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Bone-Seeking Targeted Radio-Nuclide Therapy (BT-RNT) in Management of Metastatic Castration-Resistant Prostate Cancer (mCRPC): Shifting from Palliation to Improving Survival

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Abstract

Background: The purpose of this article is to review the role of bone-seeking targeted radionuclide therapy (BT-RNT) in metastatic prostate cancer. The mechanisms of actions, radiobiology and clinical benefits of BT-RNTs will be reviewed.

Methods: Relevant studies of CRPC and targeted therapies were identified from literature and clinical trial databases, websites, and conference abstracts.

Results: BT-RNT in mCRPC has a proven beneficial palliative role in treatment of patients with mCRPC. The use of these agents as a monotherapy as well as combination with other palliative therapies are evolving. Among the various BT-RNT's the alpha emitter ^{223}Ra which is highly targeted and well tolerated has shown significant clinical benefit and survival advantage in this patient population.

Conclusion: BT-RNT represents an exciting treatment option for patients with mCRPC. ^{223}Ra represents a new treatment paradigm for patients with mCRPC.

Keywords: mCRPC; BT-RNT; Alpharidin; Radium-223; Radiotherapy; Prostate cancer

Introduction

Despite the success of various hormonal and local therapies, a significant percentage of patients with prostate cancer will recur and develop metastatic disease. Standard therapy for metastatic prostate cancer is Androgen Deprivation Therapy achieved by orchiectomy or medical castration. Inevitably patients with metastatic prostate cancer develop castrate resistant disease. Approximately 90% of patients with castration-resistant prostate cancer (CRPC) develop bone metastases. Despite the advent of novel therapies, the prognosis of castration-resistant prostate cancer (CRPC) remains poor with a median survival of approximately 24 months [1,2].

Bone metastases are a significant source of morbidity and mortality in prostate cancer [1]. When patients develop bone metastases, treatment strategies are used to palliate symptoms, reduces skeletal complications and extends survival. Palliative and survival benefits of therapy in this patient population must be weighed against toxicities of therapy. Recent agents such as carbazitaxel, Abiraterone and Enzalutamide show moderate improved survival in mCRPC; however, there is a need for interventions to further increase survival, palliate symptoms and improve quality of life in this setting [2].

Bone targeted therapies include anti-resorptive agents, bone-seeking targeted radionuclide therapy and external beam radiotherapy. Anti-resorptive agents (e.g.: zolendronic acid, denosumab) inhibit osteoclast activity and help to delay Skeletal Related Events (SREs); however, these agents have no impact on survival. Bone-seeking targeted radionuclide therapy (BT-RNT) using radiopharmaceuticals have been used for decades in mCRPC as a palliative therapy. External beam radiotherapy is routinely used to palliate painful bone metastases with high response rates.

Bone-seeking Targeted Radionuclide Therapy (BT-RNT) and Bone Metastases

Owing to the large bone tumor burden in patients with metastatic CRPC (mCRPC), there is significant interest in agents that could broadly target and eradicate prostate cancer cells in the bone. BT-RNT systemically seeks out active sites of bone metastasis and delivers tumoricidal radiation focally at the site where cancer interacts with bone. The benefit of this technique, compared to external beam radiation therapy, is that multiple sites of metastatic disease can be treated simultaneously. BT-RNT can also treat asymptomatic tumour sites in the bone which may help to reduce future complications and SRE's. In addition due to the localized targeting of cancer, there is in theory minimal radiation exposure to nearby tissues with relative sparing of normal bone, bone marrow and adjacent tissues.

Active prostate cancer cells within the bone metastasis alters the skeletal metabolic activity around it, resulting in an active bone synthesis process characterised by local increase in the uptake of

calcium, which is used to construct hydroxyapatite. It is believed that the cancer cells secrete pro-osteoblastic factors that promote bone mineralization. In addition, the cancer cells also produce pro-osteoclastic factors such as receptor activator of NFkappaB ligand (RANKL). Thus the inhibition of the prostate cancer cells using radiation would help in inhibiting both the osteoblastic and osteoclastic effects of bone metastasis. This in-turn should palliate pain and reduced risk of SREs. In addition tumoricidal effects of radionuclide therapy could lessen tumor burden and potentially improve survival [3].

BT-RNT for palliation of pain from bone metastases has been used successfully for decades [4]. In 1941, a patient with prostate cancer and painful osteoblastic bone metastases was treated with 8 mCi of Sr-89 with positive pain response, which was the first clinical use of radionuclide therapy for bone metastases [5]. Radioactive phosphorus (^{32}P) and ^{89}Sr were the first bone-seeking radiopharmaceuticals to be approved for treatment of bone metastases. However the use of ^{32}P waned due to the high rates of myelotoxicity [6]. The most popular BT-RNT agents currently in clinical use in mCRPC are the radionuclides ^{89}Sr, ^{153}Sm, ^{186}Re, ^{188}Re, and ^{223}Ra. The physical characteristics of these agents are tabulated in Table 1.

Radiopharmaceutical	Half-life (t ½)	Maximum beta (β) nergy in MeV (mean)	Mean alpha (α) energy in MeV	Mean gamma (γ) energy in keV	Maximum tissue penetration (mean)	Usual administered activity (SI units)	Typical response time	Typical response duration	Retreatment interval
Phosphorus [^{32}P]	14.3	1.71	_	None	8 mm (3 mm)	5-10 mCi (185-370 MBq)			
Strontium-89 [^{89}SrCl2] (Metastron®)	50.5 days (14 days biological T1/2)	1.46 (0.58)	-	none	5.5 mm (2.4 mm)	4 mCi/kg (1.48 MBq/kg)	14-28 days	12-26 weeks	>3 months
Samarium-153 [153Sm-EDTMP] (Quadramet®)	1.9 days	0.81 (0.22)	-	103	2.5 mm (0.6 mm	1 mCi/kg 37 MBq/kg)	2-7 days	8 weeks	>2 months
Radium-223 [^{223}RaCl2] (Alpharadin®)	11.4 days	-	5.64	-	<0.1 mm	1.35 kCi/kg (50 kBq/kg)	<10 days	Not established	Not established
Stannic-117	13. 6 days	(conversion electron)	-	159	0.2-0.3 mm	~333 MBq	5-19 days	98 days	Not established
Rhenium-186 [^{186}Re-HEDP}	3.8 days	1.07 (0.35)	-	137	4.5 mm (1.1 mm)	35 mCi (1295 MBq)	2-7 days	8-10 weeks	>2 months

Table 1: Physical characteristics of Bone seeking radiopharmaceuticals.

Mechanism of Action of BT-RNT

Bone metastases in prostate cancer are predominantly osteoblastic. The bone targeting of most radiopharmaceuticals in prostate cancer relies on selective uptake and prolonged retention of the isotopes (or their chelated complexes) at sites of increased osteoblastic activity. This enables delivery of ionizing radiation to areas of amplified osteoblastic activity in multiple sites simultaneously. The radiopharmaceuticals target both symptomatic and asymptomatic sites [7] (Figure 1). It is unclear whether the BT-RNT produces response through disruption of an onconiche (where osteoblasts provides a microenvironment which supports and sustains cancer stem cells) or due to eradication of micrometastatic disease [8].

Bone targeting agents like ^{89}Sr and ^{223}Ra are calcium mimetic, as they are members of the second group of periodic table. Similar to calcium, they are incorporated into hydroxyapatite at the sites of high osteoblastic activity. Radioisotopes such as samarium (^{153}Sm) and rhenium (^{186}Re, ^{188}Re) require complexing with a chelate such as ethylenediamine tetramethylene phosphonic acid (EDTMP) or hydroxyethylidene diphosphonate (HEDP) to achieve selective uptake to the bone. After injection, these "isotope-carrier complexes" attach to the hydroxyapatite in mineralized bone, particularly in areas of high bone turnover at metastatic sites.

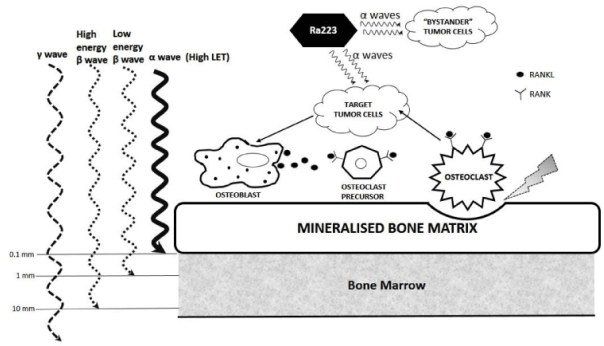

Figure 1: Schematic diagram showing the mechanism of action of ^{223}Ra. The image shows action both at the site of uptake as well as action upon bystander tumor cells which does not uptake the radionuclide. Alpha emitters have less bone marrow dose due to less penetration of alpha particles.

Once localized to bone, the radionuclides decay and emit gamma (γ) rays, alpha (α) particle, beta (β) particles or a combination of these. The particle (α, β) emissions cause cell damage directly through DNA

damage and cellular apoptosis. Additional properties of radionuclide therapy are the "bystander effect," in which cell signalling mechanisms (connexion 43 gap junctions) cause death of tumor cells adjoining the target cells [7] (Figure 1), and the "cross-fire effect" in which cells not directly targeted are killed by convergence of particle emissions from surrounding sites.

Dosimetry and Radiobiological Considerations

The dosimetry of BT-RNT is complex. The radiobiology developed for external beam radiation therapy does not apply to BT-RNT. In EBRT, there is a constant delivery of radiation dose in a short time period producing single or double strand DNA breaks in tumour cells. On the other hand, BT-RNT particle radiation is delivered in a non-uniform distribution, and continuously in decreasing amounts over a longer time period. Radiation delivery in BT-RNT depends on the physical radionuclide half-life and residence time of the administered radiopharmaceutical. Where EBRT is delivered in fractions to improve its effect, some authors consider BT-RNT to be a form of continuous fractionation.

Mechanisms of cell death by BT-RNT include effects of radiation on the cell surface through the ceramide pathway triggering cellular apoptosis. In addition, BT-RNT results in significant DNA damage with resultant cell necrosis and a secondary immunological response [9].

The actual radiation dose received by the target depends on factors such as the physical half-life, type of emission and its attendant energy and tissue penetration, biological transit time and clearance (Table 1). Depth of penetration is a significant clinical factor as different tumors extend over varying lengths. β-emitters such as ^{153}Sm, ^{89}Sr, and $^{186/188}$Re have energies high enough to penetrate the tumor but low enough to help minimize dose to the bone marrow (an important dose limiting organ in BT-RNT). γ rays penetrate deeper but are low dose and are used for post therapy imaging. The newer agent ^{223}Ra predominantly emits α rays which have a very short range (2 to 10 cell diameters). As a result the dose to surrounding normal bone marrow is minimized.

Alpha particles from ^{223}Ra have a high linear energy transfer (LET) compared to agents which emit β rays (lower LET). Low LET radiation is relatively ineffective in overcoming the radio-resistance of hypoxic tumor cells compared to oxygenated cells [10]. High-energy LET radiation (α rays) overcomes this radio-resistance compared to low LET therapies due to its low oxygen enhancement ratio. For a given absorbed dose, α radiation also has a higher relative biological effect (RBE), achieving a greater cell kill per dose compared with low LET treatments. To produce the same cell kill as α particles, it is estimated that at least 100 to 1000 times the number of β particles are required [11]. BT-RNT using α emitters also have theoretical benefits in using more than one treatments as the DNA damage induced by α particles takes longer to repair and therefore gives a high probability of accumulated damage with each treatment [10,11]. Repeat cycles of ^{223}Ra can result in progressive tumour cell killing. Analogous to fractionated external radiotherapy cancer cells with residual DNA damage may be eradicated by subsequent treatment courses with radioisotope.

Particle range influences treatment-related toxicity. Usually the energy of shorter range particles is largely absorbed within the target cell, whereas longer-range particles may irradiate more surrounding healthy tissues like bone marrow, contributing to unwanted toxicity. The physical characteristics of therapeutic radionuclides for bone pain palliation are summarized in Table 1 [4,12,13].

Clinical Endpoints of BT-RNT Therapy

Palliation of bone pain remains the main clinical indication for BT-RNT. Up to 70% of patients experience pain relief and approximately 20% experience complete pain resolution. Published clinical trials measure pain differently and hence it is difficult to cross compare studies. In addition, many of the trials had relatively small patient numbers (18). Evidence supporting the use of different radiopharmaceuticals is discussed here, and administered activities, typical responses, and re-treatment intervals are listed in Table 2 [14-29].

	Trial	Methods	No. of patients	Technique	Outcomes
^{89}Sr compared to placebo	Lewington et al. (Phase III cross over) [4].	^{89}Sr vs. placebo	32	150 MBq week 1 and 150 MBq in week 6 if needed	Pain reduction for ^{89}Sr arm ($p<0.01$)
	Buchali et al. (Phase I/II) [15].	^{89}Sr vs. placebo	49	75 MBq qmonths x 3 months	NSD# after 1-3 years improved 2 years OS (46% vs. 4%) in ^{89}Sr arm
Adjuvant ^{89}Sr compared to placebo	Porter et al. (Phase III) [16]	^{89}Sr as adjunctive therapy to local XRT compared with placebo	126	Involved field XRT and 10.8 mCi (400 MBq) injection	Fewer new pain sites in ^{89}Sr group NSD pain relief or median survival. ^{89}Sr arm better in need of analgesics, time to further XRT and further quality of life.
	Smeland et al. (phase III) [17].	EBRT + ^{89}Sr vs. EBRT + placebo	95 (64 prostate)	150 MBq	No adjuvant benefit to ^{89}Sr with EBRT No survival or QOL, PSA difference
^{89}Sr compared to EBRT	Quilty et al. (stratum I) Phase III [19].	^{89}Sr with EBRT (involved field)	148	200 MBq	NSD in pain relief or survival, decreased new sites and further XRT.
	Quilty et al. (stratum II) Phase III [19]	^{89}Sr with EBRT (hemibody RT)	157	200 MBq vs. 6 Gy upper , 8 Gy lower	NSD in pain relief or median survival ^{89}Sr reduced new pain sites

	Oosterhof et al., Phase III [20].	EBRT vs. ^{89}Sr	203	150 MBq (4 mCi)	Better OS with XRT (11 months vs. 7.2 months) No difference in PSA response
^{89}Sr vs. ^{153}Sm	Baczyk et al. [21]	^{89}Sr vs. 153Sm	50	^{89}Sr (150 MBq) vs. 153Sm (37 MBq per kg)	NSD pain relief. Better response for blastic metastasis than mixed.
^{89}Sr vs. chemotherapy alone	Tu et al. [22]	Induction chemo followed by randomisation to doxorubicin with or without 6 weekly ^{89}Sr 89	72	2·035 MBq per kg	Significant survival advantage for addition of ^{89}Sr (27.7 vs. 16.8 mo)
	Nilsson et al. [23]	^{89}Sr (18) vs. 5-FU, epirubicin, mitomycin-C	35	150 MBq (4 mCi)	At 3 weeks, pain reduced in both groups (p = 0.01 and 0.001 respectively) No differences in Karnofsky performance status or analgesic use More side effects in the chemo arm.
^{153}Sm vs. placebo	Serafini et al. [24]	^{153}Sm vs. placebo	118	0.5-1 mCi/kg (18.5-37 MBq/kg)	62–72% of patients had \pain relief with 1.0 mCi/ kg during first 4 weeks and 31% had complete/ marked relief by week 4
	Sartor et al. [25]	^{153}Sm (101) vs. placebo (51)	152	1 mCi/kg (37 MBq/kg)	Significant improvement in bone pain and analgesic use with Sm-153 (p<0.05)
^{153}Sm 0.5 vs. 1.0	Resche et al. [26]	^{153}Sm at 0.5 mCi/ kg (55) vs. 1.0 mCi/ kg (59)	114 (67 prostate)	^{153}Sm at 0.5 mCi/ kg (55) vs. 1.0 mCi/ kg (59)	55% vs. 70% pain relief between 0.5 mc 9 and 1.0 mci at week 4 (p = 0.0476) OS not different between groups
^{186}Re vs. placebo	Han et al. Phase III [27] (PLACORHEN study)	^{186}Re vs. Placebo	79	1,295 to 2,960 MBq (35–80 mCi)	Mean percentage of pain response days 27% (^{186}Re) vs. 13% (placebo), p<0.05 Median survival 37.2 weeks (placebo) vs. 30.4 weeks (^{186}Re), p > 0.05 Radiotherapy for pain required in 44% (^{186}Re) vs. 67% (placebo)
	Maxon et al. Phase III crossover [28]	^{186}Re (6) vs. Placebo	20 (9 prostate)	30-35 mCi (1110-1295 MBq)	Significantly greater relief in pain with ^{186}Re (p<0.05). Higher leukopenia in Re arm
^{223}Ra vs. placebo	Parker et al. [29] Phase III (ALSYMPCA trial)	^{223}Ra (541) vs. placebo (268)	809	(50 kBq/kg IV) q4 weeks	OS: 14 months (^{223}Ra) vs.11.2 months (placebo), HR 0.695, p = 0.001 HR time to total ALP progression: 0.163 (p<0.00001), HR for time to PSA progression: 0.671(p = 0.0002),

Table 2: Table demonstrating the various randomised trials in bone seeking radionuclide therapy. #No significant difference.

As we gain more insight into these agents there is great interest in studying clinical predictors of response to therapy. An Italian multicenter observational study in metastatic prostate cancer patients found that patients with limited skeletal disease, radiologically osteoblastic or mixed bone lesions, life expectancy more than 3 months had better responses with BT-RNTs. The flare phenomenon which was found in 14% patients did not correlate with response [30]. Zafeirakis et al. found that NTx, a potent collagenous marker of bone resorption, along with the novel NTx/PINP (N-telopeptide/ aminoterminal propeptide of type I collagen) ratio provide useful cut-off values for identifying a group of castrate-resistant prostate cancer patients who do not respond to palliative treatment with ^{186}Re-HEDP [31].

Even though radionuclide dose escalation studies have reported a dose response relationship, increasing myelotoxicity is also seen with higher doses. Due to this dose-limiting toxicity of myelosuppression, clinical trials combining BT-RNT with stem cell support are also being studied [32,33]. Nilsson et al. in their dose escalation study for ^{233}Ra also reports increasing response for pain control with increasing dose of ^{233}Ra with minimal toxicity even at the highest dose level [1]. Additional trials of dose escalation and extended duration ^{233}Ra are underway to evaluate safety and potential benefits.

The disease modifying properties of BT-RNT agents are a matter of interest as they may be useful surrogate markers of clinical benefit of therapy. In evaluating new treatment options for mCRPC serum biomarkers, such as PSA and bone ALP, are commonly used as early efficacy markers. Reduction in markers of bone turnover such as alkaline phosphatase have been reported with BT-RNT, however it is unclear whether this is due to an anti-tumor response or whether these marker changes simply reflect a modulation of the metastasis-induced bone dysregulation or due to direct toxicity to the osteoblasts [1,16,34]. A phase II randomised study demonstrated that ^{223}Ra therapy produced >50% reduction in bone ALP in 16-66% patients depending on the administered dose [35]. Some trials demonstrate a

reduction in PSA levels in prostate cancer patients in response to BT-RNT [36]. In the pivotal TAX327 chemotherapy trial, ALP normalization at 90 days occurred in 26% of patients receiving docetaxel or mitoxantrone and correlated with better survival, independent of ≥ 30% PSA declines. The ALSYMPCA trial also showed improved survival with ^{223}Ra in a phase III setting for mCRPC [22,37-39].

Specific clinical considerations for the various BT-RNT are listed below.

Phosphorus 32, ^{32}P

Oral or injectable ^{32}P (usually injectable sodium orthophosphate) is now rarely used due to its high incidence of myelotoxicity. In addition to tin, radiophosphorus has only been investigated in phase I/II trials in metastatic prostate cancer at this time [37].

Strontium 89, ^{89}Sr -Cl (Metastron®)

Strontium-89 chloride was FDA approved in 1993 as the first beta-emitting radiopharmaceutical for metastatic prostate cancer. ^{89}Sr has been evaluated in phase III trials for mCRPC. Due to its biological half-life, the toxicity profile is much better than ^{32}P. ^{89}Sr has proven efficacy in the palliation of painful bony metastases in mCRPC. (Table 2) ^{89}Sr monotherapy has not been shown to lengthen the average duration of patient survival. The evidence favoring combination of ^{89}Sr with chemotherapy is demonstrated in Table 2. The recommended dose for ^{89}Sr is 148 MBq (4 mCi) by slow intravenous injection (1-2 minutes), accompanied by intravenous or oral hydration (at least 500 mL) [37]. Onset of pain relief is generally 7-20 days. Excretion is through urine (67%) and feces (33%).

Samarium 153, ^{153}Sm-EDTMP (Quadramet®)

Samarium 153 lexidronam is currently licensed in Canada, and has been available since 2013. The recommended dose for ^{153}Sm is 37 MBq/kg (1 mCi/kg) by slow intravenous injection (1-2 minutes), accompanied by intravenous or oral hydration (at least 500 mL) [38]. Table 2 shows the randomised trials demonstrating the benefits of this radionuclide over placebo. Myelotoxicity is less than with strontium-89.

Radium-223 (^{223} Ra); ^{223}Ra-Cl (Xofigo®)

Radium-223 chloride (Xofigo®, Bayer), formerly known as Alpharadin® is a calcium mimetic, bone-seeking agent that targets new bone growth within and around metastases. ^{223}Ra emits high-energy alpha-particles within a 2- to 10-cell diameter distance, generating highly localized and intense radiation zones that induce primarily non-repairable, double stranded DNA breaks in the target areas containing metastatic cancer cells. The relatively favorable safety profile of ^{223}Ra has been demonstrated in phase I, II, and III studies of patients with bone metastases [1].

Importantly, ^{223}Ra is the first agent in this class to show an overall survival advantage in mCRPC patients with bone metastases. The recent phase III ALSYMPCA (ALpharidin in SYMptomatic Prostate Cancer) trial demonstrated an overall survival benefit compared to placebo; the trial was stopped prematurely after an interim analysis had shown an improvement in overall survival (14.9 month vs. 11.3 months), in addition to reduced frequency of SREs and increased median time to an SRE (15.6 vs. 9.8 months). The toxicity profile was favourable with low rates of bone marrow toxicity in the form of grade 3 or 4 neutropenia 1.8% vs. 0.8% and thrombocytopenia rates 4% vs. 2% compared to the placebo arm [29,40]. ^{223}Ra was approved by FDA on May 13, 2013 for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease [39]. ^{223} Ra received Health Canada approval in December 2013. Thus, ^{223}Ra is the first bone-targeted agent shown to meaningfully alter the natural history of mCRPC. In addition ^{223}Ra provided palliation of pain, quality of life benefits, delayed SRE's and had a favourable toxicity profile.

Rhenium-186 (^{186}Re-HEDP) and Rhenium-188 (^{188}Re-HEDP)

Rhenium is a transitional metal with two radioisotopes (Re-186 and Re-188) that can be attached to hydroxyethylidene diphosphonate (HEDP) for bone targeting. The PLACORHEN randomized controlled trial of ^{186}Re-HEDP vs placebo showed a significantly higher rate of pain responders (65% vs. 36%, respectively). The number of patients in this study requiring palliative EBRT was higher in the placebo group than in the treatment group (67% vs. 44%). Repeat administration of ^{186}Re-HEDP appears to be both safe and effective in select patients [27,40]. ^{188}Re-(Sn)HEDP has similar bio-distribution and radiation dosimetry characteristics as ^{186}Re-(Sn)HEDP and appears to result in similar benefits and toxicities in patients with skeletal metastases. An advantage of Re-188 is that this radionuclide can be produced in a relatively convenient generator. More data on the effectiveness of Re-188 is needed [41].

Tin-117(stannic, 4+) DTPA (Sn-117m DTPA)

The metastable isotope ^{117}mSn, chelated to diethylenetriamine pentaacetic acid (DTPA), is under investigation as a possible therapeutic radionuclide for the treatment of bone metastases. The range of electron emission is less than any other compound (micrometers), hence potentially less marrow dose. The half-life of 13.6 days is ideal as far as shipment and shelf life is concerned. Tin is a natural bone-seeker, but its highest specificity for bone occurs when the element is in its quatravalent state (4+). DTPA stabilizes tin in this preferred 4+ state, protecting it from competing redox reactions in vivo. There is also accompanying gamma photons which can be used for monitoring distributions. Preliminary clinical studies have shown promise [13].

Other investigational agents such as Lutetium-177 (^{177}Lu), Thulium-170 (^{170}Tm) are also under clinical study.

Indications

The indications for BT-RNT are treatment of symptomatic multiple skeletal metastasis of blastic or mixed type with intense uptake around painful metastases. The indications and contraindications of BT-RNTs are demonstrated in Table 3. Most common reason for failure of therapy is inappropriate patient selection. Foci of increased uptake on bone scan should be confirmed and correlated with patient's symptoms to attribute to osteoblastic metastases, since other pain aetiologies such as vertebral collapse, nerve root entrapment, fracture or visceral pain will not respond to BT-RNT. In patients with predominantly osteolytic pattern of skeletal metastases, the response may be less favourable due to the poor uptake and retention resulting in lower metastatic absorbed dose.

Indications	Contra-Indications
Known castrate-resistant prostate cancer with painful bone metastasis	Absolute pregnancy, continuing breast feeding.
Metastatic disease refractory to hormone therapy	History of hypersenstitivty to EDTMP or similar phosphonate compounds
Severe pain poorly controlled with conventional narcotics	Relative myelosuppression chronic renal failure or deterioration of renal function (urea >12 mmol/l; creatinine >150 mmol/l; GFR <30 mL/min)
Not a candidate for local or wide field radiotherapy	urinary incontinence
Positive correlation between pain sites and osteoblastic lesions on bone scan	acute or chronic spinal cord compression and/or metastases at the base of the skull
Painful sites of disease on both sides of the diaphragm	
No chemotherapy or large field radiation in the past 4-12 weeks	
Urinary catheter placed for incontinence	
Life expectancy more than 4 weeks	
Signed informed consent	
Adequate bone marrow reserve • Hemoglobin >9.0 mg/dl • Absolute WBC >3500 /dl • Absolute neutrophil >1500/dl • Platelets >1,00,000/dl	
Glomerular filtration rate >50 Ml/min; urea <12 mmol/L; creatinine <200 mmol/L	

Table 3: Criteria for patient selection for bone-seeking radionuclide therapy.

Preserved renal function is vital in clearance of most of these agents. Elderly mCRPC patients can present with modest renal impairment, so the benefits vs. risks in these patients should be carefully considered. The outflow obstruction at vesico-ureteric junction or bladder neck should be treated appropriately before BT-RNT administration. Incontinent patients may require urinary catheterization [39]. ^{223}Ra is predominantly excreted by the GI tract and does not impact on renal function. The 2013 AUA guidelines state that radionuclide therapy may be offered to patients with symptomatic mCRPC who do not want or cannot have one of the standard therapies [42]. However, these guidelines did not consider the use of ^{223}Ra which has disease modifying effect as indicated by an improved survival and delay in Skeletal Related Events.

Administration and Side Effects of BT-RNT

Generally the treatment is an outpatient based; since particle emissions are attenuated within the patient specific radiation isolation is unnecessary and universal precautions similar to those use with chemotherapy are employed. Some centres observe overnight with or without hydration. Patients should be well hydrated prior to procedure to allow for sufficient elimination of residual radionuclide. After the intravenous administration of the agent, the patient typically is followed with frequent blood counts monitoring up to 8 weeks [43].

The principal side effect of BT-RNT in general is myelosuppression, with thrombocytopenia being the most common form. Anemia and neutropenia are less common. Flare phenomenon is usually seen in 5-10% patients which is a transient and self-limiting increase in bone pain, especially in patients with high tumor burden. This usually occurs 36-72 hours post dose and the reaction is generally mild and self-limiting. Other toxicity include loose stools, nausea, asymptomatic hematuria and heart palpitations. Some patients may notice a flushing sensation following rapid (<30 sec) injection of Sr89 [43].

In the ALSYMPCA trial, the noted side effects were nausea, diarrhea, vomiting and swelling of the leg, ankle or foot. The most common abnormalities detected during blood testing were anemia, lymphocytopenia, leukopenia, thrombocytopenia and neutropenia. The haematological toxicity was less compared to the other agents [29,39]. There were no effects of [39] ^{223}Ra on renal function as it is predominantly excreted by the GI tract.

Combination with Other Prostate Cancer Therapies

Chemotherapy

Chemotherapy is known to have a synergistic effects with radiation therapy as it makes the cancer cells more susceptible to damage by radiation. Most clinical trials studying combination of chemotherapy and BT-RNT used Sr-89 as the agent. However there is no published randomised phase III trial. Sciuto et al. showed that the pain response in patients treated with Sr-89 and low dose carboplatin was superior to Sr-89 alone in terms of longer duration of pain control [44]. Small series studying low-dose cisplatin in combination with ^{89}Sr showed improved response rates compared to Sr-89 monotherapy [18]. The phase I/II Taxium trial using fractionated ^{186}Re-HEDP and 3-weekly docetaxol may give some more evidence regarding the effectiveness of this combination [45]. Phase I trials combining ^{153}Sm with weekly docetaxel and 3-weekly docetaxel showed the combination to be well tolerated [46,47]. Numerous phase II trials in mCRPC showed that ^{89}Sr or ^{153}Sm in combination with chemotherapy improved outcomes in a subset of patients [48,49]. However with newer agents like ^{223}Ra, which has better bone marrow preservation there is potential for designing clinical trials in combination with chemotherapy. The results of the ongoing phase I/IIa study of ^{223}Ra and docetaxel for mCRPC would be able to provide insights on this [50]. More evidence needs to be gathered regarding the best agents and dose regimens that need to be combined to balance toxicity and outcomes.

Radiotherapy

Porter et al. showed that the addition of Sr-89 to external beam radiotherapy was associated with lower pain scales and analgesic consumption, as well as a longer interval to the development of new sites of painful bone metastases, compared to local field radiotherapy alone in patients with mCRPC. However this study was criticised due

to the higher ^{89}Sr doses used [36]. No other trial could demonstrate this benefit [17]. This form of combination potentially helps to give extra radiation doses to larger lesions that could be radiologically localised. In a sub-analyses of ALSYMPCA it was safe to give subsequent palliative radiation to patients who have received prior ^{223}Ra.

Combination with bisphosphonates

The hypothesis against concomitant use is that the competitive interaction of bisphosphonates and the radionuclide at the hydroxyapatite crystal surface of the skeleton, could decrease the uptake and clinical effect of both agents. However the clinical evidence regarding combining bisphosphonates with BT-RNT is conflicting [6]. Storto et al., in his retrospective study, showed that sequential use of Sr-89 with zolendronic acid compared to Sr-89 alone demonstrated higher response rates in the form of reduced analgesic doses in the combined arm (96% vs. 76%) at the end of 6 months of therapy. The bone marrow toxicity was also slightly higher but tolerable [51]. However the evidence with newer agents like ^{223}Ra is still unknown. ^{223}Ra resulted in a survival advantage in patients There was comparable survival benefit for those patients who were receiving bisphosphonates vs. those patients those who were not receiving bisphosphonates in the ALSYMPCA Trial.

Re-treatment using BT-RNTs

The role for repeat administration of BT-RNT is of interest in palliation of patients with mCRPC patients who have exhausted all other treatment options. Multiple administrations of Re-188 showed an improved overall survival compared to single administration in mCRPC [52]. The feasibility of repeating ^{153}Sm therapy in mCRPC who were previous responders to therapy has been shown. The same study also showed that the magnitude of response remained the same with each dosing [25]. Due to reduced bone marrow toxicity, the use of repeat ^{223}Ra seems attractive and future trials will evaluate its safety and efficacy.

Conclusion

BT-RNT is an effective treatment option for pain palliation in patients with mCRPC. Xofigo® (^{223}Ra) is an exciting new systemic radionuclide therapy which improves survival in mCRPC. It has a favourable safety profile and has been shown to improving quality of life and delay skeletal related events. Additional clinical trials are necessary to expand on the emerging positive evidence with Xofigo® (^{223}Ra) as monotherapy as well as in combination with other systemic therapies to further improve patient outcomes.

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