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Preliminary dosimetric evaluation of ^{90}Y-BPAMD as a potential agent for bone marrow ablative therapy

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Original Article

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Abstract

Aim: Bone-seeking radiopharmaceuticals are potential therapeutic tools for bone marrow ablation in patients with multiple myeloma. In this procedure, estimation of radiation absorbed dose received by the target and non-target organs is one of the most important parameters that should be undertaken. This research revolves around the absorbed dose to human organs after ^{90}Y-BPAMD injection. *Materials and methods:* ^{90}Y-(4-{[(bis(phosphonomethyl))carbamoyl]methyl}-7,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl) acetic acid (^{90}Y-BPAMD) complex was successfully prepared under optimised conditions. The human absorbed dose of the complex was estimated based on the biodistribution data on rats using the radiation-absorbed dose-assessment resource method. The target to non-target absorbed dose ratios for the complex was compared with the ratios for ^{166}Ho-DOTMP, as the main radiopharmaceutical for bone marrow ablation. *Results:* As expected, the highest amounts of absorbed dose were observed in the bone surface and the bone marrow with 2·52 and 2·29 mGy/MBq, respectively. The red marrow to the most organ absorbed dose ratios for ^{90}Y-BPAMD are much higher than the ratios for ^{166}Ho-DOTMP. *Findings:* ^{90}Y-BPAMD has interesting characteristics compared with ^{166}Ho-DOTMP and can be considered as a high potential agent for bone marrow ablative therapy of the patient with multiple myeloma.

Introduction

Multiple myeloma is a plasma cell malignancy, mainly involving bone marrow, with the 5-year survival rate of <30%.[1–3] However, chemotherapy is known as the standard method of treatment;[4] radiation therapy and stem cell transplant are used as the other treatment methods for disease control.[5] Stem cell transplant is the common procedure in multiple myeloma treatment that is used following radiation or chemotherapy.

In the technique called bone marrow ablation, all stem cells of the haematopoietic system are destroyed to follow the bone marrow transplantation for patients with multiple myeloma.[6] Recently, some bone-seeking radiopharmaceuticals using bisphosphonates are developed for bone marrow ablation, offering a beneficial therapeutic option in patients with multiple myeloma.[7,8]

However, bisphosphonates are known as the effective drugs for transportation of the diagnostic and therapeutic radionuclides to the bone site.[9] New generation of bisphosphonates such as (4-{[(bis(phosphonomethyl))carbamoyl]methyl}-7,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl)acetic acid (BPAMD) are developed solving some requirements and restrictions of the first-generation phosphonates.[10] Lately, the radiolabelled compounds of BPAMD have shown excellent biodistribution in animal model or human studies.[11,12]

Among the different therapeutic radionuclides, Samarium-153 [^{153}Sm][13] and Holmiun-166 [^{166}Ho][7] with their high-energy β-particles have been used for bone marrow ablation in the patients with multiple myeloma. ^{166}Ho-DOTMP[7] is used as the main radiopharmaceutical for this purpose. Yttrium-90 [^{90}Y] ($E\beta^-_{max} = 2{\cdot}25$ MeV, $T_{1/2} = 2{\cdot}7$ d) is of enormous interest owing to its favourable decay characteristics and its availability in the form of ^{90}Sr–^{90}Y generator system, resulting in the preparation of radiopharmaceuticals with greater specific activity. ^{90}Y seems to be a better candidate for bone marrow ablation compared with ^{166}Ho, according to its high-energy β-particles.

^{90}Y is believed to be the most useful among the radionuclides that have been used for radiotherapeutic purposes.[14] ^{90}Y-radiopharmaceuticals are widely used for the treatment and management of different cancer types.[15] However, some radiolabelled compounds of this radionuclide, including ^{90}Y-citrate and ^{90}Y-EDTMP, are used in clinical applications.[16,17] These complexes suffer from the low stability in human serum resulting in the liver toxicity. Recently, ^{90}Y-BPAMD was prepared that showed interesting characteristics compared with the other ^{90}Y bone-seeking agents and even ^{166}Ho-BPAMD.[18]

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In this study, with respect to the importance of absorbed dose in the bone marrow and other non-target organs, as a first step to evaluate the possibility of its usage, the absorbed dose to human organs after injection of ^{90}Y-BPAMD was estimated based on the biodistribution of rats data by radiation-absorbed dose-assessment resource (RADAR) method. The resulting data were compared with ^{166}Ho-DOTMP as the only clinically used ^{166}Ho bone marrow ablative agent.

Materials and Methods

An electrochemical ^{90}Sr–^{90}Y generator "Kamadhenu" system from Isotope Technologies Dresden, ITD, Germany was used for radiolabelling purpose. BPAMD was obtained from ABX (Radeberg, Germany). The other chemical reagents and Whatman No. 2 paper were purchased from Merck (Darmstadt, Germany) and Whatman (Buckinghamshire, UK). A high-purity germanium (HPGe) detector coupled with a Canberra™ (model GC1020-500SL) multichannel analyser and a Wallac 1220 Quantulus, Perkin-Elmer, ultra-low-level liquid scintillation spectrometer (Turku, Finland) were used for the assessment of γ and β impurities. Radio-chromatography was performed by using a Bioscan AR-2000 radio thin layer chromatography scanner instrument (Bioscan, Washington, DC, USA). The male Syrian rats weighing 180–220 g kept at routine day/night light program and under common rodent diet pellets were used for biodistribution studies.

Preparation and quality control of ^{90}Y-BPAMD

An electrochemical generator based on the secular equilibrium of ^{90}Sr–^{90}Y was used to attain $^{90}YCl_3$ for radiolabelling purpose. The amounts of ^{90}Sr in $^{90}YCl_3$ solution was specified by extraction paper chromatography technique according to the previous research.[19] Radionuclidic purity and radiochemical purity of the solution were checked by an HPGe detector and instant thin layer chromatography (ITLC) method, respectively.

^{90}Y-BPAMD was prepared according to the previously reported literature.[18] Briefly, 1 mg of BPAMD was dissolved in 1 mL pure water and the aqueous solution was used for labelling studies. 60 µL (105 nmol) of the stock solution was added to the vial containing 370 MBq of $^{90}YCl_3$. The pH of the reaction mixture was adjusted to 5 and the mixture was incubated for 45 minutes at 90–100°C. To remove the non-complexed ^{90}Y from the radiolabelled compound, the mixture was passed over the strong cation exchanger (Strata-X-C 60 mg). The radiochemical purity was checked by ITLC method using the NH_4OH:MeOH:H_2O (0·2:2:4) solvent system as the mobile phase.

Biodistribution assessment of the radiolabelled complex in male Syrian rats

Final ^{90}Y-BPAMD solution with approximately 5·55 MBq radioactivity was injected intravenously into the male Syrian rats through their tail veins. The animals were sacrificed at selected times after injection using the animal care protocols. The percentage of injected dose per gram (%ID/g) for different organs was calculated by dividing the activity amount of each tissue (A) to the injected activity and the mass of each organ.

Statistical analysis

Five mice were sacrificed for each time interval. All values were expressed as mean ± SD and the data were compared using Student's *t*-test. Statistical significance was defined as $p < 0{\cdot}05$.

Calculation of accumulated activity in human organs

The accumulated activity in human organs was determined according to the previous research performed by Yousefnia et al.[20] In summary, the non-decay corrected percentage-injected dose versus time was plotted for each animal organ. Although linear approximation was used between the two experimental points of times and the curves were extrapolated to infinity by fitting the tail of each curve to a monoexponential curve, the area under the curves were counted as the accumulated activity of animal organs. Then, the accumulated activity for human organs were determined by the extrapolation of this amount for animal organs using the proposed method of Sparks and Aydogan.[21]

Equivalent and effective absorbed dose calculation

The absorbed dose in human organs was calculated by RADAR formalism based on biodistribution data of the rats[22] and in accordance with the other previously reported research.[21] Briefly, the calculated accumulated activity was multiplied by the dose factors of source organs taken from the amount presented in OLINDA/EXM software.[23]

The effective absorbed dose for each organ was computed by Equation (1):

$$E = \sum_T W_T H_T \quad (1)$$

where H_T is the equivalent absorbed dose for each organ and W_T is the tissue-weighting factor that represents a subjective balance between the different stochastic health risks.[24] W_T was obtained from the reported value in ICRP-103.[25]

Results and Discussion

Preparation and quality control of ^{90}Y-BPAMD

The radionuclidic purity and radiochemical purity of $^{90}YCl_3$ solution were calculated to be more than 99·99 and 99%, respectively. The amount of ^{90}Sr contamination in the solution was estimated to be equal to 1·05 ppm (Figure 1), which is within the permissible limit. Radiochemical purity of higher than 98% was observed for ^{90}Y-BPAMD complex (Figure 2).

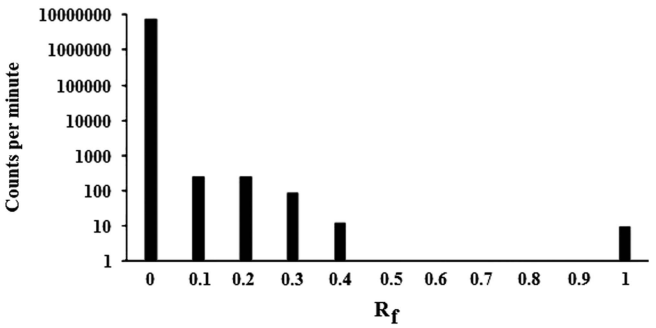

Figure 1. Extraction paper chromatography of the ^{90}Y solution used for radiolabelling.

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Table 1. The non-decay corrected %ID/g values after intravenously injection of ^{90}Y-BPAMD to the rats

	Time					
Organ	1 h	2 h	4 h	24 h	48 h	72 h
Blood	0·31 ± 0·01	0·29 ± 0·01	0·16 ± 0·01	0·07 ± 0·00	0·00 ± 0·00	0·00 ± 0·00
Urine	12·35 ± 0·42	9·95 ± 0·46	8·96 ± 0·42	3·07 ± 0·24	0·06 ± 0·00	0·05 ± 0·00
Bladder	0·41 ± 0·02	0·68 ± 0·03	0·42 ± 0·02	0·28 ± 0·01	0·21 ± 0·01	0·09 ± 0·00
Kidney	1·20 ± 0·01	1·15 ± 0·05	0·71 ± 0·03	0·24 ± 0·01	0·02 ± 0·00	0·00 ± 0·00
Liver	0·19 ± 0·01	0·26 ± 0·01	0·30 ± 0·01	0·11 ± 0·00	0·06 ± 0·00	0·05 ± 0·00
Spleen	0·11 ± 0·00	0·10 ± 0·00	0·17 ± 0·01	0·04 ± 0·00	0·01 ± 0·00	0·00 ± 0·00
Lung	0·10 ± 0·00	0·12 ± 0·00	0·23 ± 0·01	0·19 ± 0·01	0·08 ± 0·00	0·07 ± 0·00
Stomach	0·04 ± 0·00	0·09 ± 0·00	0·09 ± 0·00	0·12 ± 0·00	0·01 ± 0·00	0·01 ± 0·00
Heart	0·18 ± 0·01	0·14 ± 0·00	0·12 ± 0·00	0·06 ± 0·00	0·00 ± 0·00	0·00 ± 0·00
Intestine	0·03 ± 0·00	0·05 ± 0·00	0·10 ± 0·00	0·09 ± 0·01	0·01 ± 0·00	0·00 ± 0·00
Bone	7·12 ± 0·33	7·73 ± 0·31	8·23 ± 0·38	7·07 ± 0·30	5·36 ± 0·23	3·94 ± 0·18
Muscle	0·15 ± 0·01	0·14 ± 0·00	0·13 ± 0·00	0·02 ± 0·00	0·01 ± 0·00	0·00 ± 0·00
Skin	0·01 ± 0·00	0·01 ± 0·00	0·02 ± 0·00	0·01 ± 0·00	0·01 ± 0·00	0·00 ± 0·00

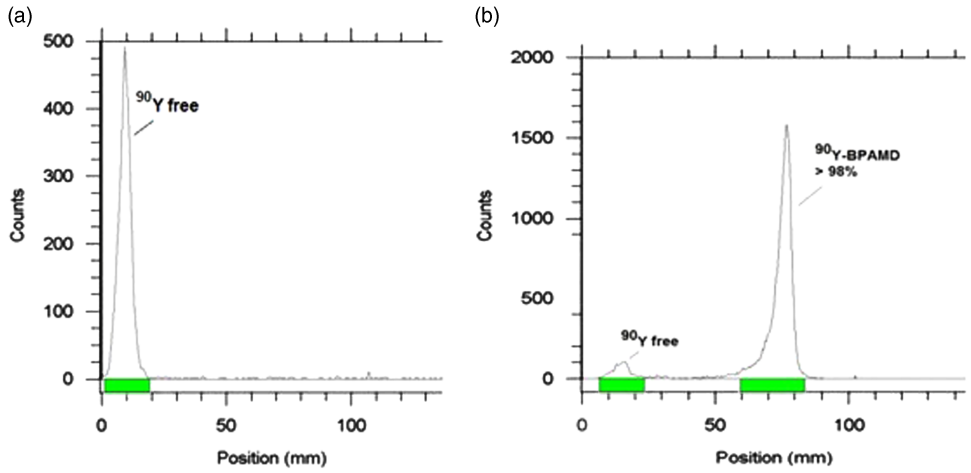

Figure 2. ITLC of $^{90}YCl_3$ (a) and ^{90}Y-BPAMD (b) in NH_4OH:MeOH:H_2O (0·2:2:4) solution on Whatman No. 2 papers.

Biodistribution assessment of the radiolabelled complex in rats

Biodistribution of ^{90}Y-BPAMD in the rats was investigated up to 72 h post injection. The non-decay corrected %ID/g for the rat organs after the injection of the complex was demonstrated in Table 1. The biodistribution of the complex showed that the radioactivity would remove from blood circulation very fast and significantly excreted from the kidneys. No considerable accumulation was observed in the liver. Based on the obtained results, it is clearly concluded that the major portion of the injected activity of the complex is accumulated in the bones.

Dosimetric studies

Dosimetric evaluation of the complex in human organs was carried out by RADAR method based on biodistribution data in the rat organs. The equivalent and effective absorbed dose in human organs after intravenous injection were presented in Table 2.

Owing to the direct relationship between the absorbed dose and response in terms of cell killing/survival, this study was done with the aim of estimating the radiation absorbed dose in human organs after injection of ^{90}Y-BPAMD. For this purpose, the biodistribution data of male Syrian rats were used. However, it should be noted that the actual percentage of the administered dose of radiation that reaches the bone/bone marrow necessarily varies from subject to subject.

Besides, extrapolation between animals and humans may lead to overestimation or underestimation of the absorbed dose, but the previous studies have demonstrated the usefulness of animal biodistribution as a model for the absorbed dose estimations in humans.[26,27] Estimation of the absorbed dose from small animals such as mice and rats is probably the most accurate procedure that has been used since the earliest days of nuclear medicine.[28]

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Table 2. Equivalent and effective absorbed dose delivered into human organs after injection of ^{90}Y-BPAMD

Target organs	Equivalent absorbed dose in humans (mGy/MBq)	Wt[a]	Effective absorbed dose in humans (mSv/MBq)
Adrenals	0	0·12	0
Brain	0	0·01	0
Breasts	0	0·12	0
GB wall	0	0·12	0
LLI wall	0·006	0·12	0·0007
Small int	0·007	0·12	0·0008
Stomach wall	0·004	0·12	0·0005
ULI wall	0·009	0·12	0·0011
Heart wall	0·009	0·12	0·0011
Kidneys	0·20	0·12	0·024
Liver	0·089	0·04	0·0036
Lungs	0·106	0·12	0·0127
Muscle	0·047	0·12	0·0056
Ovaries	0	0·08	0
Pancreas	0	0·12	0
Red marrow	2·29	0·12	0·2748
Bone surf	2·52	0·01	0·0252
Spleen	0·030	0·12	0·0036
Testes	0	0·12	0
Thymus	0	0·12	0
Thyroid	0	0·04	0
UB wall	0·004	0·04	0·0002
Total body	0·215		0·361

Note: [a]Tissue weighting factors according to international commission on radiological protection, ICRP-103 (2007).
Abbreviations: GB, gallbladder; LLI, lower large intestine; int, intestine; ULI, upper large intestine; UB Wall, urinary bladder wall.

As expected, the highest amounts of absorbed dose are observed in the bone surface and the bone marrow with 2·52 and 2·29 mGy/MBq, respectively, whereas the other organs receive insignificant absorbed dose. The bone marrow to other tissue absorbed dose ratios for ^{90}Y-BPAMD were calculated and presented in Table 3. For better comparison, the calculated ratios after injection of ^{166}Ho-DOTMP, as the only clinically used ^{166}Ho bone marrow ablative agent, to the patients with multiple myeloma are also given in Table 3.

As can be seen in Table 3, the red marrow to the most organ absorbed dose ratios for ^{90}Y-BPAMD are much higher than these ratios for ^{166}Ho-DOTMP. This means for a given dose to the bone marrow as the target organ, total body and other organs such as spleen, bone surface, brain etc. would receive lesser absorbed dose in the case of ^{90}Y-BPAMD utilisation. The absorbed dose ratios of red marrow:liver and red marrow:lung are

Table 3. Bone marrow to non-target absorbed dose ratios for ^{90}Y-BPAMD and ^{166}Ho-DOTMP

Organs	^{90}Y-BPAMD	^{166}Ho-DOTMP
Adrenals	N.D.[a]	36·9
Brain	N.D.	36·9
Breasts	N.D.	39·8
GB wall	N.D.	39·8
LLI wall	381·7	36·9
Small int.	327·1	39·8
Stomach wall	572·5	39·8
ULI wall	254·4	39·8
Heart wall	254·4	39·8
Kidneys	11·5	11·5
Liver	25·7	39·8
Lungs	21·8	36·9
Muscle	48·7	39·8
Pancreas	N.D.	39·8
Red marrow	1	1
Bone surf	0·91	0·6
Spleen	76·3	39·8
Testes	N.D.	39·8
Thymus	N.D.	39·8
Thyroid	N.D.	36·9
UB wall	572·5	1·8
Total body	10·7	8·3
Reference	This work	7

Note: [a]N.D. refers to not defined.
Abbreviations: GB, gallbladder; LLI, lower large intestine; int, intestine; ULI, upper large intestine; UB Wall, urinary bladder wall.

greater for ^{166}Ho-DOTMP, rather than ^{90}Y-BPAMD. Therefore, for delivering a certain dose to the bone marrow, these two organs would receive lesser absorbed dose in the case of ^{166}Ho-DOTMP usage.

Conclusion

The radiolabelled ^{90}Y complex was prepared with high radiochemical purity (>98%, ITLC). The biodistribution of the complex in normal rats up to 72 h post injection indicated considerable accumulation in the bones. The highest amounts of absorbed dos are observed in the bone surface and the bone marrow with 2·52 and 2·29 mGy/MBq, respectively, while the other organs receive insignificant absorbed dose. The results indicate that for a given dose to the bone marrow as the target organ, the most non-target organs would receive lesser absorbed dose in the case of ^{90}Y-BPAMD utilisation rather than ^{166}Ho-DOTMP. Generally, the dosimetric data of ^{90}Y-BPAMD showed high red marrow to non-target organs absorbed dose ratios and therefore can be considered

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as a potential agent for bone marrow ablative therapy; however, further biological studies are still needed.

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Ethical standards. All procedures contributing to this work comply with the ethical standards of the relevant national guidelines on the care and use of laboratory animals and has been approved by the NSTRI Committee.

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