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^{131}I-metaiodobenzylguanidine therapy for malignant pheochromocytoma

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^{131}I-metaiodobenzylguanidine (MIBG) therapy was given to five patients with malignant pheochromocytoma. The patients received 1–3 doses of 3.33–4.625 GBq (total dose: 3.7 to 10.73 GBq). Partial tumor regression was observed in two patients, the tumor was unchanged in two patients, and slow progression was noted in one patient. Marked improvement in clinical symptoms was achieved in four patients. The other patient had no symptoms before ^{131}I-MIBG treatment, but the serum epinephrine and dopamine decreased. There were no severe untoward responses in four patients. However, one patient developed transient but severe orthostatic hypotension, hypertension, and hyperglycemia from 1 week to 1 month after ^{131}I-MIBG administration. Although complete remission was not obtained, all the patients achieved some benefit from ^{131}I-MIBG therapy. Thus, ^{131}I-MIBG appears to be useful for the palliation of malignant pheochromocytoma.

Key words: ^{131}I-MIBG, pheochromocytoma, radionuclide therapy

INTRODUCTION

MALIGNANT PHEOCHROMOCYTOMA or metastasis to other organs occurs in about 10% of pheochromocytoma patients. This tumor is resistant to external radiotherapy or chemotherapy and there has been no effective treatment for widespread metastatic lesions.

^{131}I-metaiodobenzylguanidine (MIBG) is a useful radiopharmaceutical for imaging pheochromocytoma, neuroblastoma, and other tumors of neural crest origin.[1-5] Treatment of these tumors with high doses of ^{131}I-MIBG has also been tried and a good response has been reported in some patients.[6-9]

Between December, 1989 and August, 1993, we treated 5 malignant pheochromocytoma patients with ^{131}I-MIBG. Here we report our experience with ^{131}I-MIBG therapy for this tumor.

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PATIENTS AND METHODS

The patients characteristics are listed in Table 1. All 5 patients had recurrent pheochromocytoma. The length of time between resection of the primary tumor and ^{131}I-MIBG therapy ranged from 29 months to 13 years (mean: 63 months). Three patients had adrenal pheochromocytoma (patients 1, 3, and 4) and two patients had extra-adrenal pheochromocytoma (patients 2 and 5). A diagnostic dose of ^{131}I-MIBG or ^{123}I-MIBG was administered to the patients prior to treatment to confirm specific uptake by their tumors.

^{131}I-MIBG was supplied by Daiichi Radioisotope Laboratory (Tokyo, Japan). Its specific activity was greater than 2.22 GBq/mg.

To block thyroidal uptake of free radioiodine, the patients received 120 mg of potassium iodide daily from 1 week before administration of ^{131}I-MIBG to 3 weeks after the treatment. ^{131}I-MIBG was administered as an intravenous infusion over 1 to 1.5 hours. Patients were housed in an isolation room for one week.

Two or three weeks after administration of the therapeutic dose of ^{131}I-MIBG, scintigrams were taken with whole-body images or spot images.

In patient 5, the blood radioactivity level and the

Table 1 Clinical profile of the patients

Patient	Age	Sex	Clinical Symptoms	Metastatic Lesions
1	67	F	Malaise, Constipation	Lung, Liver, Lymph node
2	57	M	Malaise, Headache	Lung, Bone, Lymph node
3	52	M	Constipation, Back pain	Bone, Lymph node
4	17	F	Episodes of nausea and chest oppression	Liver, Lymph node
5	28	F	none	Bone, Liver, Lymph node

Table 2 Response to ^{131}I-MIBG therapy

Patient	Therapy No.	Dose (GBq)	Responses		
			Tumor	Hormone*	Symptoms
1	1	3.7	partial	partial	improved
	2	3.7	no	no	unchanged
2	1	3.33	partial	partial	improved
	2	4.625	no	no	unchanged
3	1	3.7	no	no	improved
	2	3.515	no	no	unchanged
4	1	3.33	no	no	disappeared
	2	3.7	no	no	no symptom
	3	3.7	no	no	no symptom
5	1	3.7	no	partial	no symptom

*Serum catecholamine levels.

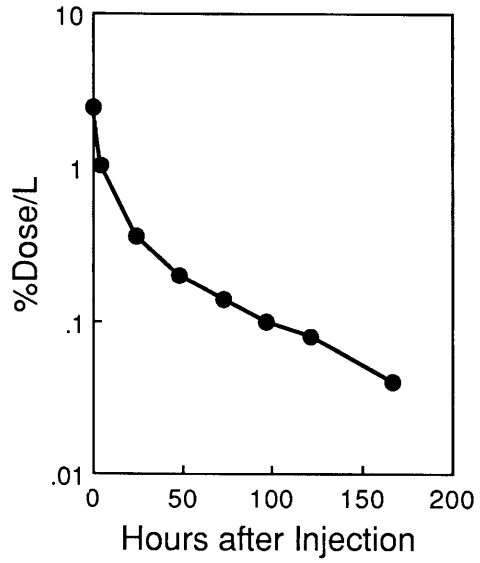

Fig. 1 Blood clearance of ^{131}I-MIBG in patient 5.

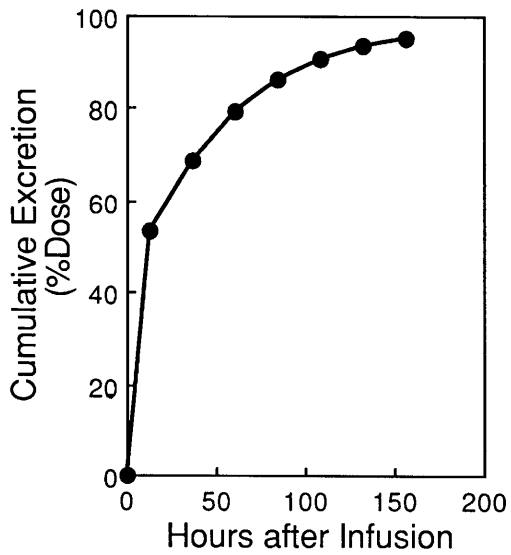

Fig. 2 Urinary excretion of ^{131}I-MIBG in patient 5.

urinary excretion of ^{131}I were measured.

RESULTS

Table 2 summarizes the results of ^{131}I-MIBG therapy. One patient received a single dose, three patients received two doses, and one patient received three doses. The mean interval between doses was 10 months (range: 4–20 months) and the cumulative dose ranged from 3.7 GBq to 10.73 GBq. Partial tumor regression was observed in two patients (patients 1 and 2), the tumor size was unchanged in two patients (patients 4 and 5), and the tumor continued to grow slowly in one patient (patient 3). Marked improvement in subjective complaints occurred in four patients. Patient 5 had no symptoms before or after treatment, but her serum epinephrine and dopamine were decreased by the therapy. Temporary but severe orthostatic hypotension, hypertension, and hyperglycemia were observed in patient 1, but there were no severe untoward reactions in the other four patients. No bone marrow suppression was seen in any of the patients.

The blood clearance of ^{131}I-MIBG was very rapid (Fig.

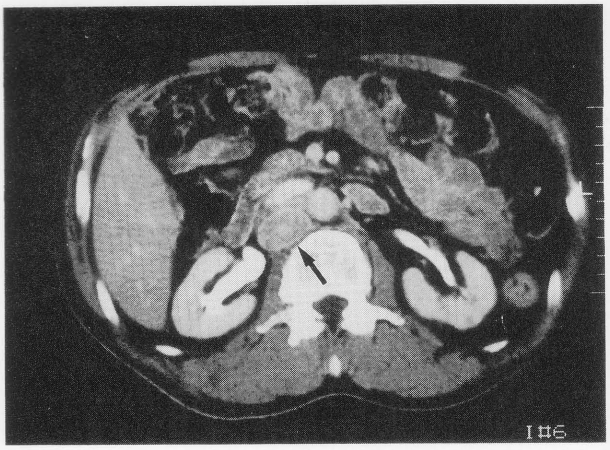

Fig. 3A Metastatic lymph node in patient 2 before ^{131}I-MIBG therapy (arrow).

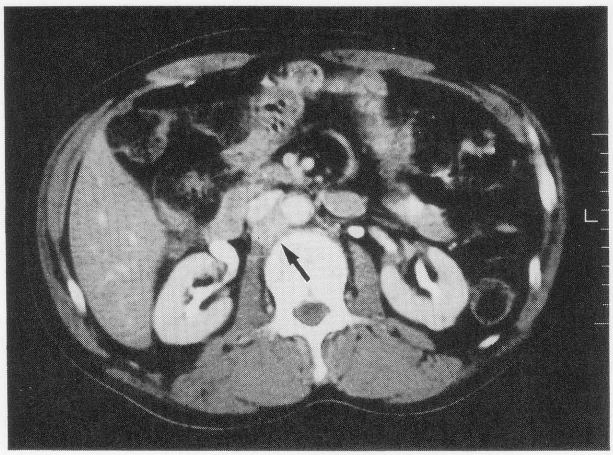

Fig. 3B After treatment, the tumor shrank by more than 50% (arrow).

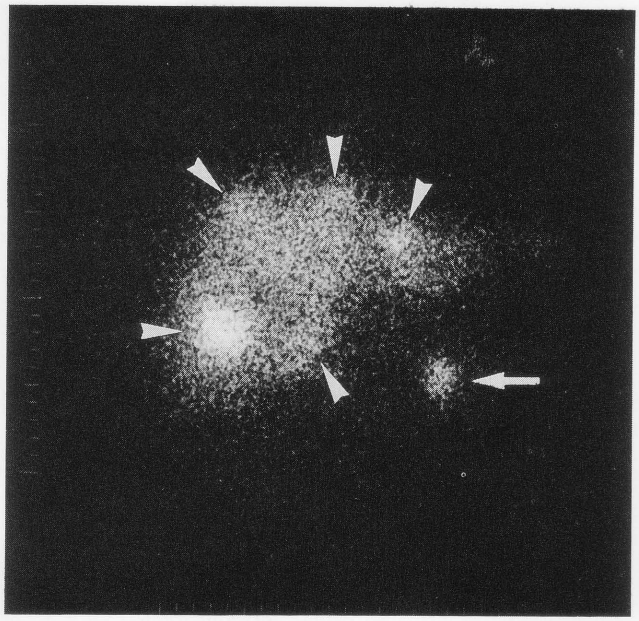

Fig. 4 ^{131}I-MIBG scintigram after administration of a therapeutic dose in patient 4. High uptake can be seen by metastatic lesions in the liver (arrowheads) and the splenic hilum (arrow).

1). At the end of the 1.5-hour infusion, only 2.5% of the injected dose remained per liter of blood. The blood volume of this patient was calculated as 3178.5 m*l* on the basis of her body weight (48.9 kg), so 7.9% of the injected dose remained in the blood at the end of infusion. The clearance curve was biphasic, with the biological half-life being 5.7 hours for the first component and 52.2 hours for the second component.

Urinary excretion of ^{131}I-MIBG is shown in Fig. 2. Fifty-three percent of the injected dose was excreted within 13 hours. If excretion of the injected radioiodine was exclusively via the urine, 762 MBq (20.6% of the injected dose) remained in the body at 3 days after administration.

Case 1

The patient developed malaise and constipation 4 years after the resection of a left adrenal pheochromocytoma. After the first ^{131}I-MIBG treatment, metastatic tumors in the lungs and liver decreased dramatically in size, but the size of the metastatic lymph nodes was unchanged. However the patient's quality of life was improved markedly. Temporary but severe orthostatic hypotension, hypertension, and hyperglycemia developed from 1 week after the administration of ^{131}I-MIBG and were resolved within 1 month. The details of this case have been reported previously.[8] After 12 months, regrowth of the metastatic tumors was confirmed on abdominal CT. She received a second dose of ^{131}I-MIBG 17 months after the first treatment. However, there was no further tumor response and she died 24 months after the first ^{131}I-MIBG treatment.

Case 2

The patient suffered from headache and malaise for 1 year after the resection of an extra-adrenal pheochromocytoma in the lower abdomen. Metastatic tumors in the lungs, bone, and lymph nodes were detected by ^{131}I-MIBG scanning. He received 3.33 MBq of ^{131}I-MIBG in the first treatment. The size of the metastatic lymph nodes decreased by more than 50% on CT scans (Fig. 3), but metastatic lesions in the lungs and bone were unchanged. A temporary decrease in serum and urinary norepinephrine was observed. The norepinephrine level was 21,316 pg/m*l* before MIBG therapy and fell to 4,586 pg/m*l* at 3 weeks after MIBG administration. The patient's antihypertensive therapy dose was decreased and his general condition improved. Because of tumor regrowth he received a second dose of ^{131}I-MIBG. However, there was no response of the metastatic tumors this time and he died 18 months after the first treatment.

Case 3

The patient received ^{131}I-MIBG therapy for multiple bone

metastases. After the first ^{131}I-MIBG treatment, his back pain was dramatically decreased and he no longer required analgesics. However, the size of the tumors was not changed. A second treatment was given 20 months after the first, but no subjective or objective response was observed. His symptoms remained well controlled by alpha-methyl-para-tyrosine except for mild bone pain until 4 years after the first ^{131}I-MIBG treatment, when enlargement of a tumor mass in the thoracic spine caused paraplegia.

Case 4

The patient developed episodic nausea and chest oppression 4 years after the resection of a left adrenal pheochromocytoma. She received a total of 3 therapeutic doses of ^{131}I-MIBG, with the intervals being 5 months and 4 months, respectively. Figure 4 shows a high level of accumulation of ^{131}I-MIBG in the metastatic lesions after the first treatment. The episodes of chest oppression and nausea continued to increase for 2 weeks, but then her symptoms disappeared by 3 weeks after the first ^{131}I-MIBG treatment. She has since been well without any symptoms for 2 years and there has been no change in tumor size.

Case 5

Recurrent tumors were detected in the lymph nodes, liver, thoracic vertebrae and lumbar vertebrae at 13 years after the resection of an extra-adrenal pheochromocytoma, but the patient was asymptomatic. Serum epinephrine and dopamine had decreased temporarily after ^{131}I-MIBG treatment. The patient's serum norepinephrine level was 7,000 pg/m*l* before treatment and it fell to 4,400 pg/m*l* at 3 weeks after MIBG administration. There was no change in tumor size. At present, she suffers from headache and chest oppression at 6 months after MIBG therapy.

DISCUSSION

Although partial tumor regression was seen in only 2 of the 5 patients, symptomatic improvement and pain relief were obtained in 4 patients. It seems to be difficult to achieve a complete cure of malignant pheochromocytoma by ^{131}I-MIBG therapy.[9] However, the palliative effect of this treatment should not be underestimated, because no other effective therapy for malignant pheochromocytoma has yet been described.

In general, it is important to estimate the radiation dose absorbed by the tumor in radionuclide therapy. Although we did not calculate the absorbed dose, Sisson et al. performed ^{131}I-MIBG therapy for malignant pheochromocytoma and reported that the estimated tumor dose was 13–82.5 Gy per 3.7 GBq, with a cumulative dose of 35.1–197.9 Gy after 2 to 4 treatments.[6] In addition, Aritake estimated the absorbed tumor dose to be 5.4–68 Gy per 3.7 GBq and stated that the relief of clinical symptoms was related to the absorbed radiation dose.[7] However, Sisson et al. suggested that factors other than the total dose also play a role in determining the response to treatment.

The tumor response was better after the first treatment than after the second treatment in patients 1 and 2. It seems likely that tumor cells which incorporate more ^{131}I-MIBG or are radiosensitive will be killed first. Accordingly, cells which incorporate less MIBG or are radioresistant will remain and show a relatively poor response to subsequent treatments.[7]

The urinary excretion of ^{131}I-MIBG was rapid in our patient and was comparable to that previously reported,[10] although the tumor uptake of ^{131}I-MIBG was not very high in this patient. The blood clearance and urinary excretion may vary among patients, reflecting differences in tumor uptake.

The severe untoward responses seen in patient 1 are noteworthy and would have resulted from catecholamine release by damaged tumor cells.[8] An increase in chest oppression was temporarily observed in patient 4 and this also probably reflected the tumor response to ^{131}I-MIBG therapy.

In conclusion, ^{131}I-MIBG therapy can be effective for the palliation of advanced pheochromocytoma.

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REFERENCES

1. Sisson JC, Frager MS, Valk TW, Gross MD, Swanson DP, Wieland DM, et al. Scintigraphic localization of pheochromocytoma. *N Engl J Med* 305: 12–17, 1981.
2. Shapiro B, Copp JE, Sisson JC, Eyre PL, Wallis J, Beierwaltes WH. Iodine-131 metaiodobenzylguanidine for the locating of suspected pheochromocytoma: experience in 400 cases. *J Nucl Med* 26: 576–585, 1985.
3. Koizumi M, Endo K, Sakahara H, Nakashima T, Nakano Y, Nakao K, et al. Computed tomography and ^{131}I-MIBG scintigraphy in the diagnosis of pheochromocytoma. *Acta Radiol Diag* 27: 305–309, 1986.
4. Endo K, Shiomi K, Kasagi K, Konishi J, Torizuka K, Nakao K, et al. Imaging of medullary thyroid cancer with ^{131}I-MIBG. *Lancet* ii: 233, 1984.
5. Hoefnagel CA, Voute PA, de Kraker J, Marcuse HR. Radionuclide diagnosis and therapy of neural crest tumors using iodine-131 metaiodobenzylguanidine. *J Nucl Med* 28: 308–314, 1987.
6. Sisson JC, Shapiro B, Beierwaltes WH, Glowniac JV, Nakajo M, Mangner TJ, et al. Radiopharmaceutical treatment of malignant pheochromocytoma. *J Nucl Med* 24: 197–206, 1984.
7. Aritake S. Radioisotope therapy of malignant pheochromocytoma with iodine-131 metaiodobenzylguanidine. Ab-

sorbed dose assessments using SPECT. *KAKU IGAKU (Jpn J Nucl Med)* 29: 667–678, 1992.
8. Okazawa H, Endo K, Saga T, Watanabe Y, Nakai T, Kasagi K, et al. Therapy of malignant pheochromocytoma using I-131 metaiodobenzylguanidine. Report of a case. *Acta Radiol Jpn* 50: 286–294, 1990
9. Hoefnagel CA. Radionuclide therapy revisited. *Eur J Nucl Med* 18: 408–431, 1991.
10. McEwan AJ, Shapiro B, Sisson JC, Beierwaltes WH, Ackery DM. Radio-iodobenzylguanidine for the scintigraphic location and therapy of adrenergic tumors. *Semin Nucl Med* 15: 132–153, 1985.