FABAD J. Pharm. Sci., 48, 2, 319-336, 2023
Doi: 10.55262/fabadeczacilik.1191048
REVIEW ARTICLE

The Role of Radiopharmaceuticals in the Bone Metastases Therapy

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SUMMARY

Cancer, having high morbidity and mortality rates, has become a significant public health problem in recent years, and it is the second leading cause of death after heart disease in the world. Metastases are one of the most serious complications of cancer and bone metastases are detected in 2/3 of metastatic cancer cases. Therapy approaches in bone metastases can be classified as surgery, bisphosphonates, radiotherapy, and radionuclide therapy. Radionuclide therapy using alpha and beta-emitting radionuclides is more selective and effective than other local and systemic treatment methods, and this feature provides superiority over other therapeutic methods. Radionuclide therapy is used in bone metastasis to reduce pain, to kill tumor cells, to prolong life span, and to improve quality of life. In recent years, alpha-emitting radiopharmaceuticals [such as Radium-223 (Ra-223) chloride] and beta-emitting radiopharmaceuticals [such as Strontium-89 (Sr-89) chloride, Lutetium-177 (Lu-177) labeled Ethylenediamine Tetra Methylene Phosphonic Acid (EDTMP), Samarium-153 (Sm-153) labeled EDTMP] are introduced in the clinic for especially the treatment of painful bone metastases and on the other hand new radiopharmaceutical development studies also continue intensively, like Actinium-225 labeled prostate-specific membrane antigen-617 (Ac-225-PSMA). Number of studies are proven that using radionuclide therapy in bone metastases improves the patient's general health, reduces pain and the risk of pathological fractures, and increases survival. This review presents an overview of radionuclide therapy used in bone metastases. In this context, following the general information about radiopharmaceuticals, the importance of radiopharmaceuticals used in bone metastases therapy is explained with experimental and clinical studies examples.

Key Words: *Cancer, Bone Metastases, Radionuclide Therapy, Radiopharmaceutical*

Kemik Metastazlarının Tedavisinde Radyofarmasötiklerin Rolü

ÖZ

Kanser, morbidite ve mortalite oranları yüksek olan ve son yıllarda büyük bir halk sağlığı sorunu haline gelen bir hastalıktır ve dünyada kalp hastalıklarından sonra ölüm nedenleri arasında 2. sırada yer almaktadır. Metastazlar kanserin en ciddi komplikasyonlarından biri olup kemik metastazları, metastatik kanser olgularının 2/3'sinde saptanmaktadır. Kemik metastazlarında genel tedavi yaklaşımları, cerrahi, bifosfanatlarla tedavi, radyoterapi ve radyonüklid tedavi olarak sınıflandırılabilir. Radyonüklid tedavinin diğer lokal ve sistemik tedavi yöntemleriyle karşılaştırıldığında daha seçici ve etkili olması yöntemi avantajlı hale getirmektedir. Alfa ve beta partikülü yayan radyonüklidlerin kullanıldığı bu tedavi yöntemi, kemik metastazı olan hastalarda sıklıkla görülen ağrının azaltılmasında, tümör hücrelerinin öldürülmesinde, yaşam süresinin uzatılmasında ve yaşam kalitesinin artırılmasında etkili bir yöntemdir. Son yıllarda alfa partikülü yayan; Radyum-223 (Ra-223) klorür, beta partikülü yayan; Stronsiyum-89 (Sr-89) klorür, Lutesyum-177 (Lu-177) işaretli Etilendiamin Tetra Metilen Fosfonik Asit (EDTMP) ve Samaryum-153 (Sm-153) işaretli EDTMP başta olmak üzere çok sayıda radyofarmasötik kemik metastazlarının tedavisinde klinik kullanıma girmişken Aktinyum-225 işaretli prostat spesifik membran antijeni-617 (PSMA-617) gibi yeni radyofarmasötiklerin geliştirilmesi üzerine de çalışmalar yoğun şekilde devam etmektedir. Yapılan birçok çalışma kemik metastazı tedavisinde radyofarmasötiklerin kullanımının hastanın genel sağlık durumunu iyileştirdiğini, ağrıları ve patolojik kırık riskini azalttığını ve sağkalımı artırdığını kanıtlamıştır. Bu derlemede kemik metastazı tedavisinde kullanılan radyonüklid tedaviye genel bir bakış açısı sunulmuştur. Bu kapsamda klinikte kullanılan ve araştırmaları devam eden radyofarmasötiklerle ilgili genel bilgiler verilmiş, deneysel ve klinik çalışma örnekleriyle kemik metastazı tedavisinde radyofarmasötiklerin kullanımının önemi açıklanmıştır.

Anahtar Kelimeler: *Kanser, Kemik metastazı, Radyonüklid Tedavi, Radyofarmasötik*

Received: 18.10.2022
Revised: 25.04.2023
Accepted: 02.05.2023

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INTRODUCTION

Cancer is a disease that occurs when some of the body's cells grow and multiply uncontrollably and spread to other areas of the body (National Cancer Institute, 2021). Cancer has become a major public health problem in recent years and has high morbidity and mortality rates. According to the World Health Organization (WHO) and Global Cancer Observatory (GLOBACON) data, approximately 19.3 million new cancer cases were encountered worldwide in 2020, and the number of cancer-related deaths was reported as approximately 10 million. In other words, one out of every eight deaths worldwide are caused by cancer. In our country, while the number of new cancer cases for 2020 is about 230.000, cancer-related deaths have been reported at about 130.000 (Global Cancer Observatory, 2020).

Metastases are one of the most critical complications of cancer (Ell & Gambhir, 2006), and 2/3 of metastatic cancer cases are bone metastases which are a widespread consequence of the spread of numerous solid cancers to distant sites (Arıkan, 2014). The primary tumors with the highest rate of bone metastases are prostate, breast, kidney, lung, and thyroid cancer (Maccauro et al., 2011; Çetin & Büyükberber, 2012). The incidence of bone metastasis of primary tumors calculated by postmortem examination is shown in Figure 1 (Coleman, 2006; Galasko, 1981).

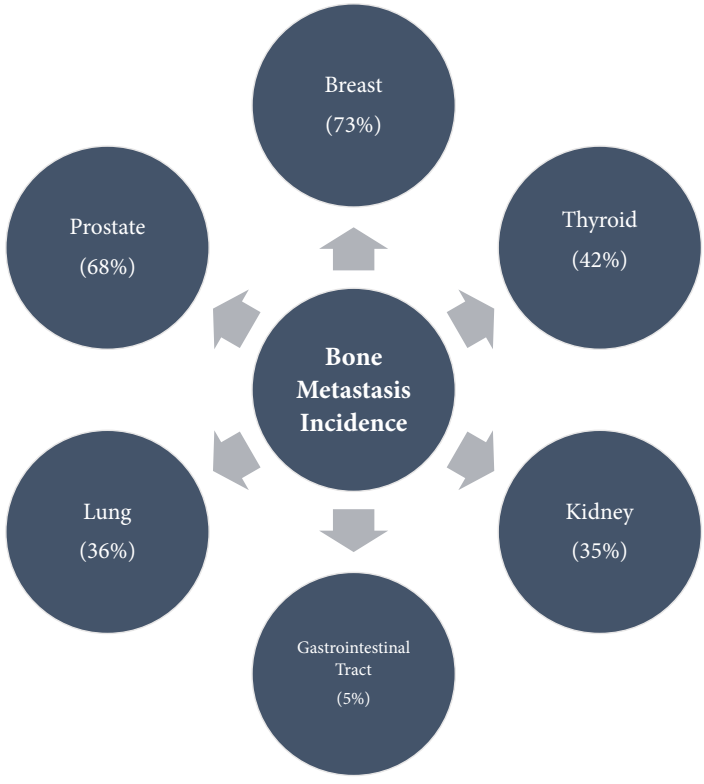

Figure 1. Incidence of bone metastases at postmortem examination in different cancers

(Data are adapted from Coleman, 2006 and Galasko, 1981 and presented as a figure)

The most common symptoms in bone metastases are severe pain, movement disorder, hypercalcemia, pathological bone fracture, spinal cord or nerve root compression, and bone marrow infiltration (Maisano et al., 2001; Macedo et al., 2017). Pain is the most widespread symptom in bone metastases. This symptom, which negatively affects the patient's quality of life, is increasingly severe at night and does not go away with sleep or lying down (Clohisy & Mantyh, 2003). In the therapy of bone metastases, it is crucial to increase the patient's survival and improve the quality of life by reducing the symptoms. For this reason, fac-

tors such as localized or widespread bone disease, the type of tumor, previous treatments, and the patient's response to previous treatments should be evaluated, and appropriate treatment should be decided. Therapy methods such as radiotherapy, endocrine therapy, chemotherapy, therapy with bisphosphonates, and radionuclide therapy come to the fore in bone metastases therapy (Maisano et al., 2001).

In this review, therapy methods for bone metastases, where primary tumors frequently metastasize and constitute a significant percentage of metastatic cancer cases, are briefly mentioned. In addition, the radiopharmaceuticals used in this therapy are summarized by emphasizing the importance of radionuclide therapy, and examples from studies on the subject are presented.

THERAPY METHODS FOR BONE METASTASES

Bone metastasis therapy aims to reduce tumor burden, to prevent further progression of tumor and metastasis, and to prevent tumor-related bone pathologies such as pathological fracture, pain, and hypercalcemia (Suva et al., 2011). It is also essential to increase survival by improving the patient's quality of life (Mayadağlı et al., 2011). Local bone metastasis treatment strategies are palliative in nature; individual lesions are surgically excised, and the tumor 'bed' irradiated, either before or after surgery. The decision for or against surgery and/or radiation, alone or in combination with select bone-targeted agents, is profoundly influenced by the extent of systemic disease at the time of treatment.

Surgery; it is difficult to treat bone metastases surgically, multidisciplinary approach that must be applied to each patient depending on the specifics of their case is necessary. In general, surgery can be applied to treat existing or potential pathological fractures, decompress spinal cord and nerve roots, relieve pain and reestablish bone continuity (Güney et al., 2008; Macedo et al., 2017).

Radiotherapy; it is the most commonly used treatment for bone metastases. Primary purpose is to reduce bone pain and prevent pathological fractures and spinal cord compression while maintaining the patient's quality of life (De Felice et al., 2017).

Therapy with bisphosphonates; bisphosphonates are analogs of pyrophosphate, a natural inhibitor of bone demineralization. It has been shown that bisphosphonates is reduced skeletal complications and vertebral fractures in bone metastases and they cause osteoclasts' apoptosis by inhibiting their development and function (Janjan, 2001; Gralow & Tripathy, 2007). Therefore, bisphosphonates, alone or in combination with cytotoxic agents, have recently started to be used, especially in treatment of tumor-induced hypercalcemia (Maisano et al., 2001).

Radionuclide therapy; it is a therapy method using alpha (α) and beta (β-) emitting radionuclides. It can be more effective when combined with other therapy methods, such as chemotherapy, bisphosphonates, and radiotherapy (Macedo et al., 2017). The aim of the radionuclide therapy is to decelerate the development of the disease by preventing the development of new metastases. Thus, it can reduce morbidity and increase survival (Hillegonds et al., 2007).

RADIONUCLIDE THERAPY

In radionuclide therapy, the destructive effects of the radiation emitted by radioactive substances on target cells are utilized. Unlike the diagnostic radiopharmaceuticals, therapeutic radiopharmaceuticals' purposes are to kill cells. Therefore, it is desired that the radionuclide used for therapy should have high energy (E_{max} > 1 MeV). In addition, the localization of the radiopharmaceutical in the target organ is significant (Önsel, 2009). Therefore, the success of radionuclide therapy depends on adequate uptake and long-term retention of the radiopharmaceutical in the target tissue (Chatal & Hoefnagel, 1999).

The radioactive material can be delivered locally into an organ or tissue or targeted to the desired tissue

with the help of metabolic carriers (Naki Sivri & Özer, 2004). Contrary to systemic treatment approaches, in radionuclidic treatment cell death selectively occurs in cancer cells while damage to healthy tissues is minimal. In this way, the rest of the body is protected from the harmful effects of radiation (Ersahin et al., 2011). However, as well as the advantages of radionuclide therapy, there are some limitations. In Table 1, the pros and cons of radionuclide therapy were summarized (Chatal & Hoefnagel, 1999; Naki Sivri & Özer, 2004; Sgouros et al., 2020).

Table 1. Advantages and disadvantages of radionuclide therapy

Advantages
It can be applied systemically or locally.
It is effective in all areas with disease involvement.
Selective.
Non-invasive method.
Palliation ability.
Low normal tissue toxicity.
Minimal side effects.
The uptake and retention of the radioactive material in the tumor can be predetermined.
Multiple therapies are possible.
Disadvantages
Patient isolation may be required (for some therapies).
Special rules are required for the disposal and storage of radioactive waste.
Difficulties may be experienced in the supply of radiopharmaceuticals.
Some new therapies are costly.
A multidisciplinary approach is required.
Dosimetry calculations is required.
Patients may be prejudiced toward radioactivity.

Radionuclide therapy in bone metastases

The failure of cancer treatments and the fact that metastases are the leading cause of cancer-related deaths have increased the attention on the development of more effective treatment methods for palliative treatment and the treatment of metastases, especially bone metastases, in recent years (Ferreira et al., 2012). Radionuclide therapy is one of these methods and mainly used for pain relief associated with bone metastases. It is applied in cases where pain due to bone metastasis, recurrent pain in the radiotherapy area, no response to opiate analgesics, pain circulating in more than one region, and more than one abnormality from a bone scan are observed (Ell & Gambhir, 2006). Although the early use of radionuclide therapy in osteoblastic metastases has proven to be a reliable method in the treatment of pain (Paes & Serafini, 2010), it is currently used as the last preferred method in cases where other treatments have failed.

In the clinic, α and β emitting radionuclides are used in the therapy of bone metastases and pain relief associated with bone metastases. These radionuclides can be selectively delivered to bone sites with enhanced osteoblastic activity (Tsukamoto et al., 2021). An ideal radiopharmaceutical to be used for the therapy of bone metastasis should have the following characteristics (Ferreira et al., 2012; Choi, 2018). It should;

- show selective, high, and long-term uptake in bone lesions,

- has limited uptake by other organs,
- excrete rapidly from non-skeletal sites,
- show low toxicity in the bone marrow and other healthy tissues,
- has a low risk of side effects,
- has easy and simple preparation methods,
- be produced in high radiochemical purity,
- be suitable for clinic use,
- be safe for patients and staff,
- provide bone pain palliation and improve survival.

Although β-emitting radionuclides, such as P-32, Sr-89, Re-186, Re-188, Lu-177 and Sm-153 have been used more frequently in the therapy of bone metastases and pain palliation associated with bone metastasis, in recent years, α-emitting radionuclides, such as Ra-223 and Ac-225 have been received increasing attention (Sathekge et al., 2019; Satapathy et al., 2020; Nava-Cabrera et al., 2021). The properties of β and α radionuclides used in radionuclide therapy are summarized in Table 2 (Zustovich & Barsanti, 2017; Choi, 2018; Marcu et al., 2018).

Table 2. Properties of β and α radionuclides used in the bone metastases.

β emitting radionuclides	**α emitting radionuclides**
Low energy	High energy
Low LET (~0.3 keV/μm)	High LET (~100 keV/μm)
Less tumoricidal activity	More tumoricidal activity
Long distance (2000–11500 μm)	Short distance (20-80 μm)
Delivers more radiation to neighboring tissue	Delivers less radiation to neighboring tissue
High risk of bone marrow toxicity	Low risk of bone marrow toxicity
Use in pain palliation	Use in pain palliation
Required patient isolation	Outpatient therapy for radium-223

In radionuclide therapy of bone metastasis, the radiation dose absorbed in the metastatic focus is a function of the activity uptake in the tumor and this function is determined by parameters such as the concentration and retention time of the radiopharmaceutical as well as the particle energy and half-life of the radionuclides. Mechanism of pain relief is not yet fully understood; however, it is thought that radiopharmaceuticals used in treating pain palliation work by adsorption or fixation in areas with increased osteoblastic activity. Tumor size is reduced by the effect of radiation, thus reducing the periosteum pressure, and as a result, the patient is relieved. It is also reported that the destruction of cells that secrete pain mediators may play a role in reducing pain, especially in the early period of metastases (Şahin et al., 1998; Ferreira et al., 2012). Bone marrow toxicity is a parameter that limits the use of radionuclides. High doses of radiation may lead to the risk of bone marrow suppression (Zustovich & Barsanti, 2017).

α-particles have particular advantageous in targeted therapy due to their high potential and specificity in addition, the distance that α particles go to in human tissue is very short (2-10 tumor cell diameter) which is especially important for dosimetry of surrounding tissue. α-particles have a high linear energy transfer (LET) (about 100 keV/μm), and thus they cause breaks in the double-stranded structure of DNA. When the double-stranded DNA structure is disrupted, it becomes difficult to repair, the unrepaired structure undergoes apoptosis (Zustovich & Barsanti, 2017).

Radiopharmaceuticals used for the therapy of bone metastases

Phosphorus-32 (P-32) Orthophosphate (Phosphotope)

P-32, the radioisotope of phosphor, is produced directly by the reactor and has a physical half-life of 14.3 days. It is a pure β emitter with high specific radioactivity (Ferreira et al., 2012). The maximum and average β particle energies are 1.71 and 0.695 MeV, respectively. The maximum and mean penetration ranges in tissues are 8 and 3 mm, respectively (Pandit-Taskar et al., 2004).

Phosphate is widely distributed throughout the body, contributing to energy metabolism, neuromuscular function, hematopoiesis, and bone metabolism. The skeletal system is the greatest pool of phosphate in the body, and phosphor, found in the bone as inorganic phosphate, binds to the hydroxyapatite matrix (Ell & Gambhir, 2006). Phosphate is eliminated mainly by the renal route, with minimal fecal excretion (Şahin et al., 1998).

P-32 was one of the first radionuclides used to decrease pain from bone metastases and was in widespread use until the 1980s. It is thought that the mechanism of action of P-32 is to cause damage to the DNA of the tumor cell as well as to reduce pain due to damage to cells that produce pain modulators (such as lymphokines). However, various toxicities, including myelosuppression and pancytopenia in patients, limited the its clinical use (Pandit-Taskar et al., 2004).

Strontium-89 (Sr-89) Chloride (Metastron™)

Sr-89 is a pure β emitter with a half-life of 50.5 days. It has a maximum energy of 1.46 MeV, an average soft tissue penetration of 2.4 mm, and high specific radioactivity (Paes & Serafini, 2010; Kuroda, 2014).

Strontium, like calcium, is a divalent cation and is incorporated into the hydroxyapatite structure in bone in rate to osteoblastic activity. In osteoblastic lesions in the bone, it is taken five times more than in normal bone areas, and long-term uptake occurs (Paes & Serafini, 2010). About 80% of Sr-89, which is not concentrated in the bone, is excreted through the kidneys and 20% through the gastrointestinal tract (Pandit-Taskar et al., 2004). It has been reported that Sr-89 chloride exerts its effect by effectively killing tumor cells and inducing tumor cell apoptosis (Ye et al., 2018).

Sr-89 labeled strontium chloride $^{89}[Sr]SrCl_2$ was the first radiopharmaceutical approved by the FDA in 1993 for bone pain therapy and is currently licensed in many countries (Paes & Serafini, 2010; Guerra Liberal et al., 2016). Pecher first reported using Sr-89 chloride to treat painful bone metastases in 1942. Studies have shown that Sr-89 is an alternative treatment method for patients with bone pain caused by metastatic prostate cancer, provides benefits in addition to External Beam Radiotherapy (EBRT), and is cost-effective (Furubayashi et al., 2015). In addition, it has been emphasized that Sr-89 can reduce the need for both EBRT and narcotic analgesics, helping reduce lifelong health costs without hospitalization (Pandit-Taskar et al., 2004).

Robinson et al. stated that in 622 patients, a response rate of 81% occurred in pain palliation therapy with Sr-89, and no myelotoxicity occurred in the patients (Robinson et al., 1995). In a study by Kuroda et al., the lethal effect of Sr-89 on the tumor, pain therapy efficacy, and survival were investigated in prostate cancer patients with bone metastases. As a result of the study, Sr-89; has been stated that it controls prostate-specific antigen (PSA) and increases survival time. However, it has been emphasized that large-scale studies are needed to examine its tumor-killing effect (Kuroda, 2014).

Ye et al. evaluated the efficacy of Sr-89 chloride in pain relief associated with bone metastasis in lung, breast, or prostate cancer patients. The study included one hundred twenty-six patients with lung cancer, 71 with breast cancer, and 49 with prostate cancer. The study's results indicated that Sr-89 chloride could safely and efficiently alleviate bone pain caused by

bone metastasis in lung cancer. However, its efficacy is lower in patients with lung cancer than in breast or prostate cancer (Ye et al., 2018).

Samarium-153 (Sm-153) Ethylenediamine Tetra Methylene Phosphonic Acid (EDTMP) (Quadramet®)

Samarium-153 is a radionuclide with a physical half-life of 1.9 days. It emits beta particles with a maximum energy of 810 keV. It emits β particle with a maximum energy of 810 keV and gamma rays with maximum energy of 103 keV. The average penetration range of Sm-153 is 0.5 mm, and Sm-152 oxide is produced with high radionuclidic purity by neutron bombardment (Rubini et al., 2014).

Goeckeler et al. (1987) reported for the first time the synthesis of a series of samarium complexes has been produced using multidentate acetate and phosphonate ligands. Of the complexes studied, Sm-153 labeled EDTMP provides the optimum combination as a result of its high bone uptake, rapid blood clearance, and low soft tissue uptake. Sm-153-labeled EDTMP, concentrated in proportion to osteoblastic activity in the skeleton (Pandit-Taskar et al., 2004), is used in the clinic for the effective palliative therapy of bone metastasis. After injection, Sm-153 labeled EDTMP is quickly excreted from the blood into the urine. Only 1% of the injected activity remains in the blood 4 hours after application, while retained in bone for a long time (Ferreira et al., 2012). Excretion from the body is carried out through the kidneys and is completed in approximately 6 hours (Paes & Serafini, 2010).

The first study, conducted in 1989, included 35 patients with bone metastases that spread from different tumor types. In 65% of patients treated with Sm-153 labeled EDTMP, pain relief was reported between 4 and 35 weeks. In addition, dose-limiting toxicity appeared to be myelosuppression, and platelet counts were reported to return to treatment baseline levels within ten weeks of therapy (Turner et al., 1989; Rubini et al., 2014).

In a study carried out to determine the clinical efficacy of Sm-153-labeled EDTMP, the following four parameters were evaluated by asking patients at each visit (before and after therapy) of all patients treated with ^{153}Sm-EDTMP in the clinic:

(i) Pain assessment according to the visual analog scale (VAS),

(ii) Pain-related sleep disorder,

(iii) Analgesic drug dose,

(iv) Answer the question, 'Do you think you have benefited from the treatment?'

In conclusion, it has been reported that Sm-153 labeled EDTMP therapy is an effective supportive treatment, especially in patients with bone metastases originating from breast or prostate cancer (Kolesnikov-Gauthier et al., 2018).

Barai et al. investigated whether combining capecitabine in radio-sensitizing dose with Sm-153-EDTMP produces superior analgesia compared to Sm alone. Capecitabine is a chemotherapeutic drug and used with external beam radiation to make the target more radiosensitive. For eight days, patients with skeletal metastases from various primaries received either Sm-153 labeled EDTMP plus capecitabine or Sm-153 labeled EDTMP plus placebo (control group) and all patients were followed up for 12 weeks to evaluate the degree and duration of pain palliation and hematologic toxicity. As a result, it was stated that the combination of radiosensitive capecitabine and ^{153}Sm-EDTMP radiopharmaceutical increased the analgesic effect without increasing bone marrow toxicity (Barai et al., 2015).

Sm-153 labeled EDTMP has been reported to be safe and effective and has been reported to cause only mild reversible bone marrow suppression in patients, while it has been reported to be safe and effective (Paes & Serafini, 2010). However, although ease of use, ability to display its distribution, and clinical results make Sm-153 labeled EDTMP attractive, the risk of developing myelosuppression limits its wider use (Pandit-Taskar et al., 2004).

Lutetium-177 (Lu-177) EDTMP

Lu-177 is a radioisotope used for both therapeutic and diagnostic purposes, with a physical half-life of 6.73 days, a maximum β energy of 497 keV, γ Energy of 113 keV (6.4%), and 208 keV (11%). Lutetium-177 is produced in nuclear reactors either directly by the ^{176}Lu (n, γ) ^{177}Lu reaction or indirectly by the ^{176}Yb (n, γ) ^{177}Yb $\xrightarrow{\beta-}$ ^{177}Lu reaction.

Lu-177 labeled EDTMP has appropriate biological and physical properties for the palliative therapy of patients with painful bone metastases (Ando et al., 1998). It was shown that the uptake of the ^{177}Lu-EDTMP compound in soft tissues is very low and high in bones. In addition, Lu-177 nuclide has an appropriate physical half-life, and its low-energy gamma-rays allow the imaging of bone lesions by scintigraphy. Furthermore, the potential for side effects is lower than the other beta-particle emitting radionuclides due to their moderate beta energy. Thus, Lu-177 is considered an alternative nuclide to clinically used radionuclides such as Sr-89 and Sm-153 (Chopra, 2004), and its clinical use is increasing rapidly.

In the phase II study, the therapeutic efficacy and safety of 177Lu-EDTMP were examined in breast cancer and hormone-resistant prostate cancer patients with bone metastases. In addition, patients were observed for pain scores, Karnofsky indices, mobility scores, and analgesic needs. The results have been reported to show that using 177Lu-EDTMP is effective and safe (Yuan et al., 2013).

In a randomized, double-blind clinical study, 153Sm-EDTMP and 177Lu-EDTMP were compared to the effectiveness of pain palliation in patients with bone metastases. Fifty patients with painful bone metastases were included in the study. It was stated that similar results were obtained in the patient groups treated with these two radiopharmaceuticals and that 153Sm-EDTMP and 177Lu-EDTMP could be used in the pain therapy of multiple bone metastases, and were effective and safe (Taheri et al., 2018).

Rhenium-186 (Re-186) Hydroxyethylidene Diphosphonate (HEDP)

Re-186 is a β^- emitting radioisotope of rhenium with a physical half-life of 3.7 days, a maximum energy of 1.07 MeV, an average energy of 0.349 MeV, and a mean penetration range of 1.1 mm. This isotope also emits a low level of 137 keV gamma radiation (Bodei et al., 2008). Re-186 is produced directly in the reactor and has moderate specific radioactivity (Ferreira et al., 2012).

Re-186 is used as a HEDP compound for palliative therapy. Mathieu et al. first reported the possible use of ^{186}Re-HEDP in the treatment of bone metastases in 1979 (Mathieu et al., 1979). Re-186-labeled HEDP binds to hydroxyapatite crystals by building hydroxide bridges in a hydrolysis reaction and is significantly concentrated in primary and metastatic bone lesions (Finlay et al., 2005; Lam et al., 2007). This process is thought to mediate the metabolic activity of osteoclastic cells. Studies on the biokinetics of ^{186}Re-HEDP have shown that it binds to plasma proteins in a time-dependent manner and is a compound with rapid blood clearance. Approximately 70% of the dose is excreted in the urine within 24 hours (Finlay et al., 2005).

In the phase II study, to evaluate the effect of the compound, 60 persons with painful bone metastases from different tumors were treated with ^{186}Re-HEDP, and 80% of the patients stated that they experienced pain relief. Of these, 31% reported that the pain was utterly relieved, 34% partially relieved, and 15% relieved at a low level. The duration of pain relief has been noted to range from 2 to 52 weeks, with moderate and transient hematological toxicity (Sciuto et al., 2000).

Kucuk et al. investigated the palliative and side effects of Re-186 HEDP in patients with different cancer types with bone metastases. Thirty-one patients were included in the study (10 prostate, ten breast, four rectum, five lung, and two nasopharyngeal cancer patients). In conclusion, it was reported that the overall response rate was 67.5%; the average response

rate was 87.5% in patients with breast and prostate cancer, 75% in patients with rectal cancer, and 20% in patients with lung cancer. Furthermore, when the side effects were evaluated, it was stated that no serious side effects were observed except for mild hematological toxicity (Küçük et al., 2000).

The Phase III study, entitled PLACORHEN, was a randomized controlled trial in which 111 patients with metastatic castration-resistant prostate cancer (mCRPC) with bone metastases received ^{186}Re-HEDP or placebo. It was reported that a higher rate of pain relief response (65% vs. 36%) was observed in the group receiving ^{186}Re-HEDP compared to the group receiving placebo, and the pain response with ^{186}Re-HEDP was longer than those associated with placebo (Han et al., 2002).

Because of the delivery of a substantial dose to bone marrow, marrow toxicity side effects such as thrombocytopenia or, most rarely, leucopenia may be observed. The baseline white blood cells and platelet counts are essential parameters for therapy. Platelets and white blood cells count decrease during therapy; however, it is reported that they return to average levels within eight weeks after administration (Argyrou et al., 2013; Sciuto et al., 2000).

Although Re-186 labeled HEDP, has been evaluated in various studies for the therapy of painful bone metastases, its use is still experimental and has not yet entered routine clinical use.

Rhenium-188 (Re-188) HEDP

Re-188, an isotope of rhenium, has a physical half-life of 16.9 hours and a maximum beta energy of 2.1 MeV, with a mean penetration range into the soft tissue of 3 mm (Li et al., 2001). Re-188 also emits 155 keV gamma radiation. This isotope's high β energy can potentially kill tumor cells. Re-188 is synthesized from the Tungsten-188/Rhenium-188 generator, so it is cheap, and a kit combined with HEDP is also available (Pandit-Taskar et al., 2004).

Re-188 is evaluated by complexing with HEDP, just like the Re-186 compound, for bone pain relief but ^{188}Re-HEDP, like ^{186}Re-HEDP, has not yet entered routine clinical use. Average biological half-life of ^{188}Re-HEDP in bone is about 16 hours, almost 40% of the radiopharmaceutical is excreted in the urine within 8 hours (Finlay et al., 2005). ^{188}Re-HEDP has high bone uptake and shows similar results to ^{186}Re-HEDP. The hematological toxicity of ^{188}Re-HEDP is a decrease in platelet and leukocyte counts, and it has been stated that these changes are reversible (Pandit-Taskar et al., 2004; Cheng et al., 2011; Rubini et al., 2014).

Although there are some studies to show its effectiveness, the information on the use of the Re-188 labeled HEDP compound is limited. In the study by Cheng et al., various doses of ^{188}Re-HEDP were administered in 64 patients, and pain reduction, blood counts, biochemical parameters, and side effects were reviewed. As a result of the study, it was reported that there were no clinically significant changes in biochemical parameters, and no vital adverse effects were observed. It has been reported that thrombopenia and leukopenia are rarely seen in patients, and thrombocyte and leukocyte levels return to baseline at the end of the therapy. In addition, it was stated that pain relief was achieved by 84.62% in patients with prostate cancer, 78.57% in patients with breast cancer, 62.50% in patients with lung cancer, and 55.56% in patients with liver cancer from specific tumor types. As a result of the study, it was pointed out that ^{188}Re-HEDP is a beneficial radiopharmaceutical to improve bone pain in patients with progressed cancer with painful bone metastases (Cheng et al., 2011).

Li et al. evaluated the therapeutic efficacy of ^{188}Re-HEDP for the palliation of painful bone metastases in patients with dissimilar types of advanced cancer. Sixty-one patients were included in the study and were treated with various doses of Re-188 HEDP. As a result, it was reported that most patients had an essential reduction in bone pain, and no serious side effects or hematopoietic toxicity were observed (Li et al., 2001).

Radium-223 (Ra-223) Dichloride (Xofigo®)

Ra-223, a radioactive isotope of radium, supplied as a radium chloride salt solution and given intrave-

nously, has a half-life of 11.4 days. It has an average path length of less than 0.1 mm in soft tissue and an alpha particle energy of 5850 keV.

Radium-223 is chemically like calcium and replaces calcium by participating in the hydroxyapatite structure ((), a bone mineral ingredient. In addition to the bone surface and skeletal metastases, it is concentrated in growth zones, including sites of bone turnover (Rubini et al., 2014; Zustovich & Barsanti, 2017). It shows its radiobiological effects mainly by the forming double helix breaks in tumor cell DNA by α particles. A cytotoxic effect occurs due to the high LET of α particles. At the same time, since the distance that α-particles can travel in the tissue is very short (2-10 cells), the suppressive effect of Ra-223 on the bone marrow is significantly less than that of β-particles (Alan Selçuk & Yencilek, 2018). Approximately 25% of the injected Ra-223 at therapeutic doses is uptake by the bones, and its elimination is primarily accomplished by the gastrointestinal tract (Pandit-Taskar et al., 2014; Alan Selçuk & Yencilek, 2018).

Studies conducted on mCRPC patients with only bone metastases and no internal organ metastases showed that radium-223 dichloride increased overall survival versus placebo, and Ra-223 had a palliative effect of 50-60%. In addition, it was emphasized that it was superior in pain relief (Alan Selçuk & Yencilek, 2018).

The first human study to examine the safety and tolerability of Ra-223 was performed by Nilsson et al. As a result of the study, it was emphasized that Ra-223 was tolerable at therapeutic doses. It could be an effective radiopharmaceutical in cancer therapy due to its pain-reducing properties and positive effects on serum markers (Nilsson et al., 2005). A randomized, double-blind, placebo-controlled multicenter phase II study conducted in 2002 indicated that adverse events, including serious ones, were more common when patients were not treated with Ra-223 (Gupta et al., 2017).

In a multicenter study with Ra-223 titled Alpha-Alphadine (Alpharadin in Symptomatic Prostate Cancer=ALSYMPCA) in Phase III Symptomatic Prostate Cancer, Ra-223 was reported to improve overall survival. In this study, the efficacy and safety of Ra-223 in mCRPC patients were compared with the placebo group. The study's results emphasized that the overall survival was prolonged, the risk of death was reduced by 30%, and the development time of symptomatic skeletal-related events was delayed in patients treated with Ra-223 compared to the placebo group. Ra-223 has also been shown to have a palliative effect on pain associated with bone metastases. It was stated that the most common side effects were anemia, thrombocytopenia, and diarrhea (Parker et al., 2013).

Ra-223 dichloride has been approved for use in CRPC patients with bone metastases and no visceral metastases. This radiopharmaceutical is commercially available under the trade name Xofigo®. Many studies are ongoing regarding extending other indications of radium-223 dichloride in patients with prostate cancer and its use in bone metastases caused by different types of cancer (Pandit-Taskar et al., 2014; Alan Selçuk & Yencilek, 2018).

Actinium-225 labeled prostate-specific membrane antigen-617 (Ac-225-PSMA-617)

Ac-225 is an α-emitting radioisotope with a half-life of 10 days. It emits four α, two β particles and two γ photons during decay. Alpha particles have 5.8 to 8.4 MeV energies, and tissue ranges from 47 to 85 μm (Hooijman et al., 2021). The emitted γ photons can be used for post-therapy monitoring and dosimetric experiments. Its favorable half-life and decay properties make Ac-225 a promising compound for targeted alpha therapy (TAT). Preclinical or early clinical trials of many Ac-225-labeled molecules (peptides, antibodies, nanobodies) are ongoing, and some of them (^{225}Ac-PSMA-617 and ^{225}Ac-DOTATATE) have reached clinical practice (Dhiman et al., 2022).

Ac-225-labeled PSMA-617, developed and characterized in 2013, has shown remarkable therapeutic efficacy in previously intensively treated mCRPC patients (Sathekge et al., 2019). Compared with the Lu-177 labeled PSMA used in the clinic, Ac-225 has higher energy, a shorter distance, and a higher tumoricidal effect. It was reported that the therapeutic re-

sponse of ^{177}Lu labeled PSMA in bone metastases is weaker than in soft tissue lesions. Nava-Cabrera et al. calculated the absorbed dose of ^{177}Lu-PSMA and ^{225}Ac-PSMA by comparing experimental data from the bone metastasis model and cellular fractionation in animals and performed a comparison study. The study's results reported that ^{225}Ac-PSMA accumulates in bone lesions and efficiently kills tumoral cells in the bone lumen (Nava-Cabrera et al., 2021). Moreover, ^{225}Ac-PSMA-617 can target any metastatic tissue and has good application potential for small tumors, diffuse cancers, and micro-metastasis. Clinical trials are being gradually conducted at multiple centers to evaluate the efficacy and safety of ^{225}Ac-PSMA-617 radiopharmaceutical in mCRPC patients (Ma et al., 2022).

^{225}Ac-PSMA-17 therapy was administered to patients with advanced prostate cancer who did not receive chemotherapy. Bone metastasis was reported in 80% of the 17 patients included in the study. Therapy efficacy was evaluated by ^{68}Ga-PSMA-11 PET scans and measuring prostate-specific antigen (PSA) values. As a result of the study, it was reported that an excellent antitumor effect was observed based on PSA levels and PET results. In addition, ^{68}Ga-PSMA-11 PET scans showeda decrease in tracer avidity in metastatic nodal and skeletal lesions and relief in bone pain after the first therapy cycle (Sathekge et al., 2019).

Satapathy et al. use the "National Comprehensive Cancer Network Functional Assessment of Cancer Therapy-Prostate Symptom Index 17 (NCCN-FACT-FPSI-17)" questionnaire to evaluate the health status of mCRPC patients (previously heavily pretreated) after ^{225}Ac-PSMA-17 therapy. As a result of the study, it was stated that PSA decreased in 5 out of 11 patients, while PSA remained stable or progressed in 3 of them. In addition, index scores before and after treatment were compared. It has been reported that the patients recorded significant improvement in physical symptoms such as pain, difficulty in urination, bone pain, fatigue, and limitation in physical activity (Satapathy et al., 2020).

The information obtained in the clinical studies with Ac-225 radiopharmaceuticals is encouraging, thus leading to the development and use of different α-emitters such as Terbium-149 (Tb-149), Astatine-211 (At-211), Lead-212 (Pb-212), Bismuth-213 (Bi-213), and Thorium-227 (Th-227) (Dhiman et al., 2022).

In addition, there are studies on different radiopharmaceuticals that can be used in the therapy of bone metastases, which are still in the research phase. These radiopharmaceuticals and their properties are summarized in Table 3 (International Atomic Energy Agency, 2021).

Table 3. Examples of radiopharmaceuticals under investigation for use in bone metastases therapy and their properties (International Atomic Energy Agency, 2021)

Radionuclide	Labeled Compound	Half-life	Radiation Type	Maximum Energy of Beta Particles (keV)	References
Sn-117m	DTPA	14 days	β^-,γ	130	(Krishnamurthy et al., 1997) (Srivastava et al., 1998)
Lu-177	DOTMP	6.734 days	β^-, γ	498	(Zakaly et al., 2020) (Bollampally et al., 2021) (Chakraborty et al., 2008)
Sm-153	DOTMP	46.27 hours	β^-	808	(Simón et al., 2012) (Chakraborty et al., 2004)
Tm-170	EDTMP	128.6 days	β^-, γ	968	(Das et al., 2009) (Das et al., 2017)
Ho-166	EDTMP	26.83 hours	β^-, γ	1854	(Louw et al., 1996) (Pedraza- López et al., 2004)

Sn: Tin; **Lu:** Lutetium; **Sm:** Samarium; **Tm:** Thulium; **Ho:** Holmium; **DTPA:** Diethylene triaminepentaacetic acid; **DOTMP:** 1,4,7,10-tetraaxacyclododecane-1,4,7,10-tetramethylene phosphonic acid

CONCLUSION

Metastases are still one of the most serious complications of cancer, and their treatment is vital for patient health. Bone metastases are seen in many primary cancer types and cause significant problems in patient survival and living standards. Radionuclide therapy is becoming increasingly important in the treatment of bone metastases. Using a targeted systemic therapy approach in radionuclide therapy and radiopharmaceuticals is more selective and effective in bone metastases therapy than other local and systemic treatments, making this therapy method advantageous. For this reason, studies on radionuclide therapy and the use of new radiopharmaceuticals in bone metastases therapy continue intensively. It can be said that promising results have been obtained with radiopharmaceuticals that have entered clinical use.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION STATEMENT

Determining the subject of study (SE), literature research (HB), preparing the study text (HB, SE), reviewing the text (SE).

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