Radionuclidic purity aspects of ^{153}Sm for radionuclide therapy

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Abstract. ^{153}Sm-EDTMP (ethylenediaminetetramethylenephosphonate) is a promising radiotherapeutic agent for palliative treatment of metastatic bone cancer pain. ^{153}Sm has a half-life of 46.3 hr. Maximum and mean beta energies (220 keV) are moderate and satisfy the criterion of short range in soft tissue. Auger electrons contribute significantly to the locally absorbd dose. The rather high yield of the 103 keV gamma rays can be successfully used for scintigraphy and for retention measurements with a wholebody counter. Measurements of 19 patients with a wholebody counter in the Department of Nuclear Medicine in the General Hospital in Vienna show gammalines in the energy spektra which correspond to ^{152}Eu ($T_{½}$=13.53 a), ^{154}Eu ($T_{½}$=8.59 a) and ^{156}Eu ($T_{½}$=15.19 d). These long-lived radionuclidic impurities are coproductions of ^{153}Sm, which is produced by neutron activation of both natural Sm_2O_3 and enriched $^{152}Sm_2O_3$. Biodistribution studies show that there is a very close similarity in the behaviour of complexes of the rare-earth elements Sm and Eu. As tests show these activities remain fix in the bone. This aspect needs to be taken into account while considering the acceptance of the additional radiation dose burden due to the radionuclidic impurities of Eu-isotpes in ^{153}Sm. Radiation absorbed dose calculations were done for these Eu-isotopes localized in bone. The highest tissue doses are those of bone and bone surface, but because of the different tissue weighting factors the equivalent dose of the red marrow contributes most to the additional effective dose followed by the dose of bone. Calculations show that 1 to 5 treatments do not really lead to a dose problem. However 10 or more treatments with this radiopharmacon can pose a problem.

1. Introduction

Patients with disseminated carcinoma often have painful bone metastases. Once these patients have developed bony metastases, pain control becomes difficult and most patients die within 6 – 12 month of inanitition with narcotic use and immobility. Patients with late stage breast or prostata cancer are an ideal group to derive benefit from systematic treatment of osteoblastic bone lesions with bone seeking radiopharmaceuticals [1, 2]. Because of this, effective pain pallation in this patient group might be associated with prolonged survival.

^{153}Samarium-EDTMP (ethylenediaminetetramethylenephosphonate) is an appropriate candidate for therapeutic use in this setting. The gamma dose rate constante is high in comparison to other lanthanoid radionuclides used in therapy. Maximum and mean beta energies (220 keV) are moderate and satisfy the criterion of short range in soft tissue. The rather high yield of the 103-keV-gamma rays can be used successfully for scintigraphy and for retention measurements.

^{153}Sm is produced by neutron capture of isotopically enriched $^{152}Sm_2O_3$ and is then dissolved in 0.1 M HCl. The radiopharmaceutical ^{153}Sm-EDTMP is then prepared by addition of Ca salt of EDTMP to the acidic ^{153}Sm solution; pH is adjusted with NaOH. Quality control tests of the radiopharmaceutical prior to administration show complexation of ^{153}Sm to EDTMP in the order of 99% an higher.

However, there is an additional radionuclidic impurity burden in the case of the ^{153}Sm-EDTMP treatment obtained from Sm_2O_3 target due to the coproduction of long-lived radionuclides, namely due to ^{152}Eu ($T_{½}$=13.53 a), ^{154}Eu ($T_{½}$=8.59 a) and ^{156}Eu ($T_{½}$=15.19 d). There is a very close similarity in the behaviour of complexes of the rare-earth elements such as Sm and Eu. The behaviour of Eu-EDTMP present with ^{153}Sm-EDTMP should be identical [3]. This aspect needs to be taken into account while considering the acceptance of the additional radiation dose burden due to these long-lived radionuclidic impurities.

2. Materials and Methods

2.1. Gammaspectrum of the Eu-impurities in ^{153}Sm-EDTMP

High resolution, gammaray spectrometry was performed using a n-type high-purity germanium (HPGe) detector. A ^{152}Eu reference source was used for energy calibration. Measurements of the ^{153}Sm-EDTMP radiopharmacon show gammalines which correspond to the mentioned isotopes of europium. The measured gammaspectrum is shown in Figure 1.

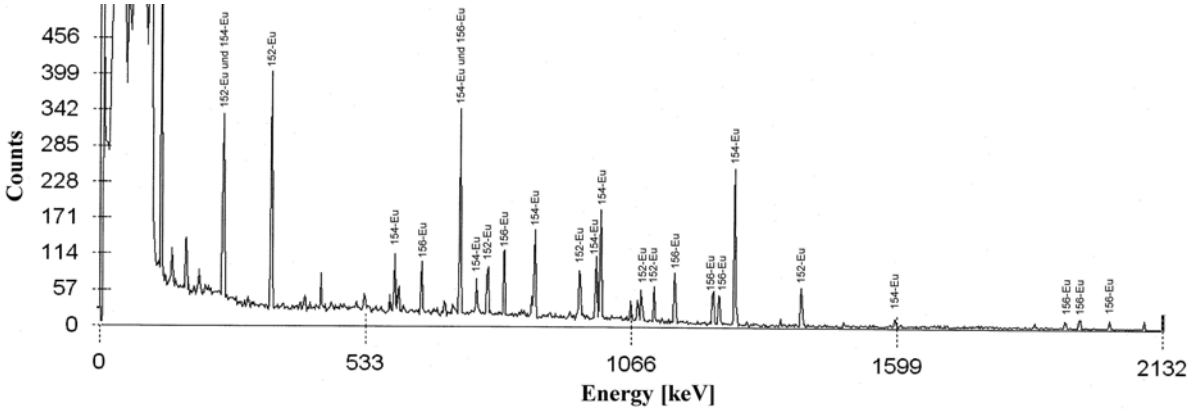

FIG.1. *Radioactive impurities in the ^{153}Sm-EDTMP-radiopharmacon. Measured with a high-purity germanium (HPGe) detector.*

2.2. Wholebody counter

Wholebody counters are devices for the identification and measurement of small quantities of gamma-emitting radionuclides and their distribution in the human body. The Department of Nuclear Medicine of the General Hospital Vienna is equipped with a clinical wholebody counter, which was constructed by the Austrian Research Center in Seibersdorf. This device consists of four 6“ x 4“ NaI(Tl) crystals, which are mounted in fixed positions: two stationary detectors above the couch and two below. The shadow shield is made of specially selected low background lead (length: 170 cm, thickness: 10 cm), which results in a total mass of 8500 kg. It is connected to a motor-driven, dead time corrected computer controlled scanning system during counting. During the measurements the computer-operated, variable-speed motor drives the couch for a preset scan time and scan length along an axis parallel to the longitudinal axis of the subject from the home-position through the measuring range to the end-position. The scan time was selected to 1000 s. The clinical wholebody counter is characterized by outstanding scan qualities due to precise adjustable slit collimators. Collimators can be adjusted between 0 mm and 300 mm in front of the detectors. Therefore this instrument is especially used for metabolic studies with patients, for research applications like the localization of small activities in the human body and for studies of the behaviour of radiopharmaceuticals, as well as for routine measurements.

2.3. Patient selection

19 patients were selected for this study. All patients had histologically documentated breast or prostata cancer with painful bone metastasis. It was the first course of treatment of bone metastasis with ^{153}Sm-EDTMP for some patients. However, many patients had courses of treatment of their bone metastasis with ^{153}Sm-EDTMP before. One patient even had 11 courses of treatment before. An activity of 1 GBq ^{153}Sm-EDTMP was administered intravenously to each patient for one course of treatment. The red marrow dose is limiting the amount of administered activity. The proposed limit of red marrow dose is 2.85 Gy [4]. A marrow dose of 1.86 mGy/MBq bone uptake is reported. Considering this value and the red marrow dose limit, the activity accumulated in bone should not exceed 1.53 GBq. Three weeks after the administration of the radiopharmacon the remained activity was measured with the wholebody counter.

2.4. Dosimetric calculations

Calculations have been undertaken to estimate the likely radiation dose received by patients undergoing treatment with ^{153}Sm-EDTMP and its impurities. The MIRD concept of absorbed dose calculations in connection with the Monte Carlo method values of the specific dose (S-values) to red marrow and bone was used for the calculations. Adopting the MIRD notation [5], the absorbed dose to a target organ, t, from a source, s, can be written

$$D(t,s) = A_S \times S(t,s)\,, \tag{1}$$

where the S-factor is given by

$$S(t,s) = \sum_k \Delta_k \times \phi_k(t,s) \tag{2}$$

The Δ_k term is the mean energy emitted per cumulated activity for radiation of type "k" and is a property of the radionuclide. $\phi_k(t, s)$ is the specific absorbed fraction that depends implicitly on radiation type, the size, shape and separation of the source and target organs.
A_S is the cumulated activity that is given by

$$A_S = \frac{A_{SK}}{\lambda}\,, \tag{3}$$

where A_{SK} is the maximum of the skeletal activity (after several hours) and λ is the decay constant (for ^{153}Sm, ^{152}Eu, ^{154}Eu and ^{156}Eu). The cumulated activity is the total number of a specific radionuclide.

The following steps describe a simplified technique for calculation of ^{153}Sm-EDTMP and its radioactive impurities:

(a) Administer 1 GBq ^{153}Sm-EDTMP
(b) Determine the remaining activity of ^{153}Sm and its impurities by a measurement with the wholebody counter three weeks after administration
(c) Calculate skeletal uptake
(d) Calculate cumulated skeletal activity (according formula (3))
(e) Calculate radiation absorbed dose to bone and red marrow (according formula (1))

3. Results

3.1. Skeletal uptake of ^{153}Sm-EDTMP

Retention measurements with the wholebody counter yield 48.2% ± 13.1% uptake in bone (mean ± SD); range: 31.7% - 87.2%). The reason for the wide range for the uptake in the skeleton is not sufficiently explainable. A correlation between the percentage of ^{153}Sm-EDTMP retention and responses to treatment could not be found.

Most of the patients (over 85%) experienced substantial relief of pain. The other patients had just a minimal improvement or no change of their pain. Duration of the pain relief from an injection ranged from 4 to about 25 weeks.

3.2. Radiation dose due to one ^{153}Sm-EDTMP treatment

The absorbed dose equivalent of ^{153}Sm-EDTMP has been determined for the main tissues. The highest tissue doses are those of bone and bone surface, but because of the different tissue weighting factors the equivalent dose of the red marrow contributes most to the effective dose followed by the doses for bone and urinary bladder Table I). The effective dose due to one treatment with ^{153}Sm-EDTMP is about 0.13 mSv/MBq.

Table I. Organ doses, dose equivalents and effective dose after one ^{153}Sm-EDTMP.

Organ/Tissue	Organ Dose D_T [mGy/MBq]	Tissue weighting factor w_T	Dose equivalent $D_T \times w_T$ [mGy/MBq]	% of the effektive dose
Gonads	0.0036	0.20	0.0007	0.5
Red marrow	0.7211	0.12	0.0865	67.5
Lung	0.0041	0.12	0.0005	0.4
Colon	0.0021	0.12	0.0003	0.2
Stomach	0.0019	0.12	0.0002	0.2
Urinary bladder	0.0018	0.05	0.0001	0.1
Thyroid	0.0043	0.05	0.0001	0.1
Liver	0.0026	0.05	0.0001	0.1
Breast	0.0018	0.05	0.0001	0.1
Bone	3.5523	0.01	0.0355	27.8
Skin	0.0027	0.01	0.0000	0.0
Whole body	0.0763	0.05	0.0038	3.0

3.3. Incorporated Eu-impurities

Measurements show gammalines which correspond to ^{152}Eu, ^{154}Eu and ^{156}Eu (Fig. 2). It is a feature of the lanthanoids (rare elemets) that the occupation of their outer electronic orbits are the same. Since their chemical behaviour is very similar and complexes of the two elements with EDTMP might be composed. The metabolism of the complex is determined above all by the phosphonate EDTMP which preferentially localizes in active bone, and specifically at sites of metastases producing site-directed radiotherapy. Therefore, ^{152}Eu-, ^{154}Eu- and ^{156}Eu-EDTMP show the same metabolism as ^{153}Sm-EDTMP and the impurities accumulate in bone after every treatment. Studies show that EDTMP remains in bone so that the complexes have no metabolism anymore after they are integrated in bone. Measurements with the wholebody counter confirm that every treatment increases the incorporated activity about 15 kBq for ^{152}Eu, 7 kBq for ^{154}Eu and 19 kBq for ^{156}Eu. However, due to the rather short half-life, ^{156}Eu decays after several weeks.

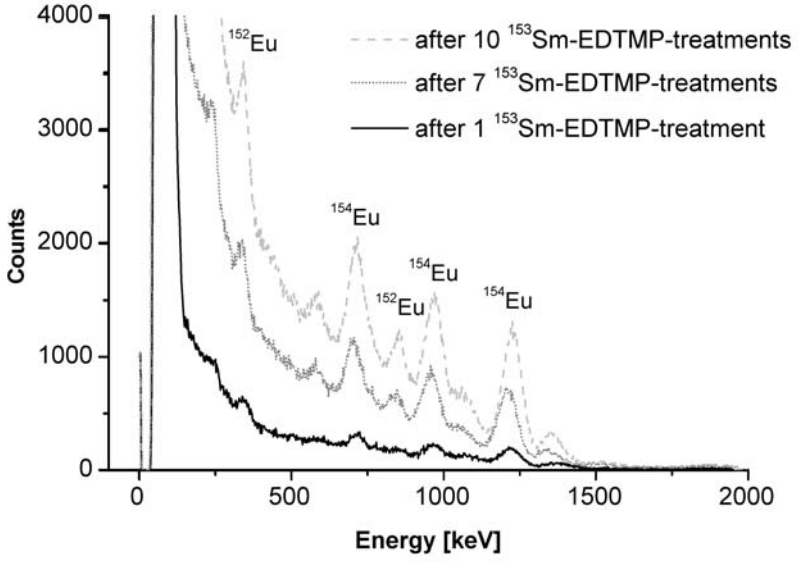

FIG.2: Radioactive Eu-impurities in bone after 1, 7 and 10 ^{153}Sm-EDTMP-treatments.

3.4. Radiation dose due to Eu-impurities

Radiation dose calculations were also done for the Eu-impurities. These calculations show that the equivalent dose of the red marrow also contributes most to the effective dose followed by the doses for bone. For a better illustration the red marrow dose for one treatment with ^{153}Sm-EDTMP is compared with the red marrow dose due to the Eu-impurities one year after 1, 5, 9, 12 and 15 treatments. The first column in Table II shows the number x of treatments, the second column shows the red marrow dose because of the Eu-impurities one year after the treatment x, and the third column presents the percentage which the dose in column 2 correspond to one treatment with ^{153}Sm-EDTMP.

Table II: Eu-impurities doses compared with the dose of one ^{153}Sm-EDTMP treatment

Number x of treatments	**Total Eu-dose 1 year after treatment x [mGy]**	**Percentage, which the total Eu-dose correspond to one treatment with ^{153}Sm-EDTMP**
1	5.7	0.8
5	42.0	5.8
9	132.1	18.3
12	259.0	35.9
15	448.5	62.2

These considerations show that the undesireable doses due to the Eu-isotopes become higher with every treatment. The additional dose after 10 treatments come in the order of one ^{153}Sm-EDTMP treatment.

4. Conclusion

Wholebody counter measurements have clearly shown gammalines which correspond to ^{152}Eu, ^{154}Eu and ^{156}Eu. The behaviour of these Eu-isotopes present with ^{153}Sm-EDTMP is identical. Dosimetric considerations have shown that after several treatments the additional dose due to the Eu-isotopes is in the order of one ^{153}Sm-EDTMP treatment. Nevertheless, in the palliative treatment of terminal cancer patients suffering from bone pain, and who have been subjected to repeat doses too, this feature of the therapeutic radiopharmaceutical would not be a limitation. For determination of the applied dose and for quality assurance wholebody counters can be a useful tool for controlling and monitoring health care.

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