

## Phase I Dose Escalation of Iodine-131–Metaiodobenzylguanidine With Myeloablative Chemotherapy and Autologous Stem-Cell Transplantation in Refractory Neuroblastoma: A New Approaches to Neuroblastoma Therapy Consortium Study

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### A B S T R A C T

#### Purpose

To determine the maximum-tolerated dose (MTD) and toxicity of iodine-131–metaiodobenzylguanidine ( $^{131}\text{I}$ -MIBG) with carboplatin, etoposide, melphalan (CEM) and autologous stem-cell transplantation (ASCT) in refractory neuroblastoma.

#### Patients and Methods

Twenty-four children with primary refractory neuroblastoma and no prior ASCT were entered; 22 were assessable for toxicity and response.  $^{131}\text{I}$ -MIBG was administered on day  $-21$ , CEM was administered on days  $-7$  to  $-4$ , and ASCT was performed on day 0, followed by 13-*cis*-retinoic acid.  $^{131}\text{I}$ -MIBG was escalated in groups of three to six patients, stratified by corrected glomerular filtration rate (GFR).

#### Results

The MTD for patients with normal GFR ( $\geq 100$  mL/min/1.73 m<sup>2</sup>) was  $^{131}\text{I}$ -MIBG 12 mCi/kg, carboplatin 1,500 mg/m<sup>2</sup>, etoposide 1,200 mg/m<sup>2</sup>, and melphalan 210 mg/m<sup>2</sup>. In the low-GFR cohort, at the initial dose level using 12 mCi/kg of  $^{131}\text{I}$ -MIBG and reduced chemotherapy, one in six patients had dose limiting toxicity (DLT), including veno-occlusive disease (VOD). Three more patients in this group had grade 3 or 4 hepatotoxicity, and two had VOD, without meeting DLT criteria. There was only one death as a result of toxicity among all 24 patients. All assessable patients engrafted, with median time for neutrophils  $\geq 500/\mu\text{L}$  of 10 days and median time for platelets  $\geq 20,000/\mu\text{L}$  of 26 days. Six of 22 assessable patients had complete or partial response, and 15 patients had mixed response or stable disease. The estimated probability of event-free survival and survival from the day of MIBG infusion for all patients at 3 years was  $0.31 \pm 0.10$  and  $0.58 \pm 0.10$ , respectively.

#### Conclusion

$^{131}\text{I}$ -MIBG with myeloablative chemotherapy is feasible and effective for patients with neuroblastoma exhibiting de novo resistance to chemotherapy.

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### INTRODUCTION

Neuroblastoma, arising in the sympathetic nervous system, is the most common extracranial childhood solid tumor. One half of patients present with metastatic disease, with a 5-year survival of only 30%, despite intensive myeloablative therapy and autologous stem-cell transplantation (ASCT).<sup>1</sup> Patients who do not achieve partial response with induction chemotherapy or have residual bone marrow disease have an even lower survival rate of below 10%.<sup>2</sup> New approaches are needed for such resistant tumors.

Metaiodobenzylguanidine (MIBG), a norepinephrine analog, is concentrated selectively in sympathetic nervous tissue, and when labeled with iodine-123 ( $^{123}\text{I}$ ), has become an integral component of staging and response evaluation in neuroblastoma.<sup>3,4</sup> MIBG labeled with iodine-131 ( $^{131}\text{I}$ ) has demonstrated activity for targeted therapy of neuroblastoma, both in relapsed and newly diagnosed patients.<sup>5-12</sup>  $^{131}\text{I}$ -MIBG as a single agent in a phase I dose-escalation study showed a response rate of 37% in children with relapsed neuroblastoma<sup>10</sup> and dose-limiting hematologic toxicity was circumvented with ASCT.<sup>13,14</sup>

Myeloablative chemotherapy also has demonstrated efficacy against neuroblastoma. Carboplatin, etoposide, and melphalan with ASCT is an effective regimen that resulted in 55% 3-year event-free survival (EFS) in patients without progressive disease, and 10% to 20% EFS in patients who had experienced relapse.<sup>1,15,16</sup> A combination of targeted <sup>131</sup>I-MIBG treatment and intensive systemic chemotherapy may lead to a higher rate of EFS for children with resistant neuroblastoma. Pilot studies of <sup>131</sup>I-MIBG with myeloablative chemotherapy and ASCT demonstrated that the therapy was well tolerated in a small number of patients,<sup>17-19</sup> and one pilot study suggested activity in patients with relapsed or resistant disease.<sup>20</sup> We report here a dose-escalation study to define the maximum-tolerated dose (MTD) of <sup>131</sup>I-MIBG with myeloablative melphalan, etoposide, and carboplatin plus ASCT in patients with refractory or relapsed neuroblastoma.

**PATIENTS AND METHODS**

**Patient Population**

Patients with high-risk neuroblastoma who were age 1 to 21 years at diagnosis were eligible if they had poorly responding neuroblastoma, defined as stable disease or partial response at the end of at least 12 weeks of any induction therapy; bone marrow containing greater than 100 tumor cells per 10<sup>5</sup> mononuclear cells by immunocytology after 12 weeks of induction therapy,<sup>2</sup> or progressive disease at any time. All patients were required to have demonstrated MIBG uptake in the skeleton or soft tissue tumor. Patients were required to have hematopoietic stem cells without detectable tumor by immunocytology, or to have no tumor in bone marrow by routine morphology before peripheral-blood stem-cell (PBSC) collection. Patients had normal organ function and glomerular filtration rate (GFR) of ≥ 60 mL/min/1.73 m<sup>2</sup>. Patients who had undergone prior myeloablative therapy were excluded. The study enrolled 24 patients from April 2000 to December 2004. The protocol was carried out by the New Approaches to Neuroblastoma Therapy (NANT) consortium ([www.nant.org](http://www.nant.org)), and was approved by the US Food and Drug Administration. Patients received MIBG infusion at University of California, San Francisco (San Francisco, CA), University of Michigan (Ann Arbor, MI), or Children's Hospital of Philadelphia (Philadelphia, PA), and then returned to their respective NANT institutions for the myeloablative chemotherapy and ASCT. The study was approved by NANT institutional review boards, and informed consent was obtained for all patients. Participating NANT investigators and institutions are listed in the Appendix.

**Study Design and Toxicity Evaluation**

Patients received an intravenous infusion of <sup>131</sup>I-MIBG during 2 hours with hydration, with thyroid protection with potassium iodide and potassium

perchlorate, and a Foley catheter for bladder protection. Patients remained in a radiation-protected isolation room for 4 to 7 days, until radiation emissions met institutional regulations.<sup>10</sup> The dose of radiation to the whole body from the <sup>131</sup>I-MIBG was calculated as described using multiple measurements from a hand-held Geiger counter or ceiling-mounted monitor.<sup>11</sup> Two weeks after MIBG infusion, the patient received carboplatin and etoposide as a continuous 96-hour infusion on days -7 to -3. Melphalan was administered by intravenous bolus at hour 0 days -7, -6, and -5. Stem cells were infused 72 hours after completion of chemotherapy. Granulocyte colony-stimulating factor was administered 4 hours after stem-cell infusion and continued to absolute neutrophil count (ANC) more than 1,500/μL. Local radiation (2.1 Gy), was administered to the primary tumor bed and to residual metastatic sites after completion of MIBG and chemotherapy, and after response evaluation. 13-*cis*-Retinoic acid or other biologic therapy was permitted after the response evaluation.

This study used the standard 3 + 3 phase I trial design.<sup>21</sup> Dose escalation, expansion, and termination of escalation were done independently in the two cohorts of patients (those with a normal GFR ≥ 100 mL/min/1.73 m<sup>2</sup> and patients with GFR between 60 and 99 mL/min/1.73 m<sup>2</sup>). The doses of <sup>131</sup>I-MIBG and chemotherapy combination were started below the previously established MTD of each agent (Table 1). Toxicity was graded according to National Cancer Institute Common Toxicity Criteria, version 2.0 (<http://ctep.cancer.gov/reporting/ctc.html>), using the Common Toxicity Criteria bone marrow transplantation-specific modifications.

Dose-limiting toxicity (DLT) was defined as any grade 4 nonhematologic toxicity excluding fever, anorexia, inner ear/hearing, vomiting requiring parenteral nutrition, metabolic/laboratory abnormalities unless life threatening or disabling, infection unless also associated with grade 3 symptoms in other organs related to the infection that do not resolve to baseline within 7 days of occurrence. The following grade 3 nonhematologic toxicities were also defined as DLT: renal toxicity excluding grade 3 hemorrhagic cystitis, dysuria, urinary frequency/urgency, and urinary electrolyte wasting; pancreatitis; CNS bleeding; cerebrovascular ischemia; seizures; and/or aphasia. Only the following hematologic toxicities were defined as DLT: grade 4 hemolysis, platelet transfusion refractoriness associated with life-threatening bleeding, hemorrhage or hemolysis associated with life-threatening anemia, grade 4 failure to engraft, or other life-threatening blood/bone marrow toxicity. The MTD was defined as the dose level where zero of six or one of six assessable patients experienced a DLT and two or more patients experienced DLT at the next higher dose. For the diagnosis of veno-occlusive disease (VOD), two of the following criteria had to be met within 20 days of transplantation: hyperbilirubinemia (total serum bilirubin > 2 mg/dL), hepatomegaly or right upper quadrant pain of liver origin, and sudden weight gain (> 2% of baseline body weight) secondary to fluid accumulation without other explanation.<sup>22</sup> Neutrophil recovery was defined as the first of 3 consecutive days of an ANC ≥ 500/uL, and platelet recovery was defined as the first of 3 consecutive days of a platelet count ≥ 20,000/μL without platelet transfusion support. The day of MIBG infusion was the starting point for Kaplan-Meier calculation of estimated overall

**Table 1.** Dose Escalation Schema

Patients With Normal GFR ≥ 100 mL/min/1.73 m <sup>2</sup>				
Level	<sup>131</sup> I-MIBG (mCi/kg)	Carboplatin (mg/m <sup>2</sup> )	Etoposide (mg/m <sup>2</sup> )	Melphalan (mg/m <sup>2</sup> )
1	12	1,500	1,200	210
2	15	1,500	1,200	210
3	18	1,500	1,200	210
4	18	1,700	1,200	210
Patients With Low GFR 60-99 mL/min/1.73 m <sup>2</sup>				
Level	<sup>131</sup> I-MIBG (mCi/kg)	Carboplatin (AUC)	Etoposide (mg/m <sup>2</sup> )	Melphalan (mg/m <sup>2</sup> )
1A	12	3.3/day	640	180
2A	15	3.3/day	640	180

Abbreviations: GFR, glomerular filtration rate; <sup>131</sup>I-MIBG, iodine-131-metaiodobenzylguanidine; AUC, area under the time-concentration curve.

survival and EFS, which was defined as time to progressive disease, second malignancy, or death.

### Response Evaluation

All responses were assessed by central review of MIBG and computed tomography (CT) scans by a radiologist and nuclear medicine physician, blinded to patient identity and outcome. Response in soft tissue lesions was evaluated according to Response Evaluation Criteria in Solid Tumors Group criteria if a measurable lesion was present on CT.<sup>23</sup> To quantify the response by MIBG scan, a score was assigned to all pretherapy and day 84 post-therapy MIBG scans; response was defined as a relative score of  $\leq 0.5$ .<sup>24,25</sup> Overall response for all patients was assigned according to the International Neuroblastoma Response Criteria, after evaluation of bone marrow, CT scan, MIBG scan, and urine catecholamines,<sup>4</sup> except for using the Response Evaluation Criteria in Solid Tumors Group method for solid lesions and use of semiquantitative MIBG score rather than technetium-99m bone scan for bone metastases.<sup>25</sup>

## RESULTS

### Patients

Twenty-four patients with refractory neuroblastoma were enrolled onto this study (Table 2). Although two patients were declared ineligible on retrospective review (one received chemotherapy 18 days before study entry and another received PBSCs that were not tested for tumor cells by immunocytology), all 24 patients are included in this report. Twenty-two were assessable for toxicity and response. Eight patients were treated at level 1, six patients were treated at level 2, four patients were treated at level 3, and six patients were treated at level 1A.

Patients had the usual high-risk characteristics at diagnosis and all the patients had extensive prior chemotherapy treatment; 22 of 24 had at least two regimens (Table 2). Most patients also had multiple sites of disease at study entry, including 10 with morphologic bone marrow tumor, 12 with soft tissue lesions, and 21 with skeletal lesions. Twenty patients had primary refractory ( $n = 12$ ) or progressive neuroblastoma ( $n = 8$ ) despite multiple regimens.

### Dose-Limiting Toxicity

In the normal GFR cohort, six assessable patients were treated at level 1 because one patient experienced DLTs after MIBG alone (Table 3). These events likely were due to complications related to bulky tumor load and ascites, exacerbated by fluid infusion for MIBG. Chemotherapy and stem cells were never administered. There were no DLTs in the remaining five assessable patients at this level. Two additional patients were treated at this level without DLTs, but were inassessable due to modified doses. At level 2, three patients were entered initially without DLTs. At level 3, the MTD was exceeded, with DLTs in two of four patients. Three additional patients were entered at level 2, with DLTs in two (Table 3). Thus, with two of six assessable patients having experienced DLTs at level 2, level 1 (with 12 mCi/kg <sup>131</sup>I-MIBG) was determined to be the MTD for the normal GFR cohort.

In the low-GFR cohort, six patients accrued to level 1A and were assessable for toxicity. One patient at this level experienced a DLT of grade 4 VOD (Table 3). This patient also had two subsequent adverse events of delayed platelet engraftment and esophageal stricture. Level 1A was expanded to accrue a total of six patients on the basis of the DLT. Although none of the other five patients experienced a DLT, four patients experienced grade 3 or 4 hepatic toxicity, and two more had VOD. As a result of this apparent high incidence of VOD, the dose was not escalated to level 2A in the low-GFR cohort.

**Table 2.** Patient Characteristics (N = 24)

Characteristic	No.	%
<b>Characteristic at diagnosis</b>		
Age, years		
Median	5.4	
Range	0.4-15.9	
Males	13	54
Females	11	46
MYCN amplification	5 of 20	25
Bone metastases	22 of 23	96
Bone marrow metastases	21 of 23	91
<b>Characteristic at study entry</b>		
Median time from diagnosis, months	9.6	
Range	4.1-48.6	
Age, years		
Median	6.6	
Range	1.5-16.9	
Bone marrow metastases	10	42
Mass on CT/MRI	12	50
Bone metastases by MIBG	21	88
Disease status		
PR	4	
SD	12	
PD	8	
No. of prior regimens*		
1	2	8
2	13	54
3	5	21
4-5	4	17
Prior radiation	1	
Low GFR, 66-99 mL/min/1.73 m <sup>2</sup> (n = 6)		
Median	72	
Range	62-97	
Normal GFR, $\geq 100$ mL/min/1.73 m <sup>2</sup> (n = 18)		
Median	127	
Range	107-185	

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; MIBG, metaiodobenzylguanidine; PR, partial response; SD, stable disease; PD, progressive disease; GFR, glomerular filtration rate.

\*Patients with prior myeloablative therapy were excluded.

There was modest incremental change in the measured whole-body radiation dose with <sup>131</sup>I-MIBG dose level, with a range of 1.11 to 3.07 Gy, and median of 2.08, 2.11, 2.13, and 2.95 Gy for levels 1A, 1, 2, and 3, respectively. There was no difference in the whole-body radiation received in the low-GFR cohort compared with the normal GFR cohort at level 1 to account for the increase in VOD among patients with low GFR attributable to radiation.

### Hematologic and Nonhematologic Toxicity

Hematologic toxicity equal to grade 3 or 4 occurred in all patients, as expected in a myeloablative protocol. All of the assessable patients engrafted, with median time to ANC more than 500/ $\mu$ L of 10 days and median time to platelets more than 20,000/ $\mu$ L of 26 days (Table 4). The one patient with delayed platelet engraftment to 224 days had other DLTs that included grade 4 VOD.

The frequent nonhematologic grade 3 and 4 toxicities were similar to those of other myeloablative regimens (Table 5). Cardiovascular toxicities included arrhythmia, capillary leak syndrome, edema, hypotension, and hypertension. Pulmonary toxicities included acute

**Table 3.** DLTs

Dose Level	No. DLTs*	No. Assessable	Patient	Toxicity
1	1	6	N003	Grade 4 acute vascular leak syndrome, edema, ascites, acidosis, hypoxia, dyspnea; grade 3 nodal/junctional arrhythmia (after MIBG only)
2	2	6	N023	Grade 4 mucositis, ARDS, arrhythmia; grade 3 renal failure; grade 3 VOD; grade 3 bilirubin, hepatomegaly, AST, weight gain, epistaxis, GI bleeding
2			N050	Grade 3 VOD; hepatomegaly with grade 3 bilirubin, AST, ALT, weight gain
3	2	4	N017	Gram-negative sepsis with grade 4 hypotension, hypoxia, dyspnea, ARDS, pleural effusion, hypokalemia; grade 3 bilirubin, AST, ALT, epistaxis
3			N018	Death as a result of toxicity from multiorgan failure with grade 4 vascular leak, VOD, ALT, AST, ascites, DIC, hypoxia, acidosis, hypotension; grade 3 renal failure.
1A	1	6	N007	Grade 4 VOD, grade 2 seizure; grade 4 esophagitis/esophageal stricture, delayed platelet engraftment

Abbreviations: DLT, dose-limiting toxicity; MIBG, metaiodobenzylguanidine; ARDS, acute respiratory distress syndrome; VOD, veno-occlusive disease; DIC, disseminated intravascular coagulation.

\*Two additional patients who were enrolled at level 1 (N0013 and N0024) were inassessable for toxicity for dose escalation purposes due to non-protocol-mandated dose alterations, but they did not have DLT.

respiratory distress syndrome, dyspnea, and hypoxia. Two patients developed grade 3 renal insufficiency. Serious infection or febrile neutropenia developed in 91% of patients. Bleeding, although a frequent toxicity, was restricted to mucous membranes and GI tract. Ninety-one percent of patients had some GI toxicity, 60% of which was related to mucositis.

Rare toxicities included one patient receiving dose level 1A with grade 2 hypothyroidism, and another in level 1A who had a grade 2 seizure on the first day of chemotherapy infusion without neurologic sequelae. One patient who had DLT at level 3 later developed lymphoproliferative disease at day +122 after receiving CD34-selected PBSC for ASCT.

Grade 3 to 4 hepatic toxicities, seen in 55% of patients, included hepatomegaly, hypoalbuminemia, and elevations in bilirubin, alkaline phosphatase, ALT, AST, and gamma-glutamyltransferase levels. Three of the six patients in the low-GFR cohort and three of 16 patients in the normal-GFR cohort developed VOD. Neither of the two inassessable patients with incorrect dosing at level 1 had VOD, although one had grade 3 AST and ALT elevation.

**Response**

Responses in the 22 assessable patients are summarized in Table 6. The overall response rate including complete and partial response was six of 22 (27%; 95% CI, 13% to 50%). It is noteworthy that four of

these six patients with a response to protocol therapy had primary refractory (n = 2) or progressive disease (n = 2) despite multiple prior regimens. If only patients who were dosed correctly and had a complete set of required follow-up scans were considered, then the response rate was six of 18 (33%). One of the patients with a mixed response had complete response in bone marrow, improvement on MIBG scan (relative MIBG score of 0.73), but persistence of abnormal catecholamines. The other patient with a mixed response had complete response in bone marrow but no change in primary tumor mass or in MIBG score. Four of 10 patients with morphologic bone marrow tumor at study entry cleared the marrow at the evaluation on day 84. The MIBG scan improved in nine patients, with a median relative MIBG score of 0.5 (Table 7). Five of 12 patients with measurable disease on CT/magnetic resonance imaging showed significant decrease in mass disease.

**EFS and Overall Survival**

The median follow-up of surviving patients was 36.5 months (range, 6.9 to 49.5+ months). The median EFS for all patients is 18.0 months (95% CI, 13.5 to 34.2 months); the median overall survival interval is 48.1 months (95% CI, 18.7 to 49.5+ months). The estimated probability of patients remaining alive and event free at 2 and 3

**Table 4.** Time to Engraftment (days from stem-cell infusion)

Dose Level	No. of Patients Entered	ANC > 500/ $\mu$ L (n = 23)*		Platelets > 20,000/ $\mu$ L (n = 22) <sup>†</sup>	
		Median	Range	Median	Range
1	8	12	10-15	45	10-60
2	6	10	8-12	21.5	12-46
3	4	10	9-11	21	14-26
1A	6	10.5	9-12	26	13-224
All patients	24	10	8-15	26	10-224

Abbreviation: ANC, absolute neutrophil count.  
<sup>\*</sup>One patient who died as a result of toxicity on day 10 at level 3 was assessable for ANC engraftment but not platelets, whereas one patient at level 1 died as a result of progressive disease prior to receiving the transplant.

**Table 5.** Patients With Grade 3 or 4 Nonhematologic Toxicities

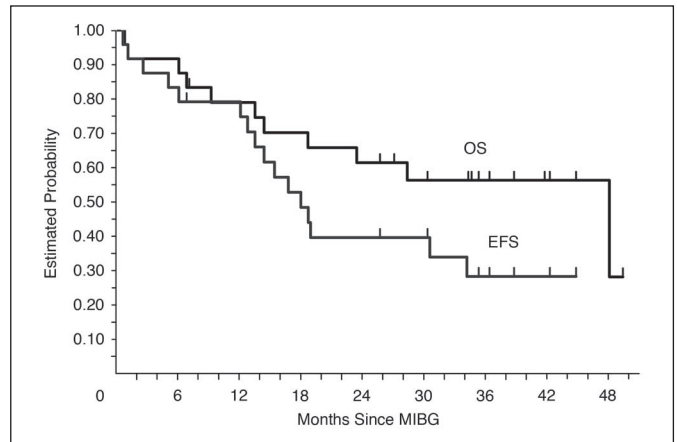
Toxicity	Level				All Levels (n = 22)	
	1 (n = 6)	2 (n = 6)	3 (n = 4)	1A (n = 6)	No.	%
Hepatic	1	5	2	4	12	55
Cardiovascular	1	1	3	2	7	32
Pulmonary	1	3	4	1	9	41
Renal insufficiency	0	1	1	0	2	9
Infection/febrile neutropenia	4	6	4	6	20	91
Hemorrhage	3	2	1	2	8	36
GI	5	6	4	5	20	91
Metabolic/laboratory	4	3	3	3	13	59
Neurology	1	1	0	0	2	9
Any	6	6	4	6	22	100

**Table 6.** Responses in All Evaluated Patients

Dose Level	Complete Response	Partial Response	Mixed Response	Stable Disease	Progressive Disease
1 (n = 7)	0	1	1	4	1
2 (n = 6)	1	2	1	2	0
3 (n = 3)	0	2	0	1	0
1A (n = 6)	0	0	0	6	0
All Levels (n = 22)	1	5	2	13	1

NOTE. Two patients were not assessable for response because of early death (one died before treatment completion as a result of disease progression and the other died as a result of toxicity on day 11 after ASCT). Two other patients at level 1, who were listed as having stable disease by clinical evaluation and persistent bone marrow disease, did not have the complete required disease evaluation; one was missing a follow-up CT scan and the other was missing the day 84 MIBG scan. The two patients treated at the incorrect dose at level 1 are included in the table.

Abbreviations: ASCT, autologous stem-cell transplantation; CT, computed tomography; MIBG, metaiodobenzylguanidine.



**Fig 1.** Overall survival (OS) and event-free survival (EFS) for all 24 patients entered onto study. The median OS was 48.1 months (95% CI, 18.7 to 49.5+ months); the median EFS was 18.0 months (95% CI, 13.5 to 34.2 months). MIBG, metaiodobenzylguanidine.

years is  $0.42 \pm 0.10$  and  $0.31 \pm 0.10$ , respectively (Fig 1). Nine patients have died as a result of progressive disease (n = 7), toxicity while on study (n = 1), and infection 14 months after study therapy (n = 1). The estimated probability of overall survival at 3 years is  $0.58 \pm 0.10$  (Fig 1).

**DISCUSSION**

This study demonstrates that the combination of <sup>131</sup>I-MIBG with carboplatin, etoposide, and melphalan followed by ASCT is feasible and effective therapy for patients with refractory neuroblastoma. The MTD for this group of heavily pretreated patients was 12 mCi/kg of <sup>131</sup>I-MIBG with carboplatin 1,500 mg/m<sup>2</sup>, etoposide 1,200 mg/m<sup>2</sup>, and melphalan 210 mg/m<sup>2</sup>. This regimen allowed the delivery of targeted radiotherapy to primary and residual metastatic neuroblastoma with little more than 2.0 Gy of measured total-body dose, which should minimize potential late effects of total-body irradiation (TBI).<sup>26</sup> Furthermore, the doses of chemotherapy in combination with <sup>131</sup>I-MIBG at the regimen MTD were only slightly decreased from their MTD when used without TBI: by 12% for carboplatin, 11% for etoposide, 0% for melphalan. The regimen MTDs were 50% greater for carboplatin and 87% greater for etoposide than when the

**Table 7.** MIBG Scores for Patients With Improvement on MIBG Scan

Patient	Overall Response	MIBG Response	Absolute MIBG Score Pretherapy	Absolute MIBG Score Post-Therapy	Relative MIBG Score
N010	CR	CR	5	0	0
N009	PR	CR	1	0	0
N016	PR	PR	12	1	0.08
N017	PR	PR	8	3	0.375
N014	PR	PR	2	1	0.50
N051	PR	PR	4	2	0.50
N020	SD	SD	5	3	0.6
N011	MR	SD	11	8	0.73
N015	SD	SD	16	14	0.875

Abbreviations: MIBG, metaiodobenzylguanidine; CR, complete response; PR, partial response; SD, stable disease.

same drugs were combined with TBI.<sup>1,27</sup> The MTD for the low-GFR cohort requires additional testing because of the excessive rate of VOD. Thus, this regimen allows delivery of 30.0 Gy or more to multiple metastatic sites,<sup>11</sup> with essentially full doses of myeloablative chemotherapy but without excessive TBI.

Although the hepatic toxicity was high, particularly in the period immediately after chemotherapy administration, the type and incidence in this study were similar to those observed in other studies of high-risk neuroblastoma patients using the same chemotherapy regimen without MIBG.<sup>22</sup> An apparently excessive rate of VOD was seen in the patients with a low GFR, suggesting that decreased clearance of either the <sup>131</sup>I-MIBG or of the chemotherapy agents, despite dose adjustment, added to the hepatic insult. The lack of difference in the received whole-body radiation dose at 12 mCi/kg in the low-GFR cohort compared with that in the normal-GFR cohort suggests that the major problem was related to the chemotherapy clearance when combined with the radiation from the MIBG. No late hepatic toxicity has been observed in surviving patients who were treated with MIBG, either alone or in combination with chemotherapy. Furthermore, no significant hepatic toxicity has been noted in patients receiving multiple infusions of <sup>131</sup>I-MIBG without chemotherapy, again suggesting that the radiotherapy effect alone is not sufficient to produce VOD.<sup>28</sup> Future studies that include patients with low GFR should use a lower <sup>131</sup>I-MIBG dose, which is still expected to be effective from previous phase I and II studies, in addition to careful toxicity monitoring or a lower dose of chemotherapy.

Other toxicities observed in this study were similar to those reported from previous studies of similar myeloablative chemotherapy.<sup>1,27,29</sup> The single death as a result of toxicity in 24 patients is also within the acceptable range for myeloablative regimens followed by ASCT. Hematopoietic reconstitution after ASCT was also equivalent to that reported from previous neuroblastoma clinical trials, suggesting that the addition of <sup>131</sup>I-MIBG does not have deleterious effects on bone marrow stroma or stem cells.

The response rate of 27% was encouraging in this population of patients with de novo refractory metastatic neuroblastoma, despite two or more intensive chemotherapy induction regimens. Four of the six patients with a complete or partial response had

demonstrated progression or no response to multiple previous treatments. This is comparable to the 30% response reported in studies of relapsed neuroblastoma with <sup>131</sup>I-MIBG.<sup>9-11,30</sup> The other encouraging result is the 28% 3-year EFS and 56% overall survival. In fact, eight of the 24 patients are surviving from 14 to 49.5 months from protocol treatment without disease progression, although most are receiving biologic therapy. This result appears to be better than the previously reported 10% EFS for patients with neuroblastoma who had poor response to induction therapy.<sup>1,31,32</sup> Furthermore, seven of 10 patients with residual bone marrow disease by morphology at the time of entry into our study are surviving at a median of 39 months (range, 12 to 44 months). This type of patient had an extremely poor outcome in a recent Children's Cancer Group study, in which less than 10% of patients with

any bone marrow tumor detectable after 12 weeks of induction chemotherapy and none of those with more than 0.1% tumor in marrow 2 to 4 weeks before ASCT survived.<sup>2</sup> Of note, all surviving patients in the current report have received additional biologic therapy, including phase I investigational agents, and the impact of such on EFS and survival is not known.

In summary, the combination of <sup>131</sup>I-MIBG with myeloablative doses of carboplatin, etoposide, and melphalan is feasible and effective in patients with refractory neuroblastoma and normal renal function. The regimen requires additional testing with appropriate dose modification for patients with a low GFR. Stem-cell support permits prompt engraftment after <sup>131</sup>I-MIBG and myeloablative chemotherapy. This regimen is now being tested in a NANT phase II study for patients with poor response to induction chemotherapy.

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**Appendix****Appendix.** List of NANT Principal Investigators Participating in N9901

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**Authors' Disclosures of Potential Conflicts of Interest**

The authors indicated no potential conflicts of interest.

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