Dealing with Dry Waste Disposal Issues Associated with 177mLu Impurities: A Long-Term Challenge for Nuclear Medicine Departments

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Short communication

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Dealing with dry waste disposal issues associated with ^{177m}Lu impurities: a long-term challenge for Nuclear Medicine departments

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Abstract:

Purpose: A strategy for management of radioactive waste associated with ^{177}Lu-dotatate (Lutathera®) treatments was established in our institution, based on predicted storage times of 3 to 5 years extrapolated from the results of a 2-year measurement study. The aim of this work was to validate the model used by identifying contaminants and confirming disposal based on the clearance level twice-the-background was within expected time frames.

Methods: We conducted a prospective series of measurements of radioactive waste associated with the first 65 treatments administered. Sequential measurements of the first 45 vials used were performed on a dose calibrator to identify contaminants. Exposure rates in contact were monitored with a dose ratemeter on a 6-monthly basis for all types of waste stored: 46 empty vials, 19 vials partially used and 67 biohazard containers.

Results: Initial median activity of the first vials used was 118 MBq [4 - 4188 MBq]. For each vial, the decay curve of activity obtained was adjusted to a bi-exponential model. The major component, representing 99.7 % of the activity, has a half-life of 6.5 ± 0.2 days, corresponding to ^{177}Lu. The second, representing only 0.3 % of the activity and having a half-life of 156 ± 24 days corresponding to ^{177m}Lu, determines necessary storage times. Partially used vials can be disposed of after 5 years, other waste after 3 years. Compliance with the regulatory clearance level is achieved within expected time frames.

Conclusion: Although only present as traces, ^{177m}Lu results in major radioactive waste disposal issues for hospitals. Availability of radiopharmaceuticals without impurities appears to be crucial for an expanding use of targeted radionuclide therapy.

Key words: ^{177}Lu-dotatate, Lutathera®, ^{177m}Lu impurities, storage, waste

Introduction

Council Directive 2013/59/Euratom of December 5, 2013 (1) re-emphasized the key role of optimization of protection, the ALARA concept, applying to all categories of exposure namely medical, occupational and public. Waste management strategies and environmental monitoring programs must be developed to ensure the best possible protection of the population. The license issued by national authorities to hold and make use of unsealed radioactive sources in Nuclear Medicine (NM) requires hospitals to control the radioactive waste that is generated. Prior analysis and measurements have to be performed each time a new radionuclide is intended to be used so that all practices can be optimized.

Lutetium-177 (^{177}Lu) is very promising for use in Targeted Radionuclide Therapy (TRT). According to recent results of the VISION trial on treatment of metastatic prostate cancer with ^{177}Lu-PSMA-617 (2), a significant increase in the number of patients treated with ^{177}Lu and consequently, in the volume of radioactive waste produced, is expected in the coming years. NM departments must therefore review and adapt their radiation risk control strategy to the characteristics and properties of this new marker. ^{177}Lu decays to stable Hafnium-177 (^{177}Hf) with a half-life of 6,64 days, emitting beta particles with maximum energy 497 keV (79 %) together with low energy and low abundance gamma rays (208 keV, 11 %; 113 keV, 6 %), resulting in a low risk of external exposure when away from the source. Safe storage of waste can be organized in facilities designed for Iodine-131 high energy gamma rays.

Assessing the impact of a growing use of ^{177}Lu in our hospital, we focused on the concerns arising when starting treatments with ^{177}Lu dotatate (Lutathera®, Advanced Accelerator Applications/Novartis), a somatostatin analogous peptide, indicated for the treatment of well-differentiated, metastatic gastro-entero-pancreatic neuroendocrine tumors (3). On-site storage of waste was initially organized according to ^{177}Lu half-life, for an expected time frame of 3 months corresponding to 13 half-lives. However, after 3 months decay, exposure rates (ER) in contact with empty vials were still 14 times higher than the clearance level and they were no longer decreasing on a weekly basis. No waste could be disposed of. A study to determine optimum waste management procedures was therefore carried out. Necessary storage times ranging from 3 to 5 years were estimated from the results of a 2-year measurement study (4). A waste management strategy was then established based on these time frames.

The purpose of this paper was to validate the model used by:

- Identifying and quantifying long-lived contaminants.
- Confirming waste can be disposed of within expected storage times.

Material and methods

Single-dose Lutathera® vials contain a ready-to-use solution for infusion whose activity is 7.4 GBq (± 10 %) at the date and time of administration. Recommended treatment regimen in adults consists of 4 infusions of 7.4 GBq each administered every 8 ± 1 weeks. A reduction in the administered activity up to 3.7 GBq may be justified for clinical reasons. In that case, a partially used vial with residual activity 3.7 GBq is discarded and stored for decay. Vials also contain metastable Lutetium (^{177m}Lu) impurities, a ^{177}Lu nuclear isomer associated with the direct production process (5). 78.6 % of ^{177m}Lu decays to ^{177}Hf and 21.4 % to ^{177}Lu with a half-life of 160.4 days via isomeric transition.

Treatments are administered in a dedicated infusion room within the NM department, where dry waste is separated and collected in appropriate containers. ER in contact with all types of waste are measured at the end of every procedure. Non-radioactive waste is discharged. Radioactive waste is identified and transferred to dedicated storage for decay. Practical optimization of the volume of storage available was achieved by considering 3 separate types of waste: biohazard containers, empty (fully used) vials and partially used vials with residual solution of high activity.

The waste management strategy was established as follows:

- Empty vials and biohazard containers are held in storage for an estimated period of 3 years before disposal based on the clearance level of twice-the-local-background (2*BKG = 0.1 $\mu Sv.h^{-1}$). Vials are discarded in bags on a 6-monthly basis.
- Partially used vials are stored in their as-delivered lead container for 3 years, before being discarded in bags on a yearly basis. Bags are then stored for 2 additional years before expected disposal.

We conducted a prospective series of measurements of waste associated with the first 65 treatments, administered on an outpatient basis from November 2017 to July 2019. Data for Lutathera® vials used are presented in Table 1.

According to batch release documents, median ^{177m}Lu activity in 25.0 mL Lutathera® vial is 1.08 MBq [0.74 - 1.61 MBq] at expiration time, when exemption level is 1 MBq (1).

Sequential measurements of the first 45 vials used were performed on a dose calibrator Veenstra Medi-404 (Medisystem, Guyancourt, FR) to identify and quantify contaminants. ER in contact were monitored with a dose ratemeter IdentiFINDER 2 (High Tech Detection Systems, Massy, FR) on a 6-monthly basis for all types of waste stored: 67 biohazard containers, 46 empty vials and 19 partially used vials.

Results

Initial median activity was 118 MBq [4 - 4188 MBq]. For each of the 45 first vials used, the decay curve of activity obtained from sequential measurements was adjusted to a bi-exponential model (Figure 1). Percentage and half-life of the 2 components identified are presented in Table 2**.** The major component, representing 99.7 % [85.6 – 99.8 %] of the activity, has a measured half-life of 6.5 ± 0.2 days corresponding to ^{177}Lu. The second, representing only 0.3 % [0.2 - 1.7 %] of the activity and having a measured half-life of 156 ± 24 days corresponding to ^{177m}Lu, determines necessary storage times.

ER measured in July 2021, in contact with all waste stored for decay since 2018, are presented in Tables 3 to 5.

Empty vials (Table 3): ER of each vial from the first semester 2018 was the local BKG (0.05 µSv.h^{-1}). In contact with the bag of 19 vials, ER was complying with the clearance level 2*BKG. This bag was disposed of.
An additional 6 months of storage were necessary for vials of the second half of 2018, 12 months for those of the first semester 2019.

Biohazard containers (Table 4): 97.1 % of waste collected in 2018 were disposed of. Only one container of the second half of 2018, with an ER of 0.3 µSv.h^{-1} (6*BKG), required one additional year of storage.
10 of the 26 containers of the first semester 2019 (38.5 %) were disposed of after only 2 years decay. The others were maintained in storage for 6 additional months.

Partially used vials (Table 5): After a median storage time of 34.6 months, median activity of the 10 vials used in 2018 was 100 kBq [26 – 165 kBq]. ER were still 4 to 14 times higher than the clearance level, requiring 2 additional years of decay. When discarded in a bag, total residual activity was about 1 MBq and ER in contact with the bag was 50 times higher than the clearance level. 3 additional years of storage were then necessary before the bag of 10 vials could be disposed of instead of 2 years if vials are disposed of on an individual basis.
Vials used in 2019 had a median activity of 210 kBq [105 – 615 kBq] and their ER was 8 to 41 times higher than the clearance level: 3 additional years of decay were required. ER in contact with the bag of 9 vials confirmed 4 additional years of storage would be necessary before disposal.
Residual ^{177m}Lu activity in these 19 vials was 3 times higher than the exemption level.

Discussion & conclusion

This study demonstrated that although only present as traces, ^{177m}Lu determines minimum storage times, below which dry waste can't be disposed of without activating the alarm of the portal monitor used for radiological output checks of containers. Long-term storage must therefore be organized according to ^{177m}Lu half-life of 160.4 days within appropriate premises. 5 years of decay are necessary before disposal of individual vials with residual solution, 3 years for empty vials and biohazard containers. The waste management strategy established ensures that compliance with the regulatory clearance level is achieved within predicted storage times and the model can be validated.

In our institution, the volume of storage available had to be doubled since the beginning of Lutathera® therapy. Additionally, a cold room, dedicated to the storage of long-lived putrescible and biohazardous waste, was built to optimize the protection of staff exposed to infectious hazard by avoiding extreme heat in the facility.

Assessing the impact of a growing use of ^{177}Lu in hospitals, waste management strategies to be developed will depend on the production process used by suppliers. ^{177m}Lu associated with the direct production route results in major waste disposal issues for NM departments. Primary emphasis must be placed on minimization of the volume of long-lived waste to ensure and maintain compliance with regulatory requirements. Availability of radiopharmaceuticals without impurities appears to be crucial for an expanding use of TRT.

Table 1: Data for the 65 Lutathera® vials used for the first treatments administered

	Treatments	Activity measured MBq (mean ± SD)		
Vials	N	At reception time	At infusion time	Discarded post infusion
Fully used (empty)	46	7562 ± 119	7404 ± 122	110 ± 14
Partially used	19		4118 ± 836	3800 ± 800

Table 2: Data for the decay curves of activity obtained with sequential measurements of the 45 first Lutathera® vials used

	Vials	Percentage (%)	Correlation coefficient	Half-life (Days)
Component	N	Median (range)	Median (range)	Median (range)
First	41	99.7 (85.6 – 99.8)	1.00 (0.96 – 1.00)	6.6 (5.7 – 7.2)
Second	45	0.3 (0.2 – 1.7)	1.00 (0.98 – 1.00)	152 (104 – 205)

Figure 1: Example of the time-related decay curve of activity obtained from sequential measurements of one of the first 45 Lutathera®vials used

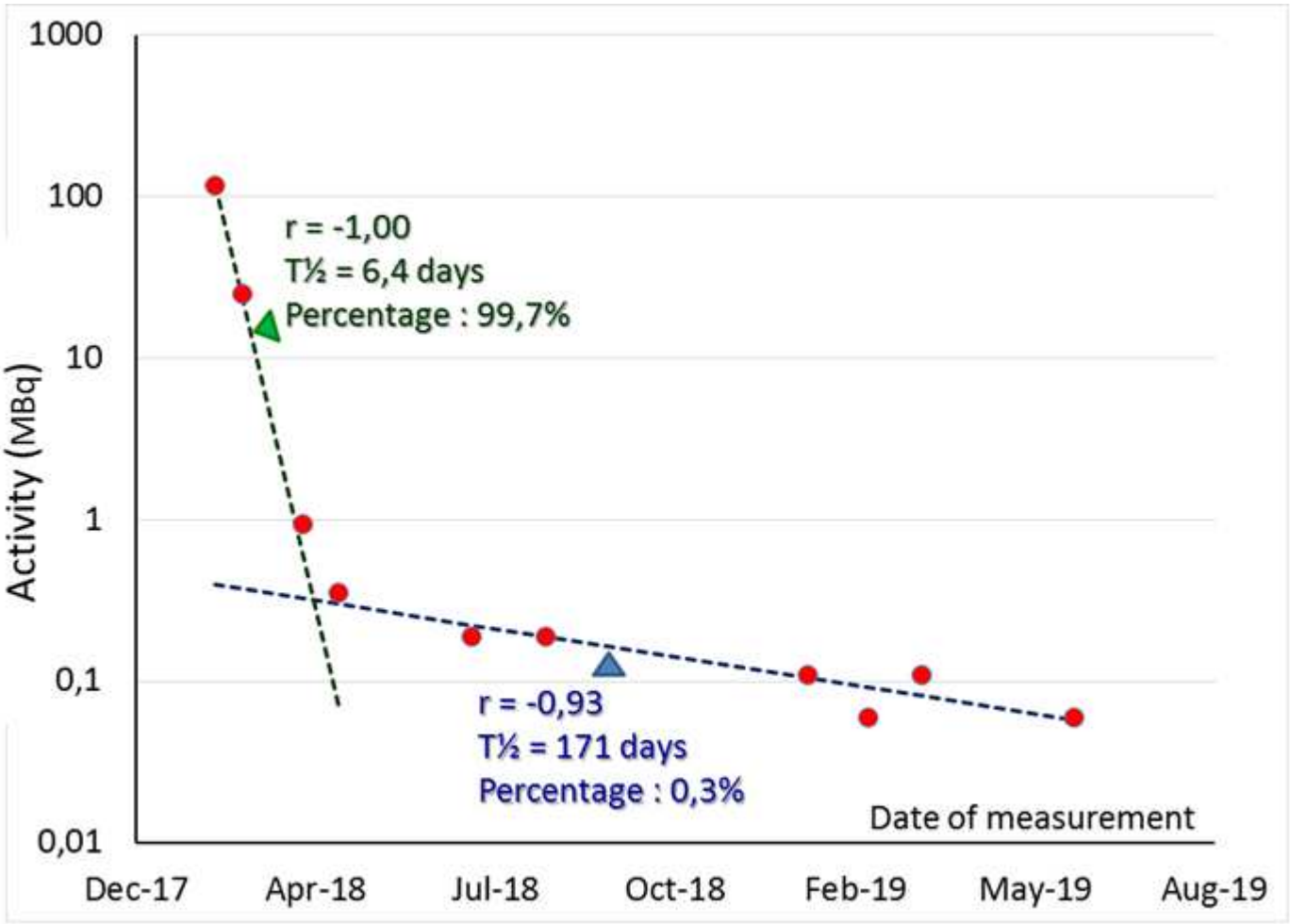

Table 3: Data for N empty vials discarded in 3 bags measured in July 2021 presented as median [range] values.

	Period of treatments		
Parameters	First half 2018	Second half 2018	First half 2019
Storage time (months)	39.4 [36.9 - 42.3]	34.6 [31.3 – 36.5]	25.5 [23.4 – 29.2]
Number of vials stored (N)	19	9	18
*(ER / 2 BKG) Ratio	0.5 [0.5 – 0.6]	0.7 [0.6 – 0.9]	1.1 [0.8 – 1.5]
Number of bags stored for decay	1	1	1
*(ER / 2 BKG) Ratio	1.0	2.1	4.5
Expected date of disposal	June 2021	December 2021	July 2022
Validation of the model	YES	YES	YES

**ER = Exposure Rate in contact; 2 BKG = regulatory clearance level twice-the-background*

Table 4: Data for N biohazard containers measured in July 2021 presented as median [range] values

	Period of treatments		
Parameters	November 2017 – June 2018	Second half of 2018	First half of 2019
Storage time (months)	40.1 [37.5 – 44.8]	34.7 [31.9 – 37.1]	26.7 [23.1 – 30.9]
Number of biohazard containers stored (N)	18	17	26
*(ER / 2 BKG) Ratio	0.7 [0.5 – 1.2]	0.7 [0.6 – 3.0]	1.1 [0.7 – 2.3]
Expected date of disposal	June 2021	December 2021	July 2022
% Waste disposed of in July 2021	100 %	94.1 %	38.5 %
Validation of the model	YES	YES	YES

**ER = Exposure Rate in contact; 2 BKG = regulatory clearance level twice-the-background*

Table 5: Data for N partially used vials discarded in 2 bags after 3 years decay, measured in July 2021 presented as median [range] values

	Period of treatments	
Parameters	December 2017 to December 2018	First half of 2019
Storage time (months)	34.6 [32.2 – 43.6]	29.1 [26.1 – 30.9]
Number of vials stored (N)	10	9
Residual activity per vial (kBq)	100 [26 – 165]	210 [105 – 615]
*(ER / 2 BKG) Ratio – Vials	8 [4.0 – 14]	15.0 [8.3 – 41.3]
Expected date of disposal	December 2023	July 2024
Validation of the model	YES	YES
Number of bags containing N vials	1	1
Total residual activity in one bag (MBq)	0.92	2.32
*(ER / 2 BKG) Ratio – Bags	50	183
Validation of the model	NO	NO

**ER = Exposure Rate in contact; 2 BKG = regulatory clearance level twice-the-background*

Declarations

- Ethics approval and consent to participate: not applicable
- Consent for publication: not applicable
- Availability of data and material: main paper
- Competing interests : not applicable
- Funding : not applicable
- Authors' contributions : not applicable
- Acknowledgements : not applicable

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