Supportive Care in the Treatment of Non-Metastatic Castration-Resistant Prostate Cancer

In 2018, there will be an estimated 164,690 new cases of prostate cancer (PC) in the U.S. and approximately 29,430 patients will die of the disease, making it the third-leading cause of cancer death in men (American Cancer Society [ACS], 2018). The majority of men with PC are treated with curative intent (i.e., with radical prostatectomy or radiation therapy) with good outcomes, but a fraction of men with locoregional PC will develop progressive disease. Men who have initial PSA/biochemical recurrence after curative treatment are a heterogeneous group of individuals with good overall prognosis, including a median metastasis-free survival (MFS) >8 years and a median overall survival (OS) of >23 years (Rozet et al., 2016).

Approximately 10%-20% of prostate cancer patients develop castration-resistant PC (CRPC) within approximately 5 years of follow-up. Decisions about clinical management (i.e., when to start treatment) are challenging because it is unclear which patients will have shorter versus longer survival, and metastatic disease is not always reliably detected with imaging (Rozet et al., 2016).

Multiple new targeted agents, including immunotherapy, second-generation hormone therapy, and androgen biosynthesis inhibitors have been recently approved. Two recently published studies (PROSPER and SPARTAN) have changed the standard of care for patients with nmCRPC.

TARGET AUDIENCE

The target audiences for these activities are urologists, medical oncologists, urology/oncology nurses, advanced practice registered nurses and nurse navigators.

EDUCATIONAL OBJECTIVES

- Use care-planning tools and resources to assess and document patient goals, preferences, and concerns, and to support shared decision-making during clinic visits.
- Describe common side effects associated with treatment of nonmetastatic castration-resistant prostate cancer (nmCRPC).
- Apply best supportive care practices for treating adverse events associated with treatment for nmCRPC.

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JOINT ACCREDITATION STATEMENT

In support of improving patient care, this activity has been planned and implemented by the Postgraduate Institute for Medicine and Carevive Systems, Inc. Postgraduate Institute for Medicine is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

PHYSICIAN CONTINUING MEDICAL EDUCATION

Credit Designation

The Postgraduate Institute for Medicine designates this enduring material for a maximum of 0.75 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Release date: April 15, 2019
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Estimated time to complete activity: 45 minutes

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Faculty Disclosures

Mary W. Dunn, RN, MSN, OCN, NP-C, has no real or apparent conflicts of interest to report.

Planners And Managers

The PIM planners and managers have nothing to disclose. The Carevive Systems, Inc. planners and managers have nothing to disclose.

METHOD OF PARTICIPATION AND REQUEST FOR CREDIT

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MEDIA

E-Monograph

HARDWARE AND SOFTWARE REQUIREMENTS

- A computer with an internet connection
- A PDF viewing software: Adobe Acrobat Reader or Apple Preview
- Internet Browser: Latest versions of Internet Explorer, Firefox, Safari, or any other W3C standards compliant browser
- Additional Software: PowerPoint, Adobe Flash Player and/or an HTML 5 capable browser maybe required for video or audio playback.

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DISCLAIMER

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications and/or dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

FEE INFORMATION

There is no fee for this educational activity.

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Recent clinical trials of apalutamide (the SPARTAN trial) and enzalutamide (the PROSPER trial), both administered concurrently with androgen deprivation therapy (ADT), demonstrated efficacy and safety of these androgen receptor inhibitors for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC). These therapies, however, are often associated with adverse events that impact health-related quality of life (HRQoL). Providing optimal supportive care for patients undergoing treatment for nmCRPC can enhance HRQoL and prolong survival by allowing them to continue treatment without disruption. The use of treatment care plans to delineate cancer care is required by the Institute of Medicine as part of value-based cancer care (IOM, 2013). Electronic care planning tools are available to help optimize supportive care, guiding clinicians in educating patients about treatment options and potential adverse events; documenting patient concerns, expectations, goals, and preferences; and engaging patients in informed, shared decision-making regarding their own care (Carevive, 2019).

COMMON ADVERSE EVENTS

FATIGUE

Fatigue is among the most common adverse event associated with cancer. It is not unique to prostate cancer, occurring in as many as 40% of all patients at initial cancer diagnosis; fatigue is exacerbated by most, if not all, cancer-treatment regimens including ADT (Hofman et al, 2007; Saad et al, 2018; NCI, 2018). Strategies advocated by the American Cancer Society (2018) for coping with fatigue involve balancing activity and rest, short naps during the day to allow for sufficient periods sleep at night, eating well, and ensuring adequate intake of fluids. Cognitive behavioral interventions such as mindfulness techniques may be helpful in managing stress and promoting relaxation and sleep (Mitchell et al, 2014). When fatigue is coupled with depression, referral to a mental health professional (i.e., counselor, psychologist, or psychiatrist) is warranted to determine whether the patient may benefit from antidepressant medications (ACS, 2016, 2018; NCI, 2018). Fatigue is often caused by more than one problem, requiring doctors, nurses, social workers, physical therapists, nutritionists, and other members of the patient's healthcare team to work together to manage concurrent symptoms (ACS, 2016; ZERO, 2019).

APALUTAMIDE (SPARTAN TRIAL)

In the SPARTAN trial, six adverse events were considered by the investigators to be related to apalutamide. In addition to fatigue, which was reported by 30.4% of patients receiving apalutamide versus 21.1% receiving placebo, apalutamide was associated with the following adverse events (Smith et al, 2018):

- **Rash**. Rash was most commonly macular or maculo-papular, occurring in 23.8% of patients receiving apalutamide versus 5.5% of patients receiving placebo (Smith et al, 2018). Median onset of rash occurred at 82 days of treatment (apalutamide prescribing information, 2018). Less severe rashes can be managed with lifestyle changes; advise patients to wear loose, non-irritating clothing, use mild soaps, and avoid sun exposure or use sunscreen. More severe rashes may require medical management with topical corticosteroids, antihistamines, or reduction or interruption of the treatment regimen. Among patients for whom the treatment drug was withheld due to rash, 50% experienced recurrence of rash when re-challenged with apalutamide (Apalutamide prescribing information, 2018). Grade 3 rashes covering more than 30% of body surface area occurred in 5.2% in the apalutamide arm, vs. 0.3% in the placebo group (Smith et al, 2018).
- **Fracture**. The incidence of fracture was 11.7% in patients receiving apalutamide, compared to 6.5% in patients receiving placebo. Median onset of fracture was 314 days on apalutamide. Optimal treatment for fracture requires evaluation by an orthopedist; minor fractures may be treated by wearing a cast or other stabilizing device but more severe fractures may require surgery. Patients also should be evaluated for increased risk for fracture, which may include advanced age, mobility concerns and use of assistive devices, and comorbidities such as hypoglycemia that predispose patients to falls that often result in fracture. Although not included in the SPARTAN trial treatment protocol, calcium (minimum 500 mg) and vitamin D (400 IU) supplements, bone density testing, and treatment for osteoporosis can help reduce risk of fractures, allowing patients to maintain HRQoL while continuing treatment for nmCRPC.
- **Falls**. Falls occurred in 15.6% of patients receiving apalutamide versus 9.0% in the placebo group (Smith et al, 2018). Optimal supportive care includes assessment for a variety of intrinsic and extrinsic factors that may increase risk for falls. Intrinsic risk factors may include history of falls hypotension, hypoglycemia, impaired mobility

(unstable gait, poor balance, musculoskeletal deformities, neurological disorders), limited endurance during physical activity, peripheral neuropathy, impaired vision, altered mental status, side effects of medications, and incontinence. Extrinsic risk factors may include conditions in the physical environment, such as poor lighting, clutter, throw rugs, slippery floors, stairs, uneven surfaces, rain, snow, ice. Calcium (minimum 500 mg) and vitamin D (400 IU) supplementation may reduce risk of falls.

- **Hypothyroidism**. The incidence of hypothyroidism was 8.1% in the apalutamide arm versus 2.0% in the placebo arm; all episodes were all grade 1 or 2 (Smith et al, 2018). The trial protocol included assessment of thyroid stimulating hormone (TSH) levels every 16 weeks; abnormal TSH level was an indication for further testing (i.e., total T3, free T4, and total T4) (Clinical Study Protocol, n.d.). Approximately one fourth of patients taking apalutamide had elevated TSH, with median onset at approximately 113 days; thyroid replacement therapy was initiated in approximately 7% of these patients (apalutamide prescribing information, 2018). These data indicate that assessment of TSH is an important element in optimal supportive care for patients with nmCRPC. Technology-driven care planning tools can help ensure clinicians are routinely assessing for THS and other factors that may not be in the typical scope of cancer care.
- **Seizure**. Seizures were rare, occurring in only two patients in the apalutamide arm and zero patients in the placebo arm (apalutamide prescribing information, 2018).

ENZALUTAMIDE

In the PROSPER trial, enzalutamide had a side-effect profile similar to that of apalutamide. Fatigue was the most common adverse event, occurring in 32.6% of patients taking enzalutamide compared to 13.8% in the placebo group (Hussain et al, 2018). An important side-effect not previously mentioned was constipation (Hussain et al, 2018; enzalutamide prescribing information, 2018).

- **Constipation**. In the PROSPER trial, 9% of patients taking enzalutamide reported experiencing constipation versus 6% in the placebo arm (Hussain et al, 2018). Although constipation is a common side effect of cancer treatment, it can result from many other factors (e.g., inadequate fluid intake, poor diet, lack of exercise) and frequently leads to development of hemorrhoids, anal fissures, and bleeding. Because constipation can have deleterious effects on HRQoL in patients with nmCRPC, supportive care planning for should include routine assessment of the patient's bowel function. First-line treatment may include increasing intake of water and fiber-rich foods (e.g., fruits, vegetables, bran, nuts). Using prebiotic fiber supplements and stool-softening medications also can help in constipation management (ACS, 2018).

ANDROGEN DEPRIVATION THERAPY

All patients in the SPARTAN and PROSPER trials, in both the treatment and placebo arms, received concurrent ADT. ADT is frequently associated with certain adverse reactions and may also exacerbate adverse events caused by treatment drugs. Fatigue is a common adverse event associated with ADT; as many as 40% of patients on ADT indicate that fatigue interferes with their activities of daily living (Mitchell et al, 2014; Challapalli et al, 2018; Patil & Bernard, 2018). In addition to strategies for managing fatigue, optimal supportive care should include routine monitoring and treatment for the follow conditions commonly associated with ADT:

- **Hot flashes.** Hot flashes are characterized by a sensation of warmth that may be accompanied by facial flushing, perspiration, chills, heart palpitations, night sweats, and feelings of anxiety. Symptoms often can be alleviated by lifestyle modifications (e.g., wearing loose cotton clothing; using fans and ice and maintaining cool room temperatures; and limiting common triggers such as caffeine, spices, and alcohol). Exercise and relaxation techniques are sometimes helpful. Hot flashes rarely require medical management; however, severe symptoms impacting quality of life may be treated with venlafaxine 37.5 mg or gabapentin (dose varies) (Kaplan & Mahon, 2014).
- **Sexual dysfunction.** Patients diagnosed with prostate cancer often experience sexual dysfunction as a consequence of the disease; prevalence increases with cancer treatments, including ADT. Decreased libido is common in men on ADT; for men with advanced prostate cancer, no effective treatment currently exists. For erectile dysfunction following ADT, effective treatments may include vacuum erection devices (VEDs), PDE5 inhibitors, medicated urethral system for erection (MUSE), intracavernosal injections, or penile implants (Dall'Era et al, 2006; Rew & Heidelbaugh, 2016). Penile shrinkage commonly occurs following medical or surgical prostatectomy; VEDs are sometimes effective for penile rehabilitation. All patients undergoing ADT should be counseled and provided with information to help them understand and cope with these common side effects of treatment (ACS, 2016; (Dall'Era et al, 2006; Patil & Bernard, 2018).
- **Osteoporosis.** Reduced testosterone due to ADT creates a hypogonadal state that accelerates bone loss and can cause osteoporosis. Osteoporosis is diagnosed by a T-score of negative 2.5 or lower on dual energy x-ray absorptiometry (DEXA) scan. Treatments to prevent or slow bone loss and alleviate symptoms of osteoporosis may include zoledronic acid (4 mg administered intravenously); side effects of this treatment may include hypocalcemia, renal dysfunction, osteonecrosis of the jaw, and flu-like symptoms. Another treatment option is denosumab, a subcutaneous injection administered every 6 months. Denosumab is a monoclonal antibody that inhibits the receptor activator of nuclear factor kappa-B ligand (RANKL), a protein involved in cancer-related bone destruction. Calcium (minimum 500 mg) and vitamin D (400 IU) supplementation and a regimen of weight-bearing

exercise are essential for maintaining bone health and strength.

Other potential adverse events associated with castrate levels of testosterone caused by ADT include gynecomastia, cardiovascular disease, insulin resistance, hyperlipidemia, cognitive deficits. Patients experiencing any of these symptoms should be referred to the appropriate medical specialists for diagnosis and guidance in weighing the risks of these conditions versus the risk of cancer progression if ADT is discontinued.

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