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Clinical Cancer Research

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Cancer Therapy: Clinical

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Phase I Study of Vincristine, Irinotecan, and ^{131}I-Metaiodobenzylguanidine for Patients with Relapsed or Refractory Neuroblastoma: A New Approaches to Neuroblastoma Therapy Trial

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Abstract

Purpose: ^{131}I-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 to 30 years old with relapsed or refractory neuroblastoma and MIBG-avid tumors were eligible. All patients had autologous hematopoietic stem cells (PBSC) available and met standard phase I organ function requirements. Irinotecan (20 mg/m^2/dose IV) was given on days 0 to 4 and 7 to 11, with vincristine (1.5 mg/m^2 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 or more.

Results: Twenty-four 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 aspartate aminotransferase 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 of 24 (25%) evaluable patients.

Conclusions: MIBG is tolerable and active at 18 mCi/kg with standard doses of vincristine and irinotecan. *Clin Cancer Res; 18(9); 2679–86. ©2012 AACR.*

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 ^{123}I and ^{131}I, has become an important tool for the diagnosis and treatment of patients with neuroblastoma (5, 6). ^{131}I-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 showed that ^{131}I-MIBG is an active agent in this patient population (9).

More recent efforts have focused on combining ^{131}I-MIBG with other agents that may augment its activity.

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Translational Relevance

^{131}I-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 use 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.

Vincristine and irinotecan have several theoretical advantages as agents to evaluate in combination with ^{131}I-MIBG. First, these chemotherapy agents each may have antitumor activity against neuroblastoma, have been used in combination, and have relatively nonoverlapping toxicities with ^{131}I-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 showed that the combination of another camptothecin, topotecan, with ^{131}I-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 to 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 per kilogram available for infusion, Lansky or Karnofsky performance score of 50 or more, and life expectancy of 6 or more weeks. Patients were eligible after a minimum of 3 weeks from last systemic therapy, 3 months from prior stem cell transplant, 2 weeks from prior small port radiation, and 3 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) of 750/mm^3 or more without growth factor support; platelet count of 50,000/mm^3 or more without platelet transfusion; hemoglobin of 8 g/dL or more; estimated creatinine clearance of 60 mL/min/1.73 m^2 or more or serum creatinine of 1.5 or less times the upper limit of age-adjusted normal value; total bilirubin of 1.5 or less times the upper limit of normal; aspartate aminotransferase (ALT) and alanine aminotransferase (AST) less than 3 times the upper limit of normal; cardiac ejection fraction of 55% or more or shortening fraction of 27% or more; 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 of grade 2 or more, 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/m^2 per dose to maximum dose of 2 mg) as an intravenous bolus on days 0 and 7. Patients received irinotecan (20 mg/m^2 per dose to maximum dose of 40 mg) as an intravenous infusion over 1 hour on days 0 to 4 and 7 to 11. 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 to 120 minutes on day 1 according to dose level assigned at study entry: 8, 12, 15, or 18 mCi/kg. The maximum allowable ^{131}I-MIBG dose was 1200 mCi. ^{131}I-MIBG was provided by Jubilant DraxImage, Inc. with a specific activity of 29.7 mCi/mg or more MIBG and a maximum allowable free iodine content of less than 5%. Packed red blood cells were transfused before ^{131}I-MIBG infusion for hemoglobin less than 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 before 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 ANC less than 200/mm^3 for 7 days despite filgrastim, platelet transfusions 2 times or more weekly for 2 consecutive weeks, or ongoing need for platelet transfusions by day 56. All patients at subsequent dose levels received a minimum of 2.0×10^6 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 (SD), 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 3 patients were treated to this dose without dose-limiting toxicity (DLT), the maximum cumulative dose was increased to 36 mCi/kg.

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Toxicity and response evaluation

Toxicity was graded according to the Common Terminology Criteria for adverse events, version 3.0. Hematologic DLT was defined as: ANC less than 500/mm^3 28 days after PBSC infusion; platelets less than 20,000/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. Nonhematologic DLT was defined as grade 3 or more 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 or less 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 New Approaches to Neuroblastoma Therapy (NANT) Response Criteria, modified from the International Neuroblastoma Response Criteria (20). These criteria use Response Evaluation Criteria in Solid Tumors 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 2 time points to confirm), CR unconfirmed (1 time point only), or progressive disease (PD). BM biopsies were not required at end of course if negative at enrollment. All MIBG scans and all radiographic reports/BM reports were centrally reviewed. Patients with SD or better had central review of CT scans and BM 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: before 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 multicompartment 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 before 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 before day 0 therapy. These 2 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 or 12 mCi/kg ^{131}I-MIBG and none experienced DLT. One of the first 3 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 3 patients treated with 18 mCi/kg developed grade 3 abdominal pain, anorexia,

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
MYCN amplified tumor	3/17
Median Curie Extension score at entry (range)	5 (1–21)
BM involved at study entry	12

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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 4 patients with DLT had estimated whole body radiation doses more than 200 cGy.

Details of nonhematologic toxicity by dose level are shown in Table 2. No protocol-associated grade 4 nonhematologic toxicity was seen. The main nonhematologic toxicity was diarrhea. The incidence of grade 3 diarrhea increased with dose level from 8 to 12 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 6 patients with grade 3 diarrhea was 274 cGy (range 176–584 cGy), compared with 201 cGy (range 75–408 cGy) for the 18 patients without grade 3 diarrhea.

Details of engraftment are shown in Table 3. One of 3 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 of 12 (25%) and 4 of 12 (33%) patients treated at the recommended phase 2 dose of 18 mCi/kg did not reach a neutrophil nadir less than 500 cells/mm^3 or platelet nadir less than 20,000 cells/mm^3, respectively.

Seven patients received multiple courses of therapy, including 4 patients who received a cumulative ^{131}I-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 ^{131}I-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.

Table 2. Nonhematologic toxicity in course 1 of therapy attributed as at least possibly related to study therapy and occurring in more than 10% of patients per dose level

		Grade	
Dose level	**Toxicity**	**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
	Hypokalemia	1	0
	Mucositis/stomatitis	1	0
4[a] ($n = 12$)	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

(Continued on the following page)

Responses

Responses are summarized in Table 5, with detailed response data provided in Supplementary Table S1. 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 with 3 of 11

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Table 2. Nonhematologic toxicity in course 1 of therapy attributed as at least possibly related to study therapy and occurring in more than 10% of patients per dose level (Cont'd)

		Grade	
Dose level	**Toxicity**	**1 or 2**	**3**
	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

[a]Table does not include 1 case each of grade 3 febrile neutropenia and grade 3 hallucinations/delusions as these episodes occurred in less than 10% of patients.

(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 with 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/m^2 (2.4–5.5 L/h/m^2) and 143 L/m^2 (69–270 L/m^2). 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 1 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 with 4 of 12 (33.3%) patients with at least one nonwild-type allele. Two of 6 (33.3%) wild-type patients had DLT in course 1 compared with 1 of 12 (8.3%) patients with at least 1 nonwild-type allele. The patient homozygous for 7 TA repeat allele did not develop grade 3 diarrhea or DLT.

Discussion

The combination of ^{131}I-MIBG with vincristine and irinotecan was generally well tolerated at the maximum dose level of 18 mCi/kg ^{131}I-MIBG evaluated in this study. Observed DLTs were typically reversible and managed with supportive care measures. This dose of ^{131}I-MIBG is the highest feasible dose typically used 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 ^{123}I-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 BM disease who per criteria used must completely clear marrow disease to be defined as an overall partial or CR (8 of 12 patients with marrow involvement at highest dose level; Supplementary Table S1). Previous

Table 3. Engraftment in course 1 of therapy ($n = 24$)

^{131}I-MIBG dose level (mCi/kg)	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 for patients with platelets <20,000/mm^3)
8	2[a]/3	2[a]/3	3	32
12	2/3	3/3	24	N/A
15	4/6	5/6	7, 11	16
18	3/12	4/12	Median 7 (range 3–15)	Median 13 (range 7–38)

[a]Two patients did not meet the criteria for stem cell infusion at this dose level (ANC <200/mm^3 for 7 days or platelet transfusion >2x/wk for 2 weeks or failure to be independent of platelets by 8 weeks posttreatment).

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Table 4. Characteristics of each patient receiving more than 1 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	

[a]Responses centrally reviewed for each course.

reports have observed that ^{131}I-MIBG therapy has lower response rates against BM disease (9, 24). These data provided some of the rationale for combining ^{131}I-MIBG with chemotherapy in this study. This phase I study lacks sufficient patient numbers to evaluate whether the addition of chemotherapy improves BM 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 with single-agent ^{131}I-MIBG, we are planning a NANT randomized phase II trial comparing these regimens.

Although 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 this study than 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. Although 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 with 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. These results support this approach and extend these earlier findings by showing 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

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.
[a]The single complete BM response was documented at 1 time point only.

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 in which 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.

This study has shown that this combination is tolerable and active in patients with relapsed and refractory neuroblastoma. Whether this combination has enhanced activity compared with 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.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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