Can response to palliative treatment with radiopharmaceuticals be further enhanced?

Abstract

Bone-seeking radiopharmaceuticals (RF) are an effective systemic pain-palliative treatment schedule in patients with disseminated bone disease. This treatment relies on selective uptake and prolonged retention of RF at sites of increased osteoblastic activity, while the potential toxicity of systemic administration is reduced by relatively selective tumour targeting. The main theoretic advantage of bone-targeted radionuclide treatment is that radiation can be delivered selectively to subclinical tumours and to metastases that are too small to be imaged and treated by surgical excision or local external beam radiotherapy. The distribution of radiation dose throughout a tumour is heterogeneous, whilst the rate of response depends upon the pre-treatment condition of the patient and other factors. To enhance the effect of treatment with RF on cancer cells, the following strategies have been investigated: Individualisation of the administered dose, higher-doses, earlier or repeated radionuclide treatment, the use of new RF, and the use of a mixture of different RF. Furthermore, external beam radiotherapy, biphosphonates or chemotherapeutic agents have been combined with RF and have scored significantly better treatment results referring to pain relief, bone disease progression, etc, without important side effects. The role of bone seeking RF can be extended beyond bone pain palliation, to a synergistic anti-tumour effect.

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Introduction

Targeted radiotherapy using bone-seeking RF could be traced back to early 1940s [1] and since then, has proved to be an effective systemic pain-palliative treatment in patients with disseminated bone metastases [2, 3]. Acting systemically, bone-seeking RF are well suited to the management of disseminated skeletal disease, relying on selective uptake and prolonged retention at sites of increased osteoblastic activity, while the potential toxicity of systemic administration is reduced by relatively selective tumour targeting [4]. Current experience has focused largely on beta-particle emitting radionuclides, such as strontium-89 chloride (^{89}Sr), rhenium-186 hydroxyethylidene diphosphonate (^{186}Re-HEDP), or more recently, rhenium-188 (^{188}Re-HEDP) and samarium-153 ethylene diamine tetramethylene phosphate (^{153}Sm-EDTMP) [5].

For many years, the practice of radionuclide treatment has been a monotherapy. Now various groups of investigators combine these RF with other cancer treatment modalities to achieve better therapeutic response [6], especially in trials referring to phase II and III of the disease [7].

To enhance the effect of radionuclide treatment on cancer cells, the following new strategies have recently been investigated: Patient-specific dosing, earlier radionuclide treatment intervention for patients with longer life expectancies and with less extensive skeletal involvement, higher-dose radionuclide treatments, repeated-dose protocols, use of newer RF with higher dose rates, combinations of different radionuclides and combined regimens of radionuclides and other treatment options, such as external beam radiotherapy, biphosphonates or various chemotherapeutic agents. With emphasis to prostate cancer (PC), the prospects of these options for the treatment of bone metastases will be discussed herein, after a brief report on pre-treatment variables that correlate with response to this kind of treatment.

Pre-treatment variables that relate to response of radionuclide treatment

When using bone-seeking RF for metastatic bone pain, pain relief will occur in a high percentage of patients, but unfortunately, a significant number of patients achieve incomplete

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pain resolution, and some patients obtain no pain relief at all. The rate of response may depend upon the pre-treatment condition of the patient, the aetiology of bone metastases, differences in the populations treated, extent of the disease and previous local or systemic treatment regimens [8]. The main theoretic advantage of targeted radionuclide treatment is that radiation can be delivered selectively to subclinical tumours and metastases that are too small to be imaged or treated by surgical excision or local external beam radiotherapy. For this sort of treatment, the absorbed radiation dose is due to the flux of ionizing particles produced by radionuclides distributed within or around the tumour [9]. The dissociation of pain relief and anti-tumour activity may be a result of an inhibitory effect of the radionuclide on the release of local mediators such as prostaglandins or growth factors or to a direct toxic effect on bone osteoclasts [10].

The distribution of radiation dose throughout a tumour depends on the biologic properties of the tumour, tumour size, the radionuclide in use and some tumour-specific factors such as the affinity of targeting molecules for the tumour cells and the extent and permeability of the tumour vasculature. In terms of physics and radiobiology, there could be also differences in response to beta-emitting RF because of the dramatically different dose rates; the range of beta-emitters is likely to be too long for efficient energy deposition within single cells. A longer mean path of the beta-particle in the marrow might yield a greater tumoricidal effect, but also perhaps greater myelosuppression. It is also important that the physical half-life of the radionuclide used matches the biologic turnover of the RF in vivo. There are several other variables that could affect tumour dose from these RF [11]: a) Intensity of uptake by the reactive bone can vary dramatically, since abnormal to normal bone ratios range from 3:1 to 15:1. b) Widespread uptake from diffuse osseous metastases would result in fewer radioactive atoms per volume of tumour. c) The greater the osteoblastic trabecular volume, the greater the deposition of these therapeutic agents, with a resultant increase in tumour dose. d) The thicker the trabeculae in a marked osteoblastic lesion, the more beta particles are locally absorbed, with a resultant reduction in tumour dose, and e) Reduced renal function will increase body and lesion dose, because all palliative RF are significantly excreted through the kidneys. This complex abovementioned situation results in a heterogeneous distribution of the radiation dose.

Patient-specific dose

An alternative to traditional fixed activity administration is to prescribe an activity based on an individualized whole-body dose, which has been shown to be safe and effective. The activity retained by the metastases is only a small fraction of the whole-body activity considering its uptake in the soft tissue and in the normal bone. because of the low bone turnover, bone uptake of the radionuclide increases with time [12] Preliminary studies suggest that the uptake of a radionuclide in every metastasis corrected for total bone area and measured on the planar scan is independent of the number of metastases [13, 14]. It may, however, be more appropriate to adjust the administered activity of the RF to patient-based factors, including body mass, renal function (GFR) and tumour bulk. By individualizing the administered activity and by combining different therapeutic regimes we can achieve a better clinical result [15].

Early treatment

As expected, early treatment is related to a better therapeutic result. Many studies have reported that the number of bone metastases AS evaluated by bone scintiscans was a significant indicator of prognosis and the overall survival [16-21]. For instance, patients with pc and one or two bone metastases had a significantly longer progression-free interval and total survival time than patients with three or more metastases [17, 22]. Various staging systems based either on the total number of lesions identified by bone scintigraphy [16], on the distribution of bone metastases (axial versus appendicular) [23], or on the presence of bone metastases outside the pelvis and lumbar spine [24], showed a significant association with survival. A different system is based on grouping according to a range of bone scan index (BSI) values. The latter is coming from a subjective interpretation of the bone scan image, in which each bone involved is assigned to constitute a given fraction of the skeleton; by summing the fractional contribution of each bone, one arrives at the total percentage for the involved skeleton. Patients with low BSI had the longest survival and vice versa [25]. Beta emitting RF would be more effective in cases with a low BSI, when the tumour is confined to a thin layer of tissue close to the bone [26, 27] and also at an early stage of the disease [28, 29]. The introduction of RF earlier in the therapeutic time line may delay repetition of treatment and the development of new painful sites [30, 31]. It has been shown that early ^{89}Sr treatment delayed the development of bone pain in pre-existing but clinically silent metastases [32]. Since 30% of patients with localised PC and normal bone scan will eventually show bone metastases, it is important to treat these patients earlier, even when bone metastases are small or undetectable by common imaging modalities [22, 33, 34], especially in patients with longer life expectancies [35].

Repeated treatment

Some investigators have also noted objective survival benefit if radionuclides are used in a repeated dosing schedule [36, 37].

On current evidence, single-administration high-activity treatment is unlikely to deliver a sustained response within acceptable toxicity limits; fractionated treatment may be more realistic [35]. Under this assumption, repeated doses could lead to an «onion-peeling» effect of larger metastatic lesions [8, 38]. It would therefore appear that this kind of treatment has the ability to reduce metastatic burden [15]. Repetitive treatments with ^{186}Re-HEDP have been used in several studies, in order to prolong the duration of response, and there has been general agreement that further pain relief

may be expected if the patient has responded previously to treatment with this RF [8]. Good results were also observed in patients receiving up to five doses of ^{89}Sr with increasing pain relief periods [39, 40]. In another series with ^{153}Sm-EDTMP, patients who received two doses of the RF had better pain relief and longer survival than those receiving a single dose [36]. Objective tumour response as evaluated by reduced serum PSA levels was indicated in 64% of hormone refractory prostate cancer (HRPC) patients treated with repeated low-dose ^{153}Sm-EDTMP treatments [41], along with a reduction in the number and volume of bone lesions after repeated standard-dose treatments [42].

Myelotoxicity is cumulative in patients receiving repeated radionuclide treatments for recurrent symptoms, but this toxicity is weighed against the good therapeutic effect [43]. Intolerable toxicity was not observed after repeated injections of ^{186}Re-HEDP provided that a) the interval between ^{186}Re-HEDP injection and chemotherapy was at least 3 months [8], b) baseline counts were not very low and not declining rapidly, and c) the time interval from previous radionuclide treatment was sufficient to permit bone marrow recovery [44].

Nonetheless, many authors argue that results of re-treatments are less favourable than those after the first radionuclide treatment, probably because candidates for re-treatments are usually at a more advanced disease stage, have more compromised clinical condition and shorter life expectancy [30, 44].

Administering much higher doses

Another approach for making radionuclide treatment for bone metastases more effective is the application of high-doses necessitating bone marrow support. Doses of ^{153}Sm-EDTMP of 37-1110MBq/kg body weight were administered by others in 30 patients with locally recurrent or metastatic osteosarcoma with skeletal metastases [45]. These patients received peripheral-blood progenitor cell (PBPC) or bone marrow support. The authors found that marrow radiation doses and the grade of cytopenia corresponded linearly to the injected amount of ^{153}Sm-EDTMP. After PBPC or marrow infusion on day 14 after ^{153}Sm-EDTMP injection, recovery of haematopoiesis was problematic in two patients who had received 1110MBq/kg body weight and less than $2x10^6$ CD34/kg of marrow infusion. However, in the remaining patients, no complications were observed. A reduction or elimination of the administration of opiates was noticed in all these patients, and there was no appetite loss or important side effects. The authors concluded that high-dose irradiation (39–241Gy) by bone-targeted treatment with ^{153}Sm-EDTMP is feasible, and that non-haematological side-effects are minimal [45]. It is reminded that the standard dose of ^{153}Sm-EDTMP for pain palliation is 37MBq/kg body weight.

More recent radiopharmaceuticals

The strategy of using new RF with higher dose rates has also shown promising results. Rhenium-188-hydroxyethylidene diphosphonate (^{188}Re-HEDP) is a beta-emitting RF that has been previously investigated for pain palliation of bone metastases. The application of ^{188}Re-HEDP in humans is safe, and pain palliation can be achieved in about 70% of the patients [46]. Further evidence of the disease-modifying potential of this new RF was suggested in a randomized study regarding patients with progressive HRPC and bone pain, who received either a single injection of ^{188}Re-HEDP or a second injection 8 weeks later. The group receiving two injections of the RF had statistically significant improvement in pain palliation and the duration of pain control. There was also an improvement in median survival for patients receiving two treatments: 12.7 versus 7 months, P=0.043 [37]. One advantage of a short-living radionuclide such as ^{188}Re-HEDP is that it can deliver a high dose rate, meaning a high radiation dose within a relatively short time. Moreover, the high electron energy (2.1MeV) of ^{188}Re would lead to cytotoxic effects in the outer layers of the tumour. By repeating treatment with ^{188}Re-HEDP within an a short interval, tumour re-growth could be avoided because the deeper tumour cell layers are eradicated («onion-peeling effect») [8, 38]. Interestingly, the toxicity of this second dose treatment regimen was not increased in comparison with the single-injection protocol [47]. Physical data of ^{188}Re and of other radionuclides applied for pain palliation treatment with RF are summarized in Table 1.

Cocktails of radiopharmaceuticals

The physical characteristics of radionuclides are important determinants of their therapeutic effect. Cure probability is

Table 1. *Physical data of radionuclides applied for pain palliation from bone metastases(5)*

RF	$T_{1/2}$ (days)	Max. E_{beta} (MeV)	Mean E_{beta} (MeV)	Max. range (mm)	Min. range (mm)	E_{gamma} MeV (% abundance)
^{32}P-phosphate	14.3	1.71	0.70	7.9	3.0	–
^{89}Sr-chloride	50.5	1.46	0.58	7.0	2.4	0.909 (0.10%)
^{186}Re-HEDP	3.8	1.07	0.33	4.5	1.1	0.137 (9%)
^{188}Re-HEDP	0.7	2.12	0.73	11.0	2.7	0.155 (10%)
^{153}Sm-EDTMP	1.9	0.81	0.23	2.5	0.6	0.103 (28%)
^{117m}Sn-DTPA	13.6	0.127*, 0.152*	–	0.27	0.2	0.159 (86%)

*Conversion electrons

higher for tumours whose diameter is close to an optimum value, which depends on the path length of the emitted beta-particle of each radionuclide. With a mathematic modelling approach, it was found that there is an optimal tumour size for curability for each of 22 beta-emitting radionuclides of possible therapeutic potential [48]. Very small tumours are less curable because of inefficient absorption of radiation energy. This is a feature of targeted radiotherapy using long-range beta emitters and does not occur with external beam irradiation. Larger tumours are less curable because of having greater cells number. It is thus suggested that single agent targeted radiotherapy should not be used for the treatment of disseminated malignancy when multiple tumours of differing size, including micro-metastases, may be present [48]. The use of several radionuclides concurrently, applied as "cocktails" to which such microscopic tumours are more vulnerable would be more effective than relying on a single radionuclide [48, 49].

The shorter-range alpha-emitting and the ultra-short range Auger electron-emitting radionuclides have a gradient of energy deposition, with most of the radiochemical damage occurring within a few cubic nanometers [50] and consequently they have the potential to provide a more favourable therapeutic index than beta-emitters [51]. Thus, it is possible to extend the range of optimal curability.

Adjuvant to external-beam radiation treatment

Several study protocols have used radionuclides as an adjuvant to external-beam radiation treatment. Exposure to high-dose-rate external-beam irradiation might be expected to alter the uptake of bone-seeking RF at the irradiated site, depending on the precise sequence of treatment delivery. A randomized, placebo-controlled, phase III study investigated the efficacy of ^{89}Sr treatment as an adjunct to external radiation treatment in 126 PC patients with multiple osseous metastases, progressive disease, and a significant pain syndrome [52]. All were irradiated by external beam treatment, and were additionally given either placebo or ^{89}Sr. Three months after radiation treatment, the rate of new osseous metastases was 66% in the placebo and 41% in the ^{89}Sr group. Also, more patients in the ^{89}Sr group demonstrated a reduction in pain within the first 4 months after treatment. This tumoricidal effect was confirmed by laboratory testing of PSA and alkaline phosphatase. These results were confirmed by another study [31] regarding 284 PC patients with bone metastases. One patients' group received either local radiation treatment or hemi-body irradiation depending on the site and extent of metastases. The other group received a single-injection treatment of ^{89}Sr. Comparing both groups, it was observed that pain reduction was equivalent; however, new pain foci were significantly less frequent in the ^{89}Sr group, when compared to hemi-body irradiation cohort. Both cited studies give evidence that radionuclide treatment with ^{89}Sr in PC patients, is pain palliative, has also a better tumoricidal effect and is ideally combined with external radiotherapy. In the cited studies, no prolongation of the overall survival was shown for ^{89}Sr. Conversely, in another double-blind randomised study, the addition of ^{89}Sr to palliative external radiotherapy for painful bone metastases from PC and breast cancer did not seem to reduce the number of patients with subjective progression at 3 months [53]. Today, the timing of isotope administration in relation to external-beam radiation treatment has not been standardized and the potential of response enhancement is still under investigation [35].

Radiolabelled phosphonates combined with biphosphonates

Available treatment options worthy of consideration in cancer patients include the administration of biphosphonates. Many studies have reported the feasibility, safety [54-56] and additive benefits [57-61] of the combined use of biphosphonates with radiolabelled phosphonates. Combining biphosphonates with ^{186}Re-HEDP [57], ^{188}Re-HEDP [58], ^{89}Sr-chloride [59], or ^{153}Sm-EDTMP [60, 61] has been an effective analgesic treatment, in patients with bone metastases including, but not limited to, HRPC. Yet, combining ^{153}Sm-EDTMP and the biphosphonate zoledronic acid had no effect on the uptake of ^{153}Sm-EDTMP in skeletal metastases [60]; this observation presumably stands for all radiolabelled phosphonates combined with zoledronic acid. On the other hand, in an interesting recent review [62], it was argued that these treatments offer significant benefit in only some aspects of the disease to be weighed against their associated toxicities.

Radiolabelled phosphonates combined with chemotherapy

Important efforts have recently been made to combine RF and chemotherapy in patients with painful metastases, mostly from advanced PC. Current evidence states that combining weekly, chemo/hormonal treatments with ^{89}Sr offers a prolonged progression-free period and overall survival with acceptable toxicity [63, 64]. In particular, the combination of ^{89}Sr and doxorubicin has been reported to improve the time to disease progression as well as overall survival [65]. In the latter trial, patients with a favourable response to induction chemotherapy were subsequently randomised to receive consolidation treatment with ^{89}Sr plus doxorubicin or doxorubicin only [65]. The patients who received ^{89}Sr plus doxorubicin had a significantly longer overall survival and pronounced PSA response compared to those who received doxorubicine only. Another study of 34 PC patients who received combined chemotherapy with doxorubicin and a single ^{89}Sr injection and subsequently received six weekly additional doses of chemotherapy only, showed that within the first 6 months of receiving ^{89}Sr no patient developed bone marrow failure [66]. The authors stated that chemotherapy combined with a single dose of ^{89}Sr did not affect the tolerance of subsequent courses of chemotherapy in a selected patients' group.

Good pain palliation and an improvement in haemoglobin, tumour markers, and bone scans were also observed in some patients with HRPC, who received a combination of 148MBq of ^{89}Sr and low-dose cisplatin infusion (35mg/m^2) [67]. In another, single institutional phase III clinical trial, including patients with metastatic HRPC, patients were randomised to receive either ^{89}Sr plus low-dose cisplatin (50mg/m^2), or ^{89}Sr plus placebo. The combination of ^{89}Sr and low-dose cisplatin scored significantly better in the evaluated aspects, such as overall pain relief, new painful bone sites, survival without new painful sites, bone disease progression and overall survival. No significant differences were found between the groups with respect to haematological toxicity [68].

In another multicenter study of HRPC patients chemotherapeutic combinations of estramustine in doses of 600mg/m^2 daily in weeks 1-4 and 7-10 and vinblastine in doses of 4mg/m^2 intravenously each week in weeks 1-4 and 7-10, combined with ^{89}Sr, 2.2MBq/kg body weight, equalling to 148MBq for a 70-kg individual were also investigated [69]. Courses were repeated every 12 weeks, meaning that repeated doses of ^{89}Sr were also applied. The authors assessed response based on a change in serum PSA level. A greater than or equal to 50% decline of PSA for at least 6 weeks was observed in 48% of the patients, with a mean duration of response of 23 weeks. Hematologic toxicity was within the expected range. This study is interesting because it shows that the addition of ^{89}Sr to chemotherapy and its repeated administration is safe, effective and has a tumoricidal effect on the PC cells.

The combination of ^{89}Sr with a further cytotoxic agent, gemcitabine was assessed in a small group of selected HRPC patients in phase II of the disease, with painful osteoblastic bone metastases and stable or responding disease [70]. It was concluded that, as 800 mg/m^2 of gemcitabine was the maximum tolerated dose for combination with ^{89}Sr, an overall response rate of more than 10% was unlikely to occur and thus the study was terminated.

Apart from the major experience regarding ^{89}Sr-chloride, there are only scanty preliminary, data on the combination of ^{153}Sm-EDTMP with chemotherapeutic agents, primarily aimed at optimizing the time of co-administration of the two agents [71]. Currently, combined treatment of ^{153}Sm-EDTMP and docetaxel for HRPC demonstrated feasibility and some therapeutic potential [72, 73]. Other similar studies are in progress regarding patients with multiple myeloma [74, 75], osteosarcoma [76] and leukaemia [77]. In these malignancies combined radionuclide treatment with chemotherapy given within a relatively short interval increased significantly median survival and showed an objective tumour response. There are virtually no studies regarding the rest beta-emitting RF.

The results obtained in these retrospective studies show that treatment with bone-seeking RF given in combination with chemotherapy yields objective benefits in HRPC patients and thus warrant further investigations to optimize the dose and the relative schedule [6, 47].

A synergistic effect probably exists between the cytotoxic activity of chemotherapy on tumour cells and the additional modulating effects of radionuclide treatment on the epithelial and/or stromal components of bone metastases. The above data also show that bone marrow failure, even after simultaneously applied chemotherapy and radionuclide treatment, is unlikely. However, for patients who have received chemotherapy, it is necessary to consider that bone marrow reserves are limited and to reduce the dose of the radionuclide. Alternatively, the administration of a reduced dosage protocol for chemotherapy would mean that side-effects could be kept on a stable level and efficiency would grow due to a higher tumoricidal effect of the combination treatment. Blood counts must be considered critical in such cases, and a certain time interval must be allowed before a new myelosuppressive treatment can be started.

Nuclear medicine departments should be able to meet the demands of the oncological community. At present, radionuclide treatment is certainly underutilized.

In conclusion, patient specific doses, early RF treatment, repeated RF treatment protocols, the use of high-activity doses, new RF, cocktails of RF, and combined protocols of RF with biphosphonates, external beam radiotherapy, or chemotherapy show promising results not only for pain relief but also for tumour control.

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