Lutathera (Lutetium Lu 177 Dotatate) First Radioactive Drug Approved for Gastroenteropancreatic Neuroendocrine Tumors

By Lisa A. Raedler, PhD, RPh, Medical Writer

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs), also known as carcinoids and islet-cell tumors, are tumors of the neuroendocrine cells that occur in the gastrointestinal (GI) tract. GEP-NETs are heterogeneous and complex. Although relatively rare, GEP-NETs are more common than other tumors of the GI tract, including stomach and pancreatic carcinomas combined.

The prognosis of patients with GEP-NETs depends on the disease stage and histology. Among >64,900 patients with NETs between 1973 and 2012, the median overall survival (OS) was approximately 9.3 years. The OS was highest in patients with localized NETs (>30 years) compared with regional NETs (10.2 years) and distant NETs (1 year).

Treatment options for patients with GEP-NETs include surgery, interventional radiotherapy, cytotoxic chemotherapy, and somatostatin analogs. Somatostatin analogs, such as octreotide (Sandostatin and Sandostatin LAR Depot), are typically used as first-line systemic therapy to control hormone secretion and tumor growth. No standard second-line systemic treatment is available for the majority of subtypes of NETs, with the exception of everolimus (Afinitor), which is used for nonfunctional NETs.

FDA Approves Lutathera for Somatostatin Receptor–Positive GEP-NETs

On January 26, 2018, the US Food and Drug Administration (FDA) approved Lutathera (lutetium Lu 177 dotatate; Advanced Accelerator Applications) injection, a radiolabeled somatostatin analog, for the treatment of adults with somatostatin receptor–positive GEP-NETs, including foregut, midgut, and hindgut NETs. Lutetium Lu 177 dotatate is the first radiopharmaceutical to be approved by the FDA for this patient population.

Data from 2 studies support the FDA approval of lutetium Lu 177 dotatate: NETTER-1, a randomized clinical trial, and ERASMUS, a study of patients who received lutetium Lu 177 dotatate as part of an expanded access program.

“GEP-NETs are a rare group of cancers with limited treatment options after initial therapy fails to keep the cancer from growing. This approval provides another treatment choice for patients with these rare cancers,” said Richard Pazdur, MD, Director, FDA’s Oncology Center of Excellence.

The FDA granted lutetium Lu 177 dotatate an orphan drug designation. It is the first peptide receptor radionuclide therapy (PRRT), a molecular-targeted drug, to be approved by the FDA for patients with GEP-NETs.

Mechanism of Action

Lutetium Lu 177 dotatate is a somatostatin analog that binds to somatostatin receptors, including subtype 2 receptors. The compound is internalized upon binding to cells that express somatostatin receptors, including malignant tumor cells. Beta emission from Lu 177 induces damage to somatostatin receptor–positive cells and the neighboring cells.

Dosing and Administration

Long-acting somatostatin analogs, such as long-acting octreotide, should be discontinued at least 4 weeks before the first dose of lutetium Lu 177 dotatate. Short-acting octreotide can be used as needed, but should be discontinued at least 24 hours before the first dose of lutetium Lu 177 dotatate.

An antiemetic and an intravenous (IV) amino acid solution should be given before each dose of lutetium Lu 177 dotatate. The antiemetic is administered 30 minutes before the amino acid solution, and the amino acid solution, which contains L-lysine and L-arginine, is administered 30 minutes before the infusion of lutetium Lu 177 dotatate. The amino acid solution should be administered during and for at least 3 hours after the infusion of lutetium Lu 177 dotatate. The amino acid solution dose should not be reduced if the dose of lutetium Lu 177 dotatate is reduced.

The recommended dosage of lutetium Lu 177 dotatate is 7.4 GBq (200 mCi) given intravenously every 8
Median duration of response, mo 

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>Lutetium Lu 177 dotatate and long-acting octreotide (30 mg) (N = 116)</th>
<th>Long-acting octreotide (60 mg) (N = 113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median progression-free survival, mo</td>
<td>NR* (95% CI, NE-NE) 8.5 (95% CI, 5.8-9.1)</td>
<td></td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.21 (95% CI, 0.13-0.32)</td>
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<tr>
<td>(P) value</td>
<td>(&lt;.0001)</td>
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</tr>
<tr>
<td>Median overall survival updated, mo</td>
<td>NR (95% CI, 31.0-NE) 27.4 (95% CI, 22.2-NE)</td>
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<tr>
<td>Hazard ratio</td>
<td>0.52 (95% CI, 0.32-0.84)</td>
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<tr>
<td>Overall response rate, %</td>
<td>13 (95% CI, 7.1-19) 4 (95% CI, 0.1-7)</td>
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<tr>
<td>(P) value</td>
<td>.0148</td>
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<tr>
<td>Median duration of response, mo</td>
<td>NR (95% CI, 2.8-NE) 1.9 (95% CI, 1.9-NE)</td>
<td></td>
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</tbody>
</table>

Table Efficacy of Lutetium Lu 177 Dotatate in the NETTER-1 Clinical Trial

In the NETTER-1 clinical trial, the most common grade 3 or 4 adverse events included myelodysplastic syndrome (MDS; 1.8%), acute leukemia (0.5%), renal failure (2%), hypotension (1%), cardiac failure (2%), myocardial infarction (1%), and neuroendocrine hormonal crisis (1%).

Lutetium Lu 177 dotatate has no contraindications.

Adverse Reactions

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Drug Interactions

Because somatostatin and its analogs competitively bind to somatostatin receptors, they may interfere with the efficacy of lutetium Lu 177 dotatate. Therefore, long-acting somatostatin analogs and short-acting octreotide should be discontinued at least 4 weeks and at least 24 hours, respectively, before each dose of lutetium Lu 177 dotatate.

Use in Specific Populations

Lutetium Lu 177 dotatate can cause fetal harm. Women and men of reproductive potential should be advised of this risk and should use effective contraception during and after treatment with lutetium Lu 177 dotatate. Women of reproductive potential should have a pregnancy test before using this drug.

Women should not breastfeed during treatment with lutetium Lu 177 dotatate and for 2.5 months after the final dose.
Lutetium Lu 177 dotatate, a somatostatin analog, is the first radiopharmaceutical and the first PRRT approved by the FDA for the treatment of adults with somatostatin receptor–positive GEP-NETs.

Warnings and Precautions

Lutetium Lu 177 dotatate contributes to patients’ cumulative radiation exposure, which increases the risk for cancer. Radiation exposure should be minimized during and after treatment with lutetium Lu 177 dotatate. At a median follow-up of 24 months, MDS was reported in 2.7% of patients who received lutetium Lu 177 dotatate plus long-acting octreotide. In the ERASMUS study, 15 (1.8%) patients had MDS and 4 (0.5%) had acute leukemia. Because lutetium Lu 177 dotatate can cause hematologic toxicity, including anemia, thrombocytopenia, and neutropenia, blood cell counts must be monitored. Treatment with lutetium Lu 177 dotatate exposes kidneys to radiation and can impair kidney function. Serum creatinine levels and creatinine clearance should be monitored, and patients should be advised to urinate frequently during and after lutetium Lu 177 dotatate therapy. To protect the kidneys, IV infusion of amino acids is required before, during, and after lutetium Lu 177 dotatate therapy.

In the ERASMUS study, <1% of patients had hepatic tumor hemorrhage, edema, or necrosis. One patient had intrahepatic congestion and cholestasis. Patients with hepatic metastasis may be at an increased risk for hepatotoxicity. Transaminase, bilirubin, and serum albumin levels should be monitored when using lutetium Lu 177 dotatate. Neuroendocrine hormonal crisis occurred in 1% of patients. Patients should be monitored for tumor-related hormonal release. Somatostatin analogs, fluids, corticosteroids, and electrolytes may be indicated. Radiation absorbed by the testis and ovaries after the recommended cumulative dose of lutetium Lu 177 dotatate may result in infertility.

Conclusion

Lutetium Lu 177 dotatate, a somatostatin analog, is the first radiopharmaceutical and the first PRRT approved by the FDA for the treatment of adults with somatostatin receptor–positive GEP-NETs. Lutetium Lu 177 dotatate, combined with long-acting octreotide, significantly prolonged PFS and OS compared with high-dose long-acting octreotide alone in the randomized, phase 3, NETTER-1 clinical trial.