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Phase I Study of Vincristine, Irinotecan, and ¹³¹I-Metaiodobenzylguanidine (¹³¹I-MIBG) for Patients with Relapsed or Refractory Neuroblastoma: A New Approaches to Neuroblastoma Therapy (NANT) Trial

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Abstract

Purpose—¹³¹I-metaiodobenzylguanidine (MIBG) is a targeted radiopharmaceutical with activity in patients with relapsed or refractory neuroblastoma. Irinotecan is a known radiosensitizer with activity in neuroblastoma. This phase I study aimed to determine the recommended phase 2 dose of MIBG together with fixed doses of vincristine and irinotecan.

Experimental Design—Patients 1–30 years old with relapsed or refractory neuroblastoma and MIBG-avid tumors were eligible. All patients had autologous hematopoietic stem cells (PBSCs)

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available and met standard phase I organ function requirements. Irinotecan (20 mg/m²/dose IV) was given on days 0–4 and 7–11, with vincristine (1.5 mg/m² IV) on days 0 and 7. MIBG was given on day 1 following a 3+3 phase I dose escalation design starting at 8 mCi/kg MIBG. PBSCs were administered at dose level 8 mCi/kg for prolonged myelosuppression and for all patients at 12 mCi/kg.

Results—24 patients evaluable for dose escalation (median age 6.7 years; range 1.9 – 26.8 years) received 1 (n=17), 2 (n=5), or 3 (n=2) cycles of therapy. Myelosuppression and diarrhea were the most common toxicities. Two of 6 patients at the 18 mCi/kg dose level had dose limiting toxicity (DLT), including one with protocol-defined DLT with prolonged mild ALT elevation. Eighteen mCi/kg was the recommended phase 2 dose. Six additional patients were treated at 18 mCi/kg, with one additional DLT. Responses (2 complete and 4 partial responses) occurred in 6/24 (25%) evaluable patients.

Conclusions—MIBG is tolerable and active at 18 mCi/kg with standard doses of vincristine and irinotecan.

Keywords

¹³¹I-MIBG; Irinotecan; Vincristine; Neuroblastoma; Relapse

Introduction

Neuroblastoma is a common pediatric cancer with a propensity for widespread metastatic disease [1]. Despite recent improvements in outcomes, patients with metastatic neuroblastoma continue to be at high-risk for treatment failure [2, 3]. Outcomes for patients with relapsed or refractory neuroblastoma remain dismal, with new therapies needed.

Neuroblastoma cells typically overexpress the norepinephrine transporter.[4] Metaiodobenzylguanidine (MIBG) is specifically taken up by cells expressing the norepinephrine transporter. MIBG labeled with radioisotopes, such as ¹²³I and ¹³¹I, has become an important tool for the diagnosis and treatment of patients with neuroblastoma [5, 6]. ¹³¹I-MIBG provides a systemic form of targeted radiotherapy. In phase I studies, myelosuppression was shown to be dose-limiting, though this toxicity can be abrogated with the use of autologous hematopoietic stem cell infusion [7, 8]. A phase II study of 164 patients with relapsed or refractory neuroblastoma treated with 18 mCi/kg demonstrated that ¹³¹I-MIBG is an active agent in this patient population [9].

More recent efforts have focused on combining ¹³¹I-MIBG with other agents that may augment its activity. Vincristine and irinotecan have several theoretical advantages as agents to evaluate in combination with ¹³¹I-MIBG. First, these chemotherapy agents each may have anti-tumor activity against neuroblastoma, have been used in combination, and have relatively non-overlapping toxicities with ¹³¹I-MIBG [10–13]. Second, camptothecins have been shown to sensitize tumor cells, including neuroblastoma, to the effects of radiation [14–16]. Third, a previous feasibility trial demonstrated that the combination of another camptothecin, topotecan, with ¹³¹I-MIBG was tolerable up to doses of 12 mCi/kg [17]. The primary aim of this phase I study was to determine the tolerability of escalating doses of

^{131}I -MIBG when given with fixed doses of vincristine and irinotecan. Additional aims included descriptions of the toxicity profile, preliminary evaluation of antitumor activity, and correlation of irinotecan pharmacokinetic and pharmacogenetic parameters with toxicity.

Materials and Methods

Patient Eligibility

Patients 1–30 years of age with relapsed or refractory neuroblastoma were eligible if they had MIBG-avid disease documented within 4 weeks of study enrollment. Patients were required to have a minimum of 2.0×10^6 CD34+ autologous hematopoietic stem cells/kg available for infusion, Lansky or Karnofsky performance score ≥ 50 , and life expectancy ≥ 6 weeks. Patients were eligible after a minimum of three weeks from last systemic therapy, three months from prior stem cell transplant, two weeks from prior small port radiation, and three months from large field radiation. Patients were excluded for prior whole abdominal or total body radiation, allogeneic transplant, or ^{131}I -MIBG therapy. Prior vincristine and/or irinotecan were allowed.

Patients were required to meet the following organ function criteria: absolute neutrophil count (ANC) $\geq 750/\text{mm}^3$ without growth factor support; platelet count $\geq 50,000/\text{mm}^3$ without platelet transfusion; hemoglobin ≥ 8 g/dL; estimated creatinine clearance ≥ 60 mL/min/1.73 m² or serum creatinine ≤ 1.5 times the upper limit of age-adjusted normal value; total bilirubin ≤ 1.5 times upper limit of normal; ALT and AST < 3 times upper limit of normal; cardiac ejection fraction $\geq 55\%$ or shortening fraction $\geq 27\%$; and lack of dyspnea at rest, exercise intolerance, pleural effusion, or oxygen requirement.

Additional exclusion criteria included: pregnancy; breast feeding; other major systemic disease; inability to tolerate radiation isolation; concomitant enzyme-inducing anticonvulsants; cephalosporin allergy; diarrhea grade 2; and active infection.

Written informed consent was obtained from patients and/or legal guardians, with assent obtained as appropriate for age. Each participating site's institutional review board approved the study protocol.

Treatment

Patients received vincristine (1.5 mg/m²/dose to maximum dose of 2 mg) as an intravenous bolus on days 0 and 7. Patients received irinotecan (20 mg/m²/dose to maximum dose of 40 mg) as an intravenous infusion over 1 hour on days 0–4 and 7–11. In order to reduce the risk of diarrhea, all patients received cefixime or cefpodoxime orally on days –5 to +21 [18].

^{131}I -MIBG was infused intravenously over 90–120 minutes on day 1 according to dose level assigned at study entry: 8 mCi/kg; 12 mCi/kg; 15 mCi/kg; or 18 mCi/kg. The maximum allowable ^{131}I -MIBG dose was 1200 mCi. ^{131}I -MIBG was provided by Jubilant DraxImage, Inc (Kirkland, Quebec, Canada) with a specific activity ≥ 29.7 mCi/mg MIBG and a maximum allowable free iodine content $< 5\%$. Packed red blood cells were transfused prior to ^{131}I -MIBG infusion for hemoglobin < 10 g/dL. Estimated whole body radiation dose was calculated as previously described [19]. Patients remained in radiation isolation until they

met local radiation safety requirements. All patients required foley catheter placement prior to the start of ^{131}I -MIBG infusion. The regimen used for thyroid blockade was as previously described [9].

Patients at the 8 mCi/kg dose level received autologous hematopoietic stem cell (PBSC) infusion for $\text{ANC} < 200/\text{mm}^3$ for 7 days despite filgrastim, platelet transfusions twice weekly for 2 consecutive weeks, or ongoing need for platelet transfusions by Day 56. All patients at subsequent dose levels received a minimum of $2.0 \times 10^6 \text{ CD34}^+$ cells/kg on day 13. For patients receiving PBSCs, the use of filgrastim followed institutional standard practice.

Patients were eligible for subsequent courses if they had at least stable disease, had recovered to baseline criteria, and had PBSCs available to support a subsequent course. Initially, a maximum lifetime cumulative dose of 24 mCi/kg was allowed. Once three patients were treated to this dose without dose-limiting toxicity (DLT), the maximum cumulative dose was increased to 36 mCi/kg.

Toxicity and Response Evaluation

Toxicity was graded according to the Common Terminology Criteria for Adverse Events, version 3.0. Hematologic DLT was defined as: $\text{ANC} < 500/\text{mm}^3$ 28 days after PBSC infusion; platelets $< 20,000/\text{mm}^3$ 56 days after PBSC infusion; need for a second PBSC infusion; grade 4 hemolysis; refractory to platelet transfusions with life-threatening bleeding; and life-threatening anemia. Non-hematologic DLT was defined as grade 3 toxicity with the exception of the following grade 3 toxicities: nausea; vomiting; anorexia; dehydration; electrolyte abnormality; diarrhea of less than 72 hours duration with prescribed supportive measures; hepatic enzyme elevation returning to grade 1 by day 56; fever; infection; and febrile neutropenia. DLT definitions included only toxicities deemed at least possibly related to therapy.

Patients underwent disease staging at baseline and then approximately 8 weeks following ^{131}I -MIBG. Response was graded according to the NANT Response Criteria, modified from the International Neuroblastoma Response Criteria [20]. These criteria utilize RECIST criteria for measurable tumors [21], Curie score for MIBG scan response [22], and bone marrow (BM) morphology. BM response was graded as stable, complete response (CR; required two time points to confirm), CR unconfirmed (one time point only), or progressive disease (PD). Bone marrow biopsies were not required at end of course if negative at enrollment. All MIBG scans and all radiographic reports/bone marrow reports were centrally reviewed. Patients with stable disease (SD) or better had central review of CT scans and bone marrow slides. An overall mixed response (MR) was defined as SD by one or more criteria with at least one of the following: BM CR; MIBG response of CR/partial response (PR); or CT response of CR/PR. Patients with overall response of PD reported by treating site did not undergo CT or BM central review and were graded as PD. Overall responses of CR or PR were considered objective responses.

Irinotecan Pharmacokinetics and Pharmacogenomics

Patients consenting to an optional irinotecan pharmacokinetic study provided blood samples around the day 9 dose of irinotecan in course 1 at the following time points: prior to infusion; end of infusion; and 0.25, 0.5, 1, 2, 4, 6, and 24 hours after the infusion. An aliquot of plasma was obtained by centrifugation and extraction with cold methanol. Irinotecan, SN-38, and SN-38G levels were determined by high-performance liquid chromatography with fluorescence detection, which allowed for measurement of lactone and carboxylate forms [23].

A multicompartiment model was fit to concentration-time data of the lactone forms of irinotecan, SN-38, and SN-38G using the importance sampling expectation maximization algorithm in NONMEM 7. Area under the concentration versus time curves (AUC) for irinotecan, SN-38, and SN-38G from the beginning of the infusion to 24 hours were calculated by integration of the simulated concentration-time data from individual model parameter estimates. As a measure of net conversion, ratios of the AUCs were calculated for SN-38/irinotecan and SN-38G/SN38.

Patients consenting to an optional irinotecan pharmacogenomics study provided a single blood sample at study entry. DNA was extracted from mononuclear cells using standard methods and then *UGT1A1* polymorphisms genotyped using standard techniques.

Statistical Methods

Dose escalation followed a classic 3+3 design, with dose escalation decisions made based on DLTs observed in the first course of therapy. Patients were considered evaluable for DLT either if they experienced a DLT prior to completion of the first course or if they completed the first course of therapy and were followed through Day 42 or hematologic recovery, whichever occurred last. The recommended phase 2 dose was defined as the highest dose level at which fewer than one third of patients had DLT in the first course. An additional 6 patients were treated in a planned expansion cohort at the recommended phase 2 dose.

Results

Patient Characteristics

Twenty-six patients enrolled. One patient was found to be ineligible. Another patient was eligible but an interruption in ^{131}I -MIBG supply prompted her withdrawal from study prior to Day 0 therapy. These two patients received only cefixime, did not experience toxicity, and were inevaluable for dose escalation and response. Characteristics of the 24 eligible and evaluable patients are shown in Table 1.

Dose Escalation and Toxicity

Three patients each were treated with 8 mCi/kg or 12 mCi/kg ^{131}I -MIBG and none experienced DLT. One of the first three patients treated with 15 mCi/kg developed dose-limiting grade 3 diarrhea. Three additional patients were treated at this dose level without DLT. One of the first three patients treated with 18 mCi/kg developed grade 3 abdominal pain, anorexia, hallucinations, hyponatremia, and nausea all as part of a single acute episode

taking place in the setting of disease progression. A possible contribution of study therapy to this episode could not be excluded and this event was considered a DLT. Three additional patients were treated at this level. One of these patients had grade 3 ALT and AST elevation that did not resolve to grade 1 by the completion of course 1. This met protocol definition of DLT, but was not clinically significant. Therefore, the 18 mCi/kg dose level was declared the recommended phase 2 dose. Six additional patients were treated at this recommended phase 2 dose per protocol design. One of these patients also experienced DLT with grade 3 ALT and AST elevation. Overall, 3 of the 12 patients treated at the recommended phase 2 dose of 18 mCi/kg had DLT. The median first course whole body dose of radiation was 223 cGy (range 75 – 584 cGy). All four patients with DLT had estimated whole body radiation doses > 200 cGy.

Details of non-hematologic toxicity by dose level are shown in Table 2. No protocol-associated grade 4 non-hematologic toxicity was seen. The main non-hematologic toxicity was diarrhea. The incidence of grade 3 diarrhea increased with dose level from 8 mCi/kg to 12 mCi/kg to 15 mCi/kg, with rates of 0%, 33%, and 50%, respectively. However, the incidence of grade 3 diarrhea was only 17% among the 12 patients treated at the 18 mCi/kg dose level. The median whole body radiation dose for the six patients with grade 3 diarrhea was 274 cGy (range 176 – 584 cGy), compared to 201 cGy (range 75 – 408 cGy) for the 18 patients without grade 3 diarrhea.

Details of engraftment are shown in Table 3. One of three patients treated with 8 mCi/kg experienced prolonged myelosuppression that met protocol criteria for autologous hematopoietic stem cell infusion. Patients at higher dose levels all received mandatory autologous hematopoietic stem cell infusion, without any episodes of delayed or failed engraftment. With this strategy, 3/12 (25%) and 4/12 (33%) patients treated at the recommended phase 2 dose of 18 mCi/kg did not reach a neutrophil nadir < 500 cells/mm³ or platelet nadir < 20,000 cells/mm³, respectively.

Seven patients received multiple courses of therapy, including 4 patients who received a cumulative ¹³¹I-MIBG dose of 36 mCi/kg (Table 4). None of these patients experienced DLT in their first or subsequent courses of therapy.

One patient developed myelodysplastic syndrome associated with monosomy 7 approximately 26 months following ¹³¹I-MIBG therapy which progressed to fatal acute myeloid leukemia. Due to multiple prior treatment regimens, the contribution of study therapy to the development of this second malignancy is not clear.

Responses

Responses are summarized in Table 5, with detailed response data provided in Supplemental Table 1. The overall objective response rate across all dose levels was 25%. Of the 12 patients previously treated with irinotecan, 3 (25%) had an objective response, compared to 3/11 (27%) of response evaluable patients without previous irinotecan treatment. The median whole body radiation dose in course 1 for patients with an objective response was 168 cGy (range 94 – 272 cGy) compared to 230 cGy (range 75 – 584 cGy) for patients without an objective response. None of the 6 patients with primary refractory disease had an

objective response such that all 6 objective responses were seen in the 18 patients with relapsed disease. Of the 7 patients treated with multiple courses of therapy, 3 (43%) had an objective response, including 2 patients whose best response occurred following a subsequent course of protocol therapy (Table 4).

Irinotecan Pharmacokinetics and Pharmacogenomics

Irinotecan pharmacokinetic parameters were analyzed for 9 patients who consented to this optional study. The median (range) for the irinotecan systemic clearance and volume of distribution was 3.8 L/h/m² (2.4 to 5.5 L/h/m²) and 143 L/m² (69 – 270 L/m²). The median (range) AUC_{0–24} values were: irinotecan lactone, 353 ng/mL*h (198 – 713 ng/mL*h); SN-38 lactone, 16.2 ng/mL*h (7.4 – 44.3 ng/mL*h); SN-38 lactone glucuronide, 62.1 ng/mL*h (30.8 – 152.4 ng/mL*h). The median (range) relative extent of conversion of irinotecan to SN-38 was 0.066 (0.035 – 0.111) and relative extent of glucuronidation of SN-38 was 2.88 (1.60 – 4.09).

UGT1A1 genotype was determined for 18 patients. Six patients were homozygous for the wild type (*UGT1A1**1 with 6 TA repeats) allele, 11 patients harbored one allele with more than 6 TA repeats (10 patients heterozygous for 7 TA repeat allele or *UGT1A1**28; 1 patient heterozygous for 8 TA repeat allele), and 1 patient was homozygous for the 7 TA repeat allele (*UGT1A1**28). Two of 6 (33.3%) wild type patients developed grade 3 diarrhea in course 1 compared to 4 of 12 (33.3%) patients with at least one non-wild type allele. Two of 6 (33.3%) wild type patients had DLT in course 1 compared to 1 of 12 (8.3%) patients with at least one non-wild type allele. The patient homozygous for 7 TA repeat allele did not develop grade 3 diarrhea or DLT.

Discussion

The combination of ¹³¹I-MIBG with vincristine and irinotecan was generally well tolerated at the maximum dose level of 18 mCi/kg ¹³¹I-MIBG evaluated in this study. Observed DLTs were typically reversible and managed with supportive care measures. This dose of ¹³¹I-MIBG is the highest feasible dose typically utilized in North America, due to radiation safety considerations. In addition, this combination shows promising activity in this advanced patient population, particularly within the context of a dose escalation study. Notably, 46% of patients had partial or complete MIBG responses based on central review of ¹²³I-MIBG scans using Curie scoring. Among 10 patients evaluable for CT response, 5 (50%) had an objective response. The lower overall response rate of 25% in all patients, and the lower overall response rate at the highest dose level, was likely due to patients with bone marrow disease who per criteria used must completely clear marrow disease to be defined as an overall partial or complete response (8 of 12 patients with marrow involvement at highest dose level; Supplemental Table 1). Previous reports have observed that ¹³¹I-MIBG therapy has lower response rates against bone marrow disease [9, 24]. These data provided some of the rationale for combining ¹³¹I-MIBG with chemotherapy in the current study. This phase I study lacks sufficient patient numbers to evaluate whether the addition of chemotherapy improves bone marrow response or whether there is a dose-response relationship with this combination. To evaluate whether the addition of vincristine and irinotecan improves

responses or outcomes compared to single agent ^{131}I -MIBG, we are planning a NANT randomized phase II trial comparing these regimens.

While the activity of this combination shows promise, the regimen is associated with more toxicity than is typically seen with single-agent ^{131}I -MIBG. Diarrhea was more common in the current study compared to other studies of ^{131}I -MIBG or of irinotecan-based chemotherapy regimens [9, 10, 12, 13]. A small amount of MIBG is excreted in the stool, resulting in some radiation exposure to the colon [25]. It is therefore possible that concomitant radiation exposure sensitized patients to the risk of irinotecan-associated diarrhea. However, calculated whole body radiation exposure did not appear to correlate with the risk of grade 3 diarrhea. While previous groups have reported increased toxicity in patients harboring the *UGT1A1**28 allele [26], we did not observe a difference in the risk of grade 3 diarrhea based on *UGT1A1* genotype. Irinotecan-associated late onset diarrhea appears to be more common with protracted dosing schedules [27]. This protracted irinotecan schedule was chosen for evaluation in this study both because it was a common schedule in use at the time of study initiation and also because it results in greater overlap between radiation and the radiation sensitizer compared to shorter irinotecan schedules. The use of a shorter irinotecan schedule may reduce the likelihood of severe diarrhea in combination with ^{131}I -MIBG, though this hypothesis is being evaluated in a single-institution study.

Other groups have evaluated ^{131}I -MIBG in combination with other chemotherapy agents that have been associated with radiation sensitizing effects. One group has evaluated lower dose ^{131}I -MIBG (absolute doses of 100 – 200 mCi) together with cisplatin [28–30]. Another group studied higher dose ^{131}I -MIBG (12 mCi/kg) together with concomitant topotecan administration [17]. Both of these combinations were shown to be feasible and to have antitumor activity. The current results support this approach and extend these earlier findings by demonstrating that irinotecan can be given concurrently with ^{131}I -MIBG at the maximum feasible single-agent dose of 18 mCi/kg.

Although a drug-drug interaction between ^{131}I -MIBG and irinotecan was not suspected, it was still possible that an interaction could have occurred through an unknown mechanism. Exposure to the active SN-38 lactone form was similar in this study to previous studies where irinotecan was given intravenously at the same dose [31, 32]. Furthermore, the AUC ratios of SN-38:irinotecan and SN-38G:SN-38 were similar to prior studies [33], indicating a lack of effect of ^{131}I -MIBG on the disposition of irinotecan.

The current study has demonstrated that this combination is tolerable and active in patients with relapsed and refractory neuroblastoma. Whether this combination has enhanced activity compared to single-agent ^{131}I -MIBG will be evaluated in a future comparative trial. Follow-up studies are evaluating a shorter irinotecan schedule that may reduce the incidence of diarrhea as well as the use of this combination in patients with newly diagnosed high-risk neuroblastoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Statement of Translational Relevance

¹³¹I-metaiodobenzylguanidine (MIBG) is a targeted radiopharmaceutical with documented single-agent activity in patients with advanced neuroblastoma. In an effort to improve upon this single-agent activity, we evaluated the combination of vincristine and irinotecan together with MIBG. We found that this combination was tolerable up to MIBG doses of 18 mCi/kg and we observed significant antitumor activity. This trial is the first study to utilize MIBG at its usual maximum feasible dose in combination with a systemic radiation sensitizer. These results support the concept that MIBG can be combined safely with systemic radiation sensitizers. Our work may inform combination studies of other targeted radiopharmaceuticals. Based on our results, the combination of vincristine, irinotecan, and MIBG will now be evaluated as a block of therapy in patients with newly diagnosed high-risk neuroblastoma.

Table 1.

Characteristics of 24 eligible and evaluable patients.

Median age at study entry (range)	6.7 years (1.9 – 26.8)
Median time from diagnosis to entry (range)	28 months (5.7 – 96.8)
Male : Female	17 : 7
Relapsed disease	18
Primary refractory disease	6
Prior myeloablative therapy	20
Prior irinotecan therapy	12
<i>MYCN</i> amplified tumor	3 / 17
Median Curie Extension score at entry (range)	5 (1 – 21)
Bone marrow involved at study entry	12

Table 2.

Non-hematologic toxicity in course 1 of therapy attributed as at least possibly related to study therapy and occurring in > 10% of patients per dose level.

Dose Level	Toxicity	Grade	
		1 or 2	3
1 (n=3)	Diarrhea	3	0
	ALT elevation	2	0
	AST elevation	1	0
	Hyperbilirubinemia	1	0
	Febrile neutropenia	0	1
	GGT elevation	1	0
	Hyperglycemia	1	0
	Pain	2	0
	Hypophosphatemia	1	0
	Hypokalemia	1	0
	Hyponatremia	1	0
	Hypothyroidism	2	0
	Nausea / Vomiting	1	0
	Weight loss	1	0
2 (n=3)	Diarrhea	1	1
	ALT elevation	1	0
	Anorexia	0	1
	Alopecia	1	0
	Nose bleed	1	0
	Nausea / Vomiting	1	0
	Headache	1	0
	Hypokalemia	0	1
	Otitis media	0	1
3 (n=6)	Diarrhea	1	3
	ALT elevation	3	0
	AST elevation	4	0
	Hypoalbuminemia	1	0
	Anorexia	4	0
	Hypocalcemia	1	0
	Fatigue	2	0
	Febrile neutropenia	0	1
	GGT elevation	2	0
	Alopecia	1	0
	Nausea / Vomiting	3	1
	Pain	3	0

Dose Level	Toxicity	Grade	
		1 or 2	3
	Hypokalemia	1	0
	Mucositis/Stomatitis	1	0
4* (n=12)	Diarrhea	7	2
	ALT elevation	7	1
	AST elevation	8	0
	Hypoalbuminemia	2	0
	Anorexia	3	2
	Hyperbilirubinemia	2	0
	Hypocalcemia	4	0
	Dehydration	2	2
	Fatigue	5	0
	Hyperglycemia	2	0
	Hypomagnesemia	2	0
	Nausea / Vomiting	8	1
	Pain	7	1
	Hypophosphatemia	3	0
	Hypokalemia	3	1
	Hyponatremia	1	1
	Weight loss	5	0
	Mucositis/Stomatitis	2	0

* Table does not include 1 case each of grade 3 febrile neutropenia and grade 3 hallucinations / delusions as these episodes occurred in < 10% of patients.

Table 3.

Engraftment in course 1 of therapy (n=24).

¹³¹ I-MIBG Dose Level	ANC never < 500/mm ³	Platelets never < 20,000/mm ³	Days from stem cell infusion to ANC > 500/mm ³ (for patients with ANC < 500/mm ³)	Days from stem cell infusion to platelets > 20,000/mm ³ Ufor patients with platelets < 20,000/mm ³)
8 mCi/kg	2 ^a /3	2 ^a /3	3	32
12 mCi/kg	2/3	3/3	24	N/A
15 mCi/kg	4/6	5/6	7, 11	16
18 mCi/kg	3/12	4/12	Median 7 (range 3 – 15)	Median 13 (range 7 – 38)

^aTwo patients did not meet the criteria for stem cell infusion at this dose level (ANC <200/mm³ for 7 days or platelet transfusion > 2x/week for 2 weeks or failure to be independent of platelets by 8 weeks post-treatment).

Table 4.

Characteristics of each patient receiving more than one cycle of therapy.

¹³¹ I-MIBG Dose Level (mCi/kg)	Total Number of Courses	Cumulative ¹³¹ I-MIBG Dose (mCi)	Stem Cell Infusion	ANC and Platelet Engraftment	Response Evaluation at Course 1 ^a	Response Evaluation at Course 2 ^a	Response Evaluation at Course 3 ^a
8	3	24	No	N/A	SD	SD	PR
12	2	24	Yes	Yes	CR	CR	
12	3	36	Yes	Yes	SD	SD	SD
15	2	30	Yes	Yes	MR	MR	
18	2	36	Yes	Yes	PR	CR	
18	2	36	Yes	Yes	MR	MR	
18	2	36	Yes	Yes	SD	MR	

^aResponses centrally reviewed for each course.

Table 5.

Best overall objective responses (CR and PR) after completion of protocol therapy according to dose level and site(s) of disease.

Dose Level	Overall Response	MIBG Response	CT Response	Bone Marrow Response
8 mCi/kg	2/3	2/3	1/1	0/0
12 mCi/kg	2/3	2/3	0/1	0/1
15 mCi/kg	0/6	1/6	2/4	1 ^a /3
18 mCi/kg	2/12	6/12	2/4	0/8
All Dose Levels	6/24 (25%)	11/24 (46%)	5/10 (50%)	1/12 (8%)

Note: denominators indicate number of patients evaluable for response at the given site.

^aThe single complete bone marrow response was documented at one timepoint only.