Tumor Response and Clinical Benefit in Neuroendocrine Tumors After 7.4 GBq ^{90}Y-DOTATOC

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The aim of this prospective phase II study was to evaluate the tumor response of neuroendocrine tumors to high-dose targeted irradiation with 7.4 GBq/m^2 of the radiolabeled somatostatin analog ^{90}Y-1,4,7,10-tetra-azacyclododecan-4,7,10-tricarboxy-methyl-1-yl-acetyl-D-Phe-Tyr^3-octreotide (DOTATOC). In addition, we investigated the clinical benefit of ^{90}Y-DOTATOC regarding the malignant carcinoid syndrome and tumor-associated pain. **Methods:** Thirty-nine patients (mean age, 55 y) with progressive neuroendocrine gastroenteropancreatic and bronchial tumors were included. The treatment consisted of 4 equal intravenous injections of a total of 7.4 GBq/m^2 ^{90}Y-DOTATOC, administered at intervals of 6 wk. After each treatment cycle, a standardized clinical benefit assessment using the National Cancer Institute grading criteria (NCI-CTC) was performed. **Results:** The objective response rate according to World Health Organization (WHO) criteria was 23%. For endocrine pancreatic tumors (13 patients), the objective response rate was 38%. Complete remissions were found in 5% (2/39), partial remissions in 18% (7/39), stable disease in 69% (27/39), and progressive disease in 8% (3/39). A significant reduction of clinical symptoms could be found in 83% of patients with diarrhea, in 46% of patients with flush, in 63% of patients with wheezing, and in 75% of patients with pellagra. The overall clinical benefit was 63%. All responses (both clinical benefit and WHO response) were ongoing for the duration of follow-up (median, 6 mo; range, 2–12 mo). Side effects were grade 3 or 4 (NCI-CTC) lymphocytopenia in 23%, grade 3 anemia in 3%, and grade 2 renal insufficiency in 3%. **Conclusion:** High-dose targeted radiotherapy with 7.4 GBq/m^2 ^{90}Y-DOTATOC is a well-tolerated treatment for neuroendocrine tumors, with remarkable clinical benefit and objective response.

Key Words: radionuclide therapy; radiopeptide; somatostatin; octreotide; neuroendocrine tumor; ^{90}Y-DOTATOC

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Neuroendocrine tumors (NETs) represent a collection of diverse tumor types derived from common cell lines and unified by the secretion of neuropeptides. The excessive secretion of neuropeptides may give rise to distinct clinical syndromes. Malignant NETs and syndromes have a poor prognosis because curative surgery can be offered to <5% of all patients (*1–5*). Nevertheless, surgery remains a cornerstone in both managing severe clinical syndromes and facilitating medical treatment. Chemotherapy was considered the treatment standard of NETs until the 1980s, when therapies with α-interferon and somatostatin analogues that could significantly improve clinical management were developed. Determination of somatostatin receptor subtype in tumor tissues and development of subtype-specific analogues for therapy are new approaches in the treatment of NETs and the carcinoid syndrome (*1–3,6–12*). In recent years, many research groups in nuclear medicine and radiopharmacy have been trying to develop a somatostatin analog that has high affinity to the somatostatin receptor and can be linked to a therapeutic β-emitting radioisotope. If isotopes emitting β-particles are used for peptide labeling, the radiation emitted from a radiolabeled peptide bound to a tumor cell may also kill neighboring cells because the pathlength of β-particles can extend over several cell diameters. The crossfire of β-particles can, in theory, destroy both somatostatin receptor-positive and somatostatin receptor-negative tumor cells. In 1996, the first promising dodecanetetraacetic acid–chelated somatostatin analog was presented (*13*)—a hydrophilic peptide vector that can be labeled stably with either the β-emitting therapeutic radionuclide yttrium (^{90}Y) or diagnostic indium (^{111}In) (*14–19*). The affinity of ^{90}Y-labeled 1,4,7,10-tetra-azacyclododecan-4,7,10-tricarboxy-methyl-1-yl-acetyl-D-Phe (*1*)-Tyr^3-octreotide (DOTATOC) to the somatostatin receptor, especially to its subtypes 2 and 5, was found to be high. In a phase I study, we found that 33% of the patients who received cumulative doses of >8.5 GBq/m^2 ^{90}Y-DOTATOC without kidney protection had dose-limiting renal toxicity (*19*). The maxi-

TABLE 1
Patient Characteristics

Patient no.	Histology	Localization and account of lesions	Onset of diagnosis/time to treatment (mo)	Pretreatments	Pre-DOTATOC medication	Tumor response to DOTATOC
1	EPT	Pancreas 1, liver > 10	8-99/6	None	None	SD
2	EPT	Liver > 10	9-98/13	Chemotherapies (STZ, 5FU, x), chemoembolizations	Octreotide	PD
3	EPT	Liver 2	11-98/4	Operations	None	PR
4	EPT	Pancreas 1, liver > 10	2-95/60	Chemotherapies (CDDP, 5FU), octreotide	None	PR
5	EPT	Pancreas 1, liver > 10	1-99/7	Operations, octreotide	Octreotide	CR
6	EPT	Pancreas 1, liver 3	3-99/5	None	None	SD
7	EPT	Abdomen 4, lymph node 1	4-98/18	Operations	None	PD
8	EPT	Pancreas 1, liver 6	9-96/38	Operations	None	SD
9	EPT	Liver > 10, bone 10	12-93/72	Chemoembolizations, octreotide	Octreotide	PR
10	EPT	Liver > 10, bone 1	7-96/32	Operations	None	SD
11	EPT	Liver > 10	9-97/9	Operations, octreotide, interferon	None	SD
12	EPT	Liver > 10, abdomen 4	3-99/2	None	None	PR
13	EPT	Liver > 10, pancreas 1	7-97/31	Chemotherapies (x), octreotide, interferon	Octreotide	SD
14	Int. NET	Abdomen 5, liver > 10	5-99/3	None	None	SD
15	Int. NET	Liver > 10, bowel 1	11-99/2	None	None	PR
16	Int. NET	Liver > 10, bone > 10	3-96/44	Chemotherapies (STZ, 5FU, doxorubicin), chemoembolizations	Octreotide	SD
17	Int. NET	Bowel 1, bone > 10, lymph node 5	7-99/7	Operations	None	SD
18	Int. NET	Bowel 1, lymph node 2	2-97/33	Operations, chemotherapies (5FU, x)	Octreotide	SD
19	Int. NET	Liver > 10, abdomen 7, bowel 1	2-00/3	Octreotide	Octreotide	SD
20	Int. NET	Liver 2	12-99/4	Operations	None	SD
21	Int. NET	Liver 1, abdomen 1	12-99/3	Operations	None	SD
22	Int. NET	Bowel 1, liver 10	12-97/8	Octreotide, interferon	Octreotide	SD
23	Int. NET	Liver 2	11-98/24	Operations, interferon, octreotide	None	SD
24	Int. NET	Liver > 10, lymph node 5	11-90/112	Chemotherapies (x), chemoembolizations, operations, octreotide	Octreotide	SD
25	Int. NET	Liver > 10, bowel > 10, lymph node 4	8-99/5	Octreotide	Octreotide	SD
26	Bronch. NET	Bone 1, mediastinum 4	7-99/3	Operations	None	SD
27	Bronch. NET	Liver > 10, mediastinum 1	7-87/152	Chemotherapies (x), chemoembolizations, radiation, operations, interferon, octreotide	Octreotide	SD
28	Bronch. NET	Liver 5, bone > 10	1-98/23	Operations, radiation, interferon	None	SD
29	NETup	Liver > 10, heart 2, rectum 4	4-96/26	Octreotide, interferon	None	PD
30	NETup	Liver > 10, mediastinum 6, abdomen 4	1-98/16	I-MIBG-therapy	None	SD
31	NETup	Liver > 10	8-95/52	Operations, octreotide, interferon, chemotherapy (dacarbacin)	Octreotide	SD
32	NETup	Liver > 10	9-96/42	Chemoembolizations, octreotide, interferon	Octreotide	PR
33	NETup	Liver > 10, bone > 10	7-99/6	Chemotherapies (ETO, CDDP)	None	PR
34	NETup	Liver > 10, lymph node 2	8-99/1	None	None	SD
35	NETup	Liver > 10, lymph node 1	12-99/5	Octreotide	Octreotide	SD
36	NETup	Liver > 10, bone 10, lymph node 3	8-94/63	Chemotherapies (x), chemoembolizations, interferon	None	SD
37	NETup	Bowel 1, lymph node 2	9-99/2	None	None	SD
38	Other	Liver 1	7-99/6	None	None	CR
39	Other	Liver 8, abdomen 4	8-93/11	Operations, radiation	None	SD

EPT = endocrine pancreatic tumor; SD = stable disease; STZ = streptozotocin; 5FU = 5-fluorouracil; x = unspecified combination; PD = progression of disease; PR = partial remission; CDDP = cisplatin; CR = complete remission; Int. NET = intestinal neuroendocrine tumor; Bronch. NET = bronchial neuroendocrine tumor; NETup = neuroendocrine tumor of unknown origin; MIBG = metaiodobenzylguanidine; ETO = etoposide.

mum tolerated dose defined in this phase I trial was 6 GBq/m^2 (33% less than 8.5 GBq/m^2) with amino acid–kidney protection, and in a phase II trial with this dose the overall response rate (according to World Health Organization [WHO] criteria) was 24% in patients with NETs of gastroenteropancreatic or bronchial origin (*20*). Therefore, this study was undertaken to evaluate the clinical benefit and objective response rate of high-dose treatment (7.4 GBq/m^2 with renal protection).

MATERIALS AND METHODS

The study was approved by the local ethical committee and the Swiss authorities.

Selection of Patients

We included 39 patients (mean age, 55 y) with gastroenteropancreatic or bronchial NETs. To be included, patients had to have a histologically confirmed diagnosis of NET, progressive disease before starting the treatment, strongly positive tumors on ^{111}In-DOTATOC or ^{111}In-pentetreotide (OctreoScan; Mallinckrodt, Inc., St. Louis, MO) scintigrams, a life expectancy $>$ 6 mo, adequate organ function, no concurrent antitumor treatment, and written informed consent. Patients were excluded if they were younger than 18 y or pregnant, had a history of life-threatening atopic reactions, or had a severe concomitant illness, including severe psychiatric disorders.

Radiotracer

A dodecanetetraacetic acid–modified somatostatin analog named DOTATOC was synthesized in a 5-step procedure performed according to good medical practice (*19–22*). ^{111}In- and ^{90}Y-DOTATOC was prepared according to previously described procedures using 8 μg DOTATOC dissolved in 190 μL 0.4 mol/L sodium acetate buffer (pH 5.5) with 7 mg gentisic acid and 222 MBq $^{111}InCl_3$ (0.05 mol/L HCl; Mallinckrodt Medical, Petten, The Netherlands). The solution was heated at 95°C for 25 min, and the quality was controlled using a Sep-Pak C_{18} cartridge (Waters, Milford, MA) and high-performance liquid chromatography. As a therapeutic radiometal, the pure β-emitter ^{90}yttrium was linked stably to DOTATOC with preservation of receptor-binding affinity (dissociation constant, 2.6 ± 0.5 nmol/L; labeling yield, >99.5%).

Treatment

A fractionated treatment protocol was performed with 4 equal-dose intravenous injections administered at 6-wk intervals, resulting in a total of 7.4 GBq/m^2 ^{90}Y-DOTATOC. For each session, patients were hospitalized for 2–3 d in accordance with the legal requirements for radioactivity protection and scintigraphic localization control. Thirty minutes before the injection of each treatment dose, 500 mL Hartmann-HEPA 8% amino acid solution (Ringer's lactated Hartmann solution, Proteinsteril [B. Braun Medical AG, Sempach, Switzerland] HEPA 8%, Mg 5-Sulfat [B. Braun Medical AG]) were given to inhibit tubular reabsorption of the radiopeptide DOTATOC, followed by an additional 2,000 mL within 2.5 h after ^{90}Y-DOTATOC bolus injection. In each ^{90}Y-DOTATOC session, 111 MBq ^{111}In-DOTATOC were injected simultaneously to control for DOTATOC binding. One, 24, and 48 h after injection, static images (5 min per image) were acquired using a gamma camera with a large field of view (Diacam; Siemens Medical Systems, Inc., Hoffman Estates, IL), equipped with a medium-energy parallel-hole collimator (matrix, 64 × 64; zoom, 1).

Evaluation of Results and Assessment of Clinical Benefit

Four weeks before the first and 8–12 wk after the last internal radiotherapy, tumor growth and tumor response were monitored by either conventional CT, sonography, or MRI. Tumor response was defined according to the WHO standard criteria and was evaluated every 3 mo along with blood counts and chemistry. In addition, complete blood cell and platelet counts were obtained every 2 wk for at least 6 wk after therapy and every 3 mo thereafter. Thyroid-stimulating hormone was measured after every treatment cycle. Side effects of ^{90}Y-DOTATOC treatment were investigated and scored according to the National Cancer Institute grading criteria (NCI-CTC).

A detailed questionnaire using the NCI-CTC was developed. The last consecutive 21 patients were asked to fill out the questionnaires about their disease history and their clinical features and score them according to the NCI-CTC before and after each cycle of treatment. For the first 18 patients, the questionnaire was not available yet.

RESULTS

Patients

The study included 13 patients with endocrine pancreatic tumors (EPT), 12 patients with NET of intestinal origin,

TABLE 2
Tumor Response (WHO Standard Criteria)

Tumor type	Progression before treatment	CR	PR	SD	Progressive disease within or after treatment	Overall tumor response	CR, PR, SD
EPT (n = 13)	13 (100%)	1	4	6	2	38%	11 (85%)
Intestinal NET (n = 12)	12 (100%)	—	1	11	—	8%	12 (100%)
Bronchial NET (n = 3)	3 (100%)	—	—	3	—	0%	3 (100%)
NET of unknown origin (n = 9)	9 (100%)	—	2	6	1	22%	8 (89%)
Others (n = 2)	2 (100%)	1	—	1	—	50%	2 (100%)
All (n = 39)	39 (100%)	2	7	27	3	23%	36 (92%)

CR = complete remission; PR = partial remission; SD = stable disease; EPT = endocrine pancreatic tumor; NET = neuroendocrine tumor.

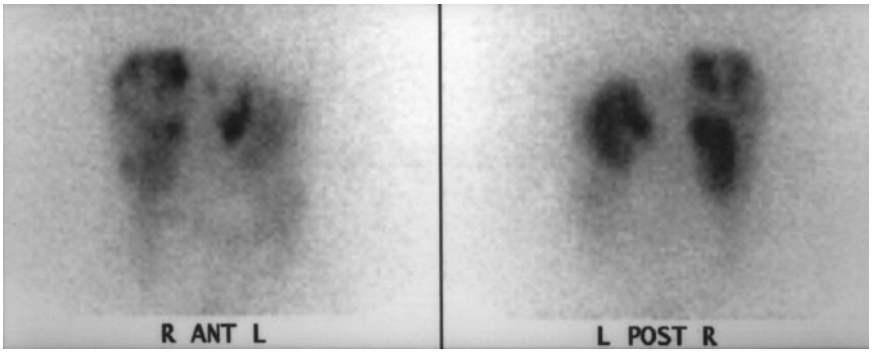

FIGURE 1. ^{111}In-DOTATOC scintigram of abdomen of 43-y-old woman with recurrence of EPT and multiple liver metastases before DOTATOC treatment. ANT = anterior; POST = posterior.

3 patients with NET of bronchial origin, 9 patients with NET of unknown origin, and 2 patients with other NET entities. All patients showed tumor growth as assessed with radiologic or scintigraphic scans before starting ^{90}Y-DOTATOC therapy. Detailed patient characteristics are listed in Table 1.

Tumor Response and Survival

The responses of the individual tumor types are listed in Table 2. For illustration, 2 scintigraphic examples of remissions are shown in Figures 1–4. Eight to 12 wk after therapy, the tumor response was monitored by CT in 30 patients, sonography in 5 patients, and MRI in 4 patients.

Complete remissions were found in 2 (5%) of 39 patients, partial remissions in 7 (18%) of 39 patients, stable disease in 27 (69%) of 39 patients, and tumor progression during or after treatment in 3 (8%) of 39 patients. The overall tumor response rate was 23%. For patients with EPT, the response rate was 38%. In 92% of patients, the disease could be stabilized (complete remission, partial remission, or stable disease).

Currently, 32 of 39 patients have no tumor progression and 4 patients have progressive disease. One patient died after the third treatment cycle because of hepatic failure caused by bacterial cholangiolitis. Two patients died within 3 mo after therapy because of tumor progression and hepatic decompensation.

Toxicity

During ^{90}Y-DOTATOC injection, nausea occurred in 48% of patients and vomiting in 29%. After each cycle, 33% had grade 1–2 nausea; grade 3 nausea was experienced by 1 patient in 1 cycle. All cases of nausea and vomiting could be treated successfully with domperidone or ondansetron.

All patients had the lowest blood counts at the final treatment. At that time, 61% of the patients (24/39) had grade 1–4 lymphocytopenia: 8% had grade 4, 15% had grade 3, and 38% had grade 1 or 2. After 3–4 wk, the values returned to baseline and all patients could receive treatment according to the protocol. Reversible anemia developed in 51% of all patients, 3% of whom had grade 3 and 48%, grade 1 or 2. No blood transfusions were needed. In 15% of all patients, grade 1 thrombocytopenia was found. Thyroid-stimulating hormone levels were normal in all patients throughout the whole trial.

With a single exception, serum creatinine values remained normal during and after treatment (median follow-up, 6 mo). Five months after the fourth cycle, the serum creatinine level of 1 patient had increased from baseline (100 μmol/L before therapy and 230 μmol/L after therapy [reference range, 45–93 μmol/L], NCI-CTC grade 2). The serum creatinine remained at this level during follow-up.

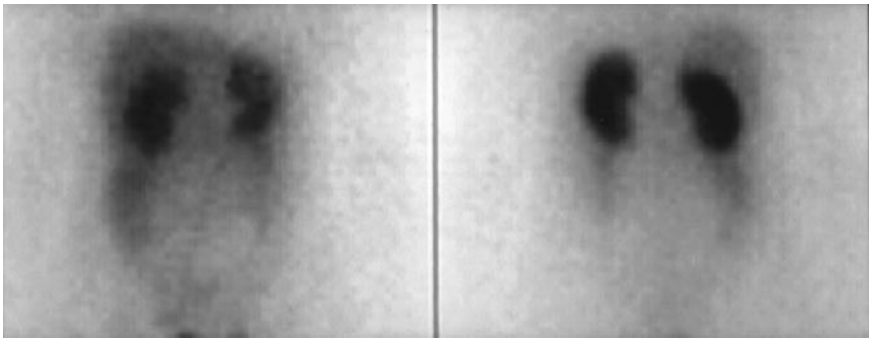

FIGURE 2. After DOTATOC treatment, ^{111}In-DOTATOC scintigram (anterior [left] and posterior [right] images) of abdomen revealed no enhancement in pancreas region or in liver. MRI finding was complete remission.

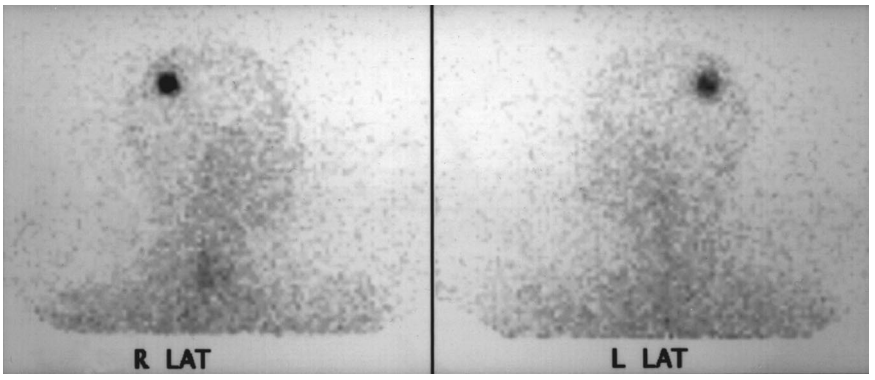

FIGURE 3. ^{111}In-DOTATOC scintigram of 43-y-old woman with neuroendocrine cerebral metastasis of EPT before DOTATOC treatment. LAT = lateral.

Assessment of Clinical Benefit

Twenty-one consecutive patients completed a clinical benefit questionnaire (18 questions) about their disease history and their clinical features (symptoms of malignant carcinoid syndrome and tumor-associated pain). They scored all symptoms according to NCI-CTC before and after each treatment cycle. An example of scoring is shown in Table 3. Specific medical questions were translated into a language that patients understood.

Malignant Carcinoid Syndrome. Fourteen (67%) of the 21 patients had malignant carcinoid syndrome despite receiving octreotide medication (Sandostatin or Sandostatin LAR; Novartis Pharmaceuticals Corp., East Hanover, NJ) before ^{90}Y-DOTATOC-therapy. Six (43%) of the 14 patients with malignant carcinoid syndrome had diarrhea: grade 4 in 2, grade 3 in 1, grade 2 in 2, and grade 1 in 1. In 3 patients (50%), the diarrhea disappeared completely, and in 3 patients (50%), the diarrhea improved by at least 1 grade.

Fourteen (67%) of the 21 patients had intermittent flushes: grade 3 in 4, grade 2 in 6, and grade 1 in 4. The flushes disappeared completely in 3 patients (23%), improved by at least 1 grade in 6 patients (46%), and deteriorated during therapy in 2 patients (15%). Eight patients (38%) had wheezing or dyspnea: grade 3 wheezing in 3, grade 2 wheezing or dyspnea in 4, and grade 1 dyspnea in 1. In 2 patients (25%), the wheezing disappeared completely; in 5 patients (63%), the wheezing or dyspnea improved by at least 1 grade; and in no patients was the wheezing exacerbated during therapy. Four patients (19%) had pellagra: grade 2 in 1 and grade 1 in 3. In 3 patients (75%), the pellagra disappeared completely.

The overall clinical benefit rate was 63%.

Tumor-Associated Pain and Abdominal Pressure. Nine of 21 patients had pain caused mainly by bone or liver metastases. Two had morphine-dependent pain; after ^{90}Y-DOTATOC treatment, the medication of the first of these patients could be changed to nonsteroidal antiinflammatory drugs, and the second patient could discontinue analgesic drugs. In 5 (56%) of 9 patients, pain improved, and is still improved, by at least 1 grade. The level of pain improvement was independent of the degree of tumor reduction. Even patients who showed progression while undergoing therapy experienced a short-term clinical benefit of a few weeks or months.

DISCUSSION

The primary objective of this study was to compare the utility of ^{90}Y-DOTATOC radionuclide therapy with that of standard treatment regimes. For advanced NET, the somatostatin analogue octreotide or lanreotide is the treatment of

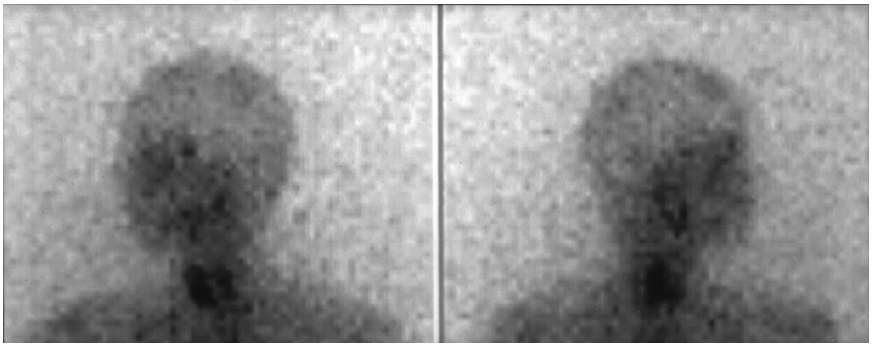

FIGURE 4. After DOTATOC treatment, ^{111}In-DOTATOC scintigram (left and right lateral images) revealed no enhancement. CCT finding was partial remission.

TABLE 3
Example of Scoring (6 of 18 Questions) According to National Cancer Institute Grading Criteria

Symptom/sign	Grade 0	1	2	3	4
Diarrhea	None	2–3 stools per day	4–6 stools per day	7–9 stools per day	>10 stools per day
Flush	None	1–10 times per month	1–10 times per week	1–10 times per day	>10 times per day
Dyspnea/wheezing	None	Abnormal function test	Only on significant exertion	At normal level of activity	At rest
Nausea	None	Able to eat	Decreased but can eat	No intake	—
Vomiting	None	1 time in 24 h	2–5 times in 24 h	6–10 times in 24 h	>10 times in 24 h
Fever	None	<38°C	<40°C	<40°C < 24 h	>40°C > 24 h

choice (*6*,*23*). Therapy with long-acting somatostatin analogues is reported to cause a tumor response in 12% of patients with EPT and a stabilization of disease in 25%–30% of patients (*24*). A Swedish research team found biochemical responses to a long-acting formulation in 40%–70% but an objective tumor response (WHO) in only 4%–10% (*6*). In a further study, in which NETs were treated with lanreotide, Ruszniewski et al. (*24*) showed subjective response rates of 50% and biochemical response rates of 42% but no objective tumor response. Alternatively, α-interferon is reported to have a biochemical response rate of 43% in patients with EPT and an objective response rate of 11% (*6*,*24*,*25*). In cases of tumor progression (clinical, biochemical, or objective) under the above-mentioned therapies, dose escalation of somatostatin analogues can be tried or, alternatively a combination of α-interferon and a somatostatin analog (*1*,*2*,*6*,*24*,*25*). If these treatments fail, patients are usually treated with chemotherapy (streptozotocin and 5-fluorouracil, or cisplatinum and etoposide) (*6*,*23*). Randomized trials have not established a standard chemotherapy protocol, and most evaluated chemotherapies have had response rates of <20% (*6*). Polychemotherapies in the treatment of NET have a high toxicity (*23*,*25*–*30*).

Compared with these standard regimes, treatment with ^{90}Y-DOTATOC resulted in an objective response of 23% overall and a remarkable 38% for patients with EPT. Many of the patients in our trial were pretreated, and all had progressive disease. In these advanced malignancies, the tumors stabilized in 92% of the patients. Nevertheless, increasing the total dose from 6 GBq/m^2, as used in our previous study, to 7.4 GBq/m^2 did not improve the tumor response significantly, but our previous results were clearly confirmed in this trial. In general, ^{90}Y-DOTATOC treatment was well tolerated and toxicity was mild; however, use of 7.4 GBq/m^2 caused a case of renal toxicity. Importantly, there was a profound palliative effect both concerning the malignant carcinoid syndrome and concerning tumor-associated pain. This benefit seemed to be independent of an objective response.

CONCLUSION

Our study suggests that ^{90}Y-DOTATOC is a remarkable therapeutic drug and an effective alternative to all chemo- and biotherapies known to us. Increasing the total dose from 6 to 7.4 GBq/m^2 did not improve the outcome. To date, the dose-limiting toxicity of ^{90}Y-DOTATOC has been renal insufficiency, starting at 7.4 GBq/m^2 (*19*). The future goal is to further reduce renal toxicity so that significantly higher doses can be applied, hopefully resulting in higher response rates and better symptom control.

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