

Safety and Efficacy of Radionuclide Therapy with High-Activity In-111 Pentetreotide in Patients with Progressive Neuroendocrine Tumors

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ABSTRACT

The intent of this study was to evaluate the safety and efficacy of high-activity ¹¹¹In-pentetreotide in patients with neuroendocrine tumors. Thirty-two patients with pentetreotide-avid neuroendocrine tumors received therapy from August 2005 to November 2006. Fourteen (14) patients received 1 treatment and 18 patients received 2 treatments. Patients were followed an average of 12.73 months (range 1.2–24.5). Seventeen (17) patients (53%) had grade I or II hematologic toxicities, and 1 patient had grade III thrombocytopenia. One patient had grade II liver toxicity, which appeared 4 weeks after therapy and resolved on week 5. No patient had renal toxicity. Of the patients who completed 2 treatment cycles, 2 of 18 patients had partial disease regression, and 16 of 18 patients with previously progressive disseminated neuroendocrine disease achieved stable disease by imaging criteria. A decrease in serum tumor markers was observed in 14 of 18 patients given 2 therapies. A clinical response was achieved in 84% of the patients. Upon interim analysis, median survival was approximately 13 months (range 1.2–24.5). These results show that high-activity ¹¹¹In-pentetreotide therapy is effective in patients with progressive disseminated neuroendocrine tumors.

Key words: neuroendocrine tumors, radionuclide therapy, pentetreotide

INTRODUCTION

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms that arise from Kulchinsky

cells that populate the thymus, bronchus, and gut. Regardless of their primary site, NETs share similar histologic, metabolic, and ultrastructural features.¹ Many NETs are found during surgery for other diagnoses, such as appendicitis, pancreatitis, or small bowel obstruction. The average time from symptom onset to diagnosis is more than 9 years.² The indolent nature of NETs lead most patients to seek treatment for their tumor when it has already metastasized, limiting their overall sur-

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vival.³ Therapeutic options for patients with advanced disease are often limited. Single-agent or combination chemotherapy regimens for management of “typical” slow-growing NETs have not been efficacious. Furthermore, external-beam radiation therapy has not demonstrated significant efficacy in establishing local control in NETs. Interferon (IFN) therapy has also been used in protocol-based management of carcinoid tumors with reported biochemical and tumor response rates of 40% and 12%, respectively.^{4,5} However, IFN therapy is associated with numerous toxicities including fever, anorexia, weight loss, fatigue, and myelosuppression. Due to the high incidence of toxicity and the low tumor response rate, the routine use of IFN for NETs is rarely recommended in the United States.

Scintigraphy with 6 mCi of Indium-111 (¹¹¹In)-labeled pentetreotide (DTPA-D-Phe1)-octreotide (OctreoScan, Mallinckrodt Medical, St. Louis, MO) is frequently used to localize previously undetected primary or metastatic NETs. At higher activities, ¹¹¹In-pentetreotide has been evaluated as a therapeutic agent. ¹¹¹In emits Auger and conversion electrons that can induce DNA strand breakage making it attractive for *in situ* radiotherapy. The first clinical trial of ¹¹¹In-pentetreotide for treatment of NETs was performed by Krenning et al. in the Netherlands in 1994. Preliminary data from this study demonstrated the safety of repeated treatments with 90–180 mCi of ¹¹¹In-pentetreotide administered every 3 weeks for 10 cycles. In this initial study, response correlated with receptor expression.⁶ Subsequent studies conducted by Krenning et al. confirmed these findings.⁷ Likewise, other researchers have reported significant responses to high-activity ¹¹¹In-pentetreotide therapy (180–500 mCi/treatment) with limited toxicity.^{6–14} These studies vary in patient selection, dosing, total activity administered, and reported outcomes, but all show significant benefits and safety of ¹¹¹In-pentetreotide therapy. Generally, studies using higher activity of ¹¹¹In (180–500 mCi) report a greater impact on disease stabilization than those using lower activity while still not reaching the maximum-tolerated dose (MTD). Although not fully comprehensive, the toxicity profile of ¹¹¹In-pentetreotide is encouraging as the MTD was not achieved in any previously published studies, and it is feasible that larger quantities of radioactivity can be administered safely. Therefore, the aim of this study was to evaluate safety and efficacy of 2 cycles of high-activity ¹¹¹In-pentetreotide at therapeutic doses of

500 mCi per cycle. Here, we report our preliminary analysis of high-activity ¹¹¹In-pentetreotide therapy in patients diagnosed with neuroendocrine tumors.

MATERIALS AND METHODS

Patient Selection and Enrollment

Patients with late-stage, progressive NETs were enrolled in a preliminary trial to evaluate the safety of high-activity ¹¹¹In-pentetreotide therapy. The patients had histologically confirmed malignant NETs with or without multiple liver metastases. Patients were qualified to receive therapy by somatostatin receptor scintigraphy for tumor localization. The tumor marker chromogranin A (CgA) or serum hormones such as serotonin, pancreastatin, gastrin, normetanephrine, alkaline phosphatase (ALP), or 24-hour urine 5-hydroxyindole acetic acid were used to monitor response to therapy. Patients who had a positive octreotide scan with an uptake grading equal to or exceeding 4 in a 5-point graded scale were eligible for therapy (grade 1 = less than background, grade 2 = background, grade 3 = more than background but less than liver, grade 4 = equal to liver, grade 5 = more than liver). All patients were in a progressive state, had Karnofsky performance status of >60, and had received and failed standard therapy before entering the study.

This study was performed under approval from the internal review board at St. Luke's Episcopal Hospital and under an Investigational New Drug application from the U.S. Food and Drug Administration. All patients understood the experimental nature of this procedure and gave informed consent prior to treatment.

Preparation of High-Dose ¹¹¹In Pentetreotide

Indium-111 chloride (¹¹¹InCl₃) was purchased from MDS Nordion (Ottawa, ON, Canada), and purified prior to radiolabeling by IsoTex Diagnostics, Inc. (Friendswood, TX). The radiolabeling procedure was adapted and modified from the procedure outlined in the package insert and performed by South Texas Nuclear Pharmacy (Houston, TX). Through calculations based on molar ratios of the somatostatin analog contained in OctreoScan commercial kits (as used in the diagnostic application), it was determined that a suitable labeling ratio with ¹¹¹InCl₃ was ~200

mCi per vial of peptide (containing 10 μg of pentetrotide). As a result, 3 commercial vials of pentetrotide were combined into a single vial prior to addition of the isotope. The final tagging was performed in the reaction vial provided by the manufacturer. The therapeutic dose of ^{111}In -pentetrotide was obtained by adding 500 mCi of ultrapure $^{111}\text{InCl}_3$ to the peptide-containing vial under aseptic conditions. Radio-high-performance liquid chromatography (HPLC) was used to assess quality control on the first 3 syntheses. Thereafter, C-18 Sep-Pak cartridges were used for purification of the final product and radiochemical purity of $>98\%$ was routinely obtained. Additionally, HPLC analysis showed that the 500 mCi dose did not adversely affect radiochemical purity or the integrity of the peptide.

Dosimetry and Biodistribution of ^{111}In -Pentetrotide

Prior to each therapy administration, ^{111}In -pentetrotide scintigraphy was performed. Patients were injected intravenously with 5–6 mCi of ^{111}In -pentetrotide (Mallinckrodt Medical, St. Louis, MO). Anterior–posterior total body sweep images were collected and a single photon emission computed tomography study was carried “out over the regions of interest (ROIs) using a dual detector gamma camera equipped with a medium-energy general-purpose collimator (Siemens E-cam; Siemens, Malvern, PA). For each patient, opposed whole-body images were captured within 30 minutes after injection (before voiding) and at 4, 24, and 48 hours postinjection. ROIs were drawn around the liver, spleen, kidneys, bladder, a constancy source, the entire frame, tumors, and the whole body (remainder). Initial organ and tumor uptakes were determined and expressed as a percentage of the total injected dose. Subsequent time period data for each ROI was then created and fitted to a monoexponential uptake/clearance curve. After curve fitting and integration, the cumulative activity and mean residence time (t) was calculated for each ROI. The radiation absorbed dose was calculated using standard Medical Internal Radiation Dose schema (<http://www.nndc.bnl.gov/mird/>) producing patient- and organ-specific conversion factors for determining absorbed dose (mGy/MBq or rad/mCi).¹⁵ Residence times were consistent within individual patients as well as for normal organ uptake across patients.

Treatment Protocol

The treatment protocol called for patients to receive 2 cycles of high-activity ^{111}In -pentetrotide therapy given 10–12 weeks apart. A Functional Living index questionnaire was completed by patients prior to each cycle of therapy.¹⁶ Patients were injected with ^{111}In -pentetrotide (average dose 489.2 mCi; range 473.5–511.6 mCi, standard deviation [SD] 11.0) as an intravenous infusion in physiologic saline using a specially designed IV pole to decrease radiation exposure to the personnel. The infusion lasted 3–5 hours and was performed in an outpatient setting with strict radiation protection instructions. No amino acid infusion was administered before or after the therapy. This infusion protocol is based on that of Louisiana State University Health Science Center (LSUHSC; New Orleans, LA) (U.S. Patent Numbers 6,630,123 and 6,180,082) and used with their permission. Patients were evaluated for hematologic, renal, and hepatic toxicities using NCI common toxicities criteria on weeks 4, 5, 6, and 7 after treatment. Analysis of tumor marker (CgA) or hormones levels and imaging studies for evaluation of tumor response to therapy were performed every 3 months thereafter. Imaging studies included OctreoScan and triple-phase computed tomography of the chest, abdomen, and pelvis. Response Evaluation Criteria in Solid Tumors (RECIST) criteria were used to evaluate radiologic response to therapy.¹⁷ The second cycle of therapy was performed 10–12 weeks following the first therapy. Interim analysis of response was performed as of August 2007.

RESULTS

Patient Demographics

Thirty-two (32) patients including 21 men and 11 women with an average age of 56 (range 16–83) years received treatment with high-activity ^{111}In -pentetrotide from August 2005–November 2006 (Table 1). Among the patients were 25 Caucasians (78%), 2 Blacks (6%), 4 Hispanics (12.5%), and 1 other (3%). All patients had progressive NETs (21 carcinoid, 7 islet cell carcinoma of the pancreas, 1 pituitary adenoma, 1 glucagonoma, and 1 pheochromocytoma) and all had failed first-line therapy (23 chemotherapy, 12 radiotherapy, 28 surgery, 23 Sandostatin, Novartis, East Hanover, NJ). As of May 2007, 14 patients received a single treatment of 500

Table 1. Patient Demographics

<i>Patient no.</i>	<i>Gender</i>	<i>Age (years)</i>	<i>Primary tumor</i>	<i>Previous therapy</i>	<i>Number of treatments</i>
1	M	16	Pituitary adenoma	C, R, S	1
2	M	47	Carcinoid	C, Sn	1
3	M	54	Carcinoid	S, Sn	1
4	M	24	Medullary thyroid cancer	C, Sn	1
5	M	62	Carcinoid	C, S, Sn	1
6	M	45	Carcinoid	C, R, S	1
7	M	37	Islet cell cancer of the pancreas	C, R, S, Sn	1
8	M	74	Carcinoid	R, S, Sn	1
9	M	70	Carcinoid	S, Sn	1
10	F	38	Carcinoid	C, R, S, Sn	1
11	F	64	Carcinoid	C, S	1
12	F	55	Islet cell cancer of the pancreas	C, S, Sn	1
13	F	63	Islet cell cancer of the pancreas	C, Sn	1
14	F	52	Carcinoid	C, R, S, Sn	1
15	F	68	Carcinoid	S	1
16	M	60	Carcinoid	I, S, Sn	2
17	M	62	Islet cell cancer of the pancreas	C, S, Sn	2
18	M	59	Carcinoid	C, R, S, Sn	2
19	M	41	Carcinoid	C, R, S	2
20	M	65	Carcinoid	C, S, Sn	2
21	M	51	Pheochromocytoma	C, R, S, Sn	2
22	M	55	Carcinoid	C, R, S	2
23	M	63	Carcinoid	S, Sn	2
24	M	62	Glucogonoma	C, S, Sn	2
25	M	57	Carcinoid	C, S, Sn	2
26	M	51	Carcinoid	C, S, Sn	2
27	M	64	Carcinoid	R, S, Sn	2
28	F	68	Carcinoid	R, S, Sn	2
29	F	83	Carcinoid	S	2
30	F	49	Islet cell cancer of the pancreas	C, S	2
31	F	61	Islet cell cancer of the pancreas	C, S, Sn	2
32	F	73	Islet cell cancer of the pancreas	C, Sn	2

C, chemotherapy; S, surgery; R, radiation; Sn, Sandostatin.

mCi ^{111}In -pentetreotide (average dose 489.2 mCi/patient, SD 10.1, range 473.5–511.6 mCi), and 18 patients received 2 treatments with an average cumulative activity of 982.8 mCi/patient (SD 16.4, range 955–1006.9 mCi). Of the patients who received only 1 cycle of therapy, 4 were deceased before they could receive the second treatment, 3 were not yet eligible for the second therapy at the time of interim analysis, and 7 patients had withdrawn from the study prior to the second treatment. All 18 patients who received 2 therapies were available for evaluation at 3 months following the second therapy. Patients were followed for an average of 12.73

months after the first cycle of treatment. (range 1.2–24.5 months).

Toxicity

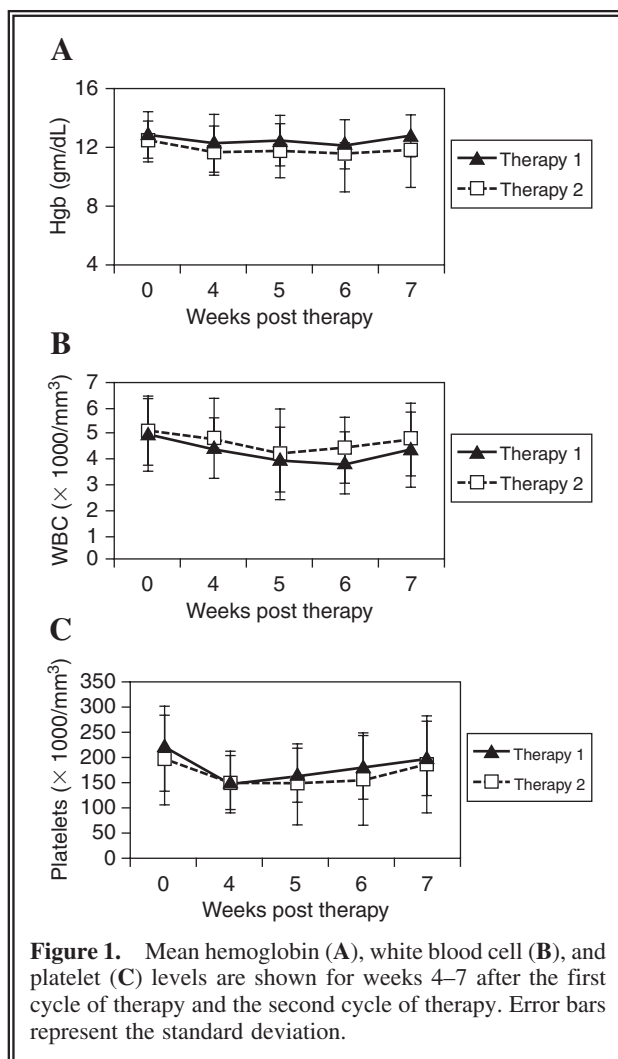
Nausea (46%), vomiting (15%), abdominal pain (10%), itching (3%), and diarrhea (6%) were noted immediately after therapy and lasted for an average of 3 days (range 1–7 days). Hematologic and liver toxicities were minimal in patients who received 1 cycle of treatment (Table 2). Four (4) of 12 patients (28%) had grade I or II hematologic toxicity and 1 patient had grade III thrombocytopenia, which did not require supportive

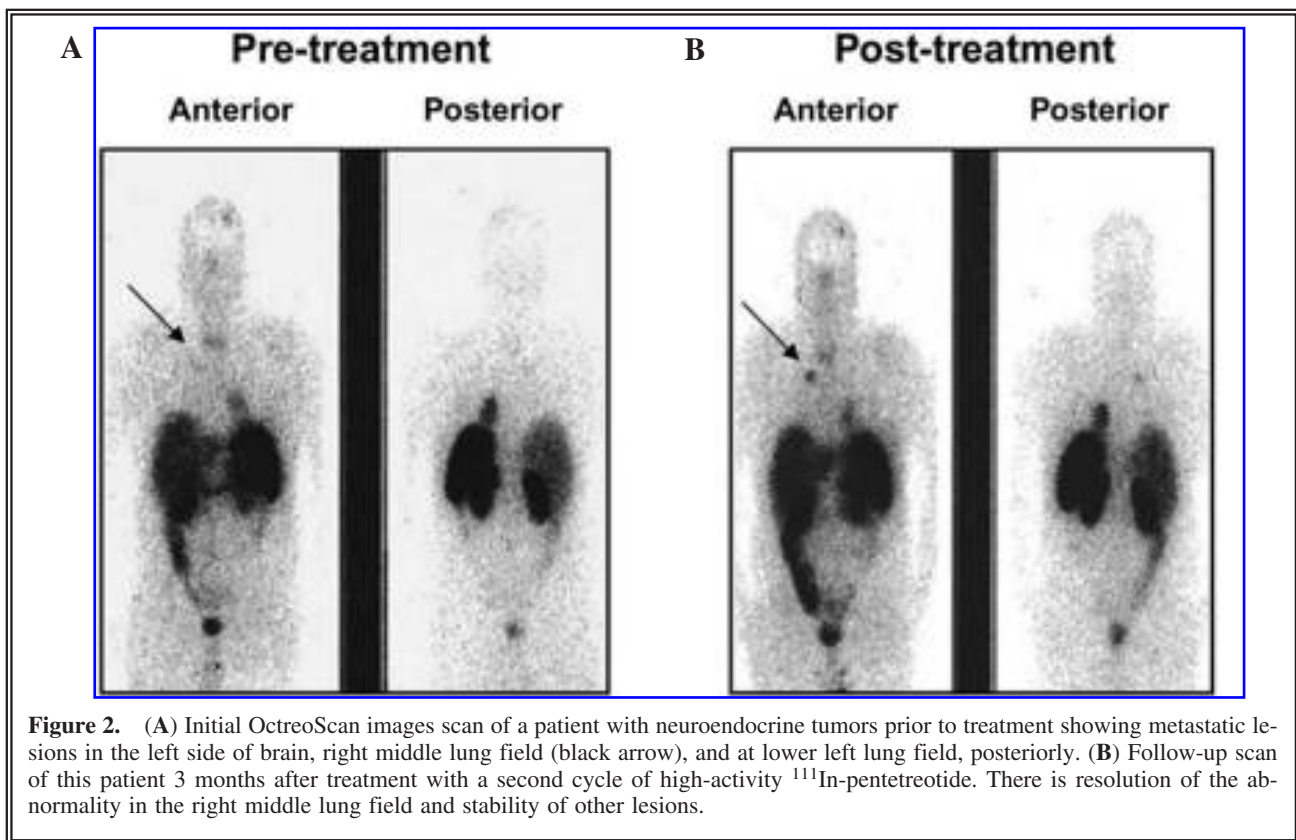
Table 2. Toxicity after 1 or 2 Cycles of High-Dose ¹¹¹In-Pentetreotide Therapy

	One treatment			Two treatments		
	Toxicity grade I	Toxicity grade II	Toxicity grade III	Toxicity grade I	Toxicity grade II	Toxicity grade III
Hematologic						
WBC	2 (14%)	2 (14%)	0 (0%)	7 (38%)	3 (22%)	0 (0%)
RBC	2 (14%)	1 (8%)	0 (0%)	6 (33%)	3 (22%)	0 (0%)
Platelets	0 (0%)	0 (0%)	1 (8%)	7 (38%)	1 (5%)	0 (0%)
Renal						
Creatinine	0 (0%)	0 (0%)	0 (0%)	5 (6%)	0 (0%)	0 (0%)
Liver						
AST	1 (8%)	1 (8%)	0 (0%)	8 (44%)	0 (0%)	0 (0%)
ALT	2 (14%)	1 (8%)	0 (0%)	6 (33%)	0 (0%)	0 (0%)

WBC, white blood cell; RBC, red blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

therapy. Three (3) of 12 patients (22%) had grade I liver toxicity and 1 of 12 had grade II liver toxicity, which appeared 4 weeks after therapy and resolved on week 5. Grade I and II hematologic toxicities were observed in 10 of 18 patients (55%) who received 2 therapy cycles, and there were no cases of grade III or IV hematologic toxicity. The mean duration of hematologic toxicities was 3 weeks (range 1–6 weeks) with the nadir for hemoglobin, white blood cells, and platelet levels occurring between weeks 5–6 post-therapy (Fig. 1A, B, and C). One patient developed nosebleeds 4 weeks after treatment and was treated symptomatically with no need for blood or platelet transfusion. One patient experienced intermittent gastrointestinal bleeding 2 months after the second cycle of therapy secondary to tumor involvement of the bowel. This resulted in low red cell and hemoglobin counts, and this patient received a blood transfusion. Eight (8) of 18 patients (44%) had grade I liver toxicity. There were no cases of grade II liver toxicity in patients receiving 2 therapy cycles. Patients with neuroendocrine liver metastases who had abnormal liver enzymes and ALP levels prior to therapy did not show any significant worsening as a result of the therapy. No significant changes in enzyme levels were found using Wilcoxon rank-sum analysis of pretreatment and post-treatment serum enzyme levels (ALP $p = 0.1221$, aspartate aminotransferase [AST] $p = 0.3271$, alanine aminotransferase [ALT] $p = 0.1676$). Patients were followed with blood urea nitrogen, creatinine, 24-hour urine creatinine clearance, and ef-





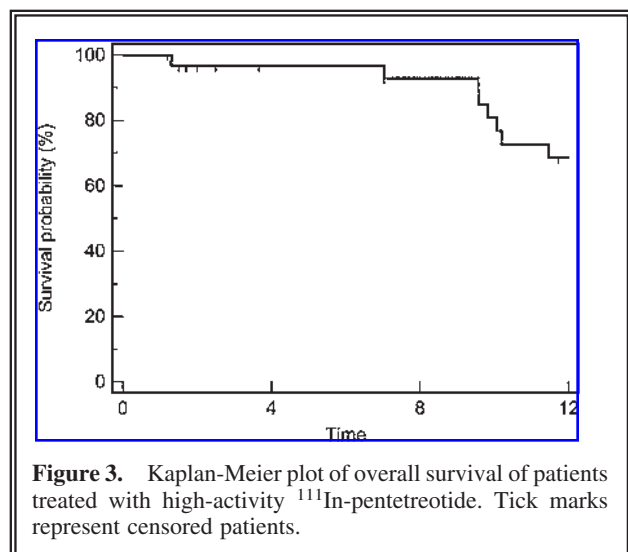
fective glomerular filtration rate. No significant short- or long-term renal toxicity was observed up to 24 months after initial therapy and 21 months after the second therapy.

Efficacy

Response to therapy was determined in the 18 patients who completed 2 cycles of therapy. Radiologic response was determined 3 months after the last therapy using RECIST criteria. Sixteen (16) out of 18 patients (88%) achieved stable disease by imaging criteria. A partial radiologic response was observed in 2 patients (11%). An example of a partial disease regression is shown in Figure 2.

Additionally, biochemical and clinical responses were determined. A significant decrease in the tumor marker CgA or hormone levels from pretreatment observations was observed in 14 of 18 patients (77%). A complete biochemical response (>50% reduction from pretreatment levels in CgA or at least 1 hormone) was observed in 8 patients (44%). A partial biochemical response in CgA or at least 1 hormonal marker (<50% but >25% decline in levels compared to

pretreatment levels) was achieved in 6 patients (33%) treated with 2 cycles of therapy. Although biochemical responses were observed, these responses were not sustained in 7 patients (39%). In these patients, there was a return to pretreatment levels or above a median of 4.8 months af-



ter the first treatment cycle (range 1.6–14.3 months, SD 4.63 months). A significant clinical response was reported in 83% of patients who received 2 cycles of therapy (15 of 18 patients).

The median survival at interim analysis was 13.3 months (95% confidence interval, range 1.2–24.5 months, SD 5.92 months). Kaplan-Meier survival analysis is shown in Figure 3. Eight (8) patients (25%) died during the course of this study. Four (4) patients died after receiving 1 cycle of therapy and 4 patients died after the second cycle. Six (6) patients died due to massive tumor burden. Two (2) patients died of hepatic failure secondary to extensive tumor involvement in the liver and abdomen. All patients had stage IV neuroendocrine disease.

DISCUSSION

Our findings are consistent with other published clinical trials of ^{111}In -pentetreotide therapy, which also demonstrated disease stabilization or partial disease regressions with cumulative activity up to 500 mCi.^{9,12–14,18,19} These studies have also reported decreases in hormone levels ranging from 0%–40% of patients and improvement in clinical symptoms in up to 60% of patients. Our study reported significantly higher hormonal and clinical responses of 77% and 83% of patients, respectively, which may be due to the higher cumulative activity used.

The long-term efficacy of high-activity ^{111}In -pentetreotide therapy is yet to be determined. A 2003 study of 16 patients given repeated doses of ^{111}In -pentetreotide (81–134 mCi), showed that while up to 70% had some short-term benefit, only 31% of patients had sustained benefit 18 months after treatment. Based upon our preliminary analysis of the current trial, radiologic responses have been observed up to 17 months after treatment. However, hormonal responses were not sustained in all patients, with hormone levels rising to pretreatment levels as soon as 7 weeks after the first cycle of therapy. Further study is needed to determine the time to disease progression for all patients enrolled in the current trial.

Treatment benefits are believed to be due to the radiation effect of Auger electron and electron conversion emitted from ^{111}In . The path length of Auger electron and electron conversion particles are in the range of 0.02–10 μm and 200–500 μm , respectively.⁹ These are relatively short path lengths when compared with other β -

emitting radioisotopes such as Y-90 (5–12 mm), Lu-177 (0.8–1.5 mm), or I-131 (0.8–2.0 mm). Due to its shorter path length, ^{111}In -pentetreotide is probably more effective in smaller tumors due to these characteristics. Larger tumors have ischemic areas in the center, and lack of blood flow prevents the radiotracer from reaching these regions. Central necrosis or ischemic areas are seen more commonly in tumors larger than 3 cm in diameter. Radioisotopes with longer path length can reach the ischemic areas of the large tumors by “cross fire” effect and therefore might be more suitable for larger tumors. On the other hand, the long path length can contribute to more collateral damage of the normal tissues in the vicinity of the tumor and more side effects in smaller tumors. Initial phase I and phase II clinical trials [^{90}Y -Y1,4,7,10-tetraazacyclododecane-N,N',N'',Noct-tetraacetic acid (DOTA)⁰Try³] octreotide (90Y-DOTATOC) with a dose escalating scheme of 4 treatment sessions up to a cumulative dose of 6 GBq (160 mCi)/m² showed overall response rates of up to 24%.²⁰ A subsequent study using 7.4 GBq (200 mCi)/m² administered in 2 sessions reported complete or partial radiologic responses in 33% of patients.²¹ Despite differences in clinical protocols, responses (either complete or partial) are reported in 10%–30% of patients in most of the studies with ^{90}Y -DOTATOC. These ranges are significantly higher than those reported with ^{111}In -pentetreotide therapy. However, significant hematologic toxicity has been reported with this treatment regimen. In a study by Chinol et al., reversible grade 3 hematologic toxicity was found in 43% of patients injected with 5.2 GBq (140 mCi).²² Furthermore, significant renal toxicity has been reported with this treatment regimen in patients who were given no amino acid renal protection prior to treatment, with one study reporting renal insufficiency in 4 of 29 patients (13%).^{20–23} Recently, clinical trials using ^{177}Lu -DOTA-octreotate have shown similar results to ^{90}Y -DOTATOC. Although limited renal toxicity has been observed with this radionuclide, all published treatment regimens report coinfusion of amino acids for kidney protection. Coinfusion of lysine and arginine are routinely used in all patients receiving ^{90}Y -DOTATOC and ^{177}Lu -DOTATATE therapies and is associated with reduced late renal toxicity in multiple clinical studies.^{18,24–32} It is of note that limited or no renal toxicity was observed in this and other published trials of ^{111}In -pentetreotide therapy without coinfusion of amino acids.

CONCLUSIONS

These results suggest that multiple 500 mCi treatments of ¹¹¹In-pentetreotide therapy are safe and effective in patients with progressive disseminated neuroendocrine tumors. There was no evidence of significant treatment-associated toxicity following an average cumulative dose of 982.8 mCi of ¹¹¹In-pentetreotide therapy for the average follow-up time of 8.69 months post-treatment. Therefore, the maximum tolerated dose has not been reached. The safety profile of this regimen suggests the opportunity for nonmyeloablative dose escalation.

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