Pilot Study of Iodine-131–Metaiodobenzylguanidine in Combination With Myeloablative Chemotherapy and Autologous Stem-Cell Support for the Treatment of Neuroblastoma


**Purpose:** The survival for children with relapsed or metastatic neuroblastoma remains poor. More effective regimens with acceptable toxicity are required to improve prognosis. Iodine-131–metaiodobenzylguanidine (131I-MIBG) selectively targets radiation to catecholamine-producing cells, including neuroblastoma cells. A pilot study was performed to examine the feasibility of a novel regimen combining 131I-MIBG and myeloablative chemotherapy with autologous stem-cell rescue.

**Patients and Methods:** Twelve patients with neuroblastoma were treated after relapse (five patients) or after induction therapy (seven patients). Eight patients had metastatic and four had localized disease at the time of therapy. All patients received 131I-MIBG 12 mCi/kg on day −21, followed by carboplatin (1,500 mg/m²), etoposide (800 mg/m²), and melphalan (210 mg/m²) administered from day −7 to day −4. Autologous peripheral-blood stem cells or bone marrow were infused on day 0. Engraftment, toxicity, and response rates were evaluated.

**Results:** The 131I-MIBG infusion and myeloablative chemotherapy were both well tolerated. Grade 2 to 3 oral mucositis was the predominant nonhematopoietic toxicity, occurring in all patients. The median times to neutrophil (> 0.5 × 10⁹/µL) and platelet (> 20 × 10⁹/µL) engraftment were 10 and 28 days, respectively. For the eight patients treated with metastatic disease, three achieved complete response and two had partial responses by day 100 after transplantation.

**Conclusion:** Treatment with 131I-MIBG in combination with myeloablative chemotherapy and hematopoietic stem-cell rescue is feasible with acceptable toxicity. Future study is warranted to examine the efficacy of this novel therapy.


**NEUROBLASTOMA** is the most common extracranial solid tumor of childhood, accounting for 8% to 10% of all childhood malignancies.¹ Despite intensive chemotherapy with autologous bone marrow transplantation followed by 13-cis-retinoic acid, the 3-year progression-free survival in patients over 1 year of age who present with metastatic disease remains less than 35%.²⁻³ Patients who did not achieve a complete response (CR) to induction therapy and patients who relapse after a prior transplant have a less than 20% event-free survival rate.⁴⁻⁶ Newer approaches for treating such high-risk patients are needed.

Studies at the University of Michigan in the 1970s identified a number of guanethidine derivatives, including metaiodobenzylguanidine (MIBG), that exhibited binding with adrenal medullary tissue.⁷ Structurally similar to noradrenaline, MIBG was found to concentrate within the neurosecretory granules of catecholamine-producing cells.⁷⁻⁸ Subsequent scintigraphic studies in the 1970s and 1980s demonstrated the effectiveness of MIBG for the localization of pheochromocytomas, neuroblastomas, and other neuroendocrine tumors.⁹⁻¹⁶ Approximately 90% of neuroblastomas concentrate MIBG, with uptake well described in both primary tumor sites and metastases.¹⁷ MIBG concentrates in tumors with favorable or unfavorable histologic patterns, amplified or nonamplified MYCN oncogene expression, and low-stage as well as advanced-stage disease.¹⁷⁻¹⁸

The use of iodine-131–metaiodobenzylguanidine (131I-MIBG) as a therapeutic agent for patients with advanced neuroblastoma has been reported in Europe, the University of California San Francisco, and the University of Michigan.¹⁹⁻²⁷ The majority of these trials were single-agent studies, with response rates ranging from 10% to 50%. The durations of response were often brief, ranging from 100 to over 500 days. Reported toxicity was mild, including nausea.
and vomiting, myelosuppression, and occasional hypothyroidism. To date, dose escalation of 131I-MIBG therapy for neuroblastoma has failed to achieve nonhematologic dose-limiting toxicity.23

Given the poor progression-free survival for patients with refractory or relapsed disease, attempts to improve prognosis with a combination of 131I-MIBG, myeloablative chemotherapy, and autologous bone marrow transplantation have been reported.24,25,27 The current pilot trial combined a fixed dose of 131I-MIBG with a high-dose chemotherapy regimen of carboplatin, etoposide, and melphalan followed by autologous marrow or stem-cell rescue. Toxicity, engraftment parameters, and response rates were determined for this patient group.

PATIENTS AND METHODS

Patient Population

Eligible patients were 1 to 18 years of age, had histologically proven neuroblastoma that had relapsed or progressed with induction therapy, and had not achieved complete remission with induction therapy. Patients were required to have evidence of MIBG avidity, as determined by a 123I-MIBG or 131I-MIBG imaging scan, before study entry. Patients who had undergone a previous autologous transplantation were eligible, provided that more than 6 months had elapsed from their initial transplantation. A glomerular filtration rate of 24-hour creatinine clearance ≥ 60 mL/min/1.73 m² was required at study entry. The study was approved by the institutional review board at the University of Michigan, and informed consent was obtained from all parents/guardians.

Autologous Marrow or Stem-Cell Harvest

A minimum of 4.0 × 10⁸ CD34⁺ cells/kg (or 2.0 × 10⁹ mononuclear cells/kg) were harvested and cryopreserved before study entry, with 2.0 × 10⁷ CD34⁺ cells/kg held in reserve in the event of delayed engraftment after transplantation. Harvested bone marrow cells were treated ex vivo with sedimentsation, filtration, and immunomagnetic beads at Children’s Hospital of Los Angeles.28 Peripheral stem-cell harvests were not required to undergo ex vivo purging. All marrow and stem-cell products were determined to be tumor-free by immunocyto logic methods.29

131I-MIBG Preparation

The MIBG was synthesized and exchanged labeled in the Phoenix Laboratory at the University at Michigan Medical Center. The 131I was supplied by MDS Nordion (Kanata, Ontario, Canada). The specific activity of 131I-MIBG was 9.0 Ci/mmol with a free iodide content of less than 5%. All products underwent radionuclidic, radiochemical, sterility, and pyrogenicity testing in the University of Michigan Nuclear Pharmacy. In all cases, the prescribed dose of 131I-MIBG was 12 mCi/kg, on the basis of the patient’s actual body weight. However, after conjugation of radiolabeled iodine to MIBG, the actual administered dosage varied within 5% of the prescribed dose.

Treatment With 131I-MIBG

Patients were admitted to a lead-shielded room in the Clinical Research Center at the University of Michigan Medical Center to receive 131I-MIBG on day −21 of therapy. Saturated solution of potassium iodide (SSKI) was begun orally (two drops bid), 12 to 24 hours before the administration of the 131I-MIBG. The SSKI continued for 28 days after 131I-MIBG infusion to inhibit thyroid uptake of 131I metabolized from 131I-MIBG. Radiation safety precautions complied with institutional, state, and federal guidelines for the administration, monitoring, and handling of the radioactive agent. Foley catheters were placed in all patients before the 131I-MIBG administration, in order to reduce radiation exposure to the bladder from the excreted 131I-MIBG, to prevent contamination of the patient’s skin and personal clothing, and to minimize health care personnel contact with radioactive urine. The urine was collected into a sterile bag housed in lead shielding. The urine collection bag was emptied every 4 hours on the first day after the 131I-MIBG infusion, and every 8 hours on subsequent days until the patient remained behind lead shields. For antiemesis, patients received intravenous granisetron for 3 consecutive days, starting 1 hour before the 131I-MIBG infusion. Patients were placed on ECG, respiratory, and blood pressure monitors during the 131I-MIBG infusion. The 131I-MIBG dose (12 mCi/kg) was diluted in 50 mL of normal saline, and infused intravenously via a central catheter over 120 minutes. Patients remained behind radiation shielding until radiation emissions were measured to be less than 3 mR at a 1-m distance from the patient. At that point, patients were discharged from isolation.

Myeloablative Chemotherapy Administration

Patients were subsequently admitted to the bone marrow transplant unit on day −7 before transplantation to receive myeloablative chemotherapy. Carboplatin (total dose, 1,500 mg/m²) and etoposide (total dose, 800 mg/m²) were administered as 96-hour continuous infusions on day −7 through day −4. Patients with a creatinine clearance ≥ 100 mL/min/1.73 m² received carboplatin at 375 mg/m²/d. Patients with a creatinine clearance 60 to 99 mL/min/1.73 m² received carboplatin dosed on the Calvert formula, targeting an area under the curve of 3.3 mg/mL/min per day.30 Melphalan (70 mg/m²/d) was administered by intravenous bolus infusion on days −7, −6, and −5. Autologous marrow or peripheral stem cells were infused on day 0.

Supportive Care

All patients received granulocyte colony-stimulating factor 5 μg/kg subcutaneously daily, beginning day 6 after transplantation and continuing until the absolute neutrophil count (ANC) was greater than 1.0 × 10⁹/μL for 2 consecutive days. Prophylactic fluconazole and acyclovir were administered through day 28. Pneumocystis carinii pneumonia prophylaxis with trimethoprim-sulfamethoxazole (or pentamidine) was administered to all patients for 6 months after transplantation.

Posttransplant Therapy

Patients were treated with oral cis-retinoic acid (120 to 160 mg/m²/d), administered over 14-day intervals, beginning approximately day 100 after transplantation. Cis-retinoic acid was continued for 1 year in patients who remained in complete remission.

Toxicity, Engraftment, and Response Evaluation

All patients underwent a 123I- or 131I-MIBG scan, computed tomography or magnetic resonance imaging scan of sites of bulk disease, and bilateral bone marrow aspirate and biopsies with immunocytochemistry at the time of study entry. For response assessment, these studies were repeated at 3 months and 6 months after transplantation and then at 6-month intervals thereafter. The International Neuroblastoma Re-
response Criteria were used to assess response. Variations in the intensity of MIBG concentration within any single target lesion were not used for determination of response to therapy.

Toxicities were graded according to the National Cancer Institute common toxicity criteria. Endocrine function was assessed by thyroid-stimulating hormone, thyroxine, adrenocorticotropic hormone, and cortisol measurements obtained before and after therapy. Cardiac function (echocardiogram, ECG) and pulmonary assessment (chest x-ray, pulmonary function testing in patients older than 6 years of age) were made before therapy, at day 100, and then yearly after transplantation.

Neutrophil recovery was defined as the first of 3 consecutive days of an ANC \( \geq 0.5 \times 10^3/\mu L \). Platelet recovery was defined as the first of 3 consecutive days with a platelet count \( \geq 20 \times 10^3/\mu L \) without platelet transfusion support.

RESULTS

Patient Characteristics

Twelve patients were treated on study between May 1998 and September 2000 (Table 1).32 All patients who had received extensive prior therapy, including eight patients who had received more than one chemotherapy regimen before study entry. Three patients (patients no. 10, 11, and 12) had undergone a previous autologous stem-cell transplantation 6 months to 3 years before enrollment on study. Four patients (patients no. 8, 9, 11, and 12) had MYCN-amplified tumors.

At the time of study entry, eight patients had metastatic and four had localized disease. Bone metastases were present in eight patients, including two patients who exhibited more than 10 sites of abnormal MIBG uptake and two patients with pathologic fractures at the time of \( ^{131}I \)-MIBG therapy. Bone marrow disease was present in six patients. In five of the six, the marrow had isolated tumor rosettes, occupying less than 5% of the marrow biopsy. In one case, the marrow involvement was greater than 50% of the biopsy specimen at the time of \( ^{131}I \)-MIBG therapy. Five patients had pulmonary or mediastinal involvement, and two patients had intra-abdominal lesions, the largest lesion measuring 10 \( \times \) 8 \( \times \) 6 cm at the time of MIBG therapy. Ten of 11 patients had a creatinine clearance greater than 100 mL/min/1.73 m\(^2\) at study entry.

Table 1. Patient Characteristics and Response

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NOTE. Group A, patients treated for progressive disease that developed during induction therapy; group B, patients treated for incomplete response to induction therapy; group C, patients treated after prior relapse. Tumor staging derived from the classification of Evans et al.32

Abbreviations: Dx, diagnosis; Tx, treatment; B, bone; BM, bone marrow; A, abdominal; T, thoracic; PD, progressive disease during induction therapy; PR, partial response to induction therapy; VGPR, very good partial response to induction therapy; ABMT, autologous bone marrow transplant; PFS, progression-free survival; OS, overall survival; DOD, died of disease.

* Multiple thoracic sites.
† A plus symbol indicates that the patient has not experienced relapse.
(patients no. 8 and 9) on day 0 of therapy. The median cell dose infused was $3.5 \times 10^{10} \text{ CD34}^{+} \text{ cells/kg}$.

**Nonhematologic Toxicity**

Regimen-related toxicities are listed in Table 2. Three patients developed mild nausea/vomiting within 24 hours of the $^{131}$I-MIBG infusion. All 12 patients experienced grade 2 to 3 mucositis, beginning day −1 to day 2 after transplantation. FEVERS Dveloped in all patients, with the onset of fever on day −1 to day 7 after transplantation. Although no episodes of sepsis were noted, two patients developed alpha-hemolytic streptococcal bacteremia while neutropenic. One episode of $P$ carinii pneumonitis occurred 150 days after transplantation. Dermatologic complications occurred in one patient, with an erythematous skin rash developing in the right axillary region 4 days after MIBG infusion. A skin biopsy specimen of the affected region revealed mild vacuolar interface dermatitis, and no cutaneous neuroblastoma. Two patients developed hematuria, with hemorrhagic cystitis documented by cystoscopy in one of the two cases. The hematuria developed 30 to 40 days after transplantation in both cases, subsequently resolving with intravenous fluids and platelet support. Urinary cultures for bacterial, fungal, and viral organisms were negative. Asymptomatic hypothyroidism, diagnosed by an elevated thyroid-stimulating hormone level at 3 months after transplantation, occurred in two patients. No cases of adrenal insufficiency (on the basis of serum adrenocorticotropic hormone and cortisol levels) have been noted. There were no toxicity-related deaths.

**Hematologic Toxicity**

Hematologic features are listed in Table 3. In all 12 patients, neutrophil counts remained stable ($>1.5 \times 10^{9} \mu\text{L}$) for 2 weeks after the $^{131}$I-MIBG administration. The median time to count nadir (ANC $<0.5 \times 10^{3} \mu\text{L}$) was day 0 of therapy (range, day −2 to day 1). The median time to neutrophil recovery was day 10 (range, day 6 to day 31). Eleven of 12 patients achieved an ANC $\geq 0.5 \times 10^{3}$ by day 15 after transplantation.

The median time to platelet nadir ($<20 \times 10^{3} \mu\text{L}$) was day 1, with a median time to platelet recovery on day 28 (range, day 7 to day 99). Two patients required platelet transfusions after day 50 because of hematuria.

**Response Rates**

For the eight patients treated with metastatic disease, three achieved CR and two achieved a partial remission after transplantation. Three of four patients treated for persistent localized disease achieved CR. Responses were seen in bone (Fig 1), soft tissue (Fig 2), and marrow. Five of six patients with marrow involvement before therapy had no evidence of disease by biopsy and immunocytology at day 100. Five of eight patients with bone involvement on pretherapy MIBG scans had resolution of MIBG activity in these sites by day 100. All three patients who previously undergone transplantation did not achieve a response by day 100 (two with no response, and one with progressive disease). Patient no. 8, who exhibited more than 10 sites of bony disease and more than 50% marrow involvement at the time of $^{131}$I-MIBG therapy, achieved a complete response by day 100, including normal marrow morphology and immunocytology (per $10^{6}$ cells).

**Relapse or disease progression** has occurred in eight patients, 2 to 13 months (median, 8.5 months) after transplantation. Relapses have occurred in previously unin-
volved bony sites (patients no. 1, 2, and 12), in previously involved bony sites (patients no. 8 and 11), in marrow (patients no. 4, 9, and 10), and in a primary abdominal mass (patient no. 11).

DISCUSSION

The feasibility of combining $^{131}$I-MIBG with myeloablative chemotherapy and hematopoietic stem-cell rescue for patients with neuroblastoma was examined in this pilot trial. The median age at the time of initial diagnosis (3.3 years), the percentage of patients with $\text{MYCN}$ amplification (33%), and the median time from diagnosis to transplantation (12 months) were similar to that reported in other neuroblastoma trials.\textsuperscript{3,5,33} Despite extensive prior therapy, toxicity was acceptable and objective responses were observed in this group of patients.

The nonhematologic toxicity of the regimen was limited, with fever/neutropenia and oral mucositis predominantly seen in all patients. Both toxicities occurred during the period of count nadir (after myeloablative chemotherapy), and presumably may have been related more to the intensive chemotherapy than to the $^{131}$I-MIBG. When given as single-agent therapy, $^{131}$I-MIBG has not been previously associated with the development of mucositis. Historically, the incidence of mucositis has been high in patients receiving myeloablative chemotherapy for the treatment of neuroblastoma.\textsuperscript{3,34,35}

The potential for bladder injury was of concern in this trial. Urinary excretion of $^{131}$I-MIBG has been previously well described, with visualization of the bladder readily seen on routine $^{123}$I- and $^{131}$I-MIBG diagnostic scans. The majority of $^{131}$I-MIBG is excreted unchanged in the urine, with 40% to 55% of an administered dose excreted in the first day, and 70% to 90% by the fifth day after administration.\textsuperscript{36,37} In order to minimize $^{131}$I-MIBG contact with bladder epithelium, all patients in this trial had indwelling urinary catheters placed and intravenous hydration administered during the $^{131}$I-MIBG administration. Despite this precaution, hematuria developed after transplantation in two patients, with hemorrhagic cystitis documented by cystos-
copy in one of the cases. The potential for bladder epithelial injury will need to be monitored in future 131I-MIBG trials.

The cause of the skin rash that developed 4 days after 131I-MIBG infusion in one patient remains unclear, as no evidence for cutaneous neuroblastoma was noted on biopsy specimens. No other dermatologic toxicities were observed in this study or in previously reported 131I-MIBG trials.

Although the follow-up has been short (median, 12 months), few late complications have been observed. The use of SSKI administration for 28 days after 131I-MIBG administration appears to have inhibited thyroid uptake of radiolabeled iodine in the majority of treated patients. The use of more vigorous measures to block thyroid uptake, such as the addition of perchlorate anion, or a greater duration of SSKI therapy may lower the incidence of hypothyroidism even further. Likewise, although 131I-MIBG will normally concentrate within the adrenal medulla, adrenal insufficiency has not been noted to date. Secondary leukemia was previously reported in a patient who received two courses of single-agent 131I-MIBG therapy. No cases of secondary leukemia have been noted in our study population to date. Because 131I-MIBG readily concentrates within the marrow, and as the majority of treated patients will have previously received high-dose alkylator and etoposide therapy, the potential for development of secondary leukemia is present in our study population.

The hematopoietic toxicity of the therapy was acceptable, with 11 of 12 patients engrafting (ANC > 0.5 × 10^3/μL) within 15 days after transplantation. The dosage of 131I-MIBG used in this trial (12 mCi/kg) has previously been shown to be myelosuppressive, but not myeloablative, if given as single-agent therapy. Delayed neutrophil recovery was only observed in one case (patient no. 8), who also had the greatest degree of marrow involvement at the time of treatment (> 50% neuroblasts). 131I-MIBG may have particularly concentrated within this patient’s marrow because of the extensive tumor involvement. 131I-MIBG concentration within the marrow, particularly within megakaryocytes, has already been well described. Whether marrow precursor cells or stromal cells selectively bind 131I-MIBG at levels that may lead to prolonged cellular injury is still under investigation.

Fig 2. Computed tomography (CT) scan of the abdomen obtained before therapy (A) and day 28 after transplantation (B) from patient no. 11. (A) Note the large intra-abdominal mass on the CT scan (dark circle). By posttransplant day 28, the mass has decreased in size by more than 50% on the CT scan and become MIBG-negative (MIBG scans not shown).

An important finding in our study was the time to onset of neutropenia (median onset, day 0). Given that marrow suppression will typically occur 21 to 40 days after infusions of 131I-MIBG, day −21 was chosen as the 131I-MIBG infusion date for this trial. As the effective half-life of 131I-MIBG in tumors is estimated to be 42 to 72 hours, therapeutic dosages of 131I-MIBG may be administered even closer to the time of transplantation. However, as radioisotope emissions are often detectable for 3 to 7 days after 131I-MIBG infusion, administering 131I-MIBG within 7 days of stem-cell/marrow infusion may pose a risk to the graft.

The response rates seen in our trial compare favorably with prior single-agent 131I-MIBG trials and trials combining 131I-MIBG with intensive chemotherapy.

Previous single-agent 131I-MIBG trials have found a threshold for tumor response, with dosages more than 9 mCi/kg achieving the greatest tumor response. Matthay et al noted responses in 37% of patients treated with single-agent therapy, with 131I-MIBG dosages ranging from 9 to 18 mCi/kg. Ten (48%) of 21 patients treated with dosages ≥ 12 mCi/kg had a response, with no apparent difference in response rates between patients treated with 12 mCi/kg versus those treated with 18 mCi/kg. Our toxicity and response rates were similar to those reported in other trials. However, direct comparisons are difficult to
make because of the heterogeneous approaches taken in these trials. Klingebiel et al.27 noted responses in eight of 11 patients treated for stage IV disease with a common induction regimen (German Neuroblastoma Trial NB90), followed by consolidation with 131I-MIBG (15.6 mCi/kg), carboplatin, etoposide, and melphalan chemotherapy, hematopoietic stem-cell rescue, and subsequent anti-GD2 murine or chimeric antibody (ch14.18). With a median observation time of 19 months, nine of 11 children were alive, eight without progression or relapse.

Whether patients in our trial relapsed because of failure of control of in situ disease, or because of reinfusion of undetected tumor cells within the stem-cell or marrow product, is difficult to determine in a trial of this size. Three of the relapses occurred in sites of new disease in patients who had received unpurged stem-cell products. It is likewise difficult to determine whether the responses seen in this trial were principally secondary to the MIBG therapy, to the high-dose chemotherapy, or to the combination of the two. No diagnostic studies were routinely performed on day −7, immediately before the chemotherapy. Prior single-agent studies have found that MIBG does not usually achieve its maximal effect for at least 4 to 6 weeks after infusion.18,20,22

The determination of optimal candidates for MIBG therapy is still under investigation. Historically, patients with relapsed neuroblastoma have an extremely poor rate of survival, especially if nonlocalized disease is present at the time of relapse.1,6 The presence of a chemoresistant relapse or relapse after transplantation are two adverse factors previously reported by Ladenstein et al.8 in a large European trial. In agreement with the report by Ladenstein et al, we noted that patients who had received a prior transplant appeared less responsive to our study therapy. Patients who have a persistent MIBG-avid tumor at the completion of induction therapy,3 or the presence of more than 100 tumor cells per 100,000 by marrow immunocytology on completion of induction therapy,9,10 are known to be at high risk for treatment failure. The addition of 131I-MIBG to consolidation therapy in these high-risk groups may be considered in the future.

As the patient population is small, larger studies will be required to more adequately assess efficacy and impact on overall survival. This pilot study examined the role of 131I-MIBG with myeloablative chemotherapy at only one dose level. A multicenter trial is currently in progress, in which dose escalation of both the 131I-MIBG and the chemotherapy regimen are being examined. In conclusion, the combination of 131I-MIBG with a fixed dose of myeloablative chemotherapy and autologous stem-cell rescue appears feasible for patients with relapsed or persistent MIBG-avid disease. Overall, therapy was well tolerated in this small group of patients, with limited nonhematopoietic toxicity, and responses were seen even in patients with progressive disease. Future trials combining 131I-MIBG with high-dose chemotherapy are warranted.

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APPENDIX

The appendix listing physicians who referred patients for therapy and provided follow-up data is available online at www.jco.org.

REFERENCES

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