



Radionuclide Therapy in the Treatment of Bone Metastases

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Introduction

The use of radionuclides for the treatment of painful bone metastases is based on the principle of targeting the metastatic foci causing the pain and delivering the radiopharmaceuticals via the systemic route. Beta-emitting radionuclides administered for pain palliation largely reach the bone metastases and micrometastases and negligibly the hematopoietic bone marrow. Systemic targeted therapy has potential pain relief with minimal side effects in diffuse metastatic disease.[1] Radionuclides used in this field include beta particle-emitting radionuclides like Phosphorus-32 (^{32}P), Strontium-89 (^{89}Sr), Rhenium-186 (^{186}Re), Rhenium-188 (^{188}Re), Samarium-153 (^{153}Sm), Lutetium-177 (^{177}Lu), and Holmium-166 (^{166}Ho), and alpha particle-emitting radionuclides such as Radium-223 (Table 1). Studies have revealed that the alpha-emitting Ra-223 prolongs the life expectancy of the patients in addition to pain palliation.[2] Radiopharmaceuticals have different advantages and disadvantages based on their pain relief period, tumoricidal effect, treatment repeatability, and toxicities. The main route for the removal of all the radionuclides, except ^{223}Ra , is renal excretion; ^{223}Ra is eliminated through gastrointestinal excretion.

Prostate cancer is typically characterized by osteoblastic metastases. However, renal cell cancer, thyroid cancer, plasmacytoma, and multiple myeloma are presented with lytic bone metastases. Mixed bone metastases consisting of both osteoblastic and osteolytic metastases are more frequently observed in breast, lung, colorectal, and pancreatic cancers.[3] In nuclear medicine, pain palliation by radionuclides is most frequently used for patients with prostate and breast cancer as it targets osteoblastic metastases.[4]

Patient Selection

Life expectancy should be at least three months in patients selected for radionuclide therapy. Bone spread of the disease should be assessed in the bone scintigraphy 4-8 weeks before the treatment, and it should be ensured that the osteoblastic metastases sites and the localization of pain symptoms are similar. Severe lytic lesions, which may cause pathological fracture or cord compression, should be excluded using radiological images. Moreover, blood counts and renal function tests should be assessed one week before the treatment. Recommended treatment limits for blood counts include >9 g/dL for hemoglobin, $>3.5 \times 10^9$ for total white cell count, and $>100 \times 10^9$ for platelet count. The patient should not have a history of chemotherapy and/or radiotherapy to a large area within the last 4-12 weeks.[5]

Contraindications

Hematological adverse effects such as neutropenia and thrombocytopenia might be seen in the patient group with a limited bone marrow reserve. In this patient group, the treatment needs to be administered with close monitoring and after a clinical benefit-risk assessment. The 'Superscan' finding in bone scintigraphy with a completely infiltrated bone marrow constitutes an absolute contraindication due to its hematological adverse effects. In the case of neurogenic pain and spinal cord compression, radionuclide therapies are not administered. Furthermore, pregnancy and lactation also constitute absolute contraindications. Therefore, the therapy should be administered after conducting a pregnancy test on the day of the treatment.[5]

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Table 1 Characteristics of the radionuclides used for the treatment of bone metastases

Radionuclide	Pharmaceutical	Half-life (days)	Emission	Energy (Maximum/Mean)	Maximum travel distance in tissue (mm)	Elimination
³² P	Orthophosphate	14.3	β	1.71/0.695	8/3	Renal
⁸⁹ Sr	Dichloride	50.5	β	1.46/0.583	6.7/2.4	Renal
¹⁵³ Sm	EDTMP	1.93	β γ	0.81/0.233	2.5/0.6	Renal
¹⁸⁶ Rhenium	HEDP	3.7	β	1.07/0.349	4.5/1.1	Renal
¹⁸⁸ Rhenium	HEDP	0.7	β	2.12/0.64	11/3	Renal
¹⁷⁷ Lutetium	EDTMP DOTMP	6.73	β γ	0.489/0.133	1.7/0.23	Renal
¹⁶⁶ Holmium	EDTMP DOTMP	1.12	β γ	1.84/0.67	8.7/4.0	Renal
²²³ Ra	Dichloride	11.4	α β γ	Maximum α Energy: 7.53, 6.88, 5.78	<0.1/0.05-0.08	Gastrointestinal

³²P: Phosphorus-32; ⁸⁹Sr: Strontium-89; ¹⁵³Sm: Samarium-153; ²²³Ra: Radium-223; EDTMP: Ethylene diamine tetramethylene phosphonic acid; HEDP: Hydroxy-ethane diphosphonic acid; DOTMP: [4,7,10-tris(phosphonomethyl)-1,4,7,10-tetrazacyclododec-1-yl]methylphosphonic acid

Radionuclides

Phosphorus-32 (³²P) is a reactor product emitting pure beta emission with a physical half-life of 14.3 days and was the first radionuclide used for pain palliation.[6] Its maximum and mean particle energies are 1.71 and 0.695 MeV, respectively. The maximum and mean travel distances in the tissue are 8 and 3 mm, respectively. It is administered at a dose of 12 millicurie (mCi). In a study by Cheung et al.,[7] ³²P orthophosphate therapy was administered to a total of 48 patients monitored for breast and prostate cancer. The pain response was observed in 51.5% of the patients with breast cancer and 93.3% of the patients with prostate cancer. No correlation was detected between the dose and the pain response of the patients. In the literature, pain response rates were described to range from 59 to 93% for prostate cancer and 52 to 94% for breast cancer patients.[8] However, its most important disadvantage is myelosuppression and pancytopenia due to the very high beta energy and low lesion-normal bone rates. Therefore, it has been replaced by other radionuclides.

Strontium-89

(⁸⁹Sr) has a physical half-life of 50.5 days, and emits beta particles with a maximum of 1.46 MeV and mean 0.58 MeV energy. Its maximum travel distance in the tissue is 6.7 mm and the mean travel distance is 2.4 mm. The

mean therapeutic dose is 4 mCi. It is mainly eliminated via the kidneys (80%), and to a lesser extent, via the gastrointestinal system (20%).[1] It has a biological half-life of 4-5 days, and approximately 20% of it is found in the metastatic bone on the 90th day. It behaves similarly to calcium and is localized in the bone proportionally to the osteoblastic activity. In their study, Kasalicky et al.[3] reported a mild pain response in 40.7% of the patients and a substantial pain response in 47.5%; no response to treatment was observed in 9% of the patients. After a single ⁸⁹SrCl dose, the patients experienced a pain response for a mean period of 3.3±2.28 months and the treatment could be repeated up to five times in some patients. In the study, it was offered as a repeatable treatment option that improved the quality of life without myelosuppression for the palliative care of metastatic bone pain especially in patients with prostate, lung, or breast cancer.

Samarium-153

(¹⁵³Sm) has a physical half-life of 1.9 days and emits beta particles with a maximum energy of 0.81 MeV and mean energy of 0.23 MeV. The maximum travel distance in the tissue is 2.5 mm, and the mean travel distance is 0.6 mm. The ¹⁵³Sm-EDTMP complex is localized in the skeletal system proportionally to the osteoblastic activity and shows a similar distribution in bone scintigraphy.[9] The usual dose for metastatic bone pain is 1mCi/

kg.[5] While 65% of the therapeutic dose remains in the skeletal system, its urinary excretion is completed within approximately 6 h.[10] The pain response starts one week after the injection and is anticipated to last up to 2-3 months. Studies have demonstrated its mean therapeutic response to be 70% (40-97%).[11-13]

Rhenium-186 and Rhenium-188 HEDP

^{186}Re has a physical half-life of 3.8 days and emits beta particles with a maximum and mean energy, 1.07 MeV and 3.49 MeV, respectively. The maximum travel distance in the tissue is 4.5 mm and the mean travel distance is 1.1 mm. The recommended dose of injection is approximately 35 mCi. After the injection, it binds to the hydroxyapatite crystals and is localized in the bone. Approximately 70% of it is eliminated via the kidneys within 24 h.[14] The pain response is around 70-80% in various malignancies with no overall serious hematological adverse effect/s.[15,16]

^{188}Re has a physical half-life of 16.9 h. Its maximum beta particle energy is 212 MeV. The maximum travel distance in the tissue is 11 mm, and the mean travel distance is 3 mm. In their study, Li et al.[17] administered the ^{188}Re therapy to a total of 61 patients with different malignancies. The overall pain response was 80%; 36% of the patients showed complete pain response, and 44% exhibited a substantial pain response. Severe adverse effects or hematological toxicities were not described in any of the patients, and the hematological counts returned to normal after eight weeks.

Lutetium-177 EDTMP

^{177}Lu -EDTMP has been described as an effective treatment alternative for painful bone metastases. It accumulates in the osteoblastic metastases in the skeletal system by binding to hydroxyapatite crystals. It has low uptake by the visceral organs (Fig. 1). Lu-177 has a physical half-life of 6.7 days and emits beta particles with maximum energy of 0.489 MeV and a mean energy of 0.133 MeV. The maximum travel distance in the tissue is 1.7 mm and its mean travel distance is 0.23 mm. In their phase II trial on a total of 44 patients, Agarwal et al.[18] compared the efficacy of administering a low dose and high dose of ^{177}Lu -EDTMP for pain palliation. The trial included patients who were diagnosed with castration-resistant prostate cancer or breast cancer and who had diffuse bone metastases. A partial pain response was observed in 48% of the pa-

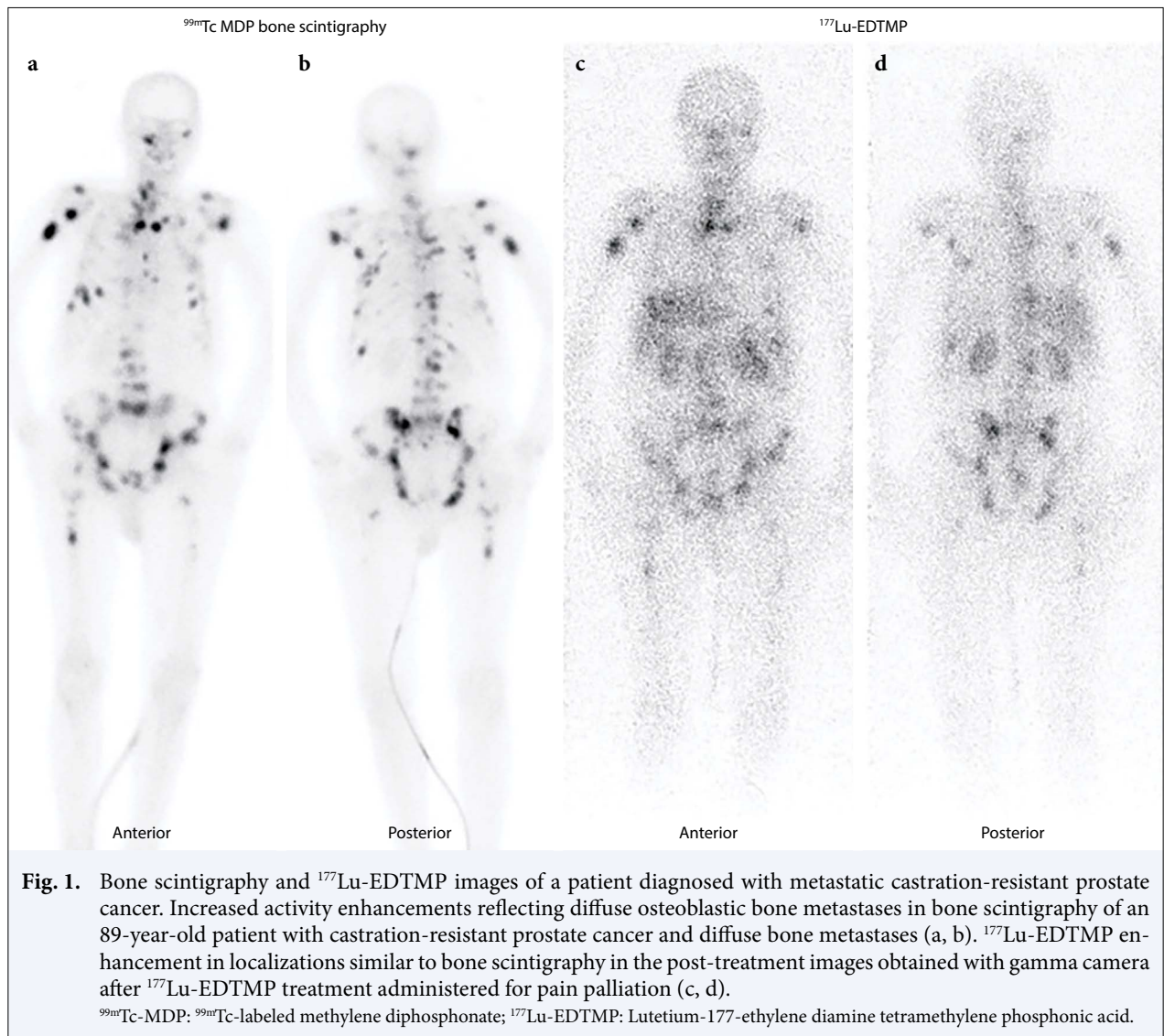
tients, complete response in 13%, and minimal pain response in 25% of the patients. The overall pain response of the patients in the high-dose group was found to be higher (77% vs. 95%). No difference was found between the low-dose and the high-dose groups in terms of toxicity. Transient Grade I/II hematological toxicity was described in 34% of the patients and transient Grade III/IV toxicity in 23% of the patients.

Holmium-166

Holmium-166 has a half-life of 1.12 days and emits beta particles with maximum energy of 1.84 MeV and mean energy of 0.67 MeV. The maximum travel distance in the tissue is 8.7 mm, and the mean travel distance is 4.0 mm. The most important advantage of ^{166}Ho is its negligible accumulation in extra-skeletal systems.[19] It is eliminated via renal excretion, similar to other beta-emitting radionuclides. Radiopharmaceuticals formed by combining ^{166}Ho with phosphate compounds are thought to be an effective treatment for bone pain palliation, especially in multiple myeloma. In their study, Giralt et al.[20] administered the Holmium-166 1, 4, 7, 10-tetraazacyclododecane-1, 4, 7, 10-tetra(methylenephosphonate) (^{166}Ho -DOTMP) treatment to 83 patients. They reported that when a dose above 40Gy was used for bone marrow, Grade II-IV nephrotoxicity was observed in approximately 30% of the patients. Complete remission was detected in 35% of the patients with a median event-free survival of 22 months. While it is a promising radionuclide in multiple myeloma, more comprehensive trials are needed in this subject.

Radium-223 (^{223}Ra)

^{223}Ra is a calcium-analog that its effects by binding to hydroxyapatite crystals similar to ^{89}Sr . It has a half-life of 11.4 days and emits alpha particles. It has a considerably higher (27.4 MeV) linear energy transfer (LET) than beta particles. It causes double-strand breaks in the DNA and irreversible cellular damage. Due to its high LET, its important advantage is that 1-10 alpha particles have a similar effect on cell death as 100-1000 beta particles. The recommended intravenous injection dose is 55 kBq/kg given in six cycles every four weeks.[2] With a very short travel distance in the tissue (shorter than 0.1 mm), it has a considerably milder and reversible hematological toxicity compared to beta-emitting radionuclides. The hematological toxicity, which can be observed 2 to four weeks after the intra-



venous injection, often resolves within six weeks. The bone concentration occurs 10 min after the injection, and 99% of it is concentrated in the bone within 24 h. Its elimination route is via the gastrointestinal system, which is different from that of the other beta-emitting radionuclides. Activity in the small intestine occurs within the first 10 min, and it is transferred toward the colon. Within 24 h, approximately 50% of the activity is observed in the colon. Thus, individuals with constipation receive higher radiation doses. In 10% of the cases, gastrointestinal symptoms such as nausea and vomiting may be observed. Generally, 75% of the activity is excreted within seven days.[21]

A survival advantage has not been described for beta-emitting radionuclides used in pain palliation.

On the other hand, ^{223}Ra has the advantage of improving overall survival with fewer adverse effects.[2,22] ^{223}Ra therapy is an approved treatment modality in the United States for patients with castration-resistant prostate cancer without visceral metastasis and lymph node metastasis above 3 cm.[23] In the controlled Phase III ALSYMPCA trial, patients with symptomatic bone metastasis without visceral metastasis were compared with the control group. All patients were monitored under the best possible care conditions. It was demonstrated that the overall survival was better in the ^{223}Ra arm (14.9 vs. 11.3 months). Moreover, the risk of symptomatic skeletal system-related events such as pathological fracture and spinal cord compression was substantially delayed in the ^{223}Ra arm (15.6 vs.

9.8 months).[2] There was no difference between the study groups in terms of the incidence of Grade III-IV hematological adverse effects. One of the most important effects described in the ^{223}Ra arm was the improved quality of life.

In a single-arm, phase III B trial performed after the ALSYMPCA trial, the safety and overall survival results of ^{223}Ra were assessed. Totally, 696 patients received at least one dose of the therapy. A total of 403 patients received six cycles of ^{223}Ra therapy. Adverse effects of Grade III and above included anemia in 5% of the patients, thrombocytopenia in 15%, neutropenia in 1%, and leukopenia in 1% of the patients. Serious adverse effects of any grade were detected in 35% of the patients. The median overall survival was 16 months. In this study, it was concluded that the combined use of ^{223}Ra with androgen receptor hormone therapies such as abiraterone and enzalutamide is considered safe and improves overall survival (mean 13 months) compared to monotherapy. Moreover, the combined use with denosumab increases the overall survival (15 months vs. 13 months).[24]

Adverse Effects and Precautions

Beta particle-emitting radiopharmaceuticals' main excretion route is renal excretion. The patients need to exercise care for toilet hygiene after the administration. This is especially of greater importance for ^{89}Sr treatment due to its longer physical half-life. The urinary excretion of the ^{153}Sm and ^{186}Re is completed within 8-12 h after the injection. Hence, care should be exercised on the first day. In patients with incontinence, catheterization is recommended before the injection.[4] The most important adverse effect of beta-emitting radiopharmaceuticals is hematological toxicity. Therefore, it is important to perform regular hematological monitoring of the patients for up to six weeks after the injection. This period might be extended to 12-16 weeks for ^{89}Sr due to its longer physical half-life.[25] There might be a transient pain aggravation called the 'flare phenomenon' in response to standard analgesics in approximately 10% of the patients; this occurs usually within the first 72 h after the administration. The flare phenomenon is usually associated with good clinical response.[26,27]

The most common non-hematological adverse effects with ^{223}Ra use include transient bone pain (bone flare) and gastrointestinal symptoms such as vomiting, nausea, and diarrhea.[2,28,29]

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