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Nucl Med Biol. Author manuscript; available in PMC 2009 August 1.

Published in final edited form as:
Nucl Med Biol. 2008 August ; 35(Suppl 1): S35–S48. doi:10.1016/j.nucmedbio.2008.05.002.

Radiolabeled Metaiodobenzylguanidine for the Treatment of Neuroblastoma

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Abstract

Introduction—Neuroblastoma is the most common pediatric extracranial solid cancer. This tumor is characterized by metaiodobenzylguanidine (MIBG) avidity in 90% of cases, prompting the use of radiolabeled MIBG for targeted radiotherapy in these tumors.

Methods—The available English language literature was reviewed for original research investigating *in vitro, in vivo*, and clinical applications of radiolabeled MIBG for neuroblastoma.

Results—MIBG is actively transported into neuroblastoma cells by the norepinephrine transporter. Preclinical studies demonstrate substantial activity of radiolabeled MIBG in neuroblastoma models, with ^{131}I-MIBG showing enhanced activity in larger tumors compared to ^{125}I-MIBG. Clinical studies of ^{131}I-MIBG in patients with relapsed or refractory neuroblastoma have identified myelosuppression as the main dose-limiting toxicity, necessitating stem cell reinfusion at higher doses. Most studies report a response rate of 30–40% with ^{131}I-MIBG in this population. More recent studies have focused on the use of ^{131}I-MIBG in combination with chemotherapy or myeloablative regimens.

Conclusions—^{131}I-MIBG is an active agent for the treatment of patients with neuroblastoma. Future studies will need to define the optimal role of this targeted radiopharmaceutical in the therapy of this disease.

Keywords

Metaiodobenzylguanidine; neuroblastoma; pediatric; radionuclide

Introduction

Neuroblastoma is the most common extracranial malignant solid tumor of childhood. The peak incidence occurs during early childhood and approximately 650 new cases are diagnosed in the United States each year [1]. The tumor is derived from the sympathetic nervous system. The most common site of origin is within the adrenal medulla, although the tumor also commonly arises elsewhere along the sympathetic chain.

Neuroblastoma is notable for its heterogeneous clinical behavior. Several key clinical and biological prognostic features have been identified that appear to influence the behavior of these tumors. The two most important clinical features are age and stage. Younger patients have a lower risk of developing recurrent disease and therefore improved overall survival. The

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threshold at which a patient is considered "young" has shifted in recent years from less than 1 year to less than 18 months of age at initial diagnosis [2,3]. All patients with newly diagnosed neuroblastoma undergo a series of staging studies to evaluate the extent of disease. Approximately 50% of patients have distant hematogenous metastases at the time of diagnosis, most commonly to the bone or bone marrow [4]. These patients will undergo dedicated imaging of the primary tumor and bone marrow biopsies. As a tumor derived from the sympathetic nervous system, these tumors typically express the norepinephrine transporter which mediates active intracellular uptake of radiolabeled metaiodobenzylguanidine (MIBG) in approximately 90% of patients [5,6]. Patients with newly-diagnosed neuroblastoma therefore typically also have a diagnostic MIBG scan performed to identify sites of bone metastasis or diffuse bone marrow involvement [7]. The results of these staging studies are used to assign a patient a stage based upon the International Neuroblastoma Staging System (INSS) [8]. In addition to these clinical features, several biological prognostic factors have also been identified. The most important biological prognostic factor is amplification of the *MYCN* oncogene, which has consistently been reported as an independent adverse prognostic factor [9]. Tumor histopathologic grading according to the Shimada classification system, tumor ploidy, gain of chromosome 17q, and deletions of 1p and 11q are other biological prognostic factors evaluated in these tumors [10–13].

The treatment of neuroblastoma depends upon a patient's estimated risk of relapse, based upon these identified clinical and biological prognostic features. For those patients with low-stage localized tumors (INSS 1 and 2) and favorable biological features, surgical resection alone is almost always curative. For patients with locally aggressive tumors (INSS 3) but favorable biology, the combination of chemotherapy and surgical resection is the standard approach with excellent outcomes [14]. Patients with metastatic disease at initial diagnosis who are greater than 18 months of age and patients with *MYCN* amplified locoregional tumors are treated with intensive multimodal therapy with chemotherapy, surgical resection, local radiation, and consolidation with high-dose therapy with autologous hematopoietic stem cell rescue [15]. These patients also benefit from 13-cis-retinoic acid given post-consolidation as a differentiating agent for minimal residual disease [15,16]. While this intensive approach has been shown to improve outcome, patients with high-risk disease frequently relapse and fewer than 50% of these patients will be long-term survivors [15,16].

The poor outcome in patients with high-risk disease and the observation that 90% of tumors are MIBG-avid provide the rationale for utilizing MIBG as a targeted radionuclide in these patients. This review will summarize the available preclinical and clinical experience of using MIBG as a therapeutic agent for neuroblastoma. The review will include a discussion of approaches that combine MIBG with other active agents for neuroblastoma. The review will conclude with an overview of the reported late effects of MIBG therapy in this patient population as well as the practical considerations involved in administering MIBG therapy to young patients.

Preclinical Studies of Radiolabeled MIBG in Neuroblastoma

A relatively small number of studies have evaluated radiolabeled MIBG in preclinical models of neuroblastoma. Most of these studies have focused on MIBG uptake into neuroblastoma cells, though other groups have also investigated mechanisms of the cytotoxicity of this agent in neuroblastoma. Early investigators observed that only a subset of neuroblastoma cell lines demonstrated specific uptake of radiolabeled MIBG, while other neuroblastoma cell lines showed only passive diffusion of the drug into cells [17]. The specific uptake is reduced by inhibition of the Na-K-ATPase and also competitively inhibited by norepinephrine [17–19]. These results suggested the possibility that MIBG is actively taken up into neuroblastoma cells by the norepinephrine transporter. This possibility was supported by studies demonstrating

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attenuation of MIBG uptake into neuroblastoma cells in the presence of imipramine, an inhibitor of norepinephrine transport [19–21]. In addition, MIBG uptake into neuroblastoma cells shows a strong correlation with norepinephrine transporter expression levels [5,22,23]. Neuroblastoma cells that do not actively take up MIBG become MIBG avid when transfected with the norepinephrine transporter gene [24]. Similarly, non-neural cells can be engineered to take up MIBG by transfection with the norepinephrine transporter gene [25,26]. These data indicate that neuroblastoma cells take up MIBG via specific active uptake by the norepinephrine transporter gene. Once taken up into neuroblastoma cells, most MIBG appears to be stored in the cytoplasm and mitochondria, rather than in the neurosecretory granules that store norepinephrine [19,21,27,28].

Several factors may modulate MIBG uptake by neuroblastoma cells (Table 1). Some of these findings may have implications for the clinical application of radiolabeled MIBG to patients with neuroblastoma. MIBG uptake appears to be reduced in the presence of hypoxia and by moderate hyperthermia [17,29]. Pretreatment with cisplatin or doxorubicin, two active chemotherapy agents used in the clinical treatment of neuroblastoma, has been shown to significantly increase MIBG uptake by neuroblastoma *in vitro* and *in vivo* [30,31]. This effect may be due to an increase in norepinephrine transporter gene expression after chemotherapy exposure [30]. Pretreatment with γ-interferon augments MIBG uptake [32,33]. The evaluation of retinoic acid pretreatment on MIBG uptake has produced mixed results depending on the cell line evaluated. In one early study, retinoic acid had no effect on MIBG uptake [32]. A separate study using a different cell line indicated that retinoic acid pretreatment improved both MIBG uptake and retention [20]. A third study showed that retinoic acid together with γ-interferon increases MIBG uptake into neuroblastoma cells [33]. The effect of retinoic acid on neuroblastoma MIBG uptake will require further study to clarify these conflicting results.

One group has evaluated the efficacy of ^{131}I-MIBG combined with topotecan in preclinical models of neuroblastoma [34]. These studies demonstrated that this combination produced synergistic inhibition of tumor cell growth, particularly when topotecan was given simultaneously with ^{131}I-MIBG. Cells treated with topotecan either simultaneously with or 24 hours after ^{131}I-MIBG treatment appeared to decrease DNA repair mechanisms [34]. These results provide the rationale for some of the combination approaches applied clinically and discussed below.

The mechanism of cytotoxicity of MIBG has been evaluated in preclinical models of neuroblastoma. Experiments in which neuroblastoma cells were exposed *in vitro* to radiolabeled or unlabeled MIBG demonstrated that unlabeled MIBG at doses < 10 μM does not contribute to the cytotoxicity of radiolabeled MIBG [35]. Instead, targeted radiation exposure accounts for all of the cytotoxicity of radiolabeled MIBG. These results were confirmed in another report indicating that unlabeled MIBG at 1–2 μM was not cytotoxic [36]. In contrast, higher dose unlabeled MIBG may be directly cytotoxic [37–39]. Higher dose unlabeled MIBG produced moderate cytotoxicity in a range of cell types, including fibroblasts, leukemia cells, and neuroblastoma cells [39]. Unlabeled MIBG at doses ≥ 10 μM results in dose-dependent inhibition of neuroblastoma cell growth and an increase in markers of oxidative stress in neuroblastoma cells [37,38]. The small contribution to cytotoxicity of unlabeled MIBG is unlikely to be clinically relevant in human therapies and even less so with a new no-carrier-added formulation (see below).

Several studies have evaluated radiolabeled MIBG in other neuroblastoma models. ^{125}I-MIBG concentrates uniformly throughout 300–400 micron neuroblastoma spheroids, while an antibody directed against neuroectodermal tissues concentrates mainly on the periphery of the spheroids [40]. ^{131}I-MIBG administered to mice with neuroblastoma xenografts concentrates in the neuroblastoma xenografts compared to normal tissues, with peak tumor uptake 6 hours

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after infusion [41]. Xenograft growth was attenuated compared to control-treated mice for up to 12 days following ^{131}I-MIBG treatment. ^{131}I-MIBG administered to produce a tumor absorbed dose of 5 Gy was as effective as 5 Gy external beam radiation in reducing tumor growth [42]. This finding is significant since the dose rate following ^{131}I-MIBG therapy is much lower than the dose rate from external beam radiation. Moreover, fractionated administration of ^{131}I-MIBG does not appear to improve the efficacy of this therapy compared to the same total dose given as a single treatment [42]. In fact, at least one experiment has suggested that multiple treatments with radiolabeled MIBG may be less effective compared with a single treatment. This experiment demonstrated that a second treatment with radiolabeled MIBG to neuroblastoma cells *in vitro* resulted in reduced cytotoxicity compared to the first treatment using the same dose [35]. The mechanism for this diminished efficacy is unclear, particularly since *in vivo* experiments have demonstrated that radiolabeled MIBG storage by neuroblastoma xenografts does not differ between initial and subsequent treatments [42].

The choice of iodine isotope for use with MIBG has been evaluated in preclinical models of neuroblastoma. Given the longer effective range of ^{131}I beta particles compared to the much shorter effective range of ^{125}I electrons, several groups have hypothesized that ^{125}I-MIBG might be better agents for the treatment of microscopic disease. In mathematical models of this issue, ^{125}I-MIBG was anticipated to produce higher dose rates in tumors ≤ 100 microns in diameter compared to ^{131}I-MIBG [43]. In contrast, ^{131}I-MIBG was anticipated to out-perform ^{125}I-MIBG for larger tumors. When this comparison was made using neuroblastoma spheroids of varying sizes, ^{125}I-MIBG and ^{131}I-MIBG were equally efficacious in the treatment of 100 micron spheroids. The effect of ^{125}I-MIBG on tumor growth remained relatively constant as spheroid size increased. In contrast, ^{131}I-MIBG became increasingly efficacious as spheroid size increased [43]. A second group replicated these findings, noting that ^{125}I-MIBG was more effective in treating neuroblastoma monolayers or 240 micron spheroids [44]. ^{125}I-MIBG was ineffective in treating 400 micron spheroids, while ^{131}I-MIBG performed well in treating these larger spheroids [36,44]. ^{125}I-MIBG has also been compared to ^{131}I-MIBG in neuroblastoma xenograft models of both macroscopic and microscopic tumors [42]. In the macroscopic tumor model, ^{125}I-MIBG was considerably less effective at slowing tumor growth compared to ^{131}I-MIBG. In the microscopic tumor model, ^{125}I-MIBG had no antitumor effect. While ^{131}I-MIBG showed some decrease in tumor growth in this microscopic disease model, the effect was much less pronounced compared with external beam total body irradiation [42]. These results support the current use of ^{131}I as the radioisotope of choice for MIBG therapy in neuroblastoma, although combination approaches may also be of future interest. These results also support the clinical observation that ^{131}I-MIBG therapy may be less efficacious for treating bone marrow micrometastatic disease (see below) [45].

An ^{131}I-MIBG formulation with no-carrier-added and therefore higher specific activity than conventional ^{131}I-MIBG has also been evaluated in preclinical models of neuroblastoma. This formulation appears to enter neuroblastoma cells using the same norepinephrine transporter as conventional ^{131}I-MIBG [46]. The cytotoxicity of the no-carrier-added formulation decreased as increasing amounts of unlabeled MIBG were added to neuroblastoma spheroids [46,47]. High specific activity ^{125}I-MIBG appeared to be more cytotoxic than conventional ^{131}I-MIBG in 500 micron neuroblastoma spheroids [48]. In neuroblastoma xenografts, tumor uptake was enhanced in mice receiving the no-carrier-added formulation compared to conventional ^{131}I-MIBG [47], although this result was not replicated by a different group [49]. Given the theoretical advantages of this formulation, no-carrier-added ^{131}I-MIBG has now entered clinical trials in children with neuroblastoma.

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Clinical Determinants of MIBG Uptake in Patients with Neuroblastoma

Only 90% of patients with neuroblastoma have MIBG-avid tumors [5,6]. The clinical determinants of MIBG-avidity remain largely unclear, though two studies have begun to address this issue. In the first study, researchers attempted to correlate the intensity of ^{123}I-MIBG tumor uptake on diagnostic scans with clinical and biologic features in 26 patients with neuroblastoma [50]. Aside from a suggestion of increased ^{123}I-MIBG uptake in larger tumors, none of the other variables correlated with intensity of ^{123}I-MIBG uptake, including degree of differentiation and *MYCN* amplification. In a second study of 54 patients with neuroblastoma, 11 tumors did not express the norepinephrine transporter by RT-PCR [5]. All six tumors that did not take up MIBG on diagnostic scans were included in this group, demonstrating a strong correlation between norepinephrine transporter expression and MIBG uptake in the clinical setting. The mechanism of MIBG uptake in the five MIBG-avid tumors that did not express the norepinephrine transporter is not clear.

Clinical Studies of MIBG Monotherapy in Neuroblastoma

Pharmacokinetics

Relatively few data describe the clearance of radiolabeled MIBG in children with neuroblastoma. In one study, six children with neuroblastoma received 100–200 mCi of ^{131}I-MIBG and had urinary MIBG levels measured following the infusion [51]. A median of 57% and 70% of the administered dose was excreted in the urine by 24 and 48 hours post-infusion, respectively. The elimination half-life during the first 44 hours post-infusion was 10.6 hours, which was slightly faster than in adult patients with neuroendocrine tumors also included in the study. A second study in seven children with neuroblastoma confirmed that 70% of the administered dose is excreted in the urine by 48 hours post-infusion [52,53]. This study included pharmacokinetic plasma sampling for one week following ^{131}I-MIBG infusion and demonstrated a mean terminal half-life of 37 hours. A third study obtained pharmacokinetic data on 17 children with neuroblastoma who received tracer doses of ^{123}I-MIBG or ^{131}I-MIBG [54]. This study demonstrated rapid clearance of MIBG from the blood, with 10% or less remaining in the blood one hour after injection. Not surprisingly, blood radioactivity did not significantly contribute to the whole body dose [55].

Early Experience

The earliest studies of MIBG therapy for patients with neuroblastoma focused mainly on the toxicity and feasibility of this approach. Some groups reported their objective response rates (complete or partial response) in these studies, though the value of this information is somewhat limited by the small sample sizes in many of these studies. The results of those pilot studies with 10 or more patients are presented here and summarized in Table 2.

Our institution treated 11 patients with refractory neuroblastoma with 100–400 mCi/m^2 of ^{131}I-MIBG [56]. The objective response rate was 18%, with two partial responses. Thrombocytopenia was the most prominent toxicity.

The Universita Cattolica in Rome treated 11 patients with refractory neuroblastoma with 70–256 mCi per cycle of therapy [57]. Seven patients received multiple cycles of therapy. The objective response rate was 18%, including one partial response and one complete response. Palliation of pain was reported in all evaluable patients.

A German study included 12 evaluable patients with relapsed or refractory neuroblastoma treated with ^{131}I-MIBG at a mean dose of 10.3 mCi/kg per cycle (range 3.6–20 mCi/kg) [58]. The objective response rate was 66%, with 2 complete responses and 6 partial responses. The

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median survival was 369 days after ^{131}I-MIBG therapy. Therapy was tolerable, with predominantly hematologic toxicity.

Another German series reported on 15 patients with relapsed or refractory neuroblastoma treated with ^{131}I-MIBG at a dose calculated to achieve 1 Gy whole body radiation dose [59]. Some patients received concomitant chemotherapy, surgery, or stem cell transplant, making treatment response difficult to assess. Nevertheless, ten patients had some degree of disease improvement with this therapy as assessed by imaging, though formal partial and complete responses were not graded.

The Children's Hospital of Philadelphia treated 17 patients with refractory neuroblastoma with ^{131}I-MIBG ranging in dose from 3.8–14.1 mCi/kg [60]. The objective response rate in evaluable patients was 31%, with all four partial responses seen in the ten patients treated with 7 mCi/kg or greater ^{131}I-MIBG. Of those patients with tumor pain at the time of MIBG therapy, 82% had a subjective decrease in pain following treatment.

An Italian center treated 21 evaluable patients with relapsed or refractory neuroblastoma [61]. Patients received 73–148 mCi of ^{131}I-MIBG per cycle of therapy. The overall response rate was 35.7%, with no complete responses reported.

The group from Genoa reported on 42 patients with relapsed or refractory neuroblastoma treated with 67–148 mCi of ^{131}I-MIBG per cycle of therapy, with 27 patients receiving more than one cycle [62]. Seven patients had a complete or partial response, for an objective response rate of 16.7%. None of the 8 patients with bone marrow involvement cleared their bone marrow with this therapy. Five patients survived for at least two years following ^{131}I-MIBG therapy.

A follow-up study from this same group included 43 patients with relapsed or refractory disease with a range of 75–162 mCi of ^{131}I-MIBG repeated up to every 4 weeks in patients benefiting from therapy [63,64]. Thirty-seven patients received multiple courses of therapy. Myelosuppression was the main toxicity. Thirteen patients (30.2%) had a complete or partial response to therapy, including one patient with a complete response.

Investigators at the University of Michigan have evaluated ^{125}I-MIBG in the treatment of relapsed or refractory neuroblastoma [65,66]. Ten patients received 224–814 mCi of ^{125}I-MIBG. Five of these patients survived for at least 18 months. At least two of these patients had bulk disease at the time of ^{125}I-MIBG therapy. This result is somewhat surprising in light of preclinical data suggesting that ^{125}I-MIBG should be most effective in treating neuroblastoma clusters less than 400 microns in size.

Formal Phase I and II Studies

Three formal phase I dose escalation studies of ^{131}I-MIBG monotherapy in patients with neuroblastoma have been performed. In the first study, 14 patients with relapsed or refractory neuroblastoma at the University of Michigan received ^{131}I-MIBG at doses escalating from 50–220 mCi [67,68]. Myelosuppression was the most notable toxicity and appeared to be more severe in patients who had previously undergone myeloablative therapy. Three patients had minor responses and one patient had a mixed response. Patients survived a median of 5.6 months following the therapy.

The United Kingdom Children's Cancer Study Group initiated another phase I study of ^{131}I-MIBG for patients with refractory stage 3 or 4 neuroblastoma [69]. Patients received a test dose of ^{131}I-MIBG followed by dosimetry studies to calculate a treatment dose that would deliver escalating whole body radiation doses. Two patients received a whole body dose of 1 Gy, 13 patients received 2 Gy, and 10 patients received 2.5 Gy. The main acute toxicities

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observed were transient mild blood pressure alterations as well as nausea and vomiting. The most prominent toxicity was myelosuppression, with the severity increasing as the whole body radiation dose increased. Thrombocytopenia was more severe than neutropenia. No patients developed febrile neutropenia. The objective response rate was 33%, with no complete responses noted. A dose-response effect was not observed. The median survival was 12 months.

In the third phase I study, 30 patients at our institution with relapsed or refractory neuroblastoma received ^{131}I-MIBG at escalating doses from 2.6 to 18.2 mCi/kg (90–819 mCi) [70]. Nonhematologic toxicity again was mild across all dose levels and consisted mainly of nausea, vomiting, transient blood pressure changes, and transient xerostomia. Myelosuppression was the most significant toxicity with this therapy and was again dose-dependent. None of the patients treated with 12 mCi/kg or less experienced prolonged neutropenia and therefore did not require autologous stem cell rescue. In contrast, 2 of 5 patients treated with 15 mCi/kg and 4 of 9 patients treated with 18 mCi/kg required stem cell rescue. The maximum tolerated dose for patients without stem cell support was therefore 12 mCi/kg. The objective response rate was 37%, with most of the responses observed in patients receiving 12 mCi/kg or higher ^{131}I-MIBG. The median survival time following treatment was 6 months.

Twenty-six patients with refractory or relapsed neuroblastoma on a French phase II study received a median of 70 mCi (range 30–108 mCi) ^{131}I-MIBG [71]. Twelve patients received multiple cycles of therapy given at a median of one month intervals between treatments. No patients had an objective response, though ten patients had stable disease for at least 8 weeks. Several patients had pain reduction. Myelosuppression was the main toxicity.

A Dutch phase II study of 53 patients with relapsed or refractory neuroblastoma prescribed 100–200 mCi of ^{131}I-MIBG [72]. The objective response rate in this study was 56%, including 7 complete responses. Only 9 patients had progressive disease as their best response to this therapy.

A phase II from UCSF, CHOP, and the University of Michigan treated 164 patients with ^{131}I-MIBG at a dose of 18 mCi/kg or 12 mCi/kg for patients with or without available autologous stem cells [45]. The overall response rate was 36%, though an additional 34% of patients had stable disease following therapy. The response rate in the 16 patients treated at the 12 mCi/kg dose level was 25% compared to 37% for patients treated at the 18 mCi/kg dose level, though this difference was not statistically significant. Predictors of response included older age, disease isolated to soft tissue alone or bone and bone marrow alone, fewer previous treatment regimens, and longer time from diagnosis to ^{131}I-MIBG treatment. The 1-year event-free survival was 18% and the 2-year overall survival was 29% (Figure 1A).

Use of Multiple MIBG Treatments in Patients with Neuroblastoma

Most of the studies described above included patients who received multiple courses of MIBG therapy. While these studies have demonstrated the feasibility of this strategy, only two reports have specifically studied multiple treatments with ^{131}I-MIBG. The first study retrospectively reported on the experience with multiple ^{131}I-MIBG treatments at our institution in 28 patients with relapsed or refractory neuroblastoma [73]. Patients in this series typically received approximately 18 mCi/kg ^{131}I-MIBG separated by a median of 98 days. Fourteen patients had a complete or partial response after the first cycle of therapy. Of the 13 patients with stable disease after the first cycle of therapy, two patients had a partial response and one patient had a mixed response after the second cycle of therapy. These results suggest that the majority of the clinical benefit with ^{131}I-MIBG therapy occurs after the first cycle of therapy, although additional responses may be observed with subsequent cycles.

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A New Approaches to Neuroblastoma Therapy (NANT) consortium study has prospectively evaluated the use of two ^{131}I-MIBG infusions given sequentially 14 days apart followed 14 days later by stem cell rescue [74]. In this phase I dose escalation study, 20 evaluable patients received a cumulative ^{131}I-MIBG dose ranging from 22 to 50 mCi/kg over the course of the two infusions. No dose limiting toxicities were noted, though 6 patients at the highest dose level developed grade 3 nonhematologic toxicities. All patients engrafted appropriately after stem cell reinfusion. The overall objective response rate was 10%, though five of 11 (45%) patients with measurable disease had a partial response based on CT scan criteria alone. Ten of 21 patients had a partial response by MIBG scan. The overall objective response rate, though, was only 10%, due mainly to persistence or progression of bone marrow disease in 13 of 15 patients. These results indicate that treatment with two sequential high doses of ^{131}I-MIBG is tolerable, but that clearing bone marrow metastatic remains a challenge with ^{131}I-MIBG monotherapy.

MIBG in Combination with Other Therapies in Neuroblastoma

Given the success of radiolabeled MIBG monotherapy in treating patients with relapsed or refractory neuroblastoma, several groups have evaluated this agent in combination with other active agents for neuroblastoma. An Italian group has reported on their experience using ^{131}I-MIBG in combination with cisplatin, an active agent against neuroblastoma and a radiation sensitizer [75,76]. Five patients with relapsed or refractory disease were treated with cisplatin on the first day of therapy and then 100 mCi ^{131}I-MIBG on the second day of therapy. This treatment was repeated one week later. Of the five patients treated with one course of this therapy, two patients had a complete response, two patients had a partial response, and one patient had a mixed response. The main reported toxicity of this regimen was myelosuppression.

This experience was extended to a larger group of patients treated with cisplatin, ^{131}I-MIBG, and other active agents in neuroblastoma [77]. Sixteen patients with relapsed or refractory neuroblastoma received cisplatin and cyclophosphamide with or without etoposide and vincristine. All patients received 200 mCi ^{131}I-MIBG on day 10. Myelosuppression was again the main toxicity. Twelve of 16 patients (75%) had a partial response with this therapy. The remaining four patients included three with stable disease and one with a mixed response. No long-term outcome data were provided in this report. The response rate with this combination therapy compares favorably with response rates of < 40% observed with ^{131}I-MIBG monotherapy, particularly given the relatively low dose of ^{131}I-MIBG used in this study.

A group in the United Kingdom has evaluated ^{131}I-MIBG together with the camptothecin topotecan [78]. Like cisplatin, topotecan is also an active drug against neuroblastoma with radiation sensitizing properties. Eight patients with relapsed neuroblastoma were treated with topotecan on Days 1–5 and 15–19 along with 12 mCi/kg of ^{131}I-MIBG on days 1 and 15. All patients received hematopoietic stem cell support on Day 27. This combination was well-tolerated and without unanticipated toxicities. Response data were not provided from this pilot study. An ongoing NANT study is evaluating the combination of ^{131}I-MIBG and another camptothecin, irinotecan, in this patient population.

Given that oxygen enhances radiation toxicity and also appears to increase MIBG uptake by neuroblastoma cells, a Dutch group evaluated ^{131}I-MIBG in combination with hyperbaric oxygen therapy [79]. All patients received 200 mCi ^{131}I-MIBG during the first cycle of therapy followed by 100 mCi in any subsequent treatments. A historical control group of 36 patients with relapsed or refractory neuroblastoma received ^{131}I-MIBG alone. This group had a mean survival of 15.4 months and an overall survival of 12% at 28 months. A second group of 27 patients received 4–5 days of hyperbaric oxygen therapy starting 2–4 days after ^{131}I-MIBG

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treatment. This group had an overall survival of 32% at 28 months. This result suggests a possible improvement in outcome with the addition of hyperbaric oxygen therapy, recognizing the limitations of drawing definitive conclusions using historic controls. Toxicity was comparable between groups. This strategy will require further study to validate these results.

MIBG as a Component of Myeloablative Therapy in Neuroblastoma

As myeloablative therapy has been demonstrated to improve the outcomes for newly diagnosed patients with advanced neuroblastoma [15,80,81], several groups have evaluated ^{131}I-MIBG in combination with myeloablative regimens. One of the first reports of this strategy treated five patients with relapsed or refractory neuroblastoma with a median of 300 mCi ^{131}I-MIBG on day 0 [82]. Patients then received high-dose chemotherapy on days 7–12 using carboplatin and melphalan with our without vincristine and etoposide. Stem cells were given on day 14. Toxicity was as expected for this type of high-dose chemotherapy regimen. All patients engrafted neutrophils. One patient with extensive bone marrow tumor involvement did not engraft platelets. Two patients survived at least 17 months following this therapy.

Another early pilot series included five patients with advanced neuroblastoma treated with ^{131}I-MIBG at a dose estimated to produce 2 Gy of whole body radiation on day 0 [83]. Patients then received melphalan on day 10 and then 12.6 Gy of total body irradiation over days 12–15 followed by stem cell infusion. Toxicity consisted mainly of expected myelosuppression and mucositis. All patients had bone marrow recovery demonstrating the feasibility of incorporating ^{131}I-MIBG into a myeloablative regimen.

Follow-up studies have focused on combining ^{131}I-MIBG with high-dose combination chemotherapy. Groups in Germany and at the University of Michigan performed pilot studies in a total of 23 patients with advanced neuroblastoma using ^{131}I-MIBG therapy followed by carboplatin, etoposide, and melphalan [84,85]. In one study, 11 patients received ^{131}I-MIBG at a median dose of 15.7 mCi/kg [84]. Once patients were released from radiation isolation, they began high-dose chemotherapy with carboplatin, etoposide, and melphalan on days -8 to -2. In the other study, 12 patients were treated with 12 mCi/kg ^{131}I-MIBG on day -21 and carboplatin, etoposide, and melphalan on days -7 to -4 [85]. Stem cells were re-infused on day 0 in both studies. Engraftment was prompt in all patients and toxicity was generally as expected for patients receiving this type of high-dose chemotherapy. Nine patients not already in complete remission achieved a complete remission with this type of therapy.

An Italian study evaluated ^{131}I-MIBG in combination with busulfan and melphalan in 17 patients with refractory neuroblastoma [86]. Patients received a median ^{131}I-MIBG dose of 7 mCi/kg followed 7–10 days later by busulfan and melphalan. Engraftment following stem cell infusion occurred as expected. Compared to a historical control group treated with similar high-dose chemotherapy but without ^{131}I-MIBG, patients treated with ^{131}I-MIBG seemed to have more gastrointestinal toxicity and required greater nutritional support. Two patients achieved a complete remission with this combination approach.

With these studies demonstrating the feasibility of incorporating ^{131}I-MIBG into autologous transplant regimens, the NANT consortium performed a phase I dose escalation study of ^{131}I-MIBG on day -21 in combination with carboplatin, etoposide, and melphalan on days -7 to -3 for patients with refractory neuroblastoma [87]. In this trial, the dose of chemotherapy was held constant and the dose of ^{131}I-MIBG was escalated starting at 12 mCi/kg. Two separate cohorts were evaluated based upon renal function at time of study enrollment, with chemotherapy dose reduction in the cohort of patients with a glomerular filtration rate of 60–99 mL/min/1.73 m^2. An ^{131}I-MIBG dose of 12 mCi/kg was identified as the maximum tolerated dose in the normal renal function cohort based on two of six and two of four patients with dose limiting toxicities at both the 15 and 18 mCi/kg dose levels, respectively. The six patients

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treated with 12 mCi/kg in the low renal function group had a higher than expected incidence of hepatic toxicity and dose escalation was not attempted in this cohort. The overall response rate was 22% with a median overall survival of 48 months (Figure 1B). Based on this promising experience in patients with refractory disease, the NANT consortium is currently conducting a phase II study of this combination in patients with refractory neuroblastoma. In addition, the Children's Oncology Group will soon open a pilot study of ^{131}I-MIBG together with carboplatin, etoposide, and melphalan followed by autologous hematopoietic stem cell transplant for consolidation in patients with newly diagnosed neuroblastoma.

MIBG Therapy for Newly Diagnosed Patients with Neuroblastoma

With the success of ^{131}I-MIBG in treating patients with relapsed or refractory neuroblastoma, several studies have incorporated this agent into the treatment of patients with newly diagnosed neuroblastoma. At one center in Amsterdam, patients with stage 4 neuroblastoma were eligible to enroll in a study of ^{131}I-MIBG given at a fixed dose of 200 mCi followed 4–6 weeks later by a second infusion of 100 mCi [88,89]. If the primary tumor was resectable after these two courses, patients proceeded to surgery. Otherwise, they received additional courses of ^{131}I-MIBG until surgery. After surgery, patients went on to receive conventional chemotherapy followed by high-dose chemotherapy with autologous stem cell rescue. Forty-one patients with stage 4 disease were treated on this protocol. The primary outcome for this study was response after two cycles of ^{131}I-MIBG. The objective response rate was 66%, including one patient with a complete response [89]. In addition, 58% of patients had a bone marrow complete response after two cycles of ^{131}I-MIBG. Of the group of 24 patients who received only ^{131}I-MIBG and surgery before initiating chemotherapy, 14 patients (58%) had a complete response after ^{131}I-MIBG and surgery. Four patients (9.8%) developed progressive disease after two courses of ^{131}I-MIBG. An additional seven patients developed progressive disease following surgery. Only 17 patients went on to receive high-dose chemotherapy with stem cell rescue. The 5-year overall survival for the 41 patients was 14.6% [89]. These results demonstrate a higher response rate of ^{131}I-MIBG in the up-front setting compared with the relapse setting. However, this agent must be incorporated into an overall treatment strategy that emphasizes the importance of both conventional chemotherapy and high-dose chemotherapy in the treatment of these patients.

Three consecutive German national trials have evaluated the role of ^{131}I-MIBG in patients with stage 4 neuroblastoma and residual MIBG-positive disease after induction therapy. In the NB85 trial, 47 patients without a complete response to induction therapy received ^{131}I-MIBG therapy with a mean dose of 8.9 mCi/kg per course [90]. The objective response rate was 46.8%. The outcome of a small subset of these patients treated with ^{131}I-MIBG and a comparison group of similar patients non-randomly chosen to not receive ^{131}I-MIBG showed no survival advantage for ^{131}I-MIBG-treated patients. In the NB97 trial, 111 patients had residual disease after induction therapy [91]. Of these patients, 36 patients non-randomly received ^{131}I-MIBG therapy prior to autologous transplant and 30 patients did not receive ^{131}I-MIBG therapy prior to transplant. The median dose of ^{131}I-MIBG on this trial was approximately 12 mCi/kg. The 3-year event-free survival for patients receiving ^{131}I-MIBG therapy was 49% compared to 33% for patients not receiving ^{131}I-MIBG. This difference was not statistically significant. The 3-year overall survival was identical between these two groups (59%). In a multivariate analysis, the use of ^{131}I-MIBG therapy did not improve outcomes. Outcomes did not differ between patients who received an ^{131}I-MIBG dose above or below the median dose of 12 mCi/kg. The ongoing NB2004 trial incorporates ^{131}I-MIBG therapy at a standard dose of 12 mCi/kg for patients with residual MIBG-positive disease after induction therapy. A prospective randomized trial of ^{131}I-MIBG combined with consolidation high-dose therapy compared to consolidation high-dose therapy alone will be required to establish the impact of ^{131}I-MIBG in consolidation.

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Use of Dosimetry and Post-treatment Scans in MIBG Therapy for Neuroblastoma

Dosimetry has been evaluated in therapeutic MIBG studies for several indications. Several groups have utilized dosimetry either from a tracer MIBG dose or from an initial therapeutic MIBG dose in order to prescribe an ^{131}I-MIBG activity calculated to produce a given whole body radiation dose [69,74,78,92]. This strategy has been effective, with calculated ^{131}I-MIBG doses typically yielding the desired whole body radiation dose. For example, one study treated 8 patients with two sequential doses of ^{131}I-MIBG with a goal total whole body radiation dose of 4 Gy [78]. The second dose of ^{131}I-MIBG was calculated based upon first dose dosimetry. The measured total whole body radiation doses ranged from 3.73 –4.65 Gy. One group determined that patients with neuroblastoma received a median of 1 cGy of whole body radiation per millicurie of ^{131}I-MIBG administered [93]. The whole body radiation dose increases approximately linearly with administered ^{131}I-MIBG dose [55]. In addition, excreted urinary activity correlates well with whole body dosimetry readings [55].

Dosimetry has also been used to estimate tumor-specific radiation dose following ^{131}I-MIBG therapy. Due to differences in intensity of tumor uptake, tumor-specific radiation dose did not correlate with prescribed ^{131}I-MIBG dose in one study [55]. In contrast, tumor-specific radiation dose correlated with treatment response, with an increased probability of treatment response in patients with tumor-specific radiation doses > 10 Gy [55]. In addition, tumor dosimetry was also used by one group to establish the effective tumor half-life of ^{131}I-MIBG in 18 patients as ranging from 35 to 95 hour [93].

A third application of dosimetry in ^{131}I-MIBG therapy has been to determine organ-specific doses. Since ^{131}I-MIBG is cleared through the urine, the bladder could receive a potentially limiting radiation dose. In five patients treated without bladder catheters, the mean bladder dose was 27 Gy, or approximately 11 cGy per mCi of ^{131}I-MIBG administered [93]. The liver and lung absorbed doses are approximately 2 and 1.3 times the whole body absorbed dose, respectively [94]. Red marrow dose appears similar to whole body dose [55].

Three reports have compared diagnostic MIBG (^{131}I-or ^{123}I-MIBG) scans with scans obtained shortly after administration of treatment doses of ^{131}I-MIBG [95–97]. In all three studies, scans performed after treatment doses of ^{131}I-MIBG revealed considerably more metastatic lesions than diagnostic scans (Figure 2). Additional sites of disease were detected in more than two-thirds of post-treatment scans. The impact of the improved sensitivity of the post-treatment scans on patient management was minimal in two of these studies as tumor stage was altered in only 2 of 15 patients and 1 of 18 patients, respectively [95,96]. Given the increased sensitivity of the post-treatment scans, it is important to compare the follow-up scan (1–2 months after treatment) to the pre-therapy scan rather than to the immediate post-treatment scan. Further study will be necessary to determine how best to utilize the additional information obtained on immediate post-treatment scans.

Acute Toxicity and Late Effects of MIBG Therapy in Patients with Neuroblastoma

Hematologic toxicity, most notably thrombocytopenia, has been reported as the main toxicity in nearly all studies of ^{131}I-MIBG therapy. The hematologic toxicity of 53 patients with relapsed or refractory neuroblastoma treated with 18 mCi/kg of ^{131}I-MIBG has been described in detail by our group [98]. In this series, 36% of patients required stem cell support for prolonged myelosuppression. Those patients who did not meet criteria for stem cell reinfusion nevertheless required platelet transfusion support for a median of 3 weeks before recovery. In contrast, patients were typically neutropenic for approximately 1 week before recovering their

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neutrophils. Hematologic toxicity was more pronounced in patients with bone marrow tumor involvement and in patients who received higher whole body radiation doses [55,98]. These results are consistent with an earlier report indicating that whole body absorbed dose was one of the best predictors of hematologic toxicity following ^{131}I-MIBG therapy [99].

In one series of nine patients with neuroblastoma treated with 12–18 mCi/kg of ^{131}I-MIBG, five patients developed bilateral parotid gland swelling shortly after ^{131}I-MIBG infusion [100]. These symptoms were associated with transient serum amylase elevations in the absence of serum lipase elevations, indicating a salivary gland process. None of the patients developed long-term xerostomia. This toxicity is not unexpected due to the known physiologic uptake of MIBG in salivary glands.

To date, MIBG therapy has mainly been used for the treatment of refractory or relapsed neuroblastoma. Since this patient population has a dismal prognosis, little is known about the late effects of MIBG therapy on these young patients. Moreover, since these patients have been heavily pre-treated with other toxic therapies, the contribution of radiolabeled MIBG to a specific late effect can be difficult to ascertain. Despite these limitations, several groups have reported their experience with thyroid dysfunction and second malignancies in patients treated with ^{131}I-MIBG for neuroblastoma.

Primary hypothyroidism appears to develop in a significant number of patients with neuroblastoma treated with ^{131}I-MIBG due to uptake of free ^{131}I by the thyroid gland. Estimates of the incidence of hypothyroidism vary widely between studies and depend upon the definition of hypothyroidism. In a series of 14 patients with neuroblastoma who survived at least two years from the time of ^{131}I-MIBG therapy, 8 patients developed symptomatic hypothyroidism requiring thyroid replacement therapy [101]. Five of these patients had not received total body external beam radiation as part of their neuroblastoma therapy. An additional 4 patients developed asymptomatic elevations in thyroid stimulating hormone (TSH) levels such that 12/14 patients (85%) in this study exhibited some degree of thyroid dysfunction despite prophylaxis with Lugol's solution for 7 days before and after ^{131}I-MIBG therapy. A larger analysis included 42 patients treated with ^{131}I-MIBG [102]. Despite 14 days of prophylaxis with Lugol's solution, thyroid uptake of ^{131}I was noted in 21% of MIBG diagnostic or post-treatment scans. Twenty-two patients (52%) developed elevations in TSH levels. In all but four patients, the TSH elevation was permanent. All patients were asymptomatic and no patients showed abnormal T4 levels. The average time to onset of TSH elevation was 1.4 years. One small series reported that a quarter of patients treated with ^{131}I-MIBG developed thyroid nodules [103].

Two reports have indicated that thyroid uptake on MIBG scans does not correlate with development of thyroid dysfunction [102,103]. In a series of 5 patients with neuroblastoma treated with multiple ^{131}I-MIBG courses ranging in dose from 50 to 150 mCi per dose, two of five patients developed hypothyroidism [104]. Thyroid dosimetry was performed on these patients and demonstrated a wide range of absorbed dose by the thyroid despite a uniform thyroid prophylaxis regimen. The results suggested that patients who developed hypothyroidism had higher thyroid absorbed doses.

The use of a more aggressive thyroid-blocking regimen may reduce the risk of thyroid toxicity. Thyroxine, methimazole, and Lugol's solution was tested in one series of patients and resulted in TSH elevations in 35% of patients [105]. At our institution and in the NANT consortium, the standard thyroid-blocking regimen consists of both potassium iodide for 45 days as well as potassium perchlorate for 5 days following ^{131}I-MIBG infusion. Following 18 mCi/kg ^{131}I-MIBG therapy, this strategy resulted in a reported incidence of 7% of hypothyroidism requiring thyroid replacement therapy [98].

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Three reports describe patients with second malignancies following ^{131}I-MIBG therapy for neuroblastoma. In one case series from our institution, three out of 95 children treated with ^{131}I-MIBG with refractory neuroblastoma developed secondary myelodysplastic syndrome (MDS) or acute myeloid leukemia [106]. These cases all developed within 1 year of ^{131}I-MIBG therapy and were characterized by variable losses of chromosome 5, 7, or 11 or by gain of chromosome 12. The cumulative incidence of developing a secondary leukemia or MDS was less than 4% at 5 years. The second report of five patients included two with leukemia, two with sarcoma, and one with malignant schwannoma diagnosed from 1.5 to 14 years following ^{131}I-MIBG therapy [107]. Curiously, the malignant schwannoma and one of the sarcomas arose within a residual differentiating neuroblastoma tumor mass, suggesting a role of the targeted radiation in secondary tumorigenesis. One patient included on the large phase II study of ^{131}I-MIBG developed peritoneal mesothelioma following therapy [45]. These cases indicate a possible increased risk of second cancers in patients treated with ^{131}I-MIBG. Given this possibility, long-term survivors after ^{131}I-MIBG therapy require ongoing surveillance.

Practical Aspects of Administering ^{131}I-MIBG Therapy to Children

Neuroblastoma is a tumor that peaks in incidence in toddlers. As such, most of the patients with neuroblastoma who receive ^{131}I-MIBG therapy are children. Use of high-dose ^{131}I-MIBG in this patient population poses challenges resulting from the radiation safety requirements associated with the administration of this therapy. These treatments require close collaboration between pediatric oncologists, nuclear medicine physicians and technologists, nursing staff, radiation safety officers, social workers, and child life specialists [108]. Potential pediatric candidates for ^{131}I-MIBG therapy should be screened carefully to ensure that they can comply with the radiation safety requirements. We routinely utilize Foley catheters during ^{131}I-MIBG treatments, particularly in young patients in order to increase their safety and the safety of their caregivers. Since it would be unacceptable for a caregiver to remain in prolonged close contact with the patient immediately following ^{131}I-MIBG administration, children must be of an appropriate developmental level to reliably remain in radiation isolation for several days. They must also be of an age at which they are not expected to remove urinary or central venous catheters if left unattended. At our institution, child life specialists provide patients with age-appropriate activities to occupy them during their time in radiation isolation. In addition, a mirror allows children in radiation isolation to see their caregivers waiting just outside of the radiation isolation room. A video camera allows the medical staff to monitor these patients without having to enter the radiation isolation room. While these strategies are very useful, in extreme circumstances, younger patients may require sedative medications in order to safely receive ^{131}I-MIBG therapy. Young children require greater assistance with meals, toileting, and personal hygiene than older patients. In order to minimize radiation exposure to nursing staff at the ^{131}I-MIBG treatment center, caregivers (typically parents) usually provide this type of care after receiving radiation safety instructions. Female caregivers should be screened for possible pregnancy prior to assuming this role. For diapered patients, soiled diapers require special handling since ^{131}I-MIBG is cleared in the urine and stool. Young children may also be reluctant to take the required oral thyroid blocking medications. Placement of a nasogastric tube for medication administration may be helpful in these instances.

Future Directions

Both preclinical and clinical data demonstrate the substantial activity of radiolabeled MIBG in neuroblastoma. Recent studies have evaluated more novel approaches. These approaches include combinations of ^{131}I-MIBG with myeloablative regimens, with chemotherapy agents with radiation sensitizing properties, or with biologic agents. As additional experience with these combination approaches is obtained, the use of these combination strategies will need to

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be rationally incorporated into the upfront management of newly diagnosed patients with high-risk disease. Combination approaches that address the decreased activity of ^{131}I-MIBG for treating small tumor deposits, such as bone marrow metastases, are required. As ^{131}I-MIBG therapy becomes more prevalent, continued study of the psychosocial implications and late effects of this treatment in a pediatric population will be necessary.

Acknowledgements

Support: Supported in part by the National Institute of Health grants PO1 CA81403, CCSG CA82103, as well by donations from the Campini Foundation, the Conner Research Fund, the Katie Dougherty Foundation, and Alex's Lemonade Stand Foundation.

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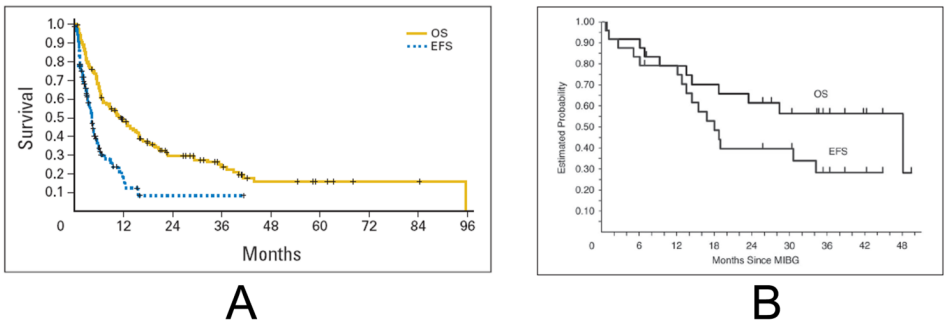

Figure 1.

A. Overall (OS) and event-free survival (EFS) of patients with relapsed or refractory neuroblastoma treated on a phase II study of high-dose ^{131}I-MIBG [45]. **B.** Overall and event-free survival of patients with refractory neuroblastoma treated on a phase I study of high-dose ^{131}I-MIBG followed by myeloablative chemotherapy with carboplatin, etoposide, and melphalan [87]. (Figures reprinted with permission from the American Society of Clinical Oncology.)

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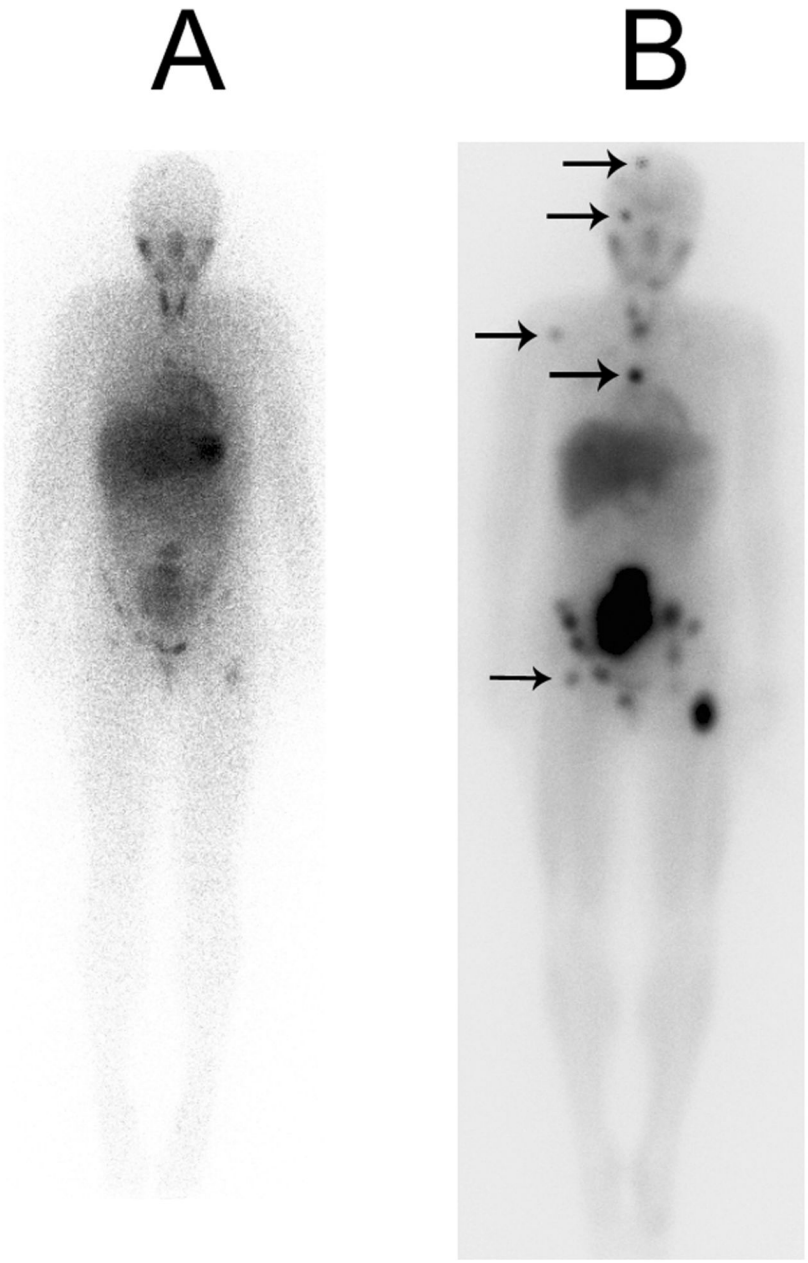

Figure 2.
Increased detection of neuroblastoma metastases on an MIBG scan obtained 5 days following 15 mCi/kg ^{131}I-MIBG (**B**) compared to a routine diagnostic scan obtained 24 hours after the administration of 5 mCi ^{123}I-MIBG (**A**). Arrows indicate tumor uptake seen on the post-treatment scan and not definitely seen on the diagnostic scan.

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Table 1

Modulators of MIBG uptake by neuroblastoma cells.

Modulator	Effect on MIBG Uptake	Reference(s)
Hypoxia	Decrease	[17]
Hyperthermia	Decrease	[29]
Chemotherapy (Cisplatin and Doxorubicin)	Increase	[30,31]
γ-Interferon	Increase	[32,33]
Cis-Retinoic Acid	Equivocal	[20,32,33]

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Table 2

^{131}I-MIBG monotherapy studies for patients with relapsed or refractory neuroblastoma. Response rate refers to percent of evaluable patients with at least a partial response to therapy as their best overall response.

Reference(s)	Number of Patients	^{131}I-MIBG Activity per Cycle	Response Rate (Complete or Partial Response)	Number of Complete Responses
Pilot or Single Institution Studies				
[56]	11	90–450 mCi (100–400 mCi/m^2)	18%	0
[57]	11	70–256 mCi	18%	1
[58]	12	Mean 10.3 mCi/kg	66%	2
[59]	15	To Yield 1 Gy Whole Body Dose	NE	NE
[60]	17	3.8–14.1 mCi/kg	31%	0
[62]	42	67–148 mCi	17%	2
[63]	43	75–162 mCi	30%	1
Formal Phase I Studies				
[67,68]	14	50–220 mCi	0	0
[69]	25	To Yield 1 Gy, 2 Gy, or 2.5 Gy Whole Body Dose	33%	0
[70]	30	90–819 mCi (2.6–18.2 mCi/kg)	37%	1
Formal Phase II Studies				
[71]	26	Median 70 mCi	0	0
[72]	53	100–200 mCi	56%	7
[45]	164	18 mCi/kg (12 mCi/kg if no stem cells)	36%	13

NE = Not evaluable

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Table 3

Combination studies of ^{131}I-MIBG in patients with relapsed or refractory neuroblastoma. Response rate refers to percent of evaluable patients with at least a partial response to therapy as their best overall response.

Reference(s)	Number of Patients	^{131}I-MIBG Activity per Cycle	Combination Regimen	Response Rate (Complete Response
Nonmyeloablative Approaches				
[75,76]	5	100 mCi × 2 doses, 1 week apart	Cisplatin 1 day prior to ^{131}IMIBG	80%
[77]	16	200 mCi on Day 10	Cisplatin and Cyclophosphamide on Days 1–4 with or without Vincristine and Etoposide	75%
[78]	8	12 mCi/kg on Days 1 and 15	Topotecan on Days 1–5 and 15–19	NR
[79]	27	200 mCi	Hyperbaric Oxygen for 4–5 Days after ^{131}I-MIBG	NR
Myeloablative Approaches				
[82]	5	300 mCi on Day 0	Carboplatin and Melphalan on Days 7–12 with or without Vincristine and Etoposide	NR
[83]	5	To Yield 2 Gy Whole Body Dose	Melphalan and 12.6 Gy Total Body Irradiation on Days 10–15	NR
[84]	11	Median of 15.7 mCi/kg ~1 Week Prior to Chemotherapy	Carboplatin, Etoposide, and Melphalan on Days -8 to -2	36%
[85]	12	12 mCi/kg on Day - 21	Carboplatin, Etoposide, Melphalan on Days -7 to -4	67%
[86]	17	Median of 7 mCi/kg	Busulfan and Melphalan 7–10 Days after ^{131}I-MIBG	47%
[87]	22	12–18 mCi/kg on Day -21	Carboplatin, Etoposide, Melphalan on Days -7 to -4	27%

NR = Not reported