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Tumor Response and Toxicity With Multiple Infusions of High Dose ^{131}I-MIBG for Refractory Neuroblastoma

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Background. ^{131}I Metaiodobenzylguanidine (^{131}I-MIBG) is an effective targeted radiotherapeutic for neuroblastoma with response rates greater than 30% in refractory disease. Toxicity is mainly limited to myelosuppression. The aim of this study was to determine the response rate and hematologic toxicity of multiple infusions of ^{131}I-MIBG. ***Procedure.*** Patients received two to four infusions of ^{131}I-MIBG at activity levels of 3–19 mCi/kg per infusion. Criteria for subsequent infusions were neutrophil recovery without stem cell support and lack of disease progression after the first infusion. ***Results.*** Sixty-two infusions were administered to 28 patients, with 24 patients receiving two infusions, two patients receiving three infusions, and two patients receiving four infusions. All patients were heavily pre-treated, including 16 with prior myeloablative therapy. Eleven patients (39%) had overall disease response to multiple therapies, including eight patients with measurable responses to each of two or three infusions, and three with a partial response (PR) after the first infusion and stable disease after the second. The main toxicity was myelosuppression, with 78% and 82% of patients requiring platelet transfusion support after the first and second infusion, respectively, while only 50% had grade 4 neutropenia, usually transient. Thirteen patients did not recover platelet transfusion independence after their final MIBG infusion; stem cell support was given in ten patients. ***Conclusions.*** Multiple therapies with ^{131}I-MIBG achieved increasing responses, but hematologic toxicity, especially to platelets, was dose limiting. More effective therapy might be given using consecutive doses in rapid succession with early stem cell support. Pediatr Blood Cancer 2005;44:232–239. © 2004 Wiley-Liss, Inc.

Key words: MIBG; myelosuppression; neuroblastoma; toxicity

INTRODUCTION

Neuroblastoma is the most common extra-cranial childhood malignancy, and is metastatic in more than 50% of patients at the time of diagnosis [1]. Patients with high-risk neuroblastoma have a 5-year survival rate of only 30–40%, even if there is a favorable response to initial therapy [2]. Due to the poor survival probability of children with metastatic neuroblastoma, it is important to develop more effective treatment.

The aralkylguanidine ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) was reported to concentrate in 91.5% of neuroblastomas in a cumulative study of 844 patients, and is a sensitive and specific indicator for neuroblastoma, as well as, a tumor-targeted vehicle for delivering therapeutic doses of radiation to neuroblastoma tumors [3]. In phase I/II trials using ^{131}I-MIBG as a targeted radiotherapy, the response rate was 30–50%, with the primary toxicity of reversible myelosuppression including marked thrombocytopenia and moderate neutropenia [4–8]. Many of these reports treated some of the patients with more than one course of therapy, but did not report detailed toxicity or differentiate the efficacy of single compared to multiple infusions. The aim of this study was to analyze the efficacy and toxicity of multiple infusions of high dose ^{131}I-MIBG for refractory neuroblastoma.

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METHODS

A retrospective chart review of 28 patients with refractory relapsed high-risk neuroblastoma treated with multiple infusions of ^{131}I-MIBG at University of California

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San Francisco (UCSF) Children's Hospital and Children's Hospital of Philadelphia (CHOP) from March 1986 to April 2003 was performed to evaluate disease response, survival, and toxicity. Patients enrolled in a phase I/II clinical trial [7–9] met the following eligibility requirements: (1) a diagnosis of neuroblastoma based on tumor histopathology or elevated vanillylmandelic acid (VMA) or homovanillylmandelic acid (HVA) with typical tumor cells in bone marrow, (2) age greater than 1 year and less than 40 years, (3) failure to achieve partial or complete response (CR) with standard therapy or progressive disease at any time, and (4) normal baseline organ function. In addition, sufficient tumor-free autologous hematopoietic stem cell product, baseline platelet count of greater than 75,000/μl, and an absolute neutrophil count (ANC) of greater than 1,000/μl were required prior to the first infusion with ^{131}I-MIBG. Patients were eligible for another treatment, 6-week post-therapy, as long as they met the requirements as described above, had responsive disease or disease stabilization after the preceding infusion, maintained platelet counts above 20,000 while requiring no more than one platelet transfusion per week, and did not require autologous hematopoietic stem cell transfusion (AHSCT) support after the preceding therapy. Requirements for AHSCT included ANC of <200/μl for 2 weeks on G-CSF, or platelet transfusion was required two or more times weekly for 4 weeks. Eight of the patients included in this study have had some of their results from the first infusion included in previous reports [7,9], but no details of the multiple infusion therapy have been reported.

Patients were infused with a median dose of 17.3 mCi/kg (range: 2.6–19.3 mCi/kg) over 90–120 min per infusion. Four patients were treated on a phase I dose escalation study [7], and 24 patients were treated on a phase II study of high dose ^{131}I-MIBG [10]. Prior to infusion with ^{131}I-MIBG, patients were treated with a loading dose of potassium iodide 6 mg/kg orally 8–12 hr prior to MIBG injection, and potassium iodide 1 mg/kg/dose every 4 hr on day 0–6, then 1 mg/kg/day through day 45 post-infusion for thyroid protection. Potassium perchlorate was also given at 8 mg/kg loading dose, then 2 mg/kg orally, every 6 hr for 5-day post-treatment. Bladder protection was provided with a urinary catheter inserted prior to ^{131}I-MIBG infusion and retained for a minimum of 72 hr, or until patient was released from radiation isolation. Patients remained in a radiation protected isolation room for 4–7 days, until radiation emissions met state regulatory requirements.

Disease response was evaluated at 6-week post-treatment, and every 3 months thereafter following the patient's final treatment with ^{131}I-MIBG. In addition, the best response achieved at any time post-therapy without other intervening treatment was also recorded. Disease evaluation included physical examination, computed tomography (CT), or magnetic resonance (MR) imaging; ^{123}I or ^{131}I-MIBG scans, ^{99}Te MDP bone scan in selected cases, bilateral bone marrow (BM) biopsy and aspirates with bone marrow immunocytochemistry, and urine catecholamines. MIBG response, CT/MR response, and BM response evaluations by each modality were recorded. Evaluation of an overall response followed the International Neuroblastoma Response Criteria (INRC): CR (no evidence of tumor), very good partial response (VGPR) (decrease by >90% of tumor, with residual bone changes allowed), partial response (PR) (decrease by >50% of tumor, with no new lesions), mixed response (MR) (decrease by >50% of any lesion, with <50% reduction in any other lesion; and <25% increase in an existing lesion; no new lesions), stable disease (SD) (<50% reduction but <25% increase in any existing lesion; no new lesions), and progressive disease (PD) (any new lesion; increase of any measurable lesion by >25%; previously negative bone marrow positive for tumor) [11]. Response by MIBG scans was evaluated by decrease in the number of lesions. Clinical improvement of performance status and pain relief was noted, but not included in the response criteria.

Toxicity was monitored, as previously described [7], with baseline and serial complete blood counts, liver, adrenal, renal, and thyroid function tests, and cardiac echo. Toxicity to therapy was recorded using NIH common toxicity criteria (CTC) version 2.0. Study protocols were approved by the UCSF and CHOP Committees on Human Research, and informed consent was obtained for all patients.

RESULTS

Patient Characteristics

Sixty-two infusions were administered to 28 patients, with 24 patients receiving a total of two infusions, two patients receiving three infusions, and two patients receiving four infusions. The on-study characteristics of the 28 patients are shown in Table I. All patients were originally high risk, except for one child with stage 4S, who subsequently progressed to stage 4, and still had refractory progressive disease after 7 years of prior chemotherapy. All patients had been heavily pre-treated with chemotherapy, surgery, and radiation including 16 patients with prior myeloablative therapy and autologous bone marrow or peripheral blood stem cell transplantation. Sites of disease prior to the first infusion included 11 patients (39%) with combined bone and/or bone marrow and soft tissue disease, 8 patients (29%) patients with bone and/or bone marrow disease only, and 9 patients (32%) with only soft tissue disease.

Timing

The median time between first and second ^{131}I-MIBG treatments for all 28 patients was 97.5 days (range:

TABLE I. Patient Characteristics

Characteristic	Value
Median age (years) at diagnosis [range]	5.8 [0.5–26.2]
Gender: M:F	14:14
Number of treatments	
2 ^{131}I-MIBG infusions	24
3 ^{131}I-MIBG infusions	2
4 ^{131}I-MIBG infusions	2
MYCN amplification at diagnosis	6/21
INSS stage at diagnosis	
3	6
4	21
4S	1
Elevated urine catecholamines	16/27
Prior therapy	
Chemotherapy	28
Surgery	20
Radiation therapy	21
Myleoablative therapy with AHSCT	16
TBI	1
Dose ^{131}I-MIBG (mCi/kg)	
First infusion: median [range]	17.5 [2.6–19.2]
Second infusion: median [range]	17.8 [3.0–19.3]
Third infusion:	4.9, 10.7, 10.9, 14.1
Fourth infusion:	9.7, 15.6
Cumulative dose	
mCi: median [range]	860 [346–2,414]
mCi/kg: median [range]	35.8 [15.3–48.0]
Sites of disease	
Soft tissue	9
Bone/bone marrow and soft tissue	11
Bone/bone marrow	8

AHSCT, autologous hematopoietic stem cell transplantation; INSS, International Neuroblastoma Staging System; TBI, total body irradiation.

42–980 days), where the most important determinant of time interval was hematologic recovery. Only four patients had rapid hematologic recovery allowing for a treatment interval of less than 8 weeks. Twelve patients had delayed intervals between their first and second treatments due to myelosuppression. Nine of the 12 patients had thrombocytopenia requiring frequent transfusion with a median interval to recovery of 92 days (range: 62–154 days), and 3 of the 12 patients had thrombocytopenia with neutropenia with intervals of 112, 157, and 189 days.

Other reasons for delays between the first and second treatments included scheduling logistics (n = 9), CR to ^{131}I-MIBG treatment with interval chemotherapy (n = 1), or intervening experimental therapy (n = 2). Nine patients with delayed treatment intervals due to personal or institutional scheduling logistics were delayed for 1–2 months after hematologic recovery with the exception of one patient (UPN 83) who was delayed for 7.5 months due to personal preference. One patient (UPN 58) had a CR to the first treatment that lasted for 18 months, with 13-*cis*-retinoic acid therapy for 6 months after the MIBG. He subsequently relapsed in bones and underwent interval chemotherapy without response, prior to returning for a second treatment of ^{131}I-MIBG 980 days after the first infusion. The time interval between the second and third ^{131}I-MIBG treatments was 42 days for one patient (UPN 5), who had a rapid hematologic recovery; 70 and 85 days for two patients (UPN 1, 40) due to scheduling; and 140 days for one patient (UPN 48), who had prolonged thrombocytopenia and anemia with platelet and red blood cell transfusion requirements. Of the two patients that received a fourth treatment of ^{131}I-MIBG, one patient (UPN 5) had a short interval of 42 days with rapid hematologic recovery, and one patient (UPN1) had an interval of 9.8 years due to a CR to the third treatment with an interval history of later surgery and multiple chemotherapies for an MIBG-negative relapse between ^{131}I-MIBG treatments.

Tumor Response to ^{131}I-MIBG Treatment

Tumor response was evaluated for all 28 patients on study, according to response to each treatment, overall response at first evaluation after all the multiple treatments, and best response achieved during or after the completion of the multiple treatments (Table II). Fourteen patients had a significant response (CR/VGPR/PR) to the first infusion, and eight had a significant response to the second infusion. One patient had a mixed response to the second infusion, with decrease in soft tissue mass but persistent bone marrow disease. Sixteen patients (57%) had a best response of CR/VGPR/PR over the course of the multiple infusion therapy. Overall disease improvement over the course of the multiple infusions was seen in 11 patients (39%), while 2 had mixed response, 6 had stable disease for at least 2 months, and 9 had overall disease progression (Table II). The time interval between the first and second infusions of ^{131}I-MIBG was a median of 108 days (range: 63–306 days) for patients with overall disease improvement, 56 days for the patients with a mixed response, median 126 days (range: 84–230 days) for patients with stable disease, and median 62 days (range: 42–980 days) for patients who had progressive disease.

Of the 11 patients who had an overall disease response to more than one infusion, nine patients received two infusions of ^{131}I-MIBG, one received three infusions of ^{131}I-MIBG, and another received four infusions of ^{131}I-MIBG. Two of the nine patients (UPN 47, 86) also received an interval therapy of 13-*cis*-retinoic acid and PS341, respectively. Of the nine patients that had an overall disease progression following ^{131}I-MIBG therapy, seven patients received two infusions of ^{131}I-MIBG, one received three infusions of ^{131}I-MIBG, and another received four infusions of ^{131}I-MIBG. Median time to progression was 47 days (range: 27–146 days) and sites of progression were bone (n = 3), bone marrow (n = 3), and soft tissue (n = 4).

TABLE II. Disease Response to Multiple ^{131}I MIBG Infusions in 28 Patients

UPN	Interval (days) Rx1–Rx2	Rx1	Rx2	Rx3	Rx4	Overall response	Best response	F/U (months)
58[a]	980	CR	SD			SD	CR	SD, 33.9
89[a]	157	CR	PR			PR	CR	DOD/BOOP, 8.8
125	56	MR	PD			PD	MR	DOD, 6.6
5	50	PR	SD	PD	PD	PD	PR	DOD, 10.5
27	112	PR	SD			PR	PR	DOD, 21.6
35	119	PR	PD			PD	PR	DOD, 7.2
40[b]	97	PR	SD	SD		PR	VGPR	PD, 50.5
47[c]	112	PR	VGPR			VGPR	VGPR	VGPR, 33.2
48	70	PR	PR	PD		PD	PR	DOD, 36.0
65	105	PR	CR			CR	CR	DOD, 12.1
79	108	PR	PR			PR	PR	DOD, 6.6
81[d]	119	PR	PR			PR	CR	CR, 9.7
86[e]	306	PR	SD			PR	PR	DOD, 13.1
87	62	PR	PD			PD	PR	DOD, 4.4
127	92	PR	SD			PR	PR	SD, 4.9
1[f]	63	SD	PR	PR	SD	PR	CR	DOD, 137
3	42	SD	PD			PD	SD	DOD, 3.7
7	49	SD	PD			PD	SD	DOD, 3.4
10	77	SD	MR			MR	MR	DOD, 7.0
19	84	SD	PR			PR	PR	DOD, 19.2
23	84	SD	SD			SD	SD	Dead AML, 14.1
41	84	SD	SD			SD	SD	DOD, 20.6
44	189	SD	PD			PD	SD	DOD, 37.3
72	98	SD	SD			SD	SD	DOD, 8.7
83	230	SD	SD			SD	SD	SD, 13.1
90	154	SD	SD			SD	SD	PD, 13.2
92	167	SD	SD			SD	SD	SD, 9.8
105	81	SD	SD			SD	SD	SD, 10.0

''Overall response'' reflects the disease status evaluated 4–8 weeks after the final treatment compared to the disease status on study. ''Best response'' refers to the best response obtained at any time during or at any time after all MIBG therapies, without other treatment.
CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease, MR, mixed response; PD, progressive disease; DOD, dead of disease; AML, acute myeloblastic leukemia; BOOP, bronchiolitis obliterans-organizing pneumonia.
[a]Both of these patients had CR, later developed disease progression and were then treated again.
[b]Patient had VGPR at 5 months follow-up post-Rx3.
[c]Patient received 13-*cis*-retinoic acid between Rx1 and Rx2.
[d]Patient had CR at 6 months follow-up post-Rx2 with no intervening therapy.
[e]Patient had rapidly progressive disease during therapy with PS341 between Rx1 and Rx2.
[f]UPN1 had successive responses to MIBG, achieved CR 1 year later without intervening therapy, then relapsed after 5 years (see text).

Hematologic Toxicity

The most prominent hematologic toxicity from the multiple infusions of ^{131}I-MIBG was marked thrombocytopenia with anemia and moderate neutropenia. Thirteen patients remained platelet transfusion dependent after their last infusion of ^{131}I-MIBG despite HSCT, 15 remained erythrocyte transfusion dependent following their final MIBG infusion, and all patients recovered neutrophils with G-CSF and/or HSCT support. By two-sided Fischer exact test, there was a significant correlation between lack of platelet recovery and bone and bone marrow tumor ($P < 0.05$), such that 12 of the 13 patients without platelet recovery had tumor in bone/bone marrow, where as only 8/15 with platelet recovery had tumor in bone/bone marrow. The detailed hematologic toxicity results are shown in Table III.

Of the 24 patients who received only two infusions of ^{131}I-MIBG, 21 patients received platelet transfusions following both treatments. Of these 21, 6 patients did not become platelet transfusion independent after the first infusion of ^{131}I-MIBG but met the eligibility criteria to receive a second infusion of ^{131}I-MIBG, and 11 patients did not become platelet transfusion independent following the second infusion of ^{131}I-MIBG. All 11 patients that did not become platelet independent following the second therapy of ^{131}I-MIBG had bone or bone marrow disease, with ten patients who had neuroblastoma in bone and/or bone marrow, and another (UPN 23) who had myelodysplasia progressing to acute myeloblastic leukemia (AML).

Out of the 24 patients receiving only two therapeutic treatments of ^{131}I-MIBG, five patients did not become erythrocyte transfusion independent following the first

TABLE III. Hematologic Toxicity Over the Course of Multiple Infusions of ^{131}I-MIBG

	Rx1 (n = 28)	Rx2 (n = 28)	Rx3[a] (n = 4)	Rx4[a] (n = 2)
Platelet nadir ($\times 10^3/\mu l$)				
Median [range]	21.5 [7–169]	20 [2–174]	21, 26, 74, 111	27, NE
Time to platelet nadir (days)				
Median [range]	26.5 [12–52]	24 [8–66]	18, 30, 35, 38	34, NE
Platelet toxicity				
Patients with grade 3 (n)	22	19	2	1
Patients with grade 4 (n)	2	4	0	0
Platelet recovery				
Platelet transfusions (n)	22	23	2	2
Platelet independent (n)	16	12	1	1
Time to platelet transfusion independence (weeks)			0[b]	0.6
Median [range]	4.4 [0–12.1]	5.2 [0.1–21.1]		
ANC nadir ($\times 10^3/\mu l$)				
Median [range]	492 [100–2,970]	590 [0–2,900]	660; 980; 1,080; 1,144	0, 250
Time to ANC nadir (days)[c]				
Median [range]	40 [17–62]	38 [10–68]	8, 18, 49, 68	32, 34
Neutrophil toxicity (n)				
grade 3	9	8	2	1
grade 4	14	13	0	1
G-CSF given	14	16	0	0
Neutrophil recovery				
ANC >500 (n)	12	13	4	2
Time with ANC <500 (weeks)				
Median [range]	1.2 [0.1–4.9]	1.8 [0.4–8.0]	0, 0, 0, 0	10, 40.7
RBC				
RBC transfusion (n)	17	23	3	2
RBC independence (n)	11	13	2	1
HSCT given	NA	8	0	2
w/ablative chemotherapy	NA	2	0	1
Indication for HSCT				
Thrombocytopenia, anemia, and neutropenia	NA	3	0	0
Thrombocytopenia and anemia	NA	3	0	1
Thrombocytopenia alone	NA	1	0	0
Neutropenia alone	NA	1	0	0
Anemia, and neutropenia	NA	0	0	1

Rx, treatment; ANC, absolute neutrophil count; RBC, red blood cell; HSCT, autologous hematopoietic stem cell transplantation.
[a]Actual values are recorded, data set too small for statistically significant median.
[b]Patient received one platelet infusion just prior to therapy, and was platelet independent from then on.
[c]ANC nadir is recorded as lowest ANC prior to G-CSF.

infusion of ^{131}I-MIBG, and ten patients did not become erythrocyte independent following the second infusion of ^{131}I-MIBG. All ten patients that did not recover erythropoiesis following the second infusion were from the same population of patients that did not recover platelets, and had bone and/or bone marrow disease including one patient (UPN 23) who had progressive AML. The only patient (UPN 125) who had refractory platelet toxicity and recovered erythropoiesis following the second infusion of ^{131}I-MIBG had a CR to ^{131}I-MIBG in the bone marrow, but progressive soft tissue disease.

Neutropenia was usually transient and without associated infection. Only two patients required prolonged G-CSF therapy between their first and second infusion of ^{131}I-MIBG, and all patients recovered their neutrophil count following their final infusion of ^{131}I-MIBG. Although most patients experienced grade 3 or 4 neutropenia, the time to recovery was rapid for most patients and was not significantly delayed with successive ^{131}I-MIBG treatments.

Hematopoietic stem cells were administered to 8 of the 24 patients receiving only two infusions of ^{131}I-MIBG, with two patients also receiving ablative chemotherapy just prior to stem cell infusion. Four of the eight patients did not have complete hematologic recovery with two patients experiencing refractory thrombocytopenia and anemia, one patient with refractory thrombocytopenia, and another (UPN 23) with refractory thrombocytopenia and anemia and myelodysplasia despite HSCT.

Four patients received greater than two infusions of ^{131}I-MIBG. Both patients with three infusions of ^{131}I-MIBG had complete hematologic recovery without

HSCT. Of the two patients that received four infusions of ^{131}I-MIBG, one patient (UPN 1) had complete hematologic recovery after stem cell infusion following the fourth ^{131}I-MIBG treatment. The other patient who received four infusions of ^{131}I-MIBG (UPN 5) experienced refractory thrombocytopenia and anemia after the third and fourth infusions of ^{131}I-MIBG with transient neutropenia after the fourth ^{131}I-MIBG treatment, was given ablative chemotherapy followed by HSCT after the fourth infusion of ^{131}I-MIBG, failed to engraft platelets and erythrocytes, and died of progressive disease in the bone marrow.

Complete hematologic recovery after the multiple infusions occurred in 15/28 patients, with 5 patients that recovered only with HSCT. Of the remaining 13 patients that did not have complete hematologic recovery, five patients did not have hematologic recovery after HSCT, and all patients had bone/bone marrow involvement on study and/or as progressive disease within the bone/bone marrow.

Non-Hematologic Toxicity

Non-hematologic toxicity was minimal. Less than 20% of patients had mild nausea and rare vomiting in the first 2 days after treatment, controlled by diphenhydramine, ondansetron, or metoclopramide. Two patients had transient grade 2 hypertension, controlled by a single dose of nifedipine. One patient had grade 1 anorexia, and another had a grade 2 skin rash, with grade 1 pruritis that resolved on its own. Three patients had grade 1 mouth dryness for 1–2 months. One patient experienced secondary amenorrhea (pre-dated MIBG therapy), and another patient had grade 2 waxing and waning gross hematuria that lasted for 2 months and cleared when platelet counts recovered. One patient developed asymptomatic hypothyroidism that was diagnosed by slightly low thyroxine and elevated thyroid stimulating hormone at 4 months post-treatment. Another patient had mild hyponatremia and mild hypomagnesemia, which was corrected by supplementation and two patients had neutropenic fevers that were resolved with antibiotics. Two grade 5 late toxicities occurred long after protocol treatment, which may have been partly attributable to the ^{131}I-MIBG therapy. One patient, as mentioned above, developed MDS/AML after her second MIBG therapy and eight prior years of chemotherapy [12]. A second patient died with bronchiolitis obliterans-organizing pneumonia (BOOP) at the time of progressive disease 5 months after her second MIBG therapy.

Survival

Progression-free survival and overall survival are shown in Figure 1. The median time from the first treatment to the last follow-up was 11.3 months (range: 3.4–136.6 months). Ten patients are still alive 5–51 months (median 12 months) from therapy including one patient who had a CR to ^{131}I-MIBG therapy, one patient with a VGPR, six patients with SD, and two patients with progressive disease at the last follow-up. Seventeen patients died of progressive disease, one patient died of secondary AML with stable neuroblastoma, and one patient (UPN 89), as noted above, who died with progressive disease also had bronchiolitis obliterans organizing pneumonia. Of the 17 patients that died of PD, 7 had progression of soft tissue only, 2 had progression of bones and soft tissue, 3 had progressive disease of bone marrow, 1 died of bone and bone marrow disease, 2 had bone progression only, 1 had soft tissue and bone marrow progression, and 1 had brain metastases.

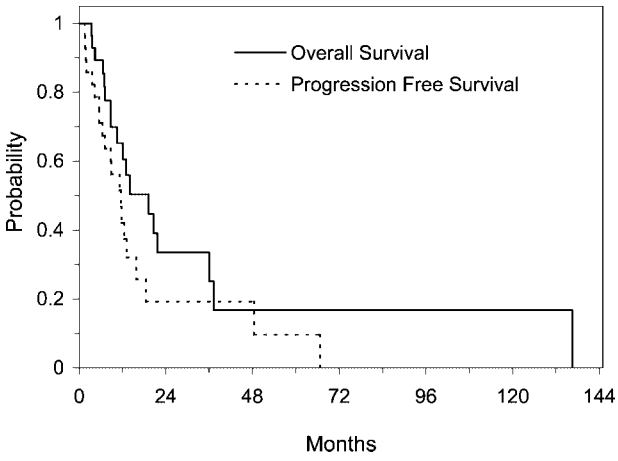

Fig. 1. Overall survival and progression-free survival from the time of first MIBG therapy for all patients.

DISCUSSION

This study shows that multiple infusions of MIBG at wide intervals are feasible and effective in children with advanced refractory neuroblastoma. However, the hematologic toxicity, particularly thrombocytopenia, limited the frequency of therapy, and was not always abrogated by HSCT, often due to ongoing bone marrow involvement.

The overall response rate to multiple infusions was 39%, comparable to response rates in previous studies with single infusions of high dose ^{131}I-MIBG [7]. In addition a delayed effect was observed in four patients with significant responses ranging from VGPR to CR at 4–12 months after treatment with ^{131}I-MIBG. The use of multiple infusions are supported by the successive response over the course of two to three infusions that were observed in 7 of the 11 responding patients. Although, some of the incremental response to the subsequent infusions might be attributed to delayed response to the first infusion, the patients who responded to the first, then actually progressed in the interval while receiving other therapy, and then responded to the second support additive activity. This suggests that increasing the

amount of activity infused will improve overall response. The median cumulative dose per kg on this study was 35.8 mCi/kg, compared to the maximum single dose of 18 mCi/kg administered in the phase I trial [7]. It is not known whether the successive responses were due to an advantage of the repetitive dosing or to an overall effect of increased total radioactivity, which would not be feasible to administer as a single infusion, due to radiation safety constraints. Some relation of increasing dose to response was suggested in our previous phase I study [7], but a linear relationship has been difficult to prove, no doubt due to multiple factors, including heterogeneity of uptake, susceptibility of differing disease sites, and differing radio-resistance of tumors.

Non-hematologic toxicity did not appear to be increased by the use of multiple infusions. The two serious toxicities resulting in death may have been partly attributable to the ^{131}I-MIBG, including the previously reported patient with myelodysplasia [12] and one patient with BOOP. The patient with myelodysplasia had a prior history of more than 8 years of prior chemotherapy and radiation, and the contribution of the cumulative radiation from the MIBG is not known. The cumulative probability of this complication in our patients has been estimated to be less than 4% at 5 years (three patients) [12]. The other unexpected toxicity is the patient with BOOP syndrome, usually seen in patients after allogeneic transplant [13–15]. This is the only case of this problem reported in more than 170 children with neuroblastoma treated with ^{131}I MIBG at UCSF and CHOP, and an undiagnosed infection could not be excluded.

The hematologic toxicity was prominent, but did not lead to toxic death, bleeding, and only rarely did the myelosuppression result in serious infection. Prolonged thrombocytopenia was the predominant manifestation, even in patients receiving hematopoietic stem cell support. Thrombocytopenia in excess of neutropenia has frequently been described as a complication of MIBG therapy even with a single infusion [6,7,16,17] and in patients treated de novo without prior therapy [18]. It is concerning that only four of eight patients given autologous HSCT after two infusions of MIBG achieved independence from transfusions. In the heavily pre-treated group seen in the current study, either bone marrow or stem cells were allowed, and the quality may have been poor in some cases, despite apparently adequate cell number, and the marrow stroma may have suffered damage in prior myeloablative regimens and radiation. Inadequate platelet engraftment was also seen in previously reported patients [17,19]. This is in contrast to our experience on an open phase I study in the New Approaches to Neuroblastoma Therapy Consortium combining a single dose of ^{131}I-MIBG with ablative chemotherapy followed by HSCT, where all 22 patients engrafted [20]. This may be due to the fact that eligibility for the ^{131}I-MIBG and myeloablative chemotherapy combination (N9901) excluded patients with prior transplant.

The other factor that significantly hindered hematologic recovery, with or without HSCT, was tumor infiltration of bone and bone marrow. Of the 13 patients that did not have complete hematologic recovery, 5 patients did not have hematologic recovery after HSCT, and all patients had bone/bone marrow involvement on study, and/or as progressive disease within the bone/bone marrow. Thus, extensive tumor may be responsible for suppression of hematopoiesis by replacement, or other effect on stem cells or stroma. It is also possible that the increased radiation to the marrow stroma from the ^{131}I-MIBG in cases of tumor involvement of bone and bone marrow may cause more damage. We noticed a similar problem in patients receiving a single dose of 18 mCi/kg of ^{131}I-MIBG, where patients with bone marrow tumor were more likely to have poor platelet recovery [8].

Multiple infusions of high dose ^{131}I-MIBG were feasible and effective in patients with refractory neuroblastoma, but were limited by hematologic toxicity, especially thrombocytopenia. Hematologic toxicity was greater in patients with bone and/or bone marrow disease, and the timing between treatments was highly dependent on the time to hematologic recovery. The successive responses seen in 25% of patients and the overall response rate of 39% suggest additional benefit from the successive infusions. In the future, it may be possible to improve the response rate and abrogate the hematologic toxicity by infusing two doses of ^{131}I-MIBG in rapid succession, supported immediately thereafter with high-quality peripheral blood stem cells. Such a study is ongoing in the New Approaches to Neuroblastoma Therapy Consortium (N 2000–01).

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