Abstract. Background: The aim of this study was to assess the efficacy and safety of targeted radionuclide therapy with $^{90}$Y-DOTATOC in patients with metastatic neuroendocrine tumors. Patients and Methods: One hundred and sixteen patients with metastatic neuroendocrine tumors were included. All patients were pretherapeutically staged with morphological imaging procedures and with somatostatin receptor scintigraphy. The scintigraphy was positive in all cases. The patients were treated with 162-200 mCi/m² body surface. In 57 patients, the quality of life was assessed with the National Cancer Institute grading criteria (NCI-CTC). Restaging was performed 8 - 12 weeks after the last treatment cycle. Blood samples were drawn every 2 weeks after the treatment to evaluate toxicity. Results: Complete remissions were found in 4%, partial remissions in 23%, stabilization in 62% and progressive disease in 11%. A significant reduction of symptoms was found in 83%. No serious adverse event occurred and the toxicity was acceptable. Conclusion: $^{90}$Y-DOTATOC is a safe and effective treatment for patients with metastatic neuroendocrine tumors.

Neuroendocrine tumors (NET) are a large, inhomogeneous group of malignancies considered to be derived from the diffuse neuroendocrine system (1). Most of these tumors show an overexpression of somatostatin receptors, mainly of subtype 2 (2). Malignant NET have a poor prognosis (1) and surgery is curative in less than 5% of all patients (3, 4), although it remains an important cornerstone in the management of these tumors. Until the 1980s, chemotherapy was the standard treatment for NETs, although single-agent chemotherapy should be considered ineffective (5-7).

Combination chemotherapy showed somewhat better results, but considerable toxicity was found. The objective response rates ranged from 0 to 33% (5, 7-9). Later, therapies with α-Interferon and somatostatin analogs significantly improved clinical management. However, in these treatments as well, the objective response rate was rather disappointing. In trials with somatostatin analogs, the response rates ranged from 0 to 9% (5, 10, 11), while in trials with Interferon it ranged from 7 to 20% (12, 13).

In recent years, radionuclide therapy with radiolabelled somatostatin analogs have become an important tool in the management of NETs (14-20). Convincing results were found for both objective tumor response and quality of life (20-22). Nevertheless controversial debates about the most suitable radionuclides and somatostatin analogs are ongoing (23).

In 1999, a phase I study with $^{90}$Y-DOTATOC identified renal toxicity as dose-limiting. The maximum tolerated dose was defined as 162 mCi/m² body surface $^{90}$Y-DOTATOC without co-infusion of an amino acid solution for kidney protection (24). A following phase II study increased the injected activity to 200 mCi/m² body surface $^{90}$Y-DOTATOC with amino acid co-infusion, achieving safe administration with tolerable toxicity (21).

Several studies with different radionuclides and different somatostatin analogs have been subsequently published. However, most of these studies deal with rather small groups of patients (14-20). This prospective study reports on the tumor response and palliative effect in a large group of patients with metastatic NET treated with $^{90}$Y-DOTATOC.

Patients and Methods

This study was approved by the local ethical committee and the Swiss authorities. All patients gave written informed consent.

Patients. One hundred and sixteen patients with metastatic NET were included. One hundred and nine of these were progressive at the time of inclusion, while 7 suffered from symptomatic, stable disease. Pretherapeutically, all patients underwent staging with
CT, 111In-pentetreotide-scintigraphy (OctreoScan®; Mallinckrodt, Inc., St. Louis, MO, USA), control of blood counts and blood chemistry. All patients had uptake on the 111In-octreotide-scintigraphy that was at least as high as the uptake in normal liver tissue. No patient was under treatment with long-acting somatostatin analogs (Octreotide LAR, Novartis Pharma; Lanreotide, Ipsen Ltd.) for at least within the 6 weeks prior to treatment, or with short-acting somatostatin analogs (Octreotide s/c, Novartis Pharma) within the last 3 days before treatment. None of the patients had prior treatment with other radiolabelled somatostatin analogs. The prerequisites for treatment were: Hb ≥100 g/l, WBC ≥2x10⁹/l, platelets ≥100x10⁹/l, serum creatinine ≤150 µmol/l and a Karnofsky Performance Score ≥50.

Methods. The somatostatin analog DOTATOC was synthesized in-house according to a previously published procedure and radiolabelled with the pure β-emitter 90Y, as published previously (24-26). Yttrium-90 was purchased from Perkin Elmer Inc. (labelling yield > 99.5%). For imaging procedures, 111 MBq of 111In-octreotide-scintigraphy (OctreoScan®; Mallinckrodt, The Netherlands) was started according to a previously published procedure and the radiopharmaceutical purity were checked using C18-RP-HPLC (Wellesley, MA, USA). The labelling yield and the radiopharmaceutical purity were checked using C18-RP-HPLC (labelling yield > 99.5%). For imaging procedures, 111 MBq of 111In-DOTATOC, prepared similarly, were added for each injection. Indium-111 was purchased from Tyco Healthcare (Petten, The Netherlands).

An infusion of amino acids (Hartmann-HEPA 8% amino acid solution; B. Braun Medical AG, Sempach, Switzerland) was started each time 30 minutes before the administration of the radiopharmaceutical and lasted up to 3 hours afterwards. The total treatment dose was 162 mCi/m² body surface for 41 patients and 200 mCi/m² for 75 patients. Eighty patients were treated in 4 sessions every 6 weeks and 36 were treated twice with an interval of 8 weeks.

Routine hematology, liver and kidney parameters were checked before every treatment cycle and every 2 weeks after the last treatment up to 8 weeks.

Fifty-seven patients filled out a detailed questionnaire using the National Cancer Institute grading criteria (NCI-CTC) before and after each cycle of treatment. For the other patients, the questionnaire was not available at the time.

Four weeks before the first and 8-12 weeks after the last treatment cycle, tumor growth and tumor response were monitored by either CT, MRI or sonography. Tumor response was defined according to the WHO standard criteria and was evaluated again 3 months later. The side-effects of 90Y-DOTATOC treatment were investigated and scored according to the NCI-CTC.

Results

The study population comprised 116 patients (mean age 53.3 years) with metastatic NET. Forty-five patients had a neuroendocrine pancreatic tumor, 28 had a NET of unknown primary, 24 had an intestinal NET, 10 had a bronchial NET and 9 patients had other NET. One hundred and nine patients were progressive at the time of inclusion and 7 patients had a symptomatic stable disease (carcinoid syndrome and/or tumor-related pain). All the patients had been pretreated with other modalities (surgery and/or chemotherapy and/or octreotide and/or external beam radiation). Eighty patients were treated with 4 treatment cycles and 36 patients with 2 treatment cycles. Of the 80 patients treated with 4 cycles, 41 received a total injected activity of 162 mCi/m² body surface 90Y-DOTATOC. The other 39 were injected with a total activity of 200 mCi/m² body surface. Thirty-six patients received 2 treatment cycles with a total injected activity of 200 mCi/m² body surface 90Y-DOTATOC.

Nausea and vomiting within the first 24 hours after the injection of the radiopharmaceutical occurred in 23% of the patients. No serious adverse events occurred during or after the treatment.

A WHO toxicity lymphopenia grade 3 or pancytopenia grade 3 occurred in 9 (8%) and 3 (3%) of the patients, respectively. One renal toxicity grade 4 with need for hemodialysis occurred. No other toxicity > grade 2 was found.

The effects of the therapy on the tumor size were evaluated in all patients. Eight to 12 weeks after the final administration, complete remissions were found in 5 patients (4%), a partial remission in 26 patients (22%) and stabilization of the disease (including minor responses) in 72 patients (62%). Thirteen (11%) of the patients remained progressive. An example of a patient who achieved a partial remission is shown in Figures 1 and 2.

Fifty-seven consecutive patients completed a detailed clinical benefit questionnaire about their disease history and their clinical features. They scored all symptoms according to the NCI-CTC before and after each treatment cycle. The symptoms of malignant carcinoid syndrome decreased significantly. A significant reduction of clinical features was found in 83% of patients with diarrhea, in 46% of patients with flushes, in 63% of patients with wheezing and in 75% of patients with pellagra. Those patients suffering from tumor-related pain achieved a significant reduction. All patients (5/57) with morphine-dependent tumor-associated pain were able to change to NSAID or to stop all pain relief medication completely.

Discussion

The results of this clinical study, on the antitumor effects and quality of life benefits in patients with NET after targeted radionuclide treatment with 90Y-DOTATOC, are most encouraging.

Several studies have shown the effectiveness of treatment with radiolabelled somatostatin analogs, however the number of patients in these studies was relatively low. Here, the use and effectiveness is shown on a collective of 116 patients. A problem faced in these studies of patients suffering from metastatic NET is the inhomogeneity of the patient cohort. There is no simple classification system available for grading the aggressiveness and the extension
of these tumors; therefore, comparison with other treatment modalities and other studies is very difficult.

We found an objective response rate of 26% in our patients. The treatment was generally well-tolerated and the toxicity was acceptable. Using an amino acid co-infusion, the renal toxicity was tolerable. The side-effects of the treatment with $^{90}$Y-DOTATOC were few and mostly transient.

The objective response rates for other modalities reported in the literature are clearly lower. For non-radiolabelled somatostatin, the objective response rate
ranged from 0 to 9% (5, 10, 11) and Interferon showed objective response rates from 7 to 20% (12, 13). Single-agent chemotherapy should be considered inactive. Studies with combinations of chemotherapy reported objective response rates from 0 to 33%. In these trials, in which high response rates were achieved, considerable side-effects were shown (5).

In this study, the results of previous studies with $^{90}$Y-DOTATOC and with other radiolabelled somatostatin analogs were confirmed.

In our opinion, targeted radionuclide therapy with radiolabelled somatostatin analogs is the most suitable treatment currently available for metastatic, progressive or symptomatic NET. The treatment achieves high objective response rates and improvements in the quality of life.

It has been shown previously, in animal experiments, that $^{90}$Y-labelled somatostatin analogs are more effective for larger tumors and that $^{177}$Lu-labelled somatostatin analogs are more effective for smaller tumors (27-29). A combination of the two radionuclides could potentially improve the results. In external beam radiation, the use of radio-sensitizers is very common (30, 31). In the near future, the use of such substances in combination with targeted radionuclide therapy should be evaluated.

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