Radionuclide Therapy for Bone Metastases

Utility of Scintigraphy and PET Imaging for Treatment Planning

Hojjat Ahmadzadehfar, MD, MSc[a,*], Markus Essler, MD[a], Kambiz Rahbar, MD[b], Ali Afshar-Oromieh, MD[c,d]

KEYWORDS

• Breast cancer • Prostate cancer • Lung cancer • Bone metastases • Radionuclide therapy • Radium-223 • PET

KEY POINTS

- A Pain relief response is seen in approximately one-half of patients treated with radionuclides for painful osseous metastases.
- FDG PET plays an important role in the detection of bony metastases with higher detection rate compared with bone scintigraphy in a majority of tumor types and consistent with clinical status of the patients as it reflects tumor activity.
- Skeletal tumor burden measured by fluoride PET correlates with OS inpatients who underwent bone targeted therapies using radionuclides.

TREATMENT OF BONE METASTASES WITH RADIONUCLIDES

The skeleton is a common site for metastases of various malignant tumors. Bone metastases are the result of complex interactions between tumor cells, bone cells, and the microenvironment.[1] Some tumor types, such as prostate cancer and breast cancer, are more frequently associated with bone metastases compared with others.[2] For inducing bone metastases, the tumor cells must detach from the primary tumor, enter the systemic circulation, evade detection by the immune system, and finally adhere to capillaries in the bone marrow, leading to extravasation into the bone marrow space.[1,3–5] Bone metastases are a major cause of morbidity and mortality and are associated with pain, pathologic fractures, spinal cord compression, and decreased survival.[6] The pain from small metastases seems to be caused by irritation of nerve endings in the endosteum by a variety of chemical mediators. Larger bone metastases produce stretching of the periosteum, which leads to pain.[7]

Bone pain palliation with radionuclides has a long history of using various β-emitters, like phosphorus-32 (^{32}P),[8] strontium-89 (^{89}Sr),[8] rhenium-186 hydroxyethylidene diphosphonate (^{186}Re-HEDP),[9] samarium-153 ethylenediamine tetramethylene phosphonate (^{153}Sm-EDTMP),[9] and, recently, lutetium-177 EDTMP (^{177}Lu-EDTMP)[10] and (4-{[(bis(phosphonomethyl))

[a] Department of Nuclear Medicine, University Hospital Bonn, Sigmund-Freud-Str. 25, Bonn 53127, Germany; [b] Department of Nuclear Medicine, University Hospital Muenster, Albert-Schweitzer-Campus 1, Muenster 48149, Germany; [c] Department of Nuclear Medicine, Heidelberg University Hospital, Im Neuenheimer Feld 400, Heidelberg 69120, Germany; [d] Clinical Cooperation Unit Nuclear Medicine, German Cancer Research Centre, Im Neuenheimer Feld 280, Heidelberg 69120, Germany
* Corresponding author. Department of Nuclear Medicine, University Hospital Bonn, Sigmund-Freud-Str. 25, Bonn 53127, Germany.
E-mail address: Hojjat.ahmadzadehfar@ukbonn.de

PET Clin 13 (2018) 491–503
https://doi.org/10.1016/j.cpet.2018.05.005

carbamoyl]methyl}-7,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl)acetic acid ^{177}Lu-BPAMD.[11] The only approved α-emitter is radium-223 (^{223}Ra).[12]

Bone-seeking radionuclides are classified into 2 groups: calcium analogs, like ^{89}Sr and ^{223}Ra, and radionuclides attached to phosphate, like ^{153}Sm-EDTMP and rhenium-186 hydroxyethylidene diphosphonate (^{188}Re-HEDP). The various radionuclides have different physical characteristics, which are shown in **Table 1**.[13] In this article, apart from introduction of different bone-specific radionuclide therapies, the value of PET imaging for the treatment planning and also its predictive value are discussed. Radionuclides that can be used for the treatment of all types of metastases (soft tissue, lymph nodes, and bone), such as ^{131}I for metastatic thyroid cancer,[14] ^{131}I-MIBG for neuroblastoma,[15] ^{177}Lu–prostate-specific membrane antigen (PSMA) for prostate cancer,[16] or ^{177}Lu-DOTATATE for neuroendocrine tumors.[17] These substances, however, are not addressed in this article.

BONE-TARGETED THERAPY WITH BONE SPECIFIC β-EMITTERS

Phosphorus-32 and strontium-89

Typical response times to different β-emitters are shown in **Box 1** and **Table 2**. Pain reduction after the injection of ^{32}P and ^{89}Sr occurs after 5 days to 14 days and 14 days to 28 days postinjection, respectively. During treatment with ^{32}P, pain relief was reported by 50% to 87% of prostate cancer patients treated with 200 MBq to 800 MBq of ^{32}P administered in daily fractions of 20 weeks to 80 MBq after androgen priming. The main disadvantage of ^{32}P therapy is a dose-limiting reversible pancytopenia due to myelosuppression with a maximum at 5 weeks to 6 weeks after administration.[18]

The first studies using ^{89}Sr have demonstrated an efficacy for pain reduction as high as 80%.[19–24] A majority of treated patients in these studies suffered from prostate or breast cancer. ^{89}Sr was the first radiopharmaceutical to be approved for systemic radionuclide therapy in the palliation of painful bone metastases. In the largest study using ^{89}Sr, 622 patients were included. Of these, 15% showed complete pain relief and a partial response was documented in 81%.[25,26] In only 4% of the patients, no response was observed. In a randomized, controlled phase III trial, James and colleagues[27,28] compared the efficacy of zoledronic acid (ZA) with ^{89}Sr regarding clinical progression-free survival (CPFS) as the primary outcome and the skeletal-related event–free interval (SREFI), total skeletal-related events (SREs), overall survival (OS), and quality of life (QOL) as secondary outcomes. Each of the compounds (ZA and ^{89}Sr) was combined with docetaxel for the treatment of bone metastases of castration-resistant prostate cancer (CRPC) patients. In this trial, 757 patients were randomized to receive 6 cycles of docetaxel combined with prednisolone, with ZA, with a single ^{89}Sr dose after the sixth cycle of docetaxel, or with both ZA and a single ^{89}Sr dose. A Cox regression analysis adjusted for stratification variables and showed a CPFS benefit for ^{89}Sr (hazard ratio [HR] = 0.845, P = .036) and confirmed no effect of ZA (P = .46). ZA showed a significant SREFI effect (HR = 0.76; P = .008), however. Neither agent affected OS (^{89}Sr, P = .74; ZA, P = .91). QOL was well maintained in all treatment arms, with differing patterns of care resulting from the effects of ^{89}Sr on the time to progression and ZA on SREFI and total SREs. The investigators concluded that ^{89}Sr combined with docetaxel improved CPFS but did not improve OS, SREFI, or total SREs. Furthermore, ZA did not improve CPFS or OS

Table 1
Summary of main physical properties of different radionuclides clinically used for pain palliation

	Emission Type	Half-Life (d)	Maximum Energy (MeV)	Maximum Tissue Penetration Range (mm)
^{32}P	ß-emitter	14.3	1.7	8.5
^{89}Sr	ß-emitter	50.5	1.46	7
Samarium-153	ß and γ-emitter	1.9	0.81	4
^{186}Re	ß and γ-emitter	3.7	1.07	5
^{188}Re	ß and γ-emitter	0.7	2.1	10
^{177}Lu	ß and γ-emitter	6.7	0.498	1.8
^{223}Ra	α-Emitter and γ-emitter	11.4	27.78	0.1

Adapted from Ahmadzadehfar H. Targeted therapy for metastatic prostate cancer with radionuclides. In: Mohan R, editor. Prostate cancer - leading-edge diagnostic procedures and treatments. Croatia: InTech; 2016.