Systemic Radionuclide Therapy Using Indium-111-DTPA-D-Phe^1-Octreotide in Midgut Carcinoid Syndrome

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A 55-yr-old woman with a midgut carcinoid syndrome due to metastatic spread of an ileal tumor to the liver, paraortic and mediastinal lymph nodes and to the skeleton was given systemic radionuclide therapy with ^{111}In-DTPA-D-Phe^1-octreotide. Before therapy, dosimetric calculations were performed on whole-body scintigraphs and ^{111}In retention was shown to be long-lasting. Excretion was mainly seen during the first 24 hr after injection; thereafter whole-body retention remained stationary at 30%. Indium-111 activity in tumor biopsies and blood was measured using a gamma counter. Very high tumor-to-blood ratios were obtained: 150 for the primary tumor and 400–650 for liver metastases, which further justified radiation therapy. Indium-111-DTPA-D-Phe^1-octreotide treatment was given on three separate occasions (3.0, 3.5 and 3.1 GBq) 8 and 4 wk apart. After each therapy, the patient experienced facial flush and pain over the skeletal lesions followed by symptomatic relief, even though no objective tumor regression was found radiologically after 5 mo. After initiation of octreotide treatment, there was a 14% reduction of the main tumor marker, urinary 5-HIAA. After three subsequent radionuclide therapies, there was a further 31% reduction of 5-HIAA levels. No adverse reactions, other than a slight decrease in leukocyte counts, were seen. The mean absorbed radiation dose after the three treatments was estimated to be about 10–12 Gy in liver metastases and 3–6 Gy in other tumors, depending on the size and location of the metastases. Assuming internalization of ^{111}In into tumor cells and a radiobiological effect from short range Auger and conversion electrons, there might be a therapeutic effect on the tumor.

Key Words: Indium-111-DTPA-D-Phe^1-octreotide; systemic radionuclide therapy; midgut carcinoid

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By binding and autoradiographic studies using radiolabeled native somatostatin, or its analogs, gut carcinoid tumors have been shown to possess a high number of somatostatin receptors (*1,2*). The use of octreotide, a long-acting somatostatin analog, has become a well-established treatment to reduce excess secretion of biogenic amines and peptides from these tumors (*3*). The introduction of ^{111}In-DTPA-D-Phe^1-octreotide scintigraphy has added important information for surgical treatment (*4–6*). Recently five subtypes of somatostatin receptors (SSTR), belonging to the superfamily of G-protein coupled receptors with seven transmembrane domains, have been cloned. The pharmacological profiles of SSTR subtypes have revealed that the affinity for octreotide is most pronounced for SSTR 2 and 5. SSTR 2 may possibly be the main target receptor for octreotide, responsible for both scintigraphic tumor visualization and antisecretory effects (*7*).

Measurements of ^{111}In activity concentration in surgical biopsies of tumor tissues and blood in patients with neuroendocrine tumors, using a gamma counter after preoperative injection with ^{111}In-DTPA-D-Phe^1-octreotide, have demonstrated very high tumor-to-blood (T/B) ratios, especially for carcinoids and certain endocrine pancreatic tumors (*8*). Our preliminary studies on primary human carcinoid tumor cell cultures after incubation with ^{111}In-DTPA-D-Phe^1-octreotide have indicated internalization of ^{111}In. Internalization of ^{111}In could lead to an enhanced radiobiological effect from Auger and conversion electrons with very short range. These findings together with the reports from Krenning et al. (*9*) encouraged us to use ^{111}In-DTPA-D-Phe^1-octreotide for systemic radionuclide therapy.

CASE REPORT

A 55-yr-old woman presented with midgut carcinoid syndrome associated with elevated urinary levels of 5-HIAA (630 μmole/24 hr; ref. <50) and attacks of severe facial flushing and hypotension. CT, octreotide scintigraphy and bone scintigraphy demonstrated metastatic spread to the liver, paraortic and mediastinal lymph nodes, and to the skeleton. CT of the liver underestimated the hepatic tumor volume because numerous small lesions (<1 cm) were not visualized. Tumor volume was better assessed by lipiodol angiography and subsequent CT scans (Fig. 1). Since the tumor burden was large (>50% of the liver volume), hepatic embolization therapy was considered to be a relatively high-risk procedure (*10*). It was therefore decided to administer systemic radionuclide therapy.

Methods

After treatment with octreotide (100 μg × 3) for 4 wk, the patient was given a second diagnostic dose of 280 MBq ^{111}In-DTPA-D-Phe^1-octreotide to enable measurements on surgical biopsies and dosimetric calculations. Repeat whole-body scintigraphy was performed 0.5, 5, 24, 48 hr and 5 and 6 days after injection (Fig. 2). A gamma camera equipped with a medium-energy, parallel-hole collimator connected to a computer system was used (*6*). The first acquisition performed 0.5 hr after injection (no voiding) was assumed to represent 100% radionuclide retention. Excretion was mainly seen during the first 24 hr after injection, whereafter whole-body retention remained stationary at approximately 30% (Figs. 2, 3). Surgery was performed on the 7th day after injection of the radiopharmaceutical. The primary tumor and three liver metastases were excised and blood samples were collected. The ^{111}In activity concentration in tumor (T) and blood (B) was measured using a gamma counter (*8*). Very high T/B ratios were obtained: 150 for the primary tumor and 400–650 for the liver metastases. Experimental studies performed on tumor cell cultures of the hepatic metastases showed binding and internalization of ^{111}In into tumor cells. Northern blot analysis of the liver

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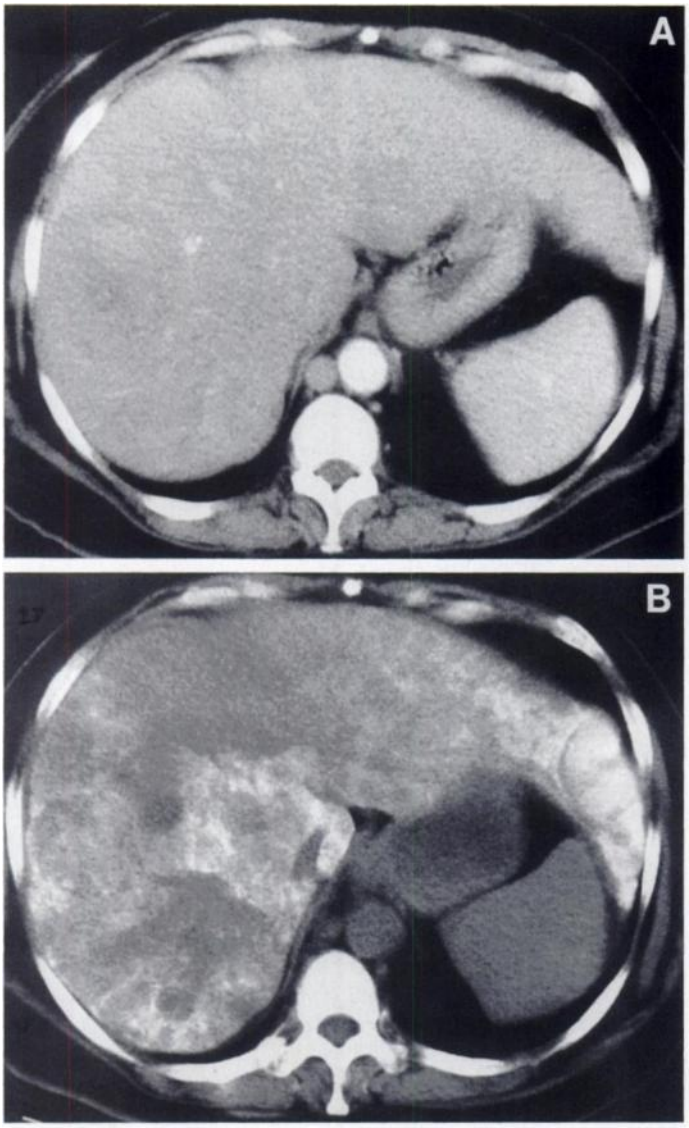

FIGURE 1. Comparison of CT before (A) and 1 day after (B) injection of lipiodol into the hepatic artery. After lipiodol injection, tumor visualization, in accordance with the surgical findings, was obtained.

metastases showed expression of SSTR 2 and 5 m-RNA, the two somatostatin receptors with the highest affinity for octreotide (Fig. 4).

Dosimetry. The mean absorbed radiation dose was calculated for several organs by quantification of organ uptake from the scintigraphic images. The calculations were performed according to the MIRD formalism (*11*). After injection of 280 MBq ^{111}In-DTPA-D-Phe^1-octreotide the estimated mean absorbed dose in the following organs were: liver (with metastases) 0.59, spleen 0.35 and kidney 0.20 mGy/MBq. A rough estimation of the maximal mean absorbed radiation dose to the red bone marrow, assuming that the whole-body content of ^{111}In minus the ^{111}In in the liver, spleen, kidneys and urinary bladder was only distributed in the red bone marrow, resulted in 0.2 mGy/MBq.

Systemic Radionuclide Therapy

Systemic radionuclide therapy with ^{111}In-DTPA-D-Phe^1-octreotide was given on three separate occasions 8 and 4 wk apart. At each therapy, the patient received 40 μg octreotide labeled with 3.0, 3.5 and 3.1 GBq ^{111}In, respectively. The radiopharmaceutical was given as 4–6 slow i.v. injections through a central venous catheter. DTPA-D-Phe^1-octreotide and $^{111}InCl_3$ were delivered in separate vials. One milliliter NaCl was added to each of the four vials containing 10 μg DTPA-D-Phe^1-octreotide. The dissolved DTPA-D-Phe^1-octreotide was then added to the vials containing

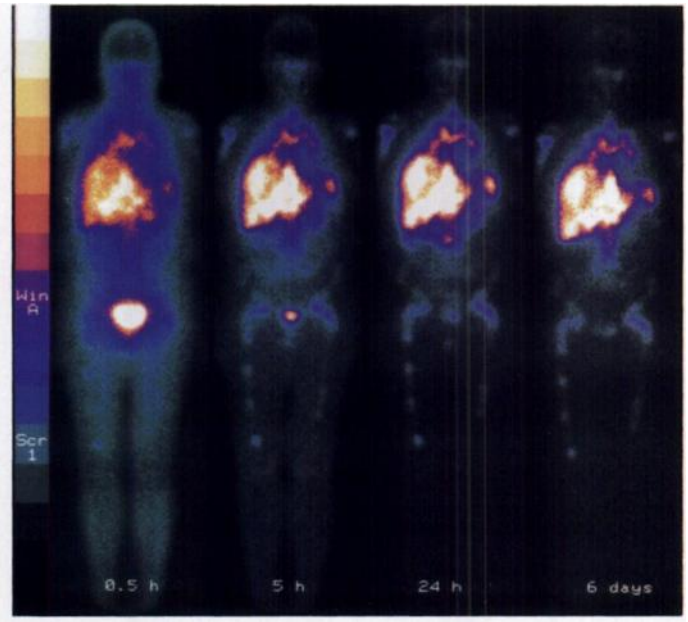

FIGURE 2. Anterior views of whole-body scintigraphy performed 0.5, 5, 24 hr and 6 days after injection of 280 MBq ^{111}In-DTPA-D-Phe^1-octreotide.

$^{111}InCl_3$. After incubation for 30 min, thin-layer chromatography of the radiopharmaceutical was performed. Silicon gel impregnated glass fiber sheets was used as the stationary phase and Na-citrate (0.1 *M*, pH 5) as the mobile. The fraction of peptide bound ^{111}In was >98%.

After each therapy, the patient stayed in a lead-shielded room under close monitoring of symptoms and biochemical responses for 3 days. The long-term treatment with octreotide was discontinued 12 hr before injection and reinstituted 12 hr later so as not to compete with ^{111}In-DTPA-D-Phe^1-octreotide uptake. Whole-body scintigraphy was performed up to 3 wk after each therapy. To avoid deadtime losses in the gamma camera when performing scintigraphy early after therapy, a 1-mm lead shield was attached to the collimator and the measured count rate was corrected for attenuation in the shield. Whole-body radiopharmaceutical retention and distribution was similar for the diagnostic and therapeutic doses (Fig. 3).

By using the diagnostic dose of ^{111}In-DTPA-D-Phe^1-octreotide for dosimetric calculations, it was estimated that the absorbed radiation dose in a liver metastasis after the three treatments would be about 10–12 Gy and in other tumors 3–6 Gy, depending on

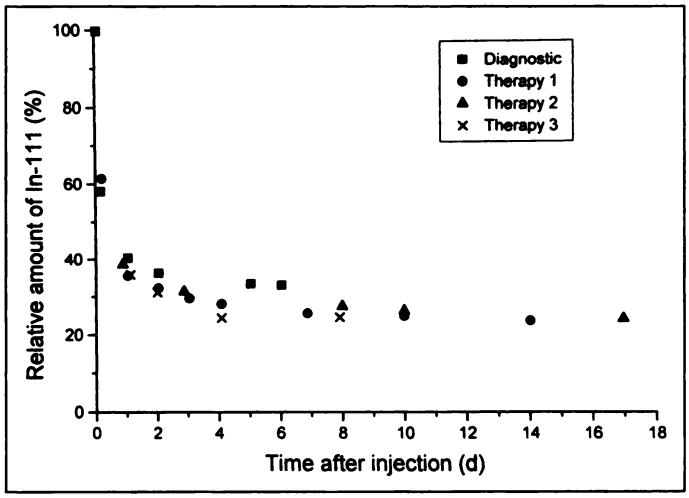

FIGURE 3. Whole-body retention of ^{111}In after injection of diagnostic and therapeutic doses of ^{111}In-DTPA-D-Phe^1-octreotide.

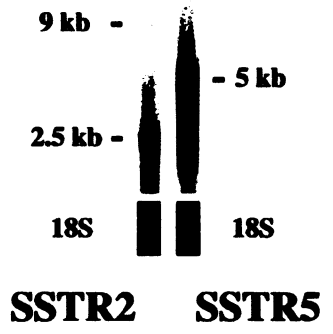

FIGURE 4. Total RNA (20 μg/lane) fractions from a liver metastasis on an agarose gel transferred to nylon membrane and probed with ^{32}P-labeled riboprobes. Moderate amounts of SSTR2 (transcript size 9 and 2.5 kb) were detected (left lane), while SSTR5 (transcript size 5 kb) was highly expressed (right lane). Ethidium bromide-stained gels indicate equal loading of samples (bottom panels).

metastases size and location. In this patient, tumor size and shape are largely unknown making the above calculations of absorbed doses uncertain.

Therapeutic Results

Symptoms. After each treatment with the radiopharmaceutical, the patient developed mild flushing and a bluish discoloration of the lips lasting for 1–2 days. She also experienced severe pain over the skeletal lesions, requiring analgesic medication for several days. No hypotensive attacks, gastrointestinal symptoms or adverse effects to the kidneys were registered.

Hematology. Before ^{111}In-DTPA-D-Phe^1-octreotide therapy, hemoglobin was 116 g/liter and 140 g/liter 4 mo later. During the first weeks after each treatment, the leukocyte count was reduced by 10%–45%. The pretreatment value was 7900/ml and 3300/ml 4 mo later. Minor reductions were seen for platelet counts after each treatment; the initial value was 297 000/ml and 240 000/ml 4 mo later.

Hormones and Tumor Markers. The patient underwent biochemical screening in serum (chromogranin A, serotonin, substance P, VIP, PP, calcitonin) and urine (5-HIAA, MelmAA, catecholamines and VMA). 5-HIAA served as the main tumor marker (Fig. 5). Before and after each treatment, the pituitary hormones (ACTH, GH, FSH, LH, prolactin and TSH), adrenocortical steroids (aldosteron and cortisol), parathyroid hormone and thyroxin were monitored for early detection of possible hyposecretion secondary to radiation therapy. In summary, octreotide treatment caused a 14% reduction of the urinary 5-HIAA levels and ^{111}In-DTPA-D-Phe^1-octreotide therapy caused a further reduction by 31% (Fig. 5). Before onset of treatment, plasma chromogranin A levels were 1500 U/liter (ref. <45). After treatment with octreotide and three systemic radionuclide therapies, the chromogranin A levels were reduced to 280 U/liter. Urinary cortisol and pituitary hormones seemed to be unaffected by the treatment, except ACTH, which showed somewhat decreased levels (from 26 pg/ml to 15 pg/ml; ref. 9–52). After the first treatment thyroxin levels were low (11.7 pmole/liter; ref. 11.7–28.0) and TSH levels increased, which necessitated substitution therapy.

Radiology. Follow-up with CT/MRI 5 mo after the first radionuclide therapy indicated stable tumor disease. No new lesions were visualized, nor was any objective regression of separate lesions demonstrated.

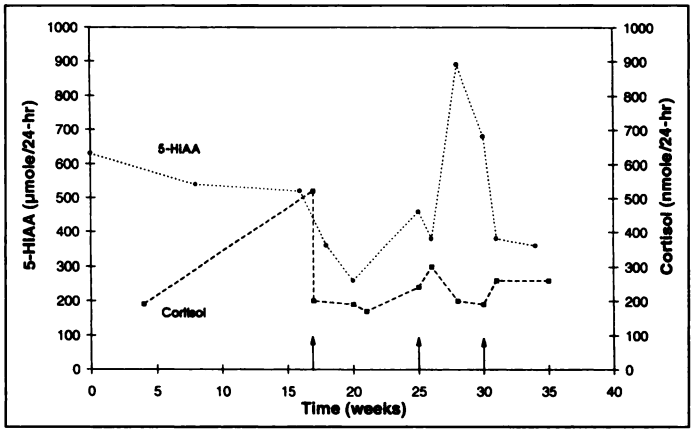

FIGURE 5. Urinary excretion of the main tumor marker (5-HIAA) and cortisol during chronic treatment with octreotide and after three treatments with ^{111}In-DTPA-D-Phe^1-octreotide (3.0, 3.5 and 3.1 GBq) (vertical arrows). Peak values observed at 28–30 wk coincided with a bronchopneumonia.

DISCUSSION

In patients with midgut carcinoid tumors, widespread metastatic disease and severe hormonal symptoms, life expectancy is limited (*12*). In this patient, surgical cure was impossible and palliation by liver arterial embolisation would be hazardous (*10*). Therefore, we attempted systemic radionuclide therapy with somatostatin receptors. This therapeutic regimen was performed after informed consent was obtained from the patient and with approval from the local and national authorities. Three treatments, totaling 9600 MBq, were given 8 and 4 wk apart. The calculated mean absorbed radiation doses in normal organs indicate that high activities of ^{111}In can be given without hazardous effects on normal tissues. Based on the assumption that ^{111}In is internalized into tumor cells, there might be an enhanced radiobiological effect from the short-range Auger and conversion electrons, despite moderate absorbed doses in the tumors judged from our estimations. This interpretation was supported by the marked reduction of 5-HIAA levels and the stationary tumor volume. There were also other clinical signs of radiopharmaceutical tumor effect: flushing and bone pain in association with radionuclide therapy (flare phenomenon) and subsequent symptom palliation.

ACKNOWLEDGMENTS

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