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ACR-ACNM-ASTRO-SNMMI Practice Parameter for Lutetium-177 (Lu-177) DOTATATE Therapy

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Objectives: This practice parameter (PP) for Lutetium-177 (Lu-177) DOTATATE peptide receptor radionuclide therapy (PRRT) aims to guide authorized users in selection of appropriate adult candidates with gastroeneropancreatic neuroendocrine tumors (GEP-NETs) from foregut, midgut, and hindgut. The essential selection criteria include somatostatin receptor-positive GEP-NETs, which are usually inoperable and progressed despite standard therapy. Lu-177 DOTATATE is a radiopharmaceutical with high avidity for somatostatin receptors that are overexpressed by these tumors. This document ensures safe handling of Lu-177 DOTATATE by the authorized users and safe management of affected patients.

Methods: The document was developed according to the systematic process developed by the American College of Radiology (ACR) and described on the ACR Web site (https://www.acr.org/Clinical-Resources/Practice-Parameters-and-Technical-Standards). The PP development was led by 2

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ACR Committees on Practice Parameters (Nuclear Medicine and Molecular Imaging and Radiation Oncology) collaboratively with the American College of Nuclear Medicine, American Society of Radiation Oncology, and Society of Nuclear Medicine and Molecular Imaging.

Results: The Lu-177 DOTATATE PP reviewed pharmacology, indications, adverse effects, personnel qualifications, and required clinical evaluation before starting the treatment, as well as the recommended posttherapy monitoring, quality assurance, documentation, and appropriate radiation safety instructions provided in written form and explained to the patients.

Conclusions: Lu-177 DOTATATE is available for therapy of inoperable and/or advanced GEP-NETs when conventional therapy had failed. It can reduce tumor size, improve symptoms, and increase the progression free survival. The PP document provides clinical guidance for authorized users to assure an appropriate, consistent, and safe practice of Lu-177 DOTATATE.

Key Words: neuroendocrine tumors, gastroenteropancreatic neuroendocrine neoplasms, peptide receptor radionuclide therapy, Lu-177 DOTATATE, receptors, somatostatin

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PREAMBLE

This document is an educational tool designed to assist practitioners in providing appropriate radiologic care for patients. Practice Parameters and Technical Standards are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care.* For these reasons and those set forth below, the American College of Radiology (ACR) and our collaborating medical specialty societies caution against the use of these documents in litigation in which the clinical decisions of a practitioner are called into question.

The ultimate judgment regarding the propriety of any specific procedure or course of action must be made by the practitioner in light of all the circumstances presented. Thus, an approach that differs from the guidance in this document, standing alone, does not necessarily imply that the approach was below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set forth in this document when, in the reasonable judgment of the practitioner, such course of action is indicated by the condition of the patient, limitations of available resources, or advances in knowledge or technology subsequent to publication of this document. However, a practitioner who uses an approach substantially different from the guidance in this document is advised to document in the patient record information sufficient to explain the approach taken.

The practice of medicine involves not only the science, but also the art of dealing with the prevention, diagnosis, alleviation, and treatment of disease. The variety and complexity of human conditions make it impossible to always reach the most appropriate diagnosis or to predict with certainty a particular response to treatment. Therefore, it should be recognized that adherence to the guidance in this document will not assure an accurate diagnosis or a successful outcome. All that should be expected is that the practitioner will follow a reasonable course of action based on current knowledge, available resources, and the needs of the patient to deliver effective and safe medical care. The sole purpose of this document is to assist practitioners in achieving this objective.

This practice parameter was developed collaboratively by the ACR, the American College of Nuclear Medicine (ACNM), the American Society for Radiation Oncology (ASTRO), and the Society of Nuclear Medicine and Molecular Imaging (SNMMI).

*Iowa Medical Society and Iowa Society of Anesthesiologists v. Iowa Board of Nursing 831 N.W.2d 826 (Iowa 2013). Iowa Supreme Court refuses to find that the ACR Technical Standard for Management of the Use of Radiation in Fluoroscopic Procedures (Revised 2008) sets a national standard for who may perform fluoroscopic procedures in light of the standard's stated purpose that ACR standards are educational tools and not intended to establish a legal standard of care. See also, Stanley v. McCarver, 63 P.3d 1076 (Ariz. App. 2003) where in a concurring opinion the Court stated that "published standards or guidelines of specialty medical organizations are useful in determining the duty owed or the standard of care applicable in a given situation" even though ACR standards themselves do not establish the standard of care.

INTRODUCTION

This practice parameter is intended to guide appropriately trained and licensed physicians performing therapy with Lutetium-177 (Lu-177) DOTATATE. Such therapy requires close cooperation and communication between the physicians who are responsible for the clinical management of the patient, those who administer radiopharmaceutical therapy, and those who manage the attendant adverse effects. Adherence to this parameter should help to maximize the efficacious use of these procedures, maintain safe conditions, and ensure compliance with applicable regulations.

Application of this parameter should be in accordance with the ACR–AAPM (American Association of Physicists in Medicine)–Society for Pediatric Radiology (SPR) Technical Standard for Therapeutic Procedures Using Radiopharmaceuticals,[1] in so far as that standard relates to the handling of radiopharmaceuticals, radiation safety, and radiation protection of patients, personnel, and the public. There must also be compliance with applicable laws and regulations.

The goal of therapy with Lu-177 DOTATATE is to slow disease progression, to palliate symptoms, or even to extend life, while minimizing untoward adverse effects and complications.

Neuroendocrine tumors (NETs) are relatively rare and typically slow-growing neoplasms that originate in neuroendocrine tissue distributed throughout the body. They secrete bioactive amines and hormones, giving rise to variable clinical presentations.[2] Surgical resection of the tumor is the preferred initial therapy; however, because of the indolent course and nonspecific presentation of the disease, many patients are diagnosed with locally advanced or metastatic disease, making curative resection difficult or impossible. Alternative conventional treatments include use of nonradioactive somatostatin analogs that take advantage of the overexpression of somatostatin receptors (SSRs) by these NETs. Use of other agents, including cytotoxic chemotherapy, can be limited because of the unwanted adverse effects and minimal effectiveness in certain grades of tumor. Despite use of these currently available conventional treatments, many patients continue to progress with life-altering signs and symptoms, such as unrelenting diarrhea, flushing, or right-sided heart disease.[3,4]

Lu-177 DOTATATE is an effective therapy for patients with inoperable, locally advanced, or metastatic NETs that progress on conventional treatments.[3–6] Improvements in disease control rates, progression-free survival, overall survival, and quality of life have advanced this radiopharmaceutical agent to a place of primary consideration in advanced disease management.[7] Lu-177 DOTATATE specifically binds to the SSRs that are overexpressed on the cell surfaces of most NETs, with highest affinity for subtype 2. The complex formed is chemically stable and is internalized into the cell resulting in a favorable position to irradiate the nucleus to induce DNA damage–related inhibition of growth and death.[8] This treatment process is called peptide receptor radionuclide therapy (PRRT). β-Emission from ^{177}Lu has a maximum energy (Q value) of 0.5 MeV, range in soft tissues of 2 mm, and half-life of 6.7 days. ^{177}Lu also emits low-energy γ-rays at 208 keV (11% abundance) and 113 keV (6.4% abundance) that can be used for γ-camera imaging and dosimetry if desired.[9] Although PRRT with Lu-177 DOTATATE has been proven to be effective in NET, there are adverse effects and safety issues that must be understood and taken into consideration by the treating physicians so that appropriate plan and required interventions can be instituted.[5]

Adverse effects associated with PRRT with Lu-177 DOTATATE can be categorized as acute, subacute, or delayed.[5] It is highly advisable that a multidisciplinary team coordinate the care of a patient being considered for treatment with Lu-177 DOTATATE.[6]

General

Abdominal pain, nausea, and vomiting can occur typically within 24 hours of treatment. In addition, patients can also experience fatigue, diarrhea, alopecia, and cough.[7] In most cases, these symptoms are self-limiting and rarely require more than supportive therapy.

Nephrotoxicity

Lu-177 DOTATATE is excreted by the kidneys through glomerular filtration and is reabsorbed by the proximal tubules where radiation damage can occur.[9] Reduction of proximal tubular reabsorption has been effectively achieved with use of other ligands that can competitively bind to the receptors in the proximal tubular cells without affecting the SSR targets of Lu-177 DOTATATE in the circulation.[10] The most efficacious solution to date to reduce renal uptake of somatostatin analogs consists of a combination of basic amino acids lysine (25 g) and arginine (25 g).[9,11] Renal toxicity is generally mild and well-tolerated with amino acid coinfusions. However, grade 1 nephrotoxicity in 20% and grade 2 nephrotoxicity in 4% of patients has been reported.[5,7] Higher-grade toxicities are rare (0% to 0.4%).[4,5] Many studies have shown improvement of renal function over time, but long-term renal impairment remains a clinical concern, with some studies reporting an annual decrease in creatinine clearance of 3.4% to 3.8%.[12,13] Details on administration are provided in the "Specific Procedures" section of this document (IV.B).

Hematologic

The bone marrow is a rapidly dividing organ and is thus radiosensitive. Mild subacute myelosuppression can be seen in the first days to weeks after treatment and typically reverses within weeks after cessation of treatment.[5] The most frequently seen effects include anemia, thrombocytopenia, and leukopenia. Grades 3 and 4 bone marrow toxicity are seen less frequently and are generally reversible without intervention within 2 to 3 months but may take up to 12 months.[4,14,15] Bone metastases can increase the likelihood of myelotoxicity.[15,16] Rarely, 1% to 2% of patients can develop leukemias and myelodysplastic syndrome, which can lead to a fatal outcome in patients heavily pretreated with myelosuppressive therapies before receiving Lu-177 DOTATATE.[4,5,13,14]

Hepatic

Liver dysfunction has been noted with increase in bilirubin and transaminases. A few patients have developed grade 3 toxicity that progressed to liver failure and death within 1 year after PRRT.[5]

Hormonal Crisis

This is a rare complication that presents as flushing and significant diarrhea and, less frequently, heart failure, emesis, and bronchoconstriction. It typically occurs within 48 hours of infusion, with greater likelihood in patients with large tumor burden.[17,18] This is a serious adverse effect requiring prompt in-hospital care for continuous somatostatin analog infusion and supportive care.

Risk of Infertility

The recommended cumulative activity of 800 mCi (29.6 GBq) Lu-177 DOTATATE results in radiation absorbed dose to the testis and ovaries within the range where temporary or permanent infertility may ensue, such as seen after pelvic external beam radiotherapy.[4,6,7,19]

Facilities and their responsible staff should consult with their radiation safety officer (RSO) to ensure that there are policies and procedures specific to Lu-177 DOTATATE that address (1) required instrumentation, calibration, and calibration frequency, and (2) ordering and receiving, recordkeeping, safe use, and waste disposal in compliance with the applicable laws and regulations as described in ACR-AAPM Radiation Safety Officer Resources.[19]

INDICATIONS

Lu-177 DOTATATE is indicated for the treatment of SSR-bearing gastroenteropancreatic NETs (GEP-NETs), including foregut, midgut, and hindgut NETs in adults.[6]

QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL

The qualifications and responsibilities of physicians and other personnel performing these therapeutic procedures should be in accordance with the ACR-AAPM-SPR Technical Standard for Therapeutic Procedures Using Radiopharmaceuticals and/or the ACR-ASTRO Practice Parameter for Radiation Oncology.[1,20]

In addition, training and experience must be in compliance with the applicable laws and regulations.

SPECIFICATIONS OF THE EXAMINATION AND TREATMENT

The written or electronic request for a Lu-177 DOTATATE procedure should provide sufficient information to demonstrate the medical necessity of the examination and allow for its proper performance.

Documentation that satisfies medical necessity includes (1) signs and symptoms and/or (2) relevant history (including known diagnoses). Additional information regarding the specific reason for the procedure or diagnosis would be helpful and may at times be needed to allow for the proper performance of the procedure.

The request for the procedure must be originated by a physician or other appropriately licensed health care provider. The accompanying clinical information should be provided by a physician or other appropriately licensed health care provider familiar with the patient's clinical problem or question and consistent with the state scope of practice requirements (ACR Resolution 35, adopted in 2006, revised in 2016, Resolution 12-b).

Clinical Evaluation

The clinical evaluation should be in concordance with the ACR-ASTRO Practice Parameter for Radiation Oncology and the ACR-ASTRO Practice Parameter for Communication: Radiation Oncology.[20,21] The treating physician's initial evaluation of the patient must include review of the patient's history, physical examination, pertinent diagnostic studies, laboratory reports, and complete history of all available records of previous pertinent therapies, including, but not limited to, myelosuppressive systemic therapy and/or radiotherapy.

1. Verification of Pathology and Indication for Therapy: A pathology report confirming diagnosis of GEP-NET should be reviewed and included in the patient's record. Efficacy of Lu-177 DOTATATE is well documented, particularly in well-differentiated NET often with Ki-67 index of <20%.[22] Because Lu-177 DOTATATE localizes to NET expressing SSR, it is of paramount importance to confirm that the NET being treated expresses the required SSR through positive ^{111}In octreotide scan or ^{68}Ga-DOTATATE PET/CT (see ACR-ACNM-SNMMI-SPR Practice Parameter for the Performance of Neuroendocrine Tumor Scintigraphy and ACR Practice Parameter for the Performance of ^{68}Ga-DOTATATE PET/CT for Neuroendocrine Tumors).[23,24]
2. Discontinuation of Somatostatin Analog Therapy With Baseline Laboratory Evaluation: If the patient is being treated with long-

acting somatostatin analog, this should be stopped for 4 weeks before Lu-177 DOTATATE infusion. Short-acting analogs can be stopped 24 hours before PRRT. In anticipation of possible adverse effects, each patient should have a complete blood count with differentials and metabolic panel including renal and hepatic function tests. Such monitoring should be performed before each infusion and as needed for hematologic monitoring in between treatments. Dose reduction based upon laboratories is discussed in Section IV.B.2. Although institution and patient-specific considerations take precedence, a creatinine clearance >50 mL/min and grade 1 to 2 or less hepatic enzyme elevation or myelosuppression is sufficient to allow therapy. Women of childbearing age should undergo pregnancy testing.[6]

3. Special Populations: Lu-177 DOTATATE has not been tested in lactating patients, and these patients should be advised to stop breastfeeding while receiving treatment and for 2.5 months after the last treatment fraction, as effects on infants have not been determined. For patients of reproductive potential, discussion should be carried out to use effective contraceptive measures during and after PRRT. For female patients, because of the possibility of fetal harm, effective contraception should be continued for 7 months after the last treatment fraction of PRRT. For male patients with female partners, contraception should be continued until 4 months after the last treatment fraction.[6] Sexual activity should be avoided after therapy for 7 days. The radiopharmaceutical has not been tested in pediatric (<18 years old) and pregnant patients. Caution should be exercised in these patient populations, with extensive discussion regarding risk of radiation.
4. Quality Management: To use radiopharmaceuticals as unsealed sources for therapy, including Lu-177 DOTATATE, a "quality management" program must be in place as required by applicable state and federal regulations (An Agreement State is any state with which the Nuclear Regulatory Commission [NRC] or the US Atomic Energy Commission has entered into an effective agreement under subsection 274.b of the Atomic Energy Act of 1954 as amended, 73 Stat, 689). Key elements of such a program include written directives, duplicative procedures for identifying patients, careful record keeping to ensure prescribed administered activity, minimization of the possibility of infiltration for radiopharmaceuticals that are administered intravenously, procedures for minimizing radiation exposure or radiopharmaceutical contamination of personnel, family members of patients, and the public (eg, alerts regarding possible current or future pregnancy), procedures for containment of radioactivity, and an audit mechanism to ensure compliance with the program.
5. Informed Consent: Informed consent must be obtained and documented. See the ACR Practice Parameter on Informed Consent–Radiation Oncology.[25]
6. Treatment: The procedure and follow-up should be performed according to an established system of procedural steps unique for Lu-177 DOTATATE.[26]
7. Radiation Precautions: Radiation precautions and patient release criteria may be regulated federally by the NRC in many states or by the state (with regulations that are closely patterned on the federal regulations and may be more restrictive). The RSO, medical physicist, or health physicist for the local facility can provide information on the applicable regulations. Details on the federal regulations can be obtained at the NRC Web site (www.nrc.gov).

Under the guidelines of federal code 10 of the Code of Federal Regulations (CFR) 35.75[27] and key sections of NUREG-1556,[28] a patient may be released to the public if the total effective dose equivalent to any other individual (including any caregiver or family member) who is exposed to the patient is not likely to exceed 5 mSv (0.5 rem). If the total effective dose equivalent is likely to exceed 1 mSv (0.1 rem) to any individual, instructions (including written instructions) must be provided to the patient on actions to limit radiation exposure to others by using the "as low as reasonably achievable" (ALARA) principle. Some states may have specific rules and regulations regarding release of patients with significant residual activity.

The dose limits specified by the National Council on Radiation Protection and Measurements (NCRP) differ somewhat from the NRC regulations.[29] Because the fetus and children are more sensitive to radiation injury than adults, the NCRP specifies that children and pregnant women, whether or not they are members of the patient's household, should be limited to 1 mSv (0.1 rem). Any individual who has no familial connection to the patient and whose presence offers no emotional benefit should also be limited to 1 mSv, which is also the NRC dose limit to a member of the public.

Many radiation meters measure exposure rates in milliroentgens per hour (mR/h). For purposes of radiation protection and for low linear energy transfer radiation (including β-particles and most x-rays and γ-rays), the authors of this document accept the approximation that 1 mR, 0.01 mSv, and 1 mrem are equivalent. Thus, an exposure rate of 7 mR/h at 1 m is an adequate approximation to the dose rate, 0.07 mSv/h (7.0 mrem/h) at 1 m.

Specific Considerations During Lu-177 DOTATATE Therapy and Patient Release

According to radiation exposure calculations based on whole-body clearance data, patients may need to be kept in radiation isolation for 4 to 5 hours after the administration of the typical dose of 200 mCi (7.4 GBq) Lu-177 DOTATATE.[30] Postinfusion survey by physics or other radiation safety is performed to determine an acceptable maximum exposure rate that conforms to the 10 CFR 35.75 requirement of <5 mSv exposure anticipated to other individuals. An established protocol for documenting this survey result should be used and available. Until the patient has been released, the patient must be kept in an area with suitable radiation shielding to protect others from unnecessary exposure. An administration of 200 mCi Lu-177 DOTATATE typically results in exposure levels on the order of 2 mR/h at 1 m immediately after administration, declining to 1 mR/h after 24 hours, allowing outpatient treatment in most cases with appropriate training, protocols, infrastructure, and patient counseling. The procedures and practical example guidance for instruction of patients upon discharge have been reviewed in published literature.[31] For further information, see Appendix A (Supplemental Digital Content, http://links.lww.com/CNM/A369).

Modeling per the NUREG-1556 assumption of 0.25 occupancy factor estimates 1.8 mSv exposure dose to other individuals, thus requiring written instructions be given to the patient on ALARA principles. During therapy, involvement of trained radiation safety personnel qualified in safe management of unsealed sources, waste, accidental contamination, and counseling of patients is important. The patient and, as relevant, caregivers should be compliant with all radiation safety precautions and instructions. Education should occur before treatment, preferably at the time of consultation so that the patient and caregivers can plan ahead. Inability to comply with the precautions may require an admission or other special accommodations to account for the realities of patient life at home, as determined by the authorized user. The specific instructions and considerations for admission or other special accommodations will vary from institution to institution, but key features are summarized below.

Urinary Contamination

Specific concern is paid to disposal of urine as the most common potential source of contamination. During therapy, a dedicated toilet is preferred, and although lead shielding is not needed because of the short range of β-emission, disposable lining of the floors and

toilet/sink surfaces is recommended to contain radioactive urine or other contamination.[31] Urinary incontinence, if present, would require catheterization before administration and for at least 2 days thereafter to minimize radiation contamination. Other simple measures used to minimize urinary contamination upon discharge include the following:

- Use of private room with its own bathroom;
- Washing of hands for 20 seconds after each use of the restroom;
- Instructing the patient to urinate while seated;
- Flushing 2 to 3 times with the toilet lid closed;
- Rinsing of sinks and showers after use; and
- Cleanup of urinary spills with damp toilet paper that can be flushed down the toilet (to minimize accumulation of waste product trash requiring long-term storage).

Other Potential Sources of Contamination

Peritoneal and hemodialysis are not contraindications for treatment, but they may impact the administered activity of ^{177}Lu given the prolonged residence time within the patient and complicate handling of hemodialysis machines because of the likelihood of retained radioactivity after use, thus requiring logistics planning with dialysis facilities and the patient. Another infrequent but special consideration for Lu-177 DOTATATE therapy given its target population is in patients with indwelling drains, such as biliary drains, which require confirmation of ability of caregivers to safely manage disposal of waste with the same precautions applied to urine. When possible, these sources of waste should be flushed down the toilet similar to urine, with use of disposable gloves by the caregiver when handling and cleaning drain equipment and collection bags.

Release to Health Care Facility/Admission to Hospital Considerations

If confinement in a health care facility is needed, it is not usually necessary to store body effluents, such as urine, stool, or vomitus. In general, for patients who have been released to the public, precautions for the patient should be according to ALARA principles and universal precautions. A discussion should be had in such cases with a facility or hospital's radiation safety department and/or involved parties (clinical leadership) to determine any additional precautions that will be taken for care workers. Furthermore, should a patient receiving Lu-177 DOTATATE require admission to a hospital or transfer to an emergency department, it is highly recommended that the administering team contact the receiving personnel for a "signout."

Although not explicitly required, examples of "extra" precautions include the following. For effluent disposal where acceptable under state or federal regulations, the toilet can be flushed 2 or 3 times after each use to ensure sufficient dilution of radioactivity. Food trays, linens, and all other contaminated products may be stored in the patient's room until monitored and cleared by radiation safety staff. The patient must stay in the room except in a medical or nonmedical (eg, fire) emergency, and access by personnel and visitors can be limited. All trash and residual nondisposable items can be monitored after the patient's release and stored until radiation levels reach the statutory level defined for safe disposal or reuse. In some jurisdictions, items in decay storage must reside there for 10 half-lives (67 days for ^{177}Lu) or until radiation levels are indistinguishable from background. Once all known contamination is removed from the room, the room must be surveyed to verify that the radiation levels and removable contamination are sufficiently low to permit its general use. The room may not be used until this survey is performed and safe level documented. Individual institution's radiation safety procedures may vary somewhat.

If the admitting physician is different from the physician who administers the radiopharmaceutical, there must be a mechanism to prevent premature discharge or release of the patient from confinement.

Waste Disposal

As aforementioned, trash and nondisposable items contaminated by patient fluids must be stored and monitored until their radiation levels reach safe disposal limits, which may vary between institutions and jurisdictions, with one prominent guideline being 10 half-lives (67 days for ^{177}Lu).

Distance of Caregivers and Considerations for Travel

There is no specific regulation on required distance of caregivers after discharge. However, to meet guidance from NUREG-1556's use of a 0.25 occupancy factor for estimating exposure of public allowing safe discharge of patients after administration, it is assumed that exposed persons will maintain a distance of 1 m (3 ft) for at least 3 days and not sleep in the same bed as the patient for 7 days. There is a further assumption of following ALARA principles to minimize exposure to potential contamination, such as may occur during use of the same toilet facilities.

Prolonged use of personal or public transportation (bus, train, etc) in the company of others for more than 1 hour is discouraged for the first 3 days after therapy. Although Title 10 of the CFR, part 35.75, does not expressly prohibit release of a radioactive patient to a location other than a private residence such as a hotel, the NRC strongly discourages this practice because it can result in radiation exposure to members of the public for which the licensee may not be able to assess full compliance with the code.

Nonetheless, when travel is unavoidable in the first 3 days after therapy, the patient should be instructed to discuss the matter with treating personnel.

Furthermore, although patients are recommended to travel immediately home, it is acknowledged that some patients may need to reside in a hotel or other public facility. Again, precautions to maximize distance from other members of the public are recommended (>1 m at a minimum) in the 3 days after Lu-177 DOTATATE administration.

Treatment Procedures for Infusion of Lu-177 DOTATATE

Preparation

Before ordering Lu-177 DOTATATE solution for PRRT, confirm that treatment with octreotide analogs has been discontinued for at least 4 weeks for long-acting preparation and for 24 hours for short-acting preparation before scheduled therapy.

Lu-177 DOTATATE is a radiopharmaceutical that requires effective radiation shielding before handling. The vial containing the radiopharmaceutical is delivered in a lead- or Plexiglas-shielded container. It is highly advised that the personnel assigned to prepare or infuse the radiopharmaceutical wear double gloves.

Before the actual administration of Lu-177 DOTATATE, patients should be started on a renoprotective amino acid infusion and may be premedicated with antiemetics according to institutional/physician preference. Depending on institutional preferences and resources, coordination should be made between all involved staff, including the referring physician and the physician administering the radiopharmaceutical to ensure that the steps and processes involved with PRRT are carried out. Two separate IV access sites are preferred: one for the amino acid infusion and one for Lu-177 DOTATATE infusion.

Dosage

The recommended dosage is 200 mCi (7.4 GBq) Lu-177 DOTATATE, administered every 8 weeks for a total of 4 doses as tolerated. Dosage can be halved, according to the US Food and

Drug Administration–approved clinical notes, in special clinical situations, such as hematological toxicity.[32]

Prophylaxis: Amino Acid Solution and Antiemetics

The Lu-177 DOTATATE solution needs to be administered with concomitant amino acid infusion to reduce radiation absorbed dose and toxicity to the kidneys. Amino acid infusion should be initiated 30 minutes before infusion of Lu-177 DOTATATE and continued for at least 4 to 5 hours after completion of PRRT. There are different amino acid formulations available. The extemporaneously compounded formulation contains only 25 g lysine HCl and 25 g arginine HCl with 1 L of appropriate sterile solvent (eg, water for injection). This formulation has lower osmolality and less patient emetic effects. The commercially available amino acid solutions have a lysine content between 18 and 24 g and arginine content between 18 and 25 g in a volume of 1.5 to 2.2 L of solution having <1050 mOsmol/L. Aminosyn II 10% used in clinical trials in the United States contained additional essential and nonessential amino acids as well as electrolytes resulting in osmolality of 1040 mOsmol/L. This preparation was associated with a high incidence of nausea and vomiting. Choice of amino acid formulations depends on institutional resources.

Due to nausea with or without vomiting observed in some patients receiving amino acid infusion, it is advised that use of prophylactic antiemetic medications be considered, as used in each institution with any chemotherapy, 30 minutes before commencing amino acid solution administration. Other adjunct treatment for persistent vomiting is reasonable depending on physicians' experiences.

Infusion Methods

It is highly preferred that the IV access for administration of Lu-177 DOTATATE solution be separate from IV access for amino acid infusion. Separate access allows removal of the radiopharmaceutical access materials from the patient after PRRT, ensuring no radioactive medical line leaves the confines of the administering facility. Before infusion, measure the source activity to confirm prescribed activity. In some centers, a double lumen peripherally inserted central catheter line can be used for infusion to avoid delivery failures.

Lu-177 DOTATATE is delivered in a vial under positive pressure. It can be administered via gravity method, infusion pump method, or via automated syringe pump injector, as detailed with illustrative figure at the available link: http://jnm.snmjournals.org/content/60/7/937/F3.expansion.html.[26] Each institution can choose the best technique of radiopharmaceutical administration.

Gravity Method

- Insert a 2.5-cm-long, 20-gauge needle (short needle) into the Lu-177 DOTATATE vial, ensuring that the beveled tip inside the vial does not touch the solution at any time during the infusion. The hub of the short needle is fastened to the IV tubing of a previously prepared 500-mL sterile 0.9% sodium chloride solution. Keep the IV tubing clamp closed until the entire setup has been completed and is ready for infusion.
- Insert a second needle that is 9-cm long, 18-gauge (long needle) into the Lu-177 DOTATATE vial, ensuring that the beveled tip of this long needle touches and is secured to the bottom of the vial during the entire infusion. Fasten a connecting tube prefilled with sterile 0.9% sodium chloride to the hub of the long needle, ensuring that there are no air bubbles inside the plastic tubing. Check the designated IV access for Lu-177 DOTATATE to ensure patency; once confirmed, fasten the male Lauer lock of the connecting tube to the IV access, keeping clamp closed.
- Do not remove the needles to reposition once the seal is punctured, as this may make the seal ineffective and prevent dose delivery by this method.
- Open the clamp in the connecting tube from the vial to the patient, and then open the clamp of the tubing from the bag of normal saline solution. Regulate the flow of the sodium chloride solution via the short needle into the Lu-177 DOTATATE vial at a rate of 50 mL/h to 100 mL/h for 5 to 10 minutes and then 200 mL/h to 300 mL/h for an additional 25 to 30 minutes. During infusion, ensure that the level of solution in the Lu-177 DOTATATE vial remains constant and that the vial does not fill up completely. Total duration of infusion is approximately 30 to 40 minutes.
- Do not administer Lu-177 DOTATATE as an IV bolus.
- Clamp the saline line once the level of radioactivity is stable for at least 5 minutes.
- Clamp the connecting line from the vial and disconnect from the long needle, taking care that no fluid spills out. Open the connecting tube again and flush with 25 mL of 0.9% sterile sodium chloride to wash off any radiopharmaceutical remaining within the tubing into the patient.
- Remove the IV access used. Measure the remaining activity in the setup, including the vial, and subtract from the measured preinfusion activity to obtain the net activity administered.

Infusion Pump Method

For the infusion pump method, the short and long needles are also used. The tubing that connects to the long needle should be primed with normal saline solution before attachment to an infusion pump. The other end of this tubing is attached to the IV access of the patient. A 3-way stopcock is connected to the hub of the short needle before it is inserted into the vial with a filter attached to the vent tip. Again, the tip of the short needle should stay above the fluid level, whereas the tip of the long needle is at the bottom of the vial. The positive pressure within the Lu-177 DOTATATE vial drives fluid into the patient and is controlled by the infusion pump, which is usually programmed to deliver 0.8 to 0.9 mL/min for total infusion time of 25 to 30 minutes. Remove the IV access used. Measure the remaining activity in the setup, including the vial, and subtract from the measured preinfusion activity to obtain the net activity administered.

Automated Syringe Pump Injector Method

Another method involves drawing the Lu-177 DOTATATE solution from inside the vial into a sterile lead-shielded syringe that is then mounted on an automated syringe pump injector to administer the Lu-177 DOTATATE. This method exposes the individual drawing the solution to radiation risk. A connecting tube prefilled with sterile 0.9% sodium chloride solution is used to connect the syringe containing the radiopharmaceutical to the IV access of the patient. Before starting the infusion, confirm patency of patient's IV access. The pump is programmed to deliver the contents of the syringe over 30 minutes, for example, 30 mL at 60 mL/h. Once infusion is completed, the connecting tube can be flushed with 25 mL of 0.9% sterile sodium chloride to wash off any radiopharmaceutical remaining within the tubing into the patient. Attention is required to safely handle the setup to avoid spillage as well as minimize radiation exposure by using tongs. Remove IV access, use and measure remaining radioactivity in the setup and vial, and subtract it from preinfusion activity to determine net activity administered.

Posttherapy Management

All personnel involved with Lu-177 DOTATATE therapy should perform a survey of their hands and clothing for any contamination, and appropriate measures should be performed if such contamination is discovered. The room used for infusion should be surveyed for contamination before releasing the room to another patient. All medical wastes associated with the PRRT should be stored as required

by radiation safety procedures, making sure that they are separated from other wastes associated with short-acting radiopharmaceuticals.

Care of the patient after Lu-177 DOTATATE therapy follows established institutional protocol for care of patient after radionuclide therapy with special consideration to ALARA principles. Therapy with octreotide LAR or lanreotide is usually given 4 to 24 hours after Lu-177 DOTATATE at the discretion of the attending oncology physician and stopped 4 weeks before subsequent PRRT. Short-acting octreotide maybe given for symptomatic management during PRRT cycles and withheld 24 hours before next dose of Lu-177 DOTATATE after determination by treating team of physicians.

If desired, posttherapy 3-dimensional imaging may be obtained for the purposes of dosimetry. Personalized dosimetry may be used to assess and estimate potential risk to organs for the individual patient, as data collection for correlative studies seeking to establish maximum organ dose thresholds or lesion treatment efficacy thresholds, or for dose reporting in case of future radiation treatments.[26]

DOCUMENTATION

Reporting should be in accordance with the ACR-ASTRO Practice Parameter for Communication: Radiation Oncology.[21]

A summary of the patient's history, pathologic findings, imaging results, and laboratory findings should be included in the report to document the indication and tolerability for treatment with Lu-177 DOTATATE. The report should include the radiopharmaceutical used, the administered activity, site and route of administration, safety precautions for other staff involved in the patient's care, and any associated incident encountered during therapy. If dosimetry is performed, salient organ absorbed dose values, both in directly calculated dose and in equivalent dose (EQD2), should be reported, and, if available, a dose map in DICOM format with the associated CT. On subsequent PRRT, interval history should include a summary of prior Lu-177 DOTATATE treatments, interval imaging to assess treatment efficacy, and pertinent laboratory findings to determine and confirm appropriateness and safety of additional therapy.[26]

STATEMENT ON THERAPEUTIC USE OF UNSEALED RADIOPHARMACEUTICAL SOURCES

On the basis of their education, training pathway(s), initial board certification(s), and maintenance of certification(s), NRC or Agreement State Authorized User (AU) status, and clinical work experience, diagnostic radiologists (DRs), nuclear radiologists (NRs), nuclear medicine physicians (NMs), and radiation oncologists (ROs) may have the qualifications to supervise and perform therapy with Lu-177 DOTATATE. Although it is recognized that individual physician variations and state and federal regulatory requirements may, of necessity, dictate site-specific practice patterns, these physicians may best participate in the practice according to their special interests and qualifications. In most clinical settings, one of the following common practice paradigms generally applies:

- Physicians who are NRC and/or Agreement State recognized, board-eligible, or board-certified in DR, NR, NM, or RO but do not hold AU status. These physicians may participate in the practice of PRRT under the supervision of an AU. Although they may not issue written directives for Lu-177 DOTATATE, they may administer such a dosage as designated and supervised by an AU.
- Physicians who are NRC and/or Agreement State–recognized and board-certified in DR, NR, NM, or RO and hold AU status based on that certification and site-specific credentialing: These physicians may administer Lu-177 DOTATATE therapy under their own AU qualifications and licensure.
- Physicians who are NRC and/or Agreement State–recognized and board-certified in DR, NR, NM, or RO and hold the appropriate AU statuses and site-specific credentialing. These physicians may practice parenteral Lu-177 DOTATATE therapy as permitted by their own specific training leading to such AU statuses.

EQUIPMENT SPECIFICATIONS

Equipment performance monitoring should be in accordance with the ACR-AAPM Technical Standard for Nuclear Medical Physics Performance Monitoring of γ-Cameras.[33]

RADIATION SAFETY

Radiologists, medical physicists, registered radiologist assistants, radiologic technologists, and all supervising physicians have a responsibility for safety in the workplace by keeping radiation exposure to staff, and to society as a whole, "as low as reasonably achievable" (ALARA) and to assure that radiation doses to individual patients are appropriate, taking into account the possible risk from radiation exposure and the diagnostic image quality necessary to achieve the clinical objective. All personnel that work with ionizing radiation must understand the key principles of occupational and public radiation protection (justification, optimization of protection, and application of dose limits) and the principles of proper management of radiation dose to patients (justification, optimization, and the use of dose reference levels) (http://www-pub.iaea.org/MTCD/Publications/PDF/Pub1578_web-57265295.pdf).

Facilities and their responsible staff should consult with the RSO to ensure that there are policies and procedures for the safe handling and administration of radiopharmaceuticals and that they are adhered to in accordance with ALARA. These policies and procedures must comply with all applicable radiation safety regulations and conditions of licensure imposed by the NRC and by state and/or other regulatory agencies. Quantities of radiopharmaceuticals should be tailored to the individual patient by prescription or protocol.

Nationally developed guidelines, such as the ACR Appropriateness Criteria, should be used to help choose the most appropriate imaging procedures to prevent unwarranted radiation exposure.

Additional information regarding patient radiation safety in imaging is available at the Image Gently for children (www.imagegently.org) and Image Wisely for adults (www.imagewisely.org) Web sites. These advocacy and awareness campaigns provide free educational materials for all stakeholders involved in imaging (patients, technologists, referring providers, medical physicists, and radiologists).

Radiation exposures or other dose indices should be measured and patient radiation dose estimated for representative examinations and types of patients by a Qualified Medical Physicist in accordance with the applicable ACR Technical Standards. Regular auditing of patient dose indices should be performed by comparing the facility's dose information with national benchmarks, such as the ACR Dose Index Registry, the NCRP Report No. 172, Reference Levels, and Achievable Doses in Medical and Dental Imaging: Recommendations for the United States or the Conference of Radiation Control Program Director's National Evaluation of X-ray Trends (ACR Resolution 17 adopted in 2006—revised in 2009, 2013, Resolution 52).

QUALITY CONTROL AND IMPROVEMENT, SAFETY, INFECTION CONTROL, AND PATIENT EDUCATION

Policies and procedures related to quality control and improvement, patient education, infection control, and safety should be developed and implemented in accordance with the ACR Policy on Quality Control and Improvement, Safety, Infection Control, and Patient Education appearing under the heading *ACR Position Statement on Quality Control and Improvement, Safety, Infection Control and Patient Education* on the ACR Web site (https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Quality-Control-and-Improvement).

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