Analysis of the Dosimetric Contribution of Radionuclides Coproduced through $^{nat}V(p,x)^{47}Sc$ Cyclotron Irradiation

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INTRODUCTION

Theranostic radiopharmaceuticals are formed by a targeting vector labelled with radionuclides which are useful for both imaging and therapy, thanks to the physical characteristics of their decay radiations. One of the most promising theranostic radionuclides is ^{47}Sc (half-life 3.35 d) thanks to the low energy (159 keV) γ-ray suitable for SPECT imaging and the intense β^- emission (mean β^- energy: 162.0 keV), useful to treat small-size tumours. Even if the therapeutic potential of ^{47}Sc has been already demonstrated preclinically, the translation of ^{47}Sc-therapeutic agents to the clinic is hampered by its limited availability. Therefore, both cyclotron- and reactor-based production routes of ^{47}Sc are currently being studied, also in the framework of the Coordinated Research Project (CRP) promoted by the International Atomic Energy Agency (IAEA) focused on "Therapeutic radiopharmaceuticals labelled with new emerging radionuclides (^{67}Cu, ^{186}Re, ^{47}Sc)" [1]. In particular, the ^{47}Sc production by medium energy cyclotrons using the $^{nat}V(p,x)^{47}Sc$ reaction was investigated within the framework of the "Production with Accelerator of ^{47}Sc for Theranostic Applications (PASTA)" research project, funded by INFN CSN5 at the Legnaro National Laboratories (LNL) [2]. This production route is particularly interesting due to the low-cost and commercially easily available ^{nat}V targets and the widespread number of medium energy proton cyclotrons, but the nuclear cross section of this reaction is quite low (approximately 12 mb at about 35 MeV) and small amounts of Sc-contaminants are co-produced for proton energies higher than 30 MeV (see [2-3] for available cross section data of ^{XX}Sc-isotopes). The main concern with these Sc-contaminants is their contribution to the patient radiation dose.

Aim of this work was therefore to evaluate the dose contributions for the three radionuclides expected to be produced through the proton irradiation of ^{nat}V target for $E_P \leq 45$ MeV, i.e. ^{48}Sc, ^{47}Sc and ^{46}Sc (whose main decay characteristics are summarized in Table 1) and using [Sc]-cm10 complex as an example of radiopharmaceutical. The DOTA-folate conjugate (cm10) is composed by a targeting vector folic acid which selectively binds to the folate receptor expressed on a variety of tumor types, the chelating agent DOTA and a small-molecular-weight albumin binding entity, which improves the blood circulation time and tissue distribution profile of folate conjugates.

Table 1. Main decay characteristics.of ^{48}Sc, ^{47}Sc and ^{46}Sc radioisotopes [4].

	E_γ (keV)	I_γ (%)	β^- (keV)	I_{β^-} (%)
^{48}Sc $T_{1/2}$: 43.67 h β^- decay to ^{48}Ti: 100%	983.526 1037.522 1312.120	100.1 97.6 100.1	158.6 227.3	10.02 89.98
^{47}Sc $T_{1/2}$: 3.3492 d β^- decay to ^{47}Ti: 100%	159.381	68.3	142.6 203.9	68.4 31.6
^{46}Sc $T_{1/2}$: 83.79 d β^- decay to ^{46}Ti: 100%	889.2771 120.545	99.9840 99.9870	111.8 580.8	99.9964 0.0036

METHODS

Detailed biodistribution data in KB tumor-bearing nude mice after [^{47}Sc]-cm10 injection [5] were used to calculate the activity curves in the main male human organs through the relative mass scaling method, which takes into account the differences in human and animal organ masses. The decay-corrected percent of injected activity for each human source organ were then plotted as a function of post injection time, fitted to a tri-exponential equation, representing the phase of accumulation, retention and elimination of the radiopharmaceutical and at last integrated, considering the physical half-lives of each radioisotope, to provide the number of disintegrations in each source organ. Dosimetric calculations were then performed with the OLINDA (Organ Level Internal Dose Assessment) software code version 2.1.1 [6] using the human male NURBS-type model [7], based on the standardized masses defined by ICRP 89 [8], to obtain the equivalent doses in each organ using the RADAR method for internal dose estimation [9] and the effective dose, *ED*, based on the tissue-weighting factor recommended by ICRP 103 [10].

Table 2. Organ equivalent doses (mSv/MBq) in the main organs and ED values calculated for [^{48}Sc]-cm10, [^{47}Sc]-cm10 and [^{46}Sc]-cm10 with the OLINDA 2.1.1 software for male ICRP 89 phantoms.

Tissues	**[^{48}Sc]-cm10**	**[^{47}Sc]-cm10**	**[^{46}Sc]-cm10**
Adrenals	0.435	0.0362	0.840
Kidneys	1.39	0.729	2.62
Liver	0.285	0.0736	0.477
Salivary Glands	0.200	0.107	0.375
ED (ICRP 103) (mSv/MBq)	0.112	0.0252	0.193

RESULTS

The equivalent doses in the main male organs calculated for [^{48}Sc]-cm10, [^{47}Sc]-cm10 and [^{46}Sc]-cm10 are reported in Table 2. The critical organs for [^{47}Sc]-cm10 are the kidneys, followed by the salivary glands and the liver. For [^{48}Sc]-cm10 and [^{46}Sc]-cm10 the critical organs are also the kidneys but followed by the adrenals and then by the liver. Due to its longer half-life, the values of organ equivalent doses calculated for [^{46}Sc]-cm10 are between 3.6 to 23.2 times higher than those calculated for [^{47}Sc]-cm10, making the [^{46}Sc]-cm10 ED value about 7.7 times higher than the [^{47}Sc]-cm10 ED. Despite ^{48}Sc shorter half-life, the equivalent dose values calculated for [^{48}Sc]-cm10 are also higher than those calculated for [^{47}Sc]-cm10, by a factor between 1.9 and 12, depending on the organ, due to the high-energy γ-emissions of ^{48}Sc (see Table 1). Therefore, [^{48}Sc]-cm10 ED value is about 4.4 times higher than the [^{47}Sc]-cm10 ED.

CONCLUSIONS

Despite extreme care should be taken when using biodistribution data from animals to predict doses to humans, results obtained in this study are useful to have an idea of the contribution of ^{48}Sc, ^{47}Sc and ^{46}Sc radioisotopes to the doses imparted to healthy individuals due to radiopharmaceuticals. Both [^{46}Sc]-cm10 and [^{48}Sc]-cm10 produce ED values higher than that due to [^{47}Sc]-cm10 (7.7 and 4.4 times, respectively). However, ^{48}Sc decays faster than the other radionuclides, so its contribution to the dose is expected to be negligible after some tens of hours. Besides this, the ^{48}Sc radioisotope is expected to be produced by the ^{nat}V(p,x)^{47}Sc reaction only for proton energy higher than 35 MeV [3]. On the other hand, ^{46}Sc is the radioisotopic impuritiy of major concern due to its quite long half-life and high energy γ emission. Considering the limit of the maximum contribution of ^{46}Sc to the total ED as 10%, the radionuclidic purity of [^{47}Sc]-cm10 radiopharmaceutical must be higher than 98.57%.

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