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Caring for Patients Receiving ^{177}Lu-DOTATATE, Lutathera®: A Treatment of Hope for Patients With Gastroenteropancreatic Neuroendocrine Tumors

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A B S T R A C T

Lutathera®, the trademark for lutetium 177Lu-DOTATATE registered to Advanced Accelerator Applications SA, is a peptide receptor radionuclide therapy used to treat gastroenteropancreatic neuroendocrine tumors positive for hormone receptor somatostatin. Lutathera specifically targets known tumor receptors and has been shown to decrease both tumor growth and spread. While available in Europe for many years, the Federal Drug Administration approved the use of 177Lu-DOTATATE in the United States in January 2018. 177Lu (lutetium) is a radioactive isotope with special precautions and considerations for safe administration of this treatment. When nuclear medicine, radiation safety, nursing, and the physicians work together as a team, the safe administration of Lutathera provides patients with another treatment option to battle cancer.

Lutathera® and GEP-NETs

Lutathera®, the trademark for ^{177}Lu-DOTATATE registered to Advanced Accelerator Applications, SA, Millburn, NJ, is a peptide receptor radionuclide therapy (PRRT) medicine used to treat gastroenteropancreatic neuroendocrine tumors (GEP-NETs) positive for hormone receptor somatostatin (Lui, 2015; LUTATHERA® Prescribing Information, 2018; Strosberg et al., 2017) (Box 1). Lutathera PRRT is an internal radioactive therapy in which ^{177}Lu (lutetium), a radioactive isotope with a half-life of 6-7 days, is bonded to the amino acid peptide, DOTATATE, and used to specifically target known tumor receptors. Initially, the drug seeks out and binds to the tumor receptor cells for DOTATATE, and then, the radioactive ^{177}Lu then works to destroy the cells (Lui, 2015; Strosberg et al., 2017). ^{177}Lu-DOTATATE, as a radionuclide therapy, must be administered by personnel trained in nuclear medicine safety protocols; therefore, radiology personnel and radiology nurses need an understanding of how to safely administer the treatment and provide quality care for the patients.

Although available in Europe for many years, the Federal Drug Administration (FDA) approved the use of ^{177}Lu-DOTATATE in the United States in January 2018. The drug completed multiphase multisite testing culminating in the recent approval that includes continued required safety tracking and reporting to be conducted through 2025 (Pazdur, 2018).

The patients being prescribed Lutathera are those with GEP-NETs. This classification includes a wide range of tumors that present along the gastrointestinal tract (Box 1). According to Schimmack et al. (2011), the incidence of GEP-NETs, which were once considered a rather rare cancer, has increased significantly to now being the second most common gastrointestinal cancer, surpassing colorectal cancer. The commonality of the symptoms makes differential diagnosis of GEP-NETs challenging. The presenting symptoms, such as sweating, flushing, palpitations, diarrhea, abdominal pain,

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Box 1
What are gastroenteropancreatic neuroendocrine tumors (GEP-NETS)?

GEP-NET refers to a group of tumors that are derived from neuroendocrine cell types along the gastrointestinal (GI) tract and pancreas. These tumors are sometimes referred to as carcinoids and islet cell tumors (Diez et al., 2013). According to Schimmack, et al. 2011, the GI tract and pancreas have 17 or more different neuroendocrine cell types from which these tumors can arise. Although these cell types present with attributes of both the neural and endocrine systems, tumors typically present from a specific area of the GI tract or pancreas. The GEP-NETs often present in patients in the age range of 50 to 60 years, a younger age of diagnosis in comparison to other carcinomas. The tumors come from a variety of cell types, and they can exhibit various clinical manifestations (Diez et al., 2013). The lack of specificity of these clinical manifestations complicates diagnosis of disease, thus delaying identification and treatment. Most patients have metastases of disease upon diagnosis (Diez et al., 2013; Schimmack et al., 2011).

Approximately half of the number of patients with GEP-NETs are classified as having tumors that actively secrete bioactive peptides and amines, and thus, they experience clinical manifestations related to this increased secretion. Symptoms will differ between patients, but some may experience glucose-management challenges from increased secretion of insulin or glucagon. Others may experience gastric pain and upset from ulcerations or hypersecretion in the stomach. An often-reported complex of symptoms known as carcinoid syndrome attributed to serotonin release in the form of 5-HT includes "diarrhea, abdominal pain, sweating, flushing, bronchospasm, tachycardia, and fibrotic heart disease" (Schimmack et al., 2011, pg 280). These symptoms are typically treated with somatostatin analogs such as octreotide. Survival for these patients depends on the timeliness of diagnosis, and if metastasized, it depends on the pattern of those metastases. Treatment of GEP-NETs has historically focused on the alleviation of symptoms and cessation of growth of the tumor and spread of the disease (Diez et al., 2013).

bronchospasm, heart disease, and bleeding (Schimmack et al., 2011), mimic multiple conditions such as irritable bowel syndrome, menopause, asthma, and peptic ulcers to name a few.

Potential adverse effects of Lutathera

Lutathera contributes to the overall radiation exposure that patients experience in their life time, and this cumulative radiation exposure is known to increase the risks for certain cancers. The most frequently identified adverse effects found in the phase 3 trial of Lutathera were gastrointestinal symptoms such as nausea, vomiting, and diarrhea, as well as abdominal pain and distension (Strosberg et al., 2017). Most patients reported these as symptoms in conjunction with the amino acids, with symptoms subsiding upon completion of the amino acid infusion. Patients may experience bone marrow suppression, with the most common condition being lymphopenia, followed by anemia, leukopenia, thrombocytopenia, and neutropenia (LUTATHERA® Prescribing Information, 2018; Strosberg et al. 2017). Patients with symptoms associated with low blood counts or resulting infections may need their treatment doses adjusted accordingly.

In addition, there is concern for patients' renal and hepatic functions, particularly in the presence of prior or ongoing disease. Lutathera therapy exposes the kidneys to radiation despite the prophylactic use of amino acids. Patients with comorbidities of impaired renal functions may be at increased risk for renal failure (Advanced Accelerator Applications, 2018). Although reported in only 1% of the patients in the clinical trials, patients with hepatic tumors may experience hemorrhage, edema, or necrosis in the liver; therefore, liver functions should be monitored and may indicate the need to adjust therapy (Advanced Accelerator Applications, 2018; LUTATHERA® Prescribing Information, 2018).

Patients may experience the symptoms of neuroendocrine hormonal crisis (Box 1) such as flushing, diarrhea, bronchospasm, and hypotension with the Lutathera therapy. The symptoms may occur both during the infusion and in the 24 hours after infusion. Hormonal crisis was reported in 1% of patients during clinical trials. Symptoms may require medical intervention as indicated by their severity (Advanced Accelerator Applications, 2018; LUTATHERA® Prescribing Information, 2018).

No studies have been conducted on the effects of Lutathera during pregnancy and breastfeeding. However, radioactive therapy has the potential to cause harm to the fetus. Therefore, all women of reproductive age need to be screened for pregnancy before Lutathera is administered. Patients (both female and male) need to be counseled to protect against pregnancy. Prophylaxis to prevent pregnancy needs to be maintained for at least 7 months after treatment is completed for women and 4 months after treatment is completed for men with female partners. In addition, there are no studies on levels of ^{177}Lu-DOTATATE in breast milk in humans or animals; however, caution needs to be taken due to the potential risk to the infant. Therefore, the recommendation is for breastfeeding to be discontinued during treatment and should not be initiated again for at least 2.5 months after treatment is complete. Both women and men are at risk for infertility with Lutathera treatment due to the radiation absorption by the ovaries and testes. The level of radiation exposure of the reproductive organs reaches the range of exposure known to cause temporary or permanent infertility (Advanced Accelerator Applications, 2018; LUTATHERA® Prescribing Information, 2018).

Patient care considerations

Prescreening

During the prescreening process by the nuclear medicine physicians who will administer the Lutathera, patient preparation for treatment has already begun. Prescreening criteria include a known GEP-NET, positive diagnostic IN-111 Octeoscan or 68 GA-Dotatate scans, and that the patient is ≥18 years of age. Diagnostic scans

Table 1
Pretreatment blood work parameters as suggested by the Federal Drug Administration

Laboratory test	Acceptable values
Serum creatinine	<1.7 mg/dL
Glomerular filtration rate	>40 mL/min/1.73m^2
Hemoglobin	>8.0 g/dL
White blood cells	>2000/mL
Absolute neutrophil count	>1000
Total bilirubin	Not >3 ULN
Serum albumin	>3.0 g/dL

ULN = upper limit of normal.

confirm the GEP-NET receptor positive, thus indicating an expected uptake of ^{177}Lu-DOTATATE by the tumor. In addition, pretreatment blood work needs to be evaluated approximately 4 weeks before treatment and then again approximately 1 week before treatment. Blood work parameters, as suggested by the FDA (Table 1), determine the ability of the kidneys to process and excrete the drug, as well as any adverse effects of treatment or disease process on the liver, kidney, and bone marrow (Chen & LaCivita, 2017). Patients' urinary continence needs to be considered before arrival for treatment to plan for issues of radiation safety associated with incontinence. This will be discussed in more detail elsewhere in the article. In addition, patients who are pregnant or breastfeeding will need additional counseling before scheduling Lutathera infusion.

Another important consideration before scheduling Lutathera is prior, current, or future scheduled therapy with short-acting or long-acting octreotide. Octreotide therapy has traditionally been used for symptom management in GEP-NET patients, and also the long-acting formula has shown some promise in slowing tumor progression (Costa & Gumz, 2013). Octreotide blocks receptor sites, inhibiting the secretion of hormones from the tumors, thus decreasing symptoms and inhibiting tumor growth. However, to improve the effectiveness of the ^{177}Lu-DOTATATE receptor binding, patients should not be receiving short-acting octreotide therapy within 24 hours before and after Lutathera infusion or 4-6 weeks before infusion for the long-acting octreotide therapy.

Room Preparation and Considerations

The setup and cleanup of the treatment area needs to be coordinated with the nuclear medicine personnel, including specific guidelines prepared by the radiation-safety officer in each institution. Although each institution will have logistical challenges specific to their environment, prior preparation of the treatment room is necessary and should be coordinated in conjunction with the radiation-safety team to protect against and prevent contamination from ^{177}Lu in the patient care area environment. Consideration should be given to protecting areas of potential contamination, such as the mattress, floor along both sides of the bed, toilet seat and lid, floor around the toilet, and the patient tray table with water-resistant padding. In addition, consider covering areas coming in direct contact with the patient, such as door handles, sinks, counter tops, and faucets. Once the procedure is completed, the room will require a comprehensive survey by the radiation-safety team for areas of contamination and the proper procedures followed for disposing contaminated items and waste.

Amino Acids and Antiemetics

According to the Lutathera-prescribing information, the patient needs one intravenous (IV) access with a three-way valve for administration of prophylactic amino acids and antiemetics as needed in conjunction with the Lutathera infusion (LUTATHERA® Prescribing Information, 2018). However, two IV access points may be more advantageous in managing the Lutathera infusion. One will be used for amnio acid infusion, medication administration, and hydration as needed, whereas the second can be used for the Lutathera infusion. Many patients may have an implanted port in place which may be used for the non-Lutathera access site.

An amino acid infusion is given before, during, and after the Lutathera infusion. The amino acids serve to provide protection to the kidneys from reuptake of the ^{177}Lu-DOTATATE, thus decreasing the radiation dose to the kidney and reducing possible renal toxicity. As per the prescribing information, the amino acids used should consist of a 1.5-L to 2.2-L volume of a combination of lysine HCL and arginine HCL, both between 18 g and 24 g each. The amino acid infusion needs to be started at least 30 minutes before the Lutathera infusion and should continue at least 3 hours after the infusion. It is not recommended to decrease the amino acid strength or volume even if the Lutathera dose is reduced (LUTATHERA® Prescribing Information, 2018). The amino acid infusion may vary depending on institutional specific policies. Patients are encouraged to void frequently to decrease radiation exposure to the urinary tract. Patients who are unable to move safely to the toilet frequently should be considered for an indwelling catheter. In all situations, the patient's urine must be handled with care to prevent contamination of ^{177}Lu in the environment, thus limiting radiation exposure to patient, health-care providers, and caregivers. Therefore, gloves must be worn when assisting patients to the bathroom, when using urinals, or emptying indwelling catheter drainage bags. Urine must be contained and not dripped or spilled on the floor and the toilet seat (see Room Preparation). The toilet should be flushed twice after every use.

Antiemetics should be given prophylactically to prevent nausea and vomiting associated with the amino acid infusion. In addition to reducing discomfort for the patient, antiemetics may reduce the potential for increased radiation contamination to the environment associated with vomiting. The movement by the patient associated with vomiting may also interfere with the ^{177}Lu-DOTATATE infusion. Therefore, prevention with antiemetics is recommended.

Lutathera Infusion

Lutathera must be administered by a nuclear medicine professional as per the state board for radiology technologists. The prescribing information describes very specific steps for administration of Lutathera, which is performed using gravity infusion (Figure 1). Lutathera should not be given as an IV bolus. Lutathera infusion is started at least 30 minutes after the amino acids infusion, and it should take approximately 30 minutes to infuse.

Institutions need a clear comprehensive policy on the administration of Lutathera, including a process for the gravity infusion method to be followed. Either infusion pump or gravity method can be used in this process; a brief explanation of the gravity method, according to the Lutathera-prescribing information, is provided here (Figure 1). The gravity method transports the Lutathera into the patient's blood stream in a controlled manner while protecting the integrity of the radioactive solution. The infusion requires a 500-mL bag of 0.9% sterile sodium chloride solution (NS) to be infused into the bottle of ^{177}Lu-DOTATATE via a short needle that is attached to an IV tubing. The short needle must not touch the ^{177}Lu-DOTATATE solution but instead stop inside the ^{177}Lu-DOTATATE solution container above the top of the solution. This NS is used as a carrier of the ^{177}Lu-DOTATATE into the patient. The NS and the short needle are not connected directly to the patient. It is important to not allow the NS to flow into the ^{177}Lu-DOTATATE solution before the start of the infusion, and do not inject the ^{177}Lu-DOTATATE directly into the NS bag. Once the infusion begins, the NS will be infused slowly at a rate of 50 mL/h to 100 mL/h for the first 5-10 minutes, and then the rate should be increased to a rate of 200 mL/h to 300 mL/h for the remaining infusion (25-30 minutes). The NS infusion rate may be regulated by a clamp or by using an infusion pump as per institutional policy. Inside the ^{177}Lu-DOTATATE solution container, a second longer needle is placed which reaches through the solution and rests on the bottom of the container. This longer needle is connected to an IV tubing that has been primed with NS and connects to the patient's peripheral IV site designated for the ^{177}Lu-DOTATATE infusion. This infusion line must be exclusive for the ^{177}Lu-DOTATATE solution. Throughout the infusion, the radioactivity of the solution must be monitored, and the infusion will be complete when the radioactivity within the

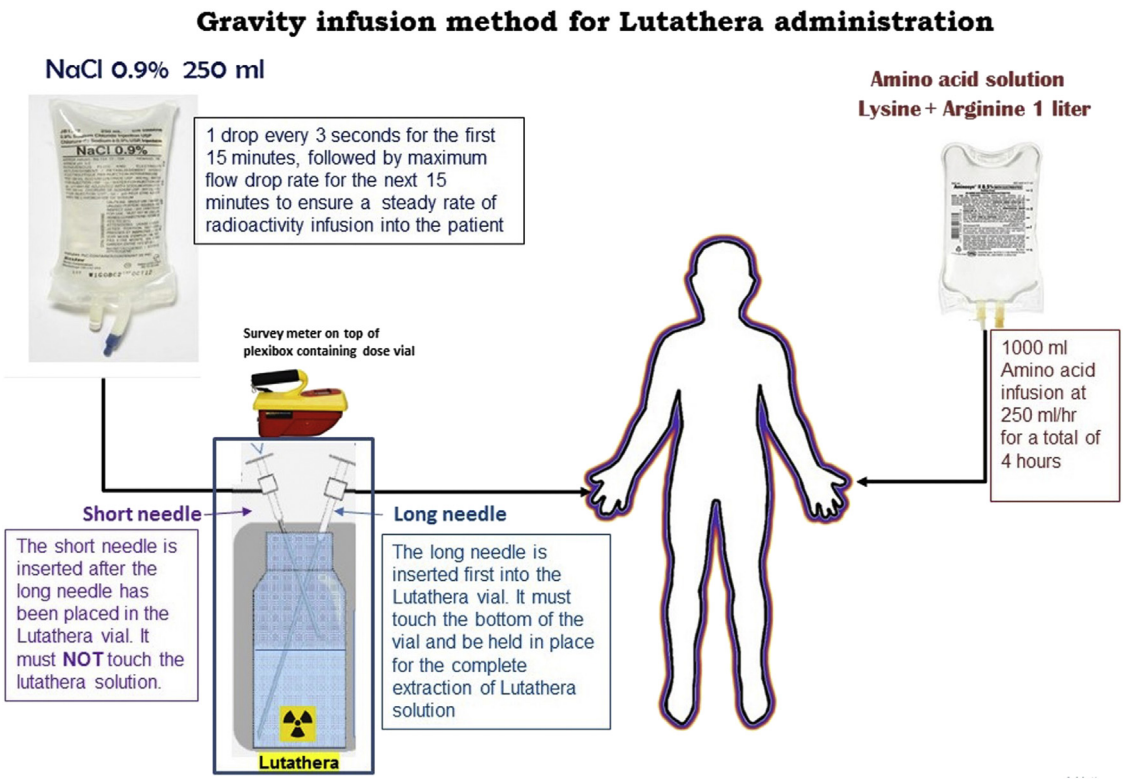

Figure 1. Gravity infusion of ^{177}Lu-DOTATATE. Reprinted with permission from UPMC Presbyterian Imaging Services. 177Lu-DOTATATE Lutathera® therapy. University of Pittsburgh Medical Center Nuclear Medicine Procedure Manual

solution container becomes stable, indicating no further infusion of radioactive material to the patient. The Lutathera-prescribing guidelines do not give specifics for these radioactive measurements, instead institutional policies should be followed. The amount of NS infused with each treatment will vary between patients. After completion of the infusion, complete the process by flushing the patient's IV with 25 mL of NS, and all unused products must be disposed of follow institutional policy for the disposal of radioactive material and items coming in contact with radioactive materials (such as floor covering, indwelling catheters, urinals, patient gowns, and so forth). Posttreatment imaging determines the distribution of the ^{177}Lu-DOTATATE throughout the body. The Lutathera treatment is repeated every 8 weeks for four treatments.

Patient Teaching

Patients discharged after Lutathera treatment need to be informed of the radiation risks and how to protect themselves, their families, and the public in the immediate days after therapy. Radiation from the Lutathera is detectable for up to 30 days in the patient's urine. Therefore, it is important to teach the patients to maintain a high level of hydration, thus protecting their urinary tract from the residual radioactive material in their system (Advanced Accelerator Applications, 2018). In addition, for 3 days after therapy when the radiation levels are the highest, patients should take extra precautions to limit potential radiation exposure for others. Patients should have a designated bathroom if possible. Encourage good personal hygiene, including frequent hand washing and using separate linens. The toilet should be flushed twice after each use, and men should sit when voiding to avoid urine splatter (UPMC, 2018).

Additional radiation-safety guidelines include limiting contact to others in those first 3 days after treatment. Patients should keep six feet between them and others as much as possible, thus minimizing close contact. This is especially important around pregnant women and young children. This would include not sharing personal items that may come in contact with saliva, urine, or sweat as all body fluids will contain radiation. Patients should sleep alone during this time, avoiding any intimate contact including kissing. Instruct patients to avoid food preparation for others and be sure to use separate tableware. For the first 3 days after treatment, it is best to avoid public places, and efforts should be made to avoid the use of public facilities and public transportation (UPMC, 2018). Medical personnel caring for the patient after Lutathera treatment need to be informed of the recent therapy and the radiation precautions in place. The radioactivity levels in the patient's body in the month after treatment may be high enough to be detected by sensitive radiation-detection devices used by homeland security. Therefore, if it is necessary to travel via airplane or entering federal facilities, it is advised to carry written verification of the recent therapy (UPMC, 2018).

Exemplars of Patient Experience with Lutathera

One patient, a wife, mother, and grandmother, reported the progression of her metastatic neuroendocrine tumors causing severe abdominal pain, fatigue, anorexia, and constant fevers. She was receiving the traditional treatments with somatostatin analogs. The patient had resigned herself to her inevitable death, refusing chemotherapy. However, with the help of her family, she was entered into a clinical trial for Lutathera. She began to see some increase in her energy levels despite continued weight loss with the first two treatments. With the third treatment, she experienced an eight-pound weight gain and began some light exercise. This renewed sense of well-being gave her and her husband the ability to take their grandchildren on a tropical vacation where she was able to play, swim, and enjoy herself without nausea or fatigue. The patient reports after her fourth and final treatment with Lutathera,

she feels a renewed sense of hope with zero pain and the energy to do the things in life she enjoys.

Another 65-year-old woman started Lutathera treatment while it was still in clinical trial. She had been coming to interventional radiology for intrahepatic chemotherapy for many years and was well known to the nursing staff. Chemotherapy was no longer working for her. The anxiety of knowing the treatments were no longer working was compounding her already debilitated condition with exhaustion, increased nausea, and perpetual worry. Throughout her treatment, she required continual emotional support to navigate the treatment process. According to her, "I am putting all my eggs in one basket. Lutathera is my last hope." She was able to complete her four rounds of Lutathera treatment, and with each subsequent treatment, her anxiety decreased and her outlook on life improved.

A husband and father of 4 began his Lutathera treatment after waiting many months to be placed on the crowded treatment schedule. After 3 years of various treatments for GEP-NETS of the pancreas with metastasis to his liver, his disease had been slowed by the treatment but was no longer responding. He was anxious to start Lutathera. When starting his third of four treatments, he reported a marked decrease in his physical symptoms and a renewed energy level. He was better able to participate in the lives of his busy family. The biggest challenge of the treatment was the posttreatment isolation. Lutathera treatment became a family effort requiring sacrifice, commitment, and planning by everyone. They followed the patient teachings closely, striving to protect the family as best they could. So, for 3 days after Lutathera, this father isolated himself in his home office. He slept on a sofa bed, ate meals alone, used disposable plates and tableware, designated one bathroom only for him, and interacted with the family only from a distance. Although difficult, he expressed the gratitude he felt for having the home situation to be able to put into place the protective precautions. The resulting well-being after treatment justified the personal and family sacrifice.

Another recently retired patient was looking forward to enjoying quality time with his wife, so he started taking better care of his health. Despite struggling with changing his eating habits, he was losing up to 10 pounds a month and experiencing constant abdominal cramping. He finally agreed to seek medical care, and after a CT, MRI, and a thorough workup, he was diagnosed with neuroendocrine tumors of the liver and pancreas. After systemic chemo and one round of transarterial chemoembolization, the tumors showed some improvement, but not quite enough, so Lutathera was recommended. With three Lutathera treatments completed, he is feeling great and thrilled with the improvement found on his scans. After the devastating diagnosis coming right at the time in his life when he should have been relaxing, traveling, and enjoying time with his wife, coupled with enduring systemic chemo which made him very sick, the patient and his wife are so thankful for Lutathera. He had suffered so much from the side effects of the chemotherapy that he contemplated just giving up. They are now amazed that the patient can receive this treatment comfortably. He experiences no nausea, watches TV with his wife, and carries on conversations during the treatment. When the treatment is over, they just go home. No suffering is experienced. But most importantly, it is working. It is giving them back their dreams of time spent together.

Conclusion—treatment of hope

Teamwork and collaboration among departments of nuclear medicine staff, radiation-safety personnel, radiology nursing, and the physicians are needed to successfully treat patients with GEP-NETs using the now FDA-approved Lutathera treatment process. Advanced Accelerator Applications (2018) provides detailed prescribing information to facilitate the creation of institution-specific policies and procedures for the administration of Lutathera while protecting patients and caregivers. Detailed and specific guidelines are needed to create a conducive environment for administration of Lutathera. In the process, patients need the emotional support of caring staff to work through their anxiety concerning this new treatment they are undertaking. Consistently, patients refer to embarking on their Lutathera treatment as a journey of hope. Hope for a better tomorrow.

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