Therapeutic Effectiveness of Iodine-131 MIBG Metastases of a Nonsecreting Paraganglioma

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This case report describes the treatment of the bone metastases of a nonfunctioning sympathetic paraganglioma, with [\(^{131}\)I]MIBG. After primary tumor excision and unsuccessful external radiotherapy, the patient received three therapeutic doses of [\(^{131}\)I]MIBG, resulting in a reduction of the number and volume of metastases, and an improvement of the general condition. At 3 yr following [\(^{131}\)I]MIBG therapy, the patient remained in remission. [\(^{131}\)I]MIBG appears to be an efficient and safe agent for treating malignant sympathetic paraganglioma.


Radiolabeled meta-iodobenzylguanidine (MIBG) is a functional scintigraphic marker of monoamine uptake (1,2). In the last years, it has been widely used for scintigraphic imaging of amine precursors uptake and decarboxylase (APUD) tumors. These tumors include mono amine secreting tumors such as the pheochromocytoma, neuroblastoma, carcinoid tumors, peptide secreting tumors such as the medullary cancer of the thyroid, and also apparently nonsecreting tumors such as nonfunctioning sympathetic paraganglioma. The latter tumors may be located throughout the body according to the neural crest topography. Aorticosympathetic retroperitoneal paraganglioma have the highest incidence of malignancy (3).

In 1984, we reported the observation of MIBG uptake into bone metastases of a malignant retroperitoneal paraganglioma (4). The aim of the present paper is to report the treatment of the patient with [\(^{131}\)I]MIBG.

CASE REPORT

The patient was a 44-yr-old woman without family history of paraganglioma. In April 1981, she underwent surgery for an abdominal mass, which was found to be a paraganglioma developed from the Zuckerkandl organ. X-ray examination revealed bone metastases in the fourth lumbar vertebra and in the right acetabulum. The results of repeated (four times) assays of urine epinephrine, norepinephrine, and their metabolites were in the normal range. Dopamine concentration in the plasma was <1 nmol.l\(^{-1}\) (normal <2 nmol.l\(^{-1}\)). On the basis of these results, the tumor was held as a nonsecreting paraganglioma. Whole-body scintigraphy after a [\(^{131}\)I]MIBG tracer dose (18.5 MBq) showed a focal uptake in the previously known metastases and the outburst of other tumors in the cervical and dorsal spine (Fig. 1). The conventional bone scintiscan with technetium-99m methylene diphosphonate showed an increase of activity on the lumbar spine and on the right pelvis, but failed to detect the cervical and dorsal metastases. The bone metastases were treated by osteosynthesis of the spine and external radiotherapy from June 1981 to May 1984—lumbar spine 46 Gy, right acetabulum 13 Gy, dorsal spine 23 Gy, cervical spine 24 Gy. Despite the treatment, the disease was rapidly progressive. In August 1984, 12 additional metastatic sites were visible on MIBG scintigraphy. Informed consent was obtained from the patient for a treatment with therapeutic doses of [\(^{131}\)I]MIBG.

The estimate of the therapeutic [\(^{131}\)I]MIBG radiation dosimetry was performed on the basis of measurements after a 18.5-MBq tracer dose (5). Assuming an exclusive urinary excretion, the whole-body retention was calculated as a function of time, from measuring the urine excretion for 7 days after injection. The radiation dose to the urinary bladder was calculated on the basis of an urine flow rate of 1,800 ml/day. The volume of the tumors was calculated from measurements on x-ray films when visible. Their shape was assumed to be spherical or ellipsoid according to measurements along three directions. When the metastatic site was not visible by x-ray and detected only by MIBG scintigraphy, the tumor mass was estimated to be <2 g. When a part or a piece of a vertebra was entirely destroyed by the tumor, the volume was evaluated by using a corpse vertebra as a reference. Taking into account the approximation due to the geometrical model, and a 10% error in diameter measurements, the range of error in the
TABLE 1
Calculated Absorbed Radiation Doses Due to [131I]MIBG Treatments*

<table>
<thead>
<tr>
<th>Tumor radiation dose (Gy)</th>
<th>Body and organ radiation dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T12</td>
<td>745</td>
</tr>
<tr>
<td>C3</td>
<td>633</td>
</tr>
<tr>
<td>Left hip</td>
<td>416</td>
</tr>
<tr>
<td>L4</td>
<td>173</td>
</tr>
<tr>
<td>T7</td>
<td>46</td>
</tr>
<tr>
<td>Right acetabulum</td>
<td>30</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>7.5</td>
</tr>
<tr>
<td>Liver</td>
<td>2.6</td>
</tr>
<tr>
<td>Whole body</td>
<td>0.26</td>
</tr>
</tbody>
</table>

* The range of error due to radioactive concentration error is 35%.

Error in counting measurements was evaluated to 5%. The error in the radioactive concentration was the sum of counting and volume determination errors, 35%. This error propagated and was reflected in the absorbed doses estimates.

The whole-body activity (A(t)) was reduced to 50% of the injected dose 17 hr after injection. The biexponential analysis of the curve resulted in the following equation:

$$A(t) = A(0) \left( 0.65 \ e^{-1.35t} + 0.35 \ e^{-0.47t} \right),$$

with t expressed in days.

FIGURE 1
Initial [131I]MIBG scan, 2/10/83. Posterior whole-body scintiscan 24 hr after 18.5 MBq of [131I]MIBG. Known metastases on the lumbar spine and on the right acetabulum (->) are depicted. Additional metastases are detected on the cervical and dorsal spine (=>).

Volume evaluation was estimated to 30%. In order to calculate the fractional dose uptake, tumor images were obtained using a gamma camera (Searle LFOV) interfaced with a computer (S2000 Sopha Medical). The system was calibrated for counts-min⁻¹ to MBq conversion. Anterior and posterior views of each tumor was obtained, and the thickness of the patient was measured at the level of the tumor, for attenuation correction.

FIGURE 2
Pretherapeutic time activity curves after a [131I]MIBG tracer dose.
Whole-body posterior scintiscan nine days after the first 2.6 GBq $[^{131}I]$MIBG treatment. In comparison with Figure 1, a multiplication of uptake sites is obvious. This is a consequence of the progression of the disease and of increasing detection sensitivity by higher injected $[^{131}I]$ MIBG dose and delayed imaging.

The tumor activity was maximum 24 hr after the injection, 7% of the injected dose, then decreased with a 3.2-day period. After the seventh postinjection day, the activity retained in the body was equal to the activity retained in the tumors (Fig. 2).

The specific activity of the $[^{131}I]$MIBG for therapy was 370 MBq·mg$^{-1}$ (Amersham Netherland, ORIS Industrie France). Five percent Lugol’s solution (30 drops/day) was given for 10 days, starting 2 days before $[^{131}I]$MIBG administration. The therapeutic doses of $[^{131}I]$MIBG were infused intravenously over a 90-min period in a 20-ml volume. The patient stayed for 15 days in a room designed for $^{131}$I thyroid cancer therapy. Three perfusions of 2.6, 3.5, and 3.6 GBq were performed over a 9-mo period. Whole-body scintiscan and tumor activity counting were obtained 3–15 days after the therapeutic dose administrations (Fig. 3). The tumor uptake was found to be 75%–79% of the uptake expected from the tracer dose measurements. This discrepancy could be explained by a difference between the kinetics of the low tracer dose and the high

**FIGURE 3**
Whole-body posterior scintiscan nine days after the first 2.6 GBq $[^{131}I]$MIBG treatment. In comparison with Figure 1, a multiplication of uptake sites is obvious. This is a consequence of the progression of the disease and of increasing detection sensitivity by higher injected $[^{131}I]$ MIBG dose and delayed imaging.

**FIGURE 4**
Comparison between scintiscans before (8/10/84), and after (3/5/87) treatment with $[^{131}I]$MIBG. Both scans are posterior views 24 hr after $[^{131}I]$MIBG 185 MBq. After $[^{131}I]$ MIBG treatment, most of tumoral fixation have disappeared, except slight residual uptake in the dorsal, lumbar, and acetabular metastases.
### TABLE 2
**Time Course of the Patient**

<table>
<thead>
<tr>
<th>Time (yr)</th>
<th>Treatment</th>
<th>Pain</th>
<th>Disability*</th>
<th>$^{[13]}$MIBG number of sites</th>
<th>Bone scan hyperfixation</th>
<th>X-ray</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Primary tumor resection Lumb. spine osteosynthesis ex. rad. L3, L5 46 Gy</td>
<td>Right hip</td>
<td>3</td>
<td>—</td>
<td>L4 lysis</td>
<td>—</td>
</tr>
<tr>
<td>1</td>
<td>Ex. rad. right acetabulum 13 Gy T6, T8 23 Gy</td>
<td>+++</td>
<td>3</td>
<td>—</td>
<td>L4, T7, right acetabulum</td>
<td>L4, right acetabulum lysis</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>3</td>
<td>3</td>
<td>No change</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>3</td>
<td>4</td>
<td>No change</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Cervical spine osteosynthesis ex. rad. C3, C4, 24 Gy $^{[13]}$MIBG 2.6 GBq</td>
<td>Neck, back</td>
<td>4</td>
<td>5</td>
<td>T2, T7, T12, L4 right acetabulum</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Left hip</td>
<td>3</td>
<td>10</td>
<td>No change</td>
<td>Left femoral demineralization</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>$^{[13]}$MIBG 3.5 GBq</td>
<td>0</td>
<td>1</td>
<td>16</td>
<td>—</td>
<td>No change</td>
</tr>
<tr>
<td>5</td>
<td>$^{[13]}$MIBG 3.6 GBq</td>
<td>Back</td>
<td>1</td>
<td>14</td>
<td>—</td>
<td>T12 body lysis</td>
</tr>
<tr>
<td>6</td>
<td>Ex. rad. T12, L1, 30 Gy</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>T12 body reconstruction</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>—</td>
<td>—</td>
<td>T12 body reconstruction</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>—</td>
<td>—</td>
<td>T12 body reconstruction</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>T7, T12</td>
<td>Left femoral remineralization</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>Right acetabulum</td>
<td>Edge of densification of the right acetabulum</td>
<td></td>
</tr>
</tbody>
</table>

* Performance status according to Ref. 7.
Ex. rad: external beam irradiation.

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**FIGURE 5**
Evolution of the right acetabulum lysis. (A) 1 yr after external beam irradiation and 1 yr before $^{[13]}$MIBG treatment—large demineralization. (B) 3 yr after $^{[13]}$MIBG treatment: remineralization of the lesion.
therapy dose due to acute radiation damage to the metastases after therapy dose (6). As a consequence, the effective calculated absorbed radiation dose was corrected in the same proportion. The range of calculated absorbed dose according to the metastatic site extended from 30 Gy in the right acetabulum to more than 633 Gy in the T12 vertebra (Table 1).

No significant change in heart rate and blood pressure was observed during and after the infusion of [131I]MIBG. Hematologic profile tests of kidney and liver function remained unchanged after the treatment.

The course of the patient and the follow-up of the indices of the disease since the onset of the disease to the last follow-up are summarized in Table 2. The response to the treatment was pain relief and a dramatic improvement of the general condition. According to the Zubrod and Schneideman scale (7), the performance status was grade 4—completely disabled—before treatment, and grade 1—ambulatory and able to do light work—after treatment. The number of metastatic sites detectable by MIBG scintigraphy fell to two, with an uptake ratio lower than 0.5%. A rapid and complete scintigraphic disappearance and radiologic remineralization were observed in the tumors that received the highest calculated radiation dose, C3, left hip, T12 (Tables 1, 2, and Fig. 4). Slower changes were observed in the early developed tumors with a large volume at the time of treatment, L4, right acetabulum (Tables 1, 2, and Fig. 4). However, in the location of the right acetabulum, which received a relatively low irradiation, an edge of radiologic condensation was observed (Fig. 5). The patient did not receive any antineoplastic treatment. At the present time, the duration of survival since the beginning of the disease is six years.

DISCUSSION

The use of [131I]MIBG for the treatment of APUD tumors has been reported in series of patients with pheochromocytomas (5), neuroblastomas (8), and in some patients with medullary thyroid carcinomas (9), and carcinoid tumors (10). A case of treatment of malignant, nonfunctional paraganglioma was reported—the patient received a single 3.85-MBq dose followed by pain relief. However, the duration of the post-therapeutic follow-up was short, 6 months (11) versus 3 yr in our study.

In the present case, the response to [131I]MIBG appears exemplary from several view points:

1. Interruption of the rapid progression of the disease.
2. Spectacular improvement of the general condition of the patient.
3. Regression of scintigraphic and radiologic tumor stigmata.
4. Remission of at least three years.

Iodine-131 MIBG treatment is a simple and safe therapeutic agent. No change either in blood pressure or in tests of autonomous functions has ever been observed in patients with pheochromocytomas (5). The calculated whole-body radiation dose is ~0.05 mGy-MBq–1. This value is in agreement with recently published results (12), and is acceptable, regarding bone marrow radiation absorbed dose. However, bone marrow depression with a marked thrombopenia was induced in two patients with diffuse neuroblastoma (8).

In the case of nonsecreting paragangliomas, no biologic tumor marker is available for the objective follow-up, especially for early detection of relapse. The level of MIBG uptake in tumors yields the most reliable and practical parameter as a guide for further therapeutic [131I]MIBG administration, if needed.
CONCLUSION

Iodine-131 MIBG provides a useful tool for the investigation and treatment of a broad spectrum of neural crest tumors. Malignant paragangliomas, as well as pheochromocytomas and neuroblastomas should be investigated and, if needed, treated with [131I]MIBG.

REFERENCES