~~Three~~ Four Years of Experience Treating Patients with Lutathera® (Lutetium, Lu-177, dotatate)

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Abstract. Lutathera® is indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) and was approved by the United States Food and Drug Administration (US FDA) for use as a commercially available therapeutic agent on January 26, 2018. Fox Chase Cancer Center first started treating patients with Lutathera® in December 2016 under a clinical trial and progressed to offer Lutathera® to patients as a treatment option in April 2018 and has administered Lutathera® 149 times as of November 2020. The radiation safety considerations for the use of Lutetium 177 (Lu-177) include radioactive materials licensing, staff training, treatment room preparation/decontamination, and radiation safety precautions for patients. Lessons learned include verifying that the toilet is not leaking in the treatment room prior to therapy, allowing patients to remain in their own clothing rather than changing into hospital gowns, requesting that all patients use a seated position when using the bathroom, patients should drink a lot of fluids but they can drink too much, we need to be aware of holiday schedules for international therapy agent production facilities, treatment room preparation is different for incontinent patients, patients can be discharged the same day as therapy under United States Nuclear Regulatory Commission regulations, and gamma well counter efficiency for Lu-177 is very low. Lessons learned are offered to help other radiation safety staff as more medical centers begin to offer Lutathera® to their patients.

KEYWORDS: *Lutetium 177, Lutathera®, Radiation Safety*

1 INTRODUCTION

Lutathera® is a peptide receptor radionuclide therapy (PRRT) "indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GRP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults [1]." Lutathera®, ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, is composed of a lutetium radionuclide chelated to a peptide. Lutetium-177 emits both beta and gamma radiations. Lutathera® is administered by intravenous (IV) injection and binds to somatostain receptors on cells[1]. The Lutathera® is then incorporated into the cancer cell and the radiation will cause cell death. In the United States, Lutathera® is approved for second line therapy after disease progression on somatostatin analogs.

Lutetium-177 has a physical half-life of 6.7 days, maximum beta energy of 498 keV(78.6%), 208 keV (11%) gamma, and 113 keV (6.4%) gamma. The beta tissue penetration is a maximum of 1.7 mm with an average tissue penetration of 0.23 mm. ^{177}Lu is effective in killing targeted tumor cells while limiting the effect on neighboring normal cells.

The patient will receive a total of 4 doses (7.4 GBq each dose) of Lutathera® spaced 8(±1) weeks apart. The patient will receive a co-infusion of amino acids to minimize the radiation dose to the kidneys. The amino acid infusion will begin 30 minutes prior to the Lutathera® infusion and will continue for approximately 3 hours after the Luthathera® infusion is completed. The therapy day for the patient is typically between 5 and 6 hours long.

A multidisciplinary team is required for Lutathera® therapies. The Lutathera® team at Fox Chase Cancer Center includes the Endocrinologist, Nuclear Medicine Authorized User, Nuclear Medicine Technologist, Nurse, Radiation Safety, Pharmacy, and a dedicated Lutathera® Patient Coordinator. The Lutathera® Patient coordinator is integral to the success of our program and is responsible for coordinating insurance approvals, completion of required imaging and blood tests, scheduling of each therapy, and coordinating the efforts of the multidisciplinary team.

2 RADIATION SAFETY CONSIDERATIONS

2.1 Patient Release

In the Unites States, some radiopharmaceutical therapy patients can be allowed to be treated as outpatients, as long as exposure criteria defined in the regulations is met. The United States Nuclear Regulatory Commission (US NRC) Consolidated Guidance About Materials Licenses Program-Specific Guidance About Medical Use Licenses NUREG-1556 Volume 9, Revision 2, Appendix U, Equation U.2 was used as the basis for determining if Lutathera® patients could be released from the hospital or would require a hospital stay[2]. The equation is as follows:

$$\text{Exposure from patient} = \frac{34.6\ \Gamma\ Q_0\ T_p\ OF}{r^2} \quad (1)$$

Γ = 0.00517 (μSv•m^2/MBq•h) [3]
Q_0 = Initial activity (use mCi in the equation) = 7.4 GBq
T_p = physical half-life = 6.7 days
OF = Occupancy Factor = 0.25 for $T_{1/2}$ > 1d
r = distance from patient = 100 cm

Solving the equation results in a value of 2.1 mSv and the US NRC allows for the release of a patient from a licensee's control if the total effective dose equivalent to any other individual from exposure to the released individual is not likely to exceed 5 mSv [4]. The patient received instructions immediately prior to each therapy on methods to reduce their exposure to other individuals as low as reasonably achievable.

2.2 Potential Sources of Contamination

2.2.1 Excretion

The majority of Lutathera® is excreted via the renal system with some also being excreted in feces. It is estimated that the patient will have excreted 44% of the activity within 5 hours, 58% within 24 hours, and 65% within 48 hours following the Lutathera® administration [5]. Greater than 99% will be eliminated within 14 days after the administration of Lutathera® [5]. Patients are encouraged to drink enough fluids necessary to urinate every hour the day of infusion and the day after the infusion. However, consuming too much fluid can cause sodium levels to drop resulting in seizures, we recommend that patients drink fluids with electrolytes.

Although excretion is primarily renal, fecal excretion is possible. This will be a consideration for patients with colostomies and will require additional radiation safety precaution training for the patient.

2.2.2 Lutathera® Vial

The Lutathera® vials are occasionally found to be externally contaminated upon receipt from the radiopharmacy. When handling the vial assume that it is contaminated and change gloves frequently to avoid cross contamination of touched surfaces.

In the United States, if the patient requires a reduced dose administration, 3.7 GBq can be administered instead of 7.4 GBq, the Nuclear Medicine Technician will be required to remove 3.7 GBq from the vial prior to administration. This is due to the fact that the radiopharmaceutical vendor does not currently have permission from the US FDA to provide a 3.7 GBq dose. Careful removal of the unwanted dose is essential for minimization of contamination.

The Lutathera® vial should be routinely visualized during the infusion to verify fluid levels inside the vial and to check for bubbling visible on the vial septum. When bubbling is observed, forceps and

gauze are used to adsorb the Lutathera® and the gauze is disposed as radioactive waste. A syringe can be used to push air into the vial and lower the fluid level.

2.3 Therapy Day

2.3.1 General Precautions

Gloves and shoe covers are used by all staff during Lutathera® administrations to minimize the potential for personal contamination and to control the spread of any potential contamination. Tongs or forceps are used when manipulating the vial. The nurse providing care the day of therapy is provided radiation dosimetry.

2.3.2 Room Preparation

Fox Chase Cancer Center has two lead shielded infusion rooms each with a private bathroom that were designed for another project but are now used for our Lutathera® patients. The therapy room(s) are prepared in advance of the patient arrival to minimize the time required to return the room to unrestricted use status. Based on nearly four years of experience our preparation has been simplified to using brown paper on the floor around the infusion chair, a brown paper path into the bathroom, brown paper under the sink, and absorbent flooring placed under and near the toilet. We cover the toilet seat and handle, the sink handle, the soap dispenser, and the television remote with plastic wrap. We cover the infusion chair with a folded sheet.

2.3.3 Lutathera® Administration

A Nuclear Medicine Technologist brings the Lutathera® dose to the infusion room from the Nuclear Medicine Department and Radiation Safety is present in the infusion suite. The Nuclear Medicine Technologist will insert the required needles into the Lutathera® vial while the nurse manages all of the patient's IV tubing connections. Once the infusion has begun, Radiation Safety will survey the Nuclear Medicine Technologist and nurse for potential contamination. Shortly after the infusion, Radiation Safety will verify, with an ionization chamber survey of the patient's IV site and abdomen, that the infusion is starting successfully. The Nuclear Medicine Technologist and Radiation Safety staff do not stay in the infusion suite for the duration of the infusion but will return to the infusion suite in approximately 30 minutes.

After approximately 30 minutes the Lutathera® IV is removed from the patient by the nurse and the Nuclear Medicine Technologist collects the IV tubing and places it in a sharps container. The nurse and nuclear medicine technologist are again surveyed by Radiation Safety for potential contamination. All the materials associated with the Lutathera® administration are removed from the area and transported back to the Nuclear Medicine department. The vial is assayed post treatment to determine administered activity.

2.3.4 Patient Exposure Measurements

The exposure rate at the Lutathera® IV site is measured with an ion chamber on contact and at 30 cm approximately 5 minutes after the completion of the Lutathera® infusion. This measurement is taken to quickly assess if an extravasation occurred. If an extravasation is identified, corrective actions will be taken to minimize potential skin effects.

Exposure readings are also taken after the completion of the amino acid infusion. Using an ion chamber, measurements are taken on contact with the abdomen, 30cm from the abdomen, and at 1m.

2.3.5 Room Decontamination

Radiation Safety surveys the infusion room and adjoining bathroom for contamination with a GM meter and decontaminates surfaces as necessary. Infusions that proceed with no spills result in infusion rooms that are typically not contaminated. Contamination is typically found in, on, around, and sometimes under the toilet. In our experience, the majority of the flooring materials used can be disposed as non-radioactive, with the notable exception of the absorbent material placed under the toilet that is frequently held for decay in storage.

After decontamination is complete, swipe surveys are taken throughout the infusion room and adjoining bathroom. The swipes surveys are counted in a liquid scintillation counter to verify that the room can be released for unrestricted use. A liquid scintillation counter is highly efficient at seeing Lu-177 whereas a gamma well counter available in nuclear medicine departments has a very low efficiency for Lu-177.

Ion chamber readings are taken throughout the infusion room and adjoining bathroom. The measured readings have all been significantly below 0.02 mSv/hr. The exposure readings are typically background with notable exception being the toilet bowl which typically reads twice background and if a patient is incontinent in the infusion chair, readings above background have been recorded.

2.3.6 Radioactive Waste

There are three main sources of radioactive waste: the Lutathera® vial containing residual Lu-177, IV tubing and items associated with the infusion that are placed in a biohazardous sharps container, and waste generated during room decontamination process. In the United States licensees are allowed to hold radioactive wastes with half-lives less than 120 days for decay-in-storage prior to disposal without regard to its radioactivity [4].

Decay-in-storage has been used successfully with sharps containers and wastes generated during room decontamination. Wastes are surveyed with a GM meter and have been found to be indistinguishable from background. However, the Lutathera® vials have been found to contain Lu-177m (half-life: 160 days), a longer lived contaminant that is not permitted for disposal using decay-in-storage. The Lutathera® vials are disposed of by transfer to a radioactive waste broker.

3 LESSONS LEARNED

3.1 Toileting Issues

Lutathera® is excreted primarily through the urine, therefore post Lutathera® infusion urine spills are radioactive contamination events. Incontinent patients are of specific concern for the infusion chair. If contaminated, the chair is likely not able to be completely decontaminated. The referring Medical Oncologist now has a conversation with patients prior to therapy to determine if they have incontinence issues. If incontinence issues are identified, an adsorbent leak proof covering will be placed on the chair prior to therapy.

Similarly, in the bathroom, male patients are requested to sit when voiding. When patients sit while voiding, splashing and dripping is minimized which ultimately aids in minimizing the amount of contamination left in the bathroom. Not all male patients honor this request, which results in extended decontamination times for these bathrooms.

3.2 Colostomy and Ileostomy Bags

Patients with colostomy and ileostomy bags may be candidates for Lutathera® therapy. The patient is instructed to empty the bag any time fluids are collected for one week. Patients are instructed to only open the bags over the toilet, even when opening just to release a build-up of air, and to rinse the bags each time they are emptied. Bags are typically changed every 3 to 7 days and changing too often or not enough can result in damaging the skin, therefore no modifications to routine practice were recommended for bag changes. We have successfully treated a patient with an ileostomy bag and no skin effects were noted at the site of the ileostomy bag over the course of the therapy and associated follow-up visits.

3.3 Hotel Stay Post-Lutathera®

Initially, patients would receive a peripherally inserted central catheter (PICC) line the morning of their Lutathera® infusion. Patients were on site from 7:00 until 16:00 or 17:00 and some patients were traveling more than 2 hours each way for the infusion. That resulted in a 14+ hour day for some cancer patients and patients asked about staying at a hotel for the night after their infusion.

Review of patient exposures post-infusion up to the point we received this question showed that the maximum exposure reading was 0.131 mSv/hr at 0.3m. Using the inverse square law gives a maximum exposure rate of 0.033 mSv/hr at 0.6 m, the distance between beds on opposite sides of a wall in hotel room [6]. Assume 8 hours in bed head to head with someone in the neighboring hotel room, maximum exposure to that neighbor would be 0.27 mGy.

The prescribing information indicates that 50% of Lutathera® is excreted in the first 4 hours post infusion and 64% is excreted in the first 24 hours. While the patient is at the hotel they may excrete up to 14% of the infused Lutathera®, up to 0.925 GBq [5]. If staff takes 5 minutes to clean the toilet, the exposure to the hotel staff member would be 0.30 mGy maximally.

Regulation in the United States required that exposure to members of the public be maintained below 1 mGy [7]. Exposures to guests in neighboring rooms and to hotel staff would be well below the regulatory limit, therefore, patients can stay in a hotel after their Lutathera® infusion if necessary.

3.4 Functioning Toilet & Sink

Lutathera® is primarily excreted through the renal system and a significant amount (up to 50%) will be excreted during the continuing amino acid infusion portion of the therapy [5]. The toilet that the patient uses will get contaminated. Identify any cracks and leaks prior to starting the infusion. We found a toilet leak after therapy was concluded that resulted in extensive bathroom floor contamination and storage of the toilet bowl for decay in storage. Similarly, check the toilet and sink for clogs prior to initiating the Lutathera® infusion. Maintenance staff will appreciate being able to make repairs prior to the introduction of radiation exposure in the room.

3.5 Extravasation

Lutathera® administration was initially administered through PICC lines but over time patients were switched to using intravenous (IV) lines. This switch shortened the length of a patient's therapy day and simplified scheduling. Extravasations are a potential consequence when using IV lines. We have experienced a single extravasation to date and while this was a new concern for the Radiation Safety staff, our infusion nurses are experienced in minimizing effects from extravasations. Prompt actions include compression, applying heat, and elevating the arm. Planar gamma camera images were obtained approximately 4, 24, and 120 hours post Lutathera® infusion. Initial images showed that the majority of Lutathera® was concentrated in the patient's left arm. Images taken at 24 hours showed that the Lutathera® was no longer concentrated in the arm and was dispersed throughout the body and incorporated in tumor sites.

Skin dose estimate was established using methodology from a published I-131 extravasation article, specifically equations 1, 2 and 3 [8]. We did not have dimensions for the extravagate site and chose to use 150 ml as the volume, the entire volume of co-infused saline, and 7.66 GBq as the total activity extravagated to establish a worst-case scenario. The dose rate calculated based on these assumptions was 0.04 Gy/min.

Exposure rates were measured using an ion chamber on contact and at 30m from the site of the extravasation and on the opposite arm (control) approximately 2, 3.5, 22.75, and 120 hours post Lutathera® infusion. A residual Lutathera® vial was measured in a dose calibrator and subsequently measured on contact and at 30 cm with the same ion chamber used to measure the exposure rates from the patient's arms. These measurements were used to estimate an activity present in the extravagated arm and these specific time points. It was observed that in approximately 2 hours the exposure rates dropped by 46%.

Combining all of this information it was estimated that the maximum skin dose was 7.8 Gy. No skin effects were identified when examined at the time of gamma camera imaging. The skin will continue to be followed during subsequent Lutathera® infusions (via PICC line) and associated follow up office visits.

3.6 Occupational Exposures

A single nurse has been involved in nearly all Lutathera® infusions since July 2018 and wears an optically stimulated luminescent dosimeter during Lutathera® therapies. The deep dose equivalent total exposure recorded on the dosimeter between July 2018 and September 2020, which included 109 Lutathera® infusions, was 1.11 mSv.

The Chief Nuclear Medicine Technologist covers nearly all Lutathera infusions and reports that Lutathera accounts for 80 to 90% of her total radiation exposure. Her annual deep dose equivalent exposures have been 1.1, 1.5, and 0.5 mSv for 2018, 2019, and 2020 respectively.

4 CONCLUSION

Lutathera® can successfully be offered as a radiopharmaceutical therapy with a well-coordinated care team organized by a single point person. The Lu-177 betas result in relatively low patient exposure rates at 1 m post infusion making this an ideal candidate for outpatient therapy. However, institutions need to be aware that Lu-177m may be present in therapy waste and will need to be disposed of accordingly. The Radiation Safety team is instrumental in answering patient's radiation safety related questions, preparing the infusion suite, monitoring for contamination throughout the therapy day, decontaminating the infusion suite post-infusion, and in responding to emergencies that arise.

5 REFERENCES

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