High-Dose $^{131}$I-Metaiodobenzylguanidine Therapy for 12 Patients with Malignant Pheochromocytoma

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Malignant pheochromocytoma and paraganglioma (extraadrenal pheochromocytoma) account for 10–20% of all cases of pheochromocytoma. Patients with malignant pheochromocytoma have a poor prognosis with an average 5-year survival of about 40%. Typically, major primary and metastatic lesions are debulked surgically. Antihypertensives and α-methyldopa block the effects or synthesis of catecholamines. However, neither treatment alters tumor growth. Systemic treatment options are limited and include chemotherapy and radioiodine-labeled metaiodobenzylguanidine (MIBG). To improve outcome, we developed a treatment protocol infusing activity of 131I-MIBG of up to 18 millicuries (mCi) per kilogram of body mass, to a maximum of about 850 mCi per treatment. These doses are larger than those previously reported.

Metaiodobenzylguanidine is a guanethidine analog that resembles norepinephrine and is concentrated similarly by adrenergic tissues. In 1981, MIBG was shown to localize pheochromocytomas. 131I-Metaiodobenzylguanidine therapy for malignant pheochromocytomas first was reported in 1984. A review of the world’s experience with 131I-MIBG for the treatment of malignant pheochromocytoma reported tumor and hormonal responses of 30% and 45%, respectively. The single-treatment dose of 131I-MIBG ranged from 96 to 300 mCi, with a mean cumulative dose of 490 mCi (range, 96–2322 mCi). There had been only five documented cases of complete responses (CR) following 131I-MIBG therapy and no reported CRs in patients with both skeletal and soft tissue metastases. However, the effect of higher treatment doses had not been determined.

A Phase I 131I-MIBG treatment dose-escalation study of children with malignant neuroblastoma reported a higher response rate with increasing 131I-MIBG activity. In that study, 1 of 9 patients was treated with 9 mCi/kg or less, and 10 of 21 patients received doses of 12 mCi/kg or more. Grade 4 hematologic toxicity occurred in greater than 80% of the patients treated with doses of 15–18 mCi/kg body weight, indicating the need for stem cell harvest before such therapy. Because pheochromocytomas are similar to neuroblastomas in many respects, we decided to determine whether therapy with higher doses of 131I-MIBG would lead to an improved response rate in patients with malignant pheochromocytoma and paraganglioma. We treated 12 patients with high-dose 131I-MIBG and report their response rates and toxicity.

**MATERIALS AND METHODS**

**Patient Eligibility**

Patients were required to have metastatic or unresectable pheochromocytoma or paraganglioma. The metastases were required to concentrate 123I-MIBG or 131I-MIBG to at least twice that of soft tissue background. Massive hepatic metastasis precluded treatment with high-dose 131I-MIBG due to concerns that such treatment might cause hepatic necrosis. Patients were required to be older than age 1 year, with a minimum life expectancy of at least 12 weeks. No chemotherapy or radiation treatments were given for at least 3 weeks before 131I-MIBG therapy. All the patients who received previous chemotherapy or radiation had documented progressive or persistent disease on computed tomography scan (CT) and 123I-MIBG before receiving 131I-MIBG therapy. Patients were required to have normal renal and cardiac function, liver enzyme levels less than twice the upper limit of normal, as well as an absolute neutrophil count (ANC) and platelet count greater than $1 \times 10^9$ and $50 \times 10^9/L$, respectively. From 1991 to 2000, 12 patients with documented pheochromocytoma or paraganglioma with metastases were treated with high-dose 131I-MIBG. Five patients have been reported already.

**Pretreatment Procedures**

Pretreatment evaluation included a history and physical examination. A 24-hour urine sample was collected to evaluate total fractionated catecholamines and metanephrines. Serum specimens were assayed for glucose, calcium, albumin, electrolytes, blood urea nitrogen, and creatinine. Pulmonary function tests were performed in patients with lung metastases. Echocardiograms were obtained for patients who had significant cardiac uptake on a 123I-MIBG scan. Bone marrow devoid of tumor was required before stem cell harvest. Two patients (Patients 1 and 3) had bone marrow harvests. The rest of our patients had stem cells collected by leukapheresis. Blood pressure was controlled before treatment. Patients did not receive medications that were known to interfere with MIBG uptake (e.g., labetalol, decongestants, phenothiazines, tricyclic antidepressants). All patients had their primary tumor resected or debulked before receiving 131I-MIBG therapy. The protocol was approved by the University of California–San Francisco (UCSF), Committee on Human Research. Informed consent was obtained from all patients or their parents.

**131I-Metaiodobenzylguanidine Preparation**

Metaiodobenzylguanidine was synthesized and exchange-labeled at UCSF as described previously. The free iodine content at the time of dosing was less than 5%. The specific activity was 10–12 Ci/mmol MIBG.
Administration

Patients were admitted to a lead-shielded room. They were hydrated with intravenous fluids beginning 12 hours before the infusion of $^{131}$I-MIBG. The maximal single treatment activity delivered was 18 mCi/kg up to a maximal single dose of 850 mCi. The intended single treatment dose of 12–18 mCi/kg varied predominately secondary to patient's weight. Patient 1 was treated during the dose escalation phase of our protocol and therefore was treated with a smaller dose of $^{131}$I-MIBG. A bladder catheter was inserted and drained into a lead-shielded container to reduce radiation exposure to the bladder. The bladder catheter was left in place and drained continuously for about 3 days following the infusion of $^{131}$I-MIBG, or until at least 75% of the isotope was excreted. The dose was administered over 2 hours from behind an additional lead shield of 2.5 cm thickness. To block thyroid uptake of unbound $^{131}$I, potassium iodide (KI) was given at least 2 hours before the infusion (6 mg/kg load), followed by 0.88 mg/kg orally every 4 hours for 7 days and then 1 mg/kg orally for 45 days after the infusion. A loading dose of 8 mg/kg potassium perchlorate was given at least 2 hours before $^{131}$I-MIBG followed by 2 mg/kg orally every 6 hours for 5 days posttreatment. The patients remained behind a lead shield until radiation decreased to less than 2 millirads (< 0.02 mSv) per hour at 1 meter.

Posttreatment Follow-Up

Whole-body gamma scans were performed 5 days and 2–3 months after $^{131}$I-MIBG therapy. A CT or magnetic resonance imaging scan was ordered at 2–3 months following $^{131}$I-MIBG treatment and regularly thereafter. A complete blood count with differential was obtained twice per week for 6 weeks and then monthly until normal. Serum liver enzyme and creatinine levels were measured once per week for 6 weeks, and then monthly for 1 year. Urine levels of catecholamines and metanephrines were measured at 3, 6, and 12 months. Thyroid function tests were obtained at 1, 2, 3, 6, and 12 months posttreatment. An autologous bone marrow or stem cell infusion was performed per physician discretion, using the following guidelines: ANC less than 200 $\times$ 10$^9$/L for more than 2 weeks or if dependent on platelet transfusions for at least 3 weeks. Platelet and red blood cell (RBC) transfusions and granulocyte–colony-stimulating factor (G-CSF) were used at the discretion of the patients’ local oncologists.

Retreatment

Repeat $^{131}$I-MIBG treatments were administered on a case-by-case basis in an effort to improve the overall response. Multiple factors were considered, such as previous response and toxicity, tumor burden, and total radiation. The median interval between treatments was 4.4 months (range, 3–7 months). Patients were required to have normal hematologic, hepatic, renal, and cardiac function before repeat $^{131}$I-MIBG treatment and to be free of active infection. The need for stem cell infusion or an autologous bone marrow transplant precluded further $^{131}$I-MIBG therapy.

Definitions

All responses were evaluated with respect to measurements obtained before the initial $^{131}$I-MIBG treatment. Hormonal responses were classified by the change in urinary total levels of catecholamines or metanephrines as follows: CR, normalization; partial response (PR), reduction by $\geq$ 50%; no change (NC), reduction by $< 50\%$ or an increase of $< 25\%$; progressive disease (PD), an increase of $\geq 25\%$. Tumor responses on CT scan were determined by the maximal tumor diameter of the predominant lesions and defined as follows: CR, complete resolution of all tumors on imaging; PR, a reduction of $\geq 50\%$ in the measured maximal tumor diameter; stable disease (SD), no change; and PD, an increase of $\geq 25\%$ in a single lesion or the development of new lesions. Metaiodobenzylguanidine responses were defined qualitatively with respect to the distribution of $^{123}$I-MIBG uptake as follows: CR, complete resolution of $^{123}$I-MIBG uptake; PR, reduction of distribution of uptake; SD, no change; and PD, an increase in the regions of uptake. Best response refers to the greatest level of response per symptom, urinary catecholamine/metanephrine levels, $^{123}$I-MIBG scan, and CT scan. The best response was maintained at follow-up, unless the patient developed PD. Hematologic toxicities were classified according to the National Cancer Institute’s common toxicity criteria, Version 2.0.

Statistical Methods

Follow-up was measured from the first $^{131}$I-MIBG treatment. The duration of response was measured from the initial $^{131}$I-MIBG treatment to the initial date of disease recurrence or PD. Except where otherwise stated, values are expressed as median (range). Student t tests using the Sigma Stat Version 2.0 statistical package (SPSS, Inc., Chicago, IL) were performed to compare age responders versus nonresponders, cumulative doses and mCi/kg values for responders and nonresponders, and platelet and ANC grade versus total cumulative dose and mCi/kg. Wilcoxon signed rank tests were used to compare nonparametric values. A two-tailed Fisher exact test was used to compare proportions. $P < 0.05$ was considered significant.
RESULTS
Patient Characteristics
Twelve patients were treated with high-dose $^{131}$I-MIBG (Table 1). Their median age was 31 years (range, 10–58 years). Five patients were younger than age 18 years. Six patients had malignant pheochromocytoma, and five had malignant paraganglioma. Patient 7 had multiple peritoneal metastases secondary to intraabdominal seeding of his tumor. These lesions were clearly visible on CT scan and were avid for $^{123}$I-MIBG.

Of the 12 patients, 10 had skeletal metastases at the time of the initial $^{131}$I-MIBG treatment. The skull was the most common site of metastasis at initial presentation; skull metastases were observed in eight patients. Other locations of metastatic disease included the vertebral spine in seven patients; the pelvis and abdominal cavity in six each; the lung in five; the liver, femur, and shoulder in four each; and the ribs and thigh soft tissue in two each. Patient 11 had reproducible $^{123}$I-MIBG and posttreatment $^{131}$I-MIBG uptake in the skull and vertebrae. Metiodobenzylguanidine scanning with reproducible uptake in bone is highly specific for metastatic pheochromocytoma. The lack of observed cortical disruption per CT scan was attributed to the smallness of the metastatic lesions. The $^{123}$I-Metiodobenzylguanidine uptake in the thigh and buttock in Patient 4 was reproducible and therefore was not attributed to urine contamination. No patients had involvement of the central nervous system.

Five patients had received chemotherapy or radiotherapy before $^{131}$I-MIBG treatment. The median time from the discovery of metastases to therapy with $^{131}$I-MIBG was 9 months (range, 1.4–53 months).

The median single treatment activity of $^{131}$I-MIBG was 800 mCi (29.2 gigabecquerels [GBq]; range, 386–866 mCi) or 11.5 mCi/kg (range, 5.6–18.3 mCi/kg). Six patients received one dose, five patients received two doses, and one patient received three doses of $^{131}$I-MIBG. The activities of repeat treatments were on average within 2% of previous treatments. The median cumulative dose was 1015 mCi (37 GBq) $^{131}$I-MIBG (range, 386–1717 mCi; Table 2).

Response to $^{131}$I-Metiodobenzylguanidine Therapy
After $^{131}$I-MIBG therapy, the tumor response was evaluated with respect to pretreatment symptoms, urinary levels of catecholamines and metanephrines, and tumor reduction per $^{123}$I-MIBG and CT scan. An initial response was measured at a median of 2.4 months (range, 1.2–4.7 months).

Pain and other symptoms were reduced in the majority of patients after treatment with $^{131}$I-MIBG (Tables 1, 2). Ten had symptoms at baseline. Patient 1 did not respond. She was treated in the dose escalation phase of our protocol with a comparatively low level of $^{131}$I-MIBG activity. A PR occurred in 4 patients, for a median duration of 6.5 months (range, 2–45 months). Patient 6 had a 2-month interval of reduced pain and was not treated with another dose of $^{131}$I-MIBG because of a surgical infection. Five patients experienced CR, for a median duration of 44 months (range, 23–101 months). Patient 10, who was dependent on opioid analgesics before treatment, had a complete resolution of her pelvic pain and administration of opioid analgesics was discontinued within 2 weeks of her initial $^{131}$I-MIBG treatment. With the exception of Patient 6, the improvement or progression of symptoms coincided with the hormonal response in all patients with secretory malignancies.

A reduction (PR or CR) in total urinary levels of catecholamine or metanephrine excretion following $^{131}$I-MIBG treatment was observed in 4 of 6 patients (Figs. 1, 2; Table 1), for a median duration of 34 months (range, 7–47 months). The tumor did not secrete catecholamines or metabolites in three patients (Patients 4, 10, and 11). Patient 7 had a complete normalization of elevated norepinephrine levels. His metanephrine levels have remained normal. Patient 9 was not evaluable secondary to surgical reduction of an intraabdominal tumor between the first and second treatments. Patient 12 had a period of normalization; however, pretreatment values were not greatly elevated, leading to a designation of NC. Urinary levels of catecholamines and metanephrines returned to normal in Patient 8 at 7 months after therapy, before PD. Serum levels of chromogranin A (CgA) were not measured in all patients. Patient 2 had an elevated level of CgA of 137 ng/mL (1.6–5.6 ng/mL) that decreased 2 months after $^{131}$I-MIBG to 56 ng/mL, increased to 470 ng/mL at 6 months, and further progressed to 1430 ng/mL in concordance with PD on imaging studies.

Of the 12 patients in the current study, 7 had a PR with respect to the $^{123}$I-MIBG scan, with a median duration of 43 months (range, 6–47 months). Three of these seven patients subsequently developed PD. A CR as determined by $^{123}$I-MIBG scanning occurred in three patients. Two patients did not respond to treatment. A CT scan of Patient 1 showed multiple pulmonary metastases that did not exhibit $^{131}$I-MIBG uptake. CT scans were available for evaluation in 11 patients. Two patients (Patients 2 and 8) had a PR before dying of PD. Five had SD on CT scan, with a median duration of 44 months (range, 25–47 months). Per CT scan, SD was observed secondary to a lack of measurable change of skeletal lesions. Patient 12 had new
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yrs)</th>
<th>Gender</th>
<th>Type</th>
<th>Metastatic locations before 131I-MIBG treatment</th>
<th>Previous treatment</th>
<th>Mean dose/treatment (mCi/kg)</th>
<th>No. of treatments</th>
<th>Cumulative dose (mCi)</th>
<th>Best response</th>
<th>Duration of response (mos)</th>
<th>F/U (mos)</th>
<th>Current status</th>
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<td>AWD</td>
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<td>770</td>
<td>PR</td>
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<td>7</td>
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<td>1155</td>
<td>None</td>
<td>25</td>
<td>32</td>
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</table>

mCi: milliCurie (1 mCi = 0.037 gigabecquerel); MIBG: metaiodobenzylguanidine; CT: computed tomography; F/U: follow-up; PD: progressive disease; DPD: died with progressive disease; Rad: internal beam radiation; PR: partial response; SD: stable disease; AWD: alive with disease; CR: complete response; NS: not secretory; AnoD: alive with no disease; Chemo: chemotherapy; NE: not evaluable.

*All patients had surgery before 131I-MIBG treatment.

Greatest response following 131I-MIBG treatment.

Interval from initial 131I-MIBG treatment to either progressive disease or follow-up.

Months of follow-up after the first 131I-MIBG treatment.

Urinary measurement not available; partial response with respect to chromogranin A.

Patient 7 had intraabdominal seeding of his primary pheochromocytoma.
skeletal metastases at 25 months of follow-up. Patients 4 and 7 had a CR per CT scan.

With respect to current status, 4 patients have died secondary to PD, after a median follow-up of 11 months (range, 8–13 months). Eight patients are alive at a median follow-up of 45 months. Of these, four have clinical signs of improvement, two with minimal disease (Patients 5 and 10). One patient has PD, and 3 have experienced a CR and currently are without evidence of disease, at a median follow-up of 45 months (range, 24–101 months). The median follow-up for all patients was 38 months (range, 8–101 months). The median duration of response was 34 months (range, 0–101 months).

Patients with a CR or PR, as evidenced by urinary levels of catecholamines/metanephrines, exhibited a reduction in tumor size as observed by an MIBG scan. In addition, imaging studies showed that patients with a urinary hormonal response had PD. Two of the three patients with a CR had nonsecretory tumors. The Student t test did not show a statistical relationship when comparing the dose of 131I-MIBG (cumulative or cumulative dose per kilogram) of those with a hormonal, symptom, 123I-MIBG, or CT response versus those with PD. The Fisher exact test showed a trend toward the occurrence of PD in patients who received external beam radiation before 131I-MIBG treatment. A greater proportion of patients older than age 18 years experienced PD within 12 months after initial 131I-MIBG treatment compared with patients who were younger than age 18 years.

Toxicity from 131I-Metaiodobenzylguanidine Therapy

Both hematologic (Table 3) and nonhematologic toxicities were common but not life-threatening. There was no clear association between treatment dose, cumulative dose, or patient age and the grade of hematologic toxicities within the treatment range utilized in this study. Grade 3 thrombocytopenia occurred in 79%

### Table 2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (range)</th>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>31 (10–58)</td>
<td>—</td>
</tr>
<tr>
<td>Follow-up after initial 131I-MIBG</td>
<td></td>
<td>—</td>
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<tr>
<td>treatment (mos)</td>
<td>38 (8–101)</td>
<td>—</td>
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<tr>
<td>Activity of 131I-MIBG per treatment (mCi)</td>
<td>800 (386–866)</td>
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<td>Activity of 131I-MIBG per treatment (mCi/kg)</td>
<td>11.5 (5.6–18.3)</td>
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<td>Cumulative activity of 131I-MIBG</td>
<td>1015 (386–1690)</td>
<td>—</td>
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<tr>
<td>Duration of response (mos)</td>
<td></td>
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<tr>
<td>Symptomatic</td>
<td></td>
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<tr>
<td>PR + CR</td>
<td>43 (2–101)</td>
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<tr>
<td>Hormonal</td>
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<td>PR + CR</td>
<td>34 (7–47)</td>
<td>4/6</td>
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<tr>
<td>MIBG</td>
<td></td>
<td>—</td>
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<tr>
<td>PR + CR</td>
<td>44 (6–101)</td>
<td>10/12</td>
</tr>
<tr>
<td>CT</td>
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<td>—</td>
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<tr>
<td>PR + CR</td>
<td>15 (6–101)</td>
<td>4/11</td>
</tr>
<tr>
<td>SD</td>
<td>44 (25–47)</td>
<td>5/11</td>
</tr>
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</table>

131I-MIBG: 131I-metaiodobenzylguanidine; mCi: millicuries (1 mCi = 0.037 gigabecquerels); PR: partial response; CR: complete response; SD: stable disease.
Grade 4 thrombocytopenia was not observed. The median onset of Grade 3 thrombocytopenia was 27 days (range, 18–40 days). The median time to normal platelet levels without the need for transfusions was 16 days (range, 1–31 days).

Grade 1–2 neutropenia occurred in 5 of 19 (26%) patients, and Grade 3 neutropenia occurred in 10 of 19 patients (53%). Grade 4 neutropenia occurred in 4 of 19 patients (19%). The median onset of Grade 3–4 neutropenia was 32 days (range, 20–41 days). An increase in the grade of hematologic toxicity was not observed in the six patients who had repeat treatments (data not shown). Patient 2 had stem cell replacement after his second treatment after experiencing 1 week of neutropenic fever. He had been treated with extensive external beam radiotherapy before receiving 131I-MIBG treatment.

Platelet and RBC transfusion data were available for 17 of 19 treatments. Platelets were transfused following 8 (47%) 131I-MIBG treatments. Packed RBCs were transfused following 6 of 17 (35%) 131I-MIBG treatments. Following 10 treatments (56%), G-CSF was used. There was no apparent association between treatment dose (mCi/kg) and the use of hematologic support.

The severity of nausea and emesis was recorded after 15 of 19 treatments. Following 131I-MIBG treatments, 12 of 15 patients continued to be able to eat. Of the 12 patients, 5 had 2–5 episodes of emesis per 24 hours following treatment. Transient episodes of hypotension were observed in three patients during the infusion of 131I-MIBG and were treated with nifedipine. Other complications included parotitis in three patients, herpes zoster in three patients, thrush in two patients, bacteremia in one patient, and pneumonia in one patient. Patient 10 was treated with a cumulative dose of 1680 mCi of 131I-MIBG and developed primary ovarian failure. No patients developed hypothyroidism.

**DISCUSSION**

Patients with malignant pheochromocytoma and paraganglioma have a median survival of 4.5 years, although tremendous variability is observed. Patients with metastases have survived for more than 10 years without tumor-reducing therapy.14,15 Recently, a patient with skeletal metastasis was reported as having a 26-year survival period without chemotherapy or radiation treatment.16 Therefore, it is difficult for a single institution to effectively evaluate therapies for this disease.

Surgery for primary lesions and large metastatic lesions can improve morbidity resulting from local tumor and systemic catecholamine effects. However, surgery cannot treat multiple diffuse metastatic lesions. Disease remissions have been reported with chemotherapy. Of 14 patients with malignant pheochromocytoma who were treated with a combination chemotherapy regimen of cyclophosphamide, vincristine, and dacarbazine (CVD), 79% had a hormone response and 57% had a tumor PR or CR.17 However, continued cycles of chemotherapy were required to maintain disease remission, and long-term follow-up was not provided. Another study reported a median survival of 67 months (range, 12–300 months) after various regimens.18 Multiple case reports have illustrated palliation with intermittent chemotherapy with a survival period of more than 4 years.19–21 Complete long-term disease remissions with chemotherapy, to our knowledge, have not been reported.

Therapy with 131I-MIBG has been administered at multiple centers throughout the world. In 1997, Loh et al. published a review of the worldwide experience involving 116 patients treated with 131I-MIBG for ma-
lignant pheochromocytoma. Overall, there was a symptomatic response in 76%, a hormonal response in 43 of 96 (45%), and tumor regression in 35 of 116 patients (30%). The activity of 131I-MIBG per single dose was 96–300 mCi, and the mean cumulative activity (± standard deviation [SD]) was 490 ± 350 mCi. Only five CRs to 131I-MIBG were reported. All patients who had CR had minimal soft tissue metastases. In 2001, Mukherjee et al.22 published a report on a series of 37 patients with neuroendocrine tumors who were treated with serial doses of 131I-MIBG. Of these patients, 15 had either malignant pheochromocytoma or paraganglioma. The symptomatic response rate was 100%, and a complete or partial hormonal response occurred in 8 of 9 patients; tumor reduction was observed in 7 of 13 patients (54%). The mean single treatment dose of 131I-MIBG was 189 mCi (range, 70–300 mCi) and the mean cumulative activity was 638 mCi (range, 200–1282 mCi). No CRs were reported in their series.

The mean single treatment and cumulative activity of 131I-MIBG used in our study was about 2–3.5 times higher than that employed at other centers.6,22,23 Following high-dose therapy with 131I-MIBG, 3 of the 12 patients in the current study experienced a CR that has been sustained with up to 8 years of follow-up. Unlike previous reports of CR, two of these patients had both skeletal and soft tissue metastases.

In addition, two patients alive with disease are asymptomatic with minimal tumor burden. A reduction in symptoms and urinary catecholamine/methanephrine levels occurred in about 70% of patients. In contrast, lower dose protocols often call for a greater number of treatments than the one to three treatments used in our series, and CVD chemotherapy must be given in repeated cycles indefinitely to maintain a response.6,17,22,23

Results for two of the patients with a CR require further clarification. Patient 7 had intraperitoneal seeding of a pheochromocytoma at the time of his original surgical resection. The natural history of this pheochromocytoma is unknown and may behave differently than that of a malignant pheochromocytoma. The patient had progression of both catecholamines and tumor burden that required a second major surgery. All tumor foci were not respectable, and further progression occurred. Although it is impossible to distinguish benign pheochromocytoma from malignant pheochromocytoma histologically, Patient 7 did not have distant metastases. However, his disease behaved aggressively and his CR following 131I-MIBG therapy was noteworthy. Patient 11 did not have skeletal metastases visible per CT scans but had reproducible uptake per 123I-MIBG scans to the skull and vertebrae. Unlike Technetium 99m bone scans, MIBG scanning with reproducible uptake in bone is highly specific for metastatic pheochromocytoma. We consider the resolution of 123I-MIBG scans in Patient 11 to be evidence of a CR to therapy. Malignant pheochromocytoma can dedifferentiate and lose avidity for 123I-MIBG uptake. However, this would be less likely in Patient 11, because there was no evidence of disease recurrence after nearly 4 years of follow-up.

The 3 patients in the current series who experienced CR had a median follow-up of 45 months. Following primary tumor resection in these patients, a small number of metastases remained. Therefore, these patients had only a relatively small tumor burden when treated with 131I-MIBG. It is not possible to say whether the relatively large dose of 131I-MIBG therapy contributed to their CRs. Our experience suggests that skeletal metastases frequently respond to 131I-MIBG therapy. In addition, two of these three patients had nonsecretory tumors (per urine levels of catecholamines/methanephrines). Nonsecretory malignant pheochromocytomas may retain the ability to concentrate 131I-MIBG. Patients with nonsecretory tumors may respond to 131I-MIBG therapy.

The SD observed per CT scan in five patients may be representative of the described patient population with stable malignant lesions. However, all of these patients had a PR per 123I-MIBG scan, improvement of symptoms, and reduction of previously elevated urinary levels of catecholamines/methanephrines. We attribute these improvements to the 131I-MIBG treatment. The lack of change per CT scan may be secondary to delayed recalcification of bone metastases.23

There was a trend toward an increased likelihood of PD for patients who had received external beam radiation before 131I-MIBG treatment. It is possible that this trend is simply the result of selection bias; patients who were treated with external beam radiation had extensive or aggressive metastatic lesions. Alternatively, previous exposure to external beam radiation may reduce the effectiveness of 131I-MIBG therapy. Patients in the current series typically had poor uptake of 131I-MIBG into areas of the tumor that previously had been treated with external beam radiation.

Serum levels of CgA are correlated with tumor weight and response to chemotherapy in patients with malignant pheochromocytoma.24,25 Serum CgA levels were not routinely available at the start of our protocol. However, we currently are employing assays of CgA routinely. As suggested by Patient 2, serum CgA levels may be helpful in following the response of malignant pheochromocytoma to 131I-MIBG therapy. Hematologic tox-
icity with the higher dose of $^{131}$I-MIBG usually was transient but was much greater than that reported with lower-dose protocols. In a series of 15 patients with a mean single activity of 127 mCi $^{131}$I-MIBG and a mean cumulative activity of 624 mCi $^{131}$I-MIBG, the platelet count decreased to 60–100 x 10^9/L in only 2 patients.23 Leukopenia at a level of 1.6–2.0 x 10^9/L occurred in 2 patients. In another recent study, only 1 of 15 patients developed bone marrow suppression when relatively low doses of $^{131}$I-MIBG were employed.22 In our study of high-dose $^{131}$I-MIBG, we observed Grade 3–4 thrombocytopenia and neutropenia in patients after about 80% of treatments. As in other series of patients with malignant pheochromocytoma treated with $^{131}$I-MIBG, we did not observe a correlation between dose (mCi/kg) and hematologic toxicity.6,23 However, because about 80% of patients with neuroblastoma who were treated with $\geq$ 12 mCi/kg developed Grade 4 hematologic toxicity,7 the lack of a correlation in the current series can be attributed to patients’ being on the plateau phase of the hematologic toxicity curve. Stem cell replacement was necessary in one patient in our series; this patient previously had been treated with extensive external beam radiotherapy for widespread skeletal metastases.

Patient 10 developed primary ovarian failure. The ovarian failure likely occurred secondary to local radiation from extensive pelvic bone metastases. Ovarian failure previously was reported in a 36-year-old woman with retroperitoneal and spinal metastases after a cumulative dose of 1233 mCi.22 The boys in our series have not shown abnormal pubertal development. Secondary to the development of hypothyroidism in a past neuroblastoma protocol using only KI, we adapted by using both KI and potassium perchlorate.7 Despite using both medications, the thyroid has been visualized on posttherapy scans. We have not observed hypothyroidism.

Patients treated with high-dose $^{131}$I-MIBG may be at a greater risk for developing secondary malignancies.7,26,27 Leukemia has been reported in several patients following treatment with $^{131}$I-MIBG as well as after $^{131}$I treatment of thyroid carcinoma, although it is not possible to dissect the relative contributions of previous extensive chemotherapy and radiation in some of these patients.7,28,29 This risk must be considered before repeat $^{131}$I-MIBG treatments.

We have demonstrated the feasibility of high-dose $^{131}$I-labeled MIBG therapy. Hematologic toxicity and other morbidity have been significant but tolerable. High-dose $^{131}$I-MIBG therapy is expensive and logistically difficult. The greatest logistic problem is that high-dose $^{131}$I-MIBG is not commercially available and must be synthesized on site by a nuclear pharmacist. In addition, the patient must be hospitalized for about a week in a lead-shielded room, and bone marrow harvesting is required. Given the rarity of malignant pheochromocytoma and the logistic constraints of high-dose $^{131}$I-MIBG, treatment with this technique is likely to be performed only at a limited number of facilities.

Other methods for enhancing the uptake of $^{131}$I-MIBG into the tumor and reducing systemic toxicity must be developed. The relatively acute infusion of $^{131}$I-MIBG (plus the much larger amount of cold $^{127}$I-MIBG in the infusate) may partially saturate the catecholamine reuptake mechanism of malignant pheochromocytomas. Prolonging the infusion time of $^{131}$I-MIBG well beyond the 2-hour infusions we used in these patients may be beneficial. However, this is logistically difficult due to the requirement for constant monitoring of the patient during a radioisotope infusion.

Improvement in the specific activity and purity of $^{131}$I-MIBG may improve uptake into metastatic pheochromocytoma tumors. Current methods for preparing $^{131}$I-MIBG rely on a catalyzed exchange reaction in which unbound $^{131}$I is incubated with a much larger molar amount of nonradioactive $^{127}$I-MIBG. The resultant product is such that only about 1% of the iodinated MIBG is $^{131}$I-MIBG. The rest is nonradioactive $^{127}$I-MIBG. There may be competitive inhibition of $^{131}$I-MIBG uptake by the larger amount of circulating $^{127}$I-MIBG. Purer synthesis of $^{131}$I-MIBG has been described by the radiiododesylation of 3-trimethylsilylbenzguanidine, resulting in no-carrier-added $^{131}$I-MIBG.30

Malignant pheochromocytomas are very rare tumors. Patients with this malignancy often have a poor prognosis. However, their prognosis is quite variable and prolonged survival may occur. Therefore, it is difficult for a single institution to run a prospective and controlled clinical trial with enough statistical power to compare different treatment modalities adequately. Patients in the current series experienced greater hematologic toxicity without attributable mortality. The overall response rate of patients in the current series to high-dose $^{131}$I-MIBG appears to be comparable with the rate reported in trials using lower doses of $^{131}$I-MIBG given repetitively. We observed a CR following high-dose $^{131}$I-MIBG therapy in two patients with pheochromocytoma metastases to the bone. This finding has not been reported in studies using lower-dose protocols.

Therapy with $^{131}$I-MIBG can lead to clinical improvements and possibly cure patients with malignant pheochromocytoma and paraganglioma. The current study demonstrates the feasibility of high-
dose $^{131}$I-labeled therapy for this and other malignancies. Refinements in $^{131}$I-MIBG specific activity, purity, dosing, and patient selection ultimately may improve therapeutic results and reduce toxicity.

REFERENCES