Peptide receptor radionuclide therapy

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Policy contains: Lutetium 177Lu-DOTATATE, neuroendocrine tumors, peptide receptor radionuclide therapy.

This policy is a Sandhills Center Clinical Coverage Policy adopted from AmeriHealth Caritas of North Carolina. These clinical policies are used to assist with making coverage determinations. Sandhills Center's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Sandhills Center when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Sandhills Center clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Sandhills Center's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Sandhills Center will update its clinical policies as necessary. Sandhills Center clinical policies are not guarantees of payment.

Coverage policy

Peptide receptor radionuclide therapy with lutetium ^{177}Lu-DOTATATE (Lutathera®, Advanced Accelerator Applications USA, Inc.) is clinically proven and, therefore, medically necessary when prescribed as treatment of inoperable or metastasized somatostatin receptor-positive gastro-enteropancreatic neuroendocrine tumors, including foregut, midgut, and hindgut neuroendocrine tumors in adults (Bodei, 2013; International Atomic Energy Agency, 2013). Four administrations every eight weeks are indicated (Abbott, 2018).

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

Routine patient evaluation and management by a network healthcare provider.

Background

Neuroendocrine tumors are a heterogeneous group of neoplasms with a common embryological origin and diverse biological behavior, derived from the neuroendocrine system, specifically from the amine precursor uptake and decarboxylation cells. They are characterized by overexpression of all five somatostatin receptors, particularly type 2.

The incidence of neuroendocrine tumors has been rising, particularly those located in the mid-gut and pancreas. U.S. incidence rose from 10.9 to 52.4 per million population from 1973 to 2004 (Yao, 2008). Nearly all neuroendocrine tumors are gastrointestinal (72%) or bronchopulmonary (25%) in origin (Bodei, 2013). For pancreatic neuroendocrine tumors, the U.S. five-year survival rate is 54%, with survival much greater for those localized cases, i.e., diagnosed while only in the pancreas (American Cancer Society, 2021).

Various treatments are now available for patients with neuroendocrine tumors presenting with metastatic disease, including somatostatin analogs, molecular targeted agents, cytotoxic chemotherapy, interferon-α, and peptide receptor radionuclide therapy (Wu, 2018). Surgical resection of the tumor is the treatment option, with a possibility of complete remission in patients with limited disease.

Peptide receptor radionuclide therapy treatment is recommended in case of non-responsiveness of the disease. The ideal candidates for this treatment are patients with unresectable disease of high and intermediate differentiation.

On January 26, 2018, the Food and Drug Administration approved ^{177}Lu-DOTATATE (Lutathera®, Advanced Accelerator Applications USA, Inc.) a radiolabeled somatostatin analog, for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors, including foregut, midgut, and hindgut neuroendocrine tumors in adults (Food and Drug Administration, 2018). Lu 177 has a half-life of 6.73 days and is a beta- and gamma-emitter (Bodei, 2013). The approval was based on a randomized clinical trial of 231 persons that began in 2012 (U.S. National Institutes of Health, 2021). Another isotope used for pancreatic neuroendocrine tumors is Yttrium (^{90}Y-DOTATOC).

Findings

The International Atomic Energy Agency published a guideline on best practices for treating neuroendocrine and gastroenteropancreatic tumors with peptide receptor radionuclide therapy. The guideline addresses therapy as a sole treatment and in combinations (International Atomic Energy Agency, 2013). The Agency then collaborated with the European Association of Nuclear Medicine and the Society of Nuclear Medicine and Molecular Imaging on a guideline that included recommended levels of administered activity, number of cycles, and time interval between cycles (Bodei, 2013).

Another guideline states the treatment generally consists of a 7.4 GBq (200 mCi) intravenous infusion of ^{177}Lu-DOTATATE given to patients every eight weeks for a total of four administrations, even though some slight variations exist among experts in the eight-week interval (Abbott, 2018). The North American Neuroendocrine Tumor Society guideline supports use of ^{177}Lu-DOTATATE on midgut neuroendocrine tumors progressing rapidly on somatostatin analog therapy (Strasberg, 2017).

A more recent guideline by the North American Neuroendocrine Tumor Society and the Society of Nuclear Medicine and Molecular Imaging endorses the 2018 dose and frequency of infusion for ^{177}Lu-DOTATATE in persons with neuroendocrine tumors. Treatment is indicated in patients whose somatostatin receptor expression on ^{111}In-pentetreotide is greater than background hepatic uptake (using scintigraphy or positron emission tomography), and whose lab values conform to standards two weeks before treatment (Hope, 2019).

A meta-analysis of seven studies (n = 414), median progression-free survival among patients with neuroendocrine tumors re-treated with peptide receptor radionuclide therapy was 12.52 months, similar as solo

therapy or in combination with ^{90}Y. Grade 3 - 4 adverse events occurred in 5% of patients, with 0% renal toxicity. Authors state that efficacy and safety of re-treatment is encouraging (Strosberg, 2021).

A systematic review/meta-analysis of nine studies (n = 426) evaluated peptide receptor radionuclide therapy for salvage treatment in patients with progressive endocrine tumors. Compared to initial therapy, salvage treatment hhad significantly lower response and disease control rates (P < .0001) and shorter progression free survival (P = .03), with similar hematologic and renal toxicity (Kim, 2021).

A systematic review/meta-analysis of 13 studies of metastatic or inoperable neuroendocrine tumors given peptide receptor radionuclide therapy reported a 27.58% disease response rate and a 79.14% disease control rate, with few adverse effects. The authors conclude that ^{177}Lu DOTATATE is an effective treatment (Zhang, 2020).

A meta-analysis included 22 studies (n = 1,758) with advanced neuroendocrine tumors treated with ^{177}Lu DOTATATE, who were classified into groups according to certain criteria. The pooled disease response rates by group were 33.0%, 35.0%, and 25.0%, while pooled disease control rates were 79.0%, 83.0%, and 82.0%. All outcomes were described as “significantly elevated” by authors (Wang, 2020).

A systematic review/meta-analysis of 12 studies (n = 201) of advanced paragangliomas, a neuroendocrine tumor, documented a response rate of 25% and a disease control rate of 84% after peptide receptor radionuclide therapy. Similar tumor response rates were found for ^{90}Y and ^{177} Lu-based agents, and adverse effects were minimal (Satapathy, 2019a).

A systematic review/meta-analysis compared Lu-DOTATATE (15 articles, n = 697) and Everolimus (12 articles, n = 946) for advanced pancreatic neuroendocrine tumors. Lu-DOTATATE had superior outcomes in objective response rate (47% versus 12%, P < .001), disease control rate (81% versus 73%, P < .001), median progression-free survival (25.7 months versus 14.7 months, P < .001), grade 3/4 hematological toxicity (5% versus 11%, P = .02), and adverse events causing discontinuation of therapy (0 of 128 versus 59 out of 371) (Satapathy, 2019b).

177Lu-DOTATATE. Two sets of criteria were used to calculate disease response rate (29.1% and 30.6%) and disease control rate (74.1% and 81.1%), described as effective (Saravana-Bawan, 2019).

A meta-analysis of 17 articles (n = 2,758) evaluated treatment of pancreatic neuroendocrine tumors, and detected tumor shrinkage ≥ 10% with chemotherapy alone ranged from 65% to 93%, while chemotherapy plus peptide receptor radionuclide therapy induced similar shrinkage, from 60% to 93% (Pozzari, 2018).

A systematic review and network meta-analysis compared outcomes for seven gastrointestinal neuroendocrine tumors, one of which was ^{177}Lu-DOTATATE combined with somatostatin analogue. This treatment ranked 2nd best of eight treatments in odds ratio of disease control; 1st best of eight for adverse events; and 6th best of 11 in adverse events grades 3/4 (Kaderli, 2019).

A systematic review of NETTER-1 and three other randomized controlled trials on treatments for advanced, unresectable, or metastatic neuroendocrine tumors found consistent improvements in progression-free survival and overall survival after treatment with everolimus, ^{177}Lu-DOTATATE and sunitinib, compared with basic

supportive care. Adverse events were more commonly reported following targeted treatments (Mujica-Mota, 2018).

A literature review concluded that ^{177}Lu-DOTATATE showed better results than other therapies for gastroenteropancreatic neuroendocrine tumors. Adverse effects from this therapy include myelotoxicity and nephrotoxicity. In addition, the review concluded Everolimus is a good and safe option in patients pretreated with ^{177}Lu-DOTATATE. (Maqsood, 2019). Another literature review also found Lu-DOTATATE to be effective in neuroendocrine tumors, both alone and as part of combination therapy (Alsadik, 2019).

A meta-analysisshowed. ^{177}Lu-DOTATATE peptide receptor radionuclide therapy response rates ranged from 27.63% to 57.35%, with a pooled random effect of 33.41%, and disease control rates ranged between 71.88% and 100%, with a pooled fixed effect of 79.32%. As for tandem-peptide receptor radionuclide therapy, disease response rates ranged between 42.11% and 66.67%, with a pooled fixed effect of 50.52%, and the disease control rate ranged between 93.33% and 100%, with a pooled fixed effect of 98.97% (Dannoon, 2017).

A meta-analysis of six studies (n = 473) evaluated the efficacy of ^{177}Lu-DOTATATE therapy in patients with inoperable or metastatic gastro-enteropancreatic tumors. Disease response rates ranged between 17.6% and 43.8% with a pooled effect of 29%. Disease control rates ranged from 71.8% to 100% (average 81%). The second study group demonstrated disease response rates ranging between 7.0% and 36.5% with a pooled effect of 23%. Disease control rates ranged from 73.9% to 89.1% (average 82%) (Kim, 2015).

A systematic review of 34 articles (n = 5,386) followed patients with neuroendocrine tumors treated with peptide receptor radionuclide therapy for 1 – 16 years. Authors revealed substantial nephrotoxicity, especially when Yttrium and Lutetium are combined (Stolniceanu, 2020).

References

On April 20, 2021, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “somatostatin analog,” “neuroendocrine tumors,” and “peptide receptor radionuclide therapy.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

5/2018: initial review date and clinical policy effective date: 7/2018

7/2019: Policy references updated. Policy ID changed to CCP.1383.

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