Systemic radiotherapy of bone metastases with radionuclides

Introduction

The development of bone metastases is a frequent occurrence in prostate, breast and lung cancers and is associated with a reduced quality of life and decreased survival [1]. Skeletal related events (SREs) including pathological bone fractures and spinal cord compression are considered to be caused by disruption of the normal balance between osteoblast and osteoclast activity, giving rise to a loss of bone integrity [2, 3]. Bone metastases are also associated with pain that can be felt continuously or can be more severe, arising spontaneously with movement [4].

Bone pain can be extremely resistant to standard first line treatment with non-steroidal anti-inflammatory drugs. External beam radiotherapy may also be used, either to target specific sites of disease or to treat a wider region of bone metastases using hemi-body radiotherapy [2]. For patients with widespread bone metastases, a range of alpha or beta particle emitting radiopharmaceuticals provide a means of specifically targeting all sites of bone disease. The physical decay properties of all the radionuclides described in this review are described in Table 1.

The first beta emitter to be used for the treatment of bone metastases was Phosphorus-32 [5]. However, higher rates of myelosuppression and pancytopenia were observed compared to other beta-emitters subsequently introduced for clinical use.

Strontium-89 (^{89}Sr)

^{89}Sr given in the form of strontium chloride is a beta emitting radionuclide with a half-life of 50.5 days. The mean and maximum energies of the beta particle spectrum are 0.58 MeV and 1.46 MeV respectively. The recommended activity is 150 MBq at 90 day intervals. Strontium behaves similarly to Calcium and is absorbed preferentially in sites of osteogenesis resulting in approximately ten times higher concentrations at sites of metastases compared to normal healthy bone [6].

A 2005 systematic review of observational studies and randomised controlled trials concluded that treatment with ^{89}Sr resulted in some degree of response in 76% of patients and complete response with respect to pain relief in 32% of cases [2]. For example, a double blinded randomised control trial of ^{89}Sr vs placebo showed no difference in pain relief between two arms but did demonstrate a survival difference at two years [7]. On the other hand a second double blinded randomised control trial of ^{89}Sr vs stable ^{88}Sr did demonstrate the effectiveness of ^{89}Sr in providing pain relief. Furthermore, this study also demonstrated that this was due to the beta radiation emitted by ^{89}Sr and not due to a placebo effect or to a chemical effect arising from the injection of Strontium.

Several early studies compared the effect of ^{89}Sr in addition to local radiotherapy or as an alternative to hemi-body radiotherapy. Porter et al described a randomised phase III study that assessed the additional effect of ^{89}Sr vs placebo on patients referred for local radiotherapy of painful metastases [8]. This study of 126 patients showed that the arm receiving ^{89}Sr had a reduced requirement for analgesics or further external beam radiotherapy as well as an improved quality of life.

A retrospective study of matched cohorts receiving either hemi-body radiotherapy or 1-3 MBq/kg ^{89}Sr for treatment of metastatic prostate cancer demonstrated similar levels of pain control between the two groups [9]. A prospective study addressing the same question also showed no significant

difference in overall survival between patients treated with 200 MBq ^{89}Sr or external beam radiotherapy. However, they did also show a reduced incidence of new pain sites in the ^{89}Sr arm [10]. A larger EORTC study of 203 patients concluded that there was no difference in time to progression or progression free survival between prostate cancer patients treated with a single injection of 150 MBq ^{89}Sr and those treated with palliative local field radiotherapy, although there was improved overall survival associated with external beam radiotherapy [11].

In general the toxicity of ^{89}Sr has been reported as low and reversible. Both white cell counts and platelet levels will fall below normal levels in the majority of patients, with the nadir commonly occurring 12-16 weeks after treatment [2, 12].

Samarium-153 (^{153}Sm)

^{153}Sm is a beta emitting radionuclide with a half-life of 1.9 days. The mean and maximum energies of the beta particle spectrum are 0.32 MeV and 0.81 MeV respectively. The recommended activity is 37 MBq/kg. Unlike ^{89}Sr, ^{153}Sm is not naturally taken up in bone. Instead, ^{153}Sm is complexed with ethylenediaminetetramethylene phophanate (EDTMP) which localises to sites of active bone turnover [13]. In common with ^{89}Sr a number of randomised trials have been used to evaluate the efficacy of ^{153}Sm-EDTMP.

For example, Sartor et al reported on a double blinded randomised prospective trial of a single administration of 37 MBq/kg ^{153}Sm-EDTMP vs a stable ^{152}Sm-EDTMP placebo. Patients on the treatment arm reported pain relief within 1-2 weeks as well as reduction in opioid use 3-4 weeks after treatment [14]. This followed an earlier double blinded placebo controlled trial which also reported fast pain relief and reduction of opioid analgesics in approximately 70% of patients receiving a single administration of 37 MBq/kg [15]. A later study reported that in cases where bone pain recurred, repeat administrations of ^{153}Sm-EDTMP were tolerated as long as haematological function was adequate at the time of injection [16]. Similarly to ^{89}Sr, toxicity was limited to transient myelosuppression with recovery to normal levels typically observed by 8 weeks post treatment [14, 17].

Both ^{89}Sr and ^{153}Sm-EDTMP have received marketing authorisation and are available as licensed products (Metastron and Quadramet respectively.)

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

Rhenium has similar chemical properties to technetium and can be used to label phosphonates such as hydroxyethylidine diphosphonate (HEDP). Therefore both ^{186}Re-HEDP and ^{188}Re-HEDP have been used to treat patients with bone metastases [18-22]. Both isotopes are beta emitters although with differing half-lives and beta particle energies. Palliation of pain was observed in 60-75% of patients treated with ^{188}Re activities of 2.6 GBq or higher [23] and multiple administrations have been shown to be well tolerated [24]. Interest in the use of ^{188}Re-HEDP continues. A clinical trial (NCT03458559) is underway aiming to compare overall survival in 402 metastatic castrate resistant prostate cancer patients treated with either ^{188}Re-HEDP or ^{223}Ra [25].

Imaging and treatment planning

Despite the demonstrated efficacy of both ^{89}Sr and ^{153}Sm-EDTMP it is clear from the literature that not all patients will respond to treatment. A common component of early studies was the inclusion of dosimetry studies designed to measure the absorbed radiation dose to the metastatic lesions themselves. As well as ^{89}Sr, tracer amounts of ^{85}Sr, a gamma photon emitting isotope of strontium were administered. Uptake in metastases was quantified using a gamma camera in order to calculate the absorbed radiation dose to those metastases [6]. Results showed that the currently recommended activity of 150 MBq would result in absorbed doses ranging from 9-90 Gy. Other authors have imaged patients without the injection of additional ^{85}Sr. The majority of these reports detail qualitative assessment of ^{89}Sr uptake and its correlation with sites of abnormal uptake identified by diagnostic bone scans [26, 27]. However one report described the quantitation of uptake seen on ^{89}Sr images as part of their routine clinical assessment of patients receiving ^{89}Sr therapy [28]. Initially it was assumed that these quantitative images were based on bremsstrahlung emissions since ^{89}Sr is a pure beta emitter. In fact, it has since been reported that detected emissions are most likely due to high energy photons emitted by ^{85}Sr impurities giving rise to characteristic x-rays from the gamma camera collimator [29, 30].

Further to in-vivo imaging and dosimetry, Ben-Josef et al performed dosimetry calculations with autoradiography to quantify uptake in ex-vivo samples of bone from patients previously treated with ^{89}Sr. They estimated absorbed doses to metastases ranging from 1.3 to 64 Gy [31] which are in accordance with the earlier work of Blake et al.

Overall it is clear that administration of the same activity results in wide variations in the absorbed dose to lesions. The reasons for this variable uptake are not precisely understood but it has been noted that better responses are observed in patients presenting with fewer metastases, and in osteoblastic lesions [32]

Variations in the absorbed doses delivered have also been observed for ^{153}Sm-EDTMP studies. Quantitative imaging of ^{153}Sm is possible due the emission of gamma photons with an energy of 103 keV (29% abundance.) Relative to ^{89}Sr treatments, lower absorbed doses to bone metastases have been reported. Van Rensburg et al reported absorbed doses to metastatic lesions ranging from 3 to 15 Gy for patients who received 55 MBq/kg or 110 MBq/kg [33]. The recommended administered activity is 37 MBq/kg.

A number of studies have explored the effect of increasing the amount of radioactivity administered. Mertens et al reviewed the early literature describing the effect of ^{89}Sr, finding a positive correlation between the administered activity and the proportion of patients who experienced complete pain relief [34]. A study comparing ^{153}Sm-EDTMP administrations of 28 MBq/kg, 55 MBq/kg and 110 MBq/kg did not demonstrate a statistically significant relationship between the administered activity and outcome [35]. Conversely Resche et al reported higher rates of pain relief in patients receiving 37 MBq/kg compared to those who were administered 17.5 MBq/kg [36]. However, it should be noted that the difference in these administered activities is relatively modest compared to the range of the reported doses described earlier. Consequently strategies involving higher administered activities were investigated.

However, it has been shown that increased radiation doses to the marrow result in an increased risk of toxicity [13]. As with the absorbed radiation dose to bone metastases, the same administered activity can result in significant inter-patient differences in the absorbed dose to the bone marrow. Therefore, treatment planning strategies were developed to administer the highest activity possible to an individual patient whilst keeping the absorbed dose to the bone marrow below a threshold level. For example, Turner et al described a protocol under which patients received an initial administration of 740 MBq ^{153}Sm-EDTMP alongside an assessment of dosimetry to the bone marrow. A second administration was then given to bring the total absorbed dose to the bone marrow to 2 Gy [37].

An alternative approach is to administer higher activities in conjunction with stem cell support. Anderson et al administered up to 1.1 GBq of ^{153}Sm EDTMP to patients with either bone metastases or osteosarcoma followed by stem cell support 14 days later [38]. At this level of activity absorbed doses to metastases ranged from 21 to 241 Gy, notably higher than the absorbed doses reported by Van Rensburg et al.

Radium-223 (^{223}Ra)

More recently, the use of beta emitting radionuclides in this field has declined [39], due to the development of ^{223}Ra as a treatment for castrate resistant prostate cancer. Radium is a calcium mimetic which targets osteoblastic cells. ^{223}Ra is an alpha particle emitter with a half-life of 11 days. The standard administration protocol is 6 cycles of 55 kBq/kg at intervals of six weeks. The Phase III double blinded randomised controlled ALSYMPCA study compared ^{223}Ra against placebo [40]. As well as a reduced time to symptomatic skeletal events, patients receiving ^{223}Ra had a longer median survival by approximately 3 months.

Treatment with ^{223}Ra is reported to result in lower toxicity in comparison to treatment with beta emitting radionuclides [41, 42] [43, 44]. Monte Carlo simulations suggest that this may be due to the much shorter path length of alpha particles. ^{223}Ra accumulates at the endosteal layer but the alpha particle path length is significantly lower than the dimension of the bone marrow cavities [45]. Therefore a significant fraction of the bone marrow is spared from irradiation. However, a recent meta-analysis of randomised controlled trials involving radionuclides concluded that there was no significant difference in haematological effects between ^{223}Ra and beta emitting radionuclides, although it did confirm the advantage of ^{223}Ra with respect to overall survival and time to symptomatic skeletal events [46].

Gamma camera imaging has been used to perform dosimetry studies of ^{223}Ra in patients [47, 48]. Figure 1 shows an example of the ^{223}Ra biodistribution compared to the corresponding ^{99m}Tc-MDP bone scan [49]. As with beta emitting radionuclides, there is a wide range in the absorbed doses delivered to metastatic lesions. Murray et al reported absorbed doses ranging from 0.6 Gy to 44 Gy following administration of 110 kBq/kg [49]. Of note, these values did not include application of a relative biological effectiveness (RBE) factor to account for the more damaging effects of alpha particles. Absorbed doses of a similar range and magnitude were also reported by Pacilio et al [50]. Murray et al also demonstrated a dose-response relationship between the absorbed lesion dose and functional changes in the lesion measured with Na^{18}F PET. The precise magnitude of the RBE that should be applied to the deterministic effects of alpha particles is uncertain. A value of 5 is commonly cited [51, 52] and this is close to specific values of 5.4-5.6 reported for Ra-223 [53].

Early trials demonstrated an increased response rate at higher administered activities [54]. Patients receiving 100 kBq/kg were more likely to respond to treatment than patients receiving lower activities of 5 kBq/kg, 25 kBq/kg or 50 kBq/kg. Conversely a recent study comparing six cycles of 55 kBq/kg vs 88 kBq/kg did not demonstrate any advantage in the cohort receiving the higher activity [55]. When considering such results, it should be noted that the range of reported doses in the literature is many times greater than the relative increase in activity. Therefore it cannot be assumed that patients treated with 1.6 times more activity received systematically higher absorbed doses to their metastases.

Combination therapies

In routine practice, radionuclides have been administered as monotherapies. However, there have been studies of radionuclides in combination with other therapies, particularly for prostate cancer. An early study found the addition of ^{89}Sr to doxorubicin chemotherapy extended overall survival by 11 months [56]. This encouraging result led to furthers studies of beta emitting bone agents in combination with chemotherapy. Docetaxel is a form of chemotherapy that has been shown to prolong survival in castrate resistant prostate cancer patients as well as reduce pain and improve quality of life [57]. A Phase I study of ^{89}Sr in combination with docetaxel concluded that both both agents coud safely be administered concomitantly [58]. Fizazi et al carried out a single arm Phase II study of ^{153}Sm-EDTMP in combination with docetaxel [59]. The authors reported that the treatment was well tolerated and suggested improved overall survival compared to reference data.

The bisphosphonate Zoledronic acid induces apoptosis of osteoclasts and reduces the risk of skeletal related events. A small number of studies have been carried out showing a synergistic effect of combing zoledronic acid with ^{89}Sr [60-63]. It has been hypothesised that this may in part be due to alteration of the ^{89}Sr kinetics leading to increased retention. Use of zoledronic acid in combination with ^{223}Ra has also been proposed to reduce the risk of symptomatic skeletal events [64]. Denusomab is a monoclonal antibody treatment which also inhibits osteoclastic activity. As well as reducing the risk of symptomatic skeletal events, review of an open label single arm study suggested that the combination of denusomab with ^{223}Ra was more effective than ^{223}Ra alone [65].

The same study also suggested an advantage in combing ^{223}Ra with abiraterone, a hormonal agent shown to be effective as a monotherapy in its own right [66]. However, the prospective ERA-223 study demonstrated an increased risk of bone fracture and reduced overall survival when ^{223}Ra was combined with abiraterone plus prednisolone/prednisone compared to abiraterone plus prednisolone/prednisone only [67].

Nonetheless, interest in this field continues with clinical trials underway investigating the combination of Ra-223 with other hormone therapies such as enzalutamide (NCT02194842, NCT02225704) or different approaches such as immunotherapy (NCT02463799).

PSMA

^{89}Sr, ^{153}Sm-EDTMP and ^{223}Ra all target osteoblastic bone cells rather than the metastatic cancer cells themselves. An alternative strategy is to target the cancer cells themselves allowing the delivery of targeted radiation to both bony and extraosseous disease. Prostate Specific Membrane Antigen (PSMA) is a transmembrane protein expressed at high levels by prostate cancer cells. A number of agents which target PSMA with high affinity have been developed as treatments for metastatic prostate cancer. Of these, ^{177}Lu-PSMA-617 is the most advanced in terms of clinical trials. ^{177}Lu is a beta emitting radionuclide with a 6.65 day half-life and also emits gamma photons thus allowing imaging.

Initial experience of the safety and efficacy of ^{177}Lu-PSMA-617 was gained through compassionate use under the German Medicinal Product Act [68-70]. These studies were followed by an Australian prospective Phase II, open-label, single arm study of 30 patients [71]. Patients received up to four cycles of ^{177}Lu-PSMA-617 (with an average activity of 7.5 GBq per cycle). A PSA decline of 50% or more was observed in 57% of patients. An objective radiological response was achieved in 87% of patients with measureable soft tissue disease as well as reductions in bone pain scores for all patients. This study also benefited from dosimetry measurements in all patients [72].The mean absorbed doses to the kidneys, salivary glands, liver, spleen and bone marrow were 0.44, 0.58, 0.1, 0.06 and 0.11 Gy/GBq respectively. In bone metastases, absorbed doses ranged from 3.4 Gy to 73.9 Gy, whilst the absorbed dose to nodes ranged from 4.4 Gy to 92.5 Gy. ^{177}Lu-PSMA-617 has been under evaluation in a Phase III setting – the VISION study (NCT 03511664) compares patients treated with standard of care vs standard of care plus ^{177}Lu-PSMA-617.

PSMA-617 has also been labelled with ^{225}Ac, an alpha emitting radionuclide with a half-life of 9.9 days. Initial studies suggest an even greater efficacy than ^{177}Lu-PSMA-617. For example in a study of 17 patients treated with an initial activity of 8 MBq followed by successively lower activities in the case of good response, a fall of PSA >90% was observed in 14 patients. All patients experienced grade 1-2 xerostomia. This is in line with initial salivary gland dosimetry estimates of 2.5 Sv/MBq for ^{225}Ac-PSMA-617 derived from ^{177}Lu-PSMA-617 biodistribution data [73].

Conclusions

Overall the use of radionuclides to treat bone metastases has been a story of steady progress. Well planned clinical trials have conclusively demonstrated the beneficial effect of internal radiation in providing palliative treatment. Efforts to improve response rates and optimise the potential of beta-emitting radionuclides by increasing the radiation dose to the disease have been well documented. In addition, studies suggest that combining these agents with complementary therapies may result in synergistic effects. The greatest improvements in patient outcomes have been seen with the development of the alpha particle emitter, ^{223}Ra which has largely replaced the use of beta emitters for treating prostate cancer patients. Nevertheless, ^{223}Ra may be superseded itself in the near future depending on the outcome of clinical trials investigating both beta and alpha emitting PSMA targeted therapies.

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Tables

Radionuclide	$T_{1/2}$ [days]	E_β [MeV] (%)	$E\alpha$ [MeV] (%)	$E\gamma$ [keV] (%)
^{32}P	14.3	0.695 (100%)	-	-
^{89}Sr	50.5	0.58 (100%)	-	-
^{153}Sm	1.9	0.200 (32.2%) 0.226 (49.6%) 0.265 (17.5%)	-	103 (29.8%)
^{186}Re	3.7	0.306 (21.5%) 0.359 (71.0%)	-	137.2 (9.4%)
^{188}Re	0.71	0.728 (25.6%) 0.795 (71.1%)	-	155.0 (15.1%)
^{177}Lu	6.73	0.048 (12.0%) 0.112 (9.1%) 0.149 (78.6%)	-	112.9 (6.4%) 208.4 (11.0%)
^{223}Ra	11.4	-	5.6 (25.7%) 5.7 (52.6%)	83.8 (24.9%) 94.9 (11.3%) 269.5 (13.7%)
^{225}Ac	10.0		5.8 (18.1%) 5.8 (50.7%)	-

Table 1: Physical decay properties of radionuclides used in the treatment of bone metastases. The physical half-life (T1/2), mean beta particle energy and percentage abundance (E_β), mean alpha particle energy and percentage abundance (E_α) and the energy of gamma photons (E_γ) relevant to imaging are shown.

Figures

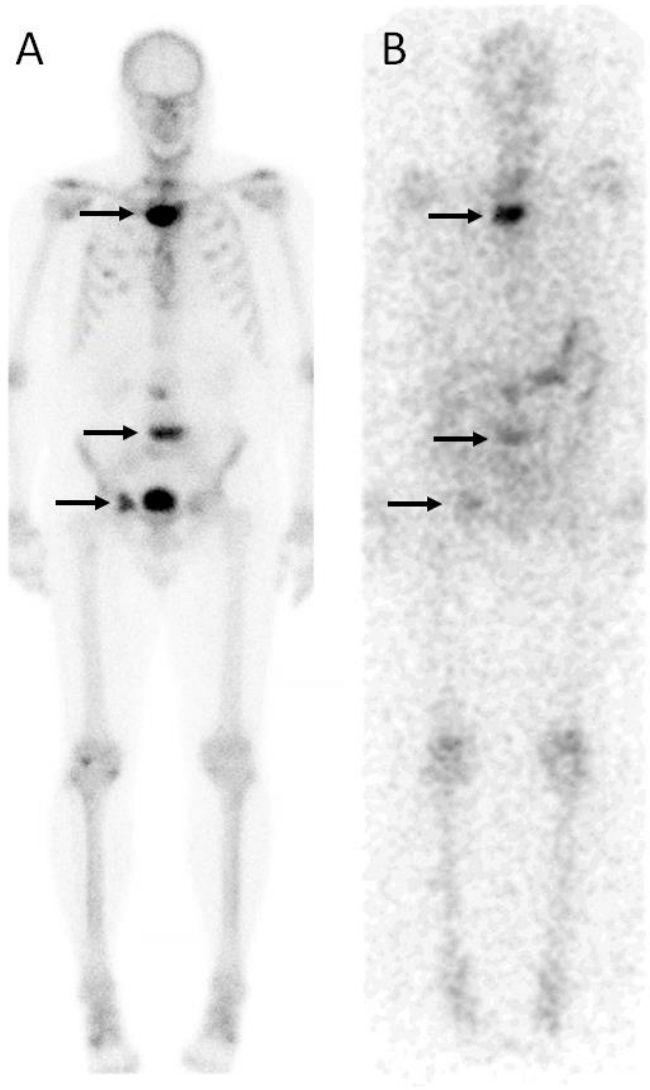

Figure 1: Anterior gamma camera images of ^{99m}Tc-MDP distribution (A) and ^{223}Ra distribution (B). Corresponding sites of increased uptake are indicated. Note the excretion of ^{223}Ra via the intestines. [49]