

Application of rhenium-188 HEDP in bone metastases therapy

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Abstract

Radionuclide bone metastases therapy is a major achievement of nuclear medicine. Development of less radiotoxic and more effective radiopharmaceuticals is therefore a challenge for radiopharmacists and industry. This paper reviews the application of rhenium-188 HEDP as a reactor- or generator-produced nuclide for bone metastases therapy.

Key words: bone metastases radionuclide therapy

Introduction

Bone metastases might occur in most of neoplastic diseases. Breast, prostate, lung and renal cancer are the most common cancers with skeletal spread. 70% of those patients suffer from bone pain [1]. Patients with bone metastases have longer survival than patients with extraosseous neoplastic dissemination [2]. Radionuclide therapy in painful bone metastases was introduced in the early 40 s [3, 4]. Today strontium-89, samarium-153 EDTMP and rhenium-186 HEDP are the most popular radiopharmaceuticals in treatment of patients with widespread skeletal metastases. Several other radiopharmaceuticals are currently introduced. One of them is rhenium-188

Rhenium-188 properties

Rhenium-188 is a relative new and attractive therapeutic radioisotope. It emits high-energy β^- radiation with mean energy of 0.76 MeV, maximal — 2.1 MeV and γ rays with energy of 155 keV. Gamma-radiation enables *in vivo* pharmacokinetic studies and

dosimetric calculations [5]. A physical half-life of rhenium-188 is 16.9 hours [6].

Rhenium-188 can be produced in two ways: in the reactor or in the generator. In the reactor it is produced by neutron irradiation of enriched rhenium-187 [7, 8]. The more common method is using a tungsten-188/rhenium-188 generator [7] similar to molybdenum-99/technetium-99m, as rhenium-188 is a chemical analog to technetium-99m [8]. Tungsten-188 parent nuclide is available in a relatively low specific activity ($< 0.15\text{--}0.19$ GBq/mg; $< 4\text{--}5$ mCi/mg) from reactor irradiation of enriched tungsten-186 [9]. The rhenium-188 daughter nuclide is obtained as sodium perhenate by elution of alumina-based tungsten-188/rhenium-188 generator with 0.9% saline. Relatively large volumes of 0.9% saline (> 15 ml) are required for elution so solutions are of relatively low specific activity concentration of rhenium-188 (< 1 GBq/ml for the 18.5 GBq generator) [9].

Therefore, this eluate needs concentration. Using tandem ion-exchange columns it is possible to concentrate rhenium-188 saline solution in active concentration of 18.5 GBq/ml (500 mCi/ml) [7]. Ammonium acetate (0.3 mole/L) is also proposed to use for generator elutions with similar results. After passage through a tandem cation-anion column system eluate of low volume (< 1 mL) of saline shows activity 11.1–14.8 GBq rhenium-188 (300–400 mCi) [9]. The generator can be used for 3 months to one year with no decrease in performance [7, 9]. Therefore rhenium-188 can be obtained easily at reasonable costs for routine preparation for treatment.

Rhenium-188 HEDP biodistribution

β^- emitters are usually labelled with diphosphonates for therapeutic application. Hsieh et al. in their study compared labelling methylene diphosphonate (MDP), hydroxymethane diphosphonate (HDP) and hydroxyethylidene diphosphonate (HEDP) with rhenium-188 [10]. They analysed the biodistributions and bone uptakes of these radiopharmaceuticals (four hours after intravenous injection of approximately 0.037 GBq (1 mCi) rhenium-188-labelled diphosphonate) in rabbits. Rhenium-188 HEDP demonstrated to be the best choice among these three bone-seeking drugs [10].

Rhenium-188 HEDP complex shows stability *in vitro* and *in vivo* [11, 12]. Rhenium-188 HEDP proves to have high bone affinity and high bone lesion uptake. The bone to soft tissue ratio is 25.06 [10], uptake in bone metastases is similar to technetium-99m bone-seeking agents [13]. The lesion/normal bone uptake ratio was 4.23 ± 0.21 in rabbits injected with rhenium-188 HEDP

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in comparison in those injected with technetium-99m MDP (4.25 ± 0.23) [6].

The biological half-life in bone is long (60.86 h). In comparison, the biological half-life in muscle and blood are short: 2.99 h and 6.21 h respectively [6].

Lin et al. in their study analysed the biodistribution following intravenous injection of rhenium-188 HEDP (0.014 Bq; 0.4 mCi) in rats [6]. They measured the radioactivity in the lung, liver, muscle, spleen, testes, blood, stool and values were all lower than 0.3 percent of injected dose per gram or per ml at 1 h post injection.

Most of the radiotracer is excreted with urine [6]. 25–32% of the administered radiopharmaceutical is eliminated via the urinary tract in the first three hours post injection, 70% of injected radiopharmaceutical is found in urine in over six hours [14].

Rhenium-188 HEDP external dosimetry

Three hours after rhenium-188 HEDP (3 GBq; 80 mCi) administration at 1 meter from the anterior mid-trunk of the patient gamma radiation dose rate values were 6.3 ± 1.0 microSv/h for gamma, and of 183 ± 40 microSv/h for beta-radiation were found [15].

This enables the same-day, outpatient therapy of disseminated skeletal metastases with rhenium-188 HEDP [8].

Rhenium-188 HEDP efficacy of bone pain palliation

Analysing the efficiency in pain palliation of bone metastases of diverse radioagents Liepe et al. compared therapeutic course utilising rhenium-188 HEDP (2.943 ± 0.609 GBq), rhenium-186 HEDP (1.341 ± 0.161 GBq) and strontium-89 (0.152 ± 0.018 GBq). 81% of patients after rhenium-188 HEDP, 77% after rhenium-186 HEDP and 80% after strontium-89 reported relief of pain. The Karnofsky-Index established by patients seems to be a little higher in group treated with rhenium-188 HEDP however this value was only statistically significant ($p = 0.001$) [16]. Comparable outcomes were achieved by Li and colleagues [17]. In this clinical trial mean administered dose of rhenium-188 HEDP was 1.1 GBq (31 mCi), moreover 23 patients received repeated treatments, with a total dose ranging from 2.3 GBq (63 mCi) to 6.9 GBq (188 mCi) resulting in a higher response. Relief of pain occurred in 49 of 61 patients (80%), with a complete response in 22 (36%) patients and with a significant response in 27 (44%) patients. In 12 (20%) cases, response was not apparent. In 38 patients treated with a single dose, 8 (21%) patients had complete pain relief, 21 (55%) patients showed significant response, and 9 (24%) patients had no response [17].

Less positive response rate was reported by Palmedo et al. with overall response 64% of patient with relief in bone pain. In this study patients received single injection of escalating doses of rhenium-188 HEDP [1.3 GBq (35 mCi), 2.6 GBq (70 mCi), 3.3 GBq (90 mCi) and 4.4 GBq (120 mCi)]. The response rate seemed to increase with higher doses, reaching 75% in the 4.4 GBq group [18].

Analgesic drug intake was studied in twenty-one patients with different cancers who were received 1.3 GBq (35 mCi) or 2.2 GBq (60 mCi) of rhenium-188 HEDP in single and multiple doses.

A decrease of 62% in analgesic drug treatment was reported for 78% of treated patients. Opiates were used in 78% of patients before radionuclide therapy and as a result of therapy 58% of patients abandoned drug intake at rest [14].

The duration of pain relief lasts from 1 to 3 months and 4.9% of patients showed a long-term effect lasting 4 to 6 months. Rebound pain ("flare phenomena") occurred in 6.5% of patients. Most of them experienced pain relief 1 week later [17].

PSA level in 23 prostate carcinoma patients with bone metastases was documented during rhenium-188 HEDP therapy for assessment of tumoricidal effect. After therapy 22% of those patients presented decrease in tumour marker level for several months [19].

Li et al. reported a case of patient with breast cancer and bone metastases proven in computed tomographic and whole-body bone scans, with heavy bone pain that did not respond to large doses of analgesics. Two weeks after a single dose of 1.11 GBq (30 mCi) rhenium-188 HEDP administration, she experienced complete relief of pain and remained pain free for 5 months. On bone scan follow-up approximately one half of the metastatic foci disappeared especially in the ribs, spine and pelvic bones [17].

Myelotoxicity and side-effects

Rhenium-188 is a radionuclide with a very high radiation energy; therefore the myelotoxicity is a limiting factor in the treatment. Thrombocytopenia and leukopenia are the most important side-effects [18] as platelets and white blood cells are being most sensitive to the effects of radiation [15]. However, short tissue range and short half-life result in the relative sparing of the bone marrow while delivering a high radiation dose to the bone metastases [5] and in fact no significant haematological toxicity was documented.

The maximum tolerated dose of rhenium-188 HEDP in prostate cancer patients with osseous metastases was assessed by Palmedo et al. [18]. Patients received a single injection of escalating doses of rhenium-188 HEDP [1.3 GBq (35 mCi), 2.6 GBq (70 mCi), 3.3 GBq (90 mCi) and 4.4 GBq (120 mCi)]. In the 1.3 GBq group, no hematological toxicity was observed. The most unfavourable results were achieved in the 4.4 GBq dose group: thrombocytopenia of grades 3 and 4 was observed respectively in one and in two patients (baseline thrombocyte count $< 200 \times 10^9/L$), leukopenia of grade 3 was showed in one patient. In patients with thrombocyte counts above $200 \times 10^9/L$, a dose of 4.4 GBq might be tolerable [18].

Liepe et al. compared level of thrombocytes before and after administration of rhenium-188 HEDP, rhenium-186 HEDP and strontium-89 in bone metastases breast and prostate carcinoma patients. In the result there was no significant difference in the bone marrow impairment between those various radionuclides [16].

The nadir of thrombocytopenia and leukopenia in majority of cases was noted at fourth week and returned to baseline level within 8 weeks [16].

Adverse side-effects including low-grade fever, nausea, vomiting and arthrodynia of the knees might appeared after rhenium-188 HEDP injection. All of which resolved spontaneously within 1 or 2 days. Li et al. observed those symptoms at 16.4% of treated patients [17].

Conclusions

Nowadays systemic radionuclide therapy is considered as effective, safe, feasible, well tolerated and cost-effective method of treatment of bone metastases. Radiopharmacotherapy is shifting towards radioisotopes with short tissue range and short half-decay time to prevent bone marrow lesion. An administration of low doses of activity (3 GBq; 80 mCi) deliver high beta-energy radiation to metastasis focus and can bring about a pain reduction without causing any clinically significant bone marrow toxicity [14].

Due to rhenium-188 HEDP physical and biological properties it could be a beneficial radionuclide for repeated application with small activity (30 mCi) used in similar manner like samarium-153 in Vienna protocol.

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