AJR FOCUS ON:

Neuroendocrine Tumor Therapy: ^{177}Lu-DOTATATE

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OBJECTIVE. The purposes of this article are to increase understanding of the concepts of theranostics and peptide receptor radionuclide therapy (PRRT) as they apply to neuroendocrine tumors (NETs); review the key 1, 2, and 3 clinical trial data leading to the approval of ^{177}Lu-tetraazacyclododecanetetraacetic acid–octreotide (^{177}Lu-DOTATATE); and foster understanding of the practical aspects and future directions of PRRT for NETs.

CONCLUSION. In January 2018, ^{177}Lu-DOTATATE therapy was approved in the United States (previously approved in Europe in September 2017) for adult patients with somatostatin receptor–positive gastroenteropancreatic neuroendocrine tumors, including those of the foregut, midgut, and hindgut. The results of the phase 3 Neuroendocrine Tumors Therapy (NETTER-1) trial show favorable outcomes with respect to the primary endpoint of progression-free survival and a host of secondary objectives, including overall survival, objective response rate, and quality of life measures. Patient selection is based on a number of specific factors and should be sequenced carefully with respect to other available therapies, ideally in multidisciplinary cancer conferences. Establishing the therapy at a new institution can be somewhat involved, but once it is established, the therapy is fairly straightforward to administer and is well tolerated with limited side-effects and toxicity. A number of approaches and issues are still to be worked out, and this therapy will continue to be studied and optimized.

Somatostatin receptor (SSTR) analogues, which are used for imaging of neuroendocrine tumors (NETs), can also be used for therapy by replacing the imaging isotope with a therapeutic isotope. This general field is referred to as peptide receptor radionuclide therapy (PRRT). PRRT is not specific to NETs, but NET therapy is currently the most advanced and only U.S. Food and Drug Administration (FDA)-approved example of it. Furthermore, this combination of imaging and therapeutic isotopes with the same target is a good example of theranostics, which is a portmanteau word consisting of "therapy" and "diagnostics." The term "theranostics" is fairly new, but the best example of it is one of the oldest isotopes, essentially originating the field of nuclear medicine, ^{131}I, which is used for simultaneous imaging and therapy.

Development of Peptide Receptor Radionuclide Therapy

NETs are well known for being heterogeneous. They can arise from a variety of different organs; can be benign or malignant; are well, moderately, or poorly differentiated, as in grade; have variable metastatic potential; and are either functional or nonfunctional (i.e., produce hormones and symptoms or do not) [1]. Symptoms can markedly reduce quality of life and are an important consideration for therapy. NETs have a low incidence but a high prevalence given the lower mortality associated with these tumors.

One commonality among NETs is expression of the G protein–coupled SSTRs, of which there are five subtypes in humans. The human somatostatin molecule, composed of 14 amino acids, is a hormone used by neuroendocrine cells for neurotransmission and cell proliferation. An abbreviated version of the human somatostatin molecule, composed of eight amino acids, is octreotide (Sandostatin, Novartis). Octreotide was FDA-approved in 1988 for symptom control in patients with functional NETs (package insert, Novartis). However, it is also known to have antiproliferative effects and is practically used in that way for patients with low- or intermediate-grade metastatic inoperable NETs [2].

Keywords: ^{177}Lu, DOTATATE, NETTER-1 trial, neuroendocrine tumors, peptide receptor radionuclide therapy

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For imaging of and therapy for NETs, several variations of the octreotide peptide have been developed and labeled with either gamma-, positron-, or beta-emitting isotopes for these various applications [3]. The isotope connects to the peptide with one of two structural linkers, either diethylenetriaminepentaacetic acid (DTPA) or tetraazacyclododecanetetraacetic acid (DOTA). Aside from octreotide, the other peptide used is octreotate (TATE). These different ligands have different binding affinities to the various subtypes of SSTRs and different dosimetry in normal organs [4–6]. Ultimately, the images and lesional dosimetry are similar but not the same [2, 4, 7].

Historically, the first approach to both nuclear imaging and therapy for NETs was with ^{111}In-DTPA-octreotide (also called ^{111}In-pentetreotide, Octreoscan, Mallinckrodt Pharmaceuticals) [3]. this radiopharmaceutical is used for gamma imaging and has been the mainstay of nuclear imaging of NETs for many decades. Therapy is also possible with ^{111}In from the auger electrons produced by the photons, which results in DNA damage. However, the efficacy is low compared with the toxicity, given the higher doses needed for therapy.

The next generation of imaging agents used the positron-emitting isotope ^{68}Ga bound to octreotide or TATE by means of the DOTA linker [4]. Similarly, the next generation of therapeutic radiopharmaceuticals used the beta-emitting isotopes ^{90}Y and ^{177}Lu bound to those same linker and peptide combinations. Both of these therapeutic isotopes are still in use (more so in Europe than in the United States), although ^{177}Lu is the only one that has both FDA and European Medicines Agency approval. It is commercially available as Lutathera (Advanced Accelerator Applications, a Novartis Company).

Although both ^{90}Y and ^{177}Lu are primarily beta-emitting radioisotopes, there are a number of differences between them. Yttrium 90 has a half-life of 2.7 days, energy of 935 keV, path length of 12 mm in soft tissue, and no gamma emission. Lutetium-177 has a half-life of 6.7 days, energy of 133 keV, path length of 2 mm in soft tissue, and additional 113-keV (6.6%) and 208-keV (11%) gamma emission. Primarily, it is theorized that the higher energy (and resulting longer path length) of ^{90}Y will provide greater efficacy for larger tumors [8]. This has been investigated in several clinical trials [9]. Unfortunately, the longer path length can also cause greater toxicity to surrounding normal tissue, such as bone marrow and kidneys, although this is still limited [8]. As such, ^{177}Lu was chosen for commercialization given similar efficacy but lower toxicity compared with ^{90}Y.

Clinical Trials

Phase 1 and 2 Experience

Because of regulatory and funding differences between the United States and Europe, much of the initial work on PRRT for NETs has been done in Europe, primarily in The Netherlands and Germany, and a few other places in the world. The first patient was treated with ^{177}Lu-DOTATATE in 1997, and since then various sites in Europe have gained considerable experience with this therapy. Although the results are valuable, most of the studies have been smaller phase 1 and 2 trials.

Even early prospective studies on ^{177}Lu-DOTATATE with only 35–50 patients showed partial response rates of 10–25%. They also showed improvements in quality of life measures in patients with metastatic NET refractory to traditional therapies [10, 11]. Follow-up studies of much larger cohorts (500–600 patients but single institutions) continued to show favorable outcomes with a 30% objective response rate, 40-month progression-free survival (PFS), and low-grade (grade 3 and 4) toxicity [12]. Current publications from these groups focus on long-term tolerability and outcomes (again in larger groups of 400–800 patients). They show favorable toxicity profiles with regard to the kidneys and bone marrow (with greater renal toxicity in those treated with ^{90}Y vs ^{177}Lu) and low levels of clinically significant toxicity otherwise, with the suggestion for individual predilections toward radiation [13]. The worst outcomes were development of acute leukemia (< 1%) or myelodysplastic syndrome (< 2%) in small percentages of patients in the context of PFS of 29 months and overall survival of 63 months [14, 15].

Neuroendocrine Tumors Therapy Trial

On the basis of many favorable phase 1 and 2 results, Advanced Accelerator Applications funded the registry trial (Neuroendocrine Tumors Therapy [NETTER-1]) of ^{177}Lu-DOTATATE (Lutathera, Advanced Accelerator Applications). This was the first phase 3 multicenter randomized controlled trial of this agent [16]. The trial was simultaneously opened in Europe and the United States with a goal of both European Medicines Agency and FDA approval.

The study design for the NETTER-1 trial is shown in Figure 1. Eligibility was for adult participants with biopsy-proven low-grade (Ki-67 level, < 20%) metastatic or locally advanced midgut NET that was inoperable and radiographically progressing with standard dose (30–40 mg) octreotide therapy. Confirmation of SSTR expression was based on planar ^{111}In-DTPA-octreotide imaging because ^{68}Ga-DOTATATE PET was not available in most centers at the time.

Participants randomized to the experimental arm received four doses of 200 mCi (7.4 GBq) of ^{177}Lu-DOTATATE once every 2 months. Long-acting octreotide was held for 1 month before each dose of ^{177}Lu-DOTATATE but could be given 4–24 hours after completion of the ^{177}Lu-DOTATATE infusion. Participants randomized to the control arm did not receive placebo. Rather, they received high-dose (60 mg) octreotide, which also has a potential therapeutic benefit. The primary endpoint of the trial was PFS. The multiple

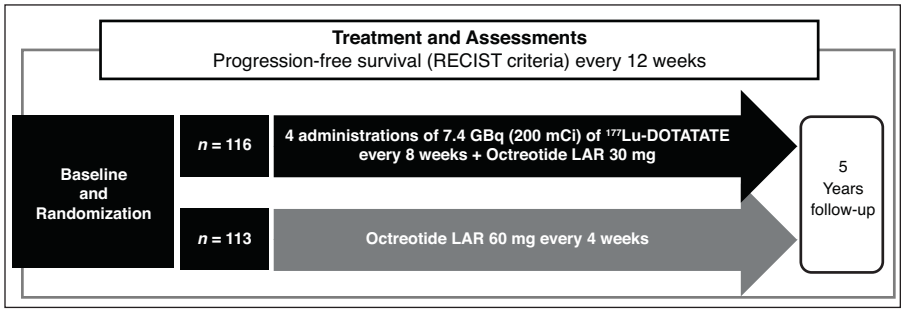
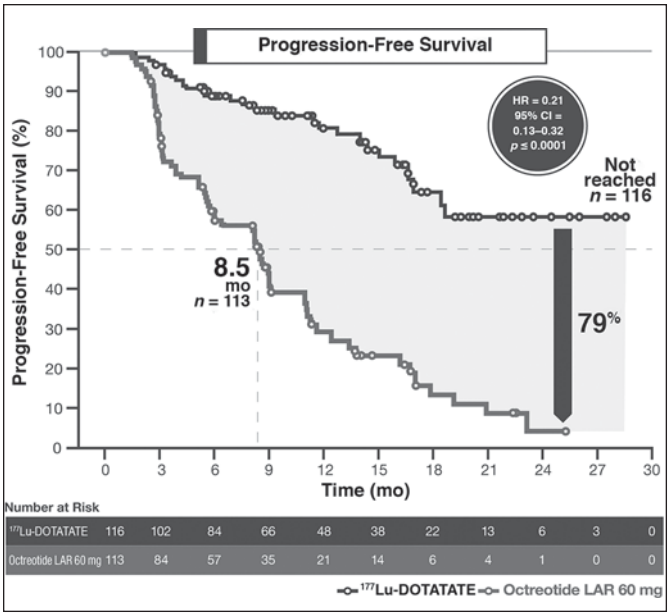


Fig. 1—Schematic shows design of Neuroendocrine Tumors Therapy trial. Study aim was to evaluate the efficacy and safety of ^{177}Lu-DOTATATE plus octreotide 30 mg compared with octreotide long-acting release (LAR) 60 mg (off-label use, U.S. Food and Drug Administration and European Medicines Agency) in patients with inoperable somatostatin receptor–positive midgut neuroendocrine tumors, progressive under octreotide LAR 30 mg (label use). Study design was international multicenter randomized comparator-controlled patient group. RECIST = Response Evaluation Criteria in Solid Tumors.



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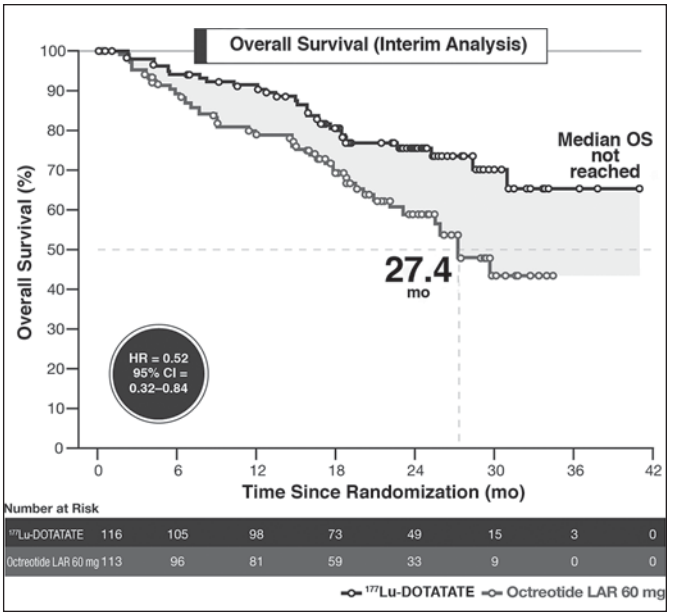

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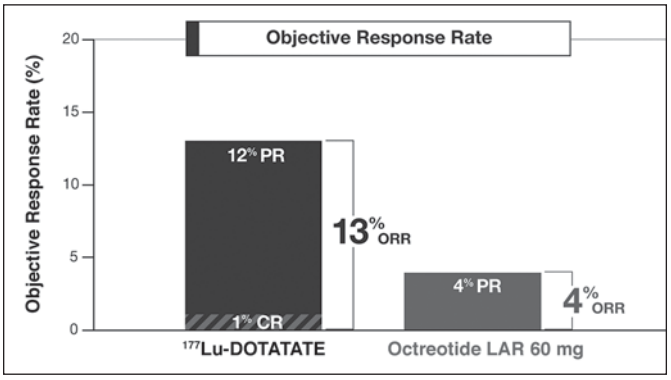

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Fig. 2—Results of Neuroendocrine Tumors Therapy (NETTER-1) trial.
A, Graph shows progression-free survival. HR = hazard ratio, LAR = long-acting release.
B, Graph shows overall survival (OS). *p* did not meet prespecified threshold for significance in interim analysis.
C, Chart shows objective response rate. PR = partial response, CR = complete response, ORR = objective response rate.

secondary endpoints included overall survival, objective response rate, toxicity, and quality of life measures.

In total, 229 patients were enrolled in the study: 116 in the experimental arm and 113 in the control arm. Overall, the results were quite favorable. The primary endpoint was reached (Fig. 2) with a strong difference between the two arms. Subjects receiving ^{177}Lu-DOTATATE had a 79% reduction in risk of progression (hazard ratio, 0.21; $p < 0.001$) with an estimated PFS of 40 months, compared with 8.4 months for high-dose octreotide therapy.

At the time of the initial NETTER-1 publication (and the writing of the current article), the overall survival data were not finalized because the 5-year follow-up phase was ongoing. But the interim analysis showed 48% lower risk of death with ^{177}Lu-DOTATATE (hazard ratio, 0.52; $p < 0.004$) (Fig. 2). The objective response rate was also significantly different between the two arms (Fig. 3). There were one complete and 17 partial responses with ^{177}Lu-DOTATATE and no complete and three partial responses with high-dose octreotide. Last, the quality of life measures showed improvements overall and specifically for diarrhea, flushing, and abdominal pain.

Lutetium-177–DOTATATE Therapy

Patient Selection

The FDA approval of ^{177}Lu-DOTATATE is for the treatment of SSTR-positive gastroenteropancreatic NETs, including foregut, midgut, and hindgut NETs in adults (package insert, Advanced Accelerator Applications). The primary considerations in patient selection for this therapy are tumor grade, SSTR density based on nuclear imaging findings, operability, distribution of disease, progression, and laboratory values. Each of these is discussed in greater detail in this section.

Tumor grade and SSTR density based on imaging findings are linked concepts. The therapy is most effective in patients who have high expression of SSTRs on their tumor cells [17]. This is typically true of well-differentiated tumors [18, 19], which is why the NETTER-1 trial required patients to have either low-grade (grade 1; Ki-67 level, < 3%) or intermediate-grade (grade 2; Ki-67 level, 3–20%) tumors. Poorly differentiated or high-grade (grade 3; Ki-67 level, > 20%) tumors are more variable in their SSTR expression. Those in the Ki-67 range of 20–50% may have high-enough SSTR expression to warrant PRRT, but those greater than 50% generally do not. The assessment of SSTR expression is based on ^{111}In-DTPA-octreotide gamma camera-imaging and SPECT or, preferably, ^{68}Ga-DOTATATE PET. Most of a patient's lesions should have uptake greater than the liver background to be eligible for

the therapy. There are ongoing studies on specific standardized uptake values (SUVs) and cutoffs to use for therapy and how they relate to outcomes [20]. Because of the aforementioned issues, ^{18}F-FDG PET may also have a role in the determination of proper patient selection and response assessment for these patients [21], especially those with poorly differentiated or high-grade tumors.

Because partial or complete surgical removal of tumors is always preferred when possible, PRRT is reserved for patients with locally aggressive and inoperable disease. Furthermore, the disease is typically metastatic to multiple sites, making other approaches, such as liver-directed therapy and external beam radiation, less appealing or impractical. Disseminated metastasis within the liver is another instance in which PRRT should likely be favored over liver-directed therapies alone. Last, the disease must be progressing with standard-dose SSTR therapy with either octreotide or lanreotide. In the clinical trials, progression was typically confirmed with either CT or MRI according to the Response Evaluation Criteria in Solid Tumors (RECIST). This general idea will likely be continued clinically, though with less stringent use of response criteria. Another area of consideration is the role of ^{111}In-DTPA-octreotide or ^{68}Ga-DOTATATE PET to show progression (e.g., if the disease is radiographically stable or only slightly enlarging but the SUV values at PET have increased substantially). This is currently an area of research. Last, patients may progress clinically but remain radiographically stable.

Patients should meet certain laboratory values to ensure that potential transient damage to the bone marrow and the kidneys will not be an issue. The laboratory cutoffs from the NETTER-1 and Expanded Access Program trials were as follows, and it would be reasonable to continue to check these same values for clinical patients at screening, between treatments, and again just before each dose of ^{177}Lu-DOTATATE. Patients should have a serum creatinine level less than 1.7 mg/dL (or creatinine clearance > 50 mL/min calculated by the Cockroft-Gault method), hemoglobin level of greater than 8 g/dL, WBC count greater than 2000/μL, platelet count greater than 75,000/μL, total bilirubin level less than three times the upper limit of normal, and a serum albumin level greater than 3 g/dL, unless the prothrombin time is within the normal range.

Sequencing Therapy

Even if a patient is eligible for PRRT on the basis of the foregoing guidelines, it may not be the best choice relative to other therapeutic options, such as surgery, mechanistic target of rapamycin (mTOR) inhibitors, chemotherapy, external beam radiation, and a variety of liver-directed therapies (bland embolization, chemoembolization, or radioembolization), for those with liver-dominant disease. This area is an active area of discussion and research, and the consideration is not only what will have great therapeutic benefit but also which will have less toxicity now and in the future [18]. Another possibility is combination therapies, which may have greater benefit than the sum of their parts, for instance by including radiosensitizing chemotherapies in conjunction with radioembolization or PRRT [22].

The European Neuroendocrine Tumor Society guidelines have long recommended PRRT as second-line therapy after disease progression with SSTR therapy, and this is a reasonable approach to consider, with the aforementioned caveats. Ultimately, the therapy sequencing decision should ideally be made in the context of a multidisciplinary conference with experts from all disciplines (oncology, surgery, radiation oncology, nuclear medicine, radiology, and pathology) represented [1]. Because in many places it is difficult to have so many NET experts, patients with progressive NET should be referred to an NET Center of Excellence (also called NET Advanced Care Center) at least once in their care.

Performing the Therapy

Compared with other radioisotope therapies, such as ^{131}I, ^{223}Ra-dichloride (Xofigo, Bayer HealthCare), and ^{131}I–ibritumomab tiuxetan (Zevalin, Spectrum), PRRT is considerably more involved. However, once the therapy program has been set up at an institution, it is fairly straightforward and requires only a reasonable amount of input.

The ^{177}Lu-DOTATATE is shipped from a radiopharmacy (either in Italy or in New Jersey) to the clinical site either the day before or on the day of therapy and arrives as a clear liquid in a glass vial. The ^{177}Lu-DOTATATE is administered over 30 minutes followed by a 10- to 20-minute infusion of saline solution to decrease the residual. There are two recommended methods of administration. The first, the gravity method (Fig. 3), requires the use of two needles inserted into the vial. The instillation of saline solution (by means of gravity or through a pump) through one needle increases the pressure within the vial and pushes the ^{177}Lu-DOTATATE out the other needle, which is attached to the patient. The second method is to manually draw out the contents of the vial into a syringe and then use a shielded, automated syringe pump to administer the agent to the patient.

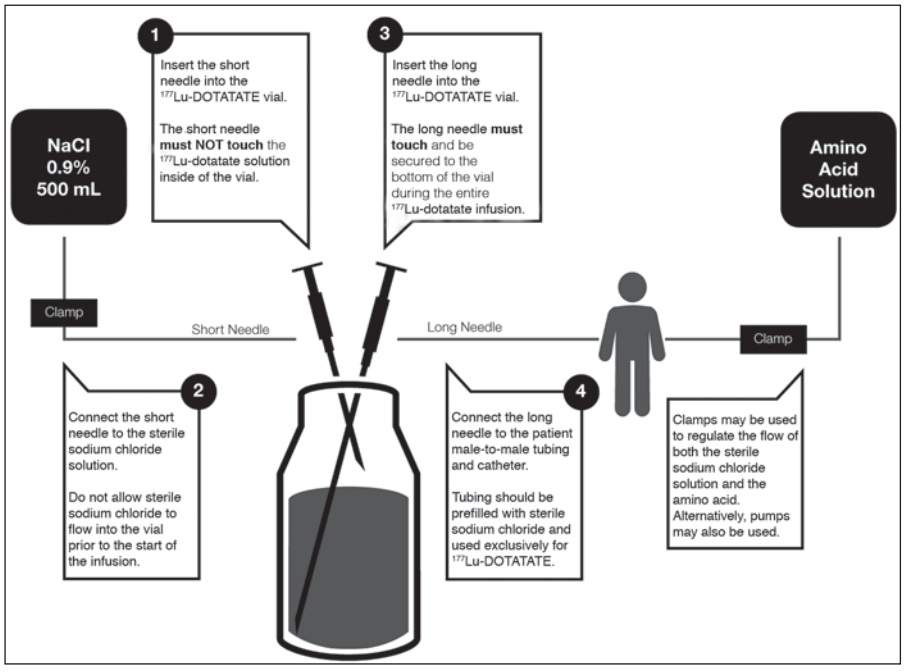

Fig. 3—Chart shows gravity method of ^{177}Lu-DOTATATE administration.

The ^{177}Lu-DOTATATE must be given in conjunction with an amino acid formulation, which is administered IV through either the same or a second IV line. Amino acids reduce the residence time of ^{177}Lu-DOTATATE in the kidneys, thereby reducing radiation toxicity. Various amino acid formulations are available with different amounts of amino acids and different osmolalities. The only two key amino acids are lysine and arginine. Purer formulations of only these two amino acids, together with a lower-osmolality solution, markedly reduce the nausea associated with their infusion. Depending on which amino acids are used (and their emetogenic potential) and the patient's sensitivity, a variable amount of antinausea premedication must be given before administration of amino acids is started. Additional as-needed antinausea medication may also be administered during the infusion.

There is a low (1–10%) but documented risk of hormone crisis either during or within a few days after PRRT administration [23, 24]. Principally based on previous experiences with similar crises that can occur with anesthetics or surgery, recommendations for management center on identifying patients at risk of hormone crisis; administering subcutaneous octreotide as a bolus or as an infusion either prophylactically (for patients at high risk) or if a crisis happens (for patients at low risk), parenteral H_1 or H_2 blockers; and resuming short- or long-acting octreotide after PRRT. There is controversy, however (again based on the surgical literature), about the utility of giving octreotide in this setting [25, 26].

On the day of treatment, probably the most important professional is the nurse who manages all supportive care, including placing the IV lines, administering the antinausea medication and amino acids, and monitoring the patient for any adverse effects. This nurse can trained in either oncology or radiology. The latter would require special training for this therapy. A technologist prepares the ^{177}Lu-DOTATATE dose and administers it to the patient. The role of the physician (who must be an authorized user) is to oversee the therapy and help with any questions or issues that arise during the process. Depending on local regulations, the authorized user may also have to be present to start the infusion of ^{177}Lu-DOTATATE.

An important point is to select an appropriate room for the therapy. It should ideally have a bathroom attached or at least close by. The toilet and surrounding floor should be lined to contain radioactive urine. The room need not be lead lined but should contain only one or more patients undergoing this same therapy. It can be located within any appropriate area, such as nuclear medicine, an oncology infusion area, or radiation oncology.

Radiation and Release Guidelines

The levels of emitted radiation especially but also the excreted radiation from this therapy are fairly low, requiring less extreme measures than for some other types of radioisotope therapy, such as ^{131}I for thyroid cancer. Typically the emitted radiation after administration of ^{177}Lu-DOTATATE is 2 mR/h (20 μSv/h) at 1 m. Within 24 hours, this has decreased to less than 1 mR/h (10 μSv/h) at 1 m. In the United States, this allows this therapy to be administered as an outpatient procedure. The patient returns home if local or stays in a hotel or motel if needed for one night before traveling home. The only need for an overnight stay in the hospital would be if medical complications occur during the day or if the patient is unable to manage their urine (i.e., is incontinent), in which case there is a high risk of contamination of the home or hotel within the first 24 hours. The patient should be encouraged to exercise good bathroom hygiene and to stay away from children, pregnant women, and crowds for approximately 3 days after the therapy. Hydration should also be encouraged during this time to promote clearance of unneeded radiopharmaceutical.

Response Assessment

Similar to confirming progression based on imaging, the clinical trials used conventional imaging (CT and MRI) with RECIST to assess response to PRRT. As such, CT and MRI remain the standard of care [27]. Response assessment is typically done 1 month after the second cycle of therapy. The patient continues with therapy if there is any outcome but progression at this time-point. Response is again assessed 1 month after completion of all four cycles of therapy, at which time the patient starts long-term follow-up.

As discussed for evaluation of progression, functional imaging (^{111}In-DTPA-octreotide or ^{68}Ga-DOTATATE PET and even FDG PET) may have an important role in the evaluation of response to PRRT, especially given that both the imaging and the therapy target the same receptor [27]. Moreover, this can be combined in the same imaging appointment with PET/CT or PET/MRI. However, the role of functional imaging for response assessment in NET has not yet been evaluated to the same degree that it has been in other malignancies (such as lymphoma). A major roadblock is the limited reimbursement for multiple ^{68}Ga-DOTATATE PET scans per year. Given the additional gamma radiation emitted by ^{177}Lu, another option is to perform gamma-camera imaging and SPECT of ^{177}Lu-DOTATATE immediately after each treatment. This has the added benefit of not requiring any additional radiation for imaging, though the resolution is more limited than that of a separate ^{68}Ga-DOTATATE PET scan [28]. Once again, however, reimbursement is an issue. The goal for the future is that more data will show the utility of imaging in this regard and lower the reimbursement hurdles.

Future Directions and Controversies

Although clinical approval of ^{177}Lu-DOTATATE has been a lengthy process, there are still many future directions for research and optimizing clinical care [29]. These include (but are not limited to) improving response assessment, optimizing the number of therapy cycles per patient, considering repeat therapy, delivering the therapy intraarterially instead of IV, clarifying the role of ^{90}Y versus ^{177}Lu, using alpha- instead of beta-emitters, improving understanding of the sequencing and combination of PRRT with other therapies, using novel peptides to bind SSTRs, and using personalized dosimetry.

The current standard of care for response assessment during and after PRRT is conventional imaging, which may have limitations due to lack of tumor shrinkage or necrosis [27]. A large unmet need is understanding the role of ^{111}In-DTPA-octreotide or ^{68}Ga-DOTATATE PET for response assessment, especially with the added value of quantitative metrics such as SUV, and different combination approaches of CT and MRI [17, 30]. This may have significant implications for improving early response assessment, prognosis after therapy, and adjusting the number of cycles of therapy. However, the uptake can change in unexpected ways (i.e., decrease in background organs and increase in metastases) after somatostatin analogue therapy, such that the scan must be interpreted in the proper context and with great care [31]. Relatedly, levels of laboratory markers,

especially liver enzymes and chromogranin A, may transiently increase after the initial cycles of therapy owing to radiation inflammation and should not be taken as progressive disease [32]. In addition, FDG PET, as in the initial evaluation of the patient, may also have a role in the response assessment of PRRT, especially because FDG-avid disease has a statistically significant negative prognostic value [33].

Most of the larger clinical trials of ^{177}Lu-DOTATATE were based on a total of four cycles of therapy. This was (somewhat arbitrarily) chosen to balance the therapeutic benefit with the toxicity. As shown by the results of the NETTER-1 trial, this schedule works well for most patients. However, some patients probably do not need all four cycles of therapy, and others could benefit from more cycles. This will allow personalized therapy with the potential for decreased toxicity and improved efficacy. Better ways to assess response to PRRT are needed to fully realize this potential.

If a patient does respond well to one course of ^{177}Lu-DOTATATE, then it is reasonable to think that the patient may respond well to another course of ^{177}Lu-DOTATATE when the disease subsequently progresses. This idea of salvage (repeat) PRRT has been evaluated to some degree in several clinical trials [34]. These studies showed that although PFS is not as long for the second cycle of PRRT compared with the initial treatment, it is still good (presumably similar to or longer than that of other therapeutic options) and the therapy is safe.

Many patients have a considerable burden of disease, but it is restricted to the liver, because this is a common site of metastatic NET from the bowel. For these patients, combining the approaches of selective internal radiation therapy and PRRT by giving ^{177}Lu-DOTATATE intraarterially via the hepatic artery has been advocated [35]. In theory, this will provide higher delivery to the tumor itself (improving efficacy) while reducing the systemic circulation (reducing side effects). This approach has been studied in a limited manner thus far [35]. Although the results are preliminary, they show that the approach can be used successfully. However, studies comparing the therapy with systemic PRRT to prove that it is indeed more beneficial have not been conducted, to my knowledge. Furthermore, the process is rather complicated, requiring the patient to lie on the interventional radiology table for approximately 4 hours, which can be burdensome to the patient and the staff.

In the initial phase of PRRT for NET, both ^{90}Y and ^{177}Lu were used as the radioisotope. Given the different physical properties of these isotopes, it has been hypothesized (and shown in smaller clinical trials) that each may provide different benefits [36]. Another approach is to give both together or sequentially to take advantage of their respective benefits [9]. Principally, ^{90}Y has higher energy and thus path length in human tissue. In theory, this would be beneficial for bulkier tumors that the lower energy and shorter path length of ^{177}Lu would not be able to penetrate. The counterargument is that as long as there is a viable blood supply to all parts of the bulky tumor, ^{177}Lu should be sufficient. Areas without a good blood supply would be prone to necrosis anyway, in which case radiation is not needed. Conversely, the longer path length of ^{90}Y will also have a greater bystander effect on normal tissues, such as bone marrow and kidneys, resulting in higher toxicity, which is generally agreed. For these reasons, ^{177}Lu was chosen as the isotope to move forward for clinical approval. However, the relative benefits of ^{90}Y and ^{177}Lu have not been rigorously studied in a comparative trial, so the topic remains open. On a similar note, the use of alpha-emitters instead of these beta-emitters is another area of active research [29].

Proper sequencing of PRRT with other available therapies has not yet been determined, and this is a major area of ongoing discussion [18, 37]. A concept related to this is the use of combination therapies, such as capecitabine as a radiosensitizer for PRRT [22] or liver-directed therapies in conjunction with systemic PRRT [37]. As the results of these trials (and others yet to be conducted) become available, we may have a better understanding of proper sequencing and combination therapies. At present, this should be discussed in the context of a multidisciplinary conference so that input from multiple experts, especially those familiar with local practices and strengths, can be considered [1].

The SSTR analogues in current use are all agonists of the SSTR. This means they activate the receptor, which ultimately becomes internalized, where the radioisotope is trapped and gives off radiation, which kills the cells. There has been considerable progress on the next generation of SSTR analogues that are antagonists to the SSTRs. These newer analogues have a higher binding specificity for the SSTR receptor such that even though they do not activate the receptor or (most likely) become internalized into the cell, they can deliver a higher dose of radiation [38]. Several ongoing studies are evaluating these newer analogues [39].

Lutetium-177–DOTATATE is not specific to the FDA-approved indication of gastroenteropancreatic NETs. In the future, PRRT will likely be extended to many other tumor types. Easily understandable is the treatment of other endocrine malignancies, such as bronchial NET, and those that are more traditionally treated with ^{131}I-metaiodobenzylguanidine (MIBG) such as paragangliomas, pheochromocytomas, and medullary thyroid cancer [40]. Beyond this, the general concept of PRRT can be extended to other cancers, including breast, prostate, gut, pancreas, and brain tumors, that have recently been found to overexpress several other peptide receptors, such as gastrin-releasing peptide, neurotensin, substance P, glucagonlike peptide 1, neuropeptide Y, and corticotropin-releasing factor receptors. To enable this therapy, a wide range of radiolabeled peptides are being developed for clinical use, including newly designed bombesin, neurotensin, substance P, neuropeptide Y, and glucagonlike peptide 1 analogues, and they have promise for future PRRT [41].

Last, but important, is the issue of personalized dosimetry. NETTER-1 and other clinical trials of ^{177}Lu-DOTATATE were conducted with a fixed dose of 200 mCi (7.4 GBq) of ^{177}Lu-DOTATATE per cycle. As can be said for all radioisotope therapies, personalized dosimetry would allow calculation of the maximum tolerated activity, which in theory should allow the greatest radiation to the tumor while limiting toxicity. This has been most well established, for instance, in patients with thyroid cancer with extensive lung or bone metastases, in which administration of as high a dose as possible is desired without risking pulmonary fibrosis or severe marrow toxicity. There is even a mandate in Europe to perform individualized dosimetry for all patients. But equal numbers in the community strongly oppose this approach, especially as a rule for all patients. Many think that giving a fixed dose works well for most patients and that there is little added gain by providing personalized dosimetry. This has been borne out in many anecdotal and single-

institution experiences but has yet to be studied in a rigorous manner. Furthermore, it is true that dosimetry is an involved and expensive endeavor that should only be undertaken at a high level. This would preclude many sites from offering these therapies.

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