PQI IN ACTION

Positive Quality Intervention

NCODA

Radium Ra 223 dichloride (Xofigo®) in Castrate-Resistant Prostate Cancer (CRPC)

INTRODUCTION

NCODA developed the peer-reviewed Positive Quality Intervention (PQI) as an easy-to-use and relatable clinical guidance resource for healthcare providers. By consolidating quality standards, real-life effective practices, clinical trial results, package insert and other guidance, PQIs equip the entire multidisciplinary care team with a comprehensive yet concise resource for managing patients receiving oral/IV oncolytics or radiopharmaceuticals.

This PQI in Action is a follow up to the Radium Ra 223 Dichloride (Xofigo) Management PQI and explores how the medically integrated teams at First Urology and Comprehensive Cancer Centers of Nevada (CCCN) collaborate and utilize the information found in the PQI as part of their daily practice. This PQI in Action focuses on the use of radium-223 in patients with CRPC.

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LOCALIZED TREATMENT OF PROSTATE CANCER
BONE METASTASES

THE bones are the most common site for metastatic spread in prostate cancer patients.[1] For those with bone metastases, treatment goals are aimed at relieving symptoms and delaying skeletal complications, such as fractures, spinal cord compression, and the need for surgical or radiation interventions.[2] While systemic therapies, including hormonal agents, can initially aid in the management of bone metastases, their effectiveness may diminish once the cancer becomes castrate resistant. In these cases, local therapies that target bone metastases directly, such as radiation therapy and radiopharmaceuticals, may be beneficial.

One such targeted radiopharmaceutical radium-223 (Xofigo®), specifically designed for prostate cancer that has metastasized to the bones, will be discussed in more detail in the following sections.

RADIUM RA 223 DICHLORIDE (XOFIGO®):
MECHANISM OF ACTION, CLINICAL DATA, AND INDICATIONS

MECHANISM OF ACTION[3]

THE active portion of Xofigo® is the isotope radium-223, which emits alpha particles. Radium-223 works by imitating calcium and forming complexes in areas where bone metastases are located. When the alpha particles are released, this causes double-strand DNA breaks within the tumor and its surrounding microenvironment, which ultimately leads to cell death.The alpha particle was designed to have a short radioactive range, which is believed to help limit damage to surrounding normal tissues and minimize side effects.

RADIUM-223 CLINICAL TRIAL DATA IN CRPC[4,5,6]

IN the pivotal phase 3 ALSYMPCA trial, 921 patients with symptomatic CRPC were randomized (2:1) to receive radium-223 or placebo. Eligible patients had two or more bone metastases, no known visceral metastases, and had either received, were ineligible for, or declined docetaxel. Radium-223 significantly improved overall survival compared to placebo (median 14.9 months vs. 11.3 months; HR, 0.70; 95% CI, 0.58-0.83; p<0.001), regardless of prior docetaxel use. It also delayed time to first skeletal-related event (median 15.6 months vs. 9.8 months). Grade 3/4 hematologic toxicity was low (3% neutropenia, 6% thrombocytopenia, 13% anemia), with mild gastrointestinal side effects (nausea, diarrhea, vomiting) and fatigue being the most common non-hematologic adverse events.[4]

ERA 223, a phase 3, placebo-controlled trial (n=806), was conducted in asymptomatic or mildly asymptomatic chemotherapy-naïve CRPC patients with at least 2 bone metastases. Patients were randomly assigned to receive abiraterone/prednisone (or prednisolone) plus or minus radium-223. The study did not meet its primary endpoint of symptomatic skeletal event-free survival and showed higher bone fracture rates, especially in patients not on bone protective agents (BPA) such as bisphosphonate or denosumab. There was no significant difference in overall survival between the groups.[5]

Early results from the Phase 3 EORTC 1333/PEACE III trial also showed a higher fracture risk at 12 months with enzalutamide plus radium-223 compared to enzalutamide alone (37.1% vs 15.8%). Following the ERA 223 trial results, the PEACE III protocol was amended to require BPA for all patients. At 1.5 years, fracture incidence with BPA was 2.8% for radium-223 plus enzalutamide and 3.9% for enzalutamide alone. Without BPA, these rates were 45.9% and 22.3%, respectively. Additionally, enzalutamide plus radium-223 improved median progression-free survival by 3 months (16 vs 19 months).[6]

INDICATIONS AND NCCN GUIDELINE RECOMMENDATIONS

IN May 2013, Xofigo® received FDA approval for treating CRPC patients with symptomatic bone metastases and no visceral metastatic disease.[3] It is a category 1 recommendation in NCCN Guidelines.[2] While the PEACE III trial indicates radium-223 can be safely combined with secondary hormone therapy if a BPA is given, NCCN is awaiting more efficacy data before recommending this combination.[2,6]

RADIUM-223 PATIENT PROFILE: HEALTHCARE PROVIDER INSIGHTS

RADIATION Oncologists from First Urology and CCCN discuss selecting prostate cancer patients with bone metastases for radium-223, aligning with prescribing information. Matthew Schwartz, MD (CCCN) states, "Ideal candidates are those with bone metastases, progressive cancer, and a history of failure with standard therapies. Xofigo® is helpful for those patients because it is like a smart bomb. It looks for the cancer, attaches specifically to the cancer in the bones and delivers a payload of radiation. This not only helps kill the cancer, but helps the patient feel better by decreasing bone pain from the cancer." Michael Anderson, MD (CCCN) adds, "We follow classic indications: metastatic prostate cancer with symptomatic bone metastases who have failed anti-androgen treatment." Ryan Malone, MD (First Urology) uses Xofigo® for patients with minimally symptomatic bone metastases, not requiring narcotics, and at least five lesions in the castrate-resistant space.

ELEVATING PATIENT CARE THROUGH THE MULTIDISCIPLINARY TEAM

A multidisciplinary team ensures optimized patient care for radiopharmaceuticals. Dr. Anderson emphasizes the need for coordination between Medical Oncology, Radiation Oncology, Urology, and Nuclear Pharmacy for Xofigo® stating "Radioisotope therapy in general is just about impossible to give without a multidisciplinary management team." Dr. Schwartz values the convenience and improved patient care from a "one-stop shopping" model, facilitating immediate consultation regarding mutual patients with physician colleagues down the hall. Julie White highlights team accountability, while Mesfin Kidane notes reduced patient stress and easier schedule management.

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– Matthew Schwartz, MD

MONITORING PATIENTS AND ADVERSE EVENT MANAGEMENT

AT both practices, a comprehensive review is completed ensuring regimens are prescribed in accordance with labeled indications/national guidelines and dosing is appropriate based on patient's weight and labs.

When it comes to counseling patients on radium-223, Urologist Dr. Malone, says that monitoring is a shared responsibility between him and the treating Radiation Oncologist and that there are "a lot of touch points when patients are on therapy". Dr. Malone likes to see his radium-223 patients halfway through the six-month treatment course, with the Radiation oncologist taking ownership of monitoring the associated labs. A complete blood count and alkaline phosphatase are required for treatment at his practice. He emphasized that for radium-223 patients, abiraterone should be discontinued due to increased risk of fractures in patients seen in the clinical trial, as reviewed above.

> "The main thing we see other than some mild fatigue is diarrhea, so we sometimes intervene with pharmacological treatment, especially if refractory to some of the OTC drugs like loperamide."
>
> – Michael Anderson, MD

Patient-Centered Activities

- Counsel patients on side effects and to report signs of bleeding or infection.
- Educate patients on the importance of monitoring and advise patients to be compliant with all followup monitoring appointments.
- Inform patients to speak with their healthcare provider about any other medications they are currently taking for prostate cancer.
- Xofigo® had increased bone fractures when used in combination with abiraterone acetate and prednisone/prednisolone.
- Advise patients to stay well hydrated and to monitor oral intake, fluid status, and urine output while being treated with Xofigo®, and instruct patients to report signs of dehydration, hypovolemia, urinary retention, or renal failure/insufficiency.
- Inform patients that there are no restrictions regarding personal contact with other people after receiving Xofigo®; follow good hygiene practices while receiving Xofigo® and for at least one week after the last injection in order to minimize radiation exposure from bodily fluids to household members and caregivers.
- Whenever possible, patients should use a toilet, and the toilet should be flushed several times with the lid closed after each use.
- Clothing soiled with patient fecal matter or urine should be washed promptly and separately from other clothing.
- Caregivers should use universal precautions for patient care, such as gloves and barrier gowns, when handling bodily fluids to avoid contamination.
- Patient Assistance: NCODA Financial Assistance Tool.

EDUCATION ENHANCES PATIENTS' UNDERSTANDING OF RADIUM-223

EDUCATION

is imperative when patients are starting treatment with radium-223. At CCCN, education is provided during the initial consultation by the Radiation Oncologist and then subsequently by the radiation technologists when patients present for radiation treatment. Dr. Anderson states, "I think the ease of administration with Xofigo® really makes education much easier. The half-life is short, it is an alpha emitter so no shielding needs to be done, and the education is quite straight forward for this isotope versus other commercially available isotopes." He emphasized that since radium-223 is mainly eliminated through the gut, he counsels patients on the risk of stool contamination with radiation, especially in those patients with fecal incontinence. Kidane highlighted that most of the education he and his team provide is centered around preventing other people from being exposed to radiation via bodily fluids. He reviews "restroom hygiene" with patients, advising that hands should be washed and toilets flushed twice and to avoid splashing because that may lead to more widespread contamination.

At First Urology, radium-223 education is provided by the urologist and APP as patients are first referred into their practice as potential candidates for treatment. For specific counseling points, Dr. Malone advises his patients to stay hydrated and to be aware of their urine output commenting, "Patients should be urinating at least their normal amount, if not more, and need to watch the urine color and monitor their symptoms." He elaborated further "If they are feeling poorly and they hydrate and that helps, that's also a signal. Of course, their lab work could reflect significant dehydration, so we watch out for this as well." At CCCN, patients are not only encouraged to hydrate at home but are also given hydration prior to the delivery of each radium-223 dose.

PQI PROCESS

- **Xofigo® comes as a premeasured, patient-ready dose from the manufacturer**
- **Calculation formula available in the package insert for reference**
- **No adjustment needed for hepatic insufficiency or mild/moderate renal impairment**
- **Supplied in single-dose vials containing 6 mL of clear, colorless solution at a concentration of 1,100 kBq/mL (30 microcurie/mL) with a total radioactivity of 6,600 kBq/vial (178 microcurie/vial) at the reference date**
- **Store at room temperature, below 40°C (104°F)**

ADMINISTRATION:

- **Flush the intravenous access line or cannula with isotonic saline before and after injection**
- **Do not dilute or mix with any solutions**
- **Administer by slow intravenous injection over 1 minute**
- **Discard any unused portion per state and local regulations**

NCODA'S PQI RESOURCE

THE PQI resource contains clinician-directed guidance and criteria that can benefit the whole team. Key segments illustrate how medically integrated pharmacists and the team support physicians by providing medical and operational expertise. The Radium Ra 223 Dichloride (Xofigo®) Management PQI covers clinical trial information, side effects, monitoring, and patient-centered educational pearls. Regarding this PQI, Dr. Schwartz states "I like that it is concise. It is helpful to have everything all in one spot." While reviewing the PQI further, Dr. Malone

NCODA's PQI Resource - continued

again emphasized the importance of advising patients to discontinue abiraterone while receiving Radium-223 and confirming the value of having this information included in the resource. At his practice site, he admits to using an "operationalized form of the PQI, but with checkboxes."

RADIUM-223 STANDARD OPERATING PROCEDURES

IN terms of operations at CCCN, Tuesday Carroll (Radiology Scheduling) states she and her team utilize a spreadsheet to help stay organized and track patients throughout their system. At the time of initial consultation with the Radiation Oncologist, the patient signs a consent form and then the treatment request is sent to the authorization department. Once authorization is obtained, Radiology Scheduling contacts the patient to review the treatment schedule including six monthly injections and six associated lab draws, planned within one week prior to each injection. Once labs have resulted and are deemed acceptable by the treating physician, the patient is placed on the treatment schedule and the radium-223 dose is ordered. Then, Kidane and his team of radiation technologists administer the radium-223 infusion once lab results are again reviewed and confirmed acceptable by the treating physician.

At First Urology, Dr. Malone's team utilizes a checklist to help facilitate the radium-223 approval process. After patients meet with Dr. Malone and the Radiation Oncologist and all in in favor of proceeding with radium-223, the drug is ordered. Treatment is administered by the Radiation Oncologist and Nuclear Medicine Technologist at the Radiation Center.

ACCESS TO THERAPY

Financial barriers not only lead to significant stress for the patient, but they can also lead to treatment delays. It is beneficial to have dedicated staff to help patients navigate the treatment authorization process.

At CCCN, Schwartz and Anderson highlighted how their site has their own team of in-house financial counselors and prior authorization personnel to help facilitate insurance approvals. Dr. Schwartz commented that for radium-223, "Approval is not usually a problem because if you select the right patients, it is on guideline, but it may take a couple of weeks for approval." Julie White, who works in the in-office dispensary at First Urology, commented that "Xofigo® can be time consuming because of the way the treatment is set up. Depending on the patient's insurance, prior authorizations can sometimes expire before the first treatment, which can necessitate a second or a third prior authorization. This is especially seen in patients who have their treatment delayed." For patients with a barrier to obtaining insurance approval, Schwartz called attention to the Bayer Access Program through the manufacturer as another potential avenue to assist patients with coverage and reimbursement.

As another point of emphasis, White discussed how some insurers push back if a patient weighs more than 150 kg, as it causes the Radium-223 dose to exceed the recommended 224 microcuries maximum. In these cases, the team is required to obtain authorization for the additional microcuries, which may take another 24-48 hours for approval. She also highlighed that certain insurance companies have a different timeframe requirement when it comes to completing labs in relation to radium-223. Although radium-223 prescribing information states ten days, some insurers require 6 days, making it important for the team to be aware of potentially different requirements amongst insurers to avoid unnecessary treatment delays.

From a practice reimbursement perspective, Dr. Anderson states that "The only financial toxicity we have run into is when we first started giving the drug. Our local Medicare Administrative Contractor (MAC) would only reimburse us for what our practice pays for the drug. When you look at that, we would actually lose money because of the cost of administration and the staff we must hire." Anderson further elaborates that "Bayer instituted a rebate program based on the volume of or amount of microcuries delivered each quarter and it has been helpful to us. Otherwise, we would be losing revenue on every Medicare patient. Bayer has done a wonderful job of making practices whole and facilitating access for patients with limited resources."

SUMMARY

RADIUM-223 is an alpha emitting radiopharmaceutical used to treat patients with CRPC with symptomatic bone metastases, offering survival benefits and delaying time to skeletal-related events. Multidisciplinary centers provide many benefits including convenience, optimized care, and authorization assistance. Important counseling points for patients initiating radium-223 include the risk of myelosuppression, gastrointestinal side effects, ensuring adequate hydration/monitoring urine output, and minimizing radiation exposure to others. Routine labs are essential, with awareness of potentially different insurer requirements. Finally, the team values concise resources such as the PQI to ensure all important tasks are completed in radium-223 patients.

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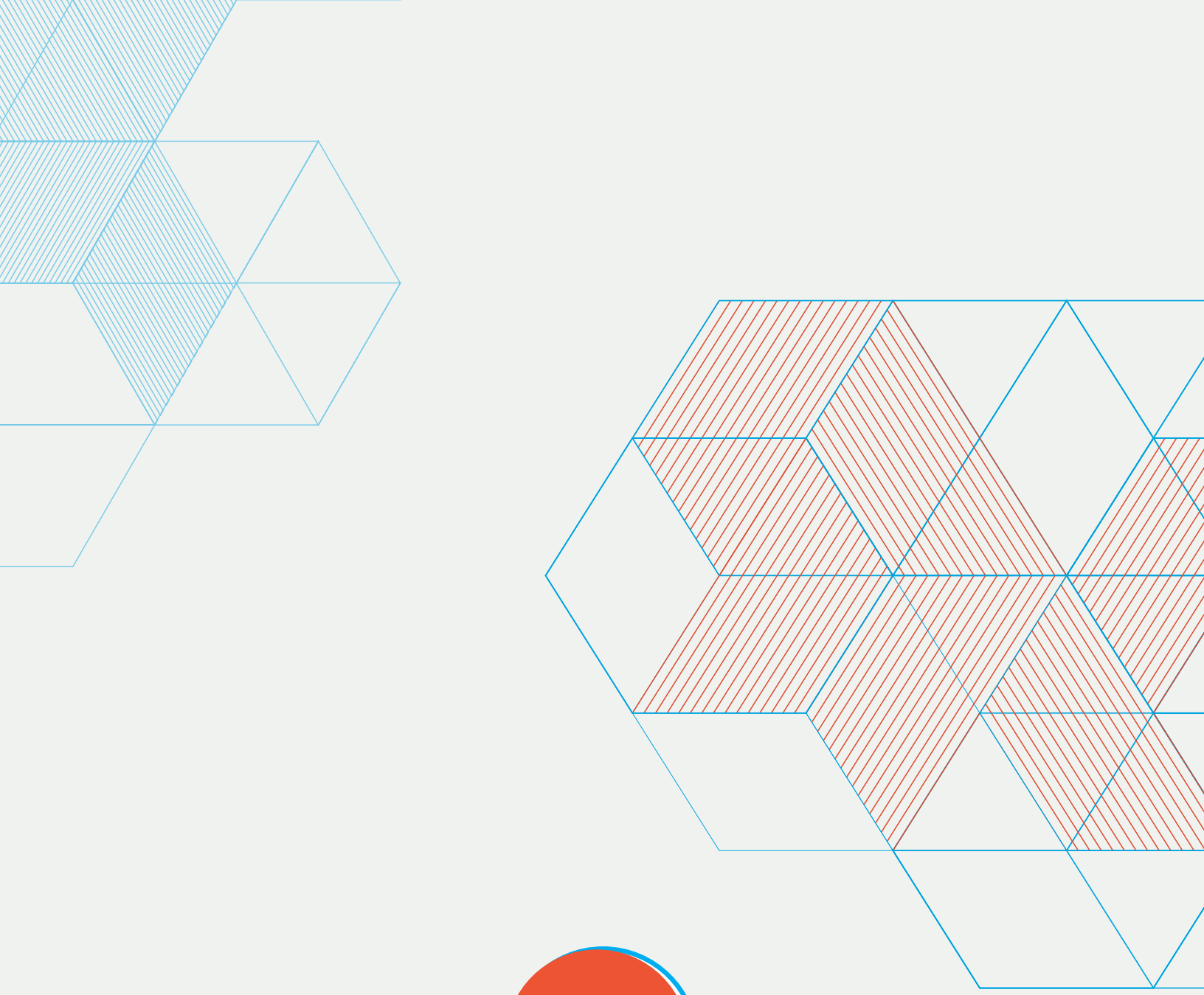

Practice panelist's comments reflect their experiences and opinions and should not be used as a substitute for medical judgment.