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Editorial

Radionuclide treatment of bone metastases – current concepts and trends

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Introduction

Painful bone metastases are an important problem in oncology and occur in 50–75% of patients with breast and prostate cancer [1, 2].

Radionuclide treatment was introduced in the early 1940s [3, 4], but this mode of treatment has been more widely implemented in the last two decades.

In recent years three trends could be seen in the development of radionuclide treatment of bone metastases:

— a re-consideration of clinical indications for this treatment: there is a shift from radionuclide palliation in patients with multiple, generalised and painful bone metastases towards an early application of this treatment in not very painful and not numerous metastases;

— a re-approach to the question of radiotoxicity, with particular emphasis on the question of myelotoxicity;

— an increasingly broader range of new radionuclides applied in this therapy, with a shift to short half-life and low-energy isotopes; however, also a return to radioactive phosphorus-32 in the treatment has recently been proposed.

Indications reconsidered

Early introduction of radionuclide treatment

Radionuclide treatment had been traditionally restricted to patients with breast and prostate cancer, with multiple bone metastases and severe pain. Today indications for radionuclide treatment apply also to patients with a small number of metastases with little or no pain. Therefore the expression "bone pain palliation" is increasingly more often being replaced by the term "treatment of bone metastases".

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Currently it is proposed that radionuclide therapy should be used at an earlier stage of metastatic disease, when the analgesic effect is more intense and durable [5, 6]. This form of treatment might be particularly beneficial in prostate cancer patients, as survival from the beginning of bone pain is relatively long — 38–69 months [7]. It is recommended either to apply complimentary external radiotherapy, or to repeat radionuclide treatment. This can lead to delaying opiate application and an improvement in ambulatory status and quality of life [5].

Moreover, the treatment of bone metastases is extended to types of carcinoma other than breast and prostate.

Bone strengthening/tumoricidal effect

The second trend in radionuclide treatment is to focus on the metastases localised in the places with a risk of pathologic fractures.

After radionuclide treatment a decrease in metabolic activity in a large portion of metastases is seen [8–10]. In post-treatment MRI studies, a major regression of bone metastases has been shown, with almost total regression of those up to 20 mm and with features of calcification in the bigger ones [9].

This is supported by in-vivo studies, where strontium-89, acting as a calcium mimic, is incorporated into newly synthesised bone matrix [11]. Other studies suggest weak tumoricidal effects of radionuclide therapy, both in clinical studies [6, 12] and animal models [13]. It may be hypothesised that both local tumoricidal effect and prevention of pathological fractures may have a positive impact on improving the clinical outcome and survival shown by some studies [12].

Therefore, not only analgesic effect but also fracture prevention seems to be a prospective aim of radionuclide therapy.

The myelotoxicity problem reconsidered

Bone marrow depression grade I and grade II occur in 15–88% of patients post radionuclide therapy, myelotoxicity of III and IV grade in 3–8% of patients [5, 14–18], depending on the radioisotope used. The nadir of blood parameters may be expected between the 3rd and 6th week after treatment, with subsequent improvement, in cases of more radiotoxic isotopes, extended to a few months.

Evaluating bone marrow side effects of particular radioisotopes, a Relative Advantage Factor (RAF), assuming the effect of the most toxic phosphorus-32 as 1.0, has been calculated for strontium — 89, rhenium — 186, samarium — 156, lutetium — 177, erbium — 169, tin — 117^m and phosphorus — 33 respectively as: 1.1, 1.5, 2.4, 3.2, 5.1, and 6.5 [19].

Repetitive radionuclide treatment does not increase myelotoxicity [20].

Is myelotoxicity life threatening? The myelotoxicity of therapeutic radionuclides is a fact to be remembered, the pre-treatment haematological parameters have to be carefully evaluated and in borderline cases the less myelotoxic therapeutic radioisotopes to be chosen. However, in the author's opinion this fact should not be exaggerated. The fears of myelotoxicity have been clearly pointed out by E.B. Silberstein [22], commenting on the paper by Sciuto et al. [6]: "to my knowledge the literature attributes only 1 death from thrombocytopenia to ^{32}P". No deaths due to bone marrow depression were reported after the use of the other radioisotopes. In practice, regarding the patient's outcome, none of the radioisotopes seems to be significantly more or less toxic than any other in any published comparative trial [22, 23].

In the author's own experience, out of about 170 patients treated in his department between 1999 and 2001, major bone marrow depression, but still not requiring in-patient care, occurred in 3 cases (unpublished data). Definitely, with prudent pre-treatment evaluation, radionuclide treatment is a relatively safe modality, safer than external sealed-sources therapy, particularly that of wide field of irradiation [24].

The choice of radioisotopes reconsidered

In the USA there is FDA approval for three radioisotopes for bone metastases therapy: phosphorus-32, samarium-153 and strontium-89. Phosphorus-32 can be omitted for its radiotoxicity, although some authors advocate its return [16, 18, 21]. The remaining two radioisotopes have both advantages and disadvantages.

Samarium-153 has a relatively fast analgesic effect, in about two weeks or less, its myelotoxicity is lower, repetitive therapy may be applied in a relatively shorter time, but the analgesic effect is shorter when compared with strontium-89.

Strontium-89 has a longer-lasting analgesic effect, sometimes even up to one year, but the start of this action is delayed, sometimes even up to one month or longer. Strontium-89 myelotoxicity is higher and repetitive therapy can be applied not earlier than 3–4 months. Also, because of higher myelosensitivity in younger patients, radiotherapy with strontium is applied rather in older patients.

Therefore:

— if the aim is a fast analgesic effect in patients with strong pain or if bone marrow shows depression due to previous radio- or chemotherapy or/and in younger patients, the agent of choice would be rather samarium-153;

— in older patients with lesser pain and with no myelodepression the choice would be either strontium-89 or combined therapy with induction with samarium-153 continued with strontium-89.

Phosphorus-32 treatment reconsidered?

It is proposed to return to bone metastases palliation with phosphorus-32 [16, 18, 21]. Phosphorus-32 has no good reputation, perhaps due to the cases of leukaemia induction after its application in the treatment of polycythemia. However, there are arguments that P-32 myelotoxicity is seriously exaggerated [22]. In the USA the costs of treatment with phosphorus-32 are roughly about 15% of the costs of treatment with strontium-89 or samarium-153 [21]. There are proposals to administer samarium-153 in early stages of disease, with prognosed longer life span, and phosphorus-32 in terminal patients. This argument may seem controversial, but at least it is worthy of consideration.

Table 1. Physical parameters of chosen therapeutic radioisotpes

Radioisotope	$T_{1/2}$* (days) **	Mean energy [keV]	Mean range in bone [mm]
Erbium-169	9.4	100	0.09
Lutetium-177	6.71	133	0.15
Phosphorus-32	14.3	695	1.7
Phosphorus-33	25.3	76	0.05
Samarium-153	1.9	225	0.32
Rhenium-186	3.8	323	0.64
Rhenium-188	0.7	220	0.11
Strontium-89	50.5	583	1.4
Tin-117^m	13.6	135	0.15

*physical half-life;
**physical half-lives and mean energies taken from (Bishayee, 2000)

Radioisotopes in trials — the future of radionuclide therapy

A further guideline in bone radionuclide therapy is a shift towards radionuclides with low-energetic radiation, therefore with a short range in tissues and short half-life, thus with little bone marrow toxicity [25–29]. For example for phosphorus-33 the absorbed dose in the bone marrow is 3–6-fold lower than for phosphorus-32 [29]. The characteristics of those radioisotopes as compared with phosphorus-32, strontium-89 and samarium-153 are given in Table 1.

Perhaps the solution for the next decade will be the generator-eluted radionuclides, such as rhenium-188; a radioisotope chemically similar to technetium-99^m and of a low production cost [30–32]. Rhenium-188, is an β-emitter with a half-life of 17 hours, obtained in the decay of wolframium-188, a radioisotope with a half-life of 69 days. Rhenium-188 is also applied in radioimmunotherapy and radionuclide brachytherapy. Rhenium-188 can be administered either as Re-188-HEDP [31], or Re-188-(V)DMSA — the latter agent targeting also medullary thyroid carcinoma and other soft tissue tumours [30].

Conclusions

Nuclear medicine is gradually shifting towards therapeutic applications. Systemic radionuclide bone metastases therapy is a relatively safe, successful and price-competitive modality when compared with external sealed sources therapy. Whereas traditional strontium-89 therapy remains a "golden standard" in therapy, it seems that several business-rivals are replacing or are about to replace this treatment modality.

Also, clinical indications for this kind of therapy are becoming broader, which, as a piece of good news, is increasing the understanding between nuclear medicine specialists and oncologists.

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