Dose Escalation Study of No-Carrier-Added ^{131}I-Metaiodobenzylguanidine for Relapsed or Refractory Neuroblastoma: New Approaches to Neuroblastoma Therapy Consortium Trial

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^{131}I-metaiodobenzylguanidine (MIBG) is specifically taken up in neuroblastoma, with a response rate of 20%–37% in relapsed disease. Nonradioactive carrier MIBG molecules inhibit uptake of ^{131}I-MIBG, theoretically resulting in less tumor radiation and increased risk of cardiovascular toxicity. Our aim was to establish the maximum tolerated dose of no-carrier-added (NCA) ^{131}I-MIBG, with secondary aims of assessing tumor and organ dosimetry and overall response. **Methods:** Eligible patients were 1–30 y old with resistant neuroblastoma, ^{131}I-MIBG uptake, and cryopreserved hematopoietic stem cells. A diagnostic dose of NCA ^{131}I-MIBG was followed by 3 dosimetry scans to assess radiation dose to critical organs and soft-tissue tumors. The treatment dose of NCA ^{131}I-MIBG (specific activity, 165 MBq/μg) was adjusted as necessary on the basis of critical organ tolerance limits. Autologous hematopoietic stem cells were infused 14 d after therapy to abrogate prolonged myelosuppression. Response and toxicity were evaluated on day 60. The NCA ^{131}I-MIBG was escalated from 444 to 777 MBq/kg (12–21 mCi/kg) using a 3 + 3 design. Dose-limiting toxicity (DLT) was failure to reconstitute neutrophils to greater than 500/μL within 28 d or platelets to greater than 20,000/μL within 56 d, or grade 3 or 4 nonhematologic toxicity by Common Terminology Criteria for Adverse Events (version 3.0) except for predefined exclusions. **Results:** Three patients each were evaluable at 444, 555, and 666 MBq/kg without DLT. The dose of 777 MBq/kg dose was not feasible because of organ dosimetry limits; however, 3 assigned patients were evaluable for a received dose of 666 MBq/kg, providing a total of 6 patients evaluable for toxicity at 666 MBq/kg without DLT. Mean whole-body radiation was 0.23 mGy/MBq, and mean organ doses were 0.92, 0.82, and 1.2 mGy/MBq of MIBG for the liver, lung, and kidney, respectively. Eight patients had 13 soft-tissue lesions with tumor-absorbed doses of 26–378 Gy. Four of 15 patients had a complete (n = 1) or partial (n = 3) response, 1 had a mixed response, 4 had stable disease, and 6 had progressive disease. **Conclusion:** NCA ^{131}I-MIBG with autologous peripheral blood stem cell transplantation is feasible at 666 MBq/kg without significant nonhematologic toxicity and with promising activity.

Key Words: ^{131}I-MIBG; no-carrier added; dosimetry; neuroblastoma

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Neuroblastoma is the most common extracranial solid malignancy of childhood. Nearly half of patients with neuroblastoma have metastatic disease at the time of presentation, with 40% survival (*1,2*). Because neuroblastoma is derived from the neural crest, the cells usually express high levels of norepinephrine transporter, providing a therapeutic target for metaiodobenzylguanidine (MIBG), a norepinephrine analog (*3*). MIBG is specifically concentrated in 90% of neuroblastoma and is an essential component of staging when labeled with ^{123}I (*4*). MIBG labeled with ^{131}I provides tumor-specific radiation and has been shown to be one of the most active therapies for relapsed neuroblastoma, with

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a 20%–37% response rate (*5–8*). Phase 1 and 2 studies suggest a dose response, and therefore patients have been treated with higher amounts of ^{131}I-MIBG supported with autologous peripheral blood stem cell transplantation (ASCT) to prevent toxicity from the myelosuppressive effects of radiation (*8–10*).

The selective uptake of MIBG by norepinephrine transporter is a competitive process. With the standard synthesis of ^{131}I-MIBG, only approximately 1/2,000 MIBG molecules are radioactive (specific activity, ~1.2 MBq/μg), whereas the others continue to bear noncytotoxic ^{127}I (*11*). Cold carrier MIBG molecules in the infusion solution potentially can diminish uptake in target organs and neuroblastoma. One strategy to increase radiation to the tumor is to increase the specific activity of ^{131}I-MIBG, using a different synthetic technique such that nearly every molecule of MIBG would include a radioactive ^{131}I isotope (specific activity, ~165 MBq/μg). Preclinical studies support the enhanced uptake of no-carrier-added (NCA) ^{131}I-MIBG, compared with the standard preparation (*11,12*). Dosimetry, followed by a phase 1 study of NCA ^{131}I-MIBG, was completed in refractory pheochromocytoma, showing safety and responses in a dose escalation from 222 to 296 MBq/kg (*13*). These data combined with the high response rate in refractory neuroblastoma using carrier-added MIBG formed the rationale for our study.

The primary aim was to establish the maximum-tolerated or recommended phase 2 dose of NCA ^{131}I-MIBG. Secondary aims were to describe toxicity, tumor and normal organ radiation dose, therapeutic response, and quality of life.

MATERIALS AND METHODS

Study Design and Statistical Methods

This study followed a 3 + 3 dose escalation design, with escalation decisions made on the basis of dose-limiting toxicity (DLT) observed in a single course of therapy. The planned dose (note that dose level is used throughout to indicate activity) levels were 444, 555, 666, and 777 MBq/kg (12, 15, 18, and 21 mCi/kg, respectively) of NCA ^{131}I-MIBG, replicating the doses used in our prior phase I study of carrier-added MIBG (*9*). The dose was not escalated unless 0 of 3 or no more than 1 of 6 evaluable patients had DLT. All patients received an imaging dose of NCA ^{131}I-MIBG, followed by dosimetry scans at 3 time points. The prescribed therapy dose of NCA ^{131}I-MIBG was adjusted such that the administered activity would deliver <23 Gy to kidneys, <30 Gy to liver, and <15 Gy to lungs. Patients received ASCT 14 ± 3 d after the therapeutic dose. Patients with an absolute neutrophil count (ANC) of <500/μL at any point after ASCT received granulocyte colony–stimulating factor (5 μg/kg/d) until the ANC was >2,000/μL. Only 1 treatment course was allowed. Patients were assessed for toxicity and response at day 60 ± 10 d after the NCA ^{131}I-MIBG therapy. The Pediatric Quality of Life Inventory was collected at baseline and 60 d after treatment.

Patients were evaluable for DLT if they experienced a DLT or if they completed therapy and were followed for at least 28 d from stem cell infusion or when ANC was >500/μL and platelets were >20,000/μL without transfusion for 3 d, whichever occurred last. The recommended phase 2 dose was defined as the highest studied assigned dose level at which fewer than one third of patients had DLT. Only patients receiving an actual infused dose within 15% of the assigned dose were included in the escalation evaluation. An expansion cohort for a total of 6 patients was planned for treatment at the recommended phase 2 dose. Responders were defined as patients having a complete response (CR), very good partial response (PR), or PR.

Patient Eligibility

Patients 1–30 y old with relapsed or refractory neuroblastoma were eligible if they had MIBG-avid disease within 6 wk of enrollment and subsequent to any chemotherapy or radiation therapy. Patients were required to have a minimum of 2.0×10^6 CD34-positive autologous hematopoietic stem cells per kilogram available, Karnofsky performance score (adults) or Lansky play score (children) ≥ 60, and life expectancy ≥ 8 wk (according to the judgment of the treating physician). Patients were eligible a minimum of 2 wk from their last systemic therapy or small port radiation, 3 mo from prior ASCT, and 3 mo from large-field radiation. Exclusions included prior whole-abdomen radiation, total-body radiation, or allogeneic bone marrow transplantation. Patients with prior carrier-added ^{131}I-MIBG therapy were eligible if more than 12 mo had elapsed.

Required organ function included ANC ≥ 750/μL without growth factor support; platelet count ≥ 20,000/μL without platelet transfusion; hemoglobin ≥ 8 g/dL (transfusions allowed); creatinine clearance ≥ 60 mL/min/1.73 m^2 or serum creatinine ≤ 1.5 times the upper limit of normal; total bilirubin ≤ 1.5 times the upper limit of normal; alanine aminotransferase and aspartate aminotransferase < 3 times the upper limit of normal; cardiac ejection fraction ≥ 50% or shortening fraction ≥ 27%; and lack of dyspnea at rest, symptomatic pleural effusion, or oxygen requirement. Exclusion criteria included pregnancy, breast-feeding, major organ system disease, inability to tolerate radiation isolation, and patient weight that would exceed a maximum allowable activity of NCA ^{131}I-MIBG (per institutional radiation safety guidelines).

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

Toxicity Evaluation

Toxicity was graded according to the Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep.cancer.gov). Hematologic DLT was defined as ANC < 500/μL 28 d after ASCT, platelets < 20,000/μL 56 d after ASCT, the need for a second ASCT, grade 4 hemolysis refractory to platelet transfusions with life-threatening bleeding, and life-threatening anemia. Nonhematologic DLT was defined as toxicity ≥ grade 3, with the exception of the following grade 3 toxicities: nausea, vomiting, anorexia, dehydration, electrolyte abnormality, hepatic enzyme elevation returning to ≤grade 1 by day 60, fever, infection, and febrile neutropenia. These definitions included only toxicities deemed at least possibly related to study therapy and required observation for at least 60 d after MIBG therapy.

Response Evaluation

Patients underwent complete disease staging (^{123}I-MIBG diagnostic scanning, bilateral bone marrow aspiration and biopsy, anatomic imaging with CT or MRI, and urine catecholamine testing) at baseline and at day 60 after NCA ^{131}I-MIBG therapy. Two independent reviewers assessed imaging response using masked

TABLE 1
Patient Characteristics at Study Entry (n = 15)

Characteristic	Data
Age (y)	
Median	8
Range	3–30
Sex (*n*)	
Male	9
Female	6
Primary refractory disease (*n*)	2
Relapsed disease (*n*)	13
Sites of disease (*n*)	
Bone marrow	4
Bone	13
Soft tissue	9
MIBG Curie score	
Median	3
Range	1–18
MYCN gene amplification (*n*)	2/11
Prior radiation (*n*)	12
Prior carrier-added MIBG therapy*	5
Prior ASCT (*n*)	8

*Patients who had received prior carrier-added MIBG therapy were eligible if more than 1 y had elapsed since that therapy before entry.

central review of original images. Response was graded using the New Approaches to Neuroblastoma Therapy Response Criteria, a modification of the International Neuroblastoma Response Criteria (*14*) in that they used the Response Evaluation Criteria in Solid Tumors 1.0 for measurable tumors (*15*) and the semiquantitative Curie score for MIBG scan response. The Curie score was obtained by dividing the patient's skeleton into 9 segments and an additional segment to assess soft-tissue involvement and assigning a score of 0–3 per segment according to the extent of involvement. Pretherapy and posttherapy extension scores were calculated by summing the segmental scores assigned by the reader (*16*). A relative score (posttherapy score divided by the pretherapy score) of ≤0.5 was rated as a PR, and a relative score of 0 as a CR. A pathologist recorded evidence of bone marrow tumor response only if there was no evidence of tumor on other staging methods. Progressive disease (PD) in bone marrow required a change from negative to morphologic involvement or an increase with doubling of tumor percentage and more than 25% tumor in marrow.

Dosimetry Procedure and Calculations

An imaging dose of NCA ^{131}I-MIBG of 3.7 MBq/kg (0.1 mCi/kg) with a maximum dose of 185 MBq (5 mCi) was given 7–28 d before therapeutic dose administration. The mean specific activity of NCA ^{131}I-MIBG was 165 MBq (range, 100–320 MBq/μg) per microgram of cold MIBG. The imaging dose was supplemented with 185 μg of cold MIBG (to mimic the level of carrier MIBG in the highest anticipated therapeutic activity) and administered over 1–3 min. In this manner, the dosimetry dose would more accurately reflect the biodistribution and biokinetics of the therapy dose, ensuring that we did not miss changes due to pharmacologic effects of the larger therapy doses. Safety monitoring with vital signs and a 12-lead electrocardiogram were obtained before and after the imaging dose. Anterior and posterior whole-body images were acquired within 1 h of administration and before bladder voiding to estimate the whole-body baseline counts and then at 24 h after the imaging dose (postvoid) and 2–5 d after the imaging dose to assess biodistribution, excretions, and tumor uptake. For each subject's planar scans, the same ^{131}I imaging standard was used. The 3 dosimetry scans were transmitted to the central imaging facility (ICON Medical Imaging) for region-of-interest analysis. The method of Coleman et al. (*13*) was used to quantify the whole-body biodistribution (including decay and

TABLE 2
NCA ^{131}I-MIBG Therapy Dose in 15 Evaluable Patients with Advanced Neuroblastoma

Patient no.	Assigned dose level at study entry (MBq/kg)	Adjusted dose based on dosimetry (MBq/kg)	Administered activity (MBq/kg)	% Assigned dose	% Adjusted dose (reason for reduction)
N190	444	444	326	73%	100%, ideal body weight
N091	444	444	440	99%	
N121	444	425	377	85%	89%, D-lung + technical
N201	555	518	488	88%	94%, D-kidney + technical
N205	555	555	551	99%	
N206	555	555	559	101%	
N141	666	666	662	99%	
N086	666	666	692	104%	
N212	666	666	681	102%	
N247	666	666	614	92%	
N219	777	666	648	83%	97%, D-lung
N222	777	566	429	55%	77%, D-lung + technical
N225	777	729	681	88%	93%, D-kidney + technical
N227	777	662	677	87%	102%, D-kidney + D-lung
N082	777	437	426	55%	97%, D-kidney + D-lung

D = dosimetry-mandated reduction to meet organ limits set for kidney, lung, or liver; technical = variation in activity infused occurred due to variation in amount received from vendor or loss of activity during transfer or infusion caused by mislabeling of volume, air bubble in tubing, or failure to flush infusion tubing.

TABLE 3
Nonhematologic Toxicities Related to Therapy

Administered dose level	Toxicity category	Maximum toxicity grade experienced			
		1	2	3	4
444 MBq/kg (n = 5)	Hepatic	3	1	0	0
	Constitutional	0	1	0	0
	Infection/febrile neutropenia	0	0	1	0
	Pain	2	0	0	0
	Gastrointestinal	2	0	0	0
	Metabolic/laboratory	2	0	0	0
	Neurology	1	0	0	0
555 MBq/kg (n = 3)	Hepatic	1	1	0	0
	Pain	0	2	0	0
	Gastrointestinal	0	1	0	0
	Dermatology/skin	0	1	0	0
	Metabolic/laboratory	1	0	0	0
	Neurology	1	0	0	0
666 MBq/kg (n = 7)	Hepatic	4	2	0	0
	Constitutional	2	1	0	0
	Cardiovascular	1	0	0	0
	Infection/febrile neutropenia	0	0	2	0
	Pain	2	3	0	0
	Gastrointestinal	1	4	0	0

camera speed corrections) into estimates of the fractional distribution of radioactivity in the whole body and organs showing appreciable accumulation of the ^{131}I.

The OLINDA/EXM software, used to estimate the radiation absorbed doses (*17*), has a complete series of dosimetry phantoms that correspond to the following body sizes: newborn, 1 y old, 5 y old, 10 y old, 15 y old (also same as adult female), and adult male. In this study, the phantom whose body weight was closest to that of each patient was used in the radiation dose estimates. Tumor dosimetry was calculated for patients with a measurable soft-tissue lesion $>$ 1 cm. The radiation dose to salivary glands and tumors was computed using spheric self-dose S values (radiation dose per unit cumulated activity) calculated from OLINDA/EXM. The organ radiation doses include cross-talk irradiation from ^{131}I decay in other organs but not from tumors (no tumors in the phantoms). The contribution of radioactivity in tumors to an organ's total radiation dose was neglected, because the contributions are less than 5% of the total received radiation dose. In cases in which the tumor was an integral part of a normal organ, such as a lung tumor, the lung radiation doses were initially calculated using all the activity in the lung, including the tumor. To determine the tumor or salivary radiation dose (mGy/MBq), the appropriate (chosen by mass) spheric S value was multiplied by the residence time (total decays in the tumor or salivary glands).

The dosimetry estimates for each subject were relayed back to the local investigator with specific recommendations on how much

TABLE 4
Organ Dosimetry with NCA ^{131}I-MIBG

Patient no.	^{131}I-MIBG activity received (MBq/kg)	Radiation dose to organ (Gy)								
		Adrenal	Brain	Thyroid	Heart	Kidney	Liver	Lungs	Red marrow	Whole body
N190	326	2.3	0.5	23.0	5.8	13.7	10.3	5.9	1.4	2.0
N121	377	3.8	2.4	28.6	25.4	13.5	15.1	14.1	2.4	3.5
N082	426	3.0	5.9	19.0	22.7	23.2	12.4	10.9	1.9	2.8
N222	429	2.0	2.4	7.8	15.3	10.3	9.1	15.3	1.5	2.2
N091	440	2.8	1.4	88.4	8.9	8.3	9.9	9.5	1.9	2.7
N201	488	3.2	1.6	45.9	8.5	22.8	9.8	7.7	2.1	2.9
N205	551	3.6	1.3	107.6	16.3	14.4	11.6	11.5	2.5	3.5
N206	559	2.5	1.6	68.1	11.9	21.6	10.5	7.9	1.5	2.3
N247	614	3.3	1.5	2.1	23.3	15.5	13.0	8.9	2.2	3.3
N219	648	3.6	2.3	34.8	18.0	14.0	10.1	13.3	2.6	3.6
N141	662	3.6	1.4	55.5	14.5	10.3	11.6	11.5	2.6	3.6
N227	677	3.9	1.5	45.2	19.5	23.4	15.7	14.7	2.6	3.7
N225	681	3.8	4.4	35.7	20.3	21.1	25.8	10.3	2.3	4.0
N212	681	3.2	2.1	29.5	12.2	16.8	12.3	14.4	2.3	3.1
N086	688	3.9	2.4	93.0	16.3	21.8	13.1	14.8	2.7	3.9

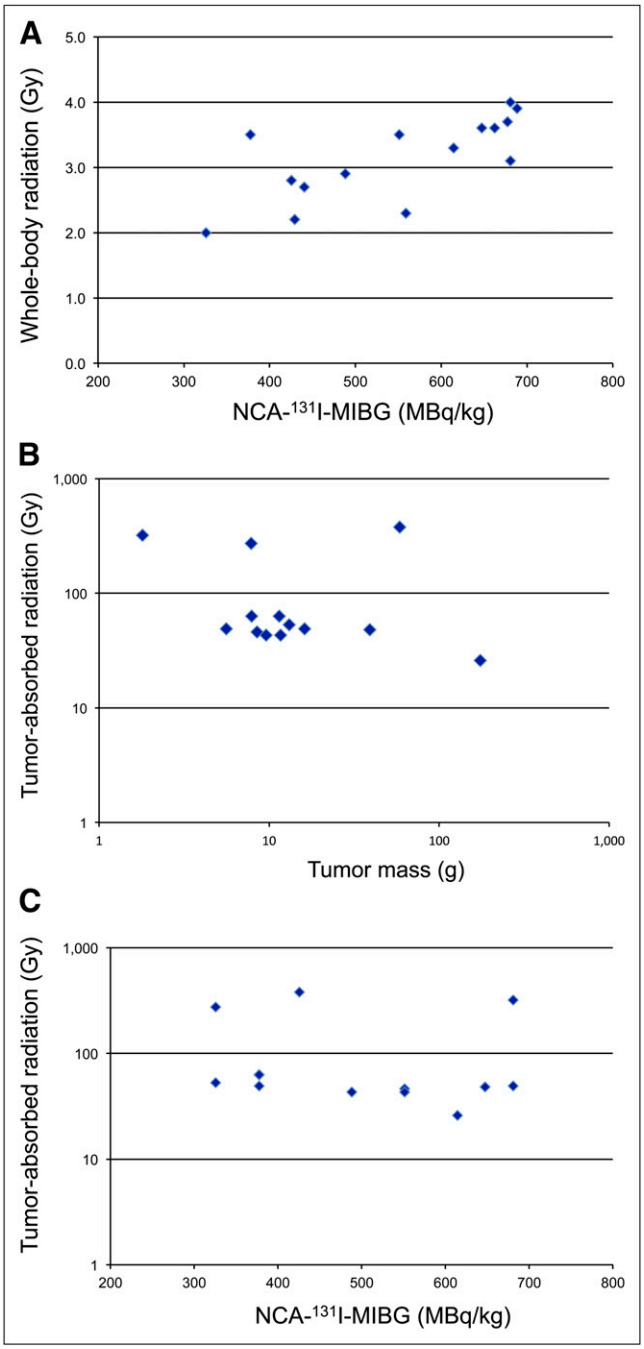

FIGURE 1. (A) Received whole-body radiation dose (Gy dose significantly depends on administered activity of NCA ^{131}I-MIBG (MBq/kg) ($n = 15$; $r = 0.75$; $P < 0.001$). (B) Tumor-absorbed radiation dose (Gy) appears to be independent of tumor mass (g) ($n = 13$; $r = -0.26$; $P = 0.40$). (C) Tumor-absorbed radiation dose (Gy) dose not correlate with activity of NCA ^{131}I-MIBG (MBq/kg) ($n = 13$; $r = -0.33$; $P = 0.27$).

to reduce the planned therapy activity should the kidney, liver, or lungs exceed total radiation dose limits established by the protocol. For example, if a subject's planned activity for therapy was 18,500 MBq (500 mCi) but the pretherapy dosimetry study showed that the kidney would receive 25.3 Gy (10% over the limit of 23 Gy), then it was recommended that the therapy activity be reduced by this percentage, so the subject in this example would receive 16,650 MBq (450 mCi). The therapy was adjusted on the basis of the pretherapy dosimetry data only.

NCA ^{131}I-MIBG therapy

NCA ^{131}I-MIBG was provided by Molecular Insight Pharmaceuticals, Inc. (investigational new drug 70,663). Ultratrace ^{131}I-iobenguane (Molecular Insight) was prepared at high specific activity via the reaction of ^{131}I-NaI with a polystrene-dibutylstannyl-m-benzylguanidine resin intermediate in the presence of oxidant and isolated using high-performance liquid chromatography. The mean specific activity of therapy doses used in this study was approximately 165 MBq per microgram of cold MIBG (*11*). Radiopurity was determined before shipment. NCA ^{131}I-MIBG was infused through a central venous catheter or a temporary indwelling catheter. The therapeutic dose was diluted in 25 mL of normal saline and infused over 30–60 min with hydration, radiation isolation, thyroid blocking with potassium perchlorate and potassium iodide, and bladder protection with a Foley catheter (*8*). Vital signs and cardiac rhythm were monitored, including a Holter monitor for 24 h. The patient remained in a radiation-protected isolation room until radiation emissions were <3 mrem/h at 1 m or met institutional or state guidelines (generally 3–5 d).

RESULTS

Patient Characteristics

Sixteen patients enrolled. One patient withdrew for rapid tumor progression before receiving the dosimetry dose. The 15 eligible and treated patients comprised the analyzed population for this report. The patients (Table 1) comprised a heavily pretreated population with median age 8 y, including 2 patients with refractory disease and 13 with relapsed disease or PD. Five patients had received prior carrier-added ^{131}I-MIBG therapy. The median MIBG score at study entry was 3 (range, 1–18).

Dose Escalation and Toxicity

Table 2 shows the dose level assigned at entry, the dose level prescribed by the pretherapy dosimetry, and the dose level actually received, which varied in 4 patients because of technical factors. Three patients were entered and treated at dose level 1 (444 MBq/kg) without DLT, including 1 obese patient whose dose was reduced using his adjusted ideal body weight. Three patients were entered and treated at dose level 2 (555 MBq/kg) without DLT. Three patients were entered and treated at dose level 3 (666 MBq/kg). None of the evaluable patients had DLT.

Because of organ dosimetry limits, none of the 5 patients enrolled at dose level 4 (777 MBq/kg) was able to receive the assigned dose. One patient had a dose reduction from assigned level 4 to level 2 based on predicted lung dose from dosimetry. This patient actually received a dose lower than allowed by dosimetry because of a technical issue with infusion (failure to flush the activity remaining in the intravenous tubing) and was evaluable at dose level 1 (444 MBq/kg). A second patient assigned to level 4 was treated at level 1 without DLT because of allowable dosimetry results for both lung and kidney. A third patient assigned to

TABLE 5
Tumor Dosimetry in 8 Patients with 13 Measurable Soft-Tissue Lesions

MIBG/kg (MBq/kg)	Tumor 1			Tumor 2			Tumor 3		
	Mass (g)	Dose (Gy)	Response	Mass (g)	Dose (Gy)	Response	Mass (g)	Dose (Gy)	Response
326	7.85	273	Stable disease	13.1	53	Stable disease			
377	5.6	49	Stable disease	7.9	63	Stable disease	11.5	63	Stable disease
426	58.6	378	Stable disease						
488	9.6	43	Stable disease						
551	11.7	43	Stable disease	8.5	46	Stable disease			
614	175.0	26	Stable disease						
648	39.0	48	PD						
681	16.2	49	Stable disease	1.8	320	Stable disease			

One patient with measurable soft-tissue lesion on CT had PR to NCA MIBG, but tumor dosimetry was not available on tumor.

level 4 was reduced to level 3 because of organ dosimetry limits but died of PD before platelet engraftment and thus was not evaluable for DLT. Three other patients assigned to level 4 received an adjusted dose of 666 MBq/kg, providing 6 patients evaluable at dose level 3 to document safety. Because the 777 MBq/kg dose was not practical because of organ dosimetry limitations and 0 of 6 evaluable patients at 666 MBq/kg had DLT, 666 MBq/kg was declared the recommended phase 2 dose.

All grade 1–4 nonhematologic toxicities definitely, probably, or possibly related to therapy are shown in Table 3. There were 3 patients with related grade 3 toxicities (fever or infection), none qualifying as DLT. One patient assigned to level 4 had a dose reduction to 432.9 MBq/kg because of dosimetry predicting a higher than allowable dose to the lungs and kidneys. The patient was admitted to the hospital for 5 d for grade 3 fever with neutropenia (blood cultures negative) 19 d after the treatment dose of NCA ^{131}I-MIBG, with associated grade 3 nausea and vomiting, grade 2 diarrhea, and pain. All toxicities were related except pain, which was attributable to the tumor. Another patient assigned and treated with 666 MBq/kg was hospitalized for fever without neutropenia 14 d after treatment with NCA ^{131}I-MIBG with a blood culture from a central venous catheter positive for coagulase negative staphylococci. The same patient was admitted 21 d after the treatment dose for grade 4 hypokalemia, which resolved with potassium supplementation (unrelated to MIBG). During this admission, the patient had fever, neutropenia, and radiographic findings consistent with asymptomatic pneumonitis. A second patient treated with 666 MBq/kg was hospitalized for fever without neutropenia. These events all resolved without sequelae and were consistent with prior reports of carrier-added ^{131}I-MIBG therapy.

Hematologic toxicity was expected and was mostly abrogated by ASCT. Only 4 of 15 evaluable patients had grade 4 neutropenia with an ANC $<$ 500 and all engrafted at 5, 7, 18, and 26 d after ASCT. Six of 15 patients had platelet counts less than 20,000, and 5 recovered above this level 4–23 d after ASCT. One patient who developed PD and died before day 60 never became independent of platelets.

There was no infusion-related toxicity and no secondary malignancies reported. One death occurred from PD on day 37 after therapy. The Pediatric Quality of Life Inventory assessments showed no significant change after therapy from baseline.

Dosimetry

Individual organ and whole-body radiation doses are shown in Table 4. The mean whole-body dose was 0.23 mGy/MBq (range, 0.071–0.43 mGy/MBq); mean doses to the liver, lungs, and kidneys were 0.92, 0.82, and 1.2 mGy/MBq, respectively. Administered activity of NCA ^{131}I-MIBG per kilogram significantly correlated with whole-body radiation (Fig. 1A). Tumor dosimetry was evaluable for 8 patients with 13 evaluable soft-tissue lesions (Table 5). Tumor masses ranged from 1.8 to 175 g, with a median delivered tumor radiation dose of 49 Gy (range, 26–378 Gy). The tumor-absorbed radiation dose did not correlate with tumor mass (Fig. 1B) or with activity of NCA-^{131}I-MIBG/kg infused (Fig. 1C). None of the patients with soft-tissue dosimetry measurements showed a significant tumor size reduction.

Response

Four of 15 patients (27%) evaluated had an objective response, including 1 with CR and 3 with PR. Additionally, 1 patient had a mixed response (MR), 6 had stable disease, and 4 had PD (Table 6). One patient treated at 555 MBq/kg had complete normalization of urine catecholamines but did not meet the criteria for MR by his unchanged CT and MIBG findings. A greater response rate was apparent at the higher dose levels, with 3 of 7 responses at 666 MBq/kg. By tumor site, 5 of 14 patients had MIBG response and 2 of 4 had bone marrow response. Only 1 of 11 patients with a measurable soft-tissue lesion had soft-tissue response, despite receiving significant tumor radiation (43–378 Gy) by dosimetry. Two patients developed new bone marrow disease at the posttherapy 60-d evaluation.

TABLE 6
Centrally Reviewed Response Overall and by Disease Site for 15 Patients Treated with NCA ^{131}I-MIBG

Dose level	^{131}I-MIBG received (MBq/kg)	MIBG semiquantitative Curie score*			CT/MRI		Bone marrow		Urine catechols†		Central review, overall response
		At entry	After Rx	Response	LD (mm)	Response	At entry	Response	At entry	Response	
444 MBq/kg	326 (444)*	9	9	Stable disease	54	Stable disease	N	N-NE	N	N	Stable disease
	377	18	14	Stable disease	184	Stable disease	N	PD	Elev	Decr	PD
	426	17	16	Stable disease	66	Stable disease	Pos	PD	Elev	Not done	PD
	429	1	1	Stable disease	43	Stable disease	N	N-NE	N	N	Stable disease
	440	7	7	Stable disease	14	Stable disease	Pos	Stable disease	Elev	Decr	Stable disease
555 MBq/kg	488	2	2§	Stable disease	24	Stable disease	N	N-NE	Elev	N	Stable disease
	551	2	2	Stable disease	91	Stable disease	N	PD	N	N	PD
	559	4	1	PR	NM	NM-NE	N	N-NE	N	N	PR
666 MBq/kg	614	2	2	Stable disease	229	Stable disease	N	N-NE	Elev	Decr	Stable disease
	648	19	Not done	Not done	40	PD	N	Not done	Elev	Not done	PD‡
	662	6	5	Stable disease	24	Stable disease	N	N-NE	N	N	Stable disease
	677	3	1	PR	NM	NM-NE	Pos	CR	N	N	PR
	681	5	2	PR	97	Stable disease	N	N-NE	N	N	MR
	681	3	0	CR	NM	NM-NE	Pos	CR‖	N	N	CR
	688	1	0	CR	26	PR	N	N-NE	Elev	Decr	PR

*For PR, ratio of posttherapy to pretherapy Curie score must be less than 0.5 (*16*).
†Catecholamines are not used to determine response except must be normal for CR/very good PR.
‡This patient had CT progression of masses and died before day 60 of PD.
§MIBG scan was done 5 mo after other scans but with no intervening therapy.
‖BM-positive (~1% tumor) at entry, negative after therapy but not verified by second BM.
MIBG score and longest diameter are average of 2 independent readers, except in case of response disagreement, when it is consensus value.
Rx = therapy; LD = sum of longest diameters of target lesions; N = negative or normal; N-NE = negative at entry and negative post therapy, so inevaluable for response at that site; Elev = elevated above normal; Decr = decreased but not normal; Pos = positive for tumor by morphology; NM = not measurable.

DISCUSSION

We have shown that NCA ^{131}I-MIBG is tolerable and feasible at a dose of 666 MBq/kg, equal to the recommended dose with carrier-added MIBG (*8*). Furthermore, NCA ^{131}I-MIBG is effective, with a centrally reviewed response rate of 27% in highly refractory relapsed neuroblastoma. The response rates were greater at the higher dose levels, with 3 of 7 patients at 666 MBq/kg with CR or PR and another with MR. A dose–response relationship has also been noted with carrier-added MIBG (*5*). Tumor dosimetry shows a median tumor-absorbed dose in our study of 49 Gy, compared with 33 Gy with the carrier added MIBG, but the small numbers and difficulty in comparing the specific tumors preclude definite conclusions (*14*). It is unusual that none of the soft-tissue lesions with dosimetry measurements showed a significant reduction in size, although response in soft tissue has frequently occurred in prior studies of carrier-added MIBG. This may be due to a resistant group of tumors in this small number of patients or a difference between the 2 preparations. A randomized trial would be necessary to demonstrate that the NCA ^{131}I-MIBG is more or less effective than the standard carrier-added formulation, although in preclinical studies there was significantly higher efficacy for NCA ^{131}I-MIBG than for carrier-added MIBG (*11*).

The lack of significant nonhematologic toxicity seen with the NCA ^{131}I-MIBG is similar to results with this agent in pheochromocytoma (*13*). The addition of ASCT allowed administration of a higher activity of the radiopharmaceutical while virtually abrogating the hematologic toxicity. Historically, 2 late toxicities of MIBG, hypothyroidism and secondary leukemia, have been reported with therapeutic doses of carrier-added ^{131}I-MIBG. Hypothyroidism is a frequent late effect of MIBG therapy, because of thyroid uptake of dissociated radioactive iodide anions (*18*). Myelodysplasia or leukemia after carrier-added MIBG has been reported, with a cumulative incidence of 4% at 4 y after therapy (*8,19*). Late toxicities have not been seen to date in our study, although a larger study with longer follow-up would be needed to determine the late toxicity of NCA ^{131}I-MIBG.

We have reported detailed whole-body, organ, and tumor dosimetry with NCA ^{131}I-MIBG. No patient assigned to 666 MBq/kg required dose reduction on the basis of dosimetry, supporting future studies using this dose without dosimetry. Similar to prior reports with carrier-added MIBG, there was a significant increase in whole-body dose with increasing activity of the NCA ^{131}I-MIBG per kilogram, with whole-body doses similar to those with carrier-added MIBG (*20*). As in prior reports, there was no correlation between MIBG activity administered and the tumor-absorbed dose (*20–22*). There was also no correlation between tumor size and the tumor-absorbed radiation dose, despite the fact that tumor dose is directly proportional to the total number of nuclear decays in the tumor and is inversely proportional to the tumor mass. This is likely due to differences in tumor perfusion, proportion of viable tumor cells, biologic body clearance rate, and tumor avidity and retention of MIBG. Perhaps improving the accuracy of the dosimetry with SPECT (*22*) or using ^{124}I-MIBG with PET would increase correlation between activity and response (*23*). Overall, the measurable tumors all received significant doses, with a median tumor dose of 49 Gy, more than twice the standard dose applied currently by external-beam radiation for newly diagnosed patients with high-risk disease (*24*).

CONCLUSION

NCA ^{131}I-MIBG is a tolerable, feasible, and effective radiopharmaceutical for the treatment of refractory neuroblastoma at activity levels that are comparable to carrier-added MIBG. This radiopharmaceutical has the theoretic advantage of lower risk of chemical pharmacologic adverse effects and the ability for more rapid infusion. Additional trials are necessary to confirm whether the efficacy differs from carrier-added MIBG and provide further safety information. Finally, NCA ^{131}I-MIBG must be tested early in the disease course to determine whether this radiopharmaceutical will improve survival.

DISCLOSURE STATEMENT

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