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Anti-Tumour Treatment

Targeted radio-nuclide therapy of skeletal metastases

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ABSTRACT

In this review, we will focus on one particular class of stromal targeted therapy, i.e. the bone seeking radiopharmaceuticals (BSRs), but will also highlight selected issues related to the bone stroma as these concepts are new, rapidly evolving, and clearly linked to the underlying BSR mechanisms of targeting and action. Herein we review clinical BSR-trials of significance with randomized trials at center stage. Furthermore, we cover a new class of BSR in late clinical development based on bone-stromal targeted alpha-particle irradiation. Lastly, we discuss potential advances in combining BSR with bisphosphonates and/or chemotherapy and emphasize the feasibility of repeated dosing.

Background

The skeleton is the most common site of symptomatic metastatic disease and cancers from prostate, breast, lung, kidney, and thyroid, as well as multiple myeloma, commonly spread into and through this organ. Though the number of patients with bone metastases is debatable, it has been estimated that approximately 400,000 such patients are diagnosed annually.[1] Prostate cancer and breast cancer are particularly important sources of bone metastases given the prevalence of these diseases, their bone tropism, and relatively prolonged natural history. Bone metastatic lesions are prone to a variety of morbid complications including pain, hypercalcemia, pathologic fracture, spinal cord and nerve root compression. Pancytopenia due to progressive growth of metastases within the axial skeleton displacing normal red bone-marrow is a common clinical problem; especially in advanced prostate cancer. These complications limit both quantity and quality of life.

A variety of treatment modalities including analgesic medications, radiation, surgery, chemotherapy, hormone treatment, bisphosphonates and/or bone-seeking radiopharmaceuticals (BSRs) may all be considered appropriate for individual patients and best treatment choices are often determined within the context of multi-disciplinary management. The appropriate choices depend on the extent of the skeletal involvement, symptoms, the underlying disease and the availability of systemic options, the life expectancy of the patient, the bone marrow function and the patient's co-morbidities.

Tumor biology of bone metastases

Though various mechanisms have been implicated in metastatic spread into the skeleton, the "seed and soil" hypothesis first promulgated by Paget in 1889[2] remains commonly accepted today. This hypothesis implicates a combination of factors including both tumor cells and a permissive stromal environment. Today there is a greater appreciation that neither the seed not the soil are static and that both tumor cells and a variety of stromal cells interact with a number of secreted paracrine factors in a "vicious cycle" that promotes the survival and proliferation of tumor cells.[3,4]

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Most studies implicate hematogenous spread as the source of tumor cells that lodge in bone. These circulating tumor cells are now increasingly well described.[5,6] It is clear that that only a small percentage of these "seeds" are capable of forming metastatic tumors and that the process of extravasation and metastatic tumor growth is complex. Molecular characterization of these events is ongoing in an effort to devise new anti-cancer strategies.

It is well recognized that the tumor cells can interact with stromal components[7–9] such as the extracellular matrix, various mesenchymal stromal cells, the immune system and vascular endothelial cells. In bone, cells such as the osteoblasts, osteoclasts, and hematopoietic cells (and their precursors) also represent components of the tumor micro-environment. Osteoclast activating factors are thought to be critical in enabling tumor growth to be established in bone, working in part through the nuclear factor-kappa B ligand (RANKL).[10] There is also evidence that malignant cell growth can be promoted by selected stromal secreted factors such as basic-FGF released.[8] Interestingly, experiments with fibroblasts derived from bone stroma combined with certain cancer cell lines display synergistic growth.[9]

There is a close balance between osteoclastic and osteoblastic activity within normal bone maintaining normal homeostasis; osteoclast and osteoblast activation by tumor disturb this balance.[11] Tumors can result in either relatively lytic metastases such as those of myeloma and renal cell cancer or relatively osteoblastic metastases; such as those present in prostate cancer. Mixed lytic/blastic lesion as are often encountered in breast cancer. It is the tumor associated upregulated osteoblastic activity that promotes new bone formation and incorporation of the 'bone seeking radioisotopes' used therapeutically.

The concept of a static bone stroma has passed but the new conceptual era of altering the bone stroma to enhance effectiveness of BSR action is only being discussed. The uptake of BSRs is proportional to the osteoblastic nature of the bone metastatic disease. Bisphosphonates are known to alter the lytic/blastic ratio in bone lesions supporting the concept of synergism when combining BSRs after chronic but not acute bisphosphonate administration. As shown in Fig. 1, a marginally bone scan positive patient with breast cancer pre-bisphosphonate is shown to have a markedly positive scan after chronic bisphosphonate therapy. This alteration in bone scan uptake should have a similar effect on BSR site-specific delivery. Similar effects might be expected after chronic but not acute administration of the RANKL antagonist denosumab. Bortezomib treatment in myeloma has also been shown to increase bone scan up take[12] (see Fig. 2).

Another approach to increase BSR uptake is through exploiting the 'flare' seen after LHRH agonists or abiraterone used in prostate cancer[13] or after hormonal therapies in breast cancer.[14] These therapies may be associated with a rises in alkaline phosphatase and increased bone scan uptake which are thought to signify healing of bone in the region of metastatic lesions. Timing BSR therapy administration to take advantage of this flare is an unexplored but attractive concept.

Chemical and radio-isotopic characterization of BSRs

The two FDA approved BSRs are beta-emitters with distinct half-lives, energies, and mechanisms of bone targeting.[15] ^{153}Sm-EDTMP (lexidronam/Quadramet) has relatively low average energy for beta emissions (0.22 MeV) and a short radioactive half-life (1.9 days). ^{89}Sr (Metastron) has a relatively prolonged half-life (50.5 days) and higher average beta emission energy (0.58 MeV). A variety of other beta-emitting isotopes have been utilized in clinical trials including ^{166}holmium, ^{177}lutetium, ^{186}rhenium, ^{188}rhenium, ^{131}iodine, and ^{90}yttrium. As seen in Table 1, the maximum and average beta energy varies considerably with each radionuclide. The highest average energy beta particle is seen with ^{90}yttrium and the lowest with ^{177}lutetium. ^{117m}tin (Sn) emits conversion electrons with two discrete energies. Conversion electrons have the same mass as beta particles and behave similarly in tissue. The energy of the conversion electrons is the lowest of any of the BSRs. Tissue penetration for the various beta particles and electrons are proportional to their energy so ^{117m}Sn emissions have the lowest penetrance of any radionuclide in this class. Tissue penetration may seem desirable on the surface but the depth of tissue penetration is also proportional to the marrow radiation, and hence hematological toxicity.

^{223}Radium is the first bone-targeted alpha emitter to be studied in clinical trials of skeletal metastases. Alpha particles are comprised of 2 protons and 2 neutrons (helium nucleus) and have a mass approximately 7300 times as large as a beta particle or

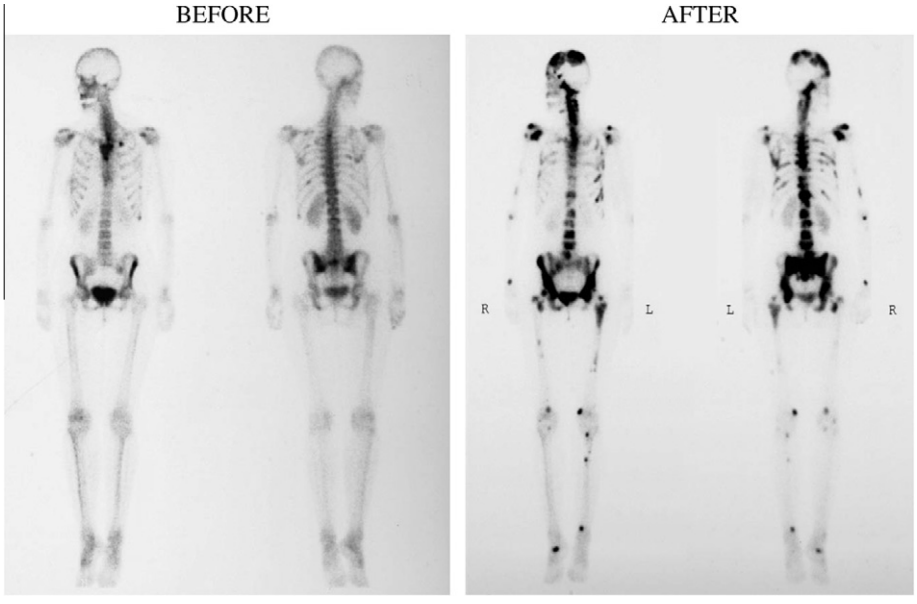

Fig. 1. Bone scans in a breast-cancer patient before/after chronic bisphosphonate therapy.

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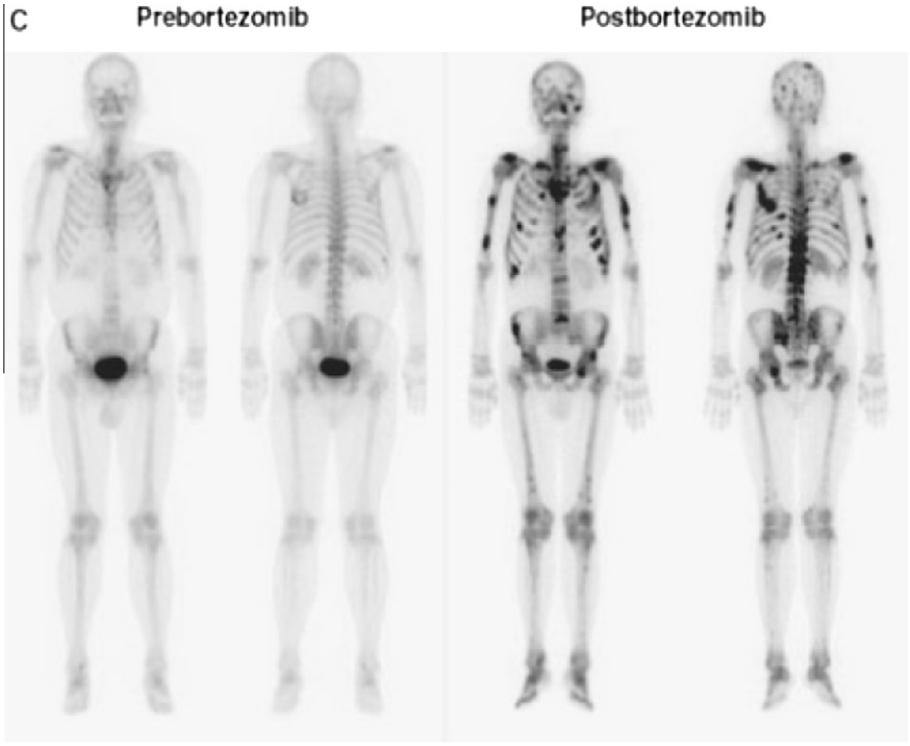

Fig. 2. Alteration of Tc-99 MDP bone scan uptake in myeloma after bortezomib treatment[12].

Table 1
Selected BSRs explored in human clinical trials.

Radionuclide	Half-life	Targeting agents	Particle type	Maximum energy (MeV)	Mean energy	Average penetration
Radium-223	11.4 days	None required	Alpha	27.78*	6.94	<0.1 mm
Strontium-89	50.5 days	None required	Beta	1.46	0.58	2.4 mm
Samarium-153	1.9 days	EDTMP	Beta	0.81	0.22	0.5 mm
Phosphorus-32	14.3 days	None required	Beta	1.71	0.69	3.0 mm
Yttrium-90	2.7 days	Citrate	Beta	2.27	0.93	4.0 mm
Lutetium-177	6.7 days	EDTMP	Beta	0.49	0.14	0.3 mm
Iodine-131	8.0 days	HDBP	Beta	0.61	0.19	0.8 mm
Rhenium-186	3.8 days	HEDP/etidronate	Beta	1.07	0.33	1.0 mm
Rhenium-188	0.7 days	HEDP	Beta	2.12	0.64	3.8 mm
Holmium-166	1.1 days	DOTMP/EDTMP	Beta	1.84	0.67	3.3 mm
Tin-117m	13.6 days	DTPA	CE**	0.15	0.14	0.2 mm

Data from nuclides 2000, nuclide explorer, version 1.2. Institute for Transuranium Elements, Karlsruhe, Germany.
* Radium-223 and daughters.
** CE is conversion electron.

conversion electron. ^{223}Radium has a physical half-life of 11.4 days with a complex radioactive decay chain that includes nuclides of radon, polonium, lead, bismuth, and thallium prior to reaching the stable lead isotope ^{207}Pb (see Fig. 3). Despite the high energy of alpha particles relative to beta particles, they are less penetrant in tissue with a maximum range of less than 0.1 mm. Alpha particles have a very high linear energy transfer,[16] consequently their biologic effects are substantial relative to beta particles. Further, cellular repair after alpha particle induced damage is much less efficient than other forms of radiation given the high propensity for lethal double stand DNA breaks. Data indicate that less than 10 alpha particle hits may be lethal in dividing cells.[17] Resistance to agents which cause double strand DNA breaks is minimal given the high lethality of this form of DNA damage.[17] Radiation with an alpha-particle is potentially advantageous in terms of inducing cell kill in the relatively quiescent clonogenic tumor stem-like cells that are capable of being killed by alpha-emissions.[18] Given that these stem cells are particularly resistant to traditional hormonal and chemotherapies, this is an important potential advantage for alpha-particle based therapies.

Potential mechanistic importance of BSRs targeting the bone stroma

This ability to target tumor cells and their micro-environment by binding to a homogenous inorganic matrix overcomes many of the issues related to drug delivery which mediate resistance to systemic chemotherapy agents such as the multi-drug resistance (MDR) pump, or changes in drug binding sites.

The action of BSRs is likely to reflect both direct action on the bone and indirect actions mediated by alterations in the metastatic tumor cells. Several markers can be readily measured that reflect both osteoblast activity and bone formation[19–21] including bone sialoprotein (BSP), type 1 procollagen amino-terminal (PINP), total alkaline phosphatase, bone-specific alkaline phosphatase (BAP), osteocalcin, osteoprotegerin (OPG) and osteoclast activity/bone resorption including N-and C-terminal peptide fragments of type 1 collagen (NTX and CTX), cross-linked variants of type 1 collagen such as pyridinoline (PYD) and deoxypyridinoline (DPD), C-terminal cross-linked telopeptide (ICTPs), and tartrate-resistant acid phosphatase type 5b (TRACP5b).

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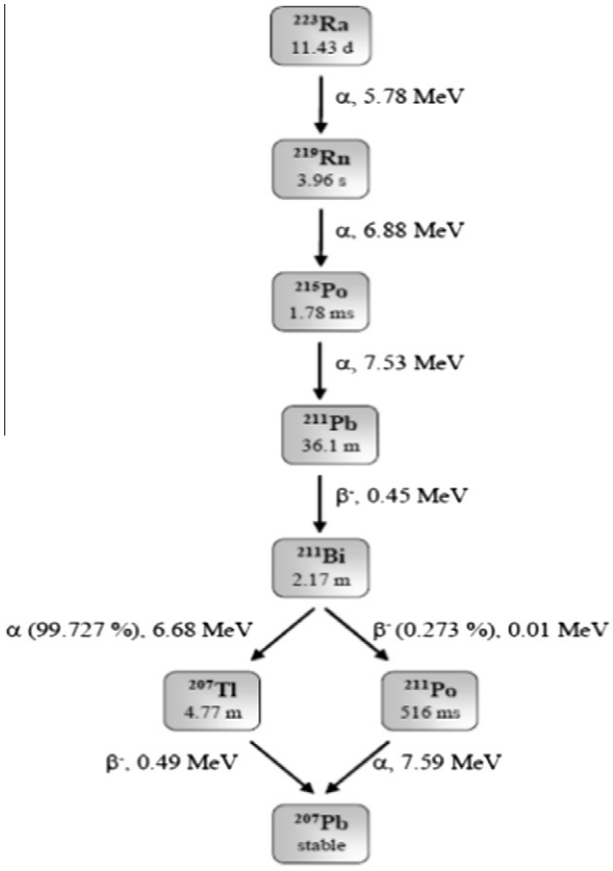

Fig. 3. Decay chain for ^{223}radium and daughters.

In bone metastatic castrate resistant prostate cancer (CRPC) patients receiving a single dose of ^{223}Ra, serum alkaline phosphatase declines slightly over 50% were noted with nadirs noted 4–6 weeks after radionuclide administration.[22] In a subsequent randomized Phase 2 study, for bone metastatic CRPC patients receiving four doses of ^{223}Ra following external beam radiation to the most painful site, alkaline phosphatase decreases of slightly less than 50% were noted. In this study, markers of osteoblastic activity, BAP and PINP, decreased a median 66% and 63% respectively. Osteoclast activity measures including CTX and ICTP were less consistently affected, either declining by 31% or increasing by 15% respectively.[23] It is noteworthy that those patients receiving only external beam radiation (in the placebo arm) had an increase of 9–43% in all markers measured.[23]

Changes with other BSRs have been less well studied. Single doses of ^{89}Sr can decrease alkaline phosphatase in men with bone-metastatic prostate cancer,[24] as can single doses of ^{186}rhenium-HEDP (^{186}Re-HEDP). In the ^{186}Re-HEDP trial, decreases of 10–15% were noted up to 6 weeks after drug administration.[25] In a single dose trial after ^{89}Sr in bone metastatic CRPC, urinary excretion of PYD and DPD was stable in patients during a 6-mo interval after ^{89}Sr-chloride palliation, whereas both of these cross-links increased significantly in patients not receiving the radionuclide.[26]

Selecting appropriate patients for BSRs: the role of imaging bone stromal elements

Each of the BSRs in contemporary use preferentially target newly formed bone at the tumor/bone interface. In prostate cancer, at least, this stromal matrix is also prevalent throughout the central part of the sclerotic metastasis. The hydroxyapatite of newly formed bone matrix is the target for both BSRs and the diphosphonate in conventional ^{99m}Tc-methylene diphosphonate (MDP) bone scans. The FDA package insert for ^{153}samarium EDTMP makes note that this agent is indicated for relief of pain in patients with confirmed osteoblastic metastatic bone lesions that enhance on radionuclide bone scan.

^{18}F sodium fluoride (^{18}F NaF) was FDA approved in 1972 for imaging areas of altered osteogenic activity. ^{18}F NaF was withdrawn from the market for technical reasons and then re-approved by the FDA as agent for diagnostic positron emission tomography (PET) imaging agent quite recently (January 2011). Data from ^{18}F sodium fluoride PET scans[27] indicate that the conventional MDP bone scans are relatively insensitive compared to ^{18}F NaF (see Fig. 4). Thus more patients may be eligible for BSRs than previously appreciated given the earlier detection of bone metastases with this newer methodology. Mechanistically, the ^{18}F NaF diffuses from vasculature to bone and chemisorption occurs at the surface of hydroxyapatite in a manner similar to the BSRs.

Clinical selection of patients for BSRs

The two BSRs having received broad regulatory approval include $^{89}SrCl_2$ and ^{153}Sm EDTMP (lexidronam). The generally accepted indications for these two agents include pain secondary to bone metastatic disease demonstrating uptake on a radionuclide bone scan. The utilization of BSRs instead of external beam radiation can include several considerations. First, those patients with multi-focal pain that would require more than one radiation field are strong candidates for BSRs. Second, BSRs may be favored in patients previously treated to maximal normal tissue tolerance with external beam radiation and having persistent, progressive, or recurrent symptoms at the treated site. There is some suggestion that strontium has greater efficacy if given relatively early in the disease course, as one study showed significantly worse responses in those with hemoglobin <10 g/dl, PSA > 100 ng/ml, or those with a 'superscan'.[28] Specific contraindications for the BSRs include bone metastatic disease with impending pathologic fracture or spinal cord compression. In addition, patients with significant thrombocytopenia, neutropenia, or renal impairment should not receive BSRs. See Table 2 for a concise description of the clinical indications for BSRs.

^{89}Strontium clinical studies

^{89}Strontium is a BSR with similarities to calcium in terms of biologic behavior. A variety of non-randomized studies ^{89}Sr have shown effective palliation of pain. The most common disease studies have been bone-metastatic prostate cancer. Some of the first reports using open-label trials suggested palliative responses in approximately 75% of treated patients with as many as 25% able to discontinue analgesics.[29] Herein we focus on double-blind prospective studies which are more reliable in terms of reporting pain outcomes.

The first randomized prospective studies with ^{89}Sr were small. Lewington et al.[30] assessed bone-metastatic CRPC and compared ^{89}Sr to placebo at a single time point 5 weeks post-dosing. Despite the short interval of follow-up, 6 patients of the 32 patients were not assessed in the analysis. The authors reported that one third of patients had a complete response and that most patients responded but the methods of pain assessment and the reporting of analgesic consumption were not well described. In another trial involving 49 patients with bone metastatic CRPC utilized 2 mCi ^{89}Sr or placebo given at monthly intervals for a total of three doses. This trial reported no significant differences in pain but did report a longer survival.[31] Given the under-powered nature of the trial and

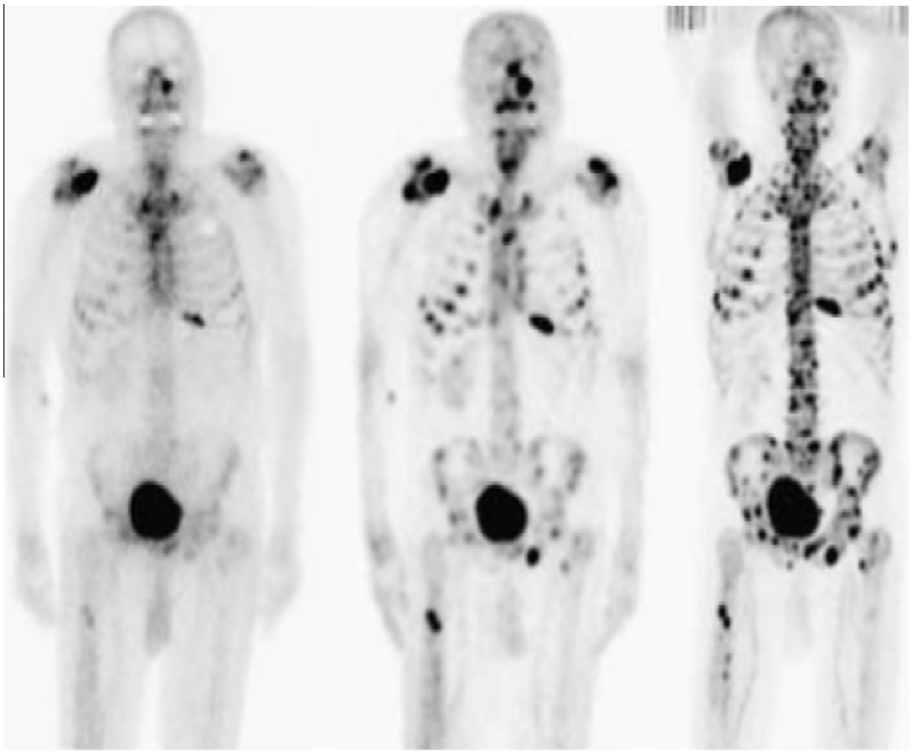

Fig. 4. Comparison of bone lesions in a prostate cancer patient detected by (left to right), conventional bone scan (2-D), multi-field of view SPECT (3-D), and F-18 fluoride PET scanning (from Even-Sapir et al. J Nucl Med 2006;47:287–297).

the fact that no other ^{89}Sr trials have demonstrated a survival advantage, we are uncertain that the conclusions were reliable.

The first relatively large multi-center ^{89}Sr prospective trial with a placebo control also involved bone-metastatic CRPC patients. This trial was termed the TransCanadian Trial and was pivotal for FDA approval.[32] All patients received external beam radiation prior to ^{89}Sr treatment. Randomized treatments after external beam included 10 mCi of intravenous ^{89}Sr or placebo in 126 patients. The dose of radionuclide in this trial was considerably higher than that used in other randomized trials. The endpoints for this trial included analgesic use, new painful sites of metastatic bone disease, reduction of pain at the sites originally radiated, and overall survival. No survival differences or differences in pain relief at the primary site were noted. There was a statistically significant improvement in the ^{89}Sr treated patients in terms of stopping analgesics (17% compared to 2%, $P < 0.05$). In addition there were fewer new sites of bone pain assessed three months after the radionuclide treatment (58.7% versus 34%, $P < 0.002$). A subsequent follow-up subset analysis indicated that the mean time to PSA progression was 19 weeks in the ^{89}Sr group as compared to 6 weeks in the placebo group.[33] The effects of ^{89}Sr on pain have not always been reproducible, however, as other trials have failed to confirm the findings.[34] Dose difference between the TransCanada Trial and other trials may account for these differences as the 10 mCi used in the TransCanada Trial has not been used elsewhere.

The European Organization for Research and Treatment of Cancer (EORTC) conducted one of the largest prospective randomized ^{89}Sr trials comparing external beam radiation to 4 mCi ^{89}Sr in 203 patients with painful bone-metastatic CRPC.[35] There were no differences between the time to subjective progression or duration of pain response in responding patients. In each group subjective progression was 3 months and duration of pain response 4 and half months. In this trial survival of the patients treated with external beam was longer than that of the ^{89}Sr treated patients (11.0 months compared to 7.2 months, $P = 0.0457$). No trial other than the EORTC trial showed a shorter survival for ^{89}Sr but given its size and multi-institutional nature, the conclusions need to be carefully considered.

Quilty et al.[36] prospectively evaluated 5.3 mCi ^{89}Sr as compared to external beam radiation in 284 patients with bone-metastatic CRPC. The trial was well designed and endpoints included pain at an index site, new sites of pain, additional external beam radiation, and overall survival. External beam radiation could be either focally administered or given in a hemi-body regimen. At the index site, there were no differences noted and each treatment arm reported pain relief in slightly more than 60% of patients. The radionuclide was more effective than focal external beam with regards to the development of new painful sites ($P < 0.05$). A smaller percentage of patients in the ^{89}Sr arm were treated with subsequent external beam radiation ($P < 0.01$). The survival was short, only 21 weeks, but there were no differences in the survival duration reported in the trial. Toxicity was minimal in both arms.

Samarium-153 EDTMP clinical studies

The first major randomized trial using ^{153}Sm EDTMP was performed as dose-controlled trial in 114 patients having painful bone metastases derived from several underlying cancers.[37] Randomized subjects received a single dose of 0.5 mCi/kg ^{153}Sm EDTMP or a 1.0 mCi/kg dose. The majority of patients had prostate cancer (59%) with most of the remainder having breast cancer (32%). Patient recorded visual analog scale (VAS) pain score and opioid analgesic use. The VAS pain scores decreased in a significant fashion ($P = 0.0476$) for the patients receiving 1.0 mCi/kg at 3 and 4 weeks after injection but the lower dose was not associated with pain improvement. Transient myelosuppression was seen with a nadir at 4 weeks and recovery by 8 weeks. A longer survival among breast cancer patients receiving the higher dose was reported (approximately 10 vs 23 months) but no differences were noted

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Table 2
Current assessments for bone seeking radiopharmaceutical therapy.

Pathologic cancer diagnosis required
Increased uptake on diagnostic radionuclide bone scan compatible with metastatic lesions
-Lack of uptake (i.e. osteolytic lesions) predicts poor BSR targeting
Bone pain correlated with bone scan findings
-Soft-tissue component of pain makes a BSR choice sub-optimal
Assessment for spinal cord compression, pathologic fracture, or high risk for pathologic fracture
-These require non-BSR management strategies
Ascertainment of past therapeutic interventions and current options
-Single lesions or regional pain may best be considered for external beam radiation
Assessment of bone marrow function by hematologic assessment
Assessment of renal function to assess radionuclide excretion
Discussions with patient on pain flare/monitoring requirements post-therapy (isotope dependent)

in the prostate cancer patients. No other trial of ^{153}Sm EDTMP has shown survival differences and caution is appropriate in interpreting these data.

Serafini et al.[38] conducted the first ^{153}Sm EDTMP prospective placebo controlled randomized trial. A total of 118 patients with painful bone metastases were treated and randomized 1:1:1 to receive a single dose ^{153}Sm EDTMP (0.5 or 1.0 mCi/kg doses) or placebo. The trial was double-blinded, thus neither the patient nor physician were aware of the underlying treatment. Bone metastatic CRPC patients comprised the majority of the patients ($n = 80$); bone metastatic breast cancer patients were also represented ($n = 21$). Patients allocated to the 1.0 mCi/kg dose had improvements in pain scores (when compared to placebo) at weeks 1, 2, 3 and 4 after dosing. The patients treated with the 0.5 mCi/kg dose had pain improvement at week 1 only. Approximately two thirds of those responding at week 4 to the 1.0 mCi/kg dose were still responding at week 16. Again falls in white count and platelets were seen but with recovery by 8 weeks and there were no cases of neutropenic fever.

In a randomized trial enrolling only bone metastatic CRPC patients, Sartor et al.[39] enrolled 152 patients randomized 2:1 to receive ^{153}Sm EDTMP or placebo. Pain was measured by two independent patient reported methods, a VAS and a pain descriptor scale. Patients on the ^{153}Sm EDTMP arm reported statistically significant improvements in VAS scores for weeks 2, 3, and 4; in the descriptor pain scores for weeks one through four. Cross-over for non-responding placebo-treated patients at four weeks prevented statistical analysis beyond that time point. Patients treated with ^{153}Sm EDTMP also had significant decreases in opioid analgesic use during weeks 3 and 4 ($P < 0.05$). Toxicity of the ^{153}Sm EDTMP was again predictable with a 45% fall in white count and 40% fall in platelets, recovering by 8 weeks.

Rhenium-186/188 clinical trials

In initial trials of ^{186}Re conducted in the early 1990s, approximately 33 mCi (1221 MBq) of ^{186}Re 1-hydroxyethylidene-1,1-diphosphonic acid (HEDP or etidronate) was administered as a single injection to 20 prostate cancer patients with osseous metastases. Pain relief was reported in 80% of patients with only mild transient marrow toxicity.[40] In a single dose escalation study, approximately 80 mCi (2960 MBq) was determined to be the maximum tolerated dose with grade 3 thrombocytopenia being dose limiting.[41] Many small or non-randomized studies were subsequently conducted that are not covered herein. In a randomized trial of with 111 prostate cancer patients (but only 79 evaluable), a dose of 35–80 mCi ^{186}Re-HEDP or placebo was administered and found to result in a greater degree of efficacy (65% vs 36%, $P < 0.05$) as compared to placebo using a patient reported 5 day minimum period of pain relief.[42] Conclusions are limited from this trial given the large number of unevaluable patients. Interestingly, toxicities were not reported. Survival was not different between arms.

In a prospective randomized trial in 64 prostate cancer patients[43] comparing one versus two doses of 70–90 mCi ^{188}Rh-HEDP (doses 8 weeks apart), pain relief was reported as being 92% in the repeat dosing arm as compared to 60% in the single dose arm ($P < 0.01$). The median duration of pain relief in the two dose arm was 5.66 vs 2.55 months in the single dose arm ($P < 0.01$). PSA declines of >50% were noted in 39% vs 7% of patients ($P < 0.01$). Survival was 12.7 vs 7.0 months, again favoring the repeat dose arm ($P < 0.05$). This result in a small trial is quite interesting but has yet to be confirmed in larger trials. Toxicity was minimal with no grade 3 toxicities. Grade 2 thrombocytopenia and/or leukopenia was noted in less than 10% of the patients.[43]

Though clearly rhenium-based BSRs have activity, regulatory agencies in the US or Europe have not recognized this compound in their compendiums thus limiting general access.

Radium-223 clinical trials

^{223}Radium localizes to bone as a consequence of being calcium mimetic (see Fig. 5). It is excreted via the gut, thus images indicate this route of excretion. A phase I trial using ^{223}Ra as a single intravenous injection has been performed in 25 patients with bone-metastatic CRPC and bone-metastatic breast cancer bone disease.[22] Injection of doses as high as 250 kBq/kg were not problematic. Three of 25 patients had grade 3 leukopenia but no grade 3 platelet toxicity was observed. There was no dose-limiting toxicity reported.

A small randomized phase II trial ($n = 64$) of external beam radiation followed by either saline or ^{223}Ra injections in bone-metastatic CRPC has been reported.[23] Four doses were administered every 4 weeks at a dose of 50 kBq/kg. The ^{223}Ra treated patients, compared to those treated with placebo, had significant decrease in PSA and bone alkaline phosphatase relative to controls. Bone marrow toxicity was minimal despite repeated doses of ^{223}Ra. An improvement in overall survival benefit was noted for the radionuclide but the small size of the trial precluded definitive conclusions other than to say that more data should be obtained.

This phase II trial served as an important precursor for the phase III trial of ^{223}Ra with 921 patients enrolled.[44] This placebo-controlled trial with six 50 kBq/kg doses of ^{223}Ra was conducted in patients with bone-metastatic CRPC. Results from this "ALSYMPCA-trial", have preliminarily been reported.[45] The trial was open to patients not suitable for additional chemotherapy. Prior chemotherapy was not required but in fact most patients had received prior docetaxel, the standard first line chemotherapy in metastatic CRPC. "Standard of care" hormonal treatment but not chemotherapy or hemi-body radiation was available while patients were on study. The trial was stopped early after meeting a prespecified stopping point at an interim analysis. The overall survival in the control group was 11.2 months and 14.0 months in the radionuclide group (hazard ratio for survival was 0.699 with $P = 0.00185$. Toxicity was minimal with 4% grade 3/4 thrombocytopenia and 2% grade 3/4 neutropenia. This is the first large phase III trial to show a clear survival benefit for BSRs and will undoubtedly influence the field for years to come. Appropriate regulatory filings in both the USA and Europe are ongoing at this time such that general availability of ^{223}Ra is expected in 2012.

Repeated BSR dosing

There are relatively limited prospective data on repeated administrations of BSRs. The data with ^{223}radium cited above

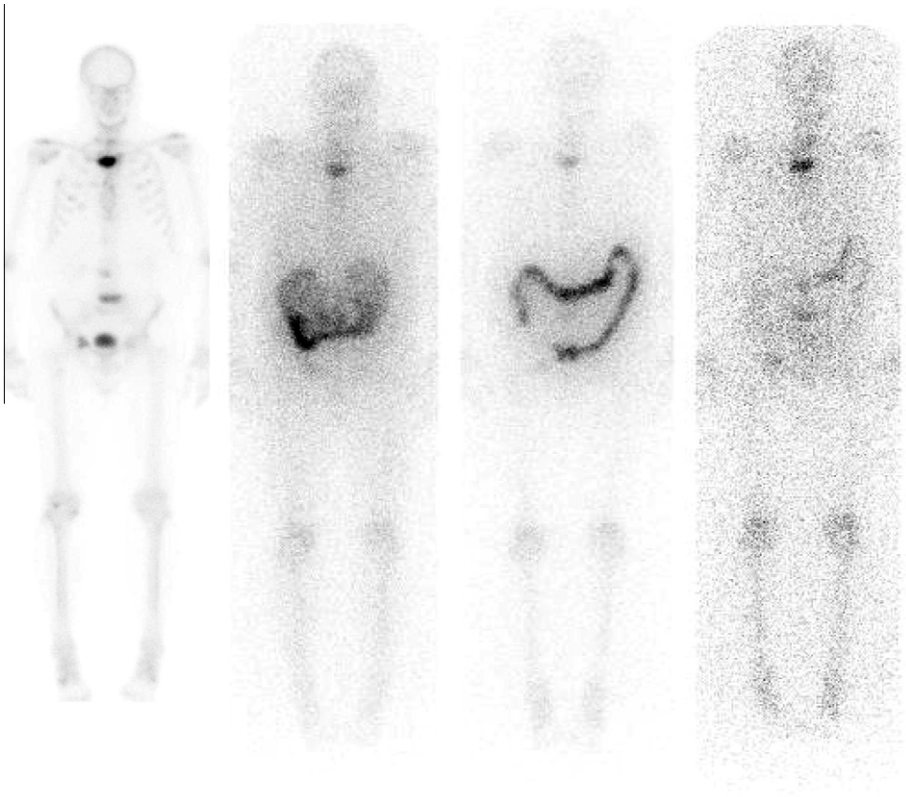

Fig. 5. Comparison of the images obtained after ^{99}Tc-MDP (A) or ^{223}radium on day 0 (B1), day 2 (B2) or day 6 (B3).

clearly indicates the feasibility of this approach with an alpha-emitter at a dose of 50 kBq/kg every four week for six doses in metastatic prostate cancer patients as this schedule and dose were used in phase III trials.[45] ^{89}Sr was used repetitively for three doses given at a monthly dose of 75 MBq (2 mCi) with no apparent safety concerns in prostate cancer patients.[31] ^{153}Sm EDTMP retreatment at 1 mCi/kg (37 MBq/kg) has been reported with good safety results in a report of a prospective study. Repeat dosing was allowed to patients having an initial palliative response was followed by symptom recurrence. In that report,[46] it is important to note that repeated doses were offered only to patients with recovery of white blood cells to >4000/mm^3 and platelets 100,000/mm^3. Efficacy as measured by pain palliation was noted in this repeated dosing cohort but caution is warranted given that pain responses were not conducted in a blinded fashion. As noted above, ^{188}Re-HEDP was well tolerated and efficacious in a prospective randomized study using two doses, as compared to one, of radionuclide 8 weeks apart.[43]

Combined treatment studies

BSRs and chemotherapy

Several clinical trials demonstrate the possibility combining chemotherapy and BRSs. The first significant trial to combine these agents was conducted with ^{89}Sr and doxorubicin in bone-metastatic CRPC patients.[47] Patients were randomized to receive either ^{89}Sr in combination with six doxorubicin weekly doses or a similar schedule of doxorubicin alone following initial chemotherapy. The initial chemotherapy consisted of KAVE (ketoconazole, adriamycin, vinblastine, and estramustine). Patient that were intolerant of KAVE, or those progressing despite the KAVE, were not randomized. These non-randomized patients clearly had a worse prognosis. The median progression free survival and the median overall survival were both improved in the ^{89}Sr arm. Trials with cisplatin and carboplatin have also shown that improved response to strontium can be achieved by the use of combined treatment with BSR and chemotherapy.[48]

There is renewed interest in combining BSRs and chemotherapy as recent studies have been reported using ^{153}Sm-EDTMP and docetaxel in bone metastatic CRPC patients.[49,50] Morris et al. combined docetaxel at 75 mg/M^2 q 3 weeks with escalating doses of ^{153}Sm-EDTMP in a repetitive fashion.[49] A one mCi/kg dose of ^{153}Sm-EDTMP q 6 weeks could be given in combination with 75 mg/M^2 docetaxel q 3 weeks for several cycles. Dose-limiting toxicity was thrombocytopenia. ''Docetaxel-refractory'' patients responded to the combinations of ^{153}Sm-EDTMP and docetaxel suggesting that combination therapy was able to reverse docetaxel resistance.

Fizazi et al.[50] planned estramustine/docetaxel q 3 weeks for 4 cycles in bone metastatic CRPC and stable/responding patients were then treated with a single dose of isotope (1 mCi/kg ^{153}Sm-EDTMP) which was combined with docetaxel at doses of 20 mg/M^2 q week $\times$ 6 doses. Toxicity was minimal, only two episodes of grade 3 thrombocytopenias were observed after combined therapy. The median overall survival was 29 months which is excellent for patients with this disease state. Large trials with docetaxel alone suggest median survivals 10 months shorter. Additional studies will be needed to determine if these results can be replicated but both the Fizazi and Morris studies indicate the promise of a combined modality approach, at least in bone-metastatic CRPC patients.

In a recent phase I trial of ^{186}Re-HEDP and docetaxel, escalating radionuclide doses were combined with conventional doses of (75 mg/M^2 q 3 weeks) docetaxel after the third and sixth cycle.

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Though conclusions regarding benefit were not possible given only 14 patients, the authors concluded that the combination was safe and a radionuclide dose of 40 MBq/kg for the first dose and 20 MBq/kg for the second dose would be tested in a randomized phase II setting.[51] Studies with ^{223}Ra and docetaxel in bone-metastatic CRPC are ongoing.[52] This combination of agents is particularly noteworthy given the low myelosuppression associated with alpha-emission, the demonstrated effectiveness of this radionuclide in prolonging survival, the possible synergy between chemotherapy and radiation therapies, and the ability to deliver multiple doses of ^{223}radium without significant toxicity.

Combination of BSRs and chemotherapy has also been reported in osteosarcoma with several interesting results. The characteristic feature of osteosarcoma is the formation of osteoid; i.e. primitive bone matrix produced by the malignant cells. Follow the initial experiences with ^{153}Sm-EDTMP alone,[53,54] fourteen patients with osteoblastic lesions were treated with doses up to 30 mCi/kg of ^{153}Sm-EDTMP and gemcitabine, a known radiosenstizer, administered one day after ^{153}Sm-EDTMP. Patients then received autologous stem cell reinfusion 2 weeks later.[55] Toxicity was restricted to bone marrow suppression which was important to know given that other potential toxicity was considered prior to therapy. At the 6–8 week assessment, there were six partial remissions and two mixed responses but unfortunately these responses were not durable.[55]

BSRs and bisphosphonates: current data

Several investigations demonstrate that the combination of BSRs and bisphosphonates is both feasible and effective in terms of palliation.[56–59] ^{89}Sr in combination with zoledronate was used to treat patients with refractory pain to conventional treatments.[56] In this study, patients received 6 doses of zoledronate (4 mg) every 3 weeks followed a single dose of 150 MBq ^{89}Sr (group A), or ^{89}Sr alone (group B), or zoledronate alone (group C). Significant pain reduction was noted for all groups but the reduction was more pronounced in group A. A total of 68 % of the group A patients had a pain response of $\geqslant$4 points, as compared to 15% and 9% of patients in groups B and C respectively.

^{153}Sm-EDTMP and bisphosphonates are the subject of only limited study.[59] Patients with bone-metastatic CRPC were treated with isotope at weeks 1 and 3 and 15. Zoledronate treatments began in week 3 and continued every 4 weeks with the bisphosphonate administered 2 days before the radionuclide. Urinary excretion and skeletal uptake of the isotope were not altered by zoledronate.

In the phase III study with ^{223}Ra, analysis of overall survival was stratified by those receiving concurrent bisphosphonates or not. This 920 patient prospective trial indicated that the subset of patients treated with prior bisphosphonate had a HR for overall survival of 0.582 (95% CI 0.397–0.854) as compared to a HR of 0.752 (95% CI 0.567–0.999). Statistical comparison of these subsets is not appropriate but clearly there was a trend toward better efficacy in patients treated with a combination of this radionuclide and bisphosphonates.

Multiple myeloma is not a usual disease studied in BSR investigations given the predominance of lytic as opposed to blastic bony involvement. We note however that pre-treatment with potent bisphosphonates or anti-RANKL monoclonals may alter the lytic/blastic ratio such that BSRs could be better targeted in this disease. This may also be of significance in other cancers with mixed lytic/blastic bone metastases such as breast (see Fig. 1), kidney, or lung cancer. Pre-clinical data with proteosome inhibitors and 153Sm-EDTMP have given synergistic results.[60] Good pain control and M-spike decreases were described in elderly patients receiving combinations of zoledronate and ^{153}Sm-EDTMP.[61] Data using ^{153}Sm-EDTMP in combination with bortezomib are provocative.[62] In this study, patients were enrolled in six cohorts. Bortezomib at doses of 1.0 or 1.3 mg/m2 were given on days 1, 4, 8, and 11 and ^{153}Sm-EDTMP was administered at doses of 0.25, 0.5, or 1.0 mCi/kg on day 3 every 56-days. Dose-limiting toxicities of neutropenia or thrombocytopenia were reached at 0.5 mCi/kg ^{153}Sm-EDTMP in combination with 1.3 mg/M^2 bortezomib. Responses in patients refractory to bortezomib were noted indicating that this strategy could have activity in chemotherapy-resistant patients, a finding similar to that reported in prostate cancer. No trials with targeted alpha-emitters have been reported in myeloma but such trials are warranted.

Summary

Bone metastatic disease is not curable with current technologies, consequently a variety of therapies targeted to diminish complications from these lesions are necessary to optimize patient care. Therapies for these patients may include surgery, radiation, analgesics, bisphosphonates, chemotherapy, hormonal therapy, and/or BSRs. It is likely that multiple therapies will be increasingly utilized in individual patients. The demonstration that a novel alpha-emitting BSR can improve survival will be impactful both in the near and distant future. Combinations of therapies with distinct mechanisms of action and different toxicities will enable further advancements in the field.

Conflict of interest

Oliver Sartor is a consultant to and member of the advisory board of Algeta ASA, as well as a consultant to and investigator for Bayer. Øyvind S. Bruland has an ownership interest in and received honoraria from Algeta ASA, as well as served as a member of the advisory board.

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