Multimodality Therapy: Bone-targeted Radioisotope Therapy of Prostate Cancer

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Abstract: Accumulating data suggest that bone-seeking radiopharmaceuticals can be used to treat prostate cancer bone metastasis and improve the clinical outcome of patients with advanced prostate cancer. It remains to be elucidated whether radiopharmaceuticals enhance the disruption of the onco-niche or the eradication of micrometastatic cells in the bone marrow. The purpose of this review is to investigate the role of bone-targeted radioisotope therapy in the setting of multimodality therapy for advanced prostate cancer. We examine available data and evaluate whether dose escalation, newer generations, or repeated dosing of radiopharmaceuticals enhance their antitumor effects and whether their combination with hormone ablative therapy, chemotherapy, or novel targeted therapy can improve clinical efficacy.

Introduction

A hallmark of metastatic prostate cancer is the development of osteoblastic bone metastasis. Almost all patients with advanced prostate cancer eventually develop bone metastasis. In most patients with prostate cancer, bone is the only site of clinical metastasis. Not surprisingly, many established prognostic factors for advanced prostate cancer (eg, performance status, alkaline phosphatase level, hemoglobin level) highlight the clinical consequences of bone metastasis. Hence, patients who develop widespread, progressive, or early bone metastasis tend to suffer more from their symptoms and fare worse with their prostate cancer. Conversely, patients who develop limited, stable, or delayed bone metastasis tend to experience less morbidity and have a better clinical outcome.

Increasingly, advanced prostate cancer is considered to be a treatable, although not curable, disease. Patients with prostate cancer and bone metastases may experience substantial palliative benefit and even a significant survival advantage from the use of hormone ablative therapy or chemotherapy. There is promise that one can gain even more from such treatments by combining them with bone-targeted agents (eg, calcitriol, atrasentan) to improve control of bone metastases. Bone-seeking radiopharmaceuticals are another therapeutic option for this very purpose.

Here, we review the underlying physical characteristics of various bone-seeking radiopharmaceuticals. We also discuss their clinical efficacy and how they may be used to overcome the putative biologic properties of prostate cancer bone metastasis. Finally, we examine ways in which the use of radiopharmaceuticals can be optimized in the setting of multimodality therapy; primarily, how they can be combined with hormone ablative therapy, chemotherapy, or targeted therapy for the treatment of prostate cancer bone metastases.

Tumor-Host Cell Interactions

For the longest time, we have focused on metastatic tumor cells in the study and treatment of metastasis. However, we now know that host cells and the microenvironment are also implicated in the metastatic process. Whether an immigrating metastatic tumor cell becomes established in a foreign tissue largely depends on favorable interactions between the metastatic tumor cell and host cells.[1,2]

The concept of tumor-host cell interactions is compatible with the concept of an onco-niche in which cancer cells interact with host cells and the microenvironment.

The Onco-niche

The osteoblast is probably the most important host cell in prostate cancer bone metastasis, which has the unique feature of being predominantly osteoblastic. It is hypothesized that prostate cancer initially stimulates an osteoblastic response by causing proliferation and differentiation of osteoblasts. In the bone marrow, the osteoblastic niche provides a microenvironment that supports and sustains hematopoetic stem cells.[3] It remains to be elucidated whether this osteoblastic niche also provides a favorable onco-niche for prostate cancer stem cells. If the sequence of events culminating in bone metastasis starts with prostate cancer-induced osteoblast overactivity, then therapeutic strategies targeting osteoblasts are logical and appropriate for the treatment of prostate cancer bone metastasis.

The concept of an onco-niche is intimately linked to that of cancer stem cells. One cannot help but notice that the prowess that allows a metastatic malignant cell to migrate, extravasate, invade, and thrive at distant sites is already ingrained within the stem cell from which it is derived. We previously postulated that the nature of the involved stem cell determines both the resultant malignant cell's predilection to metastasize and its pattern of metastasis.[4] Just as a stem-cell niche supports a normal stem cell, an onco-niche sustains a cancer stem cell. If one could manipulate the onco-niche and render it more akin to the stem-cell niche, then one might be able to keep cancer cells in check, making them more indolent, if not dormant. Therefore, the idea of an onco-niche is important because it has therapeutic implications. For a growing pool of prostate cancer stem cells, the corresponding onco-niche in the bone also needs to expand to maintain them as cancer stem cells. Thus, one way to treat prostate cancer would be to eliminate the prostate cancer stem cells. Another way would be to induce the cells to behave like normal stem cells or to differentiate into more benign or indolent entities by modulating the onco-niche. In principle, one could modulate the onco-niche by restricting its expansion (eg, by limiting osteoblastic proliferation) or by converting it back into a quasi–stem-cell niche (eg, by mitigating the effects of inflammation, oxidation, angiogenesis, and/or hypoxia in the bone marrow). The modulation of the onco-niche is especially relevant if the eradication of cancer stem cells is unlikely or impossible. The time will come when modulation of the onco-niche becomes an integral aspect of cancer therapy; it would be like managing the soil so that even if a malignant seed remains, it does not germinate or grow like a weed.

Targeting the Onco-niche

Interestingly, it has been observed that irradiated bone no longer provides a favorable niche for metastasis.

Figure 1. A bone-scan image showing a previously irradiated bone in the cervical spine (arrow) that no longer provides a favorable microenvironment (onco-niche) for subsequent prostate cancer osseous metastasis.

Table 1. Physical Characteristics of Various Bone-Seeking Radiopharmaceuticals

Agent	Carrier ligand	Half-life (days)	Maximum energy (MeV)*	γ-emission (MeV)	Maximum range (mm)
Phosphorus-32	_	14.3	1.71 (β)	None	8.5
Strontium-89	Cl$_2$	50.5	1.46 (β)	None	7
Samarium-153	EDTMP	1.9	0.81 (β)	0.103	2.5
Rhenium-186	HEDP	3.7	1.07 (β)	0.137	5
Rhenium-188	HEDP	0.7	2.12 (β)	0.155	10
Tin-117m	DTPA	13.6	0.13 and 0.16 (conversion ē)	0.159	<0.001
Radium-223	Cl$_2$	11.4	5.78 (α) average	0.154	<0.01

*Derived from the type of radiation particles emitted (in parentheses).

Cl$_2$=chlorine; DTPA=diethylenetriamine pentaacetic acid; EDTMP=ethylenediamine tetramethylene phosphonic acid; HEDP=1-hydroxy ethylidene-1,1-diphosphonic acid.

Figure 1 shows the bone-scan image of a patient with metastatic prostate cancer who had previously received external beam radiation to the cervical spine. This patient was subsequently spared from bone metastasis at the irradiated site when the prostate cancer relapsed and progressed to the skeleton. Similarly, Jacobsson and Näslund reported that previously irradiated bone (to 5,000 Gy) appeared to be protected from future metastasis.[5] We postulate that using radiopharmaceuticals to radiate multiple bone metastases in a systemic manner may similarly improve control of the bone onco-niche and treatment of bone metastases.

Therefore, when treating prostate cancer bone metastasis, it is preferable to use a treatment that not only eliminates or reduces the burden of metastatic prostate cancer cells in the bone but also alters the onco-niche by disrupting the osteoblasts, endothelial cells, and other stromal cells or factors. In principle, one can further enhance the effects of radiation therapy by combining it with hormone ablative therapy, chemotherapy, or targeted therapy that destroys the malignant cancers as well as the onco-niche. This is the basis of multimodality therapy: treating the various components of a complex disease using various therapies.

Radiopharmaceuticals

Clinical Data
Bone-seeking radiopharmaceuticals are like magic bullets or smart bombs that target bone metastases by preferential deposition at sites of increased osteoblastic activity and bone matrix synthesis. Table 1 summarizes the unique physical properties of various radiopharmaceuticals. These agents are ideally suited for the treatment of patients with multifocal osteoblastic metastases and predominant or only bone metastases. Another potential benefit of bone-seeking radiopharmaceuticals is that they can be used repeatedly for palliation of bone pain. Table 2 summarizes the clinical characteristics of various radiopharmaceuticals.

Phosphorus-32 (^{32}P) has a propensity to deposit in bone: about 85% of total body phosphorous is bound as inorganic phosphate to hydroxyapatite in the skeleton. Animal studies have shown that 3–5 times more ^{32}P is absorbed at the site of bone metastasis than in normal bone.[6] Although ^{32}P is rarely used for palliation of bone pain in the Western world, it is advantageous over other radiopharmaceuticals with respect to lower cost and convenience of administration (ie, oral). A study comparing a single oral dose of ^{32}P with intravenous (IV) strontium-89 (^{89}Sr) demonstrated similar efficacy and toxicity.[7]

^{89}Sr is a calcium analogue. Approximately 10 times more ^{89}Sr is absorbed at the site of bone metastasis than in the normal bone marrow.[8] Bone dosimetry studies suggest that light skeletal metastases (≤5 lesions) absorb approximately 4,000 Gy of radiation, moderate metastases (5–10 lesions) 8,000 Gy, and diffuse metastases 1,000 Gy.[9] In a randomized phase II study, Tu and colleagues showed that consolidation therapy using 1 dose of ^{89}Sr (55 μCi/kg) increased progression-free and overall survival in patients who had responded to induction chemotherapy.[10] An update of this study indicated that combining chemotherapy with ^{89}Sr was safe and feasible in selected patients.[11]

Table 2. Clinical Characteristics of Various Bone-Seeking Radiopharmaceuticals

Agent (dose)	Response pain (%)	Response onset (days)	Response duration (mos)	Peak effect (wks)	Recovery (wks)	Response PSA <50%*	Pain flare	Low WBC gr 3–4	Low platelets gr 3–4
Phosphorus-32 444 mBq[7]	77	5–14	3	4–5	6–7	–	–	0	11%
Strontium-89 150 mBq[23]	35	10–20	4.6	4–8	12	13%	18%	0	0
400 mBq[24]	70	–	–	–	–	50%	–	12%	33%
Samarium-153 1 mCi/kg[49]	65	5–10	4	3–4	8	9%	6%	5%	3%
Rhenium-186 1.1 mCi/kg[50]	73	2–7	2.1	4	8	<50%†	20%	0	7%
Rhenium-188 1.1 mCi/kg[14]	60	2–7	2.6	4	8	7%	10%	0	0
Repeat × 1	92	–	5.7	–	–	39%	7%	–	–
Radium-223 50 kBq/kg[16]	60	<10	–	2–4	–	–	–	–	–
Repeat × 4	–	–	–	–	–	29%	18%	3%	0

*PSA response is defined as greater than 50% decrease from baseline.

†PSA response occurred in highest treatment levels but were not generally sustained.

PSA=prostate-specific antigen; WBC=white blood cells.

Samarium-153 (^{153}Sm) lexidronam is composed of radioactive samarium and a tetraphosphonate chelator, ethylenediaminetetramethylene phosphonic acid (EDTMP). ^{153}Sm emits both beta and gamma radiation. ^{153}Sm-EDTMP collects in areas of bone turnover in association with hydroxyapatite and is rapidly taken up at sites of osteoblastic bone metastases. Compared with normal bone surfaces, osteoblastic lesions can accumulate 4–7 times as much ^{153}Sm-EDTMP.[12]

Rhenium-186 and rhenium-188 (^{186}Re and ^{188}Re) emit beta particles. Maxon and colleagues estimated the lesion-to-marrow absorbed dose ratio of ^{186}Re-1-1-hydroethylidene diphosphate (HEDP) to be between 20:1 and 30:1.[13] In a randomized phase II study, Palmedo and colleagues showed that repeated (double-injection) ^{188}Re-HEDP therapy enhanced pain palliation and improved progression-free and overall survival time of patients with hormone-refractory prostate cancer, compared with single-injection ^{188}Re-HEDP therapy.[14]

Radium-223 (^{223}Ra) is another bone-seeking radiopharmaceutical being investigated in clinical trials for the treatment of bone metastasis. ^{223}Ra emits alpha particles, which have a higher energy and travel a shorter distance than beta particles. Limited studies indicate that ^{223}Ra

has a tumor-to-marrow absorbed dose ratio of 30:1.[15] Preclinical and pilot phase I studies have not found any limiting toxicity. In a randomized, placebo-controlled, phase II study, Nilsson and colleagues demonstrated that 4 injections of ^{223}Ra (50 kBq/kg) given every 4 weeks significantly reduced bone-specific alkaline phosphatase levels and delayed time to progression of prostate-specific antigen (PSA) in patients with hormone-refractory prostate cancer.[16] Their finding that patients who received ^{223}Ra had an overall survival advantage suggests that ^{223}Ra therapy produces genuine antitumor and bone-targeted effects.

Selection and Utility

The clinical effects and toxicity profiles of radiopharmaceuticals depend on their half-life and radiation energy. Because all bone-seeking radiopharmaceuticals either directly deposit at or possess carrier ligands that bind to the bone matrix, they act near, rather than on, the cancer cells. Because they settle near the site of active bone formation, these agents are suitable for the treatment of osteoblastic metastases. Theoretically, bone-seeking radiopharmaceuticals that emit a higher energy have a longer range and will thus provide a greater palliative benefit

because of their increased antitumor potential. However, bone-marrow toxicity also increases proportionally with the energy emitted. Therefore, when using radiopharmaceuticals, one needs to strike a balance between their efficacy and their toxicity. The goals of treatment for prostate cancer bone metastasis include improved palliation of pain, decreased intake of analgesics, delayed use of or decreased need for chemotherapy/radiation therapy, enhanced quality of life, and prolonged disease-free or perhaps overall survival. Contraindications for the use of radiopharmaceuticals include thrombocytopenia ($<100 \times 10^9$/L), leucopenia ($<3 \times 10^9$/L), impending spinal-cord compression, acute renal insufficiency, and pregnancy. Because bone-seeking radiopharmaceuticals target the bone, they are not expected to alleviate pain derived from visceral origins. Like radiation therapy and chemotherapy, radiopharmaceuticals alone may not satisfactorily palliate pain due to vertebral collapse, degenerative disc disease, nerve-root impingement, or skeletal fracture.

Although no difference appears to exist in the response rate or palliative efficacy of various radiopharmaceuticals, differences do exist in their onset and duration of response as well as in their intensity and duration of toxicity (Table 2). In general, the onset of response is rapid (usually 2–3 days) after treatment with short-lived radioisotopes (eg, [153]Sm-EDTMP). In contrast, the response onset is delayed (to a few weeks) after treatment with long-lived radioisotopes (eg, ^{89}Sr). Furthermore, the duration of response is longer for the long-lived than the short-lived radioisotopes. Unfortunately, long-lived radioisotopes tend to cause more myelosuppression for a longer period of time than short-lived radioisotopes because of their greater energy of radiation and longer range of effect in bone (Table 1).

Although an ideal radiopharmaceutical does not exist, one can select an appropriate agent and make the best trade off between efficacy and toxicity in accordance with a patient's clinical presentation. Important criteria for selecting the optimal radiopharmaceutical include time to response, response duration, and bone marrow reserve. Patients with advanced metastases and severe pain tend to have a limited bone marrow reserve and require immediate pain relief. Hence, they may benefit from the use of short-lived bone-seeking radiopharmaceuticals such as [153]Sm-EDTMP and [186]Re-HEDP. These types of radiopharmaceuticals are especially useful for patients in whom hormone ablative therapy, chemotherapy, and other therapeutic options are no longer available or effective. If necessary, these patients may benefit from repeated or multiple use of such agents at relatively short time intervals (eg, every 2–3 months). However, patients with early metastases, favorable prognosis (ie, life expectancy greater than 6 months), adequate pain control (using conventional analgesics), and sufficient bone marrow reserve may benefit more from the use of long-lived radiopharmaceuticals such as [89]Sr. Importantly, when patients with progressive disease and severe pain respond to induction or frontline therapies such as hormone ablative therapy or chemotherapy, their reduced tumor burden and improved clinical condition may render multimodality therapy using long-lived, high-energy, and increased-range bone-seeking radiopharmaceuticals more tenable and practical.

Dose Response and Intensity

It remains to be determined if radiopharmaceuticals provide a dose response in antitumor activity rather than mere pain relief. Breen and colleagues reported that when a dose of 150 MBq ^{89}Sr is given, approximately 3,000 cGy at 28 days and up to 30,000 cGy at infinite time is delivered to a particular bone metastasis.[17] Perhaps this is the reason that ^{89}Sr has not been shown to provide a dose response for pain relief. Indeed, pooled results from several small studies suggest that ^{89}Sr is ineffective at doses less than 30 µCi/kg and that its activity reaches a plateau between 40 and 80 µCi/kg.[18] However, Mertens and colleagues showed that increased ^{89}Sr dosage correlated with complete pain relief.[19]

Interestingly, ^{89}Sr studies have demonstrated that increased ^{89}Sr dosage versus placebo improved pain relief and survival time (Table 3).[20,21] Increased ^{89}Sr dosage versus focal radiation therapy also delayed new pains or need for treatment of these new pains.[22,23] Furthermore, increased ^{89}Sr dose (400 vs 150 MBq) adjuvant to focal radiation therapy versus placebo prolonged time to new pains and to radiation therapy for these pains.[24,25] Additionally, increased [89]Sr (400 vs 150 MBq) and [153]Sm-EDTMP (2.5 vs 1.0 mCi/kg; Table 4) dosages provided superior antitumor effects (such as PSA responses and overall survival time) beyond mere enhanced pain relief of patients with castrate-resistant prostate cancer.[26]

Another way to intensify treatment besides increasing the dose is to repeat the treatment. Radiopharmaceuticals are particularly amenable to this dose-escalating approach because of the feasibility and safety of their repeated administration (especially for the short-acting [153]Sm-EDTMP, [188]Re-HEDP, and [223]Ra). For example, Turner and Claringbold found that repeated [153]Sm-EDTMP treatment improved the quality of pain relief and prolonged the survival time of patients with castrate-resistant prostate cancer, compared with one-time [153]Sm-EDTMP treatment.[27] Palmedo and colleagues also demonstrated that repeated (double-injection) [188]Re-HEDP therapy improved the PSA response rate, time to progression, and survival time, compared with single-dose [188]Re-HEDP therapy.[14] More recently, Nils-

Table 3. Dose Intensity and Response for 89Sr Therapy

Study, yr (phase)	Treatment (n)	Response	Survival	Comments
Lewington et al,[21] 1991 (RII)	89Sr 150 MBq (36) Placebo (26)	28% (pain relief) 15%, P<.03	–	–
Buchali et al,[20] 1988 (III)	89Sr 225 MBq (25) Placebo (24)	37% (pain relief) 50%	46% (2 yrs) 4%, P<.05	–
Oosterhof et al,[23] 2003 (III)	89Sr 150 MBq (101) Local XRT (102)	35% (pain relief) 33%	7.2 mos 11.0 mos	OS, P=.05
Quilty et al,[22] 1994 (III)	89Sr 200 MBq (76) Local XRT (72)	65% (pain relief) 67%	7.7 mos 6.5 mos	64% (no new pains) 42%, P<.05
Smeland et al,[25] 2003 (III)	89Sr 150 MBq (30) Placebo (34) (Adj to local XRT)	30% (pain relief) 20%	12 mos	Time to XRT/new pain, NS
Porter et al,[24] 1993 (III)	89Sr 400 MBq (68) Placebo (58) (Adj to local XRT)	40% (pain free) 23%, P<.05	7.1 mos	Time to XRT/new pain, P<.002

89Sr=Strontium-89; Adj=adjuvant; NS=not significant; OS=overall survival; RII=randomized phase II; XRT=external beam radiotherapy.
40 μCi=1.48 MBq; 20 cGy=1 MBq.

Table 4. Dose Intensity and Response for 153Sm-EDTMP, 188Re-HEDP, and 223Ra Therapy

Study, yr (phase)	Treatment (n)	Response	Survival (mos)	Comments
Sartor et al,[49] 2004 (III)	1.0 mCi/kg 153Sm (101) Placebo (51)	-37% (opiate use) +26%, P<.05	7.0	–
Resche et al,[51] 1997 (RII)	1.0 mCi/kg 153Sm (54) 0.5 mCi/kg (49)	70% (pain relief) 67%	4.5 7.5	OS better in breast cancer
Serafini et al,[52] 1998 (III)	1.0 mCi/kg 153Sm (39) 0.5 mCi/kg (40) Placebo (37)	31% (pain free) 28% 14%, P<.016	–	–
Collins et al,[26] 1993 (RII)	2.5 mCi/kg 153Sm (20) 1.0 mCi/kg (20)	42% (PSA <25%) 7% (8 wks)	9 6, P=.03	–
Turner et al,[27] 1991 (RII)	Repeat 153Sm (15) Single dose (23) Fixed 2 Gy to BM	87% (pain relief) 61%	9 4, P<.05	24 wks (pain relief) 8 wks, P<.05
Palmedo et al,[14] 2003 (RII)	Repeat 188Re (28) Single dose (30)	39% (PSA <50%) 7% (8 wks)	12.7 7.0, P=.04	7.0 mos (TTP) 2.3 mos, P=.001
Nilsson et al,[16] 2007 (RII)	Repeat × 4 223Ra (33) Single dose (31)	-66% (ΔBSAP) +9%, P<.0001	15.1 10.7	26 wks (TTP) 8 wks, P<.05

223Ra=Radium-223; 188Re=Rhenium-188; 153Sm=Samarium-153; BM=bone marrow; BSAP=bone-specific alkaline phosphatase; OS=overall survival; PSA=prostate-specific antigen; RII=randomized phase II; TTP=time to progression.
40 μCi=1.48 MBq; 20 cGy=1 MBq.

son and colleagues reported that repeated treatments using 223Ra after focal radiation therapy provided a disease-modifying effect by delaying time-to-PSA progression and prolonging overall survival (Table 4).[16]

These results suggest that dose intensity, if not dose response, may be appropriate and beneficial using the right agents (eg, short-acting radiopharmaceuticals like 153Sm-EDTMP, 188Re-HEDP, and 223Ra) under the right circumstances (eg, advanced prostate cancer with symptomatic bone metastases). Clearly, additional studies are needed to confirm these results. A double-blind, randomized phase III trial, ALSYMPCA (Alpharadin in

Ayymptomatic Prostate Cancer), combining 6 injections of [223]Ra 4 weeks apart with the best standard of care (ie, docetaxel) for patients with symptomatic, castrate-resistant prostate cancer is currently under way.

Multimodality Therapy

Multimodality therapy for bone metastasis involves targeting the epithelial, stromal, and endothelial components in the bone using various agents. For example, cytotoxic agents are used to eliminate the malignant epithelial cell, stromal antagonists are used to target the mesenchymal element, and vascular inhibitors are used to target the endothelial component. Hence, when treating bone metastasis, one must treat the malignant epithelial cell that has spread to the bone and the osteoblasts, osteoclasts, and endothelial cells in the bone that support and sustain it.

There are many ways to improve the therapeutic benefits of radiopharmaceuticals. However, it remains unknown whether targeting both the tumor and bone compartments would improve their therapeutic efficacy. It also remains to be established whether giving certain radiopharmaceuticals repeatedly or in combination with other treatment modalities (eg, hormone ablative therapy, chemotherapy) is safe, feasible, and advantageous over their one-time administration or their administration alone. More studies are also needed to determine the optimal sequence and schedule of these combination regimens using radiopharmaceuticals.

In general, patients with advanced widespread bone metastases may benefit from an initial response to systemic treatment (such as hormone ablative therapy) followed by consolidation bone-targeted therapy using radiopharmaceuticals. Although patients with unfavorable prognostic features, such as severe bone marrow suppression (eg, severe thrombocytopenia), proximal long bone involvement, or superscan, may not be able to tolerate or benefit from treatment using radiopharmaceuticals from the outset or alone, they could withstand the myelosuppressive effects of radiopharmaceuticals much better when their bone marrow reserve improves after response to systemic treatment.

For the same reasons, patients with advanced castrate-resistant prostate cancer and compromised bone marrow reserve may respond to secondary hormone ablative therapy (eg, ketoconazole, diethylstibesterol, low-dose dexamethasone) or even chemotherapeutic agents or regimens (eg, cyclophosphamide, vincristine, and dexamethasone [CVD][28] for patients with severe thrombocytopenia) that render consolidation therapy using radiopharmaceuticals safer and more feasible. This consideration, along with evidence that radiopharmaceuticals provide the best results

in patients with a moderate tumor burden in bone[18,29] and that treatment delays the development of new bone pain in preexisting, clinically silent sites,[22,24] suggests that earlier intervention using radiopharmaceuticals for the treatment of bone metastases may be warranted.

Hormone Ablative Therapy

There is ample evidence that radiation therapy synergizes with hormonal ablation to create an antitumor effect for the treatment of primary prostate cancer.[30,31] It is of interest to know if this synergistic antitumor effect also applies to radiopharmaceuticals for the systemic treatment of prostate cancer bone metastasis. After hormone ablative therapy, a flare reaction predicts therapeutic response and indicates rapid bone repair and increased osteoblastic activity within the affected bone metastasis.[32,33] Indeed, Bushnell and colleagues demonstrated an increased uptake of bone-seeking radiopharmaceuticals 4 weeks to 3 months following the start of hormone ablative therapy.[34] Therefore, one way to enhance the therapeutic efficacy of bone-seeking radiopharmaceuticals is to increase their tumor-absorbed dose and to deliver it at the time of a flare reaction in the bone metastases. Whether this therapeutic strategy provides improved clinical outcome remains to be determined. A randomized phase II trial (2003-922) using this strategy (chemohormonal therapy with or without one dose of ^{89}Sr) for patients with androgen-dependent prostate cancer has been completed at The University of Texas M.D. Anderson Cancer Center.

Chemotherapy

Radiosensitization is a well-recognized and widely used modality for improving the overall efficacy of radiation therapy and perhaps also that of bone-seeking radiopharmaceuticals. The cytotoxic effect of chemotherapy may render cancer cells more vulnerable to radiation damage. Geldof and colleagues demonstrated this synergism in vitro when they studied the effect of [186]Re-HEDP combined with cisplatin on prostate cancer cells.[35] Mertens and colleagues conducted clinical studies that suggest a synergy between chemotherapy and radiopharmaceuticals.[36]

It is important to point out that certain chemotherapeutic agents, such as taxanes, anthracyclines, and platins, inherently possess antitumor as well as radiosensitizing properties. Consequently, use of these cytotoxic agents is beneficial not only because they enhance the antitumor effects of radiopharmaceuticals (Table 5) but also because they are efficacious by themselves for the treatment of prostate cancer bone metastases.

A flare reaction may also occur after chemotherapy for the treatment of prostate cancer.[32] The fact that a flare reaction represents bone healing or increased bone formation within the osseous metastasis has important

Table 5. Chemoradiation Results Using Bone-seeking Radiopharmaceuticals

Study, yr (phase, n)	Treatment	Response	Survival (mos)
Pagliaro et al,[40] 2003 (I/II, 15)	^{89}Sr 55 µCi/kg + gemcitabine 800 mg/m^2 × 6	13% (PSA ≤50%)	8
Lam et al,[39] 2009 (I, 12)	^{188}Re 37 MBq/kg + capecitabine ≤2,500 mg/m^2/d	NR	NR
Sciuto et al,[53] 1996 (RII, 30)	^{89}Sr 148 MBq + carboplatin 100 mg/m^2 d1, 21	58% (pain relief) 87%, P=.025	5.7 8.1
Mertens et al,[36] 1992 (II, 17)	^{89}Sr 148 MBq + cisplatin 35 mg/m^2	55% (pain relief)	8+
Sciuto et al,[54] 2002 (RII, 70)	^{89}Sr 148 MBq + cisplatin 50 mg/m^2	63% (pain relief) 91%, P<.01	6 9
Tu et al,[55] 1996 (I/II, 25)	^{89}Sr 55 µCi/kg ≤3 + doxorubicin 20 mg/m^2 ≤ × 20	32% (PSA ≤75%)	15
Tu et al,[10] 2001 (RII, 72)	^{89}Sr 55 µCi/kg, s/p KAVE + doxorubicin 20 mg/m^2 × 6	7 mo (TTP) 14 mo, P<.001	17 28, P=.001
Akerley et al,[56] 2002 (II, 44)	^{89}Sr 2.2 MBq/kg + vinblastine 4 mg/m^2/estram × 8	48% (PSA ≤50%)	13
Amato et al,[44] 2008 (II, 29)	^{89}Sr 148 MBq + KATE	78% (PSA ≤50%)	23
Fizazi et al,[45] 2009 (II, 43)	^{153}Sm-EDTMP 37 MBq/kg, s/p docetaxel/estram + docetaxel 20 mg/m^2 × 6	77% (PSA ≤50%)	29
Tu et al,[57] 2009 (I, 18)	^{153}Sm-EDTMP 1 mCi/kg × 2 + docetaxel ≤35 mg/ m^2 d1, 8, 15	28% (PSA ≤50%)	NR
Morris et al,[58] 2009 (I, 28)	^{153}Sm-EDTMP 1 mCi/kg ≤ × 6 + docetaxel ≤75 mg/m^2 ≤ × 13	54% (PSA ≤50%)	NR

^{89}Sr=Strontium-89; ^{188}Re=Rhenium-188; ^{153}Sm=Samarium-153; EDTMP=ethylenediaminetetramethylene phosphonic acid; KATE=ketoconazole plus doxorubicin alternating with estramustine plus paclitaxel; KAVE=ketoconazole plus doxorubicin alternating with estramustine plus vinblastine; NR=not reported; PSA=prostate-specific antigen; RII=randomized phase II; TTP=time to progression.
40 µCi=1.48 MBq; 20 cGy=1 M Bq.

implications for the optimal timing of radiopharmaceutical delivery after a response to chemotherapy.

There is a caveat about the selection of chemotherapeutic agents when combined with bone-seeking radiopharmaceuticals for the treatment of prostate cancer: they ought to possess antitumor activity, have radiosensitizing properties, and be minimally myelosuppressive. Therefore, it may not be prudent to use capecitabine[37] or gemcitabine,[38] which possess some radiosensitizing properties but minimal antitumor effects, in combination with radiopharmaceuticals.[39,40] When radiopharmaceuticals are combined with chemotherapeutic agents, such as gemcitabine, that provide minimal antitumor activity but cause substantial myelosuppression in the face of diffuse tumor infiltration in the bone marrow, the benefit-risk ratio is likely to be unfavorable (Table 5).[40] Also, because the clinical efficacy of carboplatin and etoposide[41] is not guaranteed and because their hematologic toxic effects are

potentially prohibitive, these chemotherapeutic agents are also not ideal agents for combination with radiopharmaceuticals. We propose the following (modified) chemotherapeutic regimens (after prior docetaxel treatment) for the treatment of prostate cancer before the administration of radiopharmaceuticals: doxorubicin 20 mg/m^2 IV on days 1, 8, and 15 every 28 days combined with maintenance ketoconazole[42]; cyclophosphamide 150 mg orally on days 1–21 every 28 days combined with vincristine 1 mg IV weekly and maintenance dexamethasone[28]; and paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 combined with maintenance diethylstibesterol.[43] These agents or regimens have displayed efficacy; doxorubicin and paclitaxel have radiosensitizing activity and a low-dose weekly schedule, and the CVD regimen is minimally myelosuppressive.

Another important aspect of multimodality therapy that needs to be addressed is the optimal sequence for combining chemotherapy with radiopharmaceuticals.

Because not all patients will respond to either treatment alone and because any clinical benefits or toxic effects could be additive, if not synergistic, it is important to personalize care and select only patients who respond to the induction chemotherapy for consolidation bone-targeted therapy using pharmaceuticals. In this manner, the therapeutic benefit could be enhanced and the potential toxic effects reduced. It remains to be determined how to combine the right chemotherapeutic agents with the appropriate radiopharmaceuticals. For example, would it be advantageous to add a radiopharmaceutical as soon as a response is achieved (ie, after 1 cycle of chemotherapy) or after a maximum response (ie, after 4–6 cycles of chemotherapy)? Tu and colleagues,[10] Amato and coworkers,[44] and Fizazi and associates[45] have explored this therapeutic strategy using ketoconazole combined with doxorubicin alternating with estramustine combined with vinblastine (KAVE) or ketoconazole combined with doxorubicin alternating with estramustine combined with paclitaxel (KATE) with ^{89}Sr or docetaxel with [153]Sm-EDTMP, respectively. Randomized phase III trials designed to confirm these preliminary results (Table 5) are currently being conducted by the Cancer Treatment Support Unit of the National Cancer Institute (MDA-3410) and the Cancer Research UK (TRAPEZE).

Selected Targeted Agents

There is scant evidence supporting the combination of selected targeted agents with bone-seeking radiopharmaceuticals. Theoretically, any agents with radiosensitizing properties and antitumor effects may be used to enhance the therapeutic efficacy of radiopharmaceuticals. For example, certain selected targeted agents such as abiraterone, tyrosine kinase inhibitors, or COX-2 inhibitors, could affect the onco-niche in such a manner that patients with advanced prostate cancer would experience prolonged remission or increased survival time even though they still harbor viable cancer cells after treatment with these agents in combination with radiopharmaceuticals or in a maintenance fashion after radiopharmaceuticals.

It is important to point out that in Tu and colleagues' randomized phase II trial, which showed an overall survival improvement, only patients who had benefited from chemotherapy (namely KAVE) were randomized to receive [89]Sr. Furthermore, patients continued maintenance ketoconazole until disease progression.[10] Considering how well some patients responded to ketoconazole and how ketoconazole might have affected the onco-niche by inhibiting osteoblast proliferation/differentiation (unpublished data), we believe that it is plausible that

an effective maintenance drug such as ketoconazole could have contributed to the improved clinical efficacy and outcome of this particular multimodality program. It will be interesting to see whether a novel compound related to ketoconazole, namely abiraterone,[46] would provide similar, if not superior, results in a combination regimen or maintenance fashion.

Finally, it remains to be determined whether certain tyrosine kinase inhibitors, such as sunitinib (Sutent, Pfizer) and imatinib (Gleevec, Novartis),[47,48] that have radiosensitizing properties but possess only marginal antitumor activity against prostate cancer will improve the clinical efficacy of radiopharmaceuticals. It is unclear whether anti-angiogenesis agents, by promoting hypoxia, will counteract the effect of radiation, which induces the expression of proangiogenic factors. Similarly, it is unknown whether agents that target the PI3k/Akt/PTEN pathway will attenuate the effect of radiation, which mediates transient increased mTOR function. It remains to be clarified whether other radiosensitizing agents with some putative antitumor activity, such as COX-2 inhibitors, soy isoflavones, and curcumin, can be used to enhance the effects of radiopharmaceuticals or be utilized in a maintenance setting after radiopharmaceuticals for the treatment of prostate cancer bone metastases.

Conclusions

Accumulating data suggest that bone-seeking radiopharmaceuticals can be used to control bone metastasis and improve the clinical outcome of patients with prostate cancer and bone metastases. These agents target both cancer cells and the onco-niche. They should be considered as another therapeutic option in our armamentarium against bone metastases. Additional studies need to be performed to determine whether newer generations or repeated dosing of radiopharmaceuticals will accentuate their antitumor effects and whether combining radiopharmaceuticals with hormone ablative therapy, chemotherapy, or targeted therapy will their enhance clinical efficacy.

Acknowledgments

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