Clinical Cancer Research

Long-Term Efficacy, Survival, and Safety of [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate in Patients with Gastroenteropancreatic and Bronchial Neuroendocrine Tumors

Tessa Brabander[1], Wouter A. van der Zwan[1], Jaap J.M. Teunissen[1], Boen L.R. Kam[1], Richard A. Feelders[2], Wouter W. de Herder[2], Casper H.J. van Eijck[3], Gaston J.H. Franssen[3], Eric P. Krenning[1], and Dik J. Kwekkeboom[1,†]

Abstract

Purpose: Bronchial and gastroenteropancreatic neuroendocrine tumors (NET) are slow-growing tumors, which frequently express somatostatin receptors on their cell membranes. These receptors are targets for therapy with Lutetium-177–labeled somatostatin analogues. We have treated over 1,200 patients with peptide receptor radionuclide therapy (PRRT) with [^{177}Lu-DOTA^{0}, Tyr^{3}]octreotate (^{177}Lu-DOTATATE) since the year 2000 and present the results on efficacy, survival, and toxicity of this therapy.

Experimental Design: For safety analysis, 610 patients treated with a cumulative dose of at least 100 mCi (3.7 GBq) ^{177}Lu-DOTATATE were included. A subgroup of 443 Dutch patients who were treated with a cumulative dose of at least 600 mCi (22.2 GBq) ^{177}Lu-DOTATATE before 2013 was further analyzed for efficacy and survival.

Results: The objective response rate of the total group of patients was 39%. Stable disease was reached in 43% of patients. Progression-free survival (PFS) and overall survival (OS) for all NET patients were 29 months [95% confidence interval (CI), 26–33 months] and 63 months (95% CI, 55–72 months). Long-term toxicity included acute leukemia in four patients (0.7%) and myelodysplastic syndrome in nine patients (1.5%). No therapy-related long-term renal or hepatic failure occurred.

Conclusions: PRRT with ^{177}Lu-DOTATATE is a favorable therapeutic option in patients with metastatic bronchial and gastroenteropancreatic NETs that express somatostatin receptors. PRRT with ^{177}Lu-DOTATATE is safe with few side-effects and shows good response rates with PFS of 29 months and OS of 63 months. *Clin Cancer Res; 23(16); 4617–24. ©2017 AACR.*

Introduction

Neuroendocrine tumors (NET) are a heterogeneous group of tumors. A subset of this slow-growing tumor type are the gastroenteropancreatic NETs (GEP-NETs) and bronchial NETs (1). Unfortunately, the majority of GEP-NET patients have metastatic disease at time of presentation (2). Over the past decades, the incidence of GEP-NETs is rising. After the introduction of new therapies, the 5-year survival has significantly improved (3). This improvement is partly due to first-line therapy with long-acting somatostatin analogues (Octreotide LAR, Lanreotide Autogel) and targeted therapies (e.g., everolimus and sunitinib), which are approved second-line therapies for patients with progressive inoperable GEP NETs (sunitinib only being approved in pancreatic NET) (4, 5). For GEP and bronchial NETs, peptide receptor radionuclide therapy (PRRT) with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-DOTATATE) has yielded very promising results. This therapy is based on the fact that the majority of these NETs express a high number of high-affinity somatostatin receptors on their cell membranes. These receptors can be used for both imaging and therapy with radiolabeled somatostatin analogues (6). For therapy, the β-emitting radionuclide Lutetium-177, with a half-life of 6.7 days and a maximum β range of 2 mm in tissue, can be used. These parameters makes Lutetium-177 the ideal radionuclide for PRRT. Treatment with β-emitting radiolabeled somatostatin analogues results in impressive percentages of tumor regression (7–10). Also, success monitored as time to progression (TTP), progression-free survival (PFS), and overall survival (OS) has been reported in uncontrolled studies (8, 11). With the recent publication of the promising results of the NETTER-1 trial (12), the first phase III trial comparing ^{177}Lu-DOTATATE to high-dose Octreotide LAR therapy in patients with inoperable metastatic midgut NETs, it may be expected that the use of this therapy will increase in the coming years. We have previously reported on the treatment with the radiolabeled somatostatin analogue ^{177}Lu-DOTATATE (8), and have compared the side-effects and the results of this treatment with other treatment modalities and historical controls. Righteously, critical commentary arose, as to the validity of the comparisons with historical controls. Also, the high number of foreign patients that we have treated, and of

[1]Department of Radiology & Nuclear Medicine, Erasmus Medical Center, Rotterdam, the Netherlands. [2]Department of Internal Medicine, Erasmus Medical Center, ENETS Center of Excellence, Rotterdam, the Netherlands. [3]Department of Surgery, Erasmus Medical Center, Rotterdam, the Netherlands.

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

†Deceased.

Corresponding Author: Tessa Brabander, Erasmus Medical Center, s-Gravendijkwal 230, Rotterdam, 3015 CE, the Netherlands. Phone: 311-0704-0132; Fax: 311-0703-3737; E-mail: t.brabander@erasmusmc.nl

doi: 10.1158/1078-0432.CCR-16-2743

Translational Relevance

Peptide receptor radionuclide therapy (PRRT) with [^{177}Lu-DOTA^0,Tyr^3]octreotate is a therapeutic option for metastasized or inoperable gastroenteropancreatic and bronchial neuroendocrine tumors that present the somatostatin receptors on their surface. These receptors are targets for the radiolabeled somatostatin analogue [^{177}Lu-DOTA^0,Tyr^3]octreotate. This large study with a median follow-up of 78 months demonstrated a progression-free survival was 29 months, time to progression 36 months, and overall survival 63 months. These results are favorable to all other therapeutic options, which are currently available for patients with advanced, inoperable neuroendocrine tumors. Also, the limited long-term severe side-effects make this a very good therapeutic option for these patients. It is expected that in the near future this treatment will play an important role in the treatment of patients with neuroendocrine tumors.

whom a significant number was lost to follow-up might bias the percentage of reported severe adverse events. We, therefore, present now the long-term results of efficacy, survival, and toxicity of PRRT with ^{177}Lu-DOTATATE in a cohort of more than 500 Dutch patients with metastatic GEP-NETs and bronchial NETs, who all had their follow-up at our institution.

Patients and Methods

Patients

A total of 1,214 patients were treated with ^{177}Lu-DOTATATE from January 2000 to January 2015 in our institution. We selected only Dutch patients with NETs of the midgut, foregut, hindgut, and unknown primary that were treated according to a standard protocol, because of the very limited loss in follow-up in this subgroup. For safety evaluation, all patients who received at least 100 mCi (3.7 GBq) ^{177}Lu-DOTATATE were selected. For the evaluation of efficacy, patients who received at least 600 mCi (22.2 GBq) ^{177}Lu-DOTATATE before 2013 were investigated. Patients treated after 2013 returned to their referring specialist in a different institute after therapy, and imaging was not performed according to our study protocol. For safety analysis, 610 patients were available and 443 patients for efficacy and survival analysis (Fig. 1). For analysis of efficacy, NET types were divided into bronchial, pancreatic, (other) foregut, hindgut, midgut, and NET of unknown origin. Other foregut NETs included: five NETs of the stomach, five NETs of the proximal duodenum, and two NETs of the thymus. For comparison with the NETTER-1 study (12), 106 patients with progressive midgut NETs who received a cumulative dose of $\geq$100 mCi (3.7 GBq) ^{177}Lu-DOTATATE were selected. Patients were treated with ^{177}Lu-DOTATATE if the tumor uptake was at least as high as the uptake in the normal parenchyma of the liver on ^{111}In-DTPA-octreotide scintigraphy (OctreoScan) prior to the therapy. Other inclusion criteria were serum hemoglobin $\geq$6.0 mmol/L ($\geq$9.7 g/dL), total white blood cell (WBC) count $\geq 2 \times 10^9$/L, platelet count $\geq 75 \times 10^9$/L, serum creatinine concentration $\leq$150 μmol/L ($\leq$1.7 mg/dL), or creatinine clearance $\geq$40 mL/minute until 2007 or 50 mL/minute from 2007, serum albumin >30 g/L, Karnofsky performance status (KPS) $\geq$50, and no prior treatment with other radiolabeled somatostatin analogues. Preliminary results in a subgroup of these patients with GEP-NETs were reported previously (8). All patients gave written informed consent to participate in the study, which was approved by the medical ethical committee of our hospital.

Methods

[DOTA^0,Tyr^3]octreotate was obtained from BioSynthema. $^{177}LuCl_3$ was distributed by IDB-Holland. ^{177}Lu-DOTATATE was locally prepared as described previously (13). Before the infusion of the radiopharmaceutical, Granisetron 3 mg or Ondansetron 8 mg was injected intravenously. To reduce the radiation dose to the kidneys, an intravenous infusion of amino acids (2.5% arginine and 2.5% lysine in 1 L 0.9% NaCl) was started 30 minutes before the administration of the radiopharmaceutical and lasted for 4 hours. The radiopharmaceutical was coadministered intravenously using a second pump system over 30 minutes. The intended interval between treatments was 6 to 10 weeks. The treatment interval could be extended to 16 weeks in patients with longer continuing subacute hematologic toxicity. Patients were treated up to a cumulative intended dose of 750 to 800 mCi (27.8–29.6 GBq) ^{177}Lu-DOTATATE.

Routine hematology, liver, and kidney function tests were performed after each therapy cycle and at follow-up visits at 6 weeks, 3 months, and 6 months after the last treatment cycle, and thereafter at 6-month intervals. CT or MRI was performed within 3 months before the first therapy, and at every follow-up visit. Every patient was seen at the outpatient clinic by one of the investigators and a research nurse. A case report form (CRF) was completed at every follow-up visit.

In vivo measurements

Tumor response was assessed on CT or MRI according to the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) criteria (14). Radiologic disease control was defined as all patients achieving objective response (OR) or stable disease (SD) in patients with progressive disease (PD) at baseline. Uptake on the OctreoScan was scored on planar images using a 4-point scale; grade 1: less than the uptake in the normal parenchyma of the liver, grade 2: equal to the liver, grade 3: greater uptake than the liver, grade 4: higher than the uptake in the normal spleen or kidneys. The whole-body extent of disease was scored by experienced nuclear medicine physicians as: limited, moderate or extensive on OctreoScan as described previously (15).

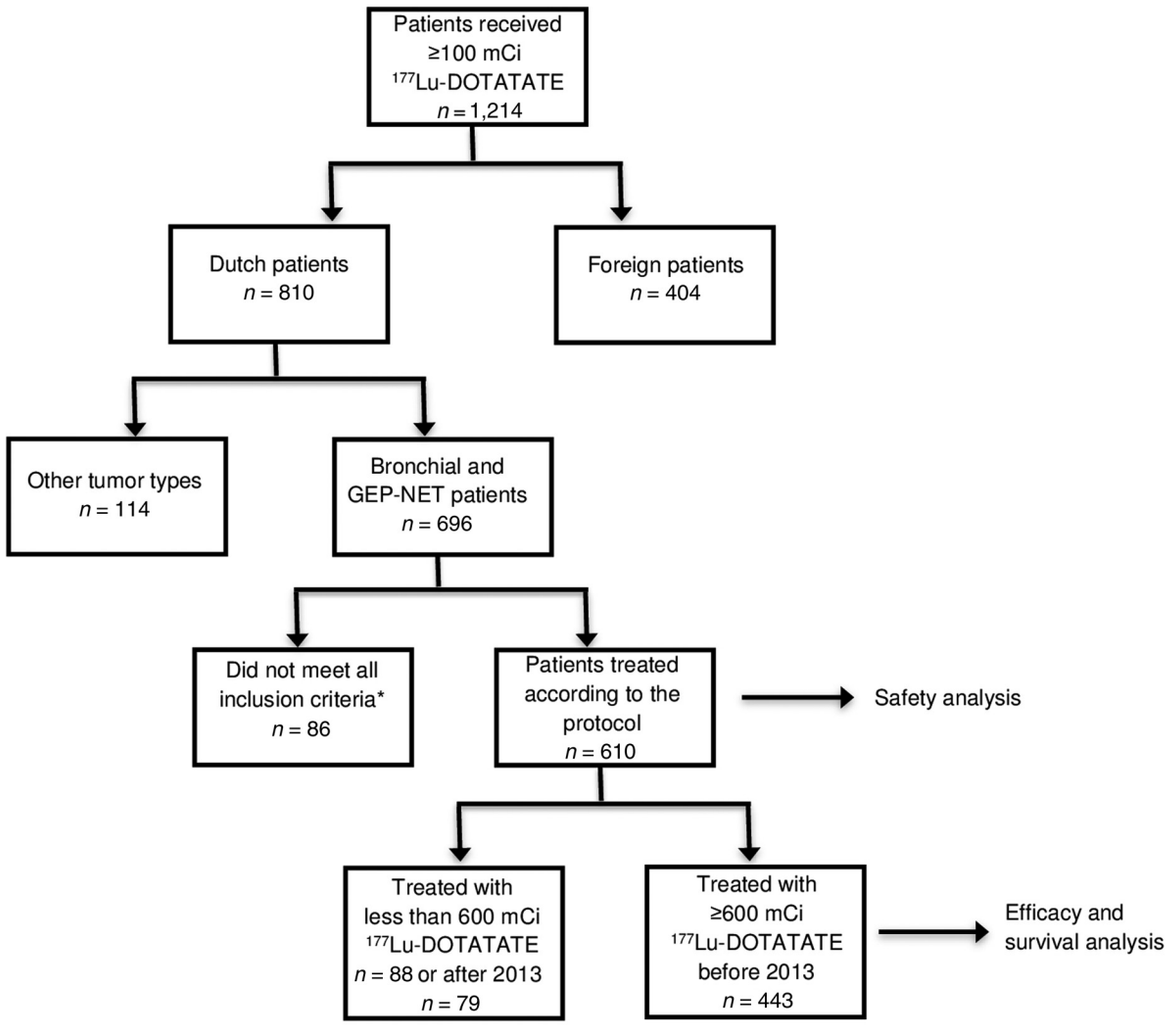
Outcomes

PFS was defined as the time from first day of treatment until day of ascertainment of objective progression or death from any cause. The TTP was calculated from the first day of treatment to the day of documented progression. Deaths were censored in the TTP analyses. OS was calculated from the first day of treatment until the day of death, or until the last date of follow-up for patients who were lost to follow-up (16).

Toxicity was scored according to the Common Terminology Criteria for Adverse Events 4.0 (CTCAE) scoring system (17).

Statistical analysis

For survival analysis, log-rank tests and Cox regression models were used. PFS and OS analyzes were performed using the



*Exclusion criteria:

Creatinine >150 umol/L (> 1.7 mg/dL)	*n* = 5
Creatinine clearance <40 ml/min	*n* = 3
Thrombocytes <75x10^9/L	*n* = 4
Albumin <30 g/L	*n* = 13
Uptake Octreoscan <2	*n* = 10
Karnofsky performance status <50	*n* = 2
Data not complete	*n* = 49

Figure 1.
Flowchart for the selection of patients.

Kaplan–Meier method. Comparison between subgroups was made using χ^2-test (or, if applicable, Fisher exact test), ANOVA, or paired *t* tests. *P* values lower than 0.05 were considered to be significant.

Results

For safety outcome, 610 patients who received ≥100 mCi (3.7 GBq) ^{177}Lu-DOTATATE were analyzed. Median follow-up time

was 64 months [95% confidence interval (CI), 58–70 months]. Mean age was 60.4 years (range 23–88). The median TTP was 35 months (95% CI, 32–39 months) and the median OS was 58 months (95% CI, 52–64 months).

CTCAE grade 3/4 toxicity of the combination of the following hematologic parameters occurred in 61 of 582 patients (10%; 95% CI, 8%–13%), grade 3/4 toxicity of platelets occurred in 30 of 582 patients (5%; 95% CI, 4%–7%), total WBC count grade 3/4 toxicity in 32 of 582 patients (5%; 95% CI, 4%–8%), hemoglobin grade 3 toxicity in 22 of 582 patients (4%; 95% CI, 2%–6%), and no grade 4 hemoglobin toxicity was observed. No data are available on the remaining 28 patients. At first follow-up visit after 3 months, these values normalized in 77% of patients. CTCAE grade 3/4 of the lymphocytes was observed in 288 of 581 patients (50%; 95% CI, 46%–54%). At 3 months follow-up, 74 of 287 patients and at 30 months follow-up 6 of 108 patients had persistent grade 3/4 lymphocyte toxicity and 53 of 108 patients had grade 1/2 lymphocyte toxicity.

An increase of aminotransferases (aspartate transaminase and/or alanine transaminase) grade 3/4 was observed in 20 of 581 patients (3%; 95% CI, 2%–5%). After 3 months follow-up, there were three patients with persistent grade 3/4 toxicity of the aminotransferases. Creatinine grade 3/4 toxicity occurred in 2 of 581 patients (0.3%; 95% CI, <1%–1%). Serum creatinine levels normalized in all patients at 3 months follow-up.

Acute leukemia occurred during follow-up in 4 patients (0.7%) after a median follow-up of 55 months after first therapy (range 32–125 months). Three of these patients died after a median follow-up of 7 months after diagnosis of acute leukemia. Myelodysplastic syndrome (MDS) occurred in nine patients (1.5%) after a median follow-up of 28 months (range 9–41 months) after first therapy. Five of these patients died after a median follow-up of 7 months after diagnosis of MDS. Of the remaining patients, no date of death is known, because these patients were referred back to their own local hospital after the diagnosis acute leukemia/MDS was made. None of these patients were treated with alkylating chemotherapy prior to PRRT (Supplementary Table S5).

Renal failure occurred in six patients (1%) during follow-up. The most probable cause of the renal failure was postrenal in one patient (hydronephrosis) and prerenal in the other patients (hypotension after gastrointestinal bleeding in one patient and in four patients dehydration caused by severe vomiting and diarrhea). No hepatic failure was observed during or after therapy.

Patient characteristics of the 443 patients who received $\geq$600 mCi (22.2 GBq) ^{177}Lu-DOTATATE and who were evaluated for efficacy and survival are presented in Table 1. Median follow-up was 78 months from the first day of treatment. The majority of all patients (61%) were treated with somatostatin analogues at referral.

Best objective response rate (ORR) was defined as the proportion of patients achieving complete response (CR) and partial response (PR) at follow-up according to the RECIST 1.1 criteria. Best response rates are presented in Table 2. The ORR in the entire patient group was 39%. SD was found in 43% of patients. PD as treatment outcome was observed in 12% of patients and 5% of patients had nonevaluable treatment outcome. In patients with midgut NETs and pancreatic NETs with PD at baseline, radiologic disease control was observed in 84% and 81%, respectively.

For the entire group of 443 NET patients, the median OS was 63 months (95% CI, 55–72 months). The median PFS was 29 months (95% CI, 26–33 months). The median TTP was 36 months (95% CI, 32–40 months; Table 2). Patients with a primary NET in the pancreas had the longest OS (Fig. 2). We identified several risk factors associated with shorter OS (Table 3). The OS was significantly shorter in patients with liver or bone metastases at baseline. Also, patients with increased alkaline phosphatase (ALP) levels (>120 IU/L) and patients with extensive disease as scored with the OctreoScan had a worse prognosis (Table 3).

Table 1. Patient, treatment, and tumor characteristics in patients with gastroenteropancreatic and bronchial NETs (n = 443)

	Yes	No	Unknown
Characteristics	**No. of patients (%)**	**No. of patients (%)**	**No. of patients (%)**
Male	230 (52)	213 (48)	
Median age (range)		60 years (30–83)	
Pretreatment			
Surgery	190 (43)	252 (57)	1 (0)
Chemotherapy[a]	28 (6)	415 (94)	0 (0)
Radiotherapy	30 (7)	412 (93)	1 (0)
Somatostatin analogues	271 (61)	172 (39)	0 (0)
Bone metastases	70 (16)	367 (83)	
Liver metastases	346 (78)	93 (21)	
Functional pancreatic NET[b]	21 (5)		
Median time since diagnosis (range)		14 months (0–371)	
Baseline progression	239 (54)	69 (16)	135 (30)
Extent of disease			
Limited	62 (14)		
Moderate	314 (71)		
Extensive	67 (15)		
Uptake on Octreoscan			
Grade 2	35 (8)		
Grade 3	278 (63)		
Grade 4	130 (29)		

[a]Including alkylating chemotherapy in 16 patients.
[b]Including vasoactive intestinal peptide-secreting tumor (VIPoma), insulinoma, gastrinoma, and glucagonoma.

Table 2. Best response, PFS, TTP, and OS after therapy with ^{177}Lu-DOTATATE

Primary NET location	Total no of pts	CR No. of pts (%)	PR No. of pts (%)	SD No. of pts (%)	PD No. of pts (%)	NE No. of pts (%)	Median PFS (months)	Median TTP (months)	Median OS (months)
Midgut	181	2 (1)	55 (30)	99 (55)	16 (9)	9 (5)	30	42	60
Non-PD	32	0 (0)	10 (31)	18 (56)	3 (9)	1 (3)	24	45	82
PD	94	1 (1)	28 (30)	50 (53)	9 (10)	6 (6)	29	40	50
Hindgut	12	0 (0)	4 (33)	6 (50)	1 (8)	1 (8)	29	29	Not defined
Pancreatic	133	6 (5)	66 (50)	40 (30)	17 (13)	4 (3)	30	31	71
Non-PD	21	1 (5)	9 (43)	10 (48)	1 (5)	0 (0)	31	31	Not defined
PD	66	2 (3)	36 (55)	15 (23)	10 (15)	3 (5)	31	36	71
Functional	21	1 (5)	12 (57)	4 (19)	3 (14)	1 (5)	30	33	Not defined
Nonfunctional	112	5 (4)	54 (48)	36 (32)	14 (13)	3 (3)	30	31	69
Bronchial	23	0 (0)	7 (30)	7 (30)	6 (26)	3 (13)	20	25	52
Other foregut[a]	12	1 (8)	4 (33)	5 (42)	2 (17)	0 (0)	25	Not defined	Not defined
Unknown	82	0 (0)	29 (35)	35 (43)	11 (13)	7 (9)	29	37	53
Total	443	9 (2)	165 (37)	192 (43)	53 (12)	24 (5)	29	36	63

[a]Including five tumors of the stomach, five of the duodenum, and two of the thymus.

Abbreviations: NE, not evaluable; Primary NET location "non-PD and PD" means "without PD and with PD" at start of therapy with ^{177}Lu-DOTATATE.

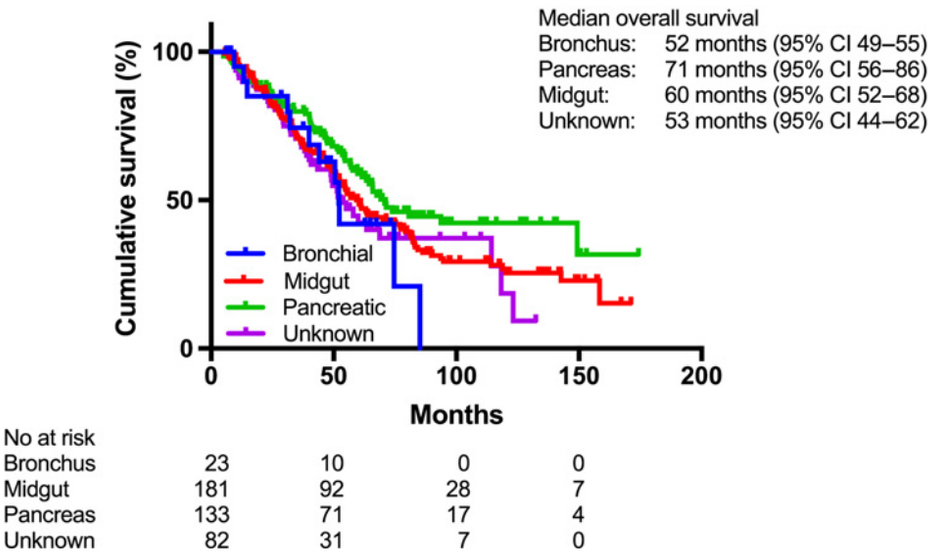


Figure 2.
Median OS in 419 NET patients treated with ^{177}Lu-DOTATATE according to location of the primary tumor. Not shown are patients with primary tumor of the hindgut ($n = 12$) and other foregut ($n = 12$) due to the small number of patients.

For the group of 239 NET patients with objective PD at baseline, the median PFS was 30 months (95% CI, 27–33 months), the median TTP 36 months (95% CI, 32–41 months), and the median OS was 58 months (95% CI, 52–64 months).

Characteristics of patients with NETs of the midgut and PD at baseline are presented in Table 4. For comparison with the NETTER-1 study, patients that received a cumulative dose of ≥100 mCi (3.7 GBq) ^{177}Lu-DOTATATE were selected. The PFS of patients with progressive midgut NETs was 24 months (95% CI, 18–30 months). OS was 46 months (95% CI, 32–60 months). The OS was significantly worse for patients with PD at baseline as compared with patients without PD at baseline (Table 2; Supplementary Fig. 3).

Discussion

The results of this study demonstrate that PRRT with ^{177}Lu-DOTATATE is an excellent therapeutic option for patients with advanced grade 1 to 2 GEP and bronchial NETs. This treatment has limited side-effects and is relatively safe.

In the last decade, various types of targeted therapies have been introduced. After the presentation of the PROMID study (18) in 2009 and the CLARINET study in 2014 (19), the use of somatostatin analogues for progressive, inoperable grade 1–2 GEP-NETs was registered. Rinke and colleagues (18) demonstrated that the median TTP in patients with metastatic midgut tumors is longer (14.3 months) with the use of 30 mg Octreotide LAR per 4 weeks as compared to placebo (6.0 months), although there seemed to be no significant effect of Octreotide LAR on the OS (20). Also for Lanreotide Autogel 120 mg per 4 weeks, Caplin and colleagues have demonstrated that the PFS in GEP-NETs with a Ki67 index < 10% was better (32.8 months) as compared with placebo (18 months; refs. 19, 21).

Recently, the first results of the NETTER-1 study were published (12). This is the first randomized phase III study comparing ^{177}Lu-DOTATATE to high dose octreotide LAR therapy in patients with inoperable, progressive midgut NETs. The dosing protocol was comparable with our protocol with four administrations of 200 mCi (7.4 GBq) ^{177}Lu-DOTATATE every 8 weeks. The PFS for the control group receiving 60 mg Octreotide LAR per 4 weeks was

Table 3. Factors predicting median OS in patients with bronchial and gastroenteropancreatic NETs

Factor	No. of patients[a]	Median OS (months)	HR (95% CI)	*P*
ALP				
<120	248	83	0.45 (0.35–0.59)	<0.01
>120	189	47		
Liver metastases				
Yes	346	57	0.46 (0.34–0.62)	<0.01
No	93	119		
Bone metastases				
Yes	70	47	0.56 (0.38–0.83)	<0.01
No	367	69		
Extent of disease				
Limited	62	123		<0.01
Moderate	314	62		
Extensive	67	46		
KPS				
≤70	35	27		<0.01
80	103	49		
90	160	65		
100	138	81		
Best response				
CR	9	Undefined		< 0.01
PR	165	82		
SD	192	61		
PD	53	24		

[a]Number of patients may vary due to missing data.

8.4 months and the PFS was not reached for the patients receiving ^{177}Lu-DOTATATE plus 30 mg Octreotide LAR per 4 weeks. For comparison with the NETTER-1 study, we selected patients with progressive midgut NETs, who received at least the same minimum cumulative dose of ≥100 mCi (3.7 GBq) of ^{177}Lu-DOTATATE. Most patient characteristics were not significantly different from patients in the NETTER-1 study (Table 4). However, tumor regional distribution seemed to be higher and tumor uptake on OctreoScan lower in our patients. The latter may be affected in the NETTER-1 study by the high dose Octreotide LAR pretreatment (22).

Table 4. Comparison between NETTER-1 study and patients with progressive midgut NETs receiving ≥100 mCi (3.7 GBq) ^{177}Lu-DOTATATE

Progressive midgut carcinoids Characteristic	NETTER 1 (*N* = 116)	Erasmus MC (*N* = 106)	*P*
Sex, *n* (%)			
Female	53 (46)	52 (49)	NS
Male	63 (54)	54 (51)	
Mean age (±SD), years	63 (±9)	62 (±10)	NS
Mean BMI (±SD), kg/m^2	25 (±5)	26 (±4)	NS
Mean KPS (±SD)	88.6 (±9.3)	85.8 (±10.2)	<0.05
Site of metastasis, *n* (%)			
Liver	97 (84)	97 (92)	NS
Bone	13 (11)	14 (13)	NS
SRS, uptake scale, *n* (%)			
Grade 2	11 (10)	7 (7)	NS
Grade 3	34 (29)	74 (70)	<0.01
Grade 4	71 (61)	25 (23)	<0.01
Extent of disease, *n* (%)			
Limited	99 (85)	4 (4)	<0.01
Moderate	13 (11)	82 (77)	<0.01
Extensive	4 (3)	20 (19)	<0.01
Previous treatments, *n* (%)			
Surgery	93 (80)	60 (57)	<0.01
Chemotherapy	11 (9)	6 (6)	NS
Radiotherapy	4 (3)	3 (3)	NS
Previous somatostatin analogue therapy (%)	116 (100)	89 (84)	<0.01
ORR, *n* (%)	18 (16)	29 (27)[a]	<0.05
PFS rate at 20 months (%)	65	58	NS
Median OS, months	NR	46	

Abbreviations: BMI, body mass index; NR, not reached.
[a]Best response used for Erasmus MC patients.

The proliferation marker Ki67 is used for the grading of NETs (23–25). In our study, the results of the Ki67 index labeling was not available in all tumors, because we started to routinely use the Ki67 index for grading of NETs in 2007. To have an estimation of the presence of high-grade NETs in our patient cohort, we took a sample of 230 GEP-NET patients who were treated after 2006. Of these 230 patients, 88 patients (38%) had WHO grade 1 NETs, 131 patients (57%) had grade 2 NETs, and 11 patients (5%) had grade 3 NETs (23–25). Because mainly grade 1–2 NETs were treated, we can conclude that PRRT is especially a therapeutic option for these tumors. Moreover, the majority of grade 3 tumors are negative on OctreoScan (26) and therefore cannot be treated with PRRT with ^{177}Lu-DOTATATE.

For progressive, metastatic grade 1–2 pancreatic NETs, both everolimus and sunitinib are approved therapies. In the RADIANT-3 study (27), comparing 10 mg everolimus orally daily to placebo, the PFS was 11.0 months for everolimus. In the study comparing sunitinib 37.5 mg orally daily to placebo (28), the PFS for sunitinib was 11.4 months. The PFS for pancreatic NETs with radiologic progression at baseline (Table 2) after therapy with ^{177}Lu-DOTATATE was 31 months and suggests being longer than with the currently available targeted therapies.

Recently, the results of the RADIANT-4 study (29) have also been published. This study compared everolimus 10 mg orally daily to placebo in patients with advanced grade 1–2 NETs of the lung and gastrointestinal origin. The PFS for everolimus was 11.0 months and thus comparable with the PFS for everolimus in the RADIANT-3 study. We found a PFS after PRRT with ^{177}Lu-DOTATATE of 29 months in the total group of patients with primary NETs in the lung or gastrointestinal tract. Although our patients were not randomized at inclusion, the current results can be compared with other studies due to the large number of patients and very long follow-up period. Therefore, not only in patients with pancreatic, but also in patients with bronchial and gastrointestinal NETs, the PFS seems to be better after ^{177}Lu-DOTATATE than the current targeted therapies which are registered for these indications.

A disadvantage of PRRT in general is the potential side-effects, especially on the bone marrow and kidneys. Because of coinfusion of lysine and arginine starting just before therapy, the radiation dose to the kidneys can be lowered and, therefore, the kidney is no longer the dose-limiting organ (13) with ^{177}Lu-DOTATATE. We have observed renal failure in six patients during follow-up after this therapy. The cause of this renal failure was probably not related to PRRT, as we found other more plausible causes in all patients. Acute leukemia and MDS are severe complications related to PRRT and occurred after a median of 28 months after the first cycle of PRRT with ^{177}Lu-DOTATATE for MDS and after a median of 55 months for acute leukemia. Although none of our patients who were diagnosed with acute leukemia/MDS received prior chemotherapy, recent reports suggest that there might be a higher risk of MDS/acute leukemia after alkylating chemotherapy (30–32).

Other therapy-related side-effects are hormone related problems. In this study, we did not focus on hormonal crises after PRRT. In a previous study, we have reported on 6 of 479 patients

(1%) with GEP-NETs and pheochromocytomas who developed severe symptoms after PRRT due to a release of bioactive substances (33). When treating patients with hormone-producing tumors, these side-effects should be taken into account as well.

Various centers in Europe use [^{90}Y-DOTA^{0},Tyr^{3}]-octreotide (^{90}Y-DOTATOC) for PRRT. The results of therapy with this radiopharmaceutical have been extensively reported in the last decade (7, 11, 34–36). Because of the higher energy of Yttrium-90, as compared with Lutetium-177, more side-effects have been reported. Imhof and colleagues (36) reported transient grade 3/4 hematologic toxicity in 12.8% of patients and permanent grade 4/5 renal toxicity in 9.2% with ^{90}Y-DOTATOC. In our opinion, ^{177}Lu is therefore the radionuclide of first choice for treating patients with NETs with PRRT because of less renal toxicity.

In 2008, we reported on 310 GEP-NET patients who were treated with ^{177}Lu-DOTATATE (8). Although part of the patients reported in the current article was included in the 2008 study, we believe that the current results are more distinctive and more unique. In contrast to the former report, in this cohort only Dutch patients with a very long follow-up in our institution were included and results of various subtypes of GEP-NETs are reported. The relative low loss to follow-up makes the current results more solid.

For this study no intention-to-treat analysis was made. We believe that an analysis of all 1,214 patients is not reliable. This group includes patients from different countries who were only treated at our institute and all follow-up was conducted in their own country. No data about this follow-up are available. This group also includes patients with different kind of malignancies, for example, thyroid cancers, paragangliomas and lymphomas. This heterogeneity will make an analysis not reliable and not representative for the investigated group of bronchial and GEP-NET patients.

The main limitation of this study is the fact that it is a nonrandomized study. However, with the selection of patients that were all treated strictly according to the inclusion criteria and an active follow-up during many years make the results very reliable. Also the inclusion of patients with stable disease at baseline is a limitation compared with other studies reporting on NETs. Patients with a very large tumor load or many symptoms of the tumor or its produced hormones were treated, because PRRT was the best available treatment option at that point in time. However, analysis of the patients with PD at baseline demonstrated only small differences in PFS, TTP, and OS compared with all GEPNET patients.

Conclusion

PRRT with ^{177}Lu-DOTATATE produces good tumor response rates for patients with grade 1–2 GEP-NETs and bronchial NETs. The side-effects are limited and in the vast majority of patients reversible on short term. Severe long-term toxicities are acute leukemia or MDS, occurring in 2% of patients. No therapy-related long-term renal or hepatic failure was observed. Although this was a nonrandomized study, the PFS and TTP for ^{177}Lu-DOTATATE are favorable to all other registered medical options that are currently available for patients with advanced or metastasized G_1–G_2 GEP-NETs and bronchial NETs.

Disclosure of Potential Conflicts of Interest

E.P. Krenning holds ownership interest (including patents) in and is a consultant/advisory board member for Advanced Accelerator Applications. D.J. Kwekkeboom held ownership interest (including patents) in Advanced Accelerator Applications. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: T. Brabander, W.A. van der Zwan, W.W. de Herder, E.P. Krenning, D.J. Kwekkeboom

Development of methodology: T. Brabander, W.A. van der Zwan, W.W. de Herder, E.P. Krenning, D.J. Kwekkeboom

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): T. Brabander, J.J.M. Teunissen, B.L.R. Kam, R.A. Feelders, W.W. de Herder, C.H.J. van Eijck, G.J.H. Franssen, E.P. Krenning, D.J. Kwekkeboom

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): T. Brabander, W.A. van der Zwan, W.W. de Herder, E.P. Krenning, D.J. Kwekkeboom

Writing, review, and/or revision of the manuscript: T. Brabander, W.A. van der Zwan, J.J.M. Teunissen, B.L.R. Kam, W.W. de Herder, C.H.J. van Eijck, E.P. Krenning, D.J. Kwekkeboom

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): T. Brabander, G.J.H. Franssen, D.J. Kwekkeboom

Study supervision: D.J. Kwekkeboom

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received October 31, 2016; revised February 21, 2017; accepted April 17, 2017; published OnlineFirst April 20, 2017.

References

1. Fraenkel M, Kim M, Faggiano A, de Herder WW, Valk GD, On behalf of the Knowledge NETwork. Incidence of gastroenteropancreatic neuroendocrine tumours: a systematic review of the literature. Endocr Relat Cancer 2014;21:R153–63.
2. Korse CM, Taal BG, van Velthuysen M-LF, Visser O. Incidence and survival of neuroendocrine tumours in the Netherlands according to histological grade: experience of two decades of cancer registry. Eur J Cancer 2013;49:1975–83.
3. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "Carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26:3063–72.
4. Kulke MH, Benson AB, Bergsland E, Berlin JD, Blaszkowsky LS, Choti MA, et al. Neuroendocrine tumors. J Natl Compr Canc Netw 2012;10:724–64.
5. Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, et al. 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;103:172–85.
6. Krenning EP, Breeman WAP, Kooij PPM, Lameris JS, Bakker WH, Koper JW, et al. Localisation of endocrine-related tumours with radioiodinated analogue of somatostatin. Lancet 1989;1:242–4.
7. Forrer F, Waldherr C, Maecke HR, Mueller-Brand J. Targeted radionuclide therapy with 90Y-DOTATOC in patients with neuroendocrine tumors. Anticancer Res 2006;26:703–7.
8. Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, et al. Treatment with the radiolabeled somatostatin analog [177Lu-DOTA0,Tyr3]octreotate: toxicity, efficacy, and survival. J Clin Oncol 2008;26:2124–30.
9. Bodei L, Cremonesi M, Grana CM, Fazio N, Iodice S, Baio SM, et al. Peptide receptor radionuclide therapy with 177Lu-DOTATATE: the IEO phase I-II study. Eur J Nucl Med Mol Imaging 2011;38:2125–35.

10. Sabet A, Dautzenberg K, Haslerud T, Aouf A, Sabet A, Simon B, et al. Specific efficacy of peptide receptor radionuclide therapy with (177)Lu-octreotate in advanced neuroendocrine tumours of the small intestine. Eur J Nucl Med Mol Imaging 2015;42:1238–46.
11. Bushnell DL, O'Dorisio TM, O'Dorisio MS, Menda Y, Hicks RJ, Van Cutsem E, et al. 90Y-edotreotide for metastatic carcinoid refractory to octreotide. J Clin Oncol 2010;28:1652–9.
12. Strosberg JR, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 trial of 177-Lu-Dotatate for midgut neuroendocrine tumors. N Engl J Med 2017;376:125–35.
13. Kwekkeboom DJ, Bakker WH, Kooij PP, Konijnenberg MW, Srinivasan A, Erion JL, et al. [177Lu-DOTAOTyr3]octreotate: comparison with [111In-DTPAo]octreotide in patients. Eur J Nucl Med 2001;28:1319–25.
14. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.
15. Kwekkeboom DJ. Radiolabeled somatostatin analog [177Lu-DOTA0, Tyr3]octreotate in patients with endocrine gastroenteropancreatic tumors. J Clin Oncol 2005;23:2754–62.
16. Pazdur R. Endpoints for assessing drug activity in clinical trials. Oncologist 2008;13:19–21.
17. US Department of Health and Human Services, National Institute of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0. 2010. Available from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.
18. Rinke A, Muller H-H, Schade-Brittinger C, Klose K-J, Barth P, Wied M, et al. 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;27:4656–63.
19. Caplin ME, Pavel M, C´wikøa JB, Phan AT, Raderer M, Sedláčková E, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med 2014;371:224–33.
20. Rinke A, Wittenberg M, Schade-Brittinger C, Aminossadati B, Ronicke E, Gress TM, et al. 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 (PROMID): results on long term survival. Neuroendocrinology [Internet]; 2016[cited 2016 Jun 8]. Available from: http://www.karger.com/?doi=10.1159/000443612
21. Caplin ME, Pavel M, C´wikøa JB, Phan AT, Raderer M, Sedláčková E, et al. Anti-tumour effects of lanreotide for pancreatic and intestinal neuroendocrine tumours: the CLARINET open-label extension study. Endocr Relat Cancer 2016;23:191–9.
22. Dörr U, Räth U, Sautter-Bihl M-L, Guzman G, Bach G, Adrian H-J, et al. Improved visualization of carcinoid liver metastases by indium-111 pentetreotide scintigraphy following treatment with cold somatostatin analogue. Eur J Nucl Med 1993;20:431–3.
23. Rindi G, Klöppel G, Alhman H, Caplin M, Couvelard A, de Herder WW, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch 2006;449:395–401.
24. Rindi G, Klöppel G, Couvelard A, Komminoth P, Körner M, Lopes JM, et al. TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. Virchows Arch 2007;451:757–62.
25. Bosman FT, World Health Organization, International Agency for Research on Cancer. WHO classification of tumours of the digestive system. 4th ed. Lyon, France: IARC Press, 2010;
26. Sorbye H, Welin S, Langer SW, Vestermark LW, Holt N, Osterlund P, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): The NORDIC NEC study. Ann Oncol 2013;24:152–60.
27. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011;364:514–23.
28. Raymond E, Dahan L, Raoul J-L, Bang Y-J, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011;364:501–13.
29. Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet 2016;387:968–77.
30. Bodei L, Kidd M, Paganelli G, Grana CM, Drozdov I, Cremonesi M, et al. Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. Eur J Nucl Med Mol Imaging 2015;42:5–19.
31. Brieau B, Hentic O, Lebtahi R, Palazzo M, Ben Reguiga M, Rebours V, et al. High risk of myelodysplastic syndrome and acute myeloid leukemia after ^{177} Lu-octreotate PRRT in NET patients heavily pretreated with alkylating chemotherapy. Endocr Relat Cancer 2016;23:L17–23.
32. Bodei L, Modlin IM, Luster M, Forrer F, Cremonesi M, Hicks RJ, et al. Myeloid neoplasms after chemotherapy and PRRT: myth and reality. Endocr Relat Cancer 2016;23:C1–7.
33. de Keizer B, van Aken MO, Feelders RA, de Herder WW, Kam BLR, van Essen M, et al. Hormonal crises following receptor radionuclide therapy with the radiolabeled somatostatin analogue [177Lu-DOTA0,Tyr3]octreotate. Eur J Nucl Med Mol Imaging 2008;35:749–55.
34. Waldherr C, Pless M, Maecke HR, Haldemann A, Mueller-Brand J. The clinical value of [90Y-DOTA]-D-Phe1-Tyr3-octreotide (90Y-DOTATOC) in the treatment of neuroendocrine tumours: a clinical phase II study. Ann Oncol 2001;12:941–5.
35. Valkema R, Pauwels S, Kvols L, Barone R, Jamar F, Bakker W, et al. Survival and response after peptide receptor radionuclide therapy with [90Y-DOTA0,Tyr3]octreotide in patients with advanced gastroenteropancreatic neuroendocrine tumors. Semin Nucl Med 2006;36:147–56.
36. Imhof A, Brunner P, Marincek N, Briel M, Schindler C, Rasch H, et al. Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. J Clin Oncol 2011;29:2416–23.