188Re HEDP etidronate

JMH de Klerk, Meander Medical Centre Amersfoort
R ter Heine, Radboud University Medical Centre Nijmegen
HJ Bloemendal, Meander Medical Centre Amersfoort

Note: The radiopharmaceutical 188Re-HEDP, the cold kits and the radionuclide generators that may be used for its production are not available as licensed drugs.

1. Introduction

Skeletal metastases frequently occur in patients with breast or prostate cancer and pain is the most common symptom of skeletal metastases. This pain can be alleviated using analgesics (usually opiates, which can cause side effects), systemic therapy such as hormonal therapy and chemotherapy or external radiation therapy.
Systemically administered bone-seeking radiopharmaceuticals can be used as an alternative, one of which is 188Re-HEDP. 188Re-HEDP is chemically similar to the previously commercially available 186Re-HEDP (Re-Bone®), the difference being that another Rhenium isotope is incorporated in the Rhenium-bisphosphonate complex. 188Re-HEDP has as the major advantage over 186Re-HEDP and all other bone seeking therapeutic radiopharmaceuticals, that upon presentation of a patient, it can be rapidly produced on-site by labelling the eluate from a Tungsten-Rhenium-188 generator to the bisphosphonate HEDP. It should be noted that the HEDP cold kits and generators are not available as approved drugs.

The most important physical characteristics of 188Re are its emission of high-energy beta particles, with a maximal energy of 2,1 MeV, and its relatively short physical half-life of 17 hours. Due to this relatively short half-life, a relatively large amount of radiopharmaceutical is required, and the dose rate is therefore also higher than when using radiopharmaceuticals with a longer half-life. The energy of the beta's is higher than those of 89Sr and 153Sm. 188Re, as a perrhenate ion, forms a complex with tin and the bisphosphonate etidronate (HEDP). The bone seeking properties of the bisphosphonate are retained after radiolabelling and through this mechanism, 188Re-HEDP specifically accumulates at the hydroxyapatite surface of bone metastases. Studies show that up to 90% of patients treated with 188Re-HEDP experience a reduction in pain. The effect is fast (within one week) and comparable for all primary tumours. It can be used for all osteoblastic metastases originating from different primary tumours. Due to its fast effect and production on site, 188Re-HEDP can be used successfully for patients who are in a lot of pain and for whom a quick response is therefore required. The treatment can be safely used in patients who have undergone prior chemotherapy after recovery of the haematological parameters, especially the total thrombocyte counts, since the toxicity is limited. Repeated treatment might be considered, as studies suggest that this results in longer survival and better pain response.

2. Methodology

This guideline is based on available scientific literature on the subject, the previous guideline (Aanbevelingen Nucleaire Geneeskunde 2007), international guidelines from EANM and/or SNMMI if available and applicable to the Dutch situation.

3. Indications

^{188}Re-HEDP is used for the treatment of painful osteoblastic skeletal metastases resulting from prostate carcinoma and other primaries. ^{188}Re-HEDP can also be used for patients experiencing recurrent pain following local radiotherapy.

Patients eligible for treatment should meet the following conditions:

a. Skeletal scintigraphy which shows uptake of bisphosphonate in the skeletal metastases.
b. The patient has metastatic bone pain.

Contraindications

Absolute contraindications are:

1. Thrombocyte levels <100x10^9/l
2. Leucocyte levels <3,0x10^9/l
3. Continued breast-feeding
4. Pain in conjunction with a neurological deficit due to metastatic invasion (urgent local external beam radiotherapy is then indicated.)
5. Pregnancy

Relative contraindications are:

1. Transient, treatable urinary incontinence. Urinary catheters provided for this purpose should remain in situ for one day
2. Serum creatinine >130 µmol/l (creatinine clearance >50 ml/min)
3. Threat of paraplegia (acute external radiotherapy is indicated if this is the case)

4. Medical information necessary for planning

a. Type of carcinoma, location of primary tumour and locations of known metastases
b. Medical history including details of hormonal treatment, chemotherapy and radiotherapy
c. Results of recent scintigraphy (2-8 weeks)
d. Blood results, in particular any recent thrombocyte and leukocyte counts, serum creatinine levels and GFR
e. Co-medication

5. Radiopharmaceutical

Rhenium-188-Hydroxyethylidenediphosphonate (^{188}Re- HEDP)

a. Kinetics

Following intravenous administration, ^{188}Re-HEDP is quickly taken up by bone, and preferentially by bone metastases with high metastasis-to-normal bone ratio. ^{188}Re-HEDP is excreted by the kidneys.

b. Dosage
A standard dose of 40 MBq/kg is given (intravenously as a bolus through a running drip). Studies have shown that the maximum tolerable dosage is 3300 MBq.
c. Dosimetry
For ^{188}Re-HEDP in patients with bone metastases, the average calculated absorbed dose (mGy/MBq) in the red marrow is 0,6, in kidneys: 0,71, in the whole body: 0,07 and in the bone metastases 3,8. A mean dose value of 0,6 mGy/MBq for the red bone marrow did not lead to any cases of clinically significant thrombocytopenia or leukopenia.
d. Toxicity/side effects
The toxicity is limited mainly to reversible bone marrow depression which manifests as a temporary drop in the thrombocyte level. The lowest point is reached approximately 4 weeks post injection. Recovery often occurs within 6-8 weeks after treatment. This reversible decline in thrombocyte and to a lesser extent in leucocyte count is not clinically relevant. A temporary 'flare response' (increase in pain) can sometimes occur. The onset is within 1 day of treatment and usually lasts 24-72 h, often followed by a particularly good response.

6. Laboratory facilities required
1. A pharmacy department compliant with GMP-z for production of non-radioactive, sterile starting materials, such as the HEDP cold kit and other necessary components.
2. A radiopharmacy department compliant with GMP-z for the radiolabelling procedure and facilities to perform thin layer chromatography, analogous to the quality control of ^{99m}Tc-bisphosphonates.

7. Preparation, method and after-care
^{188}Re-HEDP is administered as a bolus injection (using a lead syringe shield) through a free running drip.
After-care:
The radiopharmaceutical is excreted mainly into the urine and the toilet to be used should therefore be connected to sewage, and not a septic tank. Special sewage tanks are not required (see Aanbevelingen VROM (recommendations of the Dutch Ministry of Housing, Spatial Planning and Environment)). Extra hydration is recommended, particularly in patients with poor renal function. The first outpatient follow-up appointment should be scheduled for 3 weeks post treatment. In the event of a significant reduction in thrombocytes, the patient should return for weekly follow-up appointments until the thrombocyte level has returned to normal. Follow-up nuclear medicine appointments should be scheduled in collaboration with the patient's lead specialist. The patient should be instructed to use adequate contraception for the four months following treatment. Incontinent patients should be given sufficient incontinence materials to last for five days. There is no longer a preference for burial or cremation of patients who die shortly following treatment. Cremation is not considered to pose an unacceptable radiation hazard (crematorium staff can be exposed to doses of up to approximately 1 μSv).

8. Relation to other therapies
Radionuclide therapy is as effective as local external beam radiotherapy for bone

metastases. Because most patients have multiple bone metastases radionuclide therapy is to be preferred.
External radiotherapy (or even neurosurgery) is always preferable in patients with myelocompression or threatened/current neurological deficit. Extensive neurological examination should be a standard part of the analysis of patients with painful skeletal metastases. Previous external radiotherapy confined to a limited area is not a contraindication for treatment using ^{188}Re-HEDP. For recurrent pain in an area which has been irradiated previously, repeat external irradiation is often contraindicated due to myelotoxicity. These disadvantages can be prevented by using therapeutic bone-seeking radiopharmaceuticals at an earlier stage. The effectiveness of ^{188}Re-HEDP is comparable to that of external radiotherapy, it involves relatively mild toxicity and is patient-friendly.

9. Literature

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