Treatment of Bone Metastasis with Bone-Targeting Radiopharmaceuticals

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Abstract

Bone is a common metastatic site of cancer. Bone metastasis reduces life expectancy and results in serious symptoms and complications such as bone pain, pathological fractures, and spinal cord compression, decreasing quality of life by restricting sleep and mobility. Treatment for bone metastasis includes drugs (pure analgesics, hormones, cytotoxic chemotherapy, and bisphosphonates, among others), external radiation therapy, surgery, and radionuclide therapy using bone-targeting radiopharmaceuticals. Particulate radiation with α - or β -rays is used as a bone-targeting radiopharmaceutical in radionuclide therapy. β -Emitters have lower energy and a longer range than α -emitters and have less tumoricidal activity and deliver more radiation to adjacent normal tissue. Therefore, the main therapeutic effect of bone-targeting β -emitters such as ^{89}Sr -dichloride is bone pain palliation rather than enhanced survival. In contrast, α -emitters such as ^{223}Ra -dichloride have high energy and a short range, resulting in greater tumoricidal activity and less radiation damage to adjacent normal tissue. Treatment with bone-targeting α -emitters can improve survival and decrease bone pain. This review focuses on the principles and clinical utility of several clinically available bone-targeting radiopharmaceuticals in metastatic bone disease.

Keywords Bone metastasis · Pain palliation · Bone-targeting radiopharmaceutical · β -emitter · α -emitter

Introduction

Bone is a common metastatic site of cancer. The incidence of skeletal metastasis is highest in advanced breast or prostate cancer, followed by thyroid, kidney, and lung cancer. Bone metastasis reduces life expectancy and results in serious symptoms and complications such as bone pain, pathological fractures, and spinal cord compression, which decrease quality of life by restricting sleep and mobility. Therefore, appropriate treatment is essential [1, 2].

Bone metastases are typically classified into osteolytic, osteosclerotic, or mixed, based on simple radiographic findings [1–3]. If bone resorption mainly occurs in relation to increased osteoclastic activity, it results in focal bone

destruction, and the bone has an osteolytic appearance on simple radiographs. Osteolytic metastasis is commonly observed in patients with multiple myeloma, melanoma, or lung, thyroid, breast, renal, or gastrointestinal cancers. In contrast, if new bone formation is mainly due to increased osteoblastic activity, metastatic lesions have an osteosclerotic appearance on simple radiographs. Osteosclerotic metastasis is commonly observed in patients with prostate, lung, or breast cancer. However, these two bone processes usually occur simultaneously in affected bones. The type of bone metastasis usually does not affect the choice of treatment modality with the exception of bone-targeting radiopharmaceuticals.

Treatment options for bone metastasis include drugs (pure analgesics, hormones, cytotoxic chemotherapy, and bisphosphonates, among others), external radiation therapy, surgery, and radionuclide therapy using bone-targeting radiopharmaceuticals [1–4]. Each treatment modality has specific clinical indications, advantages, and disadvantages. This review focuses on the principles and clinical utility of several clinically available bone-targeting radiopharmaceuticals.

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Bone-Targeting Radiopharmaceuticals for Bone Metastasis

Requirements for optimal bone-targeting radiopharmaceuticals are: [5]

- (1) Selective uptake and prolonged retention in metastatic bones with a high metastatic-to-normal bone uptake ratio;
- (2) Rapid clearance from nonskeletal sites and fast excretion into urine or feces;
- (3) Biodistribution that can be estimated by imaging modalities such as bone scans;
- (4) Simple production process, good radiochemical stability, and clinical availability;
- (5) Cost-effectiveness;
- (6) Low toxicity and few side effects;
- (7) Radiation safety for patients and nuclear medicine staff;
- (8) Clinically proven therapeutic effects of reduced analgesic use and bone pain palliation and/or survival benefits.

Physical and radiation properties of several representative therapeutic bone-targeting radiopharmaceuticals are listed in Table 1 [5–9]. Among them, only ^{89}Sr -dichloride and ^{223}Ra -dichloride are clinically available in Korea. All therapeutic bone-targeting radiopharmaceuticals except ^{223}Ra -dichloride are β -emitters. β -Emitters have lower energy and a longer range than α -emitters and therefore have less tumoricidal activity and deliver more radiation to adjacent normal tissue than α -emitters. Therefore, the main therapeutic effect of bone-targeting β -emitters is bone pain palliation rather than survival. In contrast, α -emitters have a higher energy and shorter range than β -emitters and therefore have greater tumoricidal activity and deliver less radiation to adjacent normal tissue. With bone-targeting α -

emitters, survival benefits are possible along with bone pain palliation. Several β -emitters with abundant γ -emission such as ^{188}Re -hydroxyethylidene diphosphonic acid (HEDP), ^{153}Sm -ethylenediamine tetra methylene phosphonic acid (EDTMP), $^{117\text{m}}\text{Sn}$ -diethylenetriamine pentaacetic acid (DTPA), and ^{177}Lu -EDTMP can also be used for gamma camera imaging, which facilitates in vivo imaging for theranostics combined with tumor treatment (Fig. 1).

Pain from bone metastasis is chronic. Underlying mechanisms of pain include neurochemical changes in expression of substance P, c-Fos, and dynorphin at the spinal cord level, central sensitization, peripheral sensitization, production of algogenic substances by tumor cells and inflammatory cells, sustained activation of osteoclasts, and nerve compression and injury caused by tumor growth [10]. Among these mechanisms, the cytotoxic effects of particulate radiation on radiation-sensitive inflammatory cells such as lymphocytes appear to be most important for reducing bone pain because of the associated decrease in pain-related cytokines [9–12].

In general, bone-targeting radiopharmaceuticals have several advantages compared to other treatment modalities for symptomatic metastatic bone pain [5, 6]. Radionuclide therapy using bone-targeting radiopharmaceuticals is beneficial for diffuse bone pain caused by multiple metastases. Second, this therapy is appropriate for application in cases of poor response to other therapies or when there is concern about overuse of analgesics. Several factors should be taken into consideration when planning to use bone-targeting radiopharmaceuticals [5, 6]. Bone-targeting radiopharmaceuticals accumulate mainly in osteosclerotic, osteoblastic bone metastasis. They are therefore not suitable for treating osteolytic, osteoclastic bone metastasis. Furthermore, in metastatic bones vulnerable to fracture, local therapy such as surgery or radiation therapy should be performed prior to radionuclide therapy.

Table 1 Physical and radiation properties of representative therapeutic bone-targeting radiopharmaceuticals (modified from Refs. 5–9)

Radiopharmaceutical	Physical half-life	β -Emission (MeV) maximum, additional (% abundance)	Mean β -emission (MeV)	Maximum range in soft tissue (mm)	γ -Emission (MeV) (% abundance)
^{32}P -orthophosphate	14.3 days	1.71	0.70	8.1	None
^{89}Sr -dichloride	50.5 days	1.46, 0.58	0.58	7	0.909 (0.1%)
^{186}Re -HEDP	3.7 days	1.07, 0.93	0.33	4.5	0.137 (9%)
^{188}Re -HEDP	17.0 h	2.12, 1.97	0.64	11	0.155 (15%)
^{153}Sm -EDTMP	46.3 h	0.81, 0.71, 0.64	0.23	2.5	0.103 (29%)
$^{117\text{m}}\text{Sn}$ -DTPA	13.6 days	0.152†, 0.127†	—	0.9	0.159 (86%)
^{177}Lu -EDTMP	6.7 days	0.498, 0.385	0.14	2	0.208 (11%)
^{223}Ra -dichloride	11.4 days	α : 7.53, 6.88, 6.68, 5.78 (95.3%); β : 1.37, 0.584, 0.001 (3.6%)	—	< 100 μm	0.82, 0.154, 0.269, 0.351, 0.402 (1.1%)

†Conversion electron

Fig. 1 Posterior bone scan images after injection of ^{99m}Tc -MDP (left, 925 MBq) and ^{188}Re -HEDP (right, 1850 MBq) in a 55-year-old female patient with metastatic breast cancer. The two images are very similar except for the radioactive left scapula lesion on the ^{188}Re -HEDP bone scan. (Courtesy of Dr. Byung Hyun Byun, Department of Nuclear Medicine, Korea Cancer Center Hospital, Korea Institute of Radiological and Medical Sciences, Seoul, Korea)

There are several requirements for bone pain palliation by β -emitters [5, 6, 13]. First, osteoblastic metastasis must be confirmed by bone scintigraphy. Second, the pain should correlate with the sites of osteoblastic metastases. Third, renal function should not be impaired, and the patient should not be pregnant, breast-feeding, have spinal cord compression, impending bone fractures, or extensive bone metastasis (metastasis with a ‘super scan’ appearance). Recommended biochemical parameters of renal function are creatinine $\leq 180 \mu\text{mol/l}$ and/or glomerular filtration rate $\geq 30 \text{ ml/min}$. Fourth, patients should be hematologically stable. Relative contraindications include serum hemoglobin $< 90 \text{ g/l}$, total white blood cell count $< 3.5 \times 10^9/\text{l}$, and platelet count $< 100 \times 10^9/\text{l}$. However, in some situations, a total white blood cell count $\geq 2.4 \times 10^9/\text{l}$ and platelet count $\geq 60 \times 10^9/\text{l}$ are acceptable. Finally, the life expectancy of patients should be more than 3 months [13].

Although there are no definite differences in the efficacy of bone pain palliation among the various β -emitters available, the duration of response is longer for long-lived radioisotopes

(i.e., ^{89}Sr -dichloride) than for short-lived isotopes (i.e., ^{186}Re -HEDP and ^{153}Sm -EDTMP) [13]. In responding patients, in cases of recurrent pain, retreatment can be effective and safe if hematological parameters have fully recovered, although the quality of response can decrease with treatments. The minimum interval should be of 8 weeks for ^{153}Sm -EDTMP, 6–8 weeks for ^{186}Re -HEDP, and 12 weeks for ^{89}Sr -dichloride [14, 15]. Clinical indications of representative therapeutic bone-targeting radiopharmaceuticals along with the current authority approval status are summarized in Table 2.

^{32}P -Orthophosphate

^{32}P -orthophosphate is a reactor-produced, pure β -emitting, clinically available bone-seeking radionuclide that has been used to treat palliative bone metastasis since the 1950s [16]. It can be orally or intravenously administered at a single dose of 185–444 MBq or up to 888 MBq in multiple doses. About 85% of the administered dose is

Table 2 Clinical indications of representative therapeutic bone-targeting radiopharmaceuticals

Radiopharmaceutical	Approved by Korea MFDS	Approved by US FDA	Approved by EU	Other potential indications in literature
^{32}P -orthophosphate	None	None	None	Prostate cancer, breast cancer
^{89}Sr -dichloride	Prostate cancer	Prostate cancer	Prostate cancer	Lung cancer, breast cancer, etc.
^{186}Re -HEDP	None	None	Prostate cancer, breast cancer	
^{188}Re -HEDP	None	None	None	Prostate cancer, breast cancer
^{153}Sm -EDTMP	None	Prostate cancer, lung cancer, breast cancer, osteosarcoma, etc.	Prostate cancer, lung cancer, breast cancer, osteosarcoma, etc.	
^{117m}Sn -DTPA	None	None	None	Prostate cancer, breast cancer
^{177}Lu -EDTMP	None	None	None	Prostate cancer, breast cancer
^{223}Ra -dichloride	Prostate cancer	Prostate cancer	Prostate cancer	Breast cancer

incorporated into hydroxyapatite in the bone matrix. ^{32}P -orthophosphate is often given with an androgen such as testosterone to stimulate bone uptake in patients with metastasis from breast or prostate cancer [17–19].

Response rates for bone pain palliation in prostate cancer are between 59% and 93% (overall 77%), and those in breast cancer are between 52% and 94% (overall 84%). However, no definite dose-response relationship has been established. Pain palliation typically occurs within 14 days, with a range of 2 days to 4 weeks. Mean reported duration of pain palliation from ^{32}P -orthophosphate is 5.1 ± 2.6 months, with the longest responses noted as 16.8 ± 9.4 months for multiple doses [19].

As many as 50% of patients receiving both androgen and ^{32}P -orthophosphate experience a transient increase in pain (known as the “flare phenomenon”). A major concern with ^{32}P -orthophosphate is hematological toxicity, including bone marrow suppression. Pancytopenia dose-dependently occurs around 4–5 weeks, with recovery by 6–7 weeks. Occurrence of acute leukemia after ^{32}P -orthophosphate therapy has been reported in addition to polycythemia vera. Grade 4 leukopenia and thrombocytopenia are rare [20]. However, due to the higher toxicity of ^{32}P -orthophosphate than other bone-seeking therapeutic radiopharmaceuticals such as ^{89}Sr -dichloride, it is rarely used clinically for bone pain palliation and has not been officially approved by the US Food and Drug Administration (FDA) or Korean Ministry of Food and Drug Safety (MFDS) [21, 22].

^{89}Sr -Dichloride

Because ^{89}Sr is in the same periodic table of elements family as calcium, it localizes in bones, primarily in areas of high osteoblastic activity. The usual therapeutic dose is 148 MBq (4 mCi) or 1.48 MBq/kg (40 $\mu\text{Ci/kg}$). After intravenous injection of ^{89}Sr as $^{89}\text{SrCl}_2$, 30–35% of the radiopharmaceutical binds to the hydroxyapatite bone matrix as a substitute for calcium for 10–14 days with 20% retention at 3 months. The remaining radiopharmaceutical is excreted by renal (80%) and fecal routes (20%) and has a biological half-life of 4–5 days [23].

Response rates for bone pain palliation are between 60% and 90% (overall 76%), with complete pain relief in 5–20% of patients [20–22, 24–26]. Pain palliation occurs within 4–28 days, with a mean pain reduction duration of 3–6 months, up to 15 months. Retreatment for responders is possible at approximately 3-month intervals. Like ^{32}P -orthophosphate, the symptomatic flare phenomenon can occur in the first 1–5 days after administration, which predicts a good response. Complete pain relief and myelosuppression show a dose-response relationship [27, 28]. Hematological toxic effects are the most commonly observed side effects, with a decrease in white blood cell count of 11–65% occurring in 12–80% of

patients [26]. The platelet count decreases by about 29% in 29–80% of patients, whereas the red blood cell count does not change significantly [26]. The nadir of leukopenia and thrombocytopenia is observed at 5–8 weeks after administration, and recovery is seen at 10–16 weeks [21, 22, 28–30].

Clinical indications for ^{89}Sr -dichloride therapy are alternative or supplemental therapy for pain palliation for symptomatic osteoblastic metastasis, usually confirmed by bone scintigraphy, which leads to less opiate use and improved quality of life [25, 26]. The most positive clinical results are seen in patients with prostate, breast, or lung cancer. Promising results have also been reported for small numbers of patients with head and neck, colorectal, or urological cancer [25, 26]. Although using ^{89}Sr -dichloride therapy to prolong patient survival is still controversial, several studies have shown that ^{89}Sr -dichloride therapy can be beneficial. Patients with decreased tumor markers after ^{89}Sr -dichloride therapy lived more than twice as long as patients with no tumor marker response [31]. For prostate cancer, prolongation of mean survival was observed with use of ^{89}Sr -dichloride plus doxorubicin (vs. doxorubicin alone) or ^{89}Sr -dichloride alone (vs. placebo) [32, 33]. However, no well-designed phase III studies have shown that ^{89}Sr -dichloride therapy improves patient survival. Currently, ^{89}Sr -dichloride therapy is covered by the Korean National Healthcare Insurance, as well as approval authorities in the US and Europe, for castration-resistant prostate cancer (CRPC) with symptomatic osteoblastic metastasis only, despite positive clinical results for other kinds of cancers.

Several studies have compared the therapeutic efficacy of ^{89}Sr -dichloride to that of other bone-seeking β -emitters including ^{32}P -orthophosphate, ^{186}Re -HEDP, ^{188}Re -HEDP, and ^{153}Sm -EDTMP [21, 24, 34, 35]. These studies, including two randomized controlled trials, reported no significant difference between ^{89}Sr -dichloride and other bone-seeking radiopharmaceuticals in terms of response rate for bone pain palliation or toxic effects. Therefore, factors such as availability, cost, clinical preference, and clinical experience will determine the choice of β -emitter.

^{186}Re -HEDP

Although ^{186}Re is not a calcium analog, ^{186}Re -HEDP, a chelator of bone-seeking polyphosphonates, localizes into bones by binding to hydroxyapatite crystals, forming hydroxide bridges via hydrolysis reactions. Approximately 70% of intravenously injected activity is excreted in the urine within 24 h. Clinical studies using ^{186}Re -HEDP were performed in patients mainly with CRPC or breast cancer [36–40]. Overall response rates for pain palliation were between 38% and 82% with ^{186}Re -HEDP doses of 1295 MBq to 1406 MBq. Typically, a

pain response occurred 1–3 weeks after injection with a duration of 5–12 months. There is no definite relationship between dose and pain response [41]. Similar to ^{89}Sr -dichloride, a transient rise in pain intensity occurs 5 days after treatment with a duration of 2–10 days and is not related to overall pain response. The main side effects are hematological such as thrombocytopenia and are mild and reversible. Two placebo-controlled studies reported a significant reduction in the pain index in the ^{186}Re -HEDP group compared with the placebo group [42, 43]. However, due to the lack of well-designed phase III studies, ^{186}Re -HEDP has not been officially approved by the US FDA or Korean MFDS. However, ^{186}Re -HEDP is clinically available in Europe.

^{153}Sm -EDTMP

Although Sm, similar to ^{186}Re , is not a calcium analog, ^{153}Sm -EDTMP is a chelator of bone-seeking polyphosphonates and localizes into bone after intravenous injection (37 MBq/kg is the recommended dose) with a higher affinity for metastatic than normal bones. No specific localization occurs outside the skeleton. Free ^{153}Sm -EDTMP is excreted mainly via urine within 8 h. Pain relief occurs in 60–85% of patients within 1 week of administration, with a definite dose-response relationship. Transient myelosuppression is the most common side effect [44]. In several phase II/III clinical trials, ^{153}Sm -EDTMP has shown significant efficacy for bone pain palliation in patients with various types of cancer including breast cancer, lung cancer, osteosarcoma, and prostate cancer [45–47]. ^{153}Sm -EDTMP (Quadramet®, ^{153}Sm -Lexidronam) is approved for relief of pain in patients with osteoblastic metastatic bone lesions confirmed by radionuclide bone scan in both the US and Europe. However, ^{153}Sm -EDTMP is not clinically available in Korea. Like other bone-seeking β -emitters, there is no definite evidence that ^{153}Sm -EDTMP therapy improves patient survival.

^{223}Ra -Dichloride

^{223}Ra -dichloride is an α -emitting radioisotope of ^{226}Ra in the same periodic table of elements family as calcium. After intravenous injection, it is quickly taken up in hydroxyapatite crystals in newly forming bones. Although ^{223}Ra -dichloride is not taken up by tumor cells, high-energy ionizing α -particles from ^{223}Ra -dichloride can cause lethal double-strand DNA breaks in adjacent tumor cells in bones. These breaks can result in a highly localized antitumor effect in targeted areas containing metastatic cancer cells. In addition, the shorter range of α -particles (< 100 μm , less than 10 cell diameters) compared to β -particles contributes to lower toxicity in normal bone marrow.

In 1915–1916, radioactive radium was first used for cancer therapy as a form of external radiation therapy or brachytherapy [48]. Based on promising results from experimental skeletal metastases models [49], results of the first phase I clinical trial were reported in 2005 for patients with breast or prostate cancer [50]. Results for the first phase II clinical trial were reported in 2007 for patients with CRPC [51]. Based on the good results obtained in the phase II trial, a phase III ALSYMPCA trial was performed, and the results were published in 2013 [52]. This randomized double-blind placebo-controlled study on the use of ^{223}Ra in 921 CRPC patients with symptomatic bone metastases, no visceral metastases, and previous use of docetaxel compared with placebo showed significant improvements in overall survival, time to first symptomatic skeletal event, and biochemical response. In May 2013, the US FDA approved ^{223}Ra -dichloride (Xofigo Injection; Bayer HealthCare Pharmaceuticals, Inc.) for treatment of patients with CRPC, symptomatic bone metastases, and no known visceral metastatic disease. European FDA approval of ^{223}Ra -dichloride for the same clinical indications as in the USA occurred in November 2013, whereas the Korean MFDS approved ^{223}Ra -dichloride for the same clinical indications in January 2014.

Biodistribution, Pharmacokinetics, and Radiation Safety

After intravenous injection, ^{223}Ra -dichloride is rapidly cleared from the blood, with less than 1% activity remaining in plasma at 24 h [50, 53]. Excretion is mainly through the gastrointestinal tract. Early excretion is by the small bowel, and subsequent fecal excretion with about 52% of administered activity occurs at 24 h. There is no evidence of hepatobiliary clearance. Urinary excretion is small at less than 5% of injected activity.

The calculated absorbed dose based on the International Commission on Radiological Protection Publications 67 and 103 is highest in the bone endosteum (cortical bone), followed by the red marrow, liver, colon, and large intestine [54]. ^{223}Ra -dichloride has the highest bone surface to red bone marrow dose ratio, followed by ^{153}Sm -EDTMP and ^{89}Sr -dichloride [55].

Dose rates from patients who have undergone ^{223}Ra -dichloride therapy at 50, 100, or 200 kBq/kg of body weight have been reported to be less than 2 $\mu\text{Sv/h}$ per MBq on contact and 0.02 $\mu\text{Sv/h}$ per MBq on average at 1 m following injection [56]. Therefore, patients who undergo ^{223}Ra -dichloride therapy do not need to be hospitalized.

Toxicity

Hematological toxicity from ^{223}Ra -dichloride is relatively mild compared with other bone-seeking β -emitters. No

clinical trials have found clinically meaningful differences in the frequency of grade 3/4/5 adverse events between patients treated with ^{223}Ra -dichloride and those treated with a placebo [50, 51]. Because bone marrow suppression varies widely, serum blood cell counts of patients must be evaluated at baseline and before each administration of the radiopharmaceutical. The recommended dosing schedule for ^{223}Ra -dichloride is one intravenous injection every 4 weeks for 6 months (total six injections) at 50 kBq/kg body weight activity per injection. Before the first administration, the absolute neutrophil count (ANC) should be $\geq 1.5 \times 10^9/\text{l}$, platelet count $\geq 100 \times 10^9/\text{l}$, and hemoglobin $\geq 10.0 \text{ g/dl}$. Before subsequent administrations, ANC should be $\geq 1.0 \times 10^9/\text{l}$ and platelet count $\geq 50 \times 10^9/\text{l}$. If no recovery occurs within 6–8 weeks after final administration of ^{223}Ra -dichloride, despite standard supportive care, further treatment should be continued only after a careful risk-benefit evaluation [57]. In general, ^{223}Ra -dichloride is not indicated for patients who are pregnant, are eligible for docetaxel treatment, have visceral or brain metastasis, or have imminent or established spinal cord compression. ^{223}Ra -dichloride should be used carefully in patients with recent or ongoing cytotoxic chemotherapy, prior hemibody external radiotherapy, lymphadenopathy exceeding a 3-cm short-axis diameter, any size pelvic lymphadenopathy thought to contribute to concurrent hydronephrosis, Crohn's disease, ulcerative colitis, myelodysplastic or myeloproliferative syndromes, unstable fracture, or jaw osteonecrosis.

Very common side effects ($\geq 10\%$) include thrombocytopenia, nausea, vomiting, and diarrhea. Common side effects ($\geq 1\%$) include neutropenia, pancytopenia, leucocytopenia, and injection site reaction. Uncommon side effects ($< 1\%$) include lymphocytopenia [57]. The occurrence of a second primary cancer related to this therapy after 3 years of follow-up has not been reported.

Clinical Effectiveness

Most clinical studies of ^{223}Ra -dichloride have been performed in patients with metastatic CRPC. Metastatic CRPC is known to have a poor prognosis, with a 5-year survival rate of about 25% and a 40-month median survival. Standard therapy for CRPC with bone metastasis is docetaxel-based chemotherapy. However, if the treatment fails, no alternative therapy exists. The pivotal phase III ALSYMPCA randomized double-blind placebo-controlled trial was based on promising phase I and II studies [49–51]. The trial studied use of ^{223}Ra -dichloride in 921 patients with metastatic CRPC with symptomatic bone metastasis, previous use of analgesics or recent radiotherapy to bones, and no visceral metastasis and found significant improvements in median overall survival (14.9 months in the ^{223}Ra -dichloride group vs. 11.3 months

in the placebo group, hazard ratio = 0.70, $p < 0.001$) and median time to the first symptomatic skeletal event (15.6 months in the ^{223}Ra -dichloride group vs. 9.8 months in the placebo group, hazard ratio = 0.66, $p < 0.001$) [52]. In subgroup analyses, the ^{223}Ra -dichloride group had significantly better survival than the placebo group irrespective of baseline serum alkaline phosphatase (ALP) level, previous docetaxel use, current bisphosphonate use, or previous opioid use. For secondary end points, the ^{223}Ra -dichloride group had significantly longer median time to increased total ALP, longer median time to increased serum prostate-specific antigen, more patients with $\geq 30\%$ reduction in total ALP response, and more patients with normalization of total ALP than the placebo group. No significant differences were seen in frequency of hematological or nonhematological adverse events between the two groups.

Issues for Discussion

^{223}Ra -dichloride therapy has several important caveats. First, it is expensive, at approximately 10,000 USD (about 8,000,000 KRW in Korea) per injection. In the standard protocol, six injections are necessary. Although Medicare in the US covers ^{223}Ra -dichloride therapy if reasonable and necessary, this treatment is not covered by the National Health Insurance in Korea. Considering the variable prices and treatment durations for bone metastasis, performing a cost-benefit analysis for ^{223}Ra -dichloride therapy is difficult. In the US, six cycles of treatment with ^{223}Ra -dichloride were found to cost 69,000 USD. Although this is more than docetaxel (approximately 14,500 USD for a course of 10 cycles plus ancillary costs), it is similar to enzalutamide (approximately 60,000 USD for 8 months of treatment) and costs less than a course of sipuleucel-T (93,000 USD) [58]. The ALSYMPCA trial observed a 24% reduction in the annual number of hospitalizations and 6.5 fewer hospitalization days per patient per year in patients treated with ^{223}Ra -dichloride. This is probably due to a delay in the occurrence of symptomatic skeletal events [52, 59]. A second issue is the availability of ^{223}Ra -dichloride. Currently, ^{223}Ra -dichloride is produced only at the Institute for Energy Transfer, Isotope Laboratory, Kjeller, Norway. Delivery of ^{223}Ra -dichloride to global hospitals can take days to weeks. This delivery time limits urgent use of ^{223}Ra -dichloride. A third issue is whether ^{223}Ra -dichloride is useful for treating symptomatic bone metastasis other than CRPC. Although there are several published or ongoing clinical trials on use of ^{223}Ra -dichloride to treat various kinds of cancers with bone metastasis other than CRPC, currently no completed phase III studies regarding the utility of ^{223}Ra -dichloride therapy in such cancers are available [60].

Future Directions and Conclusion

Radionuclide therapy using bone-seeking radiopharmaceuticals is a safe and effective therapy for bone pain palliation in various kinds of cancer with bone metastasis, mainly prostate cancer. Although it is controversial whether β -emitters improve survival, the combination of radionuclide therapy with other therapies such as chemotherapy or external radiation therapy has the potential to improve patient survival. This possibility deserves further well-designed phase III trials. Radionuclide therapy using the α -emitter Ra-223 is a safe and effective therapy for CRPC with bone metastasis and can result in bone pain palliation and survival gains. Further clinical trials are needed to assess the utility of Ra-223 in other cancer types.

Compliance with Ethical Standards

Conflict of Interest Joon Young Choi declares that he has no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Not applicable.

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