Background: Radium-223 dichloride, or radium-223, is a first-in-class alpha emitter that selectively targets bone metastases with high-energy, short-range alpha particles and is approved for the treatment of patients with castration-resistant prostate cancer (CRPC), symptomatic bone metastases, and no known visceral metastatic disease. Nurses are essential in educating patients about radium-223.

Objectives: This article provides oncology nurses with information from the randomized phase III Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial, as well as important handling, administration, and safety details unique to radium-223.

Methods: Data from the ALSYMPCA trial and related published information on radium-223 were reviewed.

Findings: Radium-223 is the only alpha-emitting radiopharmaceutical that has been shown to improve overall survival in patients with CRPC, as demonstrated in the ALSYMPCA trial. In addition, radium-223 delays time to first symptomatic skeletal event, and it is well tolerated with a low incidence of myelosuppression and gastrointestinal adverse events. Delivered on an outpatient basis, radium-223 requires universal precautions for handling and administration. Because of the potential for additive myelosuppression, the concomitant use of radium-223 with chemotherapy, other systemic radioisotopes, or hemibody external radiation therapy is not recommended.

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Nurses are an essential part of the oncology team who are closely involved in the care and management of patients with castration-resistant prostate cancer (CRPC). They often are the first source of patient contact and are in a key position to intercede early in the patient care process by providing information on available treatments, discussing novel therapies, and educating about clinical trials.

About 90% of patients with CRPC have bone metastases (Armstrong, Garrett-Mayer, de Wit, Tannock, & Eisenberger, 2010; Tannock et al., 2004). Patients with bone metastases are at risk for developing skeletal complications (e.g., severe bone pain, pathologic fracture, spinal cord or nerve root compression, hypercalcemia of malignancy). Decreased survival rates have been correlated with bone metastases and skeletal events in metastatic CRPC (Sathiakumar et al., 2011). Treatment options to improve overall survival and quality of life, as well as to prevent and delay skeletal events, are of high importance when managing the care of patients with metastatic CRPC. Because nurses are crucial in managing and educating patients on novel therapies, the current authors present in this article the nursing practice implications for patient care and management in the handling, administration, and safety of radium-223. A brief review of the results of the randomized
phase III Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial, as well as recommended patient education, are also included.

Radium-223 dichloride, or radium-223, is a first-in-class alpha-emitting pharmaceutical with a potent and highly targeted antitumor effect on bone metastases (Bruland, Nilsson, Fisher, & Larsen, 2006; Henriksen, Breistøl, Bruland, Fodstad, & Larsen, 2002). Radium-223 mimics calcium to naturally target new bone growth, including areas within and around bone metastases (Bruland et al., 2006; Henriksen et al., 2002; Henriksen, Fisher, Roeske, Bruland, & Larsen, 2003), and emits high-energy, short-range alpha particles through its decay process that are highly effective in inducing double-stranded DNA breaks, which are difficult to repair and lead to cell death in the targeted areas (Henriksen et al., 2003). Radium-223 is inherently different from beta-emitting pharmaceuticals (e.g., strontium-89, samarium-153), which emit beta particles with long ranges of action that cause significant myelotoxicity. Bone-targeting therapies using beta emitters have mainly been considered palliative and have not been shown to improve survival. In contrast, alpha-emitting radium-223 has an ultrashort penetration distance (less than 100 mcm, 2–10 cell diameters), is more effective at highly localized tumor cell killing, and has shown improvement in overall patient survival (Bruland et al., 2006; Henriksen et al., 2002, 2003; Parker, Nilsson, et al., 2013). In addition, radium-223 causes minimal damage to surrounding normal tissues (e.g., bone marrow), which is a major source of toxicity for beta emitters and may limit continuation of treatment (Bruland et al., 2006; Henriksen et al., 2002, 2003).

Early studies showed that radium-223 had a dose-dependent effect on pain response. In a phase II study evaluating 25-, 50-, and 80-kBq/kg doses of radium-223, pain index data (combination of the score of item 3 on the Brief Pain Inventory and analgesic consumption) were available for 86 of 112 patients (77%). A trend toward a greater proportion of pain respondents in the 50-kBq/kg dose group than in the other two dose groups across time points (weeks 4–24) was observed (Parker, Pascoe, et al., 2013). In another phase II dose-response study, the effect of a single injection of radium-223 in 100 patients with CRPC was assessed. Pain response (i.e., pain reduction and stable analgesic consumption) was seen in as many as 71% of patients with CRPC and painful bone metastases in the two highest dose groups (50 kBq/kg and 100 kBq/kg) (Nilsson et al., 2012).

To evaluate the impact of radium-223 on overall survival, a phase III trial, ALSYMPCA, was conducted. This randomized, double-blind, placebo-controlled, multinational study compared the efficacy and safety of radium-223 plus best standard of care (BSOC) (defined as the routine care provided at each center [i.e., local external beam radiation therapy (EBRT) or treatment with glucocorticoids, antiandrogens, ketoconazole, or estrogens, such as diethylstilbestrol or estramustine]) versus placebo plus BSOC in patients with CRPC and symptomatic bone metastases (the latter of which involves the regular use of opioid or nonopioid analgesic medication or treatment with EBRT for cancer-related bone pain within the previous 12 weeks of treatment with radium-223) (Parker, Nilsson, et al., 2013). Results from ALSYMPCA led to initial approval of radium-223 by the U.S. Food and Drug Administration (FDA) in 2013; radium-223 has since been widely approved worldwide for the treatment of patients with CRPC, symptomatic bone metastases, and no known visceral metastases. It is a category 1 recommendation from the National Comprehensive Cancer Network ([NCCN], 2015) as an option in first-line and post-docetaxel settings.

Implications for Oncology Nursing Practice

Patient Management

Oncology nurses play a primary role in the management and care of patients receiving radium-223. However, nurses from a variety of disciplines (e.g., urology, medical oncology, nuclear medicine, radiation oncology) may be involved in educating patients and directing patient care using this treatment. Because this approach is multidisciplinary, all nurses involved in patient care must be educated about the properties of radium-223, as well as its therapeutic benefits and possible adverse effects. Coordination among the various disciplines is essential, and a well-defined process is necessary for managing these patients. Education directed toward the oncology nurse, initial and ongoing patient assessment, and recommended patient education will lead to optimal patient care and management.

Patient Assessment

The oncology nurse performs thorough assessments, as well as ongoing education and close monitoring, of the patient. A review and initial assessment of the patient’s current condition (e.g., extent of bone metastases, symptoms, previous treatments) will assist in identifying patients who may be eligible to receive radium-223 treatment. Eligibility criteria include history of CRPC, no visceral metastases, and symptomatic bone metastases.

Management throughout the patient’s treatment will include monitoring blood counts at baseline and before each dose of radium-223. The patient’s absolute neutrophil count (ANC) should be greater than or equal to 1.5 × 10⁹/L, the platelet count should be greater than or equal to 100 × 10⁹/L, and the hemoglobin count should be greater than or equal to 10 g/dL, all prior to the patient’s first administration of radium-223. In addition, prior to subsequent administrations, the patient’s ANC should be greater than or equal to 1 × 10⁹/L, and the platelet count should be greater than or equal to 50 × 10⁹/L (Bayer HealthCare Pharmaceuticals, Inc., 2013). Radium-223 should be discontinued if hematologic values do not recover within six to eight weeks after the last administration. A thorough and ongoing toxicity assessment must be completed throughout each cycle and prior to subsequent cycles. Monitoring the patient’s pain level throughout the course of treatment to assess response is an important component of the nurse’s assessment.

Handling and Administration

Radium-223 is provided as a ready-to-use solution for IV injection and is supplied with a shielding container and decay
correction table. An authorized user (e.g., nuclear medicine physician, radiation oncologist) administers treatment in an outpatient setting. The authorized user and outpatient department vary, depending on institutional practices. The volume to be injected must be adjusted for patient weight and radioactive decay, and each injection should be administered slowly for about one minute. Radium-223 reaches its target rapidly after IV administration, with about 60% of the injected activity taken up by the bones within four hours (Bayer HealthCare Pharmaceuticals, Inc., 2013). Excretion is predominantly fecal, with 75% excreted within one week and less than 5% excreted through urine (Bayer HealthCare Pharmaceuticals, Inc., 2013). The recommended dosing regimen is one injection (50 kBq [1.55 microcurie]) per kilogram of body weight, given every four weeks for a total of six injections; the efficacy and safety of radium-223 demonstrated in the ALSYMPCA trial are based on this regimen.

Alpha particles are relatively large and easily shielded by skin or even a sheet of paper; therefore, minimal radiation protection measures are required. Radium-223 contamination can be detected with standard instruments, including dose calibrators and gamma detectors, given the small amount of gamma decay, and radium-223 ultimately decays into a stable product, which can be discarded as normal clinical waste after 10 half-lives (about four months).

Alpharadin in Symptomatic Prostate Cancer Trial Results

The efficacy and safety of radium-223 compared with placebo were studied in the phase III ALSYMPCA trial (Parker, Nilsson, et al., 2013). A total of 921 patients were randomized 2:1 to six injections of radium-223 (50 kBq/kg every four weeks) or matching placebo; both treatment groups also continued to receive BSOC throughout the study. All patients included in ALSYMPCA had CRPC and symptomatic bone metastases and no known visceral metastases, and had either previously received docetaxel or were unfit for, did not have access to, or declined docetaxel. The trial’s primary endpoint was overall survival, and secondary endpoints included the time to first symptomatic skeletal event (SSE) and safety.

Radium-223 improved median overall survival among ALSYMPCA participants by 3.6 months compared with placebo (14.9 months for radium-223 versus 11.3 months for placebo, hazard ratio [HR] = 0.7, 95% confidence interval [CI] [0.58, 0.83], p < 0.001) (Parker, Nilsson, et al., 2013). The median time to experience a new SSE was also prolonged with radium-223 compared with the placebo (15.6 months for radium-223 versus 9.8 months for placebo, HR = 0.66, 95% CI [0.52, 0.83], p < 0.001). Various pain-related parameters indicated a positive effect on pain relief. Radium-223 versus placebo decreased the risk of EBRT for bone pain (HR = 0.67, 95% CI [0.53, 0.85], p = 0.0012) and the risk of opioids needed for pain relief (HR = 0.62, 95% CI [0.46, 0.85], p = 0.0023) (Nilsson et al., 2013; Parker, Nilsson, et al., 2013). In addition, improved pain-related quality of life scores, versus placebo, were observed over the entire trial period, including the treatment and follow-up periods (p = 0.006).

Radium-223 also exhibited a highly favorable safety profile. Radium-223 patients, versus placebo patients, had a lower incidence of total adverse events (AEs), grade 3 or 4 AEs, serious AEs, and treatment discontinuation because of AEs (see Table 1). With radium-223, the incidence of myelosuppression was low (thrombocytopenia [12% for radium-223 versus 6% for placebo], neutropenia [5% for radium-223 versus 1% for placebo]), as were rates of gastrointestinal AEs (see Table 2). The most common gastrointestinal AEs included diarrhea (25% for radium-223 versus 15% for placebo), nausea (36% for radium-223 versus 35% for placebo), and vomiting (19% for radium-223 versus 14% for placebo) (Parker, Nilsson, et al., 2013). The ALSYMPCA trial included men aged 44–94 years and demonstrated safety and efficacy across all ages, suggesting that patients within a wide age range can benefit from and tolerate radium-223 (Wiechno et al., 2013).

Recommended Patient Education

Once a patient is identified as a candidate for radium-223 treatment, education about this radiopharmaceutical should be conducted; effective communication is fundamental. Patients often have misconceptions about what to expect and may fear becoming “radioactive.” Explaining the characteristics of radium-223 and its therapeutic benefits will aid in alleviating their anxiety. Education about the alpha-emitting radiopharmaceutical’s mechanism of action increases patients’ awareness and the likelihood of a more positive view of the treatment. Information to discuss with patients regarding the efficacy of radium-223 includes reports of a meaningful improvement in quality of life, prolonged overall survival (by 3.6 months), and prolonged time to SSEs compared to the placebo (Parker, Nilsson, et al., 2013).

In addition to providing emotional and psychological support, the nurse is well positioned to provide education and self-management recommendations regarding possible side effects and symptom management. A credible education resource for patients to review is the NCCN guideline on prostate cancer for patients. Patients can review objective, evidence-based information on all available prostate cancer treatments.

| TABLE 1. Summary of Patients in the Safety Population With Adverse Events (N = 901) |
|----------------------------------|-----------|-----------|
| Radium-223 (n = 600) | Placebo (n = 301) |
| ----------------- |-------------|-----------|
| All grades       | 558         | 290        |
| Grade 3 or 4     | 339         | 188        |
| Serious          | 281         | 181        |
| Discontinuation because of event | 99          | 62         |

Note: The safety population comprised patients who received at least one dose. One patient in the placebo group received one injection of radium-223 (baseline) and is included in the radium-223 safety analysis.
Patients should be advised that radium-223 is a safe and effective treatment for individuals with CRPC and symptomatic bone metastases, and that it is distinct from chemotherapy and beta emitters in its mechanism of action and side effect profile. Describing radium-223 to patients as a form of “liquid radiation” that is administered via IV and targets all tumor cells in the bone may be helpful. Patients should be aware that radium-223 has a proven overall survival benefit and has been shown to prolong time to first SSE (Parker, Nilsson, et al., 2013).

Because of the risk for myelosuppression, patients are advised to adhere with blood cell count monitoring appointments while receiving radium-223; they should also report any signs of low blood cell counts, such as shortness of breath, tiredness, bleeding, and infection. Patients with evidence of compromised bone marrow should be monitored closely for hematologic AEs. Because of the potential for additive myelosuppression, radium-223 should not be administered during treatment with chemotherapy, other systemic radioisotopes, or hemibody external radiation therapy; patients should know that if any of these agents are administered, then radium-223 should be discontinued. However, the use of docetaxel prior to radium-223 has not been shown to affect the safety or efficacy of radium-223 and, therefore, should not affect the decision to receive radium-223. In addition to myelosuppression, patients may experience gastrointestinal AEs, most notably diarrhea and vomiting, although these usually resolve with weekly hydration and antidiarrheal medications. Patients should stay well hydrated and be instructed to recognize any signs of dehydration or urinary or kidney problems. If patients experience those signs or any other AEs (e.g., diarrhea, nausea, vomiting, peripheral edema, symptoms associated with myelosuppression, such as fatigue, bleeding, and infection), they should be instructed to report them to a healthcare professional.

Precautions to Limit Radiation Exposure

The administration of radium-223 is associated with potential risks to other persons that result from exposure to radiation or contamination from spills of bodily fluids (e.g., urine, feces, vomit). National and local regulations regarding radiation protection precautions should be followed. Those handling radium-223 should adhere to normal working procedures involving radiopharmaceuticals, as well as use universal precautions to avoid contamination (e.g., gloves, barrier gowns when handling blood and bodily fluids). In the event of skin or eye contact, the affected areas should be immediately flushed with water (Bayer HealthCare Pharmaceuticals, Inc., 2013).

Patients should be advised to follow good hygiene practices while receiving radium-223 and for at least four weeks after the last injection to minimize radiation exposure from bodily fluids to household members and caregivers. Patient contact with other people (e.g., family members, caregivers) is not restricted, but precautions should be taken to prevent contact with patients’ bodily fluids. Patients should use a toilet, flush it several times after each use, and ensure thorough hand washing. Wearing gloves and washing the hands will protect caregivers when they handle bodily fluids. If clothing is soiled with radium-223 or patient fecal matter or urine, it should be washed promptly and separately from other items (Bayer HealthCare Pharmaceuticals, Inc., 2013). In addition, patients should wear condoms if sexually active during treatment and, because of potential effects on spermatogenesis, men and their female partners who have reproductive potential should continue to use a highly effective contraceptive method for six months after the completion of treatment.

Patients with prostate cancer often focus their anxiety on prostate-specific antigen (PSA) levels because they know that an increase in PSA may be a sign of disease progression (Roth et al., 2003). However, the FDA, Prostate Cancer Clinical Trials Working Group II, and European Medicines Agency do not recommend that PSA be used as a biomarker for treatment outcome in patients with metastatic CRPC (Fleming, 2005; Scher et al., 2008). Patients must be aware that a decline in PSA is not always an expected result of radium-223 treatment and that patient benefits have been observed in the absence of a decreasing PSA. Nurses can reinforce that improvements in overall survival, the delay of SSEs (e.g., fractures), and positive effects on pain and quality of life are important indicators of the effectiveness of radium-223. Effective nurse–patient communication and clarification of the patient’s expectations are vital to the patient’s understanding of the meaning of PSA testing and may help to ease anxiety.

Reimbursement Issues

Radium-223 treatment should be covered by most insurance plans because Medicare and private insurers will provide coverage for FDA-approved cancer treatments. However, patient co-pays may vary greatly between plans. A comprehensive patient support program is available for patients from the pharmaceutical company that manufactures radium-223; the program’s website (www.xofigo-us.com/patient/resources) provides financial and reimbursement

### TABLE 2. Adverse Events of Interest in the Safety Population (N = 901)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All Grades</th>
<th>Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Radium-223</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>(n = 600)</td>
<td>(n = 301)</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>187</td>
<td>31</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>69</td>
<td>12</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
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<tr>
<td>Constipation</td>
<td>108</td>
<td>18</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>151</td>
<td>25</td>
</tr>
<tr>
<td>Nausea</td>
<td>213</td>
<td>36</td>
</tr>
<tr>
<td>Vomiting</td>
<td>111</td>
<td>19</td>
</tr>
</tbody>
</table>

*Note: The safety population comprised patients who received at least one dose. One patient in the placebo group received one injection of radium-223 (baseline) and is included in the radium-223 safety analysis.*
Implications for Practice

- Understand that radium-223 is a highly effective, well-tolerated, easy-to-administer treatment for patients with castration-resistant prostate cancer (CRPC), symptomatic bone metastases, and no known visceral metastases.
- Provide education to patients with metastatic CRPC regarding radium-223 as a new therapeutic option and its clinical relevance.
- Incorporate radium-223 knowledge into clinical practice to help guide treatment considerations and patient care.

Support and prior authorization, among other services. Information about finding locations where radium-223 is offered is available as well. Appropriate coding and classification of the patient's diagnosis is important to support medical necessity and facilitate insurance claims. ICD-9-CM 185, for a malignant prostate neoplasm, along with ICD-9-CM 198.5, for a secondary malignant neoplasm of bone, should be used when completing preauthorization forms. Nurses need to be aware of institutional procedures for verifying patient benefits, securing prior authorization, reviewing orders for radium-223, filing claims, and scheduling appointments for radium-223.

Discussion and Conclusion

Radium-223 is a safe, effective, and easy-to-administer treatment for patients with CRPC and symptomatic bone metastases and no known visceral metastases. Because radium-223 can prolong overall survival (by 3.6 months), delay time to first SSE (by 5.8 months), and result in a meaningful improvement in pain-related quality of life, it should be considered as an early treatment for patients with CRPC and symptomatic bone metastases. Effective patient communication and education about radium-223, its therapeutic benefits, and management or monitoring options for potential side effects is an essential part of the nursing role.

References