Peptide Receptor Radionuclide Therapy With ^{177}Lu-DOTATATE for Patients With Somatostatin Receptor–Expressing Neuroendocrine Tumors

The First US Phase 2 Experience

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Objectives: Peptide receptor radionuclide therapy with radiolabeled somatostatin analogs is a novel method of treatment in patients with metastatic neuroendocrine tumors (NETs). For the first time in the United States, we present preliminary results of the treatment with Lutetium 177 (^{177}Lu) DOTATATE in patients with progressive NETs.

Methods: Thirty-seven patients with grade 1 and grade 2 disseminated and progressive gastroenteropancreatic NET were enrolled in a nonrandomized, phase 2 clinical trial. Repeated cycles of 200 mCi (7.4 GBq; ±10%) were administered up to the cumulative dose of 800 mCi (29.6 GBq; ±10%).

Results: Among 32 evaluable patients, partial response and minimal response to treatment were seen in 28% and 3%, respectively, and stable disease was seen in 41% of patients. A total of 28% had progressive disease. A response to treatment was significantly associated with lower burden of disease in the liver. No significant acute or delayed hematologic or kidney toxicity was observed. An impressive improvement of performance status and quality of life were seen after ^{177}Lu-DOTATATE therapy.

Conclusions: Treatment with multiple cycles of ^{177}Lu-DOTATATE peptide receptor radionuclide therapy is well tolerated. This treatment results in control of the disease in most patients, whereas systemic toxicities are limited and reversible. Quality of life is also improved.

Key Words: neuroendocrine tumors, ^{177}Lu-DOTATATE, peptide receptor radionuclide therapy

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Neuroendocrine tumors (NETs) consist of a group of rare, usually slow-growing and heterogeneous, malignancies derived from neuroendocrine cells.[1,2] Surgical resection is the therapy of choice for patients with operable and localized disease; however, because of the slow-growing nature of the tumor and the nonspecific signs and symptoms, these tumors are often diagnosed late and present with metastatic disease, making curative surgical resection impossible.[3] The currently approved systemic therapies for NET in the United States are streptozocin, everolimus, and sunitinib, the latter 2 for primary pancreatic NET. Multiple European studies have, however, shown that systemic cytotoxic chemotherapy (cisplatin or etoposide) has a rather minimal efficacy in low-grade (grade 1 and grade 2) NET but is more effective in high-grade (grade 3) NETs.[4,5]

Somatostatin analog therapy seems to prolong the disease-free survival of midgut carcinoid, based on the data from the PROMID (placebo-controlled, randomized study of octreotide long acting release in metastatic neuroendocrine midgut tumors) study.[6] The CLARINET (clinical trial on nonfunctioning enteropancreatic endocrine tumors) study will assess the effect of lanreotide on progression-free survival (PFS) in patients with nonfunctioning enteropancreatic endocrine tumors. The final data collection for the primary outcome measure is estimated to be released by the end 2013. Scintigraphic study using ^{111}Indium-diethylene triamine pentaacetic acid octreotide (OctreoScan; Covidien, St Louis, Mo) has been widely used as a standard method of imaging for detection of somatostatin receptor–positive NETs.[7] More recently, somatostatin analogs labeled with Gallium 68—a positron emitter—have been used for positron emission tomography/computed tomography (PET/CT) tumor imaging.[8]

Neuroendocrine tumor treatment with radiolabeled somatostatin analogs has been available since the 1990s for patients with NET.[9] Peptide receptor radionuclide therapy (PRRT) initially was introduced with high doses of ^{111}Indium pentetreotide and provided some symptom relief, disease stabilization, and improvement of the quality of life.[6] Peptide receptor radionuclide therapy using multiple cycles of high dose ^{111}Indium pentetreotide is generally well tolerated with a limited systemic toxicity. We recently showed that high activity ^{111}Indium pentetreotide therapy (up to 4 cycles of 500 mCi [18.5 GBq] ^{111}Indium octreotide) seems to be a safe and effective therapy for patients with progressive metastatic NETs with no major hematologic, renal, or hepatic toxicities.[10–12] Although partial response (PR) and complete response (CR) are less likely with this treatment, stable disease (SD) is the mostly seen outcome after ^{111}Indium pentetreotide therapy in previously progressive patients. Kidney toxicity with this type of PRRT is extremely rare, and there is no need for kidney radioprotectants with this treatment.

^{90}Y-DOTA Tyr-octreotide has also been developed. ^{90}Y is a pure β emitter with a relatively long tissue penetration range (12 mm), which enables it to easily penetrate larger lesions, and a PR rate of 25% or 33% has been reported.[13–15] However, because kidney is the dose-limiting organ for this agent, PRRT

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with therapeutic dose of ^{90}Y must be accompanied with coadministration of kidney radioprotectants. In a phase 1 study performed by Otte et al,[16] ^{90}Y-DOTA Tyr-octreotide PRRT without amino acid coadministration resulted in the development of renal toxicity grade IV in 2/24 patients. The chance of occurrence of renal toxicity has been significantly decreased with amino acid co-infusion.

Since 2000, Lutetium 177 (^{177}Lu) DOTATATE has been used for PRRT. ^{177}Lu is a medium-energy β-emitter (0.498 MeV, 78.6%) with an approximate half-life of 6.7 days and with the maximal tissue penetration of 2 mm. This allows for a more localized radiation effect and less collateral damage to the normal tissues than ^{90}Y. ^{177}Lu also emits 208 KeV γ-rays, which facilitate posttherapy scintigraphic imaging, biodistribution, and dosimetry studies. When compared with ^{111}Indium, the longer particle range makes ^{177}Lu more suitable for PRRT for larger lesions.

Data from previous studies have demonstrated the safety and antitumor effect of repeated treatments with 100 to 200 mCi (3.7–7.4 GBq) of ^{177}Lu-DOTATATE. In another study performed by Kwekkeboom et al,[17] the results of ^{177}Lu-DOTATATE administration were studied in the treatment of 310 patients with NET. The data showed that the response to therapy CR, minimal response (MR), and PR (according to the Southwest Oncology Group criteria) was as high as 45%, and SD was reported in 35% of the study subjects.

Similarly, additional investigational studies have reported significant antitumor response to ^{177}Lu-DOTATATE therapy with limited toxicity.[18] Despite the fact that these studies were not similar in design, patient selection, total dosages used, and also the fact that none were randomized, all have reported tumor control in similar high percentage of patients.

The present study represents the first trial of ^{177}Lu-DOTATATE PRRT in the United States in patients with low-grade disseminated somatostatin receptor–expressing NETs. Our preliminary results of safety and effectiveness of this new treatment modality are herein reported. In addition, the role of Fluorine 18 (^{18}F) fludeoxyglucose (FDG) PET/CT imaging as a prognostic indicator is evaluated in this group of patients.

MATERIALS AND METHODS

Patient Selection and Enrollment

Thirty-seven patients with a histopathologically confirmed diagnosis of grade 1 and grade 2 gastroenteropancreatic NETs (GEP-NETs) were enrolled in a phase 2 clinical trial to evaluate the safety and efficacy of the repeated cycles of ^{177}Lu-DOTATATE therapy. This was a single-center study. All patients were treated in an outpatient setting at Excel Diagnostics and Nuclear Oncology Center, Houston, TX, under radiation safety precautions approved by the State of Texas, Department of State Health Services, Radiation Safety and Licensing Program. This study was performed under the approval from the Biomedical Research Alliance of New York institutional review board and under an approved investigational new drug application from the US Food and Drug Administration. All patients gave written informed consent before the treatment.

All enrolled patients were previously treated with different therapeutic modalities for cancer treatment before their enrollment to this trial. Twenty-eight of 37 patients were on Sandostatin. Twenty-six patients discontinued their Sandostatin after PRRT. In this group, only 1 patient had to start Sandostatin 11 months after his fourth cycle. All patients had previously demonstrated progressive disease (PD) by Response Evaluation Criteria in Solid Tumors (RECIST). All patients had Karnofsky performance status (KPS) score of higher than 60. The cost of the treatment was covered by the sponsor of the project, RITA Foundation of Houston. Patients, their family members, friends, and other institutions also made donations to the RITA Foundation. Inclusion criteria required patients to demonstrate a pathologically proven NET along with a positive ^{111}Indium octreotide scintigraphy, which is defined as tumor uptake greater than or equal to the normal liver tissue on planar imaging (grade 2 and above, Krenning score). Other prerequisites for treatment were hemoglobin concentration greater than or equal to 8.9 g/dL; white blood cell count greater than or equal to 2×10^9/L (2000/μL); platelet count greater than or equal to 100×10^9/L (100×10^3/μL), serum albumin greater than 30 g/L (3 g/dL), and serum creatinine level less than or equal to 150 μmol/L or less than or equal to 1.7 mg/dL; and a measured 24-hour creatinine clearance greater than or equal to 50 mL/min.

Most patients had multiple metastases in the liver as the most common site of distant metastasis involvement in NET.

Preparation of High-Dose ^{177}Lu-Octreotate

^{177}Lu-Cl3 was purchased from the Missouri University Research Reactor, Columbia, Mo. DOTATATE kits were manufactured by Iso-Tex, Inc in Friendswood, TX. The radiolabeled solution was compounded at the South Texas Nuclear Pharmacy (Houston, TX) and delivered to the Excel Nuclear Oncology Center in Houston, TX. Comprehensive analytical and quality assurance testing was performed at IsoTherapeutics, Inc in Angleton, TX, before administration of the dose to the patients.

Treatment Protocol

In each cycle, patients received 200 mCi (7.4 GBq; ±10%) of ^{177}Lu-DOTATATE via intravenous (IV) infusion. Initially, 2 IV lines were secured in the patient's forearms, 1 for ^{177}Lu-DOTATATE infusion and the other one for infusing the kidney protecting agents on the contralateral arm. A total of 15% Clinisol (1000 mL) was used for kidney protection. This solution is composed of a mixture of positively charged amino acids, was infused 30 minutes before ^{177}Lu therapy, and was continued for 4 hours (at a rate of 250 mL/h). After 30 minutes of infusing the amino acids, ^{177}Lu-DOTATATE infusion was then initiated and completed within 30 minutes. All these procedures were carried out in an outpatient setting. Radiation exposure at 1 m at the time of discharge was between 3 to 6 mR/h.

All patients in this study were evaluated for any adverse events immediately and after the therapy using CTCAE criteria, version 4.3. To detect any possible hematologic, renal, or hepatic toxicity, the National Cancer Institute common toxicity criteria were used. Safety monitoring included routine determinations of the complete blood cell count, comprehensive metabolic panel (including serum urea nitrogen/creatinine and total bilirubin level), and tumor markers including chromogranin A, serotonin, pancreastatin, gastrin, neurokinin A, pancreatic polypeptide, and 24-hour urine 5-hydroxyindole acetic acid 1 week before each cycle of therapy and also 4 weeks after the therapy. Patients were followed up for 3, 6, and 12 months after the fourth cycle of the therapy. Patients were eligible to receive up to 4 cycles of therapy (6–9 weeks interval, cumulative dose of 800 mCi [29.6 GBq]). Inclusion criteria for the second therapy or after were similar to the first selection criteria except for the hemoglobin concentration greater than or equal to 8.0 g/dL and platelet count greater than or equal to 75×10^3/μL. If indicated, the fourth therapy dose was adjusted to limit the cumulative radiation dose to kidneys to less than the maximum limit of 23 Gy. These patients were also evaluated for a clinical response before each cycle of therapy through history and physical examination, completion of quality of life questionnaire, and imaging studies,

TABLE 1. Demographic Data for All Patients

Diagnosis	GEP-NET	n = 37
Site of primary tumor	Pancreas	14
	Small bowel	12
	Rectal	3
	Large bowel	1
	Unknown	7
No. treatment cycles	1	5
	2	8
	3	5
	4	19
OctreoScan grade	2	4
	3	26
	4	7
No. involved metastatic sites	1	4
	2	17
	3	8
	4	8
Metastatic site	Liver	34
	Lymph nodes	16
	Bone	11
	Pancreas	8
	Lung	3
Liver burden	High	21
	Low	13
	Not evaluable	3
FDG PET scan	Positive	24
	Negative	10
RECIST	PR	9
	MR	1
	SD	13
	PD (including death)	9
Sex	Male	16
	Female	21
Adverse effects	Nausea/vomiting	30
	Skin rash	2
PFS, mo	All patients	16.1
	Patients who completed 4 cycles	16.5

such as computed tomography (CT) scan, magnetic resonance imaging (MRI), OctreoScan, and ^{18}F-FDG PET/CT scan. Aprepitant (Emend) 125 mg was used 60 to 90 minutes before the start of amino acid infusion for the prevention of nausea in cases with history of severe nausea and vomiting. Ondansetron (Zofran) 2 to 4 mg IV bolus injection was given 30 minutes into amino acid infusion and repeated every 2 hours as needed.

Statistical Analysis

Study Design

The primary end point of this trial was to determine PFS. The distributions of duration of PFS were estimated using the Kaplan-Meier method. Additional secondary end points of this trial were to determine radiological response, clinical response, and biochemical response rates This is an ongoing phase 2 pilot study and has been designed to recruit 60 patients ($\alpha = 0.05$). Analyses of variance, paired t test, Wilcoxon test, and χ^2 test were performed using GraphPad Prism 5 software (GraphPad Software, Inc, La Jolla, Calif). $P < 0.05$ was considered statistically significant. All survival times were calculated from the date of first treatment.[19,20]

RESULTS

Thirty-seven patients (16 males, 21 females; Table 1) with grade 1 and grade 2 somatostatin receptor–positive GEP-NETs underwent treatment with high activity (200 mCi [7.4 GBq]; ±10% per cycle) ^{177}Lu-DOTATATE, between October 2010 and January 2013. The mean age of patients was 63.4 years (range, 43–86 years; median, 64 years).

As of January 2013, 5 patients were treated with 1 cycle of therapy with an average dose of 198.19 mCi (7.33 GBq; range, 190.18–204.17 mCi [7.04–7.56 GBq]). Eight patients received 2 cycles of therapy with an average dose of 394.71 mCi (14.69 GBq) per patient (range, 387.99–413.26 mCi [14.35–15.30 GBq]); 5 patients received 3 cycles of therapy with an average dose of 588.82 mCi (21.78 GBq) per patient (range, 585.46–591.66 mCi [21.68–21.89 GBq]). Finally, 19 patients received 4 cycles of therapy with an average dose of 776.07 mCi (28.71 GBq; range, 727.91–797.7 mCi [26.95–29.54 GBq]); 3 completed the 6-month posttreatment follow-up assessment visits, and 7 completed the 12-month follow-up assessment visits.

No significant acute toxicity was observed during or immediately after the treatment. The most commonly seen complaint was mild to moderate nausea and vomiting, which was noted in almost 80% of the patients. Mild and transient skin redness developed in 2 cases (5.4%) after the initiation of amino acid infusion, which was resolved within few minutes, and no medical intervention was required.

Patients were extensively evaluated for any evidence of hematologic, hepatic, or renal toxicity using the National Cancer Institute common toxicity criteria and followed up for an average of 14.26 months (0.3–26.87 months; median, 16.11 months), including the 6-month and 12-month follow-up visits in applicable subjects. No patient had grade IV toxicity. Of 32 evaluable patients with 2 or more treatment cycles, 3 patients (9.4%) had grade II, and 4 patients (12.5%) developed grade III hematologic toxicity, which did not require supportive therapy. The average duration of hematologic toxicities was 12.3 weeks (range, 4–18 weeks; median, 13 weeks). Of these, 6 patients (85.7%) had a history of chemotherapy before their enrollment (averagely within 31.76 months before enrollment to our study; range, 15.4–64.8 months; median, 24.3 months). We found out that the development of hematologic toxicity after the repeated cycles of ^{177}Lu-DOTATATE therapy is statistically significantly ($P = 0.036$, χ^2 test) associated with the prior history of chemotherapy treatment. Extensive bone metastasis might be another important risk factor.

Grade I/II and III hepatic toxicity were observed in 2 (6.2%) and 3 (9.4%) patients, respectively. Importantly, ^{177}Lu-DOTATATE therapy did not impose any significant deterioration of hepatic function in patients with liver metastasis who had abnormal baseline levels of aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase before the therapy. On the contrary, in 4 patients (12.5%) with abnormal baseline liver function, complete normalization was noted in at least 1 of the hepatic indices. In addition, in 1 patient (3%), grade I or II renal toxicity occurred. Importantly, no significant (grade III or IV) renal toxicity was observed, and there was no correlation between renal toxicity and cumulative dose to the kidneys.

Radiological response to therapy was extensively studied in 32 evaluable patients for an average of 14.26 months (0.3–26.87 months). All patients who had completed more than

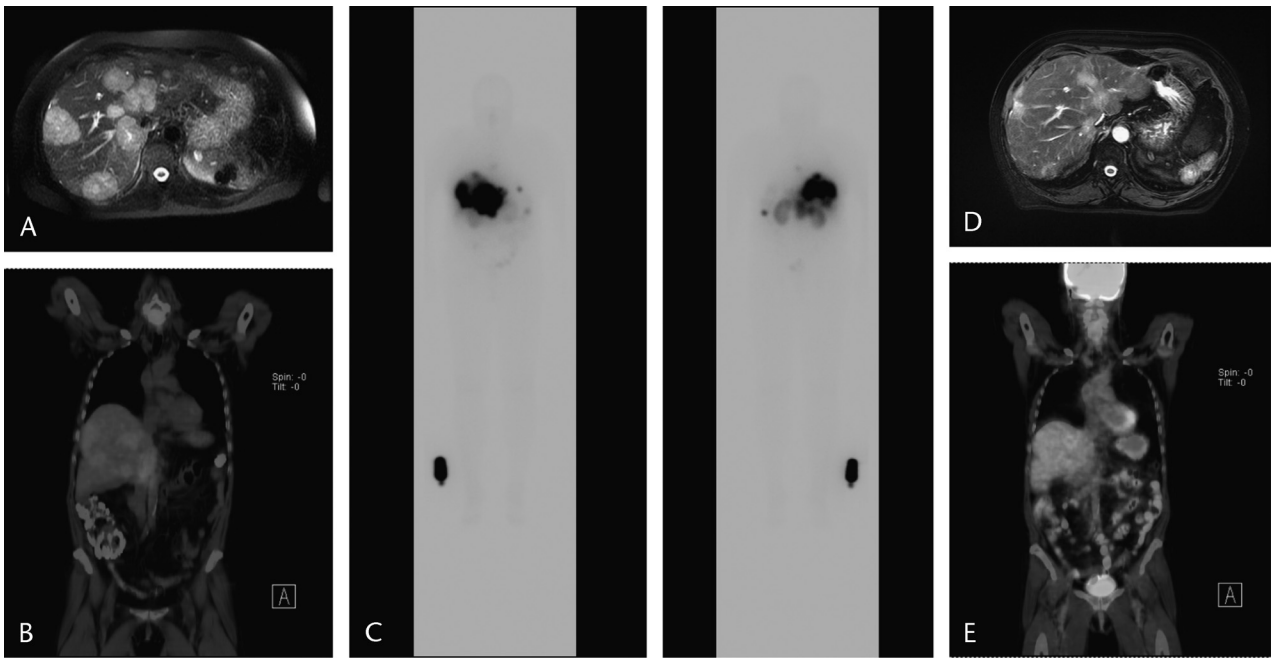

FIGURE 1. A 64-year-old female patient with pancreatic neuroendocrine cancer with significant response to treatment in liver after 2 cycles of ^{177}Lu-Octreotate; pretherapy MRI (A), pretherapy ^{18}F-FDG PET/CT scan (B), and baseline OctreoScan (C). Baseline OctreoScan shows impressive tracer uptake in the liver and periportal lymph nodes. Posttherapy MRI (D) and ^{18}F-FDG PET/CT (E) scan show significant response to the treatment.

1 cycle of treatment were studied except those patients who did not have the complete sets of data for analysis and lost the follow-up. Response assessment was performed using the modified RECIST. Among 32 evaluable patients, radiological response (PR + MR) was observed in 10 patients (total of 31%, 28% PR and 3% MR; Fig. 1). Stable disease was seen in 13 patients (41%), and PD occurred in 9 patient (28%; Table 1).

Among the total of 37 patients, 9 deaths were reported till January 2013. We believe all deaths occurred because of the huge tumor burden, as most of them had extensive involvement of the liver (high bulk group, n = 6, or 67%), and the involvement of multiple lymph nodes and bones (n = 7 or 78%) or the combination of multiple organs (n = 9 or 100%).

Progression-free survival was calculated in all patients and in those who completed all 4 cycles of treatments and were followed for at least 3 months (Table 2). As of January 2013, 28 patients were still alive. The median PFS for all patients and also those who completed all 4 cycles of treatment was 16.1 and 16.5 months, respectively. Kaplan-Meier survival curve for all patients and for those who received the 4 cycles is demonstrated in Figure 2A. Hormonal response was assessed in 19 evaluable patients who had received 3 or 4 cycles of therapy and had available baseline and posttherapy follow-up hormonal evaluation results. A significant biochemical response defined as 25% reduction from pretreatment levels, at least in 1 of the cancer-specific markers (chromogranin A, serotonin, 5-hydroxyindole acetic acid), was observed in 6 patients (32%). Two patients (10%) showed increased levels of all hormonal markers when compared with pretreatment levels.

Almost all patients (n = 36 or 97%) had either 1 or multiple local or distant metastatic lesions at the time of diagnosis. There was only 1 patient (2.7%) with localized unresectable primary tumor involving the pancreas. The pancreatic tumor in this patient was initially inoperable; however, after 2 cycles of ^{177}Lu-DOTATATE therapy (cumulative dose of 388.05 mCi) and considerable tumor shrinkage, she was referred to her surgeon for consideration of the curative surgery. There was no significant correlation (P = 0.30; t test; 95% confidence interval, −5.65 to 3.37) between PFS in patients (n = 4) with 1 anatomical site involvement (bone, lung, lymph node, mesentery, or liver; median, 8.97 months; range, 0.77–13.9 months) when compared with patients with metastatic involvement in 2 regions (n = 13; median, 8.47 months; range, 2.2–17.13 months) or those with metastases in more than 2 sites (n = 8; median, 9.86 months; range, 4.73–17.83 months; P = 0.21; t test; 95% confidence interval, −8.43 to 3.86).

To clarify whether there is any correlation between the tumor burden at start of PRRT and the PFS, we evaluated the extent of the liver involvement by using the CT or MRI of the abdomen. Thirty-four patients with available baseline CT or MRI imaging were divided into 2 groups—low bulk (n = 13) with less than 50% of liver involvement and high bulk (n = 21) with higher than 50% of liver involvement. We found that the median PFS is longer in patients with low degree of the liver involvement after the third (median, 17.3 months) and the fourth (median, 21.4 months) treatment when compared with patients with extensive liver involvement after 3 cycles (median, 16.4 months) and 4 treatments (median, 15.3 months). As a result, the PFS increased (P = 0.3, Kruskal-Wallis test) after the administration of more cycles of treatment in patients with similar degree of disease burden in the liver (high or low). Moreover, among those who had received equal number of ^{177}Lu PRRT treatments, patients with the lower disease burden had longer PFS, although the findings again did not reach the statistical significance (Kruskal-Wallis test).

In a similar approach, we studied the correlation between the degree of liver involvement and the likelihood of response to therapy. We found that favorable response to treatment

TABLE 2. Comprehensive Data for All Treated Patients

Case Number	Primary Tumor Site	OctreoScan Grade	No. Involved Metastatic Sites	Age	Sex	No. Cycles	Cumulative Dose	FDG PET/CT, Pretherapy	Burden of Liver Involvement	PFS as of January 2013
JD-Lu-0001	Rectal	4	4	59	F	2	393.17	Positive	High	1.37
NR-Lu-0002	Pancreas	3	1	62	F	2	413.26	Positive	High	26.17*
CH-Lu-0003	Pancreas	3	3	63	F	4	794.28	Positive	High	11.93
JC-Lu-0004	Pancreas	3	4	59	M	2	387.99	None	High	NA
MR-Lu-0005	Small bowel	3	2	82	F	4	784.21	Positive	Low	6.87
JI-Lu-0006	Small bowel	4	2	68	F	2	402.26	Positive	Low	24.77*
AT-Lu-0007	Pancreas	4	2	43	F	2	388.05	Positive	None	22.93*
BL-Lu-008	Pancreas	4	3	61	M	3	585.46	Positive	High	NA
NW-Lu-009	Small bowel	2	3	68	F	4	780.12	Negative	None	22.2*
MB-Lu-0010	Small bowel	3	2	66	F	4	797.7	Positive	Low	21.73*
TG-Lu-0011	Small bowel	2	4	67	M	4	789.27	Negative	Low	21.27*
GV-Lu-0012	Unknown	3	3	66	F	3	591.25	Negative	Low	21.03*
PB-Lu-0013	Unknown	3	2	53	M	1	204.17	Positive	None	0.77
NH-Lu-0014	Pancreas	3	2	64	M	4	747.75	Negative	Low	20.07*
PB-Lu-0015	Pancreas	3	4	51	F	3	585.92	Positive	High	19.13*
RB-Lu-0016	Unknown	3	4	60	M	1	197.65	Positive	High	7.03
SH-Lu-0017	Small bowel	3	3	71	F	2	397.36	Negative	Low	18.93*
LS-Lu-0018	Rectal	3	4	55	M	4	777.64	Positive	High	18.7*
LT-Lu-0019	Pancreas	4	4	67	M	3	589.85	Positive	High	5.43
GF-Lu-0020	Pancreas	3	2	57	M	4	784.5	Positive	High	16.83
MG-Lu-0021	Unknown	2	1	87	F	4	727.91	Positive	Low	18*
BB-Lu-0022	Small bowel	3	2	48	M	4	778.06	Negative	High	17.53*
HW-Lu-0023	Small bowel	3	1	65	F	4	786.32	Positive	High	17.5*
CC-Lu-0024	Small bowel	2	2	59	F	1	200.34	Negative	Low	NA
LI-Lu-0025	Small bowel	4	3	47	F	1	194.09	Positive	Low	0.67
AM-Lu-0026	Unknown	3	2	73	M	1	190.18	None	High	0.03
CC-Lu-0027	Unknown	4	3	64	F	4	777.39	Positive	High	16.33*
AF-Lu-0028	Small bowel	3	2	76	F	2	403.32	Positive	Low	16.13*
JD-Lu-0029	Pancreas	3	2	62	M	4	774.94	Negative	High	16.1*
JJ-Lu-0030	Pancreas	3	2	64	M	3	591.66	Positive	High	14.93*
MF-Lu-0031	Pancreas	3	2	63	F	4	789.04	Positive	High	NA
FL-Lu-0032	Unknown	3	2	71	M	4	789.28	Negative	High	13.57*
CS-Lu-0033	Small bowel	3	1	71	F	4	749.37	Positive	Low	12.63*
YA-Lu-0034	Rectal	3	2	42	F	4	766.73	Positive	High	12.6*
WB-Lu-0035	Large bowel	3	2	82	F	2	398.67	Negative	High	11.9*
CR-Lu-0036	Pancreas	3	3	50	M	4	784.52	Positive	Low	9.37*
SD-Lu-0037	Pancreas	3	4	45	F	4	766.3	Positive	High	11.23*

*Refers to patients with no disease progression as of January 2013

NA refers to patients who lost their follow-up, and no information is available regarding the survival.

M, male; F, female.

(PR and MR) significantly ($P = 0.04$) correlates with the degree of the liver involvement, that is, patients with lower liver burden had significantly higher chance of responding to therapy.

We also studied 34 patients who had a pretreatment ^{18}F-FDG PET/CT tumor imaging. Twenty-four patients had positive ^{18}F-FDG scans (standardized uptake value [SUV], >2.5), and 10 patients had negative scans (SUV, ≤2.5). Interestingly, our study revealed that all deaths (n = 9) happened in patients with a positive pretreatment FDG PET/CT scan (SUV range, 3–10.86). Results showed a significant correlation between a positive ^{18}F-FDG PET/CT and patient death ($P = 0.03$, χ^2 test). In addition, we found out that the chance of response to PRRT (PR and MR) was higher, although not significantly, in patients who had a negative baseline ^{18}F-FDG PET/CT imaging ($P = 0.2$, χ^2 test). The result of this observation was again confirmed when patients were matched based on the number of treatments ($P = 0.5$ and $P = 0.1$ after 3 or 4 treatments) or the degree of liver involvement ($P = 0.1$).We also compared the calculated PFS in patients with positive baseline FDG PET/CT with patients who had a negative baseline FDG PET/CT. We found that the P value was very close ($P = 0.058$) but did not reach statistical significance according to our criteria (Fig. 2B). The median PFS in patients with positive FDG PET/CT was 14.9 months versus 18.9 months for patients with negative FDG PET/CT.

Next we evaluated the association between baseline KPS score and response to treatment among patients who had

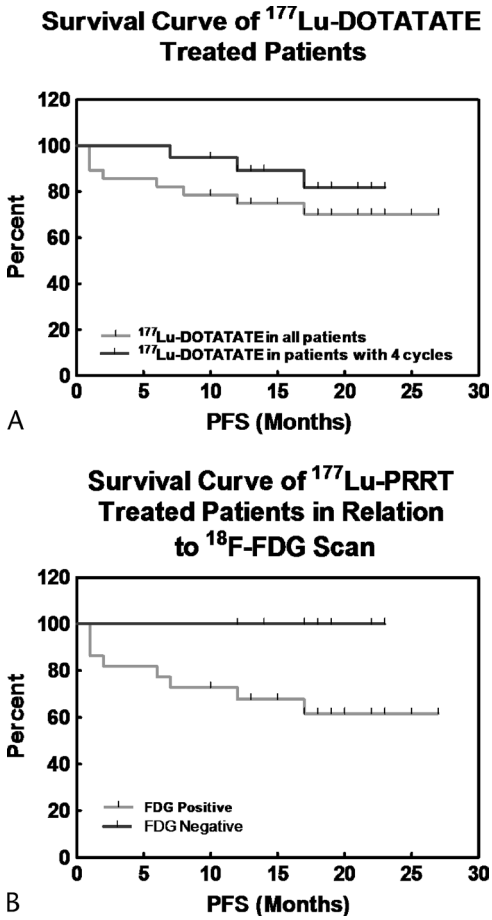

FIGURE 2. The survival cure for all patients and for those who received the 4 cycles of treatments (A). Survival graph in all patients with positive baseline FDG PET/CT comparing with all patients with negative baseline FDG PET/CT (B).

received more than 1 cycle of ^{177}Lu-DOTATATE therapy. Among 26 patients with available data, we initially noticed an impressive improvement in KPS score (patients whose KPS scores increased to more than 10 points) in 15 patients (58%) treated with more than 1 cycle of ^{177}Lu-DOTATATE. The rest of the patients (n = 11%) showed either equal or minimal increase of KPS score to less than 10 points. None of these study patients showed worsening of the KPS score.

In addition, we evaluated the influence of repeated cycles of ^{177}Lu-DOTATATE PRRT on the quality of life of patients. Patients who had died before completion of 4 cycles of treatment or those who had received only 1 cycle of therapy were excluded from this evaluation. Patients with available data (n = 27) completed the quality of life questionnaire (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30, version 3) as a self-assessment evaluation and scored themselves considering the various aspects of the well-being. Then, scores before the first therapy, after the last treatment, and at 3-month follow-up visits (if applicable) were compared. There was a significant improvement (P = 0.026, Wilcoxon test) of the overall quality of life in evaluable patients.

DISCUSSION

The radiolabeled somatostatin analogs have been introduced as a novel method of treatment for patients with somatostatin receptor–expressing NETs and provide favorable response to treatment (CR, PR, MR, and SD) in almost 80% of the patients with progressive disseminated disease, as shown in previous studies.[11,13–15,17] High expression of the somatostatin receptors allows for tumor visualization and treatment using the radiolabeled somatostatin analogs.

Preliminary data from previous studies have demonstrated the safety and effectiveness of repeated doses of 150 to 200 mCi (5.55–7.4 GBq) ^{177}Lu-DOTATATE administered every 6 to 9 weeks for a total of 4 cycles.[21–25] For the first time in the United States, in the current study, we demonstrated the efficacy and safety of ^{177}Lu-DOTATATE therapy in patients with progressive NETs, which has been used before as a promising method of treatment of disseminated NETs in other countries.[21–32]

In our evaluation, partial and minimal tumor response was noted in 28% and 3% of patients, respectively, whereas SD was the predominant outcome of treatment (41%), comparable to the findings of previous studies.[17,24,31] Progressive disease was seen in 28% of patients. All patients had previously exhausted different methods of treatment, including surgery, chemotherapy, chemoembolization, radiochemoembolization, somatostatin analogs, and external beam radiation therapy, and had PD before their enrollment to this study by RECIST. Therefore, the fact that more than 70% of patients showed either PR/MR or SD is extremely encouraging and suggests the promising role of ^{177}Lu-DOTATATE PRRT in the management of patients with progressive and/or inoperable NETs.

Mild to moderate nausea and vomiting were the leading causes of discomfort during the ^{177}Lu-DOTATATE infusion. We believe it happened primarily as a result of coadministration of the hyperosmolar solution of amino acids, and these symptoms subsided shortly after completion of the therapy.

The adverse events of treatment with ^{177}Lu-DOTATATE were not serious and mostly transient. Moderate bone marrow toxicity (grade II and III) was the most common adverse effect of the therapy, reported in about 22% of patients, most of them had a history of previous chemotherapy averaging 31.76 months before their enrollment in the PRRT program. Significant improvement in tumor-specific hormones or biomarkers was reported in 32% of patients.

As of January 2013, among the total of 37 patients, 19 received all 4 cycles of therapy. Five patients quit the study voluntarily. A total of 9 deaths were noted in this study, likely as a consequence of the high burden of underlying disease as most of them had either extensive involvement of the liver, multiple lymph nodes and bones, or the combination of multiple organs. We believe deaths were not treatment-associated adverse events because there was no definite evidence of severe hematologic, renal, or hepatic toxicity, and no other adverse effect was observed after the treatment.

We noted a significant correlation between positive baseline ^{18}F-FDG PET/CT and the occurrence of deaths. Hence, the ^{18}F-FDG PET/CT tumor imaging could be used as a prognostic tool in patients with NETs, and a positive pretreatment scan may correlate with a less favorable outcome. Comparison of survival between patients with baseline positive and negative FDG PET scan revealed that although the P value did not reach the statistical significance (P = 0.058), there is a better survival among patients with negative baseline FDG PET/CT scan as compared with patients with positive FDG PET/CT scan. A more aggressive treatment regimen including retreatment, combination PRRT, chemotherapy, or using the radiosensitizing agents may be needed in these patients.

Evaluation of response to treatment (MR and PR) among patients with different degrees of tumor burden revealed a

statistically significant correlation between lower disease burden in the liver and the chance of favorable treatment response including objective tumor shrinkage (PR and MR; modified RECIST) after ^{177}Lu PRRT. In accordance with results of the previous study performed by Kwekkeboom et al,[33] our finding clearly confirms the danger of the "watch and wait approach" when dealing with the NETs at earlier stages of disease because more favorable response is more likely to happen in patients with low disease burden. Kwekkeboom et al[33] also reported that early detection and treatment of NETs might be critical because NETs can dedifferentiate over time, rendering somatostatin receptor–based PRRT ineffective during the later stages of the disease.

In addition to objective responses, the results of subjective self-assessment evaluations revealed that repeated cycles of ^{177}Lu-DOTATATE provide a significant improvement in the quality of life of all evaluable patients.[21,22] Similarly, there was an impressive improvement of KPS score after treatment with ^{177}Lu-DOTATATE. We also realized that regardless of the treatment outcome, patients' quality of life including stamina for daily activities and diarrhea improved significantly.

One of the shortcomings of our study was the lack of randomization to compare the efficacy of different available treatment modalities in NET.[25] A randomized clinical trial has just been started in the United States and in Europe.

A multidisciplinary approach by a group of expert surgeons, interventional radiologist, medical oncologist, nuclear oncologists, and dietitians is needed to efficiently deal with patients with NETs.

There were some other limitations to this study, including limited number of enrolled patients who completed all 4 cycles of treatment and short duration of follow-up as of January of 2013. This trial is still recruiting patients and following up previously treated patients, and complete results will be reported in the future.

Future attempts to improve the effectiveness of PRRT should include tandem treatments by using the different radiolabeled somatostatin analogs or treatment with combination of radiolabeled agents and also intrahepatic administration of the radiolabeled agents in patients with predominantly liver metastases. In addition, radiosensitizers have been introduced as useful agents for increasing the chance of tumor responsiveness to PRRT. Addition of capecitabine or fluorouracil to PRRT regimens has been able to improve the tumor response rate and/or disease stabilization without imposing any additional early or late toxicity.[23,24]

CONCLUSIONS

In this study, for the first time in the United States, we studied the efficacy and safety of repeated cycles of ^{177}Lu-DOTATATE therapy in patient with progressive disseminated NETs. Treatment with multiple cycles of ^{177}Lu-DOTATATE PRRT is safe and seems to be promising for patients with metastatic progressive NETs and results in tumor control of the disease in most patients, while the systemic toxicities are manageable. The favorable response is mostly seen in patients with lower tumor burden in the liver and also those who completed the 4 treatment cycles. Therefore, early treatment may result in a better outcome. A positive pretreatment ^{18}F-FDG PET/CT tumor imaging is associated with a more aggressive tumor and may be an important predictor for an unfavorable outcome. ^{177}Lu-DOTATATE therapy also significantly improves the quality of life of the patients. A multidisciplinary approach is preferred.

The nonrandomized nature of the study, the limited number of enrolled patients, and the length of follow-up after treatment were the primary limitations of this report; hence, a randomized clinical trial with a long-term follow-up will be required to confirm the benefits of this treatment.[33,34]

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