Navigating Treatment of Metastatic Castration-Resistant Prostate Cancer: Nursing Perspectives

Frank dela Rama, RN, MS, AOCNS®, and Caroline Pratz, CRNP-AC, MSN

**Background:** Treatment of metastatic castration-resistant prostate cancer (mCRPC) has evolved rapidly. In particular, five new treatments that extend survival in mCRPC have been approved since 2010, including the chemotherapy cabazitaxel (Jevtana®), hormonal agents abiraterone (Zytiga®) and enzalutamide (Xtandi®), vaccine sipuleucel-T (Provenge®), and radiopharmaceutical radium-223 (Xofigo®); all have different indications and toxicity profiles.

**Objectives:** This review discusses treatment advances in mCRPC, including considerations for side-effect management and treatment sequencing. Studies relating to quality of care in prostate cancer are also discussed.

**Methods:** Nonsystematic searches were performed on published manuscripts and abstracts from major oncology or urology congresses, focusing on practical characteristics of the previously mentioned new treatments that extend survival in mCRPC, as well as studies relating to quality of care and the role of nurses in prostate cancer management.

**Findings:** To ensure that patients derive optimal clinical benefit, assessing overall health and proactively managing expected side effects are essential. Treatment sequencing in mCRPC is an important consideration, but clinical data in this area are limited. Despite medical advances in mCRPC, studies have identified other aspects of care in which improvement is needed. Nurses can make major contributions to addressing supportive care needs, which has been shown to improve patient care and outcomes in prostate cancer. Although patient navigation programs have improved coordination of care, inconsistent implementation among centers has been identified for prostate cancer. Greater use of outcome measures can help to identify unmet patient needs.

Prolongation of overall survival is a major goal of treatment in mCRPC. It is important to balance the potential of improvement in survival against the burden of toxicity from the treatment. One major focus of prevention and management of toxicities is to recognize early and manage potentially life-threatening situations.

**Conclusion:** This review demonstrates ongoing progress in the treatment of mCRPC and highlights areas where there is need for improvement. Future work should focus on addressing this gap in knowledge.

Key words: prostate cancer; treatment sequencing; nurse navigator; nurse; management

Digital Object Identifier: 10.1188/15.CJON.723-732

Prostate cancer is the most common cancer and second leading cause of cancer-related death in men in the United States (National Comprehensive Cancer Network [NCCN], 2015; Siegel, Ma, Zou, & Jemal, 2014). Since 2010, several therapies have received approval in the United States for the treatment of metastatic castration-resistant prostate cancer (mCRPC) (NCCN, 2015). The availability of multiple treatments, combined with the inherent heterogeneity of patients with mCRPC, complicates regimen selection and patient care. Therefore, the role of nurses and nurse navigators in prostate cancer management is becoming increasingly specialized to better coordinate care.

The current authors discuss the treatment paradigm for mCRPC, focusing on practical characteristics of newer therapies and treatment sequencing. Studies relating to quality of care and the role of nurses in prostate cancer management are discussed.

**Treatment Advances in Metastatic Prostate Cancer**

No curative options for metastatic prostate cancer exist, and choice of systemic therapy is based on patient hormonal status, specifically androgen levels. Tumor growth is heavily reliant on the androgen hormone, testosterone. Therefore, standard first-line treatment is androgen-deprivation therapy (ADT), via bilateral orchiectomy (surgical castration) or luteinizing hormone-
TABLE 1. Systemic Treatments Approved Since 2010 for Metastatic Prostate Cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Reference</th>
<th>Key Trial</th>
<th>Year of FDA Approval</th>
<th>Sequencing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone (Zytiga®)</td>
<td>de Bono et al., 2011</td>
<td>COU-AA-301</td>
<td>2011</td>
<td>Post-docetaxel</td>
</tr>
<tr>
<td></td>
<td>Ryan et al., 2013</td>
<td>COU-AA-302</td>
<td>2012</td>
<td>First-line</td>
</tr>
<tr>
<td>Cabazitaxel (Jevtana®)</td>
<td>de Bono et al., 2010</td>
<td>TROPIC</td>
<td>2010</td>
<td>Post-docetaxel</td>
</tr>
<tr>
<td>Denosumab (Xgeva®)</td>
<td>Fizazi et al., 2011</td>
<td>20050103</td>
<td>2010</td>
<td>Bone-metastatic disease</td>
</tr>
<tr>
<td>Enzalutamide (Xtandi®)</td>
<td>Beer et al., 2014</td>
<td>PREVAIL</td>
<td>2014</td>
<td>First-line</td>
</tr>
<tr>
<td></td>
<td>Scher et al., 2012</td>
<td>AFFIRM</td>
<td>2012</td>
<td>Post-docetaxel</td>
</tr>
<tr>
<td>Radium-223 (Xofigo®)</td>
<td>Parker et al., 2013</td>
<td>ALSYMPCA</td>
<td>2013</td>
<td>Bone-metastatic disease only (no known visceral metastases)</td>
</tr>
<tr>
<td>Sipuleucel-T (Provenge®)</td>
<td>Kantoff et al., 2010</td>
<td>IMPACT</td>
<td>2010</td>
<td>First-line</td>
</tr>
<tr>
<td>FDA—U.S. Food and Drug Administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

releasing hormone agonist/antagonist treatment (medicinal castration), which controls disease by lowering androgen levels. Follow-up includes physical examination, digital rectal examination, and prostate-specific antigen (PSA) testing every three to six months, with the frequency of monitoring determined by initial response to therapy. In most cases, tumors stop responding to ADT after two or three years, becoming “castration resistant,” whereby patients suffer progressive disease despite extremely low “castrate” levels of testosterone. Patients whose disease recurs should be assessed to confirm a castrate testosterone level (< 50 ng/dL) (Karantanos, Corn, & Thompson, 2013; NCCN, 2015; Peate, 2012).

Before 2004, treatments for mCRPC were limited. In 2004, the U.S. Food and Drug Administration (FDA) approved docetaxel (Taxotere®), a first-generation taxane chemotherapy, combined with prednisone for first-line treatment of mCRPC. This approval was based on two trials (TAX 327, SWOG 9916) that showed an overall survival (OS) benefit. Subsequently, docetaxel became the mainstay of treatment for mCRPC. However, about half of patients do not respond to docetaxel, and responding patients invariably develop resistance (Mukherji, Omlin, Pezaro, Shamseddine, & de Bono, 2014; NCCN, 2015; Petrylak et al., 2004; Tannock et al., 2004). Since 2010, additional therapies have shown survival benefit in phase III trials and have received FDA approval (see Table 1), including the chemotherapy cabazitaxel (Jevtana®), hormonal agents abiraterone (Zytiga®) and enzalutamide (Xtandi®), vaccine sipuleucel-T (Provenge®), and radiopharmaceutical radium-223 (Xofigo®). Associated adverse events (AEs) vary significantly, and symptom management must be tailored accordingly (see Figure 1 and Table 2).

Cabazitaxel

Cabazitaxel is a second-generation, semisynthetic taxane chemotherapy developed to overcome resistance to older taxanes (Bouchard, Semiond, Risse, & Vrignaud, 2013). Cabazitaxel is approved for patients with mCRPC who have progressed on prior docetaxel therapy based on TROPIC, a phase III, randomized, open-label study. In TROPIC, 755 patients with progression on docetaxel received cabazitaxel 25 mg/m² or mitoxantrone (Novantrone®) 12 mg/m² via IV every three weeks combined with prednisone 10 mg daily. Survival was longer with cabazitaxel than with mitoxantrone (median OS = 15.1 months versus 12.7 months, p < 0.0001), representing a 30% reduced risk of death with cabazitaxel. Median progression-free survival (PFS) was longer for cabazitaxel than for mitoxantrone (2.8 versus 1.4 months, p < 0.0001) (de Bono et al., 2010; Sanofi-Aventis U.S. LLC, 2014). Frequent toxicities associated with cabazitaxel include hematologic AEs, gastrointestinal AEs, and fatigue (Sanofi-Aventis U.S. LLC, 2014).

Abiraterone

Abiraterone acetate targets the hormone dependency of mCRPC (Attard et al., 2009) by inhibiting cytochrome p450 17 alpha-hydroxylase, an enzyme critical to androgen synthesis (Janssen Biotech, Inc., 2014). Abiraterone plus prednisone was initially approved for patients with mCRPC who had received docetaxel based on COU-AA-301, a phase III, randomized, double-blind study of oral abiraterone 1,000 mg plus prednisone 10 mg (n = 797) versus placebo plus prednisone (n = 398) in patients with previous docetaxel treatment (de Bono et al., 2011). OS was significantly longer for abiraterone than for placebo (median = 15.8 months versus 11.2 months, p < 0.0001); risk of death was reduced by 26% with abiraterone treatment (Fizazi et al., 2012). COU-AA-302 evaluated abiraterone 1,000 mg plus prednisone 10 mg (n = 546) versus placebo plus prednisone 10 mg (n = 542) in chemotherapy-naive patients with asymptomatic or mildly symptomatic disease. The study was unblinded following a positive interim analysis showing longer PFS with abiraterone (median = 16.5 months versus 8.3 months, p < 0.001). Additional follow-up confirmed longer OS with abiraterone (median unknown versus 27.2 months, p = 0.01) (Ryan et al., 2013). Based on these trials, the FDA approved abiraterone plus prednisone for treatment of mCRPC with or without prior chemotherapy (Janssen Biotech, Inc., 2014). Abiraterone may affect steroid synthesis, and associated AEs may include fluid retention, hypokalemia, and hypertension (Janssen Biotech, Inc., 2014).

Enzalutamide

Enzalutamide is an androgen-receptor inhibitor that blocks androgen binding (Astellas Pharma US, Inc., 2012). In a phase III, randomized, double-blind trial, patients with mCRPC who had received as many as two prior chemotherapy regimens...
Abiraterone Acetate (Zytiga®)

Notable AEs more frequently reported versus placebo (all-grade)
- Fatigue (39%–47%)
- Fluid retention or edema (28%–33%)
- Arthralgia (28%–30%)
- Constipation (23%–28%)
- Hot flush (22%)
- Diarrhea (20%–22%)
- Hypokalemia (17%–18%)
- Hypertension (11%–22%)

Most frequent grades 3/4 AEs
- Fatigue (9%)
- Elevated transaminases (4%–8%)
- Back pain (7%)
- Bone pain (6%)
- Cardiac disorders (5%–6%)

Other clinically significant AEs (all-grade)
- Cardiac disorders (16%–19%)
- Liver function test abnormalities (elevated transaminases; 11%–12%)

Most frequent grades 3/4 AEs in the real-world setting (early-access and/or compassionate use programs)
- Hepatotoxicity (8%)
- Hypertension (4%)
- Cardiac disorders (2%)
- Osteoporosis (1%)
- Hypokalemia (1%)
- Fluid retention or edema (1%)

Cabazitaxel (Jevtana®)

Most frequent AEs (all-grade)
- Anemia (97%)
- Leukopenia (96%)
- Neutropenia (94%)
- Thrombocytopenia (47%)
- Diarrhea (47%)
- Fatigue (37%)
- Nausea (34%)
- Vomiting (23%)

Most frequent grades 3/4 AEs
- Neutropenia (82%)
- Leukopenia (68%)
- Anemia (11%)
- Febrile neutropenia (8%)
- Diarrhea (6%)

Other clinically significant AEs (all-grade)
- Peripheral neuropathy (14%)
- Renal failure (1%)

Most frequent grades 3/4 AEs in the real-world setting (early-access and/or compassionate use programs)
- Neutropenia (18%)
- Febrile neutropenia (7%)

Enzalutamide (Xtandi®)

Notable AEs more frequently reported versus placebo (all-grade)
- Fatigue (34%–36%)
- Back pain (27%)
- Arthralgia (20%)
- Constipation (22%)
- Diarrhea (16%–21%)
- Hot flashes (18%–20%)
- Musculoskeletal pain (14%)
- Hypertension (7%–13%)
- Headache (10%–12%)

Most frequent grades 3/4 AEs
- Hypertension (7%)
- Fatigue (2%–6%)
- Back pain (3%)
- Cardiac events (1%–3%)

Other clinically significant AEs (all-grade)
- Seizure (< 1%)

Most frequent all-grade AEs in the real-world setting (early-access and/or compassionate use programs)*
- Fatigue (39%)
- Nausea (23%)
- Anorexia (15%)
- Anemia (12%)
- Peripheral edema (11%)
- Back pain (10%)
- Vomiting (10%)
- Arthralgia (10%)

Sipuleucel-T (Provenge®)

Notable AEs more frequently reported versus placebo (all-grade)b
- Chills (54%)
- Pyrexia (29%)
- Headache (16%)
- Influenza-like illness (10%)
- Myalgia (10%)
- Hypertension (7%)
- Hyperhidrosis (5%)
- Groin pain (5%)

Most frequent grades 3/4 AEs
- Back pain (4%)
- Arthralgia (2%)
- Asthenia (2%)
- Anemia (2%)
- Pain (2%)

Other clinically significant AEs (all-grade)
- Cerebrovascular events (3%)

FIGURE 1. AEs Associated With Newer Treatments for mCRPC

Note. Based on information from Beer et al., 2014; de Bono et al., 2010; Fizazi et al., 2012; Joshua et al., 2014; Kantoff et al., 2010; Malik et al., 2013; Ryan et al., 2013; Scher et al., 2012; Sternberg et al., 2014.

* All-grade AEs are given because grade 3/4 AEs were not available.

b Most AEs occurred within one day after infusion and resolved within one or two days.

AE—adverse event; mCRPC—metastatic castration-resistant prostate cancer
(including docetaxel) received oral enzalutamide (160 mg per day; n = 800) or placebo (n = 399). The trial was stopped after an interim analysis showed significantly longer OS for enzalutamide versus placebo (median = 18.4 months versus 13.6 months, p < 0.001) (Scher et al., 2012). In another randomized, double-blind, phase III study, enzalutamide or placebo were administered to 1,717 chemotherapy-naive men with asymptomatic or mildly symptomatic mCRPC. The interim analysis showed significantly longer OS for enzalutamide, with a 29% reduced risk of death (p < 0.001) (Beer et al., 2014). Based on these results, the FDA approved enzalutamide for mCRPC with or without prior docetaxel treatment. Clinically significant AEs with enzalutamide include fatigue, gastrointestinal events, and seizures (Astellas Pharma US, Inc., 2012).

### Sipuleucel-T

Sipuleucel-T is an autologous cancer vaccine prepared by collecting white blood cells from individual patients by leukapheresis, and then exposing them to a fusion protein (prostatic acid phosphatase [PAP] plus an immune cell activator) (Dendreon Corporation, 2014). Because PAP is expressed on prostate cancer cells, reinfusion of PAP-activated cells stimulates immune-mediated antitumor activity. IMPACT—a phase III, randomized, double-blind study—compared sipuleucel-T (three 60-minute IV infusions every two weeks) versus placebo in 512 patients with asymptomatic or minimally symptomatic mCRPC. To minimize infusion reactions, patients were premedicated with acetaminophen and an antihistamine. OS was longer with sipuleucel-T than with placebo (median = 25.8 months versus 21.7 months); risk of death was reduced by 22% (p = 0.03) (Dendreon Corporation, 2014; Kantoff et al., 2010). Most AEs associated with sipuleucel-T are transient and related to infusions (e.g., fever, chills) (Kantoff et al., 2010).

### Radium-223

Radium-223 dichloride is a radiopharmaceutical that selectively targets bone metastases (Bayer Healthcare Pharmaceuticals, Inc., 2013; Parker et al., 2013). ALSYMPCA was a phase III, randomized, double-blind trial of radium-223 in patients with mCRPC and bone metastases who had received, were not eligible to receive, or declined docetaxel. In total, 921 patients received six IV injections of radium-223 (50 kBq/kg body weight) or placebo, with best supportive care. OS was significantly longer in patients receiving radium-223 than in those receiving the placebo (median = 14.9 months versus 11.3 months, p < 0.001); risk of death was reduced by 30% (Parker et al., 2013). Consistent with trial eligibility criteria, radium-223 is indicated for patients with mCRPC who have symptomatic bone metastases and no known visceral metastases (Bayer Healthcare Pharmaceuticals, Inc., 2013). In ALSYMPCA, fewer patients experienced AEs with radium-223 than the placebo (93% versus 96%), and no clinically meaningful differences in grade 3 or 4 AEs were observed. One death deemed possibly related to radium-223 therapy occurred in a patient with thrombocytopenia (grade 5) who died from pneumonia with hypoxemia with no evidence of bleeding (Parker et al., 2013).

### Treatment Sequencing

Based on trial findings, sipuleucel-T and androgen-targeted agents (abiraterone, enzalutamide) are indicated for asymptomatic/mildly symptomatic patients, whereas chemotherapies (cabazitaxel, docetaxel) and androgen-targeted agents are indicated for symptomatic patients. Radium-223 is indicated for patients with symptomatic bone metastases and no known visceral metastatic disease. However, the number of available agents that should be sequenced to optimize clinical benefit is unknown. Most preliminary studies evaluating treatment sequencing are retrospective and address the post-docetaxel setting only (Sartor & Gillessen, 2014). Available data suggest that in patients previously treated with docetaxel, subsequent treatment with abiraterone followed by enzalutamide, or vice versa, reduces activity of the second agent (Bianchini et al., 2014; de Bono et al., 2011; Loriot et al., 2013; Noonan et al., 2013; Scher et al., 2012; Scheck et al., 2014). However, responses to enzalutamide are observed even after docetaxel and abiraterone failure, with more pronounced responses seen in patients who had previously responded to abiraterone (Cheng et al., 2014; Thomson, Charnley, & Parikh, 2014). Following docetaxel, response to cabazitaxel appears to be unaffected by prior abiraterone or enzalutamide treatment (de Bono et al., 2010; Peczaro et al., 2014). One study suggests that third-line abiraterone has activity after docetaxel and cabazitaxel (Wissing et al., 2013). However, whether prior abiraterone therapy decreases responses to docetaxel is unclear (Aggarwal et al., 2014; Mezynski et al., 2012). A paucity of data evaluating responses after first-line enzalutamide or post-radium-223 exists (Sartor & Gillessen, 2014).

Despite this lack of clinical evidence, sequential use of available agents is a rational approach in suitable patients. Without randomized studies that directly compare newer agents or validated factors to predict patient benefit from specific agents, treatment decisions are based on cross-trial comparisons, clinical considerations (patient preference, prior treatment, presence or absence of visceral disease) and toxicity profiles (NCCN, 2015; Sartor & Gillessen, 2014). A European expert panel published a report on contemporary mCRPC management, which included conclusions regarding treatment sequencing (Fitzpatrick et al., 2014). In particular, patients with a short response to first-line ADT (less than one year) are considered to have a higher risk of resistance to androgen-targeted agents. Several other characteristics were also linked to resistance to androgen-targeted agents, including high Gleason score, visceral metastases, rapid PSA doubling time, high testosterone level, anemia, high lactate dehydrogenase, high alkaline phosphatase, degree of bone pain, and decreased patient performance. However, no factor alone was enough to indicate that chemotherapy should be selected over androgen-targeted therapy. In addition, although a poor response to abiraterone or enzalutamide was associated with decreased probability of response to the other drug, some patients did benefit. Overall, taxanes were considered to be the therapy of choice in patients with a well-defined risk of primary resistance to androgen-targeted agents (i.e., based on multiple factors). Mechanisms of resistance are likely multifactorial and may involve constitutively active androgen-receptor splice variants (AR-Vs). A prospective biomarker study (N = 62) found that the AR-V7 splice variant in circulating tumor cells was associated...
### Table 2: Management Recommendations for Notable AEs Associated With Newer Treatments for mCRPC

<table>
<thead>
<tr>
<th>Toxicity (Drug)</th>
<th>Key Considerations</th>
<th>Management Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration and treatment preparation effects (sipuleucel-T [Provenge])</td>
<td>• Administration of sipuleucel-T is logistically intensive and requires close collaboration among the clinicians who perform the leukapheresis procedure, the manufacturers, the patient, and the infusion staff.</td>
<td>• Discuss the leukapheresis procedure in advance with patients, including the long duration (as many as four hours) and resulting need to be well hydrated, to avoid caffeine, and to consume a calcium-rich breakfast on the day of the procedure.</td>
</tr>
<tr>
<td>• Side effects of leukapheresis include perioral and digital tingling, chills, nausea, and fainting.</td>
<td>• Because the procedure can cause fatigue, advise patients to bring a caregiver.</td>
<td></td>
</tr>
<tr>
<td>Diarrhea (cabazitaxel [Jevtana], enzalutamide [Xtandi])</td>
<td>• Grade 3 or greater diarrhea can lead to dose delay or reduction.</td>
<td>• Educate patients about rehydration or anti-diarrheal medication, and administer when required.</td>
</tr>
<tr>
<td>• Diarrhea and electrolyte imbalance following treatment with cabazitaxel can lead to death; consequently, patients should be monitored.</td>
<td>• Instruct patients to maintain adequate fluid intake if diarrhea occurs.</td>
<td></td>
</tr>
<tr>
<td>• Advise dietary modifications (e.g., avoiding spicy or fried foods and dairy products) to reduce symptoms.</td>
<td>• Advise dietary modifications (e.g., avoiding spicy or fried foods and dairy products) to reduce symptoms.</td>
<td></td>
</tr>
<tr>
<td>• Obtain patient information on bowel habits pretreatment to help assess the severity of on-treatment diarrhea.</td>
<td>• Obtain patient information on bowel habits pretreatment to help assess the severity of on-treatment diarrhea.</td>
<td></td>
</tr>
<tr>
<td>• Marked increases in liver enzymes may require treatment discontinuation or a dose reduction.</td>
<td>• Marked increases in liver enzymes may require treatment discontinuation or a dose reduction.</td>
<td></td>
</tr>
<tr>
<td>Fatigue (cabazitaxel, enzalutamide)</td>
<td>• Causes of fatigue are multifactorial, and dose modification may reduce the impact on patient functioning.</td>
<td>• Inform patients that fatigue is a common side effect of cancer and cancer therapy and that severity will fluctuate between treatment cycles.</td>
</tr>
<tr>
<td>• Contributing causes other than chemotherapy may include sleep deprivation, depression, pain, and anemia.</td>
<td>• Educate patients that ongoing treatment can have a cumulative effect on fatigue.</td>
<td></td>
</tr>
<tr>
<td>Food effect (abiraterone [Zytiga])</td>
<td>• Abiraterone exposure increases by as much as 10-fold when taken with meals, increasing the likelihood of toxicity.</td>
<td>• Discuss with patients that lack of exercise, lack of sleep, poor nutrition, and anxiety and stress can contribute to fatigue.</td>
</tr>
<tr>
<td>• Educate patients about rehydration or anti-diarrheal medication, and administer when required.</td>
<td>• Investigate management options, including exercise regimens, food supplements, stress relief, counseling, cognitive behavioral therapy, and sleep medication.</td>
<td></td>
</tr>
<tr>
<td>Hematologic AEs or infection (cabazitaxel)</td>
<td>• Neutropenic deaths have been reported with cabazitaxel, so frequent blood monitoring is recommended (weekly in cycle 1, and then before each treatment cycle) to determine if growth factor (G-CSF support and/or dose modification is needed.</td>
<td>• Colony-stimulating factor (e.g., G-CSF) is recommended for all patients with cancer undergoing chemotherapy with a 20% or greater risk of febrile neutropenia.</td>
</tr>
<tr>
<td>• Consider primary prophylaxis in high-risk patients (aged older than 65 years, poor performance status, previous febrile neutropenia, extensive radiation ports, poor nutritional status, other serious comorbidities).</td>
<td>• Discuss measures to reduce the risk of infection (e.g., frequent hand washing, avoidance of large crowds and animals).</td>
<td></td>
</tr>
<tr>
<td>• Patients with cancer undergoing chemotherapy with a 20% or greater risk of febrile neutropenia.</td>
<td>• Educate patients about the high risk of infection at neutrophil nadir and how to recognize the signs of neutropenic complications (e.g., dysuria, cough, dyspnea, diarrhea, fever, chills).</td>
<td></td>
</tr>
<tr>
<td>• Advise patients to monitor their temperature and seek immediate advice should it exceed 38°C for any duration or 37.5°C for more than one hour.</td>
<td>• Advise patients that acetaminophen and NSAIDs can mask symptoms like fever.</td>
<td></td>
</tr>
<tr>
<td>• Advise patients to monitor their temperature and seek immediate advice should it exceed 38°C for any duration or 37.5°C for more than one hour.</td>
<td>• Advise patients that acetaminophen and NSAIDs can mask symptoms like fever.</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity (cabazitaxel)</td>
<td>• Before cabazitaxel infusions, all patients should receive premedication with IV antihistamine, corticosteroid, and an H2 antagonist.</td>
<td>• Should severe hypersensitivity occur, treatment should be stopped immediately.</td>
</tr>
<tr>
<td>Liver function abnormalities (abiraterone)</td>
<td>• Patients with moderate hepatic impairment should receive a reduced abiraterone dose (250 mg) and more frequent monitoring.</td>
<td>• Patients with normal transaminase levels at baseline should be monitored every two weeks for the first three months, and then monthly thereafter.</td>
</tr>
<tr>
<td>• Liver toxicities are more common in patients with elevated levels of ALT or AST at baseline; consequently, liver function tests should be performed before treatment.</td>
<td>• Marked increases in liver enzymes may require treatment discontinuation or a dose reduction.</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Based on information from Astellas Pharma US, Inc., 2012; Attard et al., 2009; de Bono et al., 2011; Doyle-Lindrud, 2012; Eaton & Tipton, 2009; Fizazi et al., 2012; Gomella et al., 2014; Hardwick, 2012; Janssen Biotech, Inc., 2014; Mostaghel & Lin, 2014; Roila et al., 2010; Roila et al., 2010; Sanofi-Aventis U.S. LLC, 2014; Wolf et al., 2008.
with poor PSA response and decreased PFS in patients receiving abiraterone or enzalutamide. Some ARV7-negative patients became positive during treatment, suggesting a mechanism for acquired resistance. This highlights the potential for biomarkers to predict resistance to androgen-targeted agents and guide treatment decisions (Antonarakis et al., 2014).

A phase III study (CHAARTED) suggests that docetaxel chemotherapy administered concurrently with ADT may extend survival in patients with metastatic castration-sensitive prostate cancer (Sweeney et al., 2014), which could further complicate treatment paradigms.

### TABLE 2. Management Recommendations for Notable AEs Associated With Newer Treatments for mCRPC (Continued)

<table>
<thead>
<tr>
<th>Toxicity (Drug)</th>
<th>Key Considerations</th>
<th>Management Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting (cabazitaxel)</td>
<td>• Prolonged periods of uncontrolled vomiting may require hospital admission for fluid replacement and parenteral antiemetics.</td>
<td>• Antiemetic medications can markedly improve symptoms.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Inform patients that antiemetics will be included in their medications for cabazitaxel.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Instruct patients to maintain adequate fluid intake.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Discuss the incidence of nausea and vomiting at each visit, potentially assisted by a patient diary.</td>
</tr>
<tr>
<td>Peripheral neuropathy (cabazitaxel)</td>
<td>• Chemotherapy-induced peripheral neuropathy can be extremely painful and lead to significant loss of functional abilities and decreased quality of life.</td>
<td>• Provide educational support and monitor symptoms over time.</td>
</tr>
<tr>
<td></td>
<td>• The clinical course commonly begins with paresthesia (tingling) and dysesthesia (e.g., pain, itching, “pins and needles”) in fingers and toes and spreads to arms and legs.</td>
<td>• No treatments are known. Interruption of chemotherapy can alleviate symptoms, but recovery tends to be slow.</td>
</tr>
<tr>
<td>Renal failure (cabazitaxel)</td>
<td>• Most cases of renal failure with cabazitaxel occurred in association with sepsis, dehydration, or obstructive uropathy.</td>
<td>• Refer patients for specialist management as needed.</td>
</tr>
<tr>
<td></td>
<td>• During cabazitaxel treatment, appropriate measures should be taken to identify causes of renal failure and treat aggressively.</td>
<td></td>
</tr>
<tr>
<td>Seizures (enzalutamide)</td>
<td>• Patients with predisposing factors for seizure were excluded from phase III trials of enzalutamide (e.g., history of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within 12 months, cerebral vascular accident, brain metastases, brain arteriovenous malformation, or use of concomitant medications that may lower the seizure threshold).</td>
<td>• Inform patients receiving enzalutamide about the risks of seizure and sudden loss of consciousness.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Advise patients not to participate in activities that could lead to serious harm should a seizure occur, such as driving a vehicle.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Note that in the phase III trial of enzalutamide, patients who developed seizures had therapy discontinued permanently, and all seizures resolved.</td>
</tr>
<tr>
<td>Toxicity associated with elevated steroid synthesis (i.e., fluid retention or edema, hypokalemia, and hypertension; abiraterone)</td>
<td>• Abiraterone treatment can lead to elevated levels of adrenocorticotropic hormone and subsequent mineralocorticoid synthesis, which is associated with fluid retention, hypertension, and hypokalemia.</td>
<td>• An accurate patient history related to cardiovascular conditions is essential.</td>
</tr>
<tr>
<td></td>
<td>• Abiraterone should be used with caution in patients with a history of cardiovascular disease, particularly where underlying medical conditions may be compromised by fluid retention, hypertension, or hypokalemia.</td>
<td>• Hypertension and hypokalemia should be controlled before and during therapy with abiraterone.</td>
</tr>
<tr>
<td></td>
<td>• Concurrent administration of abiraterone with low-dose glucocorticoids (e.g., prednisone) can ameliorate this effect.</td>
<td>• Mineralocorticoid-related side effects can be treated using the mineralocorticoid receptor antagonist eplerenone in combination with a salt-restricted diet.</td>
</tr>
<tr>
<td></td>
<td>• Patients receiving abiraterone should be monitored for fluid retention, hypertension, and hypokalemia at least once per month.</td>
<td></td>
</tr>
</tbody>
</table>

AE—adverse event; ALT—alanine aminotransferase; AST—aspartate aminotransferase; G-CSF—granulocyte–colony-stimulating factor; mCRPC—metastatic castration-resistant prostate cancer; NSAID—nonsteroidal anti-inflammatory drug

**Note.** Based on information from Astellas Pharma US, Inc., 2012; Attard et al., 2009; de Bono et al., 2011; Doyle-Lindrud, 2012; Eaton & Tipton, 2009; Fizazi et al., 2012; Gomella et al., 2014; Hardwick, 2012; Janssen Biotech, Inc., 2014; Mostaghel & Lin, 2014; Roila et al., 2010; Sanofi-Aventis U.S. LLC, 2014; Wolf et al., 2008.

### Implications for Nursing

Nurses can help in the management of patients with prostate cancer receiving newer therapies by identifying patients with existing comorbidities that overlap with toxicity profiles of therapies, monitoring for disease progression, and providing support as part of the treatment team. In general, patients with mCRPC are monitored using radiologic imaging (bone scan, computed tomography, magnetic resonance imaging [MRI], positron-emission tomography), PSA tests, and clinical examination (NCCN, 2015). Owing to moderate sensitivity
and specificity, a negative bone scan does not exclude the presence of bone metastases, particularly in patients with bone pain or rapidly rising PSA levels. In patients with bone pain and an equivocal or negative bone scan, axial skeletal MRI can be used to assess responses of bone metastases to therapy (Fitzpatrick et al., 2014). Because PSA increases or bone scan changes can be because of flare (temporary effect in an otherwise non-progressing patient) rather than true progression, therapy should continue until confirmed progression or intolerability (NCCN, 2015; Ryan et al., 2011), and imaging should be avoided within three months of starting treatment (Fitzpatrick et al., 2014). Nurses should also be aware that responses and AEs may be different when agents are used in sequences other than those examined in phase III trials.

**Importance of Nursing Care for Patients With Prostate Cancer**

A need exists to improve the quality of healthcare for men with prostate cancer (Penson, 2008; Spencer et al., 2008). In response to this need, the European Oncology Nursing Society ([EONS], n.d.) initiated the Prostate Cancer Education Project, which included a study of supportive care needs (Cockle-Hearne et al., 2013). Among 1,001 patients with stages I (16.4%), II (16.4%), III (13.6%), and IV (9.2%) prostate cancer (disease stage was unknown in 44.5%) in seven European countries, 81% had unmet supportive care needs, most commonly within the areas of psychosocial issues, sexuality, information needs, and challenges with navigating the healthcare system. Prostate-specific symptoms, reported in more than 50% of patients, included incontinence, dysuria, hormonal symptoms, and bowel problems (Cockle-Hearne et al., 2013). More than 45% of patients did not see a nurse during one or more dimensions of care (e.g., advice about screening, information and support at the time of diagnosis, help choosing treatment options), and a lack of post-treatment nursing care significantly predicted unmet needs and affected patient-reported outcomes. Progression from stage I to stages II–IV disease was among the most frequent predictors of unmet needs, and unmet psychological, patient care, and information needs remained following disease progression. Needs and outcomes of patients with prostate cancer are affected not only by effects of treatment but also by supportive nursing care.

Nurse navigators are experienced oncology nurses who provide additional patient support, and many centers have dedicated navigation programs (Wagner et al., 2014). A nurse navigator has disease-specific knowledge to provide patient-centered care and promote positive patient outcomes (Mullen, 2013). Studies report positive feedback from patients enrolled in navigation programs (Hryniuk, Simpson, McGowan, & Carter, 2014; Mullen, 2013). In one study, patients newly diagnosed with a variety of tumors reported that such navigation programs provided assistance with multiple issues during the cancer journey (Hryniuk et al., 2014). Most respondents (98%) appreciated having a designated nurse navigator, and many (52%–80%) regarded this service as important (Hryniuk et al., 2014). Several studies have evaluated the effectiveness of nurse navigator programs, and all found a neutral or positive impact on quality of care (Fiscella et al., 2012; Skrutkowski et al., 2008; Wagner et al., 2014). However, analyses performed by the Association of Community Cancer Centers (ACCC) showed that prostate cancer navigation programs in the United States are inconsistent, particularly regarding patient education and involvement in treatment decisions, as well as staff education about clinical guidelines (ACCC, 2012). Many programs were not collecting sufficient outcomes data to assess quality of care for patients with advanced or metastatic prostate cancer. Few centers had designated navigators specifically for patients with prostate cancer, with most using general, genitourinary, and urology navigators. Prostate cancer care could be improved by better implementation and coordination of navigation programs.

**Outcome Measures and Decision-Making Tools**

Outcome measurements, which assess clinical endpoints, nonclinical criteria, and patient-reported assessments, are becoming increasingly influential in clinical decision making within oncology. Nurses play an important role in assessing outcomes in patients with prostate cancer, and several scales have been used to assess these outcomes. In the EONS Prostate Cancer Education Project study (Cockle-Hearne et al., 2013), questionnaires featured three patient-reported outcome scales: (a) the Supportive Care Needs Survey, a 34-item tool for assessing patients’ unmet needs across domains of psychology, sexuality, health systems and information, physical and daily activity, and patient care and support (Boyes, Girgis, & Lecathelinais, 2009); (b) the EuroQol EQ-5D-3L, a standardized measure of mobility, self-care, usual activities, pain and discomfort, and anxiety and depression (Pickard, Wilke, Lin, & Lloyd, 2007); and (c) a custom-built scale to evaluate experiences of supportive care nursing. The second phase of the ACCC project, also previously described, aimed to identify clinical and nonclinical criteria for prostate cancer outcomes, and measures included duration of survival; time from diagnosis to ADT or ADT to chemotherapy; time to first medical oncologist visit; percentage receiving chemotherapy; use of patient navigation services and/or financial counseling; and referral to and use of palliative care.

**Implications for Practice**

- Understand that, in the absence of data comparing new prostate cancer therapies, treatment decisions are likely to be influenced by side-effect manageability, past experiences, and patient perspectives.
- Use outcome measures, including findings from clinical- and patient-reported assessments, to optimize the treatment decision-making process by identifying patient needs and enabling patients to have a more informed and involved role.
- Have an understanding of the treatment journey, be familiar with treatment options, and coordinate patient care to improve patient management, quality of experience, and outcomes in metastatic castration-resistant prostate cancer.
care, social services, oncology rehabilitation, nutrition counseling, and support groups (ACCC, 2012). Consequently, a range of measures can be used to measure outcomes in patients with prostate cancer.

Decision aids are tools that enable patients to make informed decisions with their practitioner by providing information about options and helping patients to communicate the value associated with different features. Decision aids do not recommend one option over another, and they are not intended to replace practitioner consultation (IPDAS Collaboration, 2013). The ACCC (2012) prostate cancer project investigated tools that could be used as decision aids by prostate cancer programs. Participating cancer programs were provided with the Expanded Prostate Index Composite-16 for Clinical Practice (EPIC-16 CP), a 16-question instrument evaluating patient function and quality of life (QOL) following prostate cancer treatment and assessing urinary, bowel, sexual, and hormonal function (Chang et al., 2011), along with educational materials. Urologists (83%) were most likely to use the EPIC-16 CP, followed by patient navigators (67%) and nurses (50%). Two-thirds of sites used the EPIC-16 CP at diagnosis of advanced prostate cancer; however, some also used the tool for early disease. All sites concluded that the tool provided useful information about QOL and facilitated treatment decisions. Perceived challenges included the need to explain questions to patients and difficulty sharing results across providers (ACCC, 2012). Although decision-making tools can improve care when implemented, a need exists for better tools for patients with prostate cancer.

Conclusion

Several new treatments are available for mCRPC in the predocetaxel and post-docetaxel setting. These agents provide a range of benefits, but they have different administration requirements and toxicities and are suited to different patient populations. In the absence of high-quality data comparing newer agents directly, treatment decisions can be influenced by several factors, including associated AEs, age, comorbidities, past experiences, patient perspectives, cost, and provider familiarity. Healthcare providers, including nurses, must be familiar with different treatment options to deliver optimal prostate cancer-specific care. Studies show that nurses can improve quality of care and outcomes for patients by addressing supportive care needs. Although nurse navigators have an established role in patient management in prostate cancer, more consistent implementation among centers is needed. Greater use of outcome measures can help to identify patient needs within oncology, including prostate cancer, and decision aids can enable patients to have an informed role in the decision-making process. By understanding the treatment journey and coordinating patient care, nurses have a key role to play in educating patients, managing symptoms, and improving the quality of care in men with mCRPC.

References


Malik, Z., Di Lorenzo, G., Ardavanis, A., Basaran, M., Parente, P., de Schultz, W., . . . Henideichen, A. (2013). Updated safety results from a cohort compassionate-use programme (CUP) and early access programme (EAP) with cabazitaxel (Cbz) plus prednison (P: Cbz plus P) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel (D) [Abstract 2902]. *European Journal of Cancer*, 49(Suppl. 2).


