Peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE for symptomatic control of refractory carcinoid syndrome

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ABSTRACT

Introduction: Treatment with peptide receptor radionuclide therapy (PRRT) with [Lutetium-177-DOTA^{0}-Tyr^{3}]octreotate (^{177}Lu-DOTATATE) results in an increase of progression-free survival and a decrease of carcinoid syndrome (CS) symptoms in patients with a progressive neuroendocrine tumor (NET). Our aim was to study the effect of ^{177}Lu-DOTATATE in patients with CS treated solely for symptom reduction with radiologically stable disease.

Methods: Patients with a metastatic small intestinal NET, elevated urinary 5-hydroxyindolacetic acid (5-HIAA) excretion and flushing and/or diarrhea refractory to treatment with a somatostatin were included in a retrospective analysis. Patients had a non-progressive NET and were treated with 4 cycles of ^{177}Lu-DOTATATE (intended dose 27.8–29.6 GBq) with a primary aim to reduce CS symptoms.

Results: 23 patients were included with median urinary 5-HIAA excretion of 900 µmol/day and had a mean bowel movement frequency (BMF) of 6.1 ± 3.3 per day and 4.3 ± 2.9 flushes per day. After PRRT mean BMF decreased to 4.5 ± 3.5 (p=0.005) and mean daily flushing decreased to 2.4 ± 2.7 (p=0.002). In patients with ≥2 episodes of flushing a day (n=16), 67% of patients had more than 50% decrease of daily flushing. A decrease of BMF of more than 30% occurred in 50% of patients with baseline BMF of ≥4 or more (n=18). A 5-HIAA decrease of more than 30% was seen in in 53% of patients. The EORTC-C30 diarrhea subscale score showed a trend toward improvement by an average of 17.9 points (p=0.06).

Conclusion: PRRT with ^{177}Lu-DOTATATE reduces flushing and diarrhea in patients with refractory CS and can be considered for the symptomatic treatment of CS insufficiently controlled with SSAs.

INTRODUCTION

Small intestinal neuroendocrine tumors (siNETs) arise from enterochromaffin cells which secrete serotonin to regulate gastrointestinal motility.[1,2] Locally, in the case of mesenteric lymph node metastases, the hypersecretion of serotonin and kinins by siNETS can cause mesenteric fibrosis.[3] However, as serotonin is efficiently metabolized by the liver, it can only enter the systemic circulation in case of metastatic disease.[4] Then it can cause the symptoms of flushing, diarrhea, bronchospasm and cardiac valvular fibrosis which together are known as the carcinoid syndrome (CS).[5] CS is associated with a shorter survival through the complications of fibrosis, but also because it is associated with a high tumor load and liver metastases.[6,7]

In severe CS, symptomatic control can be challenging. All patients with CS should be screened for carcinoid heart disease and valve replacement surgery can be indicated.[8] Furthermore, secretion of serotonin needs to be reduced and anti-proliferative therapy is indicated. The first step in the treatment of CS is a somatostatin analogue (SSA). This results in a decrease in serotonin secretion in more than 50% of patients and a symptomatic response in more than 65% of patients.[9] Furthermore, treatment with SSAs has been shown to increase progression-free survival when compared to placebo.[10] In patients with persisting symptoms of flushing and diarrhea despite optimal treatment with SSAs (refractory CS), several options for second-line treatment exist. In 1990's several trials with interferon-alpha demonstrated a biochemical response in 44% of patients with CS.[11,12] Recently, telotristat ethyl has also been registered for refractory CS. This drug decreases serotonin synthesis by inhibiting tryptophan hydroxylase, the rate limiting step in serotonin secretion. In a placebo-controlled trial telotristat ethyl reduced the number of daily bowel movements with –0.8 (250mg) or -1.2 (500mg) versus placebo.[13]

In patients treated with peptide radionuclide receptor therapy (PRRT) with [Lutetium-177-DOTA^{0}-Tyr^{3}]octreotate (^{177}Lu-DOTATATE) for a progressive siNET, PRRT also resulted in a decrease of diarrhea and urinary 5-HIAA excretion.[14,15]

The effects of treatment with ^{177}Lu-DOTATATE, purely for symptomatic control of CS, are largely unknown. Aim of this study was to determine the effect of ^{177}Lu-DOTATATE in patients with non-progressive low grade (WHO grade 1-2) siNET with refractory carcinoid syndrome, treated solely for symptom reduction.

METHODS

Patients

For this retrospective study, patient were selected if treated with PRRT with ^{177}Lu-DOTATATE for refractory CS. Patients were included if treated with ^{177}Lu-DOTATATE for persisting symp-

toms of CS despite treatment with a SSA (Octreotide immediate release sc, Octreotide LAR or Lanreotide Autogel). As the primary aim of the study was the effect of ^{177}Lu-DOTATATE for the indication of symptom reduction, patients with treated for radiological progressive disease (PD) as indication for PRRT who also suffered from symptoms of the carcinoid syndrome were excluded. Thus only patients with stable disease (SD) or patients treated upfront with PRRT were included. All patients treated with at least one cycle of PRRT were included if last treatment was before July 2017 (minimum of 1 year follow-up). CS was diagnosed in patients with siNETs with symptoms of diarrhea or flushing in combination with elevated urinary 5-hydroxyindoleactic acid (u5-HIAA) excretion. u5-HIAA excretion was measured as described earlier.[16] The upper limit of normal (ULN) of u5-HIAA was 50ug/24h. Patients were eligible for PRRT if hemoglobin was $\geq$ 5.5 mmol/L, white blood cell count $\geq$ 2x10^9/L, platelet count $\geq$ 75x10^9/L, and Karnofsky performance status $\geq$ 50. Furthermore, adequate tumor SSTR expression as evaluated on planar 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) expression.

PRRT Protocol

The preparation and administration of ^{177}Lu-DOTATATE has been described earlier.[17,18] The intended interval between treatments was 6–10 weeks. Patients were treated up to a cumulative intended dose of 27.8–29.6 GBq ^{177}Lu-DOTATATE. Lanreotide and Octreotide LAR was discontinued 6 weeks before therapy and short-acting octreotide was discontinued 24 hours before treatment. SSA was restarted 4 hours after administration of PRRT. All patients were admitted for one 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

At baseline patient and disease characteristics were recorded. Also the biomarkers alkaline phosphatase (ALP), lactate dehydrogenase (LDH) and chromogranin A (CgA) were included (all measured with commercially available assays according to instructions). The baseline uptake on somatostatin scintigraphy was scored on planar images; 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 on the somatostatin scintigraphy was scored as limited, moderate or extensive by experienced nuclear medicine physicians as described previously[19]. The frequency of bowel movements (BM) and flushing per day were recorded as stated in the medical chart by the treating physician. The effect on the quality of life was measured with European Organization for Research and Treatment of Cancer (EORTC) quality of life (QOL)

questionnaire (QLQ)–core module (C30).[20] The EORTC QLQ-C30 scores were transformed to 0–100 scales and the scores three months after last treatment were compared to baseline.[21]

Radiological response was assessed on CT or MRI according to the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) criteria.[22] Progression-free survival (PFS) 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 (CTCAE).

Statistics

Data were presented as mean with 95% confidence interval (95% CI) 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 non-normally distributed variables. Progression-free survival was analyzed with the Kaplan-Meier method. A p-value of <0.05 was considered statistically significant. Calculations were performed using SPSS for Windows software, (version 23.0, SPSS Inc.)

RESULTS

In this retrospective study 23 patients could be included who were treated with ^{177}Lu-DOTATATE for the reduction of CS symptoms (Table 1). Average patients' age was 62.6 ± 8.2 years and 48% was female with a median Karnosfsky score of 80 (IQR: 80-90). Patients were mainly treated previously with surgery (50%) and interferon (13%) during a median of 2.1 (IQR: 0.6-4.7) years of history with a NET. All patients were treated with a SSA, either short-acting (39%), long-acting (39%) or in combination (22%). In 91% of patients baseline imaging showed a liver burden (CT or MRI) of more than 25% with moderate or extensive disease scored with SRS. The biomarkers ALP and LDH were elevated in respectively 70% and 57% of patients with a median CgA of 1055µg/L (IQR: 542-6687).

Safety and toxicity

The complete therapy of 29.6 GBq ^{177}Lu-DOTATATE was administered to 48% of patients. Three patients were unable continue treatment after 7.8-15.6 GBq due to heart failure and two patients had clinical progression after 2 cycles. Another two patients were treated with a reduced dose due to toxicity: reversible thrombopenia in one patient and the second patient had irreversible kidney insufficiency due to urosepsis after the second cycle with further deterioration of kidney function after a third cycle. A reduced dose of 25.9 GBq was administered to two patients after previous treatment with MIBG and one patient because of high liver tumor burden. In total, 77 cycles of ^{177}Lu-DOTATATE were administered. Nausea occurred after 38% of therapies, vomiting after 13% and pain after 23% of therapies.

Subacute heamatotoxicity occurred in five patients of which one patient developed chronic thrombo- and leukopenia. There were no cases of myelodysplastic syndrome or leukemia.

All patients had severe carcinoid syndrome with median 24 hour urinary 5-HIAA excretion of 900µmol/24h (IQR: 538-1517 µmol/24h). All patients were screened with a cardiac ultrasound and 13 (56.5%) were diagnosed with carcinoid heart disease. Two patients underwent prior replacement of the tricuspid valve. All patients were using SSAs prior to PRRT, expect 1 patient with side effects of octreotide. Three patients used long-acting SSA with last administration 6 weeks prior to PRRT. Another 19 patients were treated with short-acting octreotide subcutaneously. With these prophylaxes no carcinoid crises occurred during or after therapy and all patients were safely discharged after overnight routine observation. One patient was admitted between therapies due to heart failure which was treated with diuretics.

Table 1: Baseline characteristics (n=23)

Patient characteristics		**Disease characteristic**	
Female, *n* (%)	11 (47.8)	Grade, *n* (%)	
Age (years ± SD)	62.6 ± 8.2	Grade 1	7 (30.4)
Karnofsky score (median)	80	Grade 2	7 (30.4)
Previous Treatments, *n (%)*		Unknown	9 (39.1)
Surgery	12 (52.2)	Location of Metastases, *n (%)*	
Chemotherapy	2 (8.7)	Liver	23 (100)
Interferon	3 (13.0)	Lungs	0
MIBG	2 (8.7)	Bones	6 (26.1)
Other†	3 (13.0)	Liver Burden, *n (%)**	
Somatostatin analogue n *(%)*		1-25%	2 (9.0)
Short-acting	9 (39.1)	25-50%	10 (45.5)
Long-acting	9 (39.1)	>50%	10 (45.5)
Short and long-acting	5 (21.7)	Extent of Disease (SRS), *n (%)*	
Nr. previous treatments, *n (%)*		Limited	2 (8.7)
1	11 (47.8)	Moderate	16 (69.6)
2	6 (26.1)	Extensive	5 (21.7)
≥3	6 (26.1)	Uptake on somatostatin receptor imaging, *n (%)*	
Alkaline phosphatase elevated, n *(%)*	16 (69.9)	grade 2	2 (8.7)
Lactate dehydrogenase, n *(%)*	13 (56.5)	grade 3	15 (65.2)
Chromogranin Aº (median)	1055 µg/L	grade 4	6 (26.1)

* Liver burden unevaluable in 1 patient

† includes liver embolization, radiotherapy and radiofrequency ablation.

º Upper limit of normal 94µg/L

Symptomatic and biochemical response

At start of treatment with ^{177}Lu-DOTATATE, all patients had uncontrolled symptoms of carcinoid syndrome with mean bowel movement frequency of 6.1 ± 3.3 per day and 4.3 ± 2.9 flushes per day. The symptomatic response to ^{177}Lu-DOTATATE is shown in figures 1a and 1b. After PRRT mean daily bowel movement frequency decreased to 4.5 ± 3.5 and mean daily flushing decreases to 2.4 ± 2.7. A decrease of bowel movement frequency of more than 30% occurred in 50% of patients with baseline bowel movement frequency of 4 or more (n=18). A more than 50% decrease was noted in 33% of these patients. In patients with 2 or more episodes of flushing a day (n=16), 67% of patients had more than 50% decrease of daily flushing. This was accompanied by decrease of 24 hour u5-HIAA excretion (Figure 2). Six months after last PRRT, a u5-HIAA decrease of more than 30% was seen in in 53% of patients and a decrease of more than 50% in 32% of patients. Average 24 hour u5-HIAA excretion decreased from 1140 ± 1001 µmol/24h to 782 ± 698 µmol/24h (p=0.01) in 19 patients with follow-up of more than six months. Four patients did not have u5-HIAA collection after 6 months, due to death. In an intention-to-treat model with last observation carried forward including all patients, average u5-HIAA decreased from 1262 ± 986 µmol/24h to 966 ± 803 µmol/24h (p=0.01). Of the 15 patients with a clinical response, a reduction in symptoms occurred after 1 cycle in 2 patients, after 2 cycles in 7 patients and after 3-4 cycles in 6 patients. At time of radiological progression 93% of patients also had recurrence of CS symptoms.

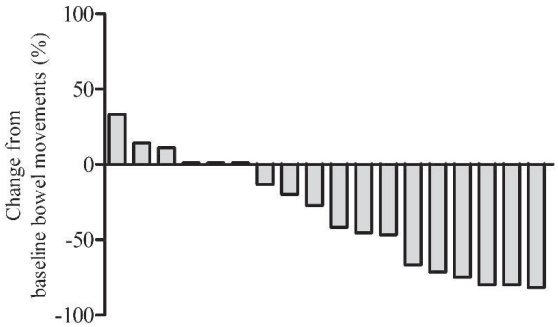

Figure 1a: Percentage of change from baseline bowel movements per patient per day (included patients with 4 or more bowel movements daily at baseline)

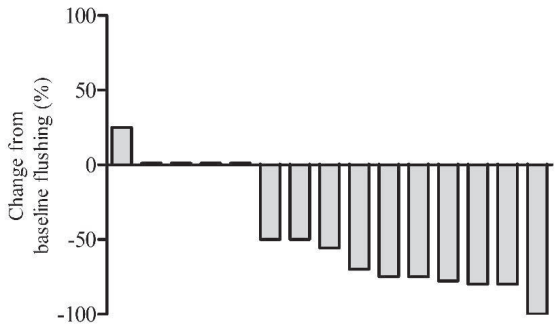

Figure 1b: Percentage of change from baseline flushing per patient per day (included patients with 2 or more flushes daily at baseline)

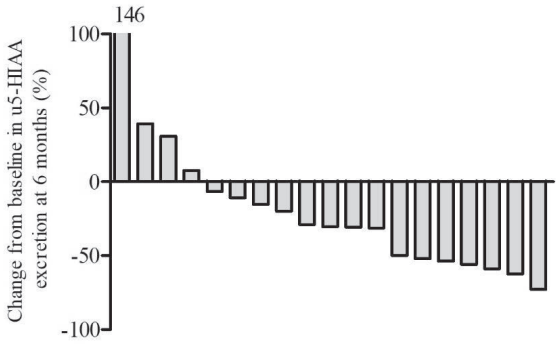

Figure 2: Percentage of change from baseline 24 hour urinary 5-HIAA excretion

Radiological response

All patients had either stable disease at baseline (n=10) or were treated with only a baseline CT-scan, thus with unknown progression (n=13). According to RECIST 1.1, PR was seen in 2 patients (9%) and stable disease in 16 patients (70%). PD occurred in 5 patients after treatment with ^{177}Lu-DOTATATE. This was heart failure in 2 patients and they both died approximately 3 and 6 months after the first cycle. Another 2 patients had 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 PFS of 34 months with a slightly longer OS of 44 months (Figure 3).

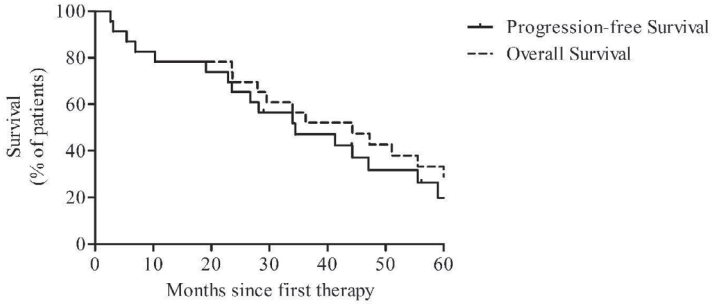

Figure 3: Progression-free and overall survival after treatment with ^{177}Lu-DOTATATE

Quality of life

EORTC QLQ-C30 scores were available for 13 patients at baseline and 3 months after last treatment. The diarrhea subscale score improved by an average of 17.9 points (on a 0-100scale), but not significant (p=0.06). There was however a decrease in cognitive functioning and emotional functioning of 9.0 points in both groups (p=0.04). All other scores showed no significant difference.

Table 2: Overview of therapy and toxicity

Treatment and toxicity (n(%))	
Cumulative dose, GBq	
7.4-14.8	5 (20.8)
18.5-22.2	4 (16.7)
25.9-27.8	3 (12.5)
29.6	11 (47.8)
Acute Toxicity (per treatment)	
Nausea	29 (37.7%)
Vomiting	10 (13.0%)
Pain	18 (23.4%)
Subacute Toxicity (per patient)	
Anaemia	
grade 3	1 (4.3%)
grade 4	0
Thrombocytopenia	
grade 3	3 (13.0%)
grade 4	1 (4.3%)
Leukopenia	
grade 3	3 (13.0%)
grade 4	1 (4.3%)
Hormone crisis	0
Chronic toxicity	
Leuko- & Trombopenia	
grade 3	1 (4.3%)
Kidney insufficiency	
grade 3	1 (4.3%)

DISCUSSION

CS is characterized mainly by diarrhea and flushing caused by secretion of serotonin and kinins by a siNET. Many patients can be treated successfully with SSAs with trials demonstrating a symptomatic response in more than 60% of patients and a decrease of u5-HIAA excretion in around 45% of patients.[9] Selected 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 50-90% of patients.[14,15,23-25] However, these patients were treated for a progressive NET and the symptomatic response was secondary to a treatment for progressive disease. In the current study patients were treated with ^{177}Lu-DOTATATE primarily for the reduction of CS symptoms. In a

cohort with severe CS, the side effect of ^{177}Lu-DOTATATE seem to be comparable with other series on PRRT for siNET.[17,26] Most patients were switched to short-acting octreotide and with this regimen no carcinoid crises occurred. However, in a group with a high incidence of carcinoid heart disease, one patient (4%) was admitted between therapies for heart failure. Adequate screening and treatment for carcinoid heart disease before PRRT remains essential, but otherwise treating patients with refractory CS with PRRT is safe.

All included patients had symptoms of CS despite treatment with a SSA and therefore the indication for treatment is comparable with the recent trials with telotristat ethyl, where 250 or 500mg of telotristat ethyl resulted in an average decrease of daily BM frequency of respectively 0.45 and 0.60 per day in the TELECAST trial[27] and 1.7 and 2.1 in the TELESTAR trial.[13] This resulted in a response (defined as ≥30% reduction of BMs in patients with >4 daily BM) in around 40% of patient. A reduction in flushing was not seen during treatment with telotristat ethyl as this only reduces serotonin secretion and not the secretion of kinines and histamines. Treatment with ^{177}Lu-DOTATATE resulted in a smaller average daily BM reduction of 1.6, but additionally did decrease average daily flushing with 1.9 a day. A decrease of BM frequency of more than 30% was observed in 50% of patients and 67% of patients had more than 50% decrease of daily flushing and therefore seems to be effective for the treatment of refractory CS. A major limitation of this study is the retrospective design, small number of patients and the absence of a control group. This causes a risk of regression toward the mean, because patients with the high symptomatic burden are selected for therapy.

Other therapies include interferon and liver-directed therapy. Interferon-alpha has been studied in several prospective studies where it resulted in highly variable clinical response of 0-90% which, combined in a meta-analyses, resulted in a decrease in flushing and diarrhea in 45% and 63% of patients.[9,28-31] However, the single randomized-controlled trial comparing octreotide in combination with interferon-alpha versus octreotide alone demonstrated no benefit of interferon.[32] Also the side-effects as fatigue and flu-like symptoms associated with interferon can be severe. Therapies based on reducing tumor burden mainly focus on the liver, like radiofrequent ablation (RFA), embolization or surgery. All together these techniques have a very high clinical response rate of 82%.[9] Head-to-head comparisons between these therapies is currently lacking. The lack of comparative trials require the selection of treatment for refractory CS to be based on patient and tumor characteristics. As the burden of evidence for SSAs and telotristat are highest these will remain first choice. Thereafter the selection of palliative treatment could possibly be based on the same principles as for progressive NET: in patients with liver dominant disease, liver directed therapy is preferred.[33] In patients with diffuse liver metastases, extra-hepatic metastases or contraindication for liver directed therapy, PRRT can be considered.

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