DRUG EVALUATION

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[¹⁷⁷Lu-DOTA⁰,Tyr³]-octreotate in the treatment of midgut neuroendocrine tumors

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Midgut neuroendocrine tumors (NETs) are relatively rare and remarkably heterogeneous. Although recent developments for pancreatic NETs have brought multiple new therapies to patients who need them, there has been little observed efficacy against midgut NETs. Peptide receptor radionuclide therapy utilizes somatostatin analogs conjugated to radioactive isotopes in order to deliver high doses of radiation directly to tumor cells, which express somatostatin receptors. Peptide receptor radionuclide therapy with [¹⁷⁷Lu-DOTA⁰,Tyr³]-octreotate (DOTATATE) has been reported and investigated for more than a decade, and the randomized controlled NETTER-1 study of this agent has recently been reported to show promising results. In this article, we will summarize and evaluate the rationale and existing clinical data for the activity of DOTATATE in midgut NETs, to give context for the interpretation of NETTER-1 results when they are fully available.

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Neuroendocrine tumors (NETs) of the GI tract are relatively rare and heterogeneous malignancies arising from enterochromaffin cells. Neuroendocrine malignancies are typically divided by histologic grade and primary site. Poorly differentiated or grade 3 cancers, defined by Ki-67 >20%, are highly aggressive malignancies beyond the scope of this review. Well-differentiated NETs are typically indolent, but the clinical course can be highly variable, and metastatic disease is generally incurable [1]. Unfortunately, the incidence of these tumors is rising, as demonstrated in an analysis of the US Surveillance, Epidemiology, and End Results (SEER) database [2]. That analysis reported the incidence of NETs to have increased from 1.09/100,000 population annually to 5.25/100,000 population annually between 1973 and 2004. Therefore, particularly in light of the relatively indolent course of these cancers, they are becoming increasingly prevalent.

Within the broad spectrum of well-differentiated NETs, tumors may be grouped according to the embryologic origin of the primary site, dividing them into foregut, midgut and hindgut NETs. Midgut NETs, arising within the duodenum, jejunum, ileum, cecum and appendix, account for 1.17 (22%) of the 5.25 tumors per 100,000 population annually in the SEER analysis. Other than those tumors arising in the appendix, midgut NETs have among the longest median overall survival duration of any metastatic well-differentiated NET, at more than 40 months for each of these sites and more than 55 months for tumors arising from the small bowel. Therefore, midgut NETs represent a significant proportion of the prevalent NETs encountered clinically.

KEYWORDS

- neuroendocrine tumors
- peptide receptor radionuclide therapy

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In addition to mass effect from disease progression and subsequent functional compromise, NETs are well known for their functional hormonal syndromes. In particular, midgut NETs have long been recognized to beget the carcinoid syndrome, classically described to include flushing, diarrhea and wheezing, later complicated by right-sided cardiac valvulopathy [3]. Carcinoid syndrome is most likely when secreted bioactive amines, such as serotonin, reach the posthepatic circulation, as can occur with hepatic metastases. The symptoms of carcinoid syndrome add an additional dimension to the management of patients with midgut NETs. Estimates of the incidence of carcinoid syndrome are highly variable, and often depend on the specific population under study, but one large analysis identified the syndrome as occurring in 7.7% of patients in a highly heterogeneous population [4].

Therapy for NETs has evolved through rigorous and systematic clinical investigation, with modern therapy based upon randomized studies of novel therapies employing prospective evaluation of defined end points. The foundation of medical therapy for midgut NETs is somatostatin analogs (SSAs). In addition to control of the symptoms of carcinoid syndrome [5], SSAs have convincing evidence from two randomized studies supporting their use to delay progression of disease in midgut NETs. In the prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors (PROMID) [6], octreotide long acting repeatable (LAR) was compared with placebo in a randomized study enrolling 85 patients. The primary end point of time to tumor progression (TTP) was significantly longer in the octreotide arm, with a hazard ratio (HR) of 0.34 (95% CI: 0.20–0.59; $p < 0.001$). Similarly the CLARINET study [7] assessed the control of tumor growth in 204 patients with progressive gastrointestinal NETs with lanreotide as compared with placebo. The primary end point of progression-free survival (PFS) was significantly longer in the lanreotide arm, with an HR of 0.47 (95% CI: 0.30–0.73; $p < 0.001$). Of note, patients could only be enrolled in CLARINET if the Ki-67 was less than 10%, they had been untreated for 6 months, and their tumor had proven avidity for somatostatin on somatostatin receptor scintigraphy. However, in a subgroup analysis of the 73 midgut NET

patients in the CLARINET study, the PFS HR was 0.35 (95% CI: 0.16–0.80) for lanreotide as compared with placebo, indistinguishable from the HR observed in PROMID. Despite the varied inclusion criteria of PROMID and CLARINET, both of which enrolled patients with midgut NETs, the data support using SSAs as integral components of the management of midgut NET patients.

Recent years have seen dramatic advances in the therapies of pancreatic NETs, but the therapeutic options for midgut NETs remain limited. Recent randomized studies have demonstrated clear improvements in the PFS for patients with pancreatic NETs using novel targeted agents such as everolimus [8], and sunitinib [9], as well as a PFS benefit with the somatostatin analog lanreotide [7] in that population. However, the evidence of benefit with these agents for NETs arising outside the pancreas has been more elusive. In the randomized Phase III RADIANT-2 study, everolimus was compared with placebo for patients with progressive NETs and carcinoid syndrome, and the primary end point was not reached [10]. Similarly, patients with extrapancreatic NETs did not appear to derive benefit from sunitinib in Phase II testing [11]. Therefore, there has been limited progress in the treatment of midgut NETs of late, prompting leaders in the neuroendocrine field to suggest that midgut NETs represent an area of urgent medical need [12].

Specialty society guidelines highlight the consensus and controversy in the management of these tumors. While SSAs are universally recommended by the US National Comprehensive Cancer Network (NCCN) [13], North American Neuroendocrine Tumor Society (NANETS) [14] and European Neuroendocrine Tumor Society (ENETS) [15], treatment beyond SSAs remains less clear. Liver-directed therapy is advised by all three groups for hepatic-predominant metastatic disease, though the appropriate timing of this intervention is difficult to determine. With respect to systemic therapy, options are limited. The NCCN panel offers a mixed recommendation for cytotoxic chemotherapy or IFN- α , while NANETS considers IFN in combination with SSA a potential option following failure of SSA, and ENETS recommends neither for disease control, instead suggesting IFN only be used for control of carcinoid syndrome.

Thus, the clinical scenario of advanced midgut NET that has progressed through SSA

remains an active area of clinical investigation. The ideal strategy is unclear, and there is significant unmet need to introduce effective therapy into this space. Additionally, as even SSAs have had limited efficacy in producing meaningful tumor shrinkage, any therapy capable of reducing tumor volume in these patients would be an important additional option in the treatment of midgut NET patients.

Overview of the treatment landscape

Progressive midgut NETs urgently need new therapies. Everolimus remains exciting as a potential new therapy, and the results of RADIANT-4, which assessed the efficacy of everolimus as compared with placebo in patients with progressive extrapancreatic NETs without carcinoid syndrome, are eagerly awaited. Additionally, a randomized Phase II study of pazopanib in progressive extrapancreatic NETs is ongoing in the cooperative group setting (NCT01841736), though significant radiographic responses of midgut NETs to pazopanib were not observed in a prior Phase II study [16]. Additionally, results of a Southwest Oncology Group study comparing bevacizumab versus IFN- α in combination with octreotide were reported at the 2015 annual meeting of the American Society of Clinical Oncology [17], and revealed the two arms to be therapeutically equivalent with respect to efficacy. As neither arm is a standard of care, however, it is unclear how to integrate these therapies into clinical practice.

In parallel with investigation using these therapies, significant effort has been invested in the evaluation of peptide receptor radionuclide therapy (PRRT), which uses radioactive somatostatin analog conjugates to direct high doses of radiation directly to neuroendocrine tumor cells. This technique derives from somatostatin receptor scintigraphy (SRS), which uses ¹¹¹Indium conjugated to octreotide in order to localize NET lesions expressing somatostatin receptors 2 and 5. Original attempts at PRRT used higher doses of the [¹¹¹In-DTPA-D-Phe¹]-octreotide used in SRS [18]. However, subsequent optimization of the PRRT technique led to the introduction of [¹⁷⁷Lu-DOTA⁰,Tyr³]-octreotate (DOTATATE), which had improved affinity for somatostatin receptor (SSTR) 2 and improved tissue penetration, resulting in a favorable therapeutic index [19]. Thus, DOTATATE has become the lead compound for investigation with PRRT.

Introduction to the compound

• Chemistry

DOTATATE is a somatostatin analog conjugated to the beta- and gamma-emitter ¹⁷⁷Lutetium at the tyrosine occupying the third position in the octapeptide. The octreotate moiety, in which the C-terminal threoninol of octreotide is replaced with threonine, demonstrated marked improvements in SSTR2 affinity as compared with conventional octreotide [20,21].

• Pharmacokinetics & metabolism

DOTATATE is injected intravenously in doses of 200 mCi every 6–9 weeks. The radioactive half-life of the ¹⁷⁷Lutetium is approximately 6.7 days [22]. However, the serum half-life of the radiation is significantly shorter, with the serum percentage of injected radioactivity dropping to less than 10% within 3 h [23]. Excretion is urinary, with approximately 75% of the injected radioactivity being excreted in the urine within 24 h. As such, DOTATATE is not meaningfully metabolized by the liver.

• Clinical efficacy

Clinical evaluation of DOTATATE PRRT has been ongoing for over a decade. Formal Phase I testing was not performed, with dosing based on the maximum safe radiation dose to the bone marrow. However, the earliest clinical study performed with this agent evaluated the tumor and bystander organ dose delivery of the agent in comparison to historical data for [¹¹¹In-DTPA⁰]-octreotide [19]. In that study, six patients with assorted malignancies received a single dose of 50 mCi of DOTATATE. Plasma, urine and organ radioactivity were assessed, as well as tumor radioactivity uptake. The authors reported significantly higher doses of radiation delivered to tumors with comparable off-target organ doses, which were further reduced to the kidney with an infusion of positively charged amino acids [19]. This study led to the conclusion that DOTATATE should be the leading candidate radiopharmaceutical for development, given its ratio of tumor to bystander organ dose.

• Phase II studies

The collected experience reported in the literature of the use of PRRT with DOTATATE is substantial, numbering in the several hundred of patients. However, we present efficacy data here collected only in prospective Phase II studies, rather than comparative cohort studies, as

their nonrandomized treatment assignments make interpretation of the comparison difficult to interpret meaningfully. Additionally, we have excluded studies that report on combinations of DOTATATE together with other PRRT technologies, though studies combining DOTATATE with sensitizing systemic chemotherapy are included.

The first efficacy report of DOTATATE was in 35 patients with gastroenteropancreatic NETs treated in The Netherlands [24]. All patients were octreotide-avid on SRS. These patients received DOTATATE in doses ranging from 100 to 200 mCi, with a total target dose of 600–800 mCi, which was successfully administered to 30 of the patients. There was no explicit primary end point or hypothesis, but patients underwent cross-sectional imaging at 6, 12 and 24 weeks after therapy. The WHO solid tumor response criteria were used to categorize changes in tumor size. While it was not an entry criterion for clinical studies at the time of the report, progressive disease within 12 months prior to entry was documented in 16 (46%) of patients. A complete response (CR) was reported in one patient (3%), partial response (PR) in 12 (35%), and stable disease (SD) in 14 (41%), with progressive disease (PD) in seven (21%). Responses appeared correlated with increased somatostatin avidity on somatostatin receptor scintigraphy. Toxicity was reported to be minimal, with abdominal pain, nausea or vomiting present in 10–30% of patients and WHO grade 3 cytopenias occurring in 2% or less of patients. Additional patients were subsequently accrued and reported. With 135 patients treated, the rates of CR (2%), PR (26%), SD (54%) and PD (18%) were comparable, and toxicities were similar as well, though a 1% incidence of renal toxicity and 1% incidence of hepatic toxicity were observed [25]. A later efficacy report in 310 patients was similar with respect to efficacy [26]. The risk–benefit ratio reported in these studies certainly appears favorable, but the lack of intention-to-treat analyses, statistical rigor, and clear patient selection criteria make the results difficult to contextualize and interpret.

The same group separately reported quality of life (QoL) outcomes in a series of 50 patients treated with DOTATATE [27]. Patients were assessed with the validated EORTC QLQ-C30, which includes 30 items across five domains and global health status, but is not specific for carcinoid syndrome symptoms. After scores are

linearly transformed onto a 0–100 scale, changes of 5–10 are considered ‘little’, 10–20 ‘moderate’ and more than 20 are considered important change, based on prior validation work. Patients received the same doses of DOTATATE as in prior protocols, and were assessed at baseline and 6 weeks after completion of therapy (mean of 7 months after baseline visit), immediately before undergoing the imaging study to determine the radiographic response to therapy, so they were unaware of the results. Over 99% of the items were complete. The global health/QoL score improved from 69 (SD: 20) at baseline to 78.2 (SD: 16.9) after therapy ($p < 0.01$), qualifying as ‘little’ improvement on the categorical scale described above. On exploratory subgroup analysis, the 24 patients with radiographic response and the six patients with radiographic progression appeared to demonstrate statistically significant QoL improvements, whereas there was no significant difference observed among the 19 patients with radiographic stable disease. Overall, DOTATATE appears to offer modest improvements in QoL for treated patients, without a clear relationship between radiographic response and QoL improvement. These data highlight the importance of control arms in order to meaningfully interpret such results.

Subsequently, QoL outcomes in 265 Dutch patients treated on a Phase II protocol of DOTATATE were reported [28]. The EORTC QLQ-C30 was used in this study as well, with the same validated categorical cut points for qualitative improvement in QoL previously described. Descriptive statistics were used to quantify changes in QoL from baseline to post-therapy assessment. When analyzing the entire group, statistically significant improvements in global QoL and multiple domains and symptoms were observed. However, the magnitude of benefit was not explicitly quantified and appears to be modest at best. Within the subgroup (95.5%) of patients experiencing QoL scores less than 100 at baseline, 36% are reported to experience improvements of 10 points or more. A greater proportion of these patients reported improvements in specific symptoms. This study demonstrated clear symptomatic improvement in a portion of the patients receiving DOTATATE, though it is not clear how to define the population most likely to benefit *a priori*.

A Phase II study examined the safety and efficacy of DOTATATE in combination with radiosensitizing doses of capecitabine [29]. In

that study, 33 patients with well-differentiated NETs and documented progressive disease within 6 months of study entry received the combination therapy of 7.8 GBq (210mCi) of DOTATATE every 8 weeks, with 14 days of capecitabine 1650 mg/m² commencing on the day of DOTATATE delivery. Efficacy and safety were assessed using descriptive statistics. Of the 33 patients, 8 (24%) experienced a PR by RECIST 1.1, with 23 (70%) experiencing SD and 2 (6%) experiencing PD at 6 months. With a median follow-up of 16 months (range: 5–33), median PFS and OS had not been reached. Three patients (9%) discontinued the capecitabine due to angina, and three (3%) experienced grade 3 thrombocytopenia. All patients experienced grade 1/2 nausea/vomiting. The authors emphasize the rate and duration of stable disease observed in this study, though historical comparisons are unavailable for similar mixtures of patients with varied grades and primary sites.

A separate Phase I/II study evaluated DOTATATE in combination with capecitabine and temozolomide chemotherapy [30]. Each patient received 7.8 GBq (210 mCi) of DOTATATE every 8 weeks, with 14 days of capecitabine 1500 mg/m² commencing 5 days before the DOTATATE delivery. All patients were octreotide-avid on SRS. Patient cohorts received escalating doses of temozolomide for the final 5 days of capecitabine administration. No dose-limiting toxicities were observed at 100 mg/m², 150 mg/m² or 200 mg/m² of temozolomide, the latter of which was declared the maximum tolerated dose. A total of 35 NET patients were treated, 2 with pulmonary primaries. Over 90% received all four cycles of therapy, and all received at least two cycles. There was no explicit primary end point or hypothesis in the Phase II portion of the study. Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 were used to measure responsiveness to therapy, though metabolic activity on SRS, PFS and OS were measured as well. By RECIST 1.1, CR was observed in five (16%), PR in 13 (41%), SD in 12 (37%) and PD in two (6%) of the 32 GEP-NET patients completing one cycle of therapy per protocol. The treatment was reported to be well tolerated, with grade 1–2 nausea/vomiting reported in ten (36%) of the patients and grade 3 nausea/vomiting reported in one (3%) of the patients. Two patients (6%) experienced grade 3 neutropenia and grade 3 angina each. When patients were divided into gastropancreatic NETs and enteric NETs, PRs were significantly more common among patients with

gastropancreatic NETs, with a PR rate of 64% (95% CI: 42–87). Multiple issues become apparent with this study on critical review. The response rate of NETs of various primary sites is not firmly established for the combination of temozolomide and capecitabine, alone or in combination. The proportion of gastric as opposed to pancreatic NETs, which likely have different response rates to alkylating chemotherapy, is not given. Therefore, it is difficult to interpret the results of this study in context, though the results certainly appear promising, particularly in light of the progressive disease on enrollment for all patients in the study.

A preliminary report from the first US Phase II study of DOTATATE was also recently published, as well [31]. Patients with octreotide-avid grade 1–2 gastroenteropancreatic NETs received up to four cycles of DOTATATE at 200 mCi per cycle. All patients had progressive disease prior to study enrollment, though the time frame of progression was not specified. The primary end point was PFS by modified RECIST, though no explicit hypothesis was reported. In this unplanned interim analysis, the PFS of the intention to treat population of 37 patients was 16.1 months. Among 32 patients deemed evaluable, PR was observed in 9 (28%), SD in 14 (44%) and PD in 9 (28%). Among the 32 evaluable patients receiving three or more cycles of therapy, grade 3 hematologic toxicity was reported in four patients (12.5%), and grade 3 hepatic toxicity was reported in three (9.4%) patients. There was no grade 3 renal toxicity. In summary, this study reported results that seem favorable, but from an unspecified mix of patients, particularly with respect to grade, and is therefore challenging to contextualize and interpret, particularly without an explicit hypothesis. Its results, along with those of the other Phase II studies, are summarized in [Table 1](#). It is important to note that different imaging criteria were used in several of the studies, making results difficult to compare directly.

• Phase III studies

No Phase III studies of DOTATATE have been published as of this writing. A study comparing treatment with DOTATATE to octreotide LAR in patients with inoperable, progressive, somatostatin receptor-positive midgut carcinoid tumors (NETTER-1; NCT01578239) is a randomized study of four doses of 200 mCi of DOTATATE compared with 60 mg of octreotide monthly in 280 patients, has been reported in abstract form and published results are expected imminently.

Table 1. Efficacy results of Phase II studies.

Study (year)	Patients (n)	Included primary sites	PD on enrollment	Additional agents	Primary end point	Outcome	Ref.
Delpassand <i>et al.</i> (2014)	37	All NETs	Yes	None	PFS	16.1 months	[31]
Claringbold <i>et al.</i> (2012)	35	All NETs	Not all	Capecitabine and temozolomide	Safety	MTD tolerated	[30]
Claringbold <i>et al.</i> (2011)	33	All NETs	Yes	Capecitabine	None	ORR 24% (95% CI: 12–36%)	[29]
Khan <i>et al.</i> (2011)	265	All NETs	No	None	None	At least ‘moderate’ QoL improvement in 36% of patients	[28]
Kwekkeboom <i>et al.</i> (2008)	310	GEPNETs	No	None	None	ORR 29% (95% CI: 24–35%)	[26]
Kwekkeboom <i>et al.</i> (2005)	131	GEPNETs	No	None	None	ORR 28% (95% CI: 20–37%)	[25]
Teunissen <i>et al.</i> (2004)	50	GEPNETs	No	None	None	‘Little’ QoL improvement overall	[27]
Kwekkeboom <i>et al.</i> (2003)	35	GEPNETs	No	None	None	ORR 38% (95% CI: 22–56%)	[24]

GEPNET: Gastroenteropancreatic neuroendocrine tumor; MTD: Maximum tolerated dose; NET: Neuroendocrine tumor; ORR: Objective response rate; PD: Progressive disease; PFS: Progression-free survival; QoL: Quality of life.

The primary end point of the study is PFS by blinded independent central radiology review. In oral presentations, the median PFS in the DOTATATE arm was not reached, whereas patients in the control arm receiving octreotide experienced a median PFS of 8.4 months (HR: 0.20; 95% CI: 0.129–0.338) [32]. We are hopeful that this study will help address whether DOTATATE specifically, and PRRT in general, is a valuable approach for the broad population of midgut NET patients encountered in routine clinical practice.

An additional randomized Phase III of DOTATATE compared with IFN-2β (CASTOR; NCT01860742) was also recently initiated in Belgium. It has an anticipated enrollment of 66 patients who have progressive disease on an SSA and will use a primary end point of PFS. However, given the small sample size and nonstandard comparator arm, it is unclear how much this study will change practice.

Safety & tolerability

In Phase II studies, DOTATATE has been generally safe and well tolerated. However,

long-term safety data have been generally lacking. Reports must be interpreted very deliberately, given the use of different grading systems in different locations and the inclusion of systemic chemotherapy in some regimens. Several studies report generally mild gastrointestinal adverse events, such as abdominal pain, nausea and/or vomiting, in 40–100% of patients. Grade 3 cytopenias occur in 2–12% of patients. Furthermore, in one series, myelodysplastic syndrome (MDS) occurred in four of 504 (0.8%) patients [25]. These results are similar to those of another series in which three of 203 (1.4%) of patients developed MDS [33]. It also bears mention that while earlier PRRT technologies were nephrotoxic, ¹⁷⁷Lu-DOTATATE is generally administered with a solution of positively charged amino acids that significantly reduce the dose of radiation delivered to the kidneys [19], likely limiting the observed toxicity. However, it is notable that the amino acid infusion is itself associated with hyperkalemia, which occurs in over 94% of patients [34]. Other PRRT compounds with greater toxicity, such as [⁹⁰Y DOTA]-octreotide, which has greater penetration depth, have a high incidence of grade 3,

Table 2. Reported toxicity outcomes in Phase II studies of DOTATATE.

Toxicity	Delpassand (2014) [31]	Claringbold (2012) [30]	Claringbold (2011) [29]	Kwekkeboom (2008) [26]	Kwekkeboom (2005) [25]
Alopecia (all grades), %	0	0	0	62	64
Abdominal Pain (all grades), %	0	0	0	10	14
Nausea (all grades), %	80	39	100	25	31
Vomiting (all grades), %	80	39	100	10	14
Nephrotoxicity (grade ≥3), %	0	0	0	<1	<1
Hepatotoxicity (grade ≥3), %	9.4	0	0	0	<1
Cytopenias (grade ≥3), %	12.5	6	3	9.5	2

Table 3. Reported toxicity outcomes in representative Phase II studies of different peptide receptor radionuclide therapies.

Toxicity	Villard (2012) [35], [⁹⁰ Y-DOTA]-octreotide	Kwekkeboom (2008) [26], [¹⁷⁷ Lu-DOTA]-octreotate	Valkema (2002) [36], [¹¹¹ In-DOTA]-octreotide
Alopecia (all grades), %	0	62	0
Abdominal pain (all grades), %	0	10	0
Nausea (all grades), %	0	25	0
Vomiting (all grades), %	0	10	0
Nephrotoxicity (grade ≥3), %	27.8	<1	0
Hepatotoxicity (grade ≥3), %	0	0	0
Cytopenias (grade ≥3), %	6.3	9.5	27

4 and 5 nephrotoxicity even when administered together with an infusion of amino acids [35]. Grade 3 hepatotoxicity was reported in nearly 10% of patients in one study, but only rarely in other reports. Similarly, alopecia (as defined by the Common Terminology Criteria for Adverse Events 4.0) is observed in more than half of the patients in some series, but is not reported in others. Safety outcomes in different studies of DOTATATE, as well as representative studies

of alternative PRRT compounds, are summarized in **Tables 2 & 3**, respectively. Of note, several toxicities vary significantly in their reported frequency, which may be due to variations in follow-up time and/or data capture.

Regulatory status

Neither DOTATATE nor any other PRRT compound is approved for marketing in the USA or EU. PRRT is frequently administered in Europe

EXECUTIVE SUMMARY

Mechanism of action

- [¹⁷⁷Lu-DOTA⁰, Tyr³]-octreotate (DOTATATE) is the beta- and gamma-emitting isotope ¹⁷⁷Lutetium conjugated to the somatostatin analog octreotate at the tyrosine occupying the third position in the octapeptide.
- Following binding of the somatostatin analog to its receptor, the ¹⁷⁷Lu delivers high doses of radiation directly to somatostatin-avid tumors.

Pharmacokinetic properties

- DOTATATE is administered as an intravenous infusion.
- It is primarily renally excreted.
- While the radioactive isotopic half-life is measured in days, serum radiation drops to less than 10% within 3 h.

Clinical efficacy

- Published reports are limited to uncontrolled Phase II studies suggesting improvements in progression-free survival, tumor shrinkage and quality of life.
- An international multicenter randomized controlled trial of DOTATATE versus octreotide LAR has been reported in oral form, and demonstrates a significant benefit with respect to progression-free survival.

Safety & tolerability

- Major toxicity concerns include marrow toxicity and nephrotoxicity.
- Renal toxicity appears to be significantly limited by the use of an amino acid infusion.
- Marrow toxicity includes transient cytopenias and an approximately 1% risk of myelodysplasia.

Drug interactions

- There are no known drug interactions.

Dosage & administration

- DOTATATE is administered as 200 mCi of radiation every 8 weeks for four doses.

as an experimental therapy. It is hoped that the results of NETTER-1 will allow for presentation of these therapies to regulatory authorities for consideration of approval.

Conclusion

Many studies have provided evidence that PRRT in general, and specifically DOTATATE, has antitumor activity in midgut NET patients. However, the heterogeneous and poorly defined patient populations, combination with other therapies of imprecisely estimated benefit, and use of descriptive statistics rather than rigorous hypothesis testing limit the interpretation of the accumulated data, despite the large number of patients who have been treated. Given the intense and urgent need for new therapies that can prolong survival and offer tumor shrinkage to patients with midgut NETs, interest in DOTATATE PRRT has been substantial across the world, and additional PRRT compounds, including somatostatin receptor antagonist

compounds with increased receptor affinity, are being investigated. As a result, the NETTER-1 study, which sought to address the question of whether this specific therapy has discrete benefit in a defined patient population using a rigorous hypothesis-testing framework, was launched, and completed accrual rapidly. As the results are fully reported, we remain hopeful that the study will fill a crucial knowledge gap in the NET field and inform us of the ultimate utility of this therapy.

Financial & competing interests disclosure

The authors participated in the randomized study of DOTATATE in scientific collaboration with Advanced Accelerator Applications. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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