

⁹⁰Y-Edotreotide for Metastatic Carcinoid Refractory to Octreotide

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ABSTRACT

Purpose

Metastatic carcinoid is an incurable malignancy whose symptoms, such as diarrhea and flushing, can be debilitating and occasionally life-threatening. Although symptom relief is available with octreotide, the disease eventually becomes refractory to octreotide, leaving no proven treatment options. The goal of this study was to evaluate the clinical effect of using ⁹⁰Y-edotreotide to treat symptomatic patients with carcinoid tumors.

Patients and Methods

Patients enrolled had metastatic carcinoid, at least one sign/symptom refractory to octreotide, and at least one measurable lesion. Study treatment consisted of three cycles of 4.4 GBq (120 mCi) ⁹⁰Y-edotreotide each, once every 6 weeks.

Results

Ninety patients were enrolled in the study. Using Southwest Oncology Group tumor response criteria, 67 (74.4%) of 90 patients (95% CI, 65.4% to 83.4%) were objectively stable or responded. A statistically significant linear trend toward improvement was demonstrated across all 12 symptoms assessed. Median progression-free survival was significantly greater ($P = .03$) for the 38 patients who had durable diarrhea improvement than the 18 patients who did not (18.2 v 7.9 months, respectively). Adverse events (AEs) were reported in 96.7% (87 of 90) of patients. These AEs consisted primarily of reversible GI events (76 of 90), which could be caused in part by concomitant administration of amino acid solution given to reduce radiation exposure to the kidneys. There was one case each of grade 3 oliguria and grade 4 renal failure, each lasting 6 days.

Conclusion

⁹⁰Y-edotreotide treatment improved symptoms associated with malignant carcinoid among subjects with no treatment alternatives. Treatment was well-tolerated and had an acceptable expected AE profile.

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INTRODUCTION

Carcinoid tumors are neuroendocrine tumors of the GI tract and bronchus. Recent estimates of GI carcinoid incidence in the United States range from 4.6 per million in 1973 to 18.1 per million in 1997 and suggest that incidence may be increasing.¹⁻³ Because many malignant carcinoids are indolent, their prevalence is approximately 76,500 total patient cases.⁴ Patients with advanced metastatic disease are at increased risk of severe symptoms due largely to secretion of large amounts of bioactive amines and peptides.

Many patients are not diagnosed until liver metastases have developed, at which time fewer than 30% survive 5 years.² In such cases, surgery may

offer palliative relief, but it is very rarely curative. Very low response rates are typically seen with chemotherapy. Temporary stabilization of disease and improvement of symptoms has been found with somatostatin analogs.^{2,5-11} Octreotide (Sandostatin and Sandostatin LAR; Novartis, Basel, Switzerland) and lanreotide (Somatuline; Ipsen Pharma Biotech, Signes, France) have been shown to control carcinoid symptoms such as diarrhea and flushing.^{12,13} However, median duration of symptom relief is about 13 months,¹² and there is no known effect on survival.

⁹⁰Y-DOTA-tyr³-octreotide consists of a somatostatin peptide analog (Tyr³-octreotide) coupled with a complexing dodecane tetraacetic acid (DOTA) moiety. It is known commonly as ⁹⁰Y-SMT487,

⁹⁰Y-DOTATOC, and ⁹⁰Y-edotreotide. This compound contains a tightly bound yttrium-90 (⁹⁰Y) atom, which is a high-energy beta emitter, while retaining its high affinity binding properties to both somatostatin receptor subtypes 2 and 3.¹⁴ Preliminary evidence suggests that ⁹⁰Y-edotreotide can selectively deliver a tumoricidal dose of radiation to somatostatin receptor–positive tumors.¹⁵

Phase I clinical trial results confirmed the safety and tolerability of the dosage and treatment schedule in this study (unpublished manuscript, Novartis). Furthermore, these data as well as phase II data¹⁶ demonstrated that administration of ⁹⁰Y-edotreotide delivered radiation doses to tumors resulting in significant and prolonged neuroendocrine tumor shrinkage. The goal of this study was to further evaluate the efficacy of this radiotherapeutic in symptomatic patients with progressive metastatic disease and carcinoid syndrome.

PATIENTS AND METHODS

Study Population

This was a single-arm multicenter phase II study of adult subjects with biopsy-proven malignant carcinoid tumors representing the first international trial in patients with malignant carcinoid tumors to our knowledge. Ninety patients were enrolled at 18 sites in five European countries and the United States. Due to the nature of this trial, sample size was based on available patients and not statistical considerations. The ethics committees or institutional review boards at the participating centers approved the protocol, and all patients freely provided written informed consent before commencing eligibility screening. Eligibility criteria were as follows: presence of one or more symptoms or signs related to their disease which was uncontrolled despite optimal somatostatin analog therapy; metastatic disease with somatostatin receptor–positive tumors identified by grade 3 to 4 uptake of ¹¹¹In-pentetreotide (OctreoScan; Mallinckrodt Imaging, Hazelwood, MO), defined as activity greater than liver on either planar or single-photon emission computed tomography images¹⁷; at least one measurable site of disease that demonstrated progression based on the response criteria of the Southwest Oncology Group (SWOG)¹⁸; a life expectancy of longer than 6 months and a Karnofsky performance status (KPS) of ≥ 60 ; and prior long-acting somatostatin analog therapy was discontinued ≥ 60 days before treatment but patients were allowed a short-acting somatostatin analog as long as it was discontinued 12 hours prior and 8 to 12 hours after study drug administration.

To ensure only patients with nonimpaired renal function were included in the study, patients were required to have either serum creatinine ≤ 150 μ mol/L or lower than 1.7 mg/dL; or a measured creatinine clearance of ≥ 60 mL/min if the serum creatinine was higher than 150 μ mol/L or 1.7 mg/dL. Exclusions included: history of congestive heart failure, unless the left ventricular ejection fraction was $\geq 40\%$; known brain metastases, unless treated and stabilized for at least 6 months before study inclusion; previous high-dose ¹¹¹In-pentetreotide or other radiolabeled somatostatin therapy; systemic radiolabeled therapy (eg, ¹³¹I-iodobenguane) for the treatment of metastatic carcinoid tumors; pregnancy; breastfeeding; or, any other significant condition, currently uncontrolled by treatment, that might interfere with study completion.

Medication

⁹⁰Y-edotreotide (Onalta; Molecular Insight Pharmaceuticals, Cambridge, MA) was infused intravenously over 10 to 15 minutes. Patients were treated in an outpatient setting and were to receive three individual doses of 4.4 GBq (120 mCi) administered in 6- to 9-week cycles apart for a total cumulative dose of 13.3 GBq (360 mCi). Two liters of an amino acid solution (Aminosyn II; Abbott Laboratories, Abbott Park, IL; or equivalent) with approximately 28 g of both lysine and arginine diluted to lower than 800 mOsmol/L were infused intravenously at 500 mL/h over 4 hours beginning 30 minutes before each ⁹⁰Y-edotreotide infusion. Patients were not eligible for re-treatment until a minimum of 6 weeks (maximum 9 weeks) had passed from the last admin-

istration of study drug. Patients had to meet the following criteria for re-treatment at each subsequent cycle: serum creatinine \leq baseline value plus 30%, or a measured creatinine clearance of ≥ 40 mL/min; absolute neutrophil count $\geq 1,500/\text{mm}^3$ and platelets $\geq 75,000/\text{mm}^3$; liver function tests (total bilirubin, aminotransferases) lower than grade 3. In addition, all grade 3 to 4 adverse events (WHO Common Toxicity Criteria, version 2.0) must have resolved to \leq grade 2.

Safety Assessments and Efficacy Measures

Safety assessments consisted of adverse events, serious adverse events, laboratory tests (hematology, clinical chemistry, urinalysis), vital signs, ECGs, and physical examinations.

The primary objective of this study was to evaluate the efficacy of ⁹⁰Y-edotreotide in relieving symptoms in patients with malignant carcinoid tumors. Patients reported on these symptoms at baseline, at day 1 of each cycle, at weeks 6 and 10 of cycle 3 (or on early discontinuation), and every 6 months for up to 5 years or death. The 12 symptoms were diarrhea, hot flushes, abdominal pain, nausea/vomiting, feeling tired, decreased strength, heartburn, loss of appetite, difficulty sleeping, pain in muscles or joints, shortness of breath, and fever. Patients reported on the presence of these symptoms in the past 2 weeks, and, if present, the impact of the symptom(s) using a 7-point Likert scale (0, not at all bothered by symptom; 6, extremely bothered).

Quality of life (QoL) was assessed with the EuroQoL EQ-5D (EQ-5D), a validated, generic QoL instrument.¹⁹ The EQ-5D has the five domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) as well as a 100-point visual analog scale (VAS), known as the health thermometer, for the patient's general health evaluation. The EQ-5D subscales assessed each variable on a 3-point intensity scale (eg, none, moderate, extreme). Patients reported on these measures at the same study time points as they did on their symptoms.

Objective tumor response was determined by the investigators based on bidimensional tumor measurements per SWOG criteria.¹⁸ Computed tomography/magnetic resonance imaging scans were scheduled at baseline, at week 4 of cycle 2, at weeks 4, 6, and 10 of cycle 3, and at 6-month intervals thereafter.

Other efficacy outcomes included body weight, octreotide use, KPS, and overall and progression-free survival. Data on the survival of patients were collected every 6 months.

Statistical Analysis

Demographic and baseline characteristics of patients were assessed. Adverse events were analyzed by body system/preferred term for WHO Common Toxicity Criteria any grade, grade 3, and grade 4, separately. Complete response (CR) or partial tumor response (PR) was defined as either completing all three cycles with a confirmed PR or CR at week 10 of cycle 3 or exhibiting a PR or CR on early discontinuation. Best objective tumor response rates are assessed by point estimates and 95% CIs. For symptoms, QoL-VAS, and KPS, linear trend of improvement was assessed by a linear mixed model accounting for random effects. A duration analysis was applied for patients who had at least three assessments for symptoms, QoL-VAS, and KPS, respectively. The durable symptom response for each was defined as an improvement from baseline sustained for at least 4 weeks since the first therapeutic dose. Overall and progression-free survival estimates were summarized by the Kaplan-Meier method.²¹ Adverse events were summarized using descriptive statistics. The SAS software system was used (SAS Institute, Cary, NC).

Study Conduct

The study was designed and analyzed originally by Novartis with additional analysis performed by Molecular Insight. The investigators had unrestricted access to the primary data. The academic authors wrote this article with editing assistance from Molecular Insight. All the coauthors contributed to the interpretation of the data and the final version of the manuscript. All the authors vouch for the accuracy and completeness of the reported data.

RESULTS

Demographics, Background Characteristics, and ⁹⁰Y-Edotreotide Treatment

A total of 96 patients were screened, and 90 patients were enrolled, prospectively. All six screened patients who did not enroll did not meet the inclusion/exclusion criteria. First and last study pa-

Table 1. Demographic and Baseline Characteristics of the Patients (N = 90)

Characteristic	No.	%
Age, years		
Mean	59.8	
Standard deviation	12.0	
Range	18-88	
Sex		
Female	35	38.9
Male	55	61.1
Prior anticancer therapy		
Any prior therapy	40	44.4
Chemotherapy	28	31.1
Immunotherapy	21	23.3
Radiotherapy	10	11.1
Prior surgery	77	85.6
Prior hormone therapy	21	23.3
Tumor site		
Liver	65	72.2
Lymph node	36	40.0
Small intestine	22	24.4
Lung	18	20.0
Bone	17	18.9
Pancreas	6	6.7
Peritoneal	6	6.7
Mesentery and omentum	5	5.6
Spinal	3	3.3
Other*	17	18.9
Using octreotide at baseline		
No	27	30
Yes	63	70
Bothered by specified symptoms (79 patients with complete self-reports)		
Diarrhea	63	79.7
Hot flushes or flashes	65	82.3
Abdominal pain	59	74.7
Nausea/vomiting	35	44.3
Feeling tired or worn out	75	94.9
Decrease in physical strength	62	78.5
Heartburn	24	30.4
Loss of appetite	40	50.6
Difficulty sleeping	44	55.7
Pain or aching in muscles or joints	47	59.5
Shortness of breath	35	44.3
Fever	14	17.7
⁹⁰ Y-edotreotide study therapy		
Received all three 4.4 GBq (120 mCi doses)	73	81.1
Received two doses	7	7.8
Received one dose	9	10.0
Received divided doses over 6 months†	1	1.1

*Includes breast (1), hypogastric (1), ileal (1), kidney (1), large intestine (2), ovary (1), pelvis (1), pituitary (1), pleural effusion (1), rectum (2), retroperitoneal mass, small bowel, ascites, serosa (1), spleen (2), stomach (1), unknown (1).
†4.4GBq (120 mCi) and four doses of 2.2 GBq (60 mCi).

tients were enrolled July 20, 2001, and August 19, 2002, respectively. The last follow-up date was April 24, 2004. The mean age of patients was 59.8 years (range, 18 to 88 years). Forty (44.4%) of 90 patients received prior anticancer therapy, including chemotherapy, immunotherapy, and/or radiotherapy. In addition, 77 (85.6%) had prior surgery and 21 (23.3%) had prior hormone therapy. Most patients (65 of 90; 72.2%) had liver involvement at baseline. Seventy-three (81.1%) of 90 patients received all three 4.4 GBq (120 mCi doses). Seven (7.8%) of 90 patients received two doses and nine patients (10.0%) received one dose. One patient (1.1%) received divided doses over 6 months, 4.4 GBq (120 mCi) and four doses of 2.2 GBq (60 mCi; Table 1).

Table 2. Adverse Events Experienced in \geq 5% of Patients (N = 90)

Body System/Preferred Term	Grade (%)		
	All	3	4
All body systems	96.7	34.4	25.6
Blood/lymphatic system			
Anemia	8.9	1.1	0.0
Leukopenia	16.7	1.1	0.0
Lymphopenia	16.7	3.3	12.2
Thrombocytopenia	17.8	0.0	0.0
Gastrointestinal disorders			
Abdominal pain	21.1	6.7	0.0
Lower	5.6	1.1	0.0
Upper	7.8	0.0	0.0
Ascites	6.7	3.3	0.0
Constipation	7.8	1.1	0.0
Diarrhea	27.8	4.4	1.1
Nausea	57.8	13.3	0.0
Vomiting	46.7	5.6	4.4
General disorders			
Asthenia	15.6	5.6	1.1
Fatigue	26.7	6.7	0.0
Edema peripheral	8.9	1.1	0.0
Pyrexia	10.0	0.0	1.1
Weakness	7.8	1.1	1.1
Infections and infestations			
Nasopharyngitis	6.7	0.0	0.0
Urinary tract infection	6.7	1.1	0.0
Investigations (weight decreased)	14.4	2.2	0.0
Metabolism and nutrition disorders			
Anorexia	20.0	5.6	0.0
Hypophosphatemia	6.7	1.1	0.0
Musculoskeletal and connective tissue disorders			
Arthralgia	6.7	1.1	0.0
Back pain	6.7	0.0	0.0
Neoplasms, benign, malignant and unspecified carcinoid syndrome	8.9	4.4	2.2
Nervous system disorders (dizziness)	8.9	0.0	0.0
Psychiatric disorders (anxiety)	5.6	0.0	0.0
Respiratory, thoracic, and mediastinal disorders			
Cough	7.8	0.0	0.0
Dyspnea	6.7	1.1	1.1
Vascular disorders			
Flushing	15.6	4.4	0.0
Flushing aggravated	6.7	3.3	0.0
Hypertension	7.8	2.2	0.0

NOTE. WHO Common Toxicity Criteria version 2.0.

Table 3. Duration of Symptom Response to ⁹⁰Y-Edotreotide

Symptoms (7-point scale: 0-6)	Patients With Baseline Symptoms		Duration (weeks)				Durable Response*	
	No.	%	Mean	Median	Minimum	Maximum	%	No.
Diarrhea	63	70	12.2	13.8	5.7	21.1	60	38/63
Hot flushes	65	72	10.5	9.7	4	19.5	51	33/65
Abdominal pain	59	66	10.7	9.3	4.1	21.1	58	34/59
Nausea/vomiting	35	39	11.0	12	4.1	18	60	21/35
Feeling tired	75	83	9.5	8.1	4.0	18	47	35/75
Decreased strength	62	69	11.1	12.5	4	15.6	52	32/62
Heartburn	24	27	10.3	9.6	4.8	19.5	54	13/24
Loss of appetite	40	44	12.1	13.0	5.7	18.0	55	22/40
Difficulty sleeping	44	49	13.2	13.9	4.0	19.5	43	19/44
Muscle/joint pain	47	52	10.5	10.6	4.0	17	55	26/47
Shortness of breath	35	39	12.1	13.6	4.0	21.1	54	19/35
Fever	14	16	11.1	12.1	4	14.7	64	9/14

*A durable response is measured as 4 or more weeks in length.

Safety Results

As presented in Table 2, 87 (96.7%) of 90 patients experienced one or more adverse events, with the majority (76; 84.4%) experiencing GI events, with nausea, vomiting, and diarrhea most frequently reported. Fifty-four (60.0%) of 90 patients had grade 3 to 4 adverse events, with lymphopenia, nausea, and vomiting most frequently reported. Three (3.3%) of 90 patients experienced grade 3 to 4 renal or urinary toxicity. One patient had grade 3 oliguria, one had grade 3 dysuria, and one had grade 4 renal failure; this latter patient had received only 4.3 GBq (115 mCi) of ⁹⁰Y-edotreotide. These renal events lasted 6, 42, and 6 days, respectively. Serum creatinine at 1 year

(mean, 1.08 mg/dL) was similar to baseline (mean, 1.14 mg/dL; *P* = .07; *n* = 55).

Twelve (13.3%) of 90 patients experienced adverse events that required a dosage adjustment or interruption of study drug treatment. Nine (10.0%) of 90 patients discontinued treatment because of adverse events, five due to GI events. The majority of patients (78 of 90; 86.7%) experienced adverse events that required significant additional therapy, mainly for nausea, vomiting, and abdominal pain. Thirty-two (35.6%) of 90 patients experienced serious adverse events, mainly GI disorders (12 patients; 13.3%). Nausea, vomiting, and abdominal pain were typically associated with amino acid infusion concomitant

Table 4. Linear Trend for Symptoms and Quality of Life (measured using the health thermometer; *N* = 90)

Symptoms (7-point scale: 0-6)	Baseline Mean Score		Estimated Mean Score at 18 weeks		<i>P</i> for Linear Trend	
	All	With Symptoms at Baseline*	All	With Symptoms at Baseline*	<i>P</i>	With Symptoms at Baseline*
Diarrhea	2.2	3.0	1.0	1.4	< .001	< .001
Hot flushes	2.2	2.7	1.4	1.4	< .001	< .001
Abdominal pain	1.8	2.6	0.7	0.9	< .001	< .001
Nausea/vomiting	0.4	1.9	-0.4	-0.2	< .001	< .001
Feeling tired	3.1	3.3	2.1	2.3	< .001	< .001
Decreased strength	2.2	3.0	1.2	1.5	< .01	< .001
Heartburn	0.3	1.5	-0.1	-0.5	< .05	< .001
Loss of appetite	0.8	2.2	-0.1	0.2	< .01	< .001
Difficulty sleeping	1.1	2.8	0.8	1.6	NS	< .001
Pain in muscles or joints	1.1	2.5	1.0	1.2	NS	< .001
Shortness of breath	0.6	2.5	0.1	0.7	< .05	< .001
Fever	-0.7	1.1	-1.0	-0.8	< .01	< .01
QoL (0-100 point scale)	65		71†		< .05	

NOTE. Patients reported on the presence of these symptoms in the past 2 weeks, and, if present, the impact of the symptom(s) using a 7-point Likert scale (0, not at all bothered by symptom; 6, extremely bothered), with -1 coded if patient reported that this symptom was absent. Improvement was relative to baseline immediately prior to cycle 1. A linear mixed model was fit to each specified outcome over the period of treatment accounting for random effects of patients with repeated measures. A decrease in symptom status from baseline to the end of treatment period indicated there was an improvement. For quality of life, an increase from baseline by the end of treatment period represents an improvement.

*Based on patients with the specific symptoms at baseline as indicated.

†Estimated at 80 weeks.

with therapy. These symptoms almost always subsided with cessation of amino acid infusion.

Eight (8.9%) of 90 study patients died. Causes of death were atherosclerosis, carcinoid crisis, coma, other malignant neoplasms (two patients), progressive disease (two patients), and sepsis. A relationship with study medication was suspected in two deaths (carcinoid crisis, coma).

Efficacy Results

Symptoms. Seventy-nine (87.8%) of 90 patients had complete self-reports of symptom assessment for analysis. The proportions of patients who had a durable response sustained for at least 4 weeks are presented in Table 3. Of the 12 symptoms, for 10 of them, more than one half of the patients who were symptomatic at baseline had a durable response. The average length of durable response after initiating treatment was 8 to 12 weeks across symptoms with an average decline of 2 points on the 7-point scale. Linear trend analysis showed that among baseline symptomatic patients, a trend toward improvement for each specified symptom was consistently demonstrated and statistically significant across all symptoms (Table 4).

EQ-5D and QoL (health thermometer)

A proportion of the 78 patients who had at least three assessments for EQ-5D subscales showed a durable improvement: 24% (n = 19) for usual activities, 28% (n = 22) for anxiety/depression, 29% (n = 23) for pain/discomfort, 21% (n = 16) for mobility, and 6% (n = 5) for self-care.

A statistically significant linear trend toward improvement from baseline was found in the EQ-5D QoL-VAS general health state scale during treatment period (Table 3). In addition, the duration of the symptom improvement is presented in Table 4. Duration analysis showed among 77 patients who had at least three assessments of QoL general health state, 61% (47) had a durable response. The average duration of response for these patients was 45 weeks with an average increase of 16 points on the 100-point scale.

Tumor Status

Objective tumor response was based on the intent-to-treat population, all 90 patients entered on-study. No patient attained a CR, four (4.4%; 95% CI, 0.2% to 8.6%) of 90 patients exhibited an (unconfirmed) PR, and 63 (70.0%) of 90 patients had stable disease. Together, 67 (74.4%; 95% CI, 65.4% to 83.4%) of 90 patients were objectively stable or responding. Eleven (12.2%) of 90 patients experienced disease progression. For 12 patients, four of whom died on study, no tumor response data were submitted.

Progression-Free Survival and Overall Survival

Median progression-free survival and overall survival were 16.3 and 26.9 months, respectively. Median progression-free survival was significantly higher for 38 patients who had durable diarrhea improvement than 18 patients who did not (18.2 v 7.9 months; log-rank test $P = .031$; Fig 1A). Figure 1B represents a subset of 51 patients all of whom had progression-free survival through month 6 with a similar result (log-rank test $P = .031$).

KPS

Linear trend analysis showed that KPS was constant over the treatment period (Table 4). Duration analysis showed among 75 pa-

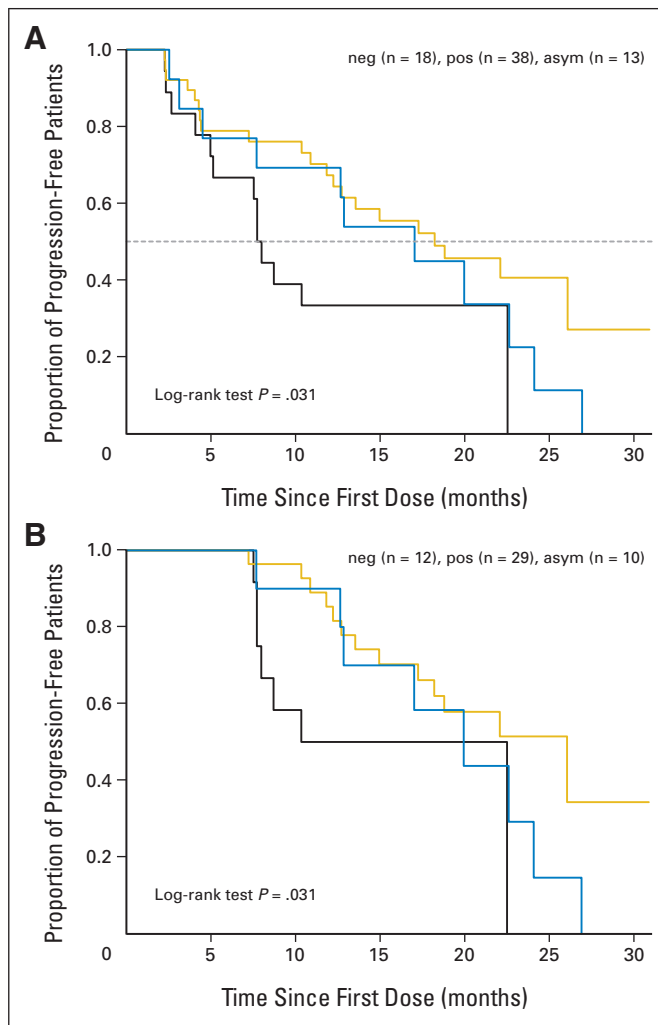


Fig 1. (A) Kaplan-Meier analyses for patients with durable diarrhea response, no durable response, and those without diarrhea at baseline. The median time for progression-free survival (PFS) in these groups was 18.2, 7.9, and 17.0 months, respectively. (B) A landmark approach was used to analyzed PFS at 6 months, with 51 patients stratified by presence of a durable response before 6 months. Only patients who were progression free through 6 months were included in the analysis. At 6 months, patients were dichotomized by whether they had durable improvement in diarrhea symptoms before 6 months. neg, negative; pos, positive; asym, asymmetrical.

tients who had at least three assessments of KPS, 20% (15) patients had a durable response from baseline for at least 4 weeks. The average duration for these patients was 10 weeks with an average increase of 12 points on the 100-point scale.

Octreotide

At baseline, 63 (70%) of 90 patients were receiving octreotide therapy and 27 (30%) were not. After receiving at least one ⁹⁰Y-edotreotide treatment on-study, 45 remained on octreotide, 22 remained off octreotide, two ceased octreotide therapy, 14 resumed octreotide therapy, and seven are unreported. Analyzing these data with the sign test shows a statistically significant increase in octreotide use during the study ($P = .004$).

Figure 2 presents pre- and post-treatment magnetic resonance imaging/computed tomography images and baseline ¹¹¹In-pentetreotide images for a subject with a typical outcome (objectively

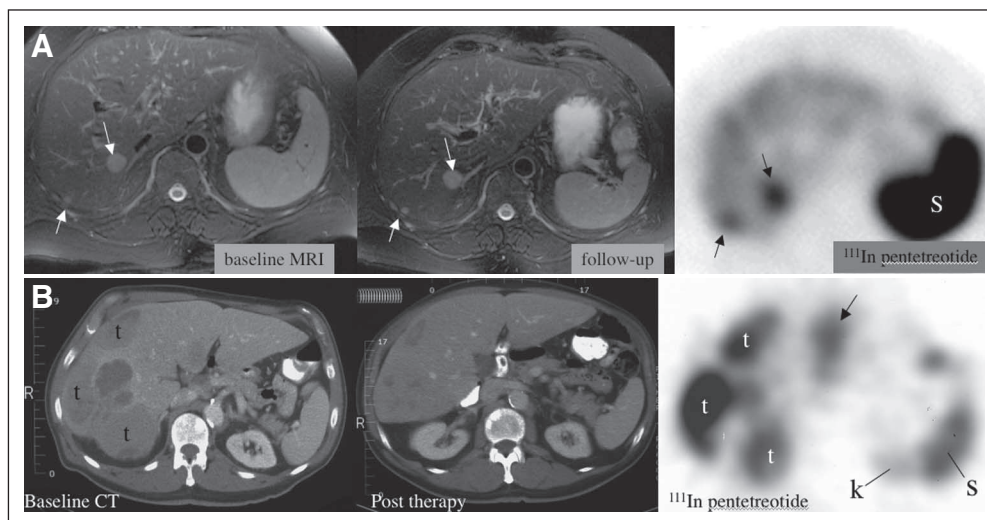


Fig 2. (A) Pretherapy (baseline) and follow-up T2 weighted axial magnetic resonance (MR) images from a patient classified as stable disease who nevertheless demonstrated substantial clinical improvement and is alive more than 5 years after treatment. These images depict two of the 11 hepatic metastases seen on the complete MR imaging (MRI) exam. The axial single-photon emission computed tomography ^{111}In -pentetreotide image on the right demonstrates significant concentration of the radiolabeled octreotide in the two lesions seen on MRI (arrows). (B) Pre- and post-therapy axial computed tomography (CT) images from a patient classified with partial response at the level of the upper pole of the left kidney and demonstrate substantial reduction in the size of multiple large hepatic metastases (t). Black arrow indicates uptake in a hepatic metastasis that is not seen on CT (S indicates spleen and K indicates upper pole of the left kidney on the pentetreotide image). This patient displayed dramatic clinical improvement as well.

stable, symptom improvement) and a subject with the optimal outcome (objective response, symptom improvement).

DISCUSSION

^{90}Y -edotreotide therapy resulted in objective tumor response or stable disease in 67 (74.4%; 95% CI, 65.4% to 83.4%) of 90 patients with metastatic carcinoid refractory to octreotide. This finding is consistent with other phase I or phase II ^{90}Y -edotreotide studies treating a variety of somatostatin receptor–positive tumors (including three unpublished Novartis trials as well as four published trials^{16,22-24}). The rates of objective response and stable disease range from 66.7% to 92.3%, and the median of these seven other studies is 75.0% objectively stable or responding.

This study's median overall survival of 26.9 months and that of 36.7 months in another ^{90}Y -edotreotide trial²⁴ compare favorably to historical controls (12.0 and 18.0 months)^{25,26} and to the most promising combination chemotherapy results for metastatic carcinoid (11.9, 15.7, 24.3 months).¹⁰

Although there was a statistically significant increase in octreotide use while on-study ($P = .004$), octreotide is unlikely to be responsible for the 74.4% objective response plus stable disease rate, since on entry into the study, all patients were refractory to this therapy. Furthermore, in four published studies of octreotide in earlier-stage patients, the median rate of objective response plus stable disease was 43%.²⁷⁻³⁰

Patients in this study had incurable, progressive disease refractory to octreotide with severe symptoms, such as flushing and diarrhea, that could themselves be life-threatening. For all 12 carcinoid-specific symptoms assessed, improvement was shown among patients who were symptomatic at baseline. Most symptoms had a substantial duration of improvement sustained for at least 4 weeks since the first treatment cycle. Patients who had diarrhea improvement appeared to

have had a progression-free survival benefit compared with those who did not show diarrhea improvement. A recent study using a scoring system designed for neuroendocrine tumor symptoms similarly found a significant clinical response after treatment with three cycles of ^{90}Y -edotreotide.³¹

Strong conclusions that would be available in a double-blind, placebo-controlled trial cannot be drawn from an open study such as this one which may be subject to biases that may have either enhanced or masked treatment effects. Two sources of potential bias include: patients may not have completed the questionnaire at certain time points when they felt too unwell, which is in part mitigated as symptoms reported are on average over the past 2 weeks; and the degree to which patients are bothered by symptoms may in theory wane over time as patients become accustomed to them, even if symptoms have not improved, which is minimized since patients had years to phase into an understanding of the range and severity of symptoms. Consequently, we believe such a bias would be notably uncommon in this clinical setting. It is useful to note that KPS, tumor response, and patient-reported symptoms correlate, which suggests that the association between these outcome measures is real.

Most patients (78 of 90; 86.7%) experienced adverse events (mainly nausea, vomiting, and abdominal pain) that required significant additional therapy. Nausea and vomiting were almost certainly due in large part to the concomitant amino acids given for renal protection.³² GI adverse events due to amino acid infusion can be mitigated by amino acid choice and/or infusion rate. Solutions containing only lysine and arginine are much better tolerated in this regard and may be a better choice for future studies.^{33,34} Importantly, only three (3.3%) of 90 patients experienced acute grade 3 to 4 renal toxicity and this toxicity was reversible.

A consistent finding of this and similar studies is that approximately 75% of patients had either an objective response or stable disease after ^{90}Y -edotreotide therapy. Most symptoms associated with

malignant carcinoid improved after ⁹⁰Y-edotreotide treatment. In conclusion, this study suggests that ⁹⁰Y-edotreotide offers an advantageous risk/benefit profile for patients with metastatic carcinoid tumor refractory to octreotide therapy.

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