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ORIGINAL REPORT

Hematologic Toxicity of High-Dose Iodine-131–Metaiodobenzylguanidine Therapy for Advanced Neuroblastoma

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ABSTRACT

Purpose
Iodine-131–metaiodobenzylguanidine (^{131}I-MIBG) has been shown to be active against refractory neuroblastoma. The primary toxicity of ^{131}I-MIBG is myelosuppression, which might necessitate autologous hematopoietic stem-cell transplantation (AHSCT). The goal of this study was to determine risk factors for myelosuppression and the need for AHSCT after ^{131}I-MIBG treatment.

Patients and Methods
Fifty-three patients with refractory or relapsed neuroblastoma were treated with 18 mCi/kg ^{131}I-MIBG on a phase I/II protocol. The median whole-body radiation dose was 2.92 Gy.

Results
Almost all patients required at least one platelet (96%) or red cell (91%) transfusion and most patients (79%) developed neutropenia ($< 0.5 \times 10^3/\mu L$). Patients reached platelet nadir earlier than neutrophil nadir ($P < .0001$). Earlier platelet nadir correlated with bone marrow tumor, more extensive bone involvement, higher whole-body radiation dose, and longer time from diagnosis to ^{131}I-MIBG therapy ($P \leq .04$). In patients who did not require AHSCT, bone marrow disease predicted longer periods of neutropenia and platelet transfusion dependence ($P \leq .03$). Nineteen patients (36%) received AHSCT for prolonged myelosuppression. Of patients who received AHSCT, 100% recovered neutrophils, 73% recovered red cells, and 60% recovered platelets. Failure to recover red cells or platelets correlated with higher whole-body radiation dose ($P \leq .04$).

Conclusion
These results demonstrate the substantial hematotoxicity associated with high-dose ^{131}I-MIBG therapy, with severe thrombocytopenia an early and nearly universal finding. Bone marrow tumor at time of treatment was the most useful predictor of hematotoxicity, whereas whole-body radiation dose was the most useful predictor of failure to recover platelets after AHSCT.

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INTRODUCTION

Neuroblastoma is the most common extracranial solid cancer in children. The majority of patients present with metastatic disease at diagnosis. Despite recent improvements in outcome with intensification of therapy for metastatic neuroblastoma, the majority of patients will ultimately experience relapse and die as a result of disease.[1]

Metaiodobenzylguanidine (MIBG) is a guanethidine derivative with specific affinity for neural crest tissues.[2] MIBG labeled with iodine-131 (^{131}I-MIBG) has been shown to be active against neuroblastoma, with one third to one half of patients with refractory or relapsed disease having some response.[3-5] Although ^{131}I-MIBG typically has been used as a single agent for patients with refractory or relapsed disease, several groups have used ^{131}I-MIBG combined with chemotherapy earlier in the course of disease.[4,6,7] With this expanding role, an understanding of the toxicity of ^{131}I-MIBG has become increasingly important.

In a phase I trial of ^{131}I-MIBG for advanced neuroblastoma, the primary toxicity

of ^{131}I-MIBG was myelosuppression, particularly thrombocytopenia.[3] At doses of 15 mCi/kg or higher, almost half of patients required autologous bone marrow or stem-cell infusion (autologous hematopoietic stem-cell transplantation [AHSCT]) for prolonged myelosuppression. Despite AHSCT, not all patients had complete bone marrow recovery. Previous reports have suggested potential risk factors for increased myelosuppression after ^{131}I-MIBG therapy, including bone marrow metastases, prior transplantation, multiple courses of ^{131}I-MIBG, increased prescribed activity of ^{131}I-MIBG, and increased radiation dose.[3,8-13] Another study suggested that possible risk factors for failure to engraft stem cells after ^{131}I-MIBG include prior transplantation, increased prescribed activity, and progressive disease after therapy.[14] The conclusions from these studies are limited by small sample sizes and differing doses used within individual studies.

The purpose of this study was to analyze the hematologic toxicity of ^{131}I-MIBG in a group of 53 patients with advanced neuroblastoma treated with a uniformly high dose of ^{131}I-MIBG. Specific risk factors for requiring AHSCT and for failure to engraft were evaluated.

PATIENTS AND METHODS

Patients

Patients older than 1 year and younger than 30 years of age were enrolled in a phase I/II trial of ^{131}I-MIBG therapy for neuroblastoma refractory to conventional therapy. Eligible patients had MIBG-avid tumors, had a minimum life expectancy of 6 weeks, and had recovered from any preceding therapy. A baseline platelet count of more than $75 \times 10^3/\mu$L and an absolute neutrophil count (ANC) of more than $1.0 \times 10^3/\mu$L were required, with exceptions made for patients with low counts because of metastatic bone marrow disease (n = 3). Because of constraints on the timing of treatment, two patients with counts still recovering from chemotherapy were treated before recovery to protocol levels. Both patients recovered counts to protocol levels before nadir counts from ^{131}I-MIBG occurred. Patients on the phase I/II trial who received a prescribed activity within 10% of the intended 18 mCi/kg (666 MBq/kg) ^{131}I-MIBG before April 1, 2002, were included in this analysis. Eight patients were treated during the phase I trial and were included in a previous report.[3] Some of the dosimetry data on 20 of the patients was reported previously.[8] Patient characteristics and sites of disease were recorded at study entry. Bone marrow involvement was defined by either positive bone marrow biopsy or positive bone marrow immunocytology (> one tumor cell per 100,000 cells). Extent of bone involvement typically was determined from the last diagnostic MIBG scan before treatment. All patients were required to have either autologous peripheral-blood stem cells (minimum 1.5×10^6 CD34$^+$ cells/kg) or purged bone marrow (minimum 1×10^8 mononuclear cells/kg) available.

Treatment

The ^{131}I-MIBG was prepared and administered during 90 to 120 minutes with thyroid protection achieved using potassium iodide and potassium perchlorate as previously described.[3] Patients were treated at the University of California, San Francisco or the Children's Hospital of Philadelphia. The study protocol was approved by the Committee on Human Research of each institution and informed consent was obtained for all patients.

Evaluation of Hematologic Toxicity

Patients were required to have CBCs obtained twice weekly for at least 6 weeks after their treatment date. Thereafter, CBCs were obtained in accordance with standard practice until counts were normal. Use of granulocyte colony-stimulating factor was recommended for neutropenia (ANC $< 0.5 \times 10^3/\mu$L). Platelet or red cell transfusions were given at the discretion of the primary oncologists, but were recommended for platelets less than 10 to 20 $\times 10^3/\mu$L and hemoglobin less than 7 g/dL. Hematologic toxicity was assessed according to the National Cancer Institute Common Toxicity Criteria, version 2.0. The ANC nadir was defined as the lowest ANC after treatment, regardless of granulocyte colony-stimulating factor administration. The platelet nadir was defined as the lowest platelet count after treatment before any platelet transfusions. Neutrophil recovery was defined as an ANC more than $0.5 \times 10^3/\mu$L after nadir ANC. The date of transfusion independence, for platelets and red cells, was defined as the date of last transfusion required to maintain counts at minimum levels, typically more than $20 \times 10^3/\mu$L for platelets. The time spent dependent on platelet transfusion was defined as the time from the first platelet transfusion to the date of platelet transfusion independence. Criteria for AHSCT were ANC less than $0.2 \times 10^3/\mu$L for more than 2 weeks despite use of hematopoietic growth factors, or requirement for platelet transfusions more frequently than once weekly for 3 to 4 weeks. In eight patients, AHSCT was not given even though criteria were met. Two patients had progressive disease and imminent death and six patients had signs of imminent marrow recovery, all six of whom had full recovery of platelets, neutrophils, and red cells.

Whole-Body Dosimetry and Red-Marrow Index Calculations

Dosimetry calculations were performed as previously described, with the exception that weight-specific interpolated rather than age-specific *S* values (mean absorbed dose to a target organ per unit cumulated activity in the source organ) were used.[8] Whole-body cumulative activity calculations for patients with insufficient exposure measurements after infusion were based on the prescribed activity and published biokinetics of ^{131}I-MIBG.[15] Weight-specific *S* values were also used for these patients.

Statistical Analysis

Clinical variables were analyzed for correlation with outcome variables related to hematologic toxicity for all patients and to engraftment for patients who required AHSCT. Clinical variables included age, bone marrow tumor at treatment, extent of bone involvement at treatment by MIBG scan, tumor not involving bone or bone marrow, prior transplantation, time from prior transplantation, time from diagnosis to ^{131}I-MIBG, prior total-body irradiation, prescribed total activity of ^{131}I-MIBG, whole-body and red-marrow radiation dose received, use of stem cells or bone marrow for AHSCT, time from ^{131}I-MIBG to AHSCT, number of cells infused for AHSCT, use of purged cells for AHSCT, use of cells harvested after a prior transplantation, time from diagnosis to cell harvest, and disease status at time of AHSCT. Outcome variables included timing of platelet and neutrophil nadir counts, platelet and neutrophil counts at nadir, duration of thrombocytopenia and neutropenia, need for red cell transfusions, need for AHSCT, and failure to engraft after AHSCT. Statistical analyses

were performed with STATA 6.0 (StataCorp, College Station, TX). Associations between groups were tested using the Wilcoxon rank sum test for continuous outcomes and the Fisher's exact test for categoric outcomes. Paired comparisons used the signed rank test for continuous outcomes and the McNemar test for paired proportions. Associations between two continuous variables were assessed with the Spearman rank correlation. Right-censored variables were compared between groups using the log-rank test for unpaired comparisons. Paired comparisons used the stratified log-rank test, with each patient defining a stratum.

RESULTS

Patient Characteristics

A total of 53 patients received ^{131}I-MIBG at 18 mCi/kg and were eligible for analysis (Table 1). Patients had advanced disease and were heavily pretreated, including 43 patients (81%) who had experienced relapse after prior myeloablative therapy. Twenty-eight percent of patients had detectable bone marrow tumor by morphology and/or immunocytology at the time of ^{131}I-MIBG therapy. The median whole-body and red-marrow radiation doses received were 2.92 Gy (range, 1.73 to 4.18 Gy) and 3.47 Gy (range, 2.06 to 5.02 Gy), respectively.

Hematologic Toxicity

Details of the hematologic toxicity after a single treatment with ^{131}I-MIBG are shown in Table 2. Almost all patients required at least one platelet (96%) or red cell (91%) transfusion and most patients (79%) developed neutropenia. Patients reached nadir platelet count earlier than nadir ANC (median, 24 *v* 42 days; $P < .0001$). The clinical variables listed above were analyzed for their effect on hematologic toxicity (Table 3). Patients with bone marrow tumor at treatment had lower nadir ANC than patients without bone marrow disease, but this difference was not statistically significant (0.09 *v* 0.22 $\times$ $10^3/\mu$L; $P = .08$). Patients with bone marrow disease at treatment reached nadir platelet count earlier than patients without bone marrow disease, but the difference was small (median, 22 *v* 24.5 days; $P = .01$). Among patients with any degree of bone involvement, patients with more than five sites of bone involvement reached nadir platelet count earlier than patients with fewer than five sites of bone involvement (median, 22 *v* 27.5 days; $P = .001$). Patients with combined involvement of the bony spine and pelvis reached nadir platelet count earlier than patients without combined involvement of the spine and pelvis (median, 22 *v* 26.5 days; $P = .01$). Earlier platelet nadir correlated with higher whole-body radiation dose received ($P = .03$) and higher red-marrow radiation dose received ($P = .03$). Earlier platelet nadir also correlated with longer time interval from neuroblastoma diagnosis to ^{131}I-MIBG therapy ($P = .04$), possibly reflecting the effect of prior cumulative bone marrow toxicity.

Table 1. Characteristics of Patients Receiving Treatment With 18 mCi/kg ^{131}I-MIBG (n = 53)

Characteristic	Data
Age at treatment, years	
Median	6.9
Range	2.3-24.0
Sex	
Male	35
Female	18
INSS stage at diagnosis	
1	1
3	10
4S	1
4	41
MYCN amplification	
No. of patients	17 amplified, 44 tested
%	38.6
Time from diagnosis to treatment, months	
Median	27.4
Range	10.0-142.2
Prior transplantation	
No. of Patients	43
%	81.1
Time from prior transplantation, months	
Median	19.5
Range	3.2-123.4
Prior total-body irradiation	
No. of patients	7
%	13.2
Bone marrow tumor at ^{131}I-MIBG*	
No. of patients	15
%	28.3
Dose ^{131}I-MIBG, mCi/kg	
Median	18.2
Range	16.2-20.8
Prescribed total activity ^{131}I-MIBG, mCi	
Median	366
Range	198-895
Whole-body radiation dose, Gy	
Median	2.92
Range	1.73-4.18
Red-marrow radiation dose, Gy	
Median	3.47
Range	2.06-5.02

Abbreviations: ^{131}I-MIBG, iodine-131-metaiodobenzylguanidine; INSS, International Neuroblastoma Staging System.
*Defined by positive bone marrow morphology or immunocytology.

Of the 53 patients, three patients who died within 2 months of ^{131}I-MIBG therapy and one patient who received a second course of ^{131}I-MIBG therapy before marrow recovery were included in the above analyses of hematologic toxicity, but were not fully assessable for platelet, ANC, or red cell recovery or need for AHSCT. In addition, platelet, ANC, and red cell recovery for the patients who required AHSCT were evaluated separately from patients who did not require AHSCT.

The time course of hematologic recovery for the patients who did not require AHSCT is shown in Fig 1.

Table 2. Hematologic Toxicity After a Single Treatment With ^{131}I-MIBG in 53 Patients

Parameter	Platelets	Neutrophils	Hemoglobin
Pretherapy counts			
Median	240 × $10^3/\mu$L	2.16 × $10^3/\mu$L	10.2 g/dL
Range	17-482	0.66-7.65	7.8-13.6
Nadir of count			
Median	18 × $10^3/\mu$L	0.160 × $10^3/\mu$L	
Range	4-51	0-3.40	
Time to nadir, days			
Median	24	42	
Range	8-47	10-66	
Required platelet or RBC transfusion			
No. of patients	51		48
%	96.2		90.6
Time platelet transfusion dependent,* weeks			
Median	5.4		
Range	0-12.6†		
ANC < 0.5 × $10^3/\mu$L			
No. of Patients		42	
%		79.2	
G-CSF given			
No. of patients		39 of 51	
%		76.5	
Time with ANC < 0.5 × $10^3/\mu$L,* weeks			
Median		0.7	
Range		0-6.6‡	
Indication for AHSCT, no. of patients			
Thrombocytopenia	7		
Neutropenia		4	
Thrombocytopenia with neutropenia	8		

Abbreviations: ^{131}I-MIBG, iodine-131-metaiodobenzylguanidine; G-CSF, granulocyte colony-stimulating factor; ANC, absolute neutrophil count; AHSCT, autologous hematopoietic stem-cell transplantation.

*Includes only patients who did not require AHSCT.

†Four patients were not assessable for platelet recovery, as described in the text. In addition, two patients did not become platelet transfusion independent prior to death from progressive disease. These patients did not receive AHSCT because of imminent death. They required platelet transfusions for 9.3 and 13.0 weeks, respectively.

‡One patient was not assessable for neutrophil recovery, as described in the text.

Patients were platelet transfusion dependent more than seven times longer than they were neutropenic (median of 5 days neutropenic *v* 5.4 weeks platelet transfusion dependent; $P <$ .0001). This difference remained significant even after excluding patients who never required platelets or became neutropenic (median, 1.4 weeks neutropenic *v* 5.4 weeks platelet transfusion dependent; $P <$ .0001). After excluding the eight patients described above who met criteria for AHSCT but did not receive AHSCT, the median time spent platelet transfusion dependent was 3.8 weeks (range, 0 to 8.7 weeks). Patients with bone marrow tumor were neutropenic longer than patients without bone marrow disease (median, 2.1 *v* 0.43 weeks; $P =$ .009). Patients with bone marrow tumor required platelet transfusions for longer than patients without bone marrow disease (median, 6.4 *v* 5.4 weeks; $P =$ .03). History of prior transplantation or total activity administered did not predict any aspect of platelet or neutrophil toxicity. Two patients with rapidly progressive disease did not receive AHSCT and remained dependent on platelet and red cell transfusion until the time of death; 2.7 and 3.8 months, respectively, from ^{131}I-MIBG treatment.

Infectious complications were rare and included four patients with fever and neutropenia, one patient with a central line infection, and one patient with *Pneumocystis carinii* pneumonitis. The only significant bleeding complication was a subdural hematoma without preceding history of trauma in a patient with a platelet count of 4 × $10^3/\mu$L after ^{131}I-MIBG. The patient was managed with platelet transfusions and recovered fully.

Engraftment After AHSCT

Nineteen patients (36%) received AHSCT. Of these, 15 patients (79%) received AHSCT for either isolated thrombocytopenia or thrombocytopenia with neutropenia, and four patients received AHSCT for isolated neutropenia. None of the clinical variables examined, including bone marrow tumor, were able to predict which patients received AHSCT. In an attempt to determine if certain patients were

Table 3. Predictors of Hematologic Toxicity After ^{131}I-MIBG Treatment

Outcome Variable	Predicted by Clinical Variables	*P*
Earlier platelet nadir	Bone marrow tumor at ^{131}I-MIBG	.01
	≥ 5 Bone sites with tumor at ^{131}I-MIBG	.001*
	Spine and pelvis with tumor at ^{131}I-MIBG	.01*
	Longer time from diagnosis to ^{131}I-MIBG	.04
	Higher whole-body radiation dose	.03
	Higher red-marrow radiation dose	.03
Earlier neutrophil nadir	No significant predictors	
Lower platelet nadir	No significant predictors	
Lower neutrophil nadir	No significant predictors	
Need for red cell transfusions†	No significant predictors	
Need for AHSCT†	No significant predictors	
Longer thrombocytopenia (no AHSCT)	Bone marrow tumor at ^{131}I-MIBG	.03
Longer thrombocytopenia (AHSCT)	No significant predictors	
Longer neutropenia (no AHSCT)	Bone marrow tumor at ^{131}I-MIBG	.009
Longer neutropenia (AHSCT)	No significant predictors	
Longer time to platelet engraftment‡	No significant predictors	
Longer time to neutrophil engraftment‡	Shorter time from ^{131}I-MIBG to AHSCT	.04
Failure to engraft platelets after AHSCT†‡	Higher whole-body radiation dose	.04
Failure to engraft red cells after AHSCT†‡	Higher red-marrow radiation dose	.04
	Higher whole-body radiation dose	.02
	Higher red-marrow radiation dose	.02

NOTE. A full list of the clinical patient characteristics and treatment variables analyzed for effect on hematologic toxicity is included in Patients and Methods. Outcome variables were analyzed as continuous variables, unless otherwise indicated.
Abbreviations: ^{131}I-MIBG, iodine-131-metaiodobenzylguanidine; AHSCT, autologous hematopoietic stem-cell transfusion.
*Includes only patients with any degree of bone involvement.
†Analyzed as a dichotomous variable.
‡Includes only patients who required AHSCT.

at low risk for requiring AHSCT, a logistic regression analysis was performed to evaluate bone marrow tumor, history of prior transplantation, time from prior transplantation, and extent of bone disease. No combination of these variables provided a profile of patients at low risk for requiring AHSCT.

Of the 19 patients who received AHSCT, three patients received chemotherapy before AHSCT infusion and one patient died as a result of progressive disease 5.6 weeks after ^{131}I-MIBG treatment. The characteristics of the remaining 15 patients who received AHSCT and were assessable for engraftment are listed in Table 4. The clinical features of this group did not differ significantly from the group of patients who did not receive AHSCT, except that patients who required AHSCT were more likely to be female (data not shown; $P = .03$).

The time course of engraftment is shown in Figure 2. All assessable patients had neutrophil recovery. Neutro-

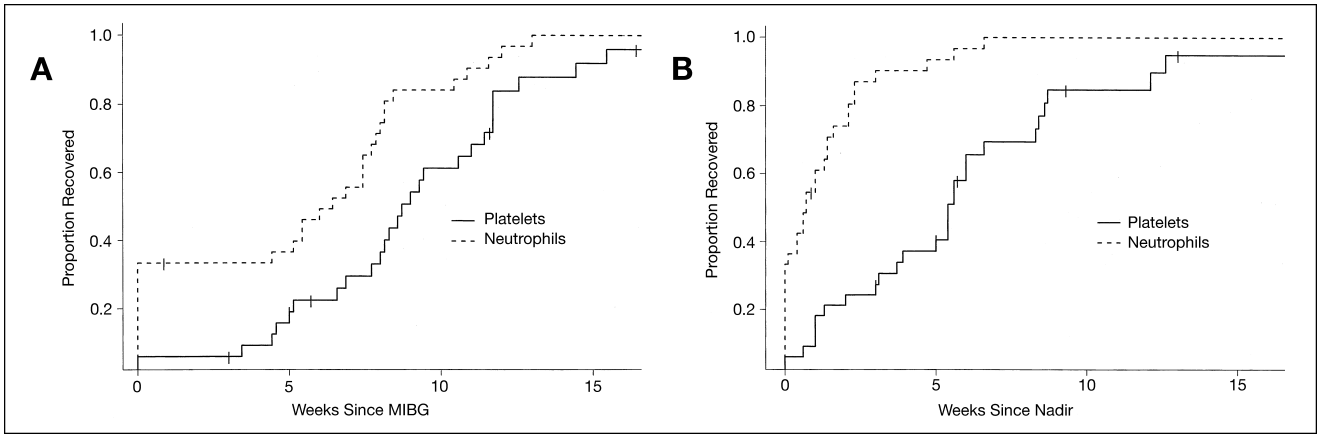

Fig 1. Neutrophil recovery to more than $0.5 \times 10^3/\mu L$ and platelet recovery to transfusion independence in 34 patients without autologous hematopoietic stem-cell transplantation. Tic marks indicate time to last follow-up for patients not assessable for recovery. (A) Recovery from iodine-131–metaiodobenzylguanidine (^{131}I-MIBG) treatment. (B) Recovery from nadir count.

Table 4. Characteristics of 15 Patients Who Required Infusion of Bone Marrow or Stem Cells After Treatment With ^{131}I-MIBG and Were Assessable for Engraftment

Characteristic	Data
Prior hematopoietic stem cell transplant	
No. of Patients	12
%	80.0
Bone marrow tumor at ^{131}I-MIBG *	
No. of Patients	4
%	26.7
Prescribed total activity ^{131}I-MIBG, mCi	
Median	366
Range	271-720
Whole-body radiation dose, Gy	
Median	2.79
Range	1.73-3.84
Red-marrow radiation dose, Gy	
Median	3.32
Range	2.06-4.57
Infused bone marrow	
No. of patients	6
%	40.0
Mononuclear cells infused, $\times 10^8$ cells/kg	
Median	1.62
Range	1.17-2.75
Received purged marrow	
No. of patients	5 of 6
%	83.3
Infused stem cells	
No. of patients	9
%	60.0
CD34 + cells infused, $\times 10^6$ cells/kg	
Median	2.55
Range	0.87-8.97
Received purged cells	
No. of patients	2 of 9
%	22.2
Time from ^{131}I-MIBG to AHSCT, weeks	
Median	7.7
Range	4.4-10.0
Became independent of platelet transfusions	
No. of patients	9
%	60.0
Platelet nadir to platelet independence, weeks	
Median	6.1
Range	2.0-8.7
AHSCT to platelet independence, weeks	
Median	1.4
Range	0.57-5
Recovered ANC $> 0.5 \times 10^3/\mu$L	
No. of patients	15
%	100
ANC nadir to ANC $> 0.5 \times 10^3/\mu$L, weeks	
Median	2.7
Range	0.6-5.6
AHSCT to ANC $> 0.5 \times 10^3/\mu$L, weeks	
Median	2.1
Range	0-4.7
Became independent of red cell transfusions	
No. of patients	11
%	73.3

Abbreviations: ^{131}I-MIBG, iodine-131-metaiodobenzylguanidine; AHSCT, autologous hematopoietic stem-cell transfusion; ANC, absolute neutrophil count.
*Defined by positive bone marrow morphology or immunocytology.

phil engraftment was complete by a median of 2.1 weeks from AHSCT. Clinical variables were analyzed for their effect on hematologic toxicity in patients receiving AHSCT (Table 3). There was a trend suggesting that higher whole-body and red-marrow radiation doses correlated with a longer period from neutrophil nadir to neutrophil recovery ($P = .066$). A longer time period from ^{131}I-MIBG to AHSCT correlated with a shorter time to neutrophil engraftment ($P = .04$).

Of the 15 assessable patients who received AHSCT, nine patients had platelet engraftment. Platelet engraftment occurred in synchrony with neutrophil engraftment (Fig 2) and was complete by a median of 1.4 weeks from AHSCT. Patients who failed to engraft platelets had received higher whole-body and red-marrow radiation doses than patients who engrafted (median whole-body doses, 3.09 *v* 2.49 Gy; median red-marrow doses, 3.73 *v* 2.98 Gy; $P = .039$ for both comparisons).

Six assessable patients failed to engraft platelets by the time of death after AHSCT (Table 5). The median time from ^{131}I-MIBG to death or additional myelosuppressive therapy for these patients was 24.9 weeks (range, 12.7 to 51.6 weeks). Three of these patients had bone marrow tumor at the time of ^{131}I-MIBG treatment. An additional two patients developed new bone marrow tumor at the time of disease progression, such that five of the six patients with failure to engraft platelets had bone marrow tumor involvement around the time of treatment. Nevertheless, bone marrow tumor at treatment was not significantly correlated with failure to engraft platelets.

Four patients continued to require red cell transfusions at the time of death or last follow-up and were considered to have experienced failure of red cell engraftment. Patients who failed to engraft RBCs received higher whole-body and red-marrow radiation doses than patients who engrafted (median whole-body doses, 3.49 *v* 2.51 Gy; median red-marrow doses, 4.16 *v* 3.01 Gy; $P = .016$ for both comparisons).

Late Effects and Nonhematologic Toxicity

Two patients developed myelodysplastic syndrome with leukemia more than 6 months after treatment with ^{131}I-MIBG and are described in a separate report.[16] Nonhematologic toxicity after ^{131}I-MIBG treatment was rare. Four patients developed hypothyroidism requiring therapy. One patient with a history of intracranial metastasis and who later developed progressive leptomeningeal disease had a self-limited seizure the day after ^{131}I-MIBG treatment. Prolonged dry mouth (n = 1), prolonged diarrhea (n = 1), hypertension during ^{131}I-MIBG infusion (n = 1), and posttreatment hypertension (n = 1) were the only other significant toxicities reported.

DISCUSSION

^{131}I-MIBG administered at 18 mCi/kg to heavily pretreated patients has substantial hematologic toxicity, with 36% of

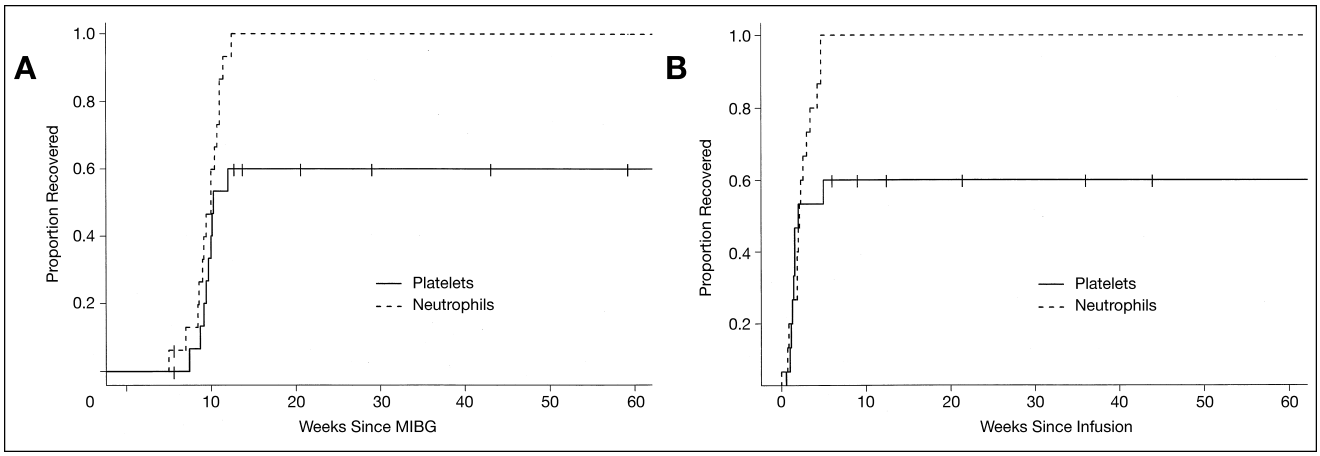

Fig 2. Neutrophil recovery to more than $0.5 \times 10^3/\mu L$ and platelet recovery to transfusion independence in 16 patients who received autologous hematopoietic stem-cell transplantation (AHSCT). Tic marks indicate time to last follow-up for patients not assessable for recovery. (A) Recovery from iodine-131–metaiodobenzylguanidine (^{131}I-MIBG) treatment. (B) Recovery from AHSCT.

patients receiving AHSCT for prolonged myelosuppression. Consistent with previous findings that higher administered activities per kilogram of ^{131}I-MIBG correlate with greater hematotoxicity,[3,8,10,11] the degree of hematotoxicity in this group of patients treated at a uniformly high dose was greater than that described previously. Thrombocytopenia requiring transfusion and neutropenia were more frequent, platelet nadir count occurred earlier, and the duration of thrombocytopenia and neutropenia was greater than in previous reports of ^{131}I-MIBG at lower doses.[3,5,9,11-13,17]

As in previous studies, ^{131}I-MIBG therapy resulted in more prominent thrombocytopenia than neutropenia.[3,5,11,18] This differential toxicity might, in part, be related to selective uptake of ^{131}I-MIBG by platelets and possibly by mature megakaryocytes as well.[19-21] In vitro work has suggested that specific blockade with selective serotonin reuptake inhibitors may provide one method of reducing thrombocytopenia after ^{131}I-MIBG treatment.[19]

Although previous studies have suggested that bone marrow tumor involvement might result in more pronounced myelosuppression after treatment with ^{131}I-MIBG,[3,9,22] our study is the first to demonstrate significant differences between patients with and without bone marrow tumor involvement in terms of timing and duration of thrombocytopenia and neutropenia. The differences observed, despite being statistically significant, were not major. These findings suggest that patients with bone marrow tumor should be monitored more closely for hematotoxicity, but the impact is not so great as to preclude the use of ^{131}I-MIBG in these patients. Bone marrow tumor might

Table 5. Features of the Six Patients Who Did Not Engraft Platelets After AHSCT

Feature	Patient					
	22	28	29	32	61	77
Prior hematopoietic stem cell transplantation	N	Y	Y	Y	Y	Y
Prior total-body irradiation	N	Y	N	N	N	N
Bone marrow tumor at ^{131}I-MIBG*	N	N	N	Y	Y	Y
Whole-body radiation dose, Gy	3.84	3.78	2.34	2.87	2.99	3.20
Red-marrow radiation dose, Gy	4.57	4.49	2.82	3.40	3.62	3.84
AHSCT type	PBM	UBM	PBM	PBM	UPBSC	UPBSC
Cell dose/kg, $\times 10^8$ MNC for BM or $\times 10^6$ CD34 for PBSC	2.8	2.4	1.2	1.3	1.9	1.8
Harvest to AHSCT, months	16	28	2	2	13	43
Cell harvest after prior transplantation	N	N	Y	Y	N	N
New marrow tumor progression after ^{131}I-MIBG	Y	Y	N	Y	N	N
Red cell engraftment	N	Y	Y	N	Y	N
Weeks of follow-up†	29.2	43.0	51.6	12.7	13.7	20.6

Abbreviations: AHSCT, autologous hematopoietic stem-cell transplantation; N, no; Y, yes; ^{131}I-MIBG, iodine-131-metaiodobenzylguanidine; PBM, purged bone marrow; UBM, unpurged bone marrow; UPBSC, unpurged peripheral-blood stem cell; MNC, mononuclear cell; BM, bone marrow; PBSC, peripheral-blood stem cell.

*Defined by positive bone marrow morphology or immunocytology.

†Follow-up from ^{131}I-MIBG treatment to death, or for patient 77, to next myelosuppressive therapy.

result in more severe myelosuppression through two possible mechanisms. First, bone marrow tumor that is not completely responsive to ^{131}I-MIBG therapy will result in bone marrow progression and myelosuppression. Second, because of the long path length of radiation from ^{131}I, ^{131}I-MIBG taken up by neuroblastoma cells in the bone marrow might damage adjacent hematopoietic and stromal cells.[23] The use of a radiolabel, such as iodine-125, with a shorter range might diminish this effect.[4]

Previous studies also have suggested greater hematotoxicity in patients who had previously received myeloablative therapy with transplantation.[3,9,13,24] Although the rationale that patients posttransplantation have less marrow reserve is appealing, a history of prior transplantation did not predict any measure of hematotoxicity in the current study. Given that only 10 patients in the current study were not posttransplantation, it is possible that a study with a more heterogeneous population might demonstrate differences in hematotoxicity on the basis of transplantation status.

Prior reports of patients treated with varying doses of ^{131}I-MIBG have demonstrated a significant relationship between higher whole-body radiation dose and lower nadir platelet and neutrophil counts.[8,10] Our study was unable to confirm these findings, despite the fact that a wide range of whole-body radiation doses was obtained. Although these associations likely exist, they might have been obscured by the uniformly high dose of ^{131}I-MIBG, resulting in severe hematotoxicity in all patients. The importance of whole-body radiation dose in predicting hematotoxicity was instead demonstrated in this study by evaluating other variables, including timing of nadir and duration of myelosuppression. These variables were correlated significantly or nearly significantly with whole-body radiation dose. Whole-body radiation dose also was shown to correlate with failure to engraft platelets or red cells in those patients requiring AHSCT. It is possible that high whole-body radiation doses of ^{131}I-MIBG might damage marrow stromal cells, resulting in an unfavorable environment for engraftment.

Of particular concern are the six patients with prolonged thrombocytopenia despite AHSCT. Other than having received higher whole-body and red-marrow radiation doses, no other clinical variables predicted failure to engraft. Although whole-body radiation dose plays a part in predicting failure to recover platelets, previous researchers using more moderate doses of ^{131}I-MIBG also have described patients with prolonged thrombocytopenia after treatment.[3,12,13,25] In contrast, three separate groups have reported a total of 40 patients treated with ^{131}I-MIBG combined with myeloablative chemotherapy and stem-cell rescue.[7,26,27] All 40 patients recovered platelets. It is possible that chemotherapy before ^{131}I-MIBG therapy facilitates marrow recovery by clearing micrometastases resistant to ^{131}I-MIBG. Alternatively, the patients in the reported series might have had less prior damage to their marrow stroma because of a much lower frequency of prior myeloablative therapy. It also is likely that the whole-body radiation dose received was lower in these other studies in which the activity infused generally was less than 15 mCi/kg. Earlier reinfusion of stem cells after ^{131}I-MIBG therapy might also favor recovery, although the results of our study failed to demonstrate a significant relationship between timing of infusion and failure to engraft platelets over the range of intervals observed in this study.

In fact, earlier AHSCT correlated with a longer time to neutrophil engraftment. It is possible that patients with a longer time from ^{131}I-MIBG to AHSCT were beginning to recover neutrophils on their own, resulting in a shorter observed time to recovery. Given the late neutrophil nadir with ^{131}I-MIBG, patients who received earlier AHSCT might still not have reached their neutrophil nadir, resulting in a longer observed time to recovery. Another possibility is that earlier AHSCT might expose cells to residual ^{131}I-MIBG activity and therefore slow engraftment. Reports from other studies using lower doses of ^{131}I-MIBG with routine early infusion of stem cells, which have shown excellent engraftment, argue against this possibility.[7,26] Finally, patients who received AHSCT earlier might have had less bone marrow reserve, resulting in a longer time to engraftment.

The substantial hematotoxicity of high-dose ^{131}I-MIBG was manageable with transfusion and cytokine support. Despite a long period of platelet dependence, the frequency of platelet transfusions often diminished to less than once per week during recovery. No toxic deaths were observed and hospitalization for infection was rare. However, the duration of myelosuppression after treatment with ^{131}I-MIBG could delay additional treatment of an aggressive tumor. Additional studies should prospectively evaluate strategies for diminishing the hematotoxicity of ^{131}I-MIBG without compromising its efficacy in treating neuroblastoma. Some potential strategies currently being evaluated by the New Approaches to Neuroblastoma Therapy consortium include incorporating early empiric stem-cell support with consecutive treatments of ^{131}I-MIBG given in rapid sequence or ^{131}I-MIBG combined with myeloablative chemotherapy.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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