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Published in:
Journal of Clinical Endocrinology and Metabolism

DOI:
[10.1210/clinem/dgab289](https://doi.org/10.1210/clinem/dgab289)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Zandee, W. T., Brabander, T., Blažević, A., Minczeles, N. S., Feelders, R. A., de Herder, W. W., & Hofland, J. (2021). Peptide receptor radionuclide therapy with ¹⁷⁷Lu-DOTATATE for symptomatic control of refractory carcinoid syndrome. *Journal of Clinical Endocrinology and Metabolism*, 106(9), e3665-e3672. <https://doi.org/10.1210/clinem/dgab289>

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Clinical Research Article

Peptide Receptor Radionuclide Therapy With ¹⁷⁷Lu-DOTATATE for Symptomatic Control of Refractory Carcinoid Syndrome

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Abbreviations: ¹⁷⁷Lu-DOTATATE, [Lutetium-177-DOTA⁰-Tyr³]octreotate; BMF, bowel movement frequency; CS, carcinoid syndrome; CT, computed tomography; EORTC, European Organization for Research and Treatment of Cancer; IQR, interquartile range; MRI, magnetic resonance imaging; NEN, neuroendocrine neoplasm; QLQ-C30, quality of life questionnaire—core module; PRRT, peptide radionuclide receptor therapy; SSA, somatostatin analog; u5-HIAA, urinary 5-hydroxyindoleacetic acid

Received: 27 January 2021; Editorial Decision: 25 April 2021; First Published Online: 4 May 2021; Corrected and Typeset: 1 June 2021.

Abstract

Context: Peptide receptor radionuclide therapy (PRRT) with [Lutetium-177-DOTA⁰-Tyr³] octreotate (¹⁷⁷Lu-DOTATATE) results in an increase of progression-free survival and quality of life in patients with progressive, well-differentiated neuroendocrine neoplasms (NENs).

Objective: To study the effect of ¹⁷⁷Lu-DOTATATE in patients with carcinoid syndrome and radiologically stable or newly diagnosed disease treated solely for the purpose of symptom reduction.

Design: Retrospective cohort study.

Setting: Tertiary care hospital.

Patients: Twenty-two patients with a metastatic midgut NEN, elevated urinary 5-hydroxyindoleacetic acid excretion, and flushing and/or diarrhea despite treatment with a somatostatin analog, without documented disease progression.

Intervention: PRRT with ^{177}Lu -DOTATATE (intended cumulative dose: 29.6 GBq) with a primary aim to reduce symptoms.

Results: After PRRT, mean bowel movement frequency (BMF) decreased from 6.1 ± 3.4 to 4.6 ± 3.6 per day ($P = 0.009$). Flushes decreased from 4.3 ± 2.9 to 2.4 ± 2.7 flushes per day ($P = 0.002$). A decrease of BMF of more than 30% occurred in 47% of patients with baseline BMF of 4 or more ($n = 17$). In patients with ≥ 2 episodes of flushing a day ($n = 15$), 67% of patients had more than 50% decrease of daily flushing. A decrease in urinary 5-hydroxyindolacetic acid excretion of more than 30% was seen in 56% of patients. The European Organization for Research and Treatment of Cancer–Core Module diarrhea subscale score showed a trend toward improvement by an average of 16.7 ± 33.3 points ($P = 0.11$).

Conclusion: PRRT with ^{177}Lu -DOTATATE effectively reduced diarrhea and flushing in patients with carcinoid syndrome and can be considered for symptomatic treatment of carcinoid syndrome insufficiently controlled with somatostatin analogs.

Key Words: neuroendocrine tumor, PRRT, carcinoid syndrome

Midgut neuroendocrine neoplasms (NENs) arise from enterochromaffin cells that secrete a plethora of peptides and amines to regulate gastrointestinal motility (1, 2). Locally, in the case of mesenteric lymph node metastases, the hypersecretion of serotonin and kinins by midgut NENs can cause mesenteric fibrosis (3). However, because serotonin is efficiently metabolized by the liver, it can only enter the systemic circulation in the case of metastatic disease (4). Then, it can cause diarrhea and cardiac valvular fibrosis. Hypersecretion of kinins and histamines can cause flushing and bronchospasm. Together, all these symptoms are known as the carcinoid syndrome (CS) (5). CS is associated with impaired overall survival, mainly because it is associated with a high tumor load and liver metastases, as well as with reduced quality of life (6–8).

In severe CS, symptomatic control can be challenging and should encompass management of tumor growth as well as hormonal secretion. The first step in the treatment of CS is initiation of a somatostatin analog (SSA). This results in a decrease in serotonin secretion in 45% of patients and a symptomatic response in more than 65% of patients (9). Furthermore, treatment with SSAs has been shown to increase time to progression of patients with advanced midgut NENs when compared with placebo (10). In patients with persisting symptoms of flushing and diarrhea despite optimal treatment with SSAs, several options for second-line treatment exist. First, decreasing the administration interval of SSAs or adding rescue injections can already further decrease symptoms of CS (11). In the 1990s, several trials with interferon-alpha demonstrated a biochemical response in 44% of patients with CS (12, 13). The serotonin synthesis inhibitor telotristat ethyl reduced daily bowel movement frequency (BMF) with 0.8 vs placebo in a controlled randomized trial (14). Also, a symptomatic response of 82% has been reported after liver-directed therapies including embolization, tumor-debulking liver surgery, and radiofrequency ablation (9).

Peptide radionuclide receptor therapy (PRRT) with [Lutetium-177-DOTA⁰-Tyr³]octreotate (^{177}Lu -DOTATATE) is registered for the treatment of advanced inoperable well-differentiated gastroenteropancreatic NENs in Europe and the United States and bronchial NENs in the United States. The phase 3 Study Comparing Treatment With ^{177}Lu -DOTA⁰-Tyr³-Octreotate to Octreotide LAR in Patients With Inoperable, Progressive, Somatostatin Receptor Positive Midgut Carcinoid Tumours trial showed that PRRT improves progression-free survival in patients with advanced well-differentiated midgut NENs compared with an above-label dose of long-acting SSAs (15). In a post hoc analysis of the study as well as in our Erasmus Medical Center phase 2 study, PRRT has been shown to result in a decrease of diarrhea and urinary 5-hydroxyindoleacetic acid (u5-HIAA) excretion in patients with advanced well-differentiated midgut NENs that were progressive before the start of therapy (16, 17).

Given its potent effects on NEN-associated pancreatic hormonal syndromes (18), PRRT could also be effective in treating patients that suffer from refractory hormonal complaints in the context of CS. However, the effects of treatment with ^{177}Lu -DOTATATE, purely for symptomatic control of CS, have not been reported. The aim of this study was to determine the effect of ^{177}Lu -DOTATATE in patients with nonprogressive low-grade (World Health Organization grade 1–2) midgut NEN with refractory CS, treated because of uncontrolled symptoms.

Methods

Patients

For this study, patients were selected from the prospective phase 2 PRRT study at the Erasmus Medical Center if

treated with ^{177}Lu -DOTATATE because of a treatment-refractory CS. Patients with advanced midgut NEN were included if treated with ^{177}Lu -DOTATATE for persisting symptoms of CS despite treatment with an SSA (Octreotide immediate release subcutaneously, Octreotide LAR, or Lanreotide Autogel). Because the primary aim of the study was the effect of ^{177}Lu -DOTATATE on symptom reduction, patients with refractory CS were excluded if they had radiological progressive disease. Thus, only patients without documented disease progression on consecutive scans or patients treated early with PRRT before follow-up imaging occurred (with a minimal treatment duration with SSA of 3 months) were included. Patients treated with at least 1 cycle of PRRT and a minimum of 1-year follow-up were included. CS was diagnosed in patients with midgut NENs with symptoms of secretory diarrhea and/or flushing in combination with elevated u5-HIAA excretion. u5-HIAA excretion was measured as described earlier with an upper limit of normal of 50 $\mu\text{mol}/24$ hours (19).

Patients were eligible for PRRT if hemoglobin was ≥ 5.5 mmol/L, white blood cell count $\geq 2 \times 10^9/\text{L}$, platelet count $\geq 75 \times 10^9/\text{L}$, and Karnofsky performance status ≥ 50 . Furthermore, adequate tumor SSTR expression as evaluated on planar scintigraphy (somatostatin receptor scintigraphy) with ^{111}In -DTPA-octreotide (OctreoScan) was required: uptake equal to (Krenning scale grade 2) or greater than normal liver tissue (grade 3) or greater than kidneys/spleen (grade 4). This study was performed in accordance with the principles of the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, and all applicable regulations including approval of the local Medical Ethical Committee. All the patients provided written informed consent.

PRRT protocol

The preparation and administration of ^{177}Lu -DOTATATE has been described earlier (20, 21). The intended interval between treatments was 6 to 10 weeks. Patients were treated with 4 cycles up to a cumulative intended dose of 27.8 to 29.6 GBq ^{177}Lu -DOTATATE. Lanreotide and Octreotide LAR were discontinued a minimum of 6 weeks before therapy and short-acting octreotide was discontinued at least 24 hours before treatment. SSA treatment was restarted at least 4 hours after the administration of the radiopharmaceutical. All patients were admitted for 1-night clinical observation. Follow-up visits were at 6 weeks, 3 months, and 6 months after the last treatment cycle, and thereafter at 6-month intervals. At each follow-up visit, routine hematology, liver, and kidney function tests were performed and a computed

tomography (CT) or magnetic resonance imaging (MRI) was performed.

Measurements and outcomes

Baseline patient and disease characteristics, radiology, and nuclear imaging were obtained from the prospective Erasmus Medical Center PRRT database. The whole-body extent of disease on the somatostatin scintigraphy was scored as limited, moderate, or extensive by experienced nuclear medicine physicians, as described previously (22). The effect on the quality of life was measured with European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-core module (C30) (23). The EORTC QLQ-C30 scores were transformed to 0 to 100 scales and the scores 3 months after last treatment were compared with baseline (24). Radiological response was assessed on CT or MRI scans according to the Response Evaluation Criteria in Solid Tumors 1.1 criteria (25). Progression-free survival was defined as the time from first day of treatment until day of objective progression, new line of treatment, or death from any cause. Toxicity was scored according to the Common Terminology Criteria for Adverse Events 4.03. Retrospectively, the daily BMF and flushing episodes were recorded as stated in the medical chart by the treating physician.

Statistics

Data were presented as mean with standard deviation or median and interquartile range (IQR: 25th-75th percentiles) as appropriate. A paired *t* test was used for comparison of continuous normally distributed variables. The Wilcoxon signed-rank test was used for nonnormally distributed variables. Logistic regression was used to identify potential predictors of a symptomatic response. Progression-free survival was analyzed with the Kaplan-Meier method. A 2-sided *P* value < 0.05 was considered statistically significant. Calculations were performed using SPSS for Windows software (version 23.0, SPSS Inc.).

Results

For this study, 22 patients could be included that were treated with ^{177}Lu -DOTATATE because of refractory CS symptoms (Table 1). The average patients' age was 62.7 ± 8.2 years, 46% was female, and the median Karnofsky score was 80 (IQR: 80-90). Patients had previously undergone a surgical resection of the primary tumor (55%) or an ovarian metastasis (5%). All patients were treated with a first-generation SSA, either short-acting (41%), long-acting (36%), or a combination (23%) during a median of 9.1 months (IQR:

Table 1. Baseline characteristics (n = 22)

Patient characteristics		Disease characteristic	
Female, n (%)	10 (46)	Grade, n (%)	
Age (y ± SD)	62.7 ± 8.2	1	7 (32)
Karnofsky score (median, IQR)	80 (80–90)	2	7 (32)
Previous treatments, n (%)		Unknown	8 (36)
Surgery	13 (59)	Location of metastases, n (%)	
Chemotherapy	2 (9)	Liver	22 (100)
Interferon	3 (14)	Lungs	0
MIBG	2 (9)	Bones	6 (27)
Other ^a	3 (14)	Liver burden, n (%) ^b	
Somatostatin analog, n (%)		1%-25%	2 (10)
Short-acting	9 (41)	25%-50%	9 (43)
Daily dose (median, IQR)	600 (375-1500) µg/day	>50%	10 (48)
Long-acting	8 (36)	Extent of disease (somatostatin receptor scintigraphy), n (%)	
Above-label dose ^c , n (%)	4 (50)	Limited	2 (9)
Short and long-acting	5 (23)	Moderate	15 (68)
No. previous treatments, n (%)		Extensive	5 (23)
1	10 (46)	Uptake on somatostatin receptor imaging, n (%)	
2	6 (27)	Grade 2	2 (9)
≥3	6 (27)	Grade 3	14 (64)
Alkaline phosphatase elevated, n (%)	15 (68)	Grade 4	6 (27)
Lactate dehydrogenase, n (%)	12 (55)		
Chromogranin A ^d (median)	1572 µg/L		

Abbreviation: IQR, interquartile ratio.

^aIncludes liver embolization, radiotherapy, and radiofrequency ablation.

^bLiver burden unevaluable in 1 patient.

^cDose of long-acting somatostatin analogs above lanreotide 120 mg or Octreotide LAR 30 mg every 4 weeks.

^dUpper limit of normal 94 µg/L.

4.9-26.5). Sixteen patients (73%) were treated with a SSA dose above the regular dose (octreotide subcutaneously 100 µg 3 times a day or lanreotide 120 mg deeply subcutaneously/octreotide LAR 30 mg IM every 28 days). One patient had to discontinue SSAs because of worsening diarrhea after the start of octreotide LAR.

All patients had stage IV disease with liver metastases. In 90% of patients, baseline imaging showed a liver burden (CT or MRI) of more than 25% with moderate or extensive disease scored with somatostatin receptor scintigraphy, suggesting large tumor bulk. All patients had severe CS with median 24-hour u5-HIAA excretion of 869 µmol/24 hours (IQR: 526-1557). All patients were screened with a cardiac ultrasound and 12 (55%) were diagnosed with carcinoid heart disease. Two patients underwent prior replacement of the tricuspid valve. One patient was treated early with PRRT after only a baseline CT scan; all others had radiological stable disease on consecutive scans.

Symptomatic and biochemical response

The intended dose of 27.8 to 29.6 GBq ¹⁷⁷Lu-DOTATATE was administered in 50% of patients and the median dose

was 26.8 GBq (IQR: 17.6-29.6). A reduced intended dose of 25.9 GBq was administered in 2 patients after previous treatment with MIBG and in 1 patient because of high liver tumor burden. Three patients were treated with a reduced dose because of toxicity, and 5 patients discontinued PRRT because of clinical progression (n = 2) or progression of heart failure (n = 3). The symptomatic response to ¹⁷⁷Lu-DOTATATE is shown in Fig. 1. At start of treatment with ¹⁷⁷Lu-DOTATATE, all patients had uncontrolled symptoms of CS with mean BMF of 6.1 ± 3.4 per day and 4.3 ± 2.9 flushes per day. After PRRT mean BMF decreased to 4.6 ± 3.6 (P = 0.009) and mean daily flushing decreased to 2.4 ± 2.7 (P = 0.002). A decrease of BMF of more than 30% occurred in 47% of patients with baseline BMF of 4 or more (n = 17). A more than 50% decrease was noted in 29% of these patients. In patients with 2 or more episodes of flushing per day (n = 15); 67% of patients had more than 50% decrease of daily flushing. Of the 14 patients with a clinical response, a reduction in symptoms occurred after 1 cycle in 1 patient, after 2 cycles in 7 patients, and after 3 to 4 cycles in 6 patients. In this small cohort, the tumor grade, liver burden, extent of disease, baseline 24-hour u5-HIAA excretion, and uptake on somatostatin receptor imaging

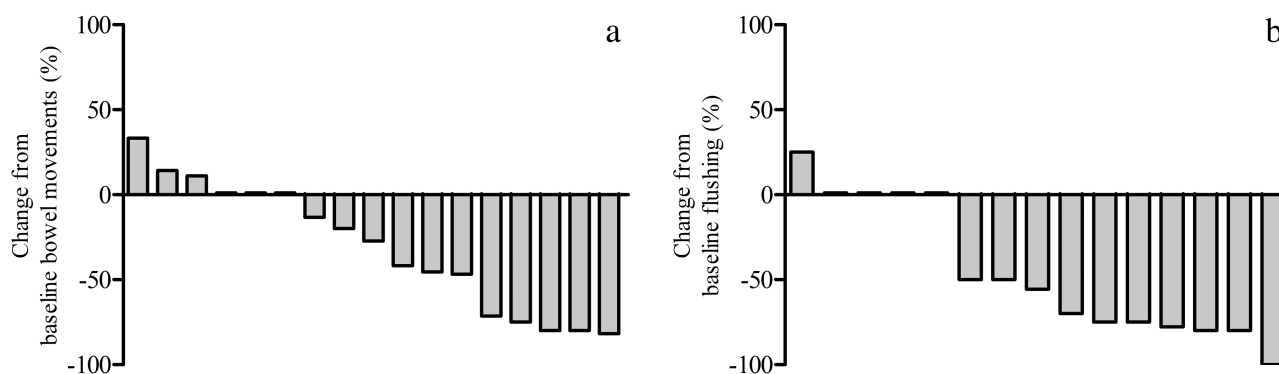


Figure 1. (A) Percentage of change from baseline bowel movements per patient per day (included patients with 4 or more bowel movements daily at baseline). (B) Percentage of change from baseline flushing per patient per day (included patients with 2 or more flushes daily at baseline).

were not found to be predictors of a symptomatic response with logistic regression.

The symptomatic responses were accompanied by decrease of 24-hour u5-HIAA excretion (Fig. 2). In 18 patients with follow-up of more than 6 months, the median 24-hour u5-HIAA excretion decreased from 775 $\mu\text{mol}/24$ hours (IQR: 471-1290) to 530 $\mu\text{mol}/24$ hours (IQR: 393-858, $P = 0.01$). Four patients did not have u5-HIAA collection after 6 months because of death. In an intention-to-treat model with last observation carried forward including all patients, median u5-HIAA decreased from 869 $\mu\text{mol}/24$ hours (IQR: 526-1557) to 657 $\mu\text{mol}/24$ hours (IQR: 422-1156, $P = 0.01$). Six months after the last cycle of PRRT, a u5-HIAA decrease of more than 30% was seen in 56% of patients and a decrease of more than 50% in 33% of patients with u5-HIAA available. In the same 18 patients with follow-up of more than 6 months, there was a nonsignificant decrease of median chromogranin A (upper limit of normal: 94 $\mu\text{g}/\text{L}$) from 1572 $\mu\text{g}/\text{L}$ (IQR: 475-7661) at baseline to 798 $\mu\text{g}/\text{L}$ (IQR: 455-1896, $P = 0.08$) 6 months after last PRRT.

Radiological response

Following PRRT with ^{177}Lu -DOTATATE, a partial response was observed in 2 patients (9%) and stable disease in 15 patients (68%). Progressive disease occurred in 5 patients after starting treatment with ^{177}Lu -DOTATATE. This was due to symptomatic deterioration in 4 patients: 2 patients had heart failure and they both died approximately 3 and 6 months after the first cycle. Another 2 patients experienced clinical progression after 2 cycles and died 3 and 7 months after first therapy. In this cohort, treatment with ^{177}Lu -DOTATATE resulted in a median progression-free survival of 28 months and an overall survival of 36 months (Fig. 3). At the time of radiological tumor progression,

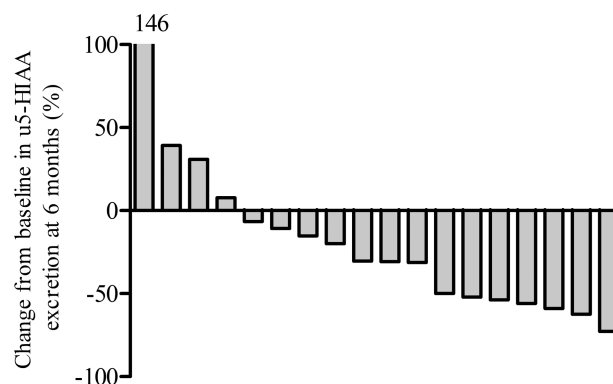


Figure 2. Percentage of change from baseline 24-hour u5-HIAA excretion. u5-HIAA, urinary 5-hydroxyindoleacetic acid.

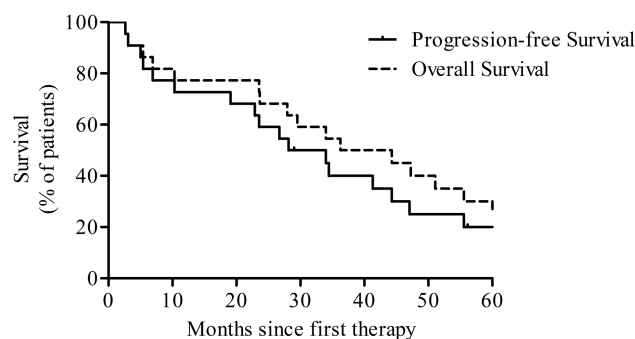


Figure 3. Progression-free and overall survival after treatment with ^{177}Lu -DOTATATE. ^{177}Lu -DOTATATE, [Lutetium-177-DOTA⁰-Tyr³]octreotate.

16 patients (94%) also experienced a recurrence of CS symptoms.

Toxicity

One patient was treated with 22.2 GBq because the maximum kidney dose was reached after 3 cycles of PRRT. One patient was treated with a reduced dose because of

reversible grade 3 thrombopenia. Another patient had irreversible kidney insufficiency from urosepsis after the second cycle, with further deterioration of kidney function after the third cycle.

In total, 73 cycles of ^{177}Lu -DOTATATE were administered. Nausea occurred after 40% of therapies, vomiting after 14%, and (increase of) pain after 25% of therapies (Table 2). Subacute hematotoxicity (grade 3-4) occurred in 5 patients. There was no development of myelodysplastic syndrome or leukemia in our patients during a median follow-up of 37 months.

Three patients used long-acting SSA with last administration 6 weeks before PRRT, without intermittent short-acting octreotide. One patient did not tolerate SSAs. The other 18 patients were treated with short-acting octreotide subcutaneously up to 24 hours before PRRT. With these prophylaxes, no carcinoid crises occurred during or after PRRT and all patients were safely discharged after overnight routine observation. One patient was admitted between therapies because of heart failure, which was deemed unrelated to PRRT and treated with diuretics.

Quality of life

EORTC QLQ-C30 scores were available for 12 patients at baseline and 3 months after last treatment. The diarrhea

Table 2. Treatment and toxicity, n (%)

Cumulative dose, GBq	
7.4-14.8	5 (23)
18.5-22.2	4 (18)
25.9	2 (9)
27.8	1 (5)
29.6	10 (46)
Acute toxicity (per cycle)	
Nausea	29 (40)
Vomiting	10 (14)
Pain	18 (25)
Subacute toxicity (per patient)	
Anemia	
Grade 3	1 (5)
Grade 4	0
Thrombocytopenia	
Grade 3	3 (14)
Grade 4	0
Leukopenia	
Grade 3	3 (14)
Grade 4	0
Hormonal crisis	0
Chronic toxicity	
Renal toxicity	
Grade 3	1 (5)

subscale score improved by an average of 16.7 ± 33.3 points (on a 0-100 scale), but not significantly ($P = 0.11$). There was, however, a significant decrease in cognitive functioning of 11.0 ± 13.0 points 3 months after PRRT ($P = 0.04$). All other scores showed no significant difference.

Discussion

Carcinoid syndrome is characterized by diarrhea and flushing as a result of hypersecretion of serotonin and other peptides by a metastatic midgut NEN. SSAs form the cornerstone of treatment of CS, both for hormonal and tumor control. Our recent systematic review and meta-analysis showed that SSAs are capable of inducing a symptomatic response in more than 65% of patients and a decrease of u5-HIAA excretion in ~45% of patients with CS (9). However, a subgroup of patients will remain symptomatic despite treatment with a SSA (including dose escalation) and will require additional treatment for symptom reduction.

PRRT with ^{177}Lu -DOTATATE has been shown to reduce symptoms of CS in 50% to 90% of patients (16, 17, 26-28). However, these patients were treated for a progressive NEN and the symptomatic response was secondary to a treatment initiated because of progressive disease. In the current study, patients were treated with ^{177}Lu -DOTATATE primarily for the reduction of CS symptoms and without radiological evidence of progressive disease. In this cohort of patients with severe CS, the adverse effects of ^{177}Lu -DOTATATE seem to be comparable with other series on PRRT for midgut NEN (15, 20). One of the severe complications of PRRT for hormonal active tumors is a carcinoid crisis. In our study, most patients switched to short-acting octreotide in between cycles and with this regimen no carcinoid crises occurred. However, in this group with a high incidence of carcinoid heart disease, 3 patients discontinued PRRT because of heart failure. Adequate screening and treatment for carcinoid heart disease before PRRT remains essential for this patient group. Otherwise, treating patients with refractory CS with PRRT was safe and well tolerated in this small cohort.

All included patients had persistent symptoms of CS despite treatment with an SSA and therefore the indication for treatment is comparable with the recent clinical trials with telotristat ethyl. In SSA-refractory CS patients, 250 or 500 mg of telotristat ethyl resulted in an average decrease of BMF of, respectively, 0.45 and 0.60 per day in the Telotristat Etiprate for Carcinoid Syndrome Therapy trial (29) and 1.7 and 2.1 in the TELESTAR trial (14). This resulted in a response (defined as $\geq 30\%$ reduction of BMs in patients with >4 daily BM) in ~40% of patients. A reduction in flushing was not seen during treatment with

telotristat ethyl because this drug only reduces serotonin secretion and not the secretion of other mediators of CS, such as kinins and histamines. The patients in our current cohort have a higher mean baseline u5-HIAA excretion and had more severe disease burden than the patients in the registration trials with telotristat ethyl, suggesting that our patients had a more severe form of CS. Still, treatment with ^{177}Lu -DOTATATE resulted in a comparable average BMF reduction of 1.5 and on top of this reduced average flushing by 1.9 times per day. A decrease of BMF of more than 30% was observed in 47% of patients and 67% of patients had more than 50% decrease of daily flushing and therefore ^{177}Lu -DOTATATE could potentially constitute a more effective and comprehensive treatment of refractory CS. Limitations of our study include the small number of patients, selection of high disease burden, and the absence of a control group. This causes a risk of regression toward the mean because patients with the high symptomatic burden were selected for therapy.

Other second-line therapies for CS include interferon and liver-directed therapy. Interferon-alpha has been studied in several prospective studies, where it resulted in highly variable clinical response of 0% to 90% that, combined in a meta-analysis, resulted in a decrease in flushing and diarrhea in 45% and 63% of patients (9, 30-33). However, the single randomized-controlled trial comparing octreotide in combination with interferon-alpha vs octreotide alone demonstrated no additional benefit of interferon (34). Also, the adverse effects as fatigue and flulike symptoms associated with interferon can be severe. Therapies based on reducing tumor burden are mainly focused on the liver, like radiofrequency ablation, embolization, or surgery. Altogether, these techniques have a very high clinical response rate of 82%, but are limited to patients with liver-dominant disease (9). Head-to-head comparisons between these therapies is currently lacking.

This lack of comparative trials requires the selection of treatment for SSA-refractory CS to be based on patient and tumor characteristics. Given the availability of randomized clinical trials, telotristat ethyl compromises the preferred second-line option in the case of refractory diarrhea and radiologically stable disease. Our series adds to the growing literature that PRRT has long-term potent effects on symptomatic control of CS, but its single-arm design does not discriminate between different third-line options. ^{177}Lu -DOTATATE for CS can especially be considered for patients with extrahepatic localizations or severe symptoms of flushing. In patients with liver-dominant disease, liver-directed therapy has also been reported to be a safe and effective modulator of CS symptoms (35). Whether PRRT or liver-directed therapy in liver-dominant disease is superior for control of CS should be the subject of future studies.

In conclusion, our study shows that PRRT with ^{177}Lu -DOTATATE for symptomatic control of refractory CS is a viable, safe, and effective option for patients with stable and recently diagnosed advanced midgut NENs.

Additional Information

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Disclosures: W. T. Z., A. B., and N. S. M. have nothing to declare. T. B. has received speaker and travel fees from Ipsen and Novartis and has joined an advisory board for Novartis. J. H. has received speaker fees from Ipsen and has joined advisory boards for Novartis and Ipsen. R. A. F. has received research support from Ipsen. W. W. d. H. has received speaker fees from Novartis AAA and Ipsen and research support from Ipsen.

Data Availability: Restrictions apply to the availability of data generated or analyzed during this study to preserve patient confidentiality. The corresponding author will, on request, detail the restrictions and any conditions under which access to some data may be provided.

References

- Bellono NW, Bayrer JR, Leitch DB, et al. Enterochromaffin cells are gut chemosensors that couple to sensory neural pathways. *Cell*. 2017;170(1):185-198.e16.
- Erspamer V, Asero B. Identification of enteramine, the specific hormone of the enterochromaffin cell system, as 5-hydroxytryptamine. *Nature*. 1952;169(4306):800-801.
- Blažević A, Zandee WT, Franssen GJH, et al. Mesenteric fibrosis and palliative surgery in small intestinal neuroendocrine tumours. *Endocr Relat Cancer*. 2018;25(3):245-254.
- Grahame-Smith DG. Progress report: the carcinoid syndrome. *Gut*. 1970;11(2):189-192.
- Hofland J, Kaltsas G, de Herder WW. Advances in the diagnosis and management of well-differentiated neuroendocrine neoplasms. *Endocr Rev*. 2020;41(2):371-403.
- Halperin DM, Shen C, Dasari A. Frequency of carcinoid syndrome at neuroendocrine tumour diagnosis: a population-based study. *Lancet Oncol*. 2017;18(4):525-534.
- Zandee WT, Kamp K, van Adrichem RC, Feelders RA, de Herder WW. Effect of hormone secretory syndromes on neuroendocrine tumor prognosis. *Endocr Relat Cancer*. 2017;24(7):R261-R274.
- Beaumont JL, Cella D, Phan AT, Choi S, Liu Z, Yao JC. Comparison of health-related quality of life in patients with neuroendocrine tumors with quality of life in the general US population. *Pancreas*. 2012;41(3):461-466.
- Hofland J, Herrera-Martínez AD, Zandee WT, de Herder WW. Management of carcinoid syndrome: a systematic review and meta-analysis. *Endocr Relat Cancer*. 2019;26(3):R145-R156.
- Rinke A, Müller HH, Schade-Brittinger C, et al.; PROMID Study Group. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control

- of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol*. 2009;27(28):4656-4663.
11. Ferolla P, Faggiano A, Grimaldi F, et al. Shortened interval of long-acting octreotide administration is effective in patients with well-differentiated neuroendocrine carcinomas in progression on standard doses. *J Endocrinol Invest*. 2012;35(3):326-331.
 12. Oberg K. Interferon-alpha versus somatostatin or the combination of both in gastro-enteropancreatic tumours. *Digestion*. 1996;57 Suppl 1:81-83.
 13. Oberg K, Eriksson B. The role of interferons in the management of carcinoid tumours. *Br J Haematol*. 1991;79 Suppl 1:74-77.
 14. Kulke MH, Hörsch D, Caplin ME, et al. Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. *J Clin Oncol*. 2017;35(1):14-23.
 15. Strosberg J, El-Haddad G, Wolin E, et al.; NETTER-1 Trial Investigators. Phase 3 trial of 177Lu-Dotatate for midgut neuroendocrine tumors. *N Engl J Med*. 2017;376(2):125-135.
 16. Strosberg J, Wolin E, Chasen B, et al. Health-related quality of life in patients with progressive midgut neuroendocrine tumors treated with (177)Lu-Dotatate in the phase III NETTER-1 trial. *J Clin Oncol*. 2018;36(25):2578-2584.
 17. Khan S, Krenning EP, van Essen M, Kam BL, Teunissen JJ, Kwekkeboom DJ. Quality of life in 265 patients with gastroenteropancreatic or bronchial neuroendocrine tumors treated with [177Lu-DOTA0,Tyr3]octreotate. *J Nucl Med*. 2011;52(9):1361-1368.
 18. Zandee WT, Brabander T, Blažević A, et al. Symptomatic and radiological response to 177Lu-DOTATATE for the treatment of functioning pancreatic neuroendocrine tumors. *J Clin Endocrinol Metab*. 2019;104(4):1336-1344.
 19. Zandee WT, Kamp K, van Adrichem RC, Feelders RA, de Herder WW. Limited value for urinary 5-HIAA excretion as prognostic marker in gastrointestinal neuroendocrine tumours. *Eur J Endocrinol*. 2016;175(5):361-366.
 20. Brabander T, van der Zwan WA, Teunissen JJM, et al. Long-term efficacy, survival, and safety of [177Lu-DOTA0,Tyr3]octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. *Clin Cancer Res*. 2017;23(16):4617-4624.
 21. Kwekkeboom DJ, Bakker WH, Kooij PP, et al. [177Lu-DOTA0,Tyr3]octreotate: comparison with [111In-DTPA0]octreotide in patients. *Eur J Nucl Med*. 2001;28(9):1319-1325.
 22. Kwekkeboom DJ, Teunissen JJ, Bakker WH, et al. Radiolabeled somatostatin analog [177Lu-DOTA0,Tyr3]octreotate in patients with endocrine gastroenteropancreatic tumors. *J Clin Oncol*. 2005;23(12):2754-2762.
 23. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365-376.
 24. Fayers PM, Aaronson NK, Bjordal K, Grønqvold M, Curran D, Bottomley A. *EORTC QLQ-C30 Scoring Manual*. European Organisation for Research and Treatment of Cancer; 2001.
 25. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.
 26. Seregni E, Maccauro M, Chiesa C, et al. Treatment with tandem [90Y]DOTA-TATE and [177Lu]DOTA-TATE of neuroendocrine tumours refractory to conventional therapy. *Eur J Nucl Med Mol Imaging*. 2014;41(2):223-230.
 27. Waldherr C, Pless M, Maecke HR, et al. Tumor response and clinical benefit in neuroendocrine tumors after 7.4 GBq (90)Y-DOTATOC. *J Nucl Med*. 2002;43(5):610-616.
 28. Hamiditabar M, Ali M, Roys J, et al. Peptide receptor radionuclide therapy with 177Lu-Octreotate in patients with somatostatin receptor expressing neuroendocrine tumors: six years' assessment. *Clin Nucl Med*. 2017;42(6):436-443.
 29. Pavel M, Gross DJ, Benavent M, et al. Telotristat ethyl in carcinoid syndrome: safety and efficacy in the TELECAST phase 3 trial. *Endocr Relat Cancer*. 2018;25(3):309-322.
 30. Moertel CG, Rubin J, Kvols LK. Therapy of metastatic carcinoid tumor and the malignant carcinoid syndrome with recombinant leukocyte A interferon. *J Clin Oncol*. 1989;7(7):865-868.
 31. Nobin A, Lindblom A, Månsson B, Sundberg M. Interferon treatment in patients with malignant carcinoids. *Acta Oncol*. 1989;28(3):445-449.
 32. Veenhof CH, de Wit R, Taal BG, et al. A dose-escalation study of recombinant interferon-alpha in patients with a metastatic carcinoid tumour. *Eur J Cancer*. 1992;28(1):75-78.
 33. Di Bartolomeo M, Bajetta E, Zilembo N, et al. Treatment of carcinoid syndrome with recombinant interferon alpha-2a. *Acta Oncol*. 1993;32(2):235-238.
 34. Arnold R, Rinke A, Klose KJ, et al. Octreotide versus octreotide plus interferon-alpha in endocrine gastroenteropancreatic tumors: a randomized trial. *Clin Gastroenterol Hepatol*. 2005;3(8):761-771.
 35. Pavel M, O'Toole D, Costa F, et al.; Vienna Consensus Conference participants. ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. *Neuroendocrinology*. 2016;103(2):172-185.