Treatment with High Dose [^{111}In-DTPA-D-PHE^{1}]-Octreotide in Patients with Neuroendocrine Tumors

Evaluation of Therapeutic and Toxic Effects

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Carcinoid tumors and endocrine pancreatic tumors often express somatostatin receptors (sst). Tumor spread may be visualized by sst scintigraphy using [^{111}In-DTPA-D-Phe^{1}]-octreotide. In this study, tumor targeting therapy with [^{111}In-DTPA-D-Phe^{1}]-octreotide at high doses (6 GBq every third week) was used to treat patients with sst-expressing tumors. Five patients entered the protocol and three were evaluable for response, while all could be evaluated for toxicity. Two patient responded with a significant reduction in tumor markers ($> 50\%$). The third patient showed increasing levels of tumor markers. Side effects were expressed as depression of bone-marrow function. In one patient a grade 4 reduction in platelet count was observed requiring several thrombocyte transfusions. In another two patients platelet counts decreased significantly. We conclude that treatment with [^{111}In-DTPA-D-Phe^{1}]-octreotide can be used in patients with neuroendocrine tumors but blood parameters have to be carefully monitored to avoid severe side effects.

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Somatostatin receptors (sst) are expressed in many different human tumors, including neuroendocrine tumors such as carcinoid and endocrine pancreatic tumors, breast cancers and pheochromocytomas (1). The sst family belongs to the seven transmembrane receptor family and five different subtypes have been cloned (2–4). The presence of the receptors was initially shown by autoradiography on tissue sections (5). The subtype expression can now be detected by in situ hybridization for subtype specific mRNA (6). For clinical use the in vivo method with sst scintigraphy has become widely used and is now part of the basic diagnostic procedure for patients with neuroendocrine tumors (7).

The ligand somatostatin acts as an inhibitory peptide and decreases the secretion of other hormones such as growth hormone, glucagon and gastrin (8). Natural somatostatin has a short half-life in plasma and therefore long-acting analogues have been developed (9). In clinical practice patients with neuroendocrine tumors are treated with these synthetic somatostatin analogues, such as octreotide, in order to reduce hormone levels and related symptoms (10).

The scintigraphic technique is frequently used to visualize and stage patients with sst-expressing tumors (11, 12). Studies of the biodistribution show a high uptake of octreotide in these tumors. In fact, tumor to blood ratios of 200 have been obtained in patients injected with between 100 and 200 MBq [^{111}In-DTPA-D-Phe^{1}]-octreotide, which is 0.254% of injected dose. However, the dose in the liver, kidney and spleen could be considerably high (0.01–0.075% of injected dose) and this may cause side effects (13). No data on bone marrow uptake are available so far. The possibility of using the scintigraphic compound for tumor targeting therapy has drawn much attention during the past few years and both [^{111}In-DTPA-D-Phe^{1}]-octreotide and other radioactively labeled somatostatin analogues have been used in small clinical trials (14, 15). We have used this compound since 1995 for treatment purposes, and our initial schedule included treatment with 3 GBq of [^{111}In-DTPA-D-Phe^{1}]-octreotide every fourth

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Table 1

Patients characteristics

No.	Sex	Age*	Diagnosis	No. of octreoscan treatments	Previous treatment
1	F	46	Midgut carcinoid tumor	8	Interferon, octreotide, chemotherapy
2	F	65	Non-functioning endocrine pancreatic tumor	4	Interferon, octreotide, chemotherapy
3	F	48	Insulinoma	2	Interferon, octreotide, chemotherapy
4	M	49	Midgut carcinoid tumor	6	Interferon, octreotide
5	M	52	Midgut carcinoid tumor	2	Interferon, octreotide, chemotherapy

* Years.

week. Altogether, we have treated 7 patients with neuroendocrine tumors according to this dose regimen. All these patients were in the very late stages of the disease and received 1–3 treatments. Thus, all of these patients received only a few treatments and all progressed during treatment. None of the patients responded either by a reduction in hormone levels or by a decrease in tumor size. No side effects were noted.

Since this dose regimen was ineffective, a new schedule was initiated with higher doses of [^{111}In-DTPA-D-Phe^{1}]-octreotide being administered. Only patients with a high tumor uptake of radionuclide were included and the interval between doses was shorter. We anticipated that this regimen should induce a higher rate of clinical responses, but also that there might be side effects. In this paper we report on our experiences from the first five patients treated with the new dose regimen.

MATERIAL AND METHODS

Patients

Five patients with neuroendocrine tumors have so far been included in this study (for patients characteristics, see Table 1). The patients had malignant tumors with multiple liver metastases and had received standard medication before entering the study. All patients were in a progressive state and all had an uptake grading equal to or exceeding 4 in a 5-point graded scale (Table 2.). All patients had a Karnofsky performance status of over 70.

Diagnostic sst scintigraphy

Sst scintigraphy for visualization of tumor spread and assessment of radionuclide uptake intensity was performed as described previously (16). Patients were injected intravenously with 100–200 MBq [^{111}In-DTPA-D-Phe^{1}]-octreotide (Mallinckrodt Medical of Petten, The Netherlands). About 24 h after the injection, static anterior–posterior images were collected, and a SPECT investigation (single photon emission computed tomography) was carried out over the abdomen using a gamma scintillation SPECT camera equipped with a medium-energy general purpose collimator (Nuclear Diagnostics, Hägersten, Sweden and London, UK). The collection of original data for the SPECT images was performed using a 64-step rotation of 360° in a 64×64 word matrix. Energy windows of 173 and 247 keV ($\pm$ 10%) were used. The collection time for each angle was 40 s, giving a total of about 30000 to 40000 counts/angle. For the reconstruction of SPECT images a Wiener filter was applied to the original data. The radionuclide uptake in the tumors was assessed and quantified in 5 degrees (see Table 2), and only patients with grade 4–5 uptake were included.

[^{111}In-DTPA-D-Phe^{1}]-octreotide therapy

Patients were injected with [^{111}In-DTPA-D-Phe^{1}]-octreotide at a dose of 6 GBq as an intravenous infusion in 100 ml physiological saline in a system primed with albumin. The infusion took about 10 min. A special device was used to rinse the system of radioactivity before disconnecting the system from the patient. The amount of octreotide administered was 40 μg and this dose was given every fourth week.

Monitoring

Patients were monitored for bone-marrow function (hemoglobin, leukocyte count and thrombocyte count) before and every second week between treatments and for liver and kidney function (bilirubin, liver enzymes and

Table 2

The grading of radionuclide uptake at somatostatin receptor scintigraphy

Grade	Appearance at somatostatin receptor scintigraphy
1	No radionuclide accumulation in known tumor lesions
2	Suspected but not certain radionuclide uptake in known tumor lesions
3	Radionuclide accumulation in known liver metastases, intensity less or the same as normal liver uptake
4	Pathological uptake of radionuclide in known liver metastases, higher intensity than normal liver uptake
5	Very high radionuclide uptake in known metastases

creatinin) before each treatment. Relevant hormone levels were checked before inclusion into the study and thereafter before every treatment. At least three doses of [^{111}In-DTPA-D-Phe^{1}]-octreotide had to be given before the outcome of the treatment could be assessed. In the carcinoid patients plasma levels of chromogranin A and urinary levels of 5-hydroxyindoleacetic acid were measured. In patients with endocrine pancreatic tumors, levels of chromogranin A were determined together with hormones produced by the tumor including gastrin, insulin and glucagon. For evaluation of tumor size, computed tomography and ultrasound investigations were used. Scintigraphic images for verification were performed 24, 48 and 72 h after each treatment session. In addition, emission of radioactivity was monitored by external measurements daily until the emission was below 20 mSv/h. During the time the emission was greater than 20 mSv/h the patient had to be isolated in the hospital in accordance with Swedish radiation safety regulations.

RESULTS

Objective response

Treatment could be evaluated in 3 patients, while toxicity could be evaluated in all 5 patients treated. In the two patients who were not evaluated for response, only two courses of treatment were administered (see Table 1). Two of the three patients evaluable for clinical response showed a decrease in hormone levels during treatment with [^{111}In-DTPA-D-Phe^{1}]-octreotide. One of these patients (patient no. 4) had a midgut carcinoid tumor and in this patient chromogranin A levels in plasma decreased from 10.7 ng/mL before start of treatment to 5.3 ng/mL after five treatments with [^{111}In-DTPA-D-Phe^{1}]-octreotide. In this patient urinary levels of 5-hydroxyindoleacetic acid remained stable. In the other responding patient (patient no. 2) chromogranin A levels decreased from 230 to 43 ng/mL, gastrin levels from 178 to 54 pmol/L and glucagon from 565 to 55 pg/mL (see Figs. 1 and 2). This patient showed an improvement in performance status and a marked decrease in symptoms. The third evaluable patient who had received [^{111}In-DTPA-D-Phe^{1}]-octreotide treatment showed an increase in both chromogranin A levels from 42 to 97 ng/mL and in urinary 5-hydroxyindoleacetic acid from 1 272 to 1 757 μmols/24 h.

Tumor size remained unchanged in all patients.

Scintigraphy

No change in the uptake pattern of the [^{111}In-DTPA-D-Phe^{1}]-octreotide was seen during the 24–72 h post-injection interval or after each treatment in the patients.

Toxicity

During treatment, patients were monitored for hematology, liver function and kidney function. In three patients blood parameters including hemoglobin concentration, leukocyte count and platelet count fell during treatment. In one patient the platelet count decreased to $< 10 \times 10^{9}$/l after two injections of [^{111}In-DTPA-D-Phe^{1}]-octreotide, and this patient required transfusions with platelets several

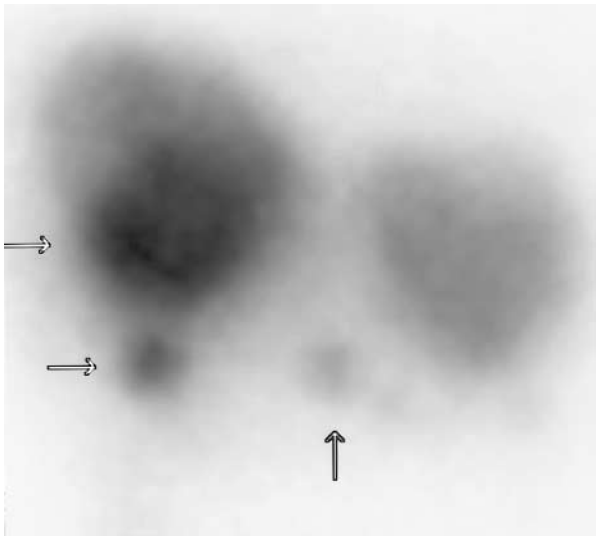

Fig. 1. Frontal planar scintigraphic image over the abdomen of patient no. 4. The image is collected 24 h after administration of 6 Gbq [^{111}In-DTPA-D-Phe^{1}]-octreotide. Arrows show uptake grade 4 in the liver and uptake grade 2 in a lymph node metastasis in the center of the abdomen.

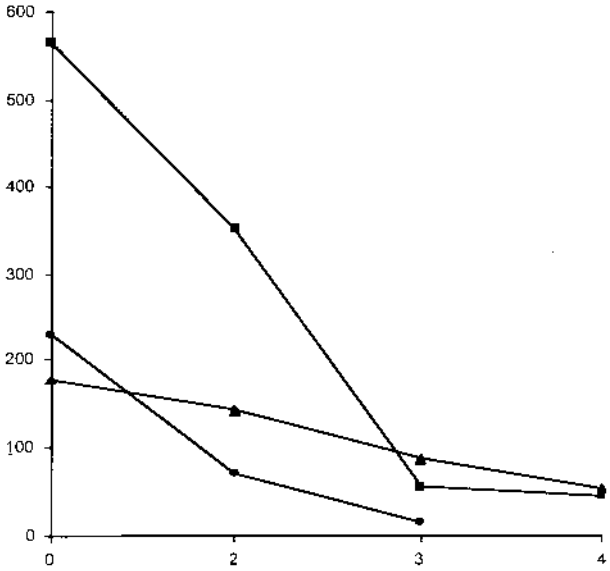

Fig. 2. Hormone levels in the patient with a non-functioning endocrine pancreatic tumor before and during treatment. Levels of all hormones measured, chromogranin A, glucagon and gastrin, decrease during treatment. 0 indicates basal levels, before first treatment, 2 indicates levels before second treatment, 3 indicates levels before third treatment and 4 levels before fourth treatment. CgA: chromogranin A. ● CgA ng/ml, ▲ gastrin pmol/L, ■ glucagon pg/ml.

times before the levels began to increase. In two other patients platelet counts fell to below 100×10^9/l, and in these patients treatment had to be postponed for 1–2 weeks. It is worth noting that severe thrombocytopenia was observed mainly in those patients who recently had received chemotherapy. There was also a slight decrease in hemoglobin levels in four patients, but none needed transfusions. Leukocyte count fell from normal levels to $< 3 \times 10^9$/l in two patients, but there were no associated infections and none of the patients needed injections with granulocyte-stimulating factors. There was commensurate fall in granulocyte and lymphocyte counts, and liver and kidney function tests remained stable and normal during the treatment courses.

DISCUSSION

Treatment with tumor-targeting agents has attracted much attention during the past few years. Previously, treatment with radiolabeled monoclonal antibodies was used in B-cell lymphomas (17, 18) and radioactively labeled metaiodobenzylguanidine for neuroblastomas (19) with encouraging results. Five years ago speculation was raised about the possibility of treating patients with sst-expressing tumors and in 1996 the first report on this type of treatment was published (14).

Our data show high uptake in tumor tissue, but to varying degrees (13). Some of the variation may, in carcinoid patients, be caused by different degrees of fibrosis in the tumor. It has been suggested that the [^{111}In-DTPA-D-Phe^1]-octreotide molecule has to be internalized into the cell interior to be effective (14). The gamma rays emitted by ^{111}In have too high an energy level to cause cell damage and the radiobiological effect has been designated to Auger electrons emitted by the isotope (20). In order to be internalized the [^{111}In-DTPA-D-Phe^1]-octreotide has to bind to ssts on the tumor cells and there are data suggesting that internalization is most effective in cells expressing sst subtypes 3 and 5 (21). Therefore it might prove to be important not only to evaluate the uptake of [^{111}In-DTPA-D-Phe^1]-octreotide on the scintigram, but also to check each patient's set of sst subtypes expressed. Such studies are now being initiated.

In our study it has been shown that treatment with [^{111}In-DTPA-D-Phe^1]-octreotide is effective and we have seen both objective responses with decrease in tumor markers and subjective responses. The dose used in the present study is higher than previously reported (14) and we have seen severe toxicities expressed as depression of bone-marrow function with reduction in platelet counts. It is worth noting that the same kind of side effect was also seen in patients treated with an alternative isotope, the ^{90}Y-[DOTA-D-Phe^1-Tyr^3]-octreotide (22), and in the recently published study with [^{111}In-DTPA-D-Phe^1]-octreotide (15). The patient in our study who had a grade 4 toxicity with a severe decrease in platelet count had previously been treated with chemotherapy including a combination of cisplatinum and etoposide, and another combination of Taxol and doxorubicin. Thus, the bone marrow had already been depressed by these previous treatments. We therefore suggest that patients intended for [^{111}In-DTPA-D-Phe^1]-octreotide treatment should have normal bone-marrow function before treatment is initiated, and blood parameters should be carefully monitored between treatments.

We suggest that treatment with [^{111}In-DTPA-D-Phe^1]-octreotide can be used in patients with neuroendocrine tumors with a high expression of ssts when other treatment has failed. Depression of bone-marrow function has in our material been the dose-limiting factor. Careful monitoring of blood parameters must be carried out during treatment periods before each therapy session and in-between therapies. The maximum number of treatments until toxicity appears in other organs has still to be established. Using the present therapy concept, the kidneys receive a high dose of irradiation. Kidney toxicity will most likely appear when many treatments have been administered. In our department we will proceed with the study administering 6 Gbq every month up to a total of 12 treatments.

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