TROPIC trial). The primary end point of the trial was to evaluate the efficacy and safety of cabazitaxel in patients with CRPC previously treated with docetaxel. Patients were randomized to prednisone, 10 mg/d, plus mitoxantrone, 12 mg/m^2, or cabazitaxel, 25 mg/m^2, every 21 days. After a median follow-up of 12.8 months, patients treated with cabazitaxel had a statistically significantly longer overall survival (15.1 vs. 12.7 months), resulting in a 30% reduced risk of death, in addition to statistically significantly longer progression-free survival (2.8 vs. 1.4 months) and response rates to tumor assessments.[28,29]

Cabazitaxel is well tolerated overall. The most commonly seen grade 3 or 4 adverse effects are neutropenia, febrile neutropenia, anemia, leukopenia, diarrhea, fatigue, and asthenia. The approximate neutrophil nadir is 12 days, and cabazitaxel carries a black box warning against giving the drug to patients with neutrophil counts of 1500 cells/mm^3 or lower. In addition, primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is recommended in high-risk patients. A dose reduction to 20 mg/m^2 may be considered for patients who experience prolonged grade 3 or higher neutropenia despite G-CSF treatment; febrile neutropenia; grade 3 or higher diarrhea; or persistent diarrhea despite appropriate treatment.

Cabazitaxel carries 2 additional black box warnings: it has been associated with severe hypersensitivity reactions and is contraindicated in patients with hypersensitivity to drugs formulated with poly-

sorbate 80. The manufacturer recommends that patients receive premedication with diphenhydramine, dexamethasone, and ranitidine (or equivalents) to reduce the incidence of hypersensitivity reactions, and if one occurs or is suspected, to slow the infusion rate. Other considerations for this medication are that it is a mild irritant like other taxanes, and that it is extensively metabolized by CYP3A4/5. Therefore, caution should be given when it is used with strong inhibitors or inducers of CYP3A4/5. Furthermore, it should not be given to patients with hepatic impairment (total bilirubin upper limit of normal or higher, or AST or ALT ≥ 1.5 times upper limit of normal).

As with other taxanes, PVC-free equipment should be used for preparation and administration. It requires a 2-step dilution process: the initial step should use the supplied diluent to achieve a concentration of 10 mg/mL, and then a further 250 mL of either 0.9% sodium chloride or 5% dextrose should be mixed in, resulting in a final solution not to exceed 0.26 mg/mL. Larger doses would require the use of a larger final volume. During dilution, the needle should be directed onto the inside wall of the vial and the solution injected slowly to prevent foaming. The solution should be gently mixed with repeated inversions of the vial for at least 45 seconds; the vial should not be shaken. The resultant solution is stable for 8 hours at room temperature and 24 hours when refrigerated. It is supersaturated; therefore, inspection for crystallization before administration is necessary. The final product also requires filtration with a 0.22 micron filter and should be infused over 1 hour.[28]

There may be some initial payment issues with cabazitaxel, as with any newly approved medication, until C- and J-codes are given for Medicare reimbursement. In the meantime, some patients may be able to use a Patient Assistance Program (e.g., sanofi-aventis PACT+ program), if they qualify. The PACT+ program offers reimbursement support services and other services to eligible patients in financial need.[30] Table 3 provides some clinical considerations for cabazitaxel.

The NCCN Guidelines for Prostate Cancer bases treatment recommendations for CRPC on metastasis status and symptomatology (available at www.NCCN.org). Patients treated with primary androgen-deprivation therapy who have confirmed relapse should undergo tests to confirm castrate levels of testosterone. Patients without distant metastases should be evaluated for a clinical trial; an appropriate second option is observation. Anti-androgen withdrawal should be used for patients with complete androgen blockade. Another valid option, although not currently proven to prolong overall survival, is secondary hormonal therapy with an anti-androgen, ketoconazole with or without steroids, or estrogen/progesterone.

Patients with distant metastases may undergo chemotherapy, immunotherapy, or secondary hormonal therapy. Those with bony metastases may receive bisphosphonates or radionuclide therapy using samarium or strontium. Zoledronic acid is recommended every 3 to 4 weeks to prevent skeletal complications in patients with bone metastases. A common first-line chemotherapy regimen is 3-week docetaxel and steroids, keeping in mind that a PSA rise alone does not constitute docetaxel failure. Sipuleucel-T is a valid option for patients on androgen-deprivation therapy who develop metastatic disease but have no visceral disease,

Table 3 Clinical Considerations for Cabazitaxel

- Contraindicated with neutrophil counts ≤ 1500 cells/mm^3
- Primary prophylaxis with granulocyte colony-stimulating factor recommended for patients at high risk
- Premedicate with diphenhydramine, dexamethasone, and ranitidine (or equivalents) to prevent hypersensitivity reactions
- Contraindicated in patients with polysorbate 80 hypersensitivity
- Extensively metabolized by CYP3A4/5; monitor for drug interactions
- Contraindicated in patients with hepatic impairment (total bilirubin ≥ ULN, or AST/ALT ≥ 1.5 x ULN)
- Use non-PVC containing infusion sets and containers
- In-line filtration with 0.22 micron filter required
- Stable for 8 hours at room temperature; 24 hours if refrigerated
- A patient assistance program is available (1-800-996-6626)

Data from Jetvana (cabazitaxel) Package Insert.[28]
Abbreviation: ULN, upper limit of normal.

minimal to no symptoms, a life expectancy longer than 6 months, and good performance status (ECOG 0-1).

Assessing for treatment response may prove difficult because the typical markers used, such as a decline in PSA and improvement in bone or CT scans, may not be seen in this population. For patients with symptomatic bone metastases, bone pain, or impending fractures, glucocorticoids and external-beam radiation are recommended for palliation. When using samarium or strontium with systemic radiotherapy, it is important to remember the effects on bone marrow, because future chemotherapy may be affected.

Chemotherapy with mitoxantrone and prednisone is another palliative option for symptomatic bone metastases; however, survival impact after first-line docetaxel has not been elucidated. Although no consensus exists on the exact treatment of patients for whom first-line docetaxel therapy has failed, valid options include a clinical trial, other chemotherapy regimens using cabazitaxel or mitoxantrone, and best supportive care. Sipuleucel-T may also be an option after more information is obtained regarding its use in this setting.[26] Table 4 shows a summary interpretation of the NCCN Guidelines for CRPC (available at www.NCCN.org).

Case Update: Assessment and Plan

The patient was a 68-year-old man with metastatic CRPC and an ECOG performance status of 2. He was in good general health aside from the cancer. He presented with disease progression after 6 cycles of docetaxel chemotherapy. The patient's liver and kidney functions and the latest CBC results were within normal limits.

How Should This Patient Be Treated?

The patient had symptomatic disease with an ECOG performance status of 2 and therefore did not meet criteria to receive sipuleucel-T according the NCCN Guidelines for Prostate Cancer (available at www.NCCN.org). His cancer was already deemed to be castration-resistant, and first-line chemotherapy using docetaxel failed. The most appropriate choice for this symptomatic patient, given good baseline laboratory values that included kidney and liver function, is second-line chemotherapy or a clinical trial. Because of his significant bone metastases, the patient should also continue zoledronic acid as long as renal function remains stable and his creatinine clearance rate is greater than 30 mL/min.

The most appropriate treatment options available for him at this stage in his disease are:

- cabazitaxel + prednisone
- mitoxantrone + prednisone
- clinical trial

Toxicities and Other Considerations

In this case, as when considering most chemotherapy treatments, pretreatment assessment of liver and kidney function are needed. In addition, a CBC count

Table 4 Summary of NCCN Guidelines for CRPC[26]*

Confirm relapse in patients treated with primary androgen-deprivation therapy with testosterone level

If without distant metastases, evaluate for clinical trial or observation:

- Anti-androgen withdrawal may be considered for those on complete androgen blockade
- Secondary androgen-deprivation therapy (e.g., ketoconazole with or without steroids) may be considered

Options for positive distant metastases:

- Bisphosphonates: zoledronic acid recommended every 3 to 4 weeks to prevent skeletal complications
- Palliative radiation therapy or radionuclide therapy (with samarium or strontium) for symptomatic bone disease
- Secondary androgen-deprivation therapy (e.g., ketoconazole with or without steroids) may be considered
- Chemotherapy:
  - Docetaxel + steroids every 3 weeks (first-line)
  - Mitoxantrone + steroids (first or second-line)
  - Cabazitaxel + steroids (second-line)
  - Immunotherapy: sipuleucel-T if no visceral disease, minimal to no symptoms, life expectancy greater than 6 months, and ECOG performance status of 0 to 1

*To view the most recent version of the NCCN Guidelines for Prostate Cancer, visit the NCCN Web site at www.NCCN.org.

with differential should be performed to determine if the patient is eligible to receive the treatment.

In this case, the patient did have some baseline renal insufficiency, with an estimated creatinine clearance of 56 mL/min. Both mitoxantrone and cabazitaxel are metabolized in the liver; therefore, the patient would be eligible to receive either of these medications because his baseline liver function tests were normal. However, his renal insufficiency could be problematic with certain clinical trial medications. Therefore, if the patient was interested in entering a clinical trial, he would need to undergo specific assessments based on each protocol's inclusion and exclusion criteria.

The patient had also undergone 6 cycles of docetaxel therapy. Therefore, his baseline CBC count with differential was also important. Although it is not necessary when using mitoxantrone, primary prophylaxis with WBC growth factor support should be considered for treatment with cabazitaxel.

Because of potential toxicities, additional monitoring is also necessary:

- Baseline cardiac function testing is necessary for all patients for whom mitoxantrone is considered. In this case, the patient had hypercholesterolemia, hyperlipidemia, and hypertension, but none of these conditions would preclude him from receiving mitoxantrone because he did not otherwise have a significant cardiac history.
- Line status is an important pretreatment consideration because mitoxantrone is considered a vesicant and cabazitaxel is considered a mild irritant. For patients receiving mitoxantrone, clinicians should consider using a central line to decrease risk of extravasation. A central line could also benefit the patient by allowing blood to be drawn more easily for other pretreatment laboratory tests.
- Patients receiving chemotherapy should undergo continued PSA monitoring and imaging scans after every 2 to 3 cycles to assess treatment response.
- Treatment with zoledronic acid and monitoring for osteolytic bone metastases should be continued, with dosing based on kidney function.
- Patients should undergo assessment of pain and performance status after kyphoplasty to ensure adequate pain control and continued ability to walk without difficulty.
- Bowel function should be monitored closely, because patients taking opioids often need a prophylactic bowel regimen. Clinicians should also consider that cabazitaxel can be associated with significant diarrhea.
- Patients must be monitored closely for drug interactions. In this case, the patient was not taking any medications that would interact specifically with cabazitaxel. However, it is important to remember that cabazitaxel is extensively metabolized by CYP3A4/5, and caution should be taken when it is used with strong inhibitors or inducers.

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Post-test

New Options for the Management of Castration Resistant Prostate Cancer: Self-Assessment Questions

1. What is the most appropriate terminology for prostate cancer that is considered hormone-refractory?
   a. Hormone refractory prostate cancer (HRPC)
   b. Androgen-independent prostate cancer (AIPC)
   c. Castration-resistant prostate cancer (CRPC)
   d. None of the above
   e. All of the above

2. Which of the following chemotherapy regimens improved survival as the first-line treatment of CRPC?
   a. Mitoxantrone + Prednisone
   b. Docetaxel + Prednisone
   c. Cabazitaxel
   d. Carboplatin + Paclitaxel
   e. A & B

3. Which hormonal therapy has the most promise for treatment of CRPC patients, even if heavily pretreated?
   a. Aminoglutethimide
   b. Ketoconazole
   c. Abiraterone
   d. Hydrocortisone
   e. None of the above

4. Which of the following immune-based therapies are being investigated for use in CRPC?
   a. Sipuleucel-T vaccine
   b. Ipilumumab
   c. Dendritic cell vaccines
   d. All of the above
   e. None of the above

5. Sipuleucel-T is FDA approved for asymptomatic or minimally symptomatic metastatic CRPC patients. Which of the following is true regarding results of the phase III trials that aided its FDA approval?
   a. It is the first immunotherapy product used in prostate cancer patients to product a survival advantage.
   b. The primary endpoint of time to progression was statistically significant in favor of Sipuleucel-T
   c. The median overall survival of 4.1 months seen with Sipuleucel-T was statistically significant over placebo
   d. A & C
   e. All of the above

6. Cabazitaxel is FDA approved for:
   a. Concomitant use with prednisone
   b. Patients with CRPC who were previously treated with docetaxel
   c. First-line treatment of CRPC
   d. A & B
   e. A & C

7. Cabazitaxel has a black box warning for the following:
   a. Treatment with neutrophil counts ≤ 1500 cells/mm^3
   b. Severe hypersensitivity reactions
   c. Contraindicated in patients with hypersensitivity to drugs formulated with polysorbate 80
   d. All of the above
   e. A & B only

8. Which of the following is true regarding cabazitaxel?
   a. Requires non-PVC containing equipment for preparation and administration
   b. Does NOT need to be filtered
   c. May be used in patients with a total bilirubin up to 5
   d. Is contraindicated in patients with a CrCl less than 50 mL/min
   e. All of the above

9. Which of the following is true regarding zoledronic acid use in prostate cancer?
   a. Should not be used in patients with CrCl less than 30mL/min
   b. Is recommended every 3 to 4 weeks to prevent skeletal complications
   c. Should not be used in patients with total bilirubin greater than 5
   d. None of the above
   e. A & B only

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