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GUIDELINES

EANM procedure guideline for treatment of refractory metastatic bone pain

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Abstract
Introduction Bone pain is a common symptom of metastatic disease in cancer, experienced with various intensities by about 30% of cancer patients, during the development of their disease, up to 60–90% in the latest phases.
Discussion In addition to other therapies, such as analgesics, bisphosphonates, chemotherapy, hormonal therapy and external beam radiotherapy, bone-seeking radiopharmaceuticals are also used for the palliation of pain from bone metastases. Substantial advantages of bone palliation radionuclide therapy include the ability to simultaneously treat multiple sites of disease with a more probable therapeutic effect in earlier phases of metastatic disease, the ease of administration, the repeatability and the potential integration with the other treatments.
Conclusion The Therapy, Oncology and Dosimetry Committees have worked together to revise the EANM guidelines on the use of bone-seeking radiopharmaceuticals. The purpose of this guideline is to assist the nuclear medicine physician in treating and managing patients undergoing such treatment.

Keywords Guidelines · Nuclear medicine · Bone palliation · ^{89}Sr · ^{153}Sm-lexidronam · ^{186}Re-etidronate

Purpose

The purpose of this guideline is to assist nuclear medicine practitioners in:

1. Evaluating patients who might be candidates for treatment to palliate refractory, metastatic bone pain using ^{89}Sr (approved in Europe for prostate cancer), ^{153}Sm-lexidronam (^{153}Sm-EDTMP; approved in Europe for

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osteoblastic metastases) or ^{186}Re-etidronate (^{186}Re-HEDP; approved in some European countries).
2. Providing information for performing these treatments.
3. Understanding and evaluating the consequences of therapy.

Background information and definitions

Bone pain is a common symptom of metastatic disease in cancer, experienced with various intensities by about 30% of cancer patients, during the development of their disease, up to 60–90% in the latest phases [1]. In addition to other therapies, such as analgesics, bisphosphonates, chemotherapy, hormonal therapy and external beam radiotherapy, bone-seeking radiopharmaceuticals are also used for the palliation of pain from bone metastases. Substantial advantages of bone palliation radionuclide therapy include the ability to simultaneously treat multiple sites of disease with a more probable therapeutic effect in earlier phases of metastatic disease, the ease of administration, the repeatability, and the potential integration with the other treatments.

Definitions

1. Metastatic bone pain in this context means bone pain arising from secondary skeletal malignancy.
2. Bone palliation means conventionally the treatment of metastatic bone pain resistant or intolerant to conventional treatments such as analgesics, bisphosphonates, anti-tumour therapy (chemotherapy or hormone manipulation) or arising from multiple sites not easily controlled by external beam radiotherapy or surgery.
3. Radionuclide therapy in this context means the intravenous administration of ^{89}Sr-chloride in aqueous solution, *or* ^{153}Sm-lexidronam (^{153}Sm-ethylene-diamine-tetramethylene-phosphonate [EDTMP]), *or* ^{186}Re-etidronate (^{186}Re-hyroxyethylidine-diphosphonate] [HEDP]).
4. Bone-seeking radiopharmaceuticals efficacy relies on their selective uptake and prolonged retention at sites of increased osteoblastic activity. The exact mechanism of action is not fully understood, but involves the reduction of cytokines and growth factors released by tumour and inflammatory cells at the interface between tumour and normal bone and radiation-induced mechanical factors, such as reduction of periosteal swelling [2].
5. Osteoblastic means focal increased skeletal metabolic activity, namely, sclerosis, caused by osseous reaction to bone metastases, as evidenced by increased activity on bone scintigraphy. Osteolytic means focal areas of bone destruction caused by the action of osteoclasts. A mixed pattern, however, is common in many lesions [3]. Bone-seeking radiopharmaceuticals may be also used for the treatment of primary and metastatic bone tumours, such as osteosarcoma, inducing an osteoblastic reaction.

Background

Bone-seeking radiopharmaceuticals are one of the therapeutic tools available for palliation of bone pain and should be used within a multidisciplinary approach to choose the best option for each patient in a correct sequence.

A careful patient selection should be performed before treatment with bone-seeking radiopharmaceuticals, which should be preferably administered early in the metastatic phase, to increase the rate of therapeutic responses. Haematological function at peripheral blood cell count, bone (marrow) involvement at pre-therapy bone scintigraphy, performance status, recent use of myelosuppressive therapies, and expectancy of life should be considered before indicating radionuclide therapy [4, 5].

1. ^{89}Sr emits a beta particle with a maximum energy of 1.46 MeV, mean energy of 0.58 MeV, average soft-tissue range of 2.4 mm and 0.01% abundant gamma emission with a 0.91-MeV photo peak. The physical half-life is 50.5 days [6].
2. ^{153}Sm emits a beta particle with a maximum energy of 0.81 MeV, mean energy of 0.23 MeV, average soft-tissue range of 0.6 mm and a 28% abundant gamma emission with a 0.103-MeV photo peak. The physical half-life is 1.9 days [7].
3. ^{186}Re emits a beta particle with a maximum energy of 1.07 MeV, mean energy of 0.349 MeV, average soft-tissue range of 1.1 mm and a 9% abundant gamma emission with a 0.137-MeV photo peak. The physical half-life is 3.7 days [8].

Indications

Intravenous injection of ^{89}Sr-chloride, ^{153}Sm-lexidronam or ^{186}Re-etidronate is used for the treatment of bone pain due to osteoblastic metastases or mixed osteoblastic lesions from prostate or breast carcinomas (established indications) or any other tumour presenting osteoblastic lesions seen as areas of intense uptake at bone scan.

Approval for the clinical use of radiopharmaceuticals may vary in different countries. The choice of the radiopharmaceutical is based on the physic characteristics of the radionuclide in relation to the extent of metastatic disease, the bone marrow reserve and the availability of the radiopharmaceutical in single countries [9].

Contraindications

Absolute Pregnancy; breastfeeding.

Relative Low blood cell count, within certain limits, may represent a relative contraindication to the use of bone-seeking radiopharmaceuticals for the possible myelotoxicity. Nevertheless, the precise lower limit is not well-defined in literature and the use of granulocyte CSFs may lower further the limit. Routinely, the following values can be considered [5, 7, 8, 10]:

1. Haemoglobin <90 gl^{-1},
2. Total white cell count $<3.5\times10^{9}$ l^{-1},
3. Platelet count $<100\times10^{9}$ l^{-1}.

In selected situations, however, lower values can be considered: values of WBC $\geq2.4\times10^{9}$ l^{-1} may be used; values of PLT, such as $\geq60\times10^{9}$ l^{-1}, can be considered, provided that chronic disseminated intravascular coagulation (DIC) can be excluded by means of coagulation tests.

The presence of bone marrow involvement does not represent per se a contraindication, provided that blood figures remain within the cited parameters and the extent of substitution does not trespass a threshold beyond which severe myelotoxicity is expected. Bone scintigraphy may help to describe the extent of bone marrow involvement. Usually a superscan appearance on bone scintigraphy corresponds to an important bone marrow involvement and this represents a contraindication, except for selected situation in which bone marrow figures are within limits.

Blood cell figures should be stable before undertaking bone palliation therapy. If there are any doubts to perform the therapy due to low blood cell counts, it might be worthwhile to repeat with a new blood sample within a short time frame to exclude a rapid deterioration in blood cell counts before the decision.

Poor renal function reduces the plasma clearance of bone-seeking radiopharmaceuticals, thus leading to a higher whole-body dose and risk of myelotoxicity. Therefore, patients with severely reduced renal function: creatinine >180 μmol/l and/or GFR <30 ml/min should be excluded.

The safety and toxicity of treatment in patients with renal insufficiency has not been thoroughly investigated. However, an increase of myelosuppressive toxicity is expected because of the impairment of renal excretion. It is, therefore, advised to lower the administered dose by 50% in patients with creatinine clearance <50 ml/min (according to the Cockroft and Gault formula for creatinine clearance in ml/min: $[(140-\text{age})\times\text{weight (kg)}\times C]/(\text{plasma creatinine}\times 0.814)$ in which C=1 if male, C=0.85 if female; plasma creatinine in μmol/l). In this case, ^{153}Sm-lexidronam and ^{186}Re-etidronate are the treatments of choice. Repeated treatment in the case of acceptable toxicity must be considered after 8 weeks [4, 11].

^{89}Sr, ^{153}Sm-lexidronam and ^{186}Re-etidronate have no place in the management of acute spinal cord compression or in treating pathological fractures. Metastases at risk of such complications should be appropriately evaluated on the basis of clinical and neurological symptoms, examination and, if necessary, radiology. In particularly selected cases, "chronic" spinal cord compression can be evaluated for radionuclide therapy, together with high-dose corticosteroid administration and a careful clinical observation [4, 12, 13].

Therapy with ^{89}Sr, ^{153}Sm-lexidronam or ^{186}Re-etidronate is inappropriate for patients with a life expectancy less than 4 weeks [5] and, considering the latency in the onset of the palliative effect, is more beneficial in patients with a relatively long life expectancy.

Procedure

Facility and personnel

The facilities required will depend on the national legislation for the emission of pure beta- or beta–gamma-emitting therapy agents. If in-patient treatment is required by national legislation, this should take place in an approved facility with appropriately shielded rooms and en-suite bathroom facilities.

The facility in which treatment is administered must have appropriate personnel, radiation safety equipment, procedures available for waste handling and disposal, handling of contamination, monitoring personnel for accidental contamination and controlling contamination spread [5].

The administration of ^{89}Sr, ^{153}Sm-lexidronam or ^{186}Re-etidronate should be undertaken by appropriately trained medical staff with supporting physics and nursing staff.

Physicians responsible for treating patients should have an understanding of the clinical pathophysiology and natural history of the disease processes, should be familiar with other forms of therapy and should be able to liaise closely with other physicians involved in managing the patient.

Clinicians involved in unsealed source therapy must be knowledgeable about and compliant with all applicable national and local legislation and regulations.

Patient preparation and data required

Patients considered for ^{89}Sr, ^{153}Sm-lexidronam or ^{186}Re-etidronate therapy will have pain that limits normal activities and/or is not easily controlled by regular analgesics. Patients

may have failed conventional analgesics, bisphosphonates and anti-tumour therapy (chemotherapy, hormone manipulation), but better candidates to bone-seeking radiopharmaceuticals, to obtain a better response, are those in earlier phases of bone metastatisation [4, 14].

Patients will have undergone recent (within 4 weeks or less) bone scintigraphy documenting increased osteoblastic activity at painful sites. Radiographs demonstrating osteosclerotic lesions are inadequate, as increased bone density does not always result in increased uptake on radionuclide imaging. Abnormalities on bone scintigraphy must be correlated with appropriate physical examination to exclude other causes of chronic pain, which would be unlikely to respond to treatment using bone-seeking radiopharmaceuticals. Neurogenic pain and pathological fractures should be specifically excluded.

Clinical practice and experimental studies demonstrated that treatment can be safely performed after local field external beam radiotherapy. The use of wide field (hemi-body) radiotherapy within 3 months of ^{89}Sr, ^{153}Sm-lexidronam or ^{186}Re-etidronate administration is likely to result in increased myelosuppression and is relatively contraindicated [15–17]. Except for experimental clinical trials exploring the anti-tumour potential of combined chemotherapy and bone-seeking radiopharmaceuticals, long-acting myelosuppressive chemotherapy should be discontinued at least 4 weeks *before* the administration of ^{89}Sr, ^{153}Sm-lexidronam or ^{186}Re-etidronate and withheld for 6–12 weeks post-therapy to avoid concomitant myelosuppression [4, 5].

A full haematological and biochemical profile should be obtained within 7 days of proposed treatment. Recommended reference levels are listed in Section Indications.

DIC may be a risk factor for severe thrombocytopenia post-therapy. Pre-treatment clotting studies to identify patients with subclinical DIC should be performed [18].

There are conflicting data as to whether bisphosphonates inhibit the uptake of radiolabelled phosphonates in bone metastases. This discussion is based on the hypothesis that as both drugs interact at the hydroxyapatite crystal surface of the skeleton, competition might exist for uptake by bone. At present, there is no evidence of competition between bisphosphonates and ^{153}Sm-lexidronam, ^{186}Re-etidronate or ^{89}Sr. Therefore, they may be used concomitantly [19, 20].

Patient Information and instruction

Patients should receive both written and verbal information about the procedure before receiving therapy. Informed written consent must be obtained from the patient, if required by local legislation.

Patients should be told that 60–80% of patients benefit from ^{89}Sr, ^{153}Sm-lexidronam or ^{186}Re-etidronate therapy.

Patients should be warned of the risk of temporary increase in bone pain (pain flare).

The patient should be told that pain reduction is unlikely within the first week, more probable in the second week and could occur as late as 4 weeks or longer after injection, particularly for long-lived isotopes. Patients should continue prescribed analgesics until bone pain decreases and receive advice regarding subsequent analgesic dose reduction where appropriate.

Patients should also be informed on the duration of the analgesic effect, generally of 2–6 months and that re-treatment is possible.

The patient should understand that ^{89}Sr, ^{153}Sm-lexidronam or ^{186}Re-etidronate are palliative treatments especially designed for treating bone pain and are unlikely to cure metastatic cancer [21].

Administration

^{89}Sr, ^{153}Sm-lexidronam and ^{186}Re-etidronate are supplied in solution to be used at room temperature. ^{89}Sr, ^{153}Sm-lexidronam and ^{186}Re-etidronate should be administered by slow infusion via an indwelling intravenous butterfly or cannula followed by 0.9% saline flush. Care should be taken to avoid extravasation of the radiopharmaceutical.

Recommended administered activities are as follows:

^{89}Sr=150 MBq,
^{153}Sm-lexidronam=37 MBq/kg,
^{186}Re-etidronate=1,295 MBq.

The use of bone-seeking radiopharmaceuticals is associated with improved pain control and decreased analgesic consumption. To evaluate the therapeutic effect, patients should be monitored by means of objective parameters, such as the visual analogue scale or quality of life assessment forms or the course of analgesic intake.

Important differences between the radiopharmaceuticals are physical half-life, energy of gamma emission and beta emission. These differences determine both the clinical benefit and the side effects. Although no clear difference in treatment response between ^{89}Sr, ^{153}Sm-lexidronam and ^{186}Re-etidronate was reported, differences in onset of response, duration of response and toxicity do exist. The onset of response is rapid after treatment with short-lived isotopes (i.e. ^{153}Sm-lexidronam and ^{186}Re-etidronate). After treatment with long-lived isotopes (^{89}Sr), the onset is prolonged for a few weeks. The duration of response, on the other hand, is longer for long-lived radioisotopes than for short-lived isotopes [4, 5, 9].

Patients with progressive disease and pain, for whom rapid relief is warranted, are best treated with short-lived isotopes. Relief will be quick and toxicity acceptable [4]. If needed, patients can be re-treated. Patients with a somewhat

better prognosis and better clinical condition may be treated with long-lived isotopes. The duration of response will be longer. However, care must be taken for myelosuppressive toxicity, as stated before.

In responding patients, in case of recurrent pain, re-treatment can be effective and safe, provided that haematological parameters are fully recovered, although the quality of response may decrease with treatments. The minimum should be of 8 weeks for ^{153}Sm-lexidronam, 6–8 weeks for ^{186}Re-etidronate or 12 weeks for ^{89}Sr [22, 23].

Starting from the observation of biochemical response reported on tumour and bone resorption markers, presently, multiple phase I/II studies are focussing on the tumouricidal effect of the combination of radiosensitising chemotherapeutic agents and bone-seeking radiopharmaceuticals [24, 25]. In this case, the different physical properties of each radiopharmaceutical will influence on the toxicity profile of the particular combination [5, 26, 27].

At the moment, signals from literature indicate that, despite the fact that a conclusive statement is not possible to date, the use of bone-seeking radiopharmaceuticals may improve survival especially when used in earlier phases of metastatic disease or in combination with chemotherapy or radiotherapy [26, 28–31].

Precautions, follow-up and side effects

The treating clinician must advise the patient on reducing unnecessary radiation exposure to family members and the public.

Following treatment, patients should thoroughly avoid pregnancy for at least 6 months after ^{153}Sm-lexidronam and ^{186}Re-etidronate, and even longer for ^{89}Sr. In reality, it is unlikely that women of childbearing age will be eligible for this therapy [32].

Patients should be appropriately hydrated before and after therapy. If the treatment is performed on an out-patient basis, patients should remain in the nuclear medicine facility for the first 4–6 h after administration.

Urinary radiopharmaceutical excretion is of particular concern during the first 2–3 days post-administration, particularly for ^{89}Sr. Urinary excretion of ^{186}Re-etidronate takes place mostly during the first 24 h after administration. For ^{153}Sm-lexidronam, it is nearly completed after the first 8–12 h after administration. Patients should be advised to observe rigorous hygiene to avoid contaminating groups at risk using the same toilet facility. Patients should be warned to avoid soiling underclothing or areas around toilet bowls for 1 week post-injection and that significantly soiled clothing should be washed separately. A double toilet flush is recommended after urination. Patients should wash their hands after urination. If contaminated with urine, patients should wash their hands abundantly with cold water without scrubbing [5].

Because urinary excretion of ^{153}Sm-lexidronam and ^{186}Re-etidronate is fast and takes place predominantly during the first 8–12 h after injection, special caution for urinary contamination should be taken during this first period.

Incontinent patients should be catheterised before radiopharmaceutical administration for radioprotection of relatives and/or caring personnel. The catheter should remain in place for an appropriate period of time (^{89}Sr=4 days, ^{186}Re-etidronate=2–3 days, ^{153}Sm-lexidronam=24 h). Catheter bags should be emptied frequently. Gloves should be worn by staff caring for catheterised patients.

If in-patient treatment is required, nursing personnel must be instructed in radiation safety. Any significant medical conditions should be noted and contingency plans made in case radiation precautions must be breached for a medical emergency. Concern about radiation exposure should not interfere with the prompt appropriate medical treatment of the patient.

Haematological toxicity is the main side effect of bone-seeking radiopharmaceuticals. Therefore, periodical haematological monitoring may be useful up to 6 weeks post-therapy (^{153}Sm-lexidronam, ^{186}Re-etidronate) to exclude significant myelosuppression in high-risk patients. After treatment with ^{89}Sr, longer follow-up is necessary because of prolonged myelosuppressive toxicity (12–16 weeks) [33].

Post-therapy scintigraphy, when feasible, may be of value to check tumour extent and radiopharmaceutical distribution and to perform dosimetry calculations.

Side effects

"Flare" phenomena: increase of pain symptoms, in about 10% of the patients, usually within 72 h, typically transient, usually mild and self-limiting and usually responding to standard analgesics. Generally, flare phenomena are associated with good clinical response [4, 5, 6, 9, 34].

When cervicodorsal spinal metastases are present, an increase rate of spinal cord compression is possible. Prophylactic corticosteroids may be considered according to local protocols.

A decrease of thrombocytes and leucocytes count in peripheral blood, as a result of myelosuppression, is frequently observed and has a nadir of 3–5 weeks (^{153}Sm-lexidronam, ^{186}Re-etidronate) or 12–16 weeks (^{89}Sr). The occurrence of grade 3 or 4 toxicity is dependent on previous (myelosuppressive) therapy and bone marrow disease. Haematological toxicity is usually temporary with complete or partial recover over the next 3 months. The rate of recovery depends on the administered activity and the bone marrow reserve.

Calcium-like flushing sensation, described with the use of ^{89}Sr, should not occur if the compound is infused slowly, as recommended.

Radiopharmaceutical

1. *Pharmaceutical name*: ^{89}Sr-strontium-chloride
   Labelling: The radiopharmaceutical is supplied in aqueous solution.
   Radiation dosimetry [35]:

Organ	mGy/MBq	rad/mCi
Bone surface	17	63
Red bone marrow	11.0	41
Lower bowel wall	4.7	17
Bladder wall	1.3	4.8
Testes	0.80	3.0
Ovaries	0.80	3.0
Uterine wall	0.80	3.0
Kidneys	0.80	3.0

2. *Pharmaceutical name*: ^{153}Sm-samarium-lexidronam (EDTMP)
   Labelling: The radiopharmaceutical is supplied in aqueous solution.
   Radiation dosimetry [36]:

Organ	mGy/MBq	rad/mCi
Bone surface	6.8	25
Red bone marrow	1.5	5.6
Lower bowel wall	0.010	0.037
Bladder wall	1.0	3.7
Testes	0.0050	0.019
Ovaries	0.0090	0.033
Kidneys	0.020	0.074

3. *Pharmaceutical name*: ^{186}Re-rhenium-etidronate (HEDP)
   Labelling: The radiopharmaceutical is supplied in aqueous solution.
   Radiation dosimetry [37]:

Organ	mGy/MBq	rad/mCi
Bone surface	1.4	5.19
Red bone marrow	1.3	4.95
Lower bowel wall	0.57	2.12
Bladder	0.54	1.98
Testes	0.008	0.03
Ovaries	0.019	0.07
Kidneys	1.5	5.6

Quality control

The amount of activity to be administered should be checked using an isotope calibrator [38].

Either of the following two methods can be used to measure the amount of ^{89}Sr to be administered:

1. Follow the "Guidelines for the Calibration of Metastron (Strontium-89-chloride injection)," available from Amersham Corporation (800/554-0157) or
2. Use a dose calibrator specially configured to quantify beta emissions.

Issues requiring further clarification

1. Beneficial effect of combined treatment, such as chemotherapy with bone-seeking radiopharmaceuticals, on the survival of patients.
2. Beneficial effects of bone-seeking radiopharmaceuticals in patients receiving bisphosphonates concomitantly.
3. Safety of bone-seeking radiopharmaceuticals in patients with extensive bone marrow substitution ("superscan" appearance at bone scintigraphy).

Disclaimer

The European Association of Nuclear Medicine has written and approved guidelines to promote the cost-effective use of high-quality nuclear medicine therapeutic procedures. These generic recommendations cannot be rigidly applied to all patients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures or exclusive of other procedures reasonably directed to obtaining the same results. Advances in medicine occur at a rapid rate. The date of a guideline should always be considered in determining its current applicability.

Conflict of interest statement None of the authors have any conflict or duality of interests.

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