4 Radiopharmaceuticals for Treatment of Osteosarcoma

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Abstract

Although trace amounts of radioactivity are routinely used to detect osteosarcoma, the use of larger therapeutic amounts of radiation is often an unrecognized opportunity to treat metastatic osteosarcoma. This chapter will review a number of approaches to use ionizing radiation in the form of injectable radiopharmaceuticals. Since bone metastases are a common pattern of metastatic spread of cancer in general, a number of bone-seeking radiopharmaceuticals have been developed and FDA approved for treatment of bone metastases. Although osteosarcoma, a bone-forming cancer, would seem ideally suited to be treated with bone seekers, patterns of relapse involving non-ossifying metastases remain a major problem to be overcome. Thus, this review will not only describe experience using a number of bone-seeking radiopharmaceuticals such as 153-samarium-EDTMP, 153-samarium-DOTMP, and 223-radium against osteosarcoma, but also approaches to identify patients who may benefit as well as some means to the improve overall efficacy including combination therapy with routine agents and using nuclear imaging to develop best strategy for use. These include imaging with not only ^{99m}Tc-MDP standard bone scans, but also ^{99m}Tc-MDP bone scans with SPECT CT, bone-specific sodium fluoride PET-CT ($Na^{18}F$), and ^{18}FDG-PET-CT. Accurate knowledge of oligometastatic active disease can facilitate more effective use of combination therapy, including radiosensitizers and local control measures, for example, stereotactic body radiotherapy (SBRT) and/or cryoablation to reduce disease burden as well as manage and prevent micrometastatic disease from growing and metastasizing. Finally, a new tumor-specific radiopharmaceutical, CLR 131, may also provide another radiopharmaceutical to treat both osteoblastic and non-ossifying areas of osteosarcoma.

Keywords

Strontium · Samarium · Radium · Radiosensitizer · Sodium fluoride PET · SPECT CT · Ifosfamide · Doxorubicin liposomes · Denosumab · Zolendronate · Pazopanib · Gemcitabine · Beta emitter · Alpha emitter · Stereotactic body radiotherapy (SBRT) · Cryoablation · Lipid raft-seeking radiopharmaceutical

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Introduction

Osteosarcoma is a bone-forming tumor; alkaline phosphatase is a tumor marker associated with high osteoblastic activity. Metastatic osteosarcoma at diagnosis with high alkaline phosphatase in more than two organs (e.g., bone and lung) was associated with significantly inferior survival [1]. The initial bone-seeking radiopharmaceuticals, ^{89}SrCl and ^{32}P, were limited by a long half-life (50 days and 14 days, respectively) and nonspecific uptake of ^{32}P in other tissues. These were generally used for one and done palliation of bone pain [2]. The next era of radiopharmaceuticals with bone-seeking specificity used metal chelates to deliver a radioactive payload which tightly binds bone matrix (Table 4.1). 133-Ho-DOTMP development was halted because of renal toxicity which occurred when radiopharmaceutical that did not bind bone passed through the kidneys into the urine. 186-Re-HEDP and 188-HEDP were used for skeletal metastases in 1997–2007 [3–6] but are not currently available in North America.

Samarium

Goeckeler tested a number of chelates and ethylene diamine tetramethylene phosphonate (EDTMP) was shown to not only have very high bone specificity, but also very high retention in bone [7, 8]. Canine osteosarcoma studies with 153-Sm-EDTMP showed activity excellent against osteoblastic osteosarcoma [9]. 153-Sm-EDMP that does not bind bone is excreted into the urine unchanged [10]. Thus, when Anderson et al. dose escalated 153-Sm-EDTMP with stem cell rescue, the protocol used saline hydration, furosemide to increase urine output, and instructions to void frequently for 6 hours to reduce renal and bladder exposure to unbound radiopharmaceutical [11]. In this study, hypocalcemia from carrier EDTMP was found to be the dose-limiting toxicity when 153-Sm-EDTMP was escalated 30-fold from a standard dose of 1 mCi/kg to 30 mCi/kg. Others have successfully used high-dose samarium for osteosarcoma [12–14]. Loeb et al. also showed tandem dosing was possible in osteosarcoma [15].

Use of gemcitabine as a radiosensitizer after the highly bone-specific binding of high-dose 153-Sm-EDTMP resulted in improved imaging responses [16]. Total body measurements after 153-Sm-EDTMP then gemcitabine were 1.08+/−0.4 mCi (<3.6 mCi for safe infusion of stem cells) after 6–7 half-lives (12–14 days) [16] and all patients recovered hematologic function within 2 weeks after getting the stem cells (Fig. 4.1).

Standard dose 153-Sm-ETMP usefulness in osteosarcoma has been reviewed previously [17, 18]; the dose-limiting toxicity of 153-Sm-EDTP is delayed thrombocytopenia. This generally occurs 3–4 weeks after administration and resolves within 4–6 weeks. To date there are no reports of use of TPO agonists such as eltrombopag or romiplostim after 153-Sm-EDTMP to limit duration and/or severity of this side effect. Although 153-Sm decays to stable 153-Eu by beta decay, trace quantities of 154-Eu are produces during synthesis of 153-Sm via neutron capture. Thus, although not associated with any clinical effects, patients need a letter about prior 153-

Table 4.1 Bone-seeking radiopharmaceuticals for osteosarcoma

Radioisotope	$T_{1/2}$ (days)	Particle	Range (mm)	Bone tumor-seeking ligand
89-Sr	50.6	Beta	7	Alkaline earth metal (like calcium)
32-P	14.3	Beta	9	Metabolized into hydroxyapatite
133-Ho	1.2	Beta	9	DOTMP
186-Re	3.7	Beta	5	HEDP
188-Re	0.7	Beta	10	HEDP
153-Sm	1.9	Beta	4	EDTMP or DOTMP
223-Ra	11.4	Alpha	0.001	Alkaline earth metal (like calcium)

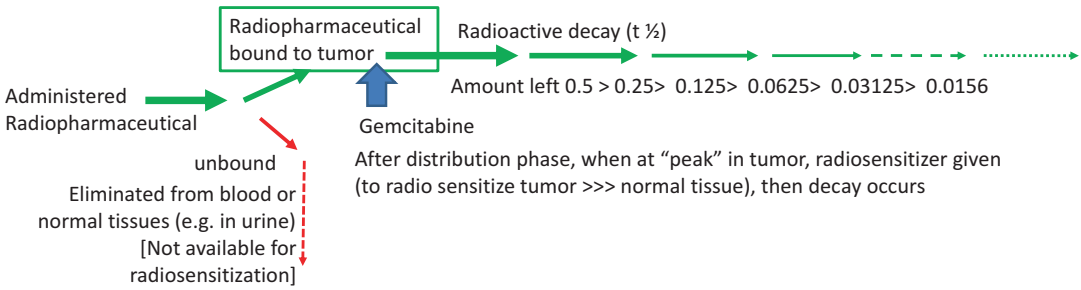

Fig. 4.1 The "Double Tap" for increased tumor-specific lethality. After elimination of unbound agent (e.g., unbound 153-Sm-EDTMP or 153-Sm-DOTMP is eliminated in the urine within 3- 6 hours), only bone bound agent remains when a radiosensitizer (e.g., gemcitabine, ifosfamide, or doxorubicin liposomes) is given later. Specifically bound radiopharmaceutical then decays; this leaves ½ the amount of radioactivity in the tumor after each half-life. Thus, after 7 half-lives 1/128th of the initial radiation is present

Sm therapy when traveling because of the extremely sensitive radiation detectors in airports will detect emissions form 145-Eu [18]. Loeb also described detection of 152-Eu in treated patients, too [19].

One approach to the saturation effect and excess EDTMP at high doses of 153-Sm-EDTMP is to synthesize a different chelate with higher purity and specific activity such as 153-Sm-DOTMP [20, 21]. This preparation has been termed "CycloSam". With high doses it may be avoid hyopcalcemia and 153-Sm-DOTA may become useful for both osteosarcoma and total skeletal irradiation.

Even high-dose samarium patients seem to have only temporary benefit. Isolated limb perfusion (ILP) of 153-Sm-EDTMP of dogs with osteosarcoma at provided some insights about potential reasons for osteosarcoma relapses after bone-seeking radiopharmaceutical administration. Autoradiography showed heterogeneous bone tumor distribution despite achieving a high dose for a short time using ILP. Lung metastases are often another pattern of osteosarcoma relapse or progression after bone-seeking radiopharmaceuticals because some lung metastases have very low amount of bone formation compared to bone metastases. Finally, the mass energy of a beta emitter is much less than alpha emitters which readily cause double-strand breaks.

Radium

Alpha-emitting radiopharmaceuticals have some advantages compared to beta-emitting agents. These include not only very high linear energy transfer (LET) because of high mass (an alpha particle has 2 protons and 2 neutrons), but also safer handling and lower radiation exposure of nontarget tissues [22, 23]. 226-radium was used >100 years ago but the major naturally occurring 226-radium isotope has not only an extremely long half-life but also long-lived radon daughters and thus was abandoned because of safety concerns [22]. Larsen, Henriksen, Nilsson, and Bruland were responsible for early development of 223-radium as a safe and effective agent for bone metastases [23–28]. Preclinical and early clinical trials work established an extremely favorable safety profile including low marrow toxicity and few side effects [27, 28]. Phase 2 studies showed safety, improved pain, and better survival in prostate cancer patients [27–30]. A subsequent randomized, placebo, double-blind phase 3 clinical trial showed improved pain and was stopped early because of a significantly improved survival benefit; this resulted in FDA and EMEA approval [31, 32]. Since prostate cancer causes osteoblastic reactive bone around the neoplastic cells, the 223-Ra may act to kill and contain the viable rim of a bone metastasis.

223-radium was first used for recurrent, progressive, metastatic osteosarcoma using the FDA compassionate access IND mechanism. In these patients not only pain but also the tumor marker, alkaline phosphatase, improved [22, 33]. Subsequently 223-radium has become part of the NCCN guidelines for relapsed osteosarcoma. Subbiah et al. showed safety of 1.5–3.0 microCi/kg [34] and blood-brain barrier penetration of 223-radium in osteosarcoma [35]. This group also demonstrated usefulness of $Na^{18}F$ PET for screening and monitoring of response [36]. The next step was combination therapy using radiotherapy (RT) and stereotactic body radiotherapy (SBRT) with other agents as detailed in Table 4.2.

Denosumab is an agent useful in the treatment of giant cell tumor and osteosarcoma [37], reducing osteopenia, and preventing complications of skeletal metastases. Since I have observed that denosumab also causes increased ossification of osteoblastic osteosarcoma tumors, the agent can be used improve the therapeutic index of 223-radium by facilitating increase 223-radium uptake. At Cleveland Clinic, 14 of 15 recent patients have also had denosumab as part of the 223-radium treatment regimen. It is possible that zolendronate may also be active in this respect and if osteosarcoma cells are like giant cell tumor zolendronate may also have an antiapoptotic effect [38]. Since zolendronate is now generic and has become inexpensive future use would be expected to increase in the treatment of osteosarcoma skeletal metastases, especially in combination with 223-radium. Figure 4.2 shows activity of combined use of continuous infusion 14-day ifosfamide/mesna and 223-radium.

Table 4.2 Agents that have been used with 223-radium (Cleveland Clinic)

Agent	Class of agent	Dose/route/frequency
Denosumab	Rank ligand antibody	120 mg sc monthly
Zolendronate	Bisphosphonate	4 mg iv monthly
Ifosfamide/mesna	Alkylating agent	1 gm/m2/d iv (CI[a]) × 14 days q month
Cyclophosphamide	Alkylating agent	25–50 mg po daily
Pazopanib	TKI[a]	400–600 mg po daily
Sorafenib	TKI[a]	400 mg po twice/day
Sirolimus	mTOR inhibitor	2–4 mg po daily
Everolimus	mTOR inhibitor	5 mg po daily
Nivolumab	Anti-PD1 antibody	480 mg iv monthly
Doxorubicin liposomes	Anthracycline	30 mg/m2 iv monthly

[a]TKI-tyrosine kinase inhibitor (mostly anti-VEGF)

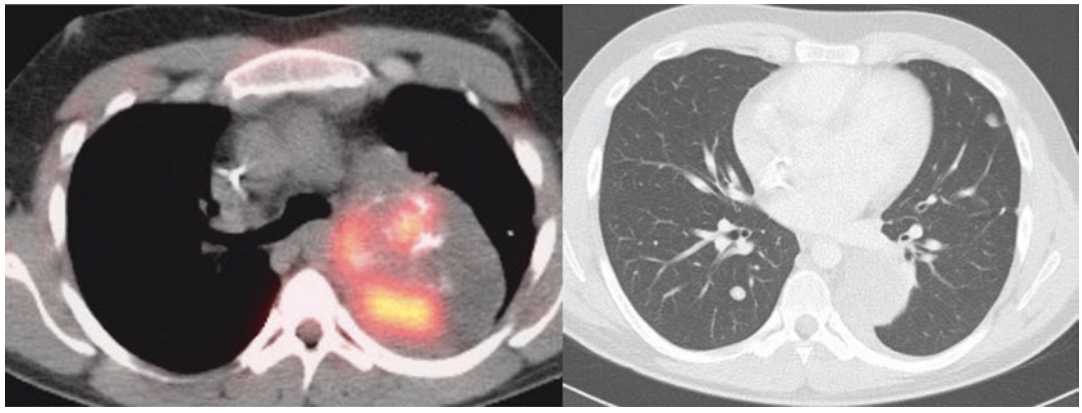

Fig. 4.2 Ifosfamide +223-radium combination therapy. Heterogeneous osteoblastic activity of an osteosarcoma lung metastasis using ^{99m}Tc-MDP bone scan/SPECT CT. This patient had an excellent response to the combination of denosumab+14-day continuous infusion ifosfamide/mesna and monthly 223-radium after two cycles. This allowed thoracic surgery to be done to remove the large mass

Choice of cytotoxic agents to combine with 223-radium was driven by agents and combinations with low marrow toxicity so as not to delay monthly 223-radium infusions. For example, oral cyclophosphamide can be adjusted to keep ANC > 1000–1500, and anemia and thrombocytopenia are rarely problematic. Although high-dose ifosfamide has high activity against relapsed osteosarcoma [39] including bone metastases [40], the 5-day regimen results in pancytopenia and would not be suitable for use with 223-radium. However, high-dose ifosfamide/mesna (14 gm/cycle but given as a continuous at 1 gm/m^2/day) has very low potential to cause thrombocytopenia; neutropenia can be overcome using PEG-GCSF [41–44].

Another means to attempt to overcome the problem of heterogeneous biodistribution of 223-radium is to use additional external beam radiation as either SBRT or RT if normal structures (e.g., trachea, carina, heart, mediastinum, stomach) do not permit SBRT to be safely given. In 15 patients treated with 223-radium treated at Cleveland Clinic >50 sites of osteosarcoma metastases have had SBRT or RT to improve both pain and/or durability of responses. Figure 4.3 shows an example to SBRT to the sacrum.

Other means of improving 223-radium efficacy have included use of TKI agents such as pazopanib, sorafenib, and regorafenib to provide radiosensitization and antiproliferative effects [45–47]. Although pazopanib, sorafenib, and regorafenib have activity against metastatic osteosarcoma [47–51], side effect profile for each is different. Since pazopanib seems to have fewer problems with rash and GI toxicity, this has been used in more of our 223-radium patients than other TKI agents at our institution. Finally, doxo-

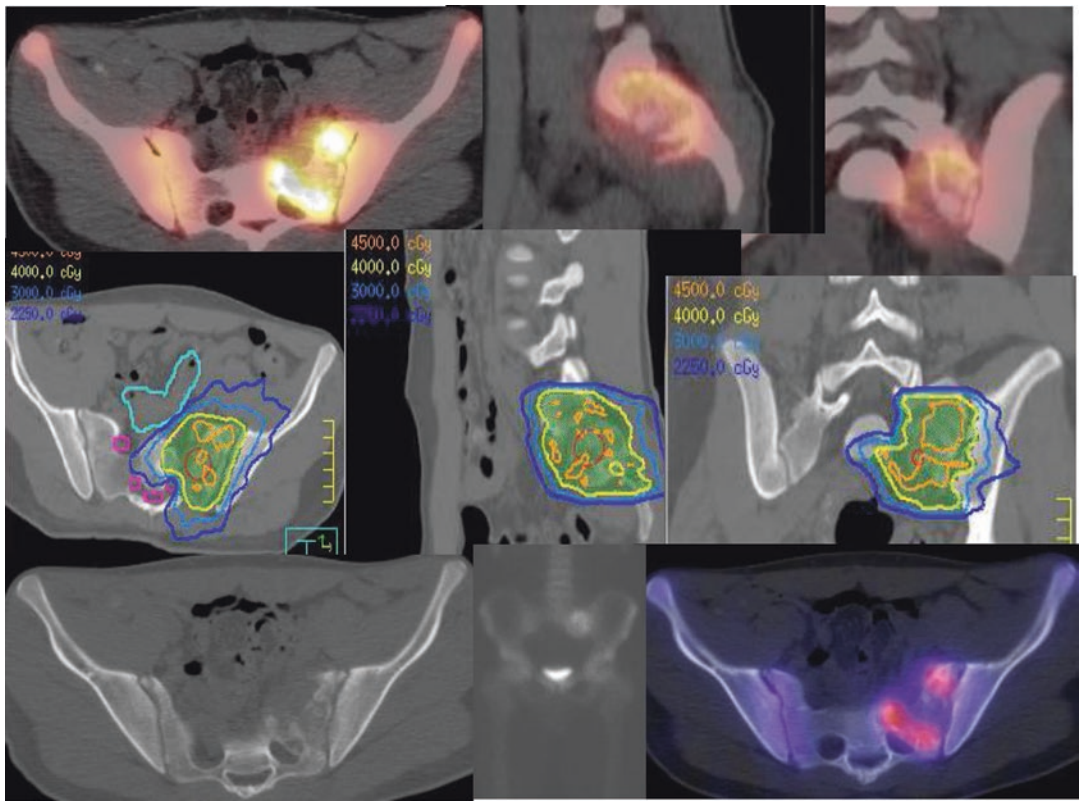

Fig. 4.3 Scan images and SBRT plans of osteosarcoma involving sacrum treated with denosumab, pazopanib, and 223-radium. Top: PET-CT showing ^{18}FDG activity; middle: SBRT plan (8 Gy × 5 = 40Gy; bottom: CT, planar ^{99m}Tc-MDP bone scan, and SPECT CT of lesion. This patient had a durable response in this location to the combination therapy and was able to participate fully in activities including climbing again and attending college

rubicin liposomes have been used with 223-radium because this agent is outpatient and well tolerated (Table 4.2). The anthracycline liposomal formulation, unlike the parent drug, has very low hematologic and heart toxicity [52] and may also have an effect on sarcoma stem cells in combination with mTOR inhibition [53, 54]. Nevertheless, relapse of metastatic osteosarcoma after 223-radium in non-osseous sites is common. In our series of patients with osteosarcoma osteoblastic metastases, 6/15 alive after 1 year and 3/15 > 2 years.

Another Radiopharmaceutical for Osteosarcoma: CLR 131

A new radiopharmaceutical with other tumor-specific properties is CLR 131. This agent has specificity for tumors via [36] lipid rafts which are highly expressed on tumor cells but not normal tissues [55].Thus, CLR 131 can deliver a nuclear payload containing iodine to osteosarcoma tumor deposits, even when these do not make bone. Preclinical models also show synergy with external bean radiation in vivo [56]. Preclinical work with pediatric cancers including neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, and osteosarcoma demonstrated in vivo concentration ~6× in tumors as well as antitumor efficacy [57, 58]. The University of Wisconsin has a clinical trial testing this agent in children and college-aged young adults with solid tumors including osteosarcoma (NCT03478462). Escalation using stem cells (like MIBG) and/or gemcitabine radiosensitization should also be possible with the CLR 131 agent.

Patient Selection for Radiopharmaceuticals for Osteosarcoma: Practical Considerations

Table 4.3 reviews some aspects of how specific nuclear medicine scans can help make plans and/or decide on suitability (or not) as well as following response(s).

Table 4.3 Scans for plans: Imaging of osteosarcoma for control of oligometastatic disease

Imaging modality	Principle	Comment
^{99m}Tc-MDP SPECT CT	Three-dimensional imaging of bone formation	223-Ra or 153-Sm-DOTMP screening and/or dosimetry
Na^{18}F PET-CT	More sensitive than ^{99m}Tc-MDP	Follow response
^{18}FDG PET-CT	Shows metabolic activity	Follow response RT plans
CT	Sensitive detection of lung metastases (lung and bone windows) CT guidance into tumors CT guidance into tumors	Follow response RT plans Biopsy + cryoablation
MRI	Axial (head and neck, spine, and pelvis)	RT plans

Although planar ^{99m}Tc-MDP bone scan can give a yes or no about lesion being osteoblastic (avid) and 223-radium suitability, combining this imaging with SPECT CT can help one know more about location and heterogeneity of uptake as well and to develop plans for other local control measures (e.g., brachytherapy, RT, SBRT, or cryoablation) [59–61]. Sodium fluoride PET is perhaps the most sensitive means to follow osteoblastic lesions after 223-radium [36].

Table 4.4 shows an example of multiple osteoblastic lesions responding using Na^{18}F PET-CT as a means to show improvement. ^{18}FDG is the best means to follow non-osteoblastic bone or visceral lesions since these may not change much in size and/or be detected by the bone-specific ^{99m}Tc-MDP or Na^{18}F bone scans. Sometimes CT done with PET scans is not of diagnostic quality and a dedicated chest CT with and without contrast is the most specific and sensitive means to follow lung metastases. Instead of relying on tumor specificity of radiopharmaceuticals, treatment of oligometastatic disease using SBRT or cryoablation using CT guidance [59–61], may offer additional modalities to reduce osteosarcoma disease burden.

Table 4.4 Decrease in $Na^{18}F$ bone PET uptake of osteoblastic metastases after 223-radium

	SUV pre 223-radium	SUV post 223-radium × 2	Difference	
Bone lesion location			SUV	Percent less
Skull base (clivus)	9.3	5.1	−4.2	−46%
C-spine (C3)	21.2	8.2	−13.0	−61%
T-spine (T2)	26.9	7.8	−19.1	−71%
T-spine (T12)	30.1	25.3	−4.8	−16%
L-spine (L4)	24.9	10.6	−14.3	−57%
Sacrum	26.8	18.8	−8.0	−30%
Pelvis (femoral head)	24.7	6.9	−17.8	−72%
Ribs (post left 6th)	18.5	6.0	−12.5	−68%
Humerus (proximal right)	35.8	19.5	−16.3	−46%
Ankle (left distal tibia)	32.6	16.0	−16.6	−51%
Median	25.8	9.4	−15.8	−54%
Mean	25.1	12.4	−12.7	−51.8%

Summary and Obtaining Access to Radiopharmaceuticals for Osteosarcoma

Bone-seeking radiopharmaceuticals 153-Sm-EDTMP and 223-radium may improve pain and provide an underutilized means to treat osteoblastic metastases of osteosarcoma. Although dose escalation of 153-Sm-EDTMP and 153-Sm-DOTA is possible, osteoblastic heterogeneity may limit long-term effectiveness (cannot hit the target if there is no uptake). Because of low marrow toxicity and ease of administration, 223-radium can be used in combination with other agents. Nevertheless, other control strategies (e.g., SBRT, cryoablation) then immune therapy such as Cincinnati Children's trial of pembrolizumab, decitabine, and SBRT (NCT 03445858) or CLR 131 at the University of Wisconsin (NCT03478462) may be other options to consider.

Radiopharmaceuticals can provide benefit to osteosarcoma patients. This is an evolving field. The author uses virtual visits to help patients and caregivers understand what options are not only feasible but with a likelihood of benefit and also how to get access to these remarkable agents [62].

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