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Thyroid and Hepatic Function After High-Dose ^{131}I-Metaiodobenzylguanidine (^{131}I-MIBG) Therapy for Neuroblastoma

Alekist Quach, BA,[1] Lingyun Ji, MS,[2] Vikash Mishra, MD,[1] Aimee Sznewajs, MS, PNP,[1] Janet Veatch, RN, MN,[1] John Huberty, MS,[3] Benjamin Franc, MD,[3] Richard Sposto, PhD,[2,4] Susan Groshen, PhD,[4] Denice Wei, MS,[4] Paul Fitzgerald, MD,[1] John M. Maris, MD,[5,6] Gregory Yanik, MD,[7] Randall A. Hawkins, MD,[3] Judith G. Villablanca, MD,[2] and Katherine K. Matthay, MD[1]*

Background. ^{131}I-Metaiodobenzylguanidine (^{131}I-MIBG) provides targeted radiotherapy for children with neuroblastoma, a malignancy of the sympathetic nervous system. Dissociated radioactive iodide may concentrate in the thyroid, and ^{131}I-MIBG is concentrated in the liver after ^{131}I-MIBG therapy. The aim of our study was to analyze the effects of ^{131}I-MIBG therapy on thyroid and liver function. ***Procedure.*** Pre- and post-therapy thyroid and liver functions were reviewed in a total of 194 neuroblastoma patients treated with ^{131}I-MIBG therapy. The cumulative incidence over time was estimated for both thyroid and liver toxicities. The relationship to cumulative dose/kg, number of treatments, time from treatment to follow-up, sex, and patient age was examined. ***Results.*** In patients who presented with Grade 0 or 1 thyroid toxicity at baseline, $12 \pm 4\%$ experienced onset of or worsening to Grade 2 hypothyroidism and one patient developed Grade 2 hyperthyroidism by 2 years after ^{131}I-MIBG therapy. At 2 years post-^{131}I-MIBG therapy, $76 \pm 4\%$ patients experienced onset or worsening of hepatic toxicity to any grade, and $23 \pm 5\%$ experienced onset of or worsening to Grade 3 or 4 liver toxicity. Liver toxicity was usually transient asymptomatic transaminase elevation, frequently confounded by disease progression and other therapies. ***Conclusion.*** The prophylactic regimen of potassium iodide and potassium perchlorate with ^{131}I-MIBG therapy resulted in a low rate of significant hypothyroidism. Liver abnormalities following ^{131}I-MIBG therapy were primarily reversible and did not result in late toxicity. ^{131}I-MIBG therapy is a promising treatment for children with relapsed neuroblastoma with a relatively low rate of symptomatic thyroid or hepatic dysfunction. Pediatr Blood Cancer 2011;56:191–201. © 2010 Wiley-Liss, Inc.

Key words: hypothyroidism; ^{131}I-MIBG; neuroblastoma

INTRODUCTION

Neuroblastoma, the most common extra-cranial solid tumor in children, is an embryonal tumor derived from the peripheral sympathetic nervous system. It is highly malignant, with metastatic disease at diagnosis in half of cases. Despite improvement in outcome with intensification therapy and treatment of minimal residual disease, 15% of patients have disease that is refractory to induction chemotherapy, and more than 50% of patients who achieve initial remission ultimately relapse and die as a result of their disease [1].

Metaiodobenzylguanidine (MIBG) is a guanethidine derivative and analogue of norepinephrine with specific affinity for neural crest tissues. When labeled with iodine-131 (^{131}I-MIBG), MIBG has shown activity against neuroblastoma, with response rates for refractory disease varying from 20% to 37% [2–10]. In a Phase II clinical trial of 164 patients, the response rate (complete and partial) for all patients was 36% [2]. While ^{131}I-MIBG has typically been used as a single agent in relapsed disease, several groups have increasingly used ^{131}I-MIBG alone earlier in the course of disease or combined with chemotherapy [11–16]. With this expanding role, an understanding of the late toxicity of ^{131}I-MIBG has become increasingly important.

The most common toxicities associated with high-dose ^{131}I-MIBG targeted radiotherapy are primarily hematologic, with almost all patients requiring at least one platelet or red cell transfusion and with most patients developing neutropenia. Approximately 36% of patients also require autologous hematopoietic stem-cell rescue (ASCR) after ^{131}I-MIBG treatment [17]. The chief non-hematological toxicities reported with ^{131}I-MIBG therapy include transient nausea and vomiting, sialoadenitis, transient hepatic abnormalities, later adrenal insufficiency (<1%), and variable rates of hypothyroidism [18–24]. Secondary malignancies such as acute myelogenous leukemia and myelodysplastic syndrome have also been reported in 3–5% of children who have received ^{131}I-MIBG therapy to treat relapsed or refractory neuroblastoma [2,25,26].

Thyroid function and liver function after ^{131}I-MIBG therapy are of particular interest because the radioactivity is often concentrated in these organs. Both the thyroid and the liver can be visualized

[1]Department of Pediatrics, UCSF Children's Hospital, University of California, San Francisco, California; [2]Children's Center for Cancer and Blood Diseases, Children's Hospital Los Angeles, Los Angeles, California; [3]Nuclear Medicine Program, Department of Radiology, University of California San Francisco, UCSF Children's Hospital, San Francisco, California; [4]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California; [5]Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; [6]University of Pennsylvania, Philadelphia, Pennsylvania; [7]Department of Pediatrics, University of Michigan and Mott Children's Hospital, Ann Arbor, Michigan

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*Correspondence to: Katherine K. Matthay, Department of Pediatrics, University of California San Francisco, 505 Parnassus, M647, San Francisco, CA 94143-0106. E-mail: matthayk@peds.ucsf.edu

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on the 96 hr post infusion ^{131}I-MIBG scan after ^{131}I-MIBG therapy and the dissociated anion may be specifically concentrated in the thyroid. However, limited data are available to assess the acute and late effects of ^{131}I-MIBG therapy on thyroid and liver function. Reports of hypothyroidism following ^{131}I-MIBG therapy have been highly variable, with incidence rates ranging from 15% to 64% of patients. There has also been little systematic examination and no reports of late liver dysfunction associated with ^{131}I-MIBG therapy [19–23].

We report here an analysis of thyroid and liver function for neuroblastoma patients with follow-up data after receiving therapy with ^{131}I-MIBG. We examined the relationship between liver and thyroid toxicity incidence and cumulative ^{131}I-MIBG dose/kg, number of treatments, sex, and patient age at the time of therapy. We also analyzed the relation of thyroid dysfunction with thyroid visualization on post-therapy 96 hr scans.

METHODS

Study Subjects

All evaluated patients either failed to achieve partial or complete response with standard induction therapy or developed progressive disease at any time prior to ^{131}I-MIBG therapy. All patients had demonstrated ^{131}I-MIBG uptake in skeletal or soft tissue prior to treatment. The vast majority of patients were heavily pre-treated, with a median of three prior regimens, and almost all had prior radiation therapy and surgery. All patients had total bilirubin $\leq 2\times$ normal for age and aspartate transaminase (AST) and alanine transaminase (ALT) $<5\times$ normal for age. All patients were fully recovered from the toxic effects of prior therapy.

Eligibility for inclusion in this analysis included evaluation of baseline thyroid and liver function and at least one post-therapy value for thyroid function tests (thyroid stimulating hormone (TSH), free T4, or T4) and/or liver function tests (AST, ALT, total bilirubin). Patients were enrolled on therapeutic trials with ^{131}I-MIBG, and appropriate informed consent was obtained for all patients with approval by the institutional human research review board and radiation safety committee at treating institutions.

Treatment

Patients were treated between August 30, 1996 and May 1, 2008 on six clinical trials using ^{131}I-MIBG therapy. These studies included patients from the following clinical trials: a multi-institutional Phase II study of 18 mCi/kg [2], an ongoing UCSF compassionate use study of ^{131}I-MIBG, NANT 99–01—a Phase I study of ^{131}I-MIBG with myeloablative chemotherapy [11], NANT 2000–01—a double infusion of ^{131}I-MIBG (24–42 mCi/kg) [27], NANT 2001–02—^{131}I-MIBG (12 mCi/kg) with myeloablative chemotherapy, and NANT 2004–06—irinotecan and vincristine with ^{131}I-MIBG (8–15 mCi/kg) (www.nant.org).

The ^{131}I-MIBG for the studies was supplied either by the Michigan Memorial Phoenix Laboratory at the University of Michigan (Investigational New Drug 17,239; Ann Arbor, MI), Draximage Radiopharmaceuticals (Investigational New Drug 76,227; Kirkland, Quebec, Canada), or the University of California at San Francisco (Investigational New Drug 32,147; San Francisco, CA). Patients received ^{131}I-MIBG infusions at the University of California, San Francisco, Children's Hospital of Philadelphia, University of Michigan, and Cincinnati Children's Hospital Medical Center. All ^{131}I-MIBG products had a free iodide content of $<5\%$. Patients who were treated on NANT 99–01, NANT 2001–02, and NANT 2004–06 received chemotherapy in combination with ^{131}I-MIBG therapy and were therefore excluded from liver function analyses.

Patients were treated with 1–3 therapeutic doses of ^{131}I-MIBG, given intravenously over 1–2 hr with hydration and a Foley catheter for bladder protection. All patients remained in radiation-protected isolation for 2–7 days until radiation emissions met institutional regulations. The dose of radiation to the whole body from ^{131}I-MIBG was calculated for every patient using multiple measurements from a hand-held or ceiling-mounted Geiger counter [28].

Thyroid Protection

To protect the thyroid from any dissociated 131-iodide from the therapeutic doses of ^{131}I-MIBG, patients were given an oral loading dose of 6 mg/kg of KI solution 8–12 hr prior to ^{131}I-MIBG infusion, then 1 mg/kg every 4 hr on days 0–6, and 1 mg/kg/day through day 45 post-infusion. Potassium perchlorate was also given as an additional oral blocking agent for 5 days post-infusion with a loading dose of 8 mg/kg, then 2 mg/kg every 6 hr on days 0–4, beginning 4 hr after the start of ^{131}I-MIBG infusion.

Monitoring

Patients on all studies were monitored weekly for a minimum of 6 weeks or until recovery from toxicity. Tumor response evaluations and hematologic, hepatic, renal, and endocrine toxicity evaluations were required at 3-month intervals for 1 year, then every 6 months, or until the patient died or went on to other therapy. Baseline abnormalities were noted if available.

Scan Review

A post-infusion ^{131}I-MIBG scan (median time of 96 hr post-infusion (range: 72–120 hr)) was performed for all patients receiving ^{131}I-MIBG therapy. Post-therapy scans were reviewed by a nuclear medicine radiologist at the University of California, San Francisco for thyroid visualization. ^{131}I-MIBG uptake in the thyroid was semi-quantitatively scored using a point scale: 0 = no uptake, 1 = faint uptake, 2 = definite uptake, 3 = intense uptake. For patients who had more than one scan available, the scan with the highest review assessment was used in the analyses.

Evaluation of Thyroid Dysfunction at Baseline and After ^{131}I-MIBG Therapy

Pre- and post-therapy TSH and T4 (free T4 when available) values were collected from medical records. Any symptomatology and/or use of thyroid hormone replacement therapy were noted. Abnormal thyroid function at baseline or time points after ^{131}I-MIBG treatment was defined as TSH and/or T4 concentrations outside of the institutional normal ranges or if patients were noted to be receiving thyroid hormone replacement therapy at that time. Toxicity grade was determined based on CTC v3.0. For TSH and T4 lab values that did not have normal ranges, national age and sex-adjusted normal ranges were used. If one of the two thyroid function measures was not available for a particular time point, only the available measure was evaluated for thyroid function. This type of missing

data was very limited, and treating missing TSH or T4 values as normal did not significantly influence the results of the analyses.

Evaluation of Liver Dysfunction at Baseline and After ^{131}I-MIBG Therapy

Liver function tests, including AST, ALT, and total bilirubin, were closely monitored and recorded pre-therapy and then weekly for the first 6 weeks after therapy and repeated at 3-month intervals for 1 year, then every 6 months, or until the patient died or went on to other therapy. Pre- and post-therapy liver functions were collected and hepatic toxicity was compared to the institutional normal ranges and graded using CTC v2.0 or CTC v3.0 per study protocol. If a normal range at a time point was missing for a patient, the normal range from another time point for the same patient was used, considering that the normal ranges were very similar across different time points. If one or two of the three liver function measures were not available for a particular time point, only the available measures were evaluated for liver toxicity. This type of missing data was limited, and treating missing lab values as normal did not significantly influence the results of the analyses.

Statistical Methods

The cumulative incidence function over time was estimated for both thyroid and liver toxicities [29]. In the analysis of the thyroid data, we evaluated (a) the onset or worsening of thyroid toxicity to Grade 2 (the highest grade of thyroid toxicity in our data) after ^{131}I-MIBG therapy and (b) the onset or worsening of thyroid toxicity to any grade (Grade 1 or 2) after ^{131}I-MIBG treatment. In (a), a change from baseline Grade 0 or 1 to Grade 2 thyroid toxicity post-^{131}I-MIBG therapy was considered an event. In (b), a change from baseline Grade 0 to Grade 1 or 2 after ^{131}I-MIBG treatment, or a change from baseline Grade 1 to Grade 2 after ^{131}I-MIBG treatment was considered an event. Patients who did not experience events defined above were censored at the time of the last test date. Patients with Grade 2 thyroid abnormality at baseline were excluded from the cumulative incidence analysis because medical management of thyroid abnormality made it unlikely for these patients to experience a further worsening of thyroid function after ^{131}I-MIBG treatment. Similarly, in the analysis of the liver data, we evaluated (a) the onset or worsening of liver toxicity to Grade 3 and 4 after ^{131}I-MIBG treatment and (b) the onset or worsening of liver toxicity to any grade (Grade 1, 2, 3, or 4). In (a), a change from baseline Grade 0, 1, or 2 liver abnormality to Grade 3 or 4 after ^{131}I-MIBG therapy was considered an event, and in (b), a change from baseline Grade 0 to Grade $\geq$1, or a change from baseline Grade 1 to Grade $\geq$2, or a change from baseline Grade 2 to Grade $\geq$3 was considered an event. Patients who did not experience an event defined above were censored at the time of the last test date. The "time 0" reference for all cumulative incidence analysis was the date of the first ^{131}I-MIBG treatment.

Analysis of toxicity cumulative incidence and its dependence on patient and disease characteristics was based on the log-rank test, product-limit (Kaplan–Meier) estimator, and univariate and multivariate Cox regression analysis [30]. The cumulative dose of ^{131}I-MIBG/kg was included as a time-dependent covariate in the Cox regression analysis. Missing data for variables used in multivariate analysis were included in the models as a "missing" category. All *P*-values are two-sided. Estimates of hazard ratio are presented with 95% confidence intervals. Statistical computation was performed using Stata 9.2 [31].

RESULTS

Analysis Cohort

A total of 194 patients were reviewed for thyroid and liver function. Of these patients, 160 had documented thyroid function values before and after ^{131}I-MIBG therapy and were evaluable for thyroid toxicity, and 136 had documented liver function values before and after ^{131}I-MIBG therapy and were evaluable for liver toxicity (Table I). Thyroid and liver data were both available in 102 patients.

Table I, patient characteristics, shows that this was a heavily pre-treated group of patients, and that approximately 25% of them had more than one ^{131}I-MIBG therapy. The median cumulative ^{131}I-MIBG dose was 18.2 mCi/kg (range: 5.0, 54.2). The median time to the last follow-up thyroid function test was 3.5 months, but 36 patients had follow-up thyroid function test results that were obtained 12 months or more after ^{131}I-MIBG therapy. Thirty-eight (24%) patients presented with abnormal thyroid function values at baseline, including one patient with an X-linked TBG deficiency that pre-disposed him to hypothyroidism, and seven patients who were on L-thyroxine prior to receiving ^{131}I-MIBG therapy. Among the 136 patients evaluable for liver toxicity, the distribution of age, sex, the number of prior regimens, and cumulative ^{131}I-MIBG dose was very similar to that with thyroid data (Table I). Thirty-eight (28%) patients showed baseline liver function abnormality.

Thyroid Abnormalities Following ^{131}I-MIBG Therapy

Of the 160 patients evaluable for thyroid function following ^{131}I-MIBG therapy, 7 patients had Grade 2 thyroid toxicity at baseline and remained Grade 2 after ^{131}I-MIBG treatment. Thirty-one had Grade 1 abnormalities at baseline, and of these, 6 progressed to Grade 2 hypothyroidism, and 14 normalized without intervention. Of the 122 patients with normal baseline thyroid function, 3 developed Grade 2 hypothyroidism and 1 patient developed Grave's disease and had subsequent thyroidectomy. In all, 36 patients experienced an onset or worsening of thyroid function tests after ^{131}I-MIBG therapy, including 9 who developed Grade 2 hypothyroidism requiring treatment with L-thyroxine (Fig. 1).

Table II and Figure 2A summarize cumulative incidence of onset or worsening of thyroid toxicities after ^{131}I-MIBG therapy and its relationship with other factors. The seven patients who had Grade 2 thyroid function abnormality at baseline were excluded from the cumulative incidence analysis. In the remaining patients, $15 \pm 5\%$ experienced onset of or worsening to Grade 2 hypothyroidism or hyperthyroidism by 2 years after ^{131}I-MIBG treatment, and $40 \pm 7\%$ of patients experienced onset or worsening of any grade (Fig. 2A). In univariate and multivariate Cox regression analyses, the risk of Grade 2 toxicity was significantly higher in patients with baseline Grade 1 thyroid abnormality compared to those with normal baseline thyroid function (Table II). The 2-year cumulative incidence rates in these two groups were $35 \pm 14\%$ and $10 \pm 5\%$, respectively. In the analyses of onset or worsening of any grade thyroid toxicity, there was no significant association with baseline thyroid function. Age, sex, the number of previous chemotherapy and biotherapy regimens, thyroid uptake, and cumulative ^{131}I-MIBG dose did not have a significant impact on thyroid toxicity.

TABLE I. Characteristics of Patients With Thyroid and/or Liver Data

Patient characteristics[a]	Thyroid, all patients (N = 160)	Liver, all patients (N = 136)
Age at study entry (years)		
Median (range)	6.8 (1.5–30.2)	6.9 (1.4–30.2)
<12	127 (79%)	109 (80%)
12–21	29 (18%)	24 (18%)
>21	4 (3%)	3 (2%)
Sex		
Males	101 (63%)	82 (60%)
Females	59 (37%)	54 (40%)
Number of prior regimens		
Median (range)	3 (1–11)	3 (1–11)
1	11 (7%)	6 (5%)
2	43 (27%)	22 (16%)
3	45 (28%)	44 (32%)
4	22 (14%)	25 (18%)
5–11	39 (24%)	39 (29%)
^{131}I-MIBG Clinical Trial (number of patients evaluated)		
Phase II ^{131}I-MIBG, compassionate use ^{131}I-MIBG (^{131}I-MIBG alone)	99 (62%)	116 (85%)
NANT 99–01, NANT 2001–02 (^{131}I-MIBG + CEM + AHSCT)	33 (21%)	—
NANT 2000–01 (rapid double sequence ^{131}I-MIBG)	19 (12%)	20 (15%)
NANT 2004–06 (^{131}I-MIBG + irinotecan + vincristine)	9 (5%)	—
Number of ^{131}I-MIBG treatments		
1 treatment (%)	121 (76%)	106 (78%)
2 treatments (%)	32 (20%)	25 (18%)
3 treatments (%)	7 (4%)	5 (4%)
Cumulative ^{131}I-MIBG dose/kg (mCi)		
Median (range)	18.2 (5.0–54.2)	18.5 (6.3–54.2)
Length of time from treatment to furthest follow-up (months)		
Median (range)	3.5 (0.8–88.2)	7.4 (0.1–90.5)
<3 months	75 (47%)	40 (29%)
≥3 to <6 months	25 (16%)	20 (15%)
≥6 to <12 months	24 (15%)	27 (20%)
≥12 to <24 months	12 (7%)	20 (15%)
≥24 months	24 (15%)	29 (21%)
Patients with baseline abnormalities		
Yes	38 (24%)	38 (28%)
No	122 (76%)	98 (72%)
Thyroid uptake seen on post-96 hr ^{131}I-MIBG scan		
None	54 (52%)	—
Faint	20 (19%)	—
Definite	25 (24%)	—
Strong	5 (5%)	—
Not evaluable	11	—
Missing/no scan	45	—

[a]One hundred ninety-four total individual patients reviewed; 102 patients had both thyroid and liver data. Evaluable patients for liver and thyroid toxicity evaluations were those with submitted laboratory values. Patients who did not have submitted thyroid and/or liver data either died <3 months after receiving ^{131}I-MIBG therapy, started new therapy <3 months after receiving ^{131}I-MIBG therapy, or were lost to follow-up. Only patients who received ^{131}I-MIBG therapy alone, without chemotherapy, were evaluable for liver toxicity.

Analysis of the cumulative incidence of hypothyroidism alone after ^{131}I-MIBG therapy showed that at 2 years after treatment, $32 \pm 6\%$ of patients experienced an onset or worsening of any grade hypothyroidism, and $12 \pm 4\%$ had experienced onset of or worsening to Grade 2 hypothyroidism.

Liver Function Following ^{131}I-MIBG Therapy

Out of the 136 patients with documented liver function values following ^{131}I-MIBG therapy, 98 had normal liver function at baseline, of whom 20 remained normal after ^{131}I-MIBG therapy, 14 experienced Grade 3 or 4 hepatic toxicities, and 64 experienced Grade 1 or 2 toxicity after treatment. Thirty-eight patients had Grade 1 or 2 liver toxicity at baseline, of whom 7 worsened to Grade 3 or 4 after ^{131}I-MIBG therapy, 7 worsened from Grade 1 to Grade 2, 17 remained the same grade, 1 decreased from Grade 2 to Grade 1, and 6 normalized without intervention. No patient had Grade 3 or 4 liver abnormalities at baseline. Of the 136 patients, a total of 18 patients experienced Grade 3 elevation of at least one measure, and a total of 3 patients experienced Grade 4 elevations (Table III).

At 2 years post-^{131}I-MIBG therapy, $76 \pm 4\%$ patients had experienced onset or worsening of hepatic toxicities to any grade (Grade

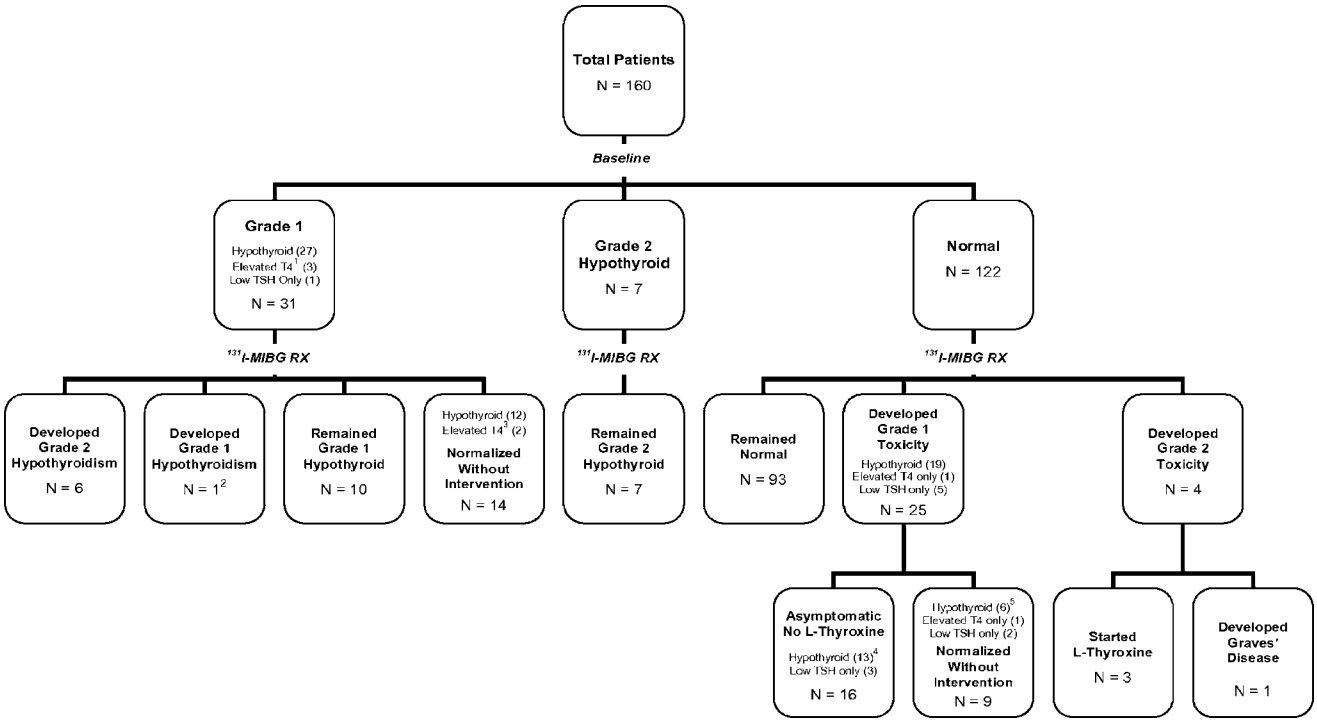

Fig. 1. Flowchart of all patients with pre- and post-therapy thyroid data. [1]Two patients had elevated T4 only, and one patient had both elevated T4 and low TSH. [2]This patient had Grade 1 low TSH only at baseline, but devloped Grade 1 hypothyroidism after ^{131}I-MIBG treatment. [3]One pateint had elevated T4 only and one patient had both elevated T4 and low TSH. [4]Of these patients, nine developed compensated hypothyroidism. [5]Of these patients, three developed compensated hypothyroidism.

1, 2, 3, or 4) (Fig. 2B). Most of these toxicities were of Grade 1 or 2. $23 \pm 5\%$ of patients had experienced onset of or worsening to Grade 3 and 4 liver toxicity (Fig. 2B). Table IV summarizes the relationship between cumulative incidence of onset or worsening of liver toxicities after ^{131}I-MIBG treatment and the other factors among patients reviewed for liver function. In Cox regression analysis, there was no significant association between baseline liver function and the risk of Grade 3 or 4 liver toxicity (Table IV). However, there was a significant association between baseline liver functioning and onset or worsening of any grade liver toxicity. Patients with abnormal liver function at baseline had a significantly lower risk of progressing to a higher grade toxicity than patients with normal liver function at baseline ($P < 0.0001$ in both the univariate and multivariate analyses; Table IV). By 2 years after ^{131}I-MIBG treatment, $84 \pm 4\%$ of patients with normal liver function at baseline and $48 \pm 10\%$ of patients with abnormal liver function at baseline had progressed to higher grade toxicity. The above results indicated that the risk of worsening to Grade 3 or 4 liver toxicity post-^{131}I-MIBG treatment was similar between patients with normal (Grade 0) or abnormal (Grade 1 or 2) baseline liver function, but the risk of worsening into Grade 1 or 2 after ^{131}I-MIBG treatment for patients who were normal at baseline was higher than the risk of worsening into Grade 2 for patients who had Grade 1 liver abnormality at baseline. Age, gender, and the number of previous chemotherapy or biotherapy regimens were not significantly associated with onset of or worsening to Grade 3 and 4 or onset or worsening of any grade hepatic toxicity. However, cumulative ^{131}I-MIBG dose showed a trend to be associated with onset or worsening of liver toxicities of any grade ($P = 0.079$ in the univariate analysis and was significantly associated ($P = 0.027$) in the multivariate analysis), but it was not associated with incidence of Grade 3 and 4 hepatic toxicity.

Of the 21 patients who had Grade 3 or 4 hepatic toxicities after ^{131}I-MIBG therapy, only 8 were considered to be possibly related to the ^{131}I-MIBG therapy; the remainder were coded as "unlikely." For these eight patients, the median follow-up time to the date of first abnormality was 1 month (range: 0.5–9 months). All abnormal values returned to normal after a median time of 15 days (Table III). The Grade 3 or 4 toxicities for the remaining 13 patients were deemed to be unlikely related to the ^{131}I-MIBG therapy (Table III). The recorded abnormal post-therapy values for those 13 patients occurred at a median time of 6 months (range: 2–44 months) after ^{131}I-MIBG therapy. The factors that probably contributed towards the occurrence of the Grade 3 or 4 liver toxicities among those 13 patients included: other subsequent therapy for neuroblastoma (N = 4), active infections (N = 2), progressive disease (N = 3), or progressive disease and other therapy (N = 4). Other therapies included hu14.18-IL2, myeloablative chemotherapy in preparation for hematopoietic cell transplant, and 13-*cis*-retinoic acid [32].

DISCUSSION

This large follow-up study including 194 patients after ^{131}I-MIBG therapy shows that with proper preventive therapy, damage to the thyroid gland is uncommon and rarely clinically significant. Permanent serious damage to the liver was not evident; most changes

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TABLE II. Cox Proportional Hazards Model of Cumulative Incidence of Onset or Worsening of Thyroid Toxicity From the Start of ^{131}I-MIBG Treatment

		Onset of or worsening to Grade 2[a]				Onset of or worsening to any grade (Grades 1 and 2)[b]			
		Univariate		Multivariate		Univariate		Multivariate	
Variables	N	HR[c]	95% CI[c]	HR[d]	95% CI[d]	HR[c]	95% CI[c]	HR[d]	95% CI[d]
Age at study entry									
<12 years	122	1.0	—	1.0	—	1.0	—	1.0	—
≥12 years	31	0.61	0.13, 2.9	0.44	0.08, 2.3	1.1	0.52, 2.4	1.3	0.58, 2.8
		$P=0.51$		$P=0.30$		$P=0.76$		$P=0.54$	
Sex									
Female	58	1.0	—	1.0	—	1.0	—	1.0	—
Male	95	0.77	0.22, 2.7	0.82	0.21, 3.2	1.9	0.87, 4.2	1.9	0.84, 4.3
		$P=0.69$		$P=0.77$		$P=0.09$		$P=0.11$	
Baseline thyroid function									
Normal	122	1.0	—	1.0	—	1.0	—	1.0	—
Abnormal	31	5.0	1.4, 18.1	5.6	1.4, 21.3	0.79	0.34, 1.9	0.83	0.35, 2.0
		$P=0.014$		$P=0.013$		$P=0.58$		$P=0.66$	
Number of previous chemotherapy and biotherapy regimens[e]									
Relative risk increase per regimen	153	0.90	0.60, 1.4	0.91	0.57, 1.5	1.1	0.92, 1.3	1.1	0.89, 1.3
		$P=0.60$		$P=0.70$		$P=0.29$		$P=0.45$	
Thyroid uptake[f]									
No	50	1.0	—	1.0	—	1.0	—	1.0	—
Yes (faint, definite, or strong)	49	1.3	0.22, 7.1	1.8	0.31, 10.6	1.0	0.44, 2.3	0.9	0.37, 2.2
Missing/no scan/not evaluable	54	$P=0.80$		$P=0.50$		$P=0.98$		$P=0.81$	
Cumulative ^{131}I-MIBG dose/kg (mCi)[e]									
Relative risk increase per 18 mCi/kg	153	1.3	0.41, 4.5	1.1	0.35, 3.5	1.02	0.51, 2.0	1.03	0.49, 2.1
		$P=0.63$		$P=0.87$		$P=0.96$		$P=0.94$	

HR, hazard ratio; CI, confidence interval. [a]Events included an increase in thyroid toxicity from baseline Grade 0 to Grade 2 after ^{131}I-MIBG treatment, or from baseline Grade 1 to Grade 2 after ^{131}I-MIBG treatment; [b]Events included an increase in thyroid toxicity from baseline Grade 0 to Grade 1 or 2 after ^{131}I-MIBG treatment, or from baseline Grade 1 to Grade 2 after ^{131}I-MIBG treatment; [c]HR's and CI's from univariate Cox models; [d]HR's and CI's from Cox models adjusting the other variables in the table; [e]Variables were treated as continuous in the models; [f]Missing data for these variables were included in the models as a "missing" category.

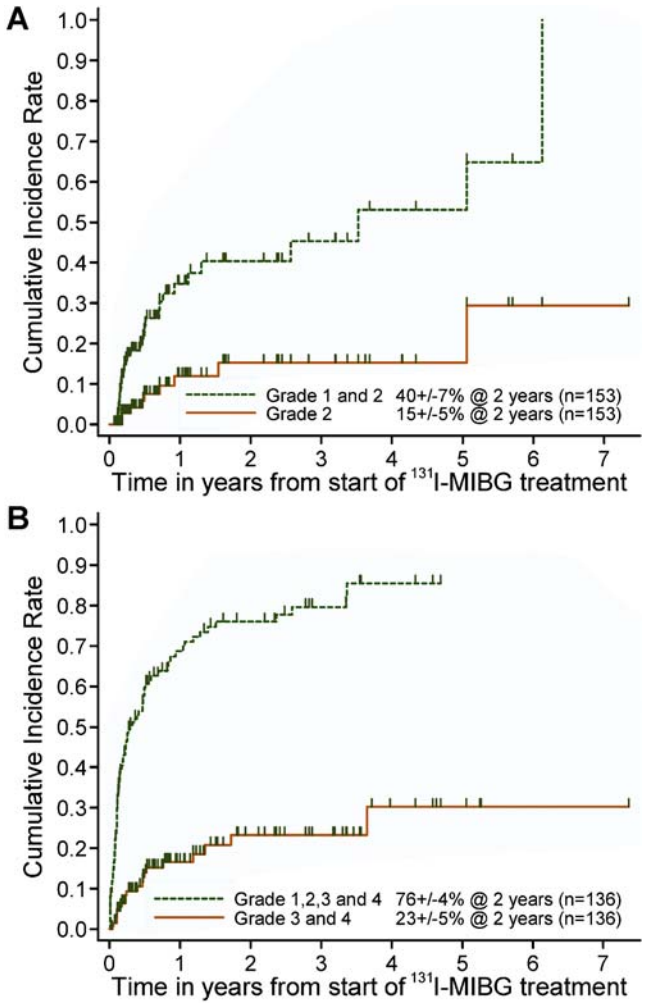

Fig. 2. Cumulative incidence of increased thyroid and liver toxicity after ^{131}I-MIBG treatment (see the Statistical Methods Section). **A**: Soild line is cumulative incidence of onset of or worsening to Grade 2 thyroid toxicity compared to baseline. Dashed line is cumulative incidence of onset of or worsening to either Grade 1 or 2 thyroid toxicity compared to baseline. **B**: Solid line is cumulative incidence of onset of or worsening to Grade 3 or 4 liver toxicity compared to baseline. Dashed line is cumulative incidence of onset or worsening of any grade liver toxicity compared to baseline.

were reversible and not clinically significant. In our study, the onset of symptomatic (Grade 2) hypothyroidism at 2 years post-therapy was only $12 \pm 4\%$, while worsening of thyroid function of any degree occurred in $40 \pm 7\%$ of children by 2 years after ^{131}I-MIBG therapy. Elevations of liver function tests were more common, with elevations to Grade 3 or 4 seen in $23 \pm 5\%$ of patients by 2 years. The liver toxicity, however, was significantly confounded by other contributing conditions, including other therapies, infections, and disease progression. Out of the 136 patients evaluated for liver toxicity, only 8 had early ^{131}I-MIBG-related Grade 3 and/or Grade 4 hepatic toxicity, without other concomitant conditions, almost always transient.

Due to some dissociation of ^{131}I-MIBG, free iodide contamination of the product, and the biologic degradation of ^{131}I-MIBG by the liver, free radioiodide is released and may be taken up by the thyroid gland, leading to radiation damage [21,33]. In order to prevent damage to the thyroid, stable, non-radioactive iodide ion such as potassium iodide is administered to patients prior to ^{131}I-MIBG therapy to pre-saturate the thyroid. However, based on a study by Picco et al. [22], primary hypothyroidism occurred in 12/14 patients after ^{131}I-MIBG therapy, typically within 6–12 months of administration, despite using potassium iodide as a thyroid blocking agent. In another study of 10 patients conducted by Brans et al. [23], 40% of patients developed hypothyroidism after a mean follow-up time of 11 months, indicating that potassium iodide administration alone was inadequate to protect the thyroid. H.M. van Santen et al. similarly concluded in a separate study that using potassium iodide only for radiation protection of the thyroid gland during ^{131}I-MIBG treatment in children was less effective than expected. In van Santen's study, up to 64% of 42 children with neuroblastoma treated with ^{131}I-MIBG (median three therapies) developed TSH elevation, indicating thyroid dysfunction, after an average of 2.3 years [21].

To decrease hypothyroidism in patients who receive ^{131}I-MIBG therapy, van Santen conducted another study using a combination of thyroxine, methimazole, and potassium iodide for thyroid protection and demonstrated that this combination appeared more effective than using potassium iodide alone. With the combination of thyroxine, methimazole, and potassium iodide, the hypothyroidism rate in 23 patients with median follow-up of 19 months dropped to 14% thyroid dysfunction following ^{131}I-MIBG therapy [20].

Using CTC v.3 criteria, the results of our study revealed a $40 \pm 7\%$ cumulative incidence rate of onset or worsening of thyroid toxicity of any grade at 2 years after ^{131}I-MIBG therapy in the patients who used a thyroid protection regimen of both potassium iodide and potassium perchlorate. The cumulative incidence rate of onset of or worsening to symptomatic hypothyroidism alone was $12 \pm 4\%$. Using thyroid toxicity evaluation criteria similar to that of Picco and van Santen who both used elevated TSH to determine thyroid toxicity in their studies, our study showed 12 out of 122 patients with normal baseline thyroid function presented with Grade 1 compensated hypothyroidism after ^{131}I-MIBG therapy, and 3 out of 122 patients required hormone replacement therapy after treatment, including 1 patient with a family history of hypothyroidism.

The most significant difference between prior studies and the current study was the thyroid blocking regimen used before and after ^{131}I-MIBG treatment. Rather than using potassium iodide alone or in combination with thyroxine and methimazole, prolonged 6 weeks of administration of potassium iodide was used with 5 days of potassium perchlorate in all six clinical trials reviewed for this study. Based on the decreased incidence of symptomatic hypothyroidism observed in this study, the combination of potassium iodide and potassium perchlorate appears to be more effective than most of the previously used regimens in protecting the thyroid from ^{131}I-MIBG therapy. However, even with the use of potassium iodide and potassium perchlorate, 29% of patients with evaluable immediate post-therapy scans showed definite or strong thyroid uptake, and 19% of patients showed faint thyroid uptake. However, none of the three patients with normal baseline who were treated with L-thyroxine post-therapy had definite or intense thyroid uptake on their post-therapy scans. Cox regression analyses did not reveal significant association between thyroid uptake and the cumulative incidence of onset or worsening of thyroid toxicity (Table II). This is consistent with van Santen, who also reported no correlation between thyroid dysfunction and thyroid visualization after ^{131}I-MIBG administration.

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TABLE III. Summary of Grade 3 and 4 Liver Toxicities Post-^{131}I-MIBG Therapy

PT #	Liver toxicity attribution[a]	Number of RXs prior to toxicity	Baseline liver status	mCi/kg	Months RX–FX[b]	Highest toxicity grade			Days to <Grade 3 resolution	Comments
						AST	ALT	Total bili.		
1	Possibly	1	Normal	10.9	1	NA	4	NA	9	ALT decreased from 695 to 53 on within 8 days
2	Possibly	1	Gr1 AST	12.1	1	4	4	—	Unknown	PD, died 1 month later
3	Possibly	1	Normal	18.3	1	1	0	3	Patient died	PD, died 6 days later
4	Possibly	1	Normal	18.6	1	1	3	0	2	No concomitant medications or conditions
5	Possibly	1	Normal	18.8	1	3	2	0	2	Other therapy: conditioning for transplant
6	Possibly	1	Gr2 ALT	19.3	0.5	3	4	0	61	History of Gr2–Gr3 AST/ALT elevations prior to ^{131}I-MIBG therapy. Liver functions fluctuated, resolved to <Gr3 and rose again to Gr3
7	Possibly	2	Normal	36.1	9/3	2	3	0	22	Received 2nd ^{131}I-MIBG therapy 3 months prior
8	Possibly	1	Gr1 ALT	37.7	3	3	3	0	14	No concomitant medications or conditions
9	Unlikely	1	Gr1 ALT	12.3	2	2	3	0	13	Other therapy: *cis*-RA; PD, died 1 month after Gr3 ALT
10	Unlikely	1	Normal	18.0	21	3	1	0	3	Other therapy: Hu 14.18 IL3
11	Unlikely	1	Normal	18.2	3	3	2	2	Patient died	Other therapy: vincristine and irinotecan; PD, died 1 day post last Gr3 AST
12	Unlikely	1	Normal	18.3	14	3	0	1	Patient died	PD, died 11 days later
13	Unlikely	1	Normal	18.4	6	4	NA	3	Patient died	PD, died 1 day after Gr4 AST and Gr3 T. Bili. elevation
14	Unlikely	1	Gr1 AST, Gr2 ALT	18.6	6	2	1	3	Patient died	Other therapy: fenretinide; PD, died 2 days later
15	Unlikely	1	Normal	18.6	6	1	1	3	Patient died	Other therapy: irinotecan; PD, died 14 days later
16	Unlikely	1	Gr1 ALT	18.8	2	2	3	0	1	Other therapy: *cis*-RA; Active infection: acute URI
17	Unlikely	1	Normal	20.9	5	2	3	—	49	Other therapy: *cis*-RA
18	Unlikely	2	Normal	32.2	16/10	2	3	0	Unknown	PD, patient had rapidly progressive disease, liver tests were discontinued
19	Unlikely	3	Normal	32.5	44/41/38	—	1	3	14	Other therapy: Hu 14.18 IL2
20	Unlikely	2	Normal	36.8	6/4	2	0	3	Unknown	Other therapy: zoledronic acid and cyclophosphamide
21	Unlikely	1	Gr1 AST, Gr1 ALT	43.3	3	3	2	2	6	Active infection: sepsis

RX, ^{131}I-MIBG treatment; FX, liver function test; PD, progressive disease. [a]No Grade 3 or 4 hepatic toxicities were considered definitely or probably related to ^{131}I-MIBG therapy, all were considered either unlikely or possibly related; [b]Time in months from each ^{131}I-MIBG treatment to the occurrence of Grade 3 or 4 liver toxicity.

TABLE IV. Cox Proportional Hazards Model of Cumulative Incidence of Onset or Worsening of Liver Toxicity From the Start of ^{131}I-MIBG Treatment

		Onset of or worsening to Grades 3 and 4[a]				Onset of or worsening to any Grade[b]			
		Univariate		Multivariate		Univariate		Multivariate	
Variables	N	HR[c]	95% CI[c]	HR[d]	95% CI[d]	HR[c]	95% CI[c]	HR[d]	95% CI[d]
Age at study entry									
<12 years	109	1.0	—	1.0	—	1.0	—	1.0	—
≥12 years	27	0.70	0.24, 2.1	0.75	0.25, 2.3	1.1	0.70, 1.9	1.2	0.71, 1.9
		$P = 0.52$		$P = 0.61$		$P = 0.60$		$P = 0.55$	
Sex									
Female	54	1.0	—	1.0	—	1.0	—	1.0	—
Male	82	1.4	0.55, 3.7	1.3	0.50, 3.6	0.85	0.56, 1.3	0.87	0.56, 1.3
		$P = 0.45$		$P = 0.55$		$P = 0.45$		$P = 0.53$	
Baseline liver function									
Normal	98	1.0	—	1.0	—	1.0	—	1.0	—
Abnormal	38	1.5	0.60, 3.6	1.4	0.56, 3.6	0.34	0.19, 0.60	0.34	0.19, 0.6
		$P = 0.41$		$P = 0.48$		$P < 0.0001$		$P < 0.0001$	
Number of previous chemotherapy and biotherapy regimens[e]									
Relative risk increase per regimen	136	1.0	0.78, 1.3	0.99	0.77, 1.3	1.1	0.97, 1.2	1.1	0.94, 1.2
		$P = 0.98$		$P = 0.95$		$P = 0.14$		$P = 0.30$	
Cumulative ^{131}I-MIBG dose/kg (mCi)[e]									
Relative risk increase per 18 mCi/kg	136	1.2	0.53, 2.8	1.1	0.49, 2.7	1.5	0.97, 2.3	1.7	1.1, 2.6
		$P = 0.64$		$P = 0.77$		$P = 0.079$		$P = 0.027$	

HR, hazard ratio; CI, confidence interval. [a]Events included an increase in hepatic toxicity from baseline Grade 0 to Grade 3 or 4 after ^{131}I-MIBG treatment, or from baseline Grade 1 or 2 to Grade 3 or 4 after ^{131}I-MIBG treatment; [b]Events included an increase in hepatic toxicity from baseline Grade 0 to Grade 1, 2, 3, or 4 after ^{131}I-MIBG treatment, or from baseline Grade 1 to Grade 2, 3 or 4 after ^{131}I-MIBG treatment, or from baseline Grade 2 to Grade 3 or 4 after ^{131}I-MIBG treatment; [c]HR's and CI's from univariate Cox models; [d]HR's and CI's from Cox models adjusting the other variables in the table; [e]Variables were treated as continuous in the models.

In addition to the thyroid blocking regimen, the lower rate of hypothyroidism reported in this study may also be attributed to a shorter median time from ^{131}I-MIBG therapy to thyroid function follow-up, and a lower median number of therapies. While other studies report the appearance of thyroid dysfunction half a year or more after ^{131}I-MIBG treatment, the median time to follow-up for this study was 3.5 months. However, 36 patients in this study were followed for more than 1 year. In addition, in only two of the patients who developed asymptomatic elevation of TSH did this occur more than 1 year post-therapy; for the three patients with both elevated TSH and low T4, including two who required hormone therapy, the abnormality developed <6 months after ^{131}I-MIBG treatment. Because the patient population consisted of refractory or relapsed neuroblastoma patients, many patients either moved on to another therapy shortly after ^{131}I-MIBG treatment or died, which limited the amount of long-term endocrine data collected and available for analysis.

A number of patients (n = 38; 24%) presented with abnormal thyroid function at baseline. This baseline abnormality may again have had to do with the study population, which included a majority of patients who had already been heavily pre-treated prior to ^{131}I-MIBG therapy. Non-thyroidal illnesses that cause transient disruption in thyroid function may have also played a role in some of the aberrant thyroid functions collected at baseline and may have contributed to some of the thyroid function abnormalities seen after ^{131}I-MIBG therapy [34]. Family history and the effects of prior therapy, as well as other treatments received after ^{131}I-MIBG therapy, such as IL-2 or neck irradiation, also may have been contributory factors to thyroid function abnormalities.

Overall, the prophylactic regimen of potassium iodide and potassium perchlorate with ^{131}I-MIBG therapy is an effective method of protecting the thyroid, resulting in a low incidence rate of clinically significant hypothyroidism. Long-term multi-year follow-up of patients receiving ^{131}I-MIBG will be necessary as this therapy is moved to front-line to determine if thyroid cancer, as yet unreported, is also a risk, as this is a known late consequence of radiation therapy to the neck or whole body [35,36].

The liver is also a target organ for ^{131}I-MIBG concentration [37]. Uptake within the organ has been consistently shown on conjugate planar imaging and one-third of injected ^{131}I-MIBG is found within the liver following diagnostic and therapeutic doses. ^{131}I-MIBG is uniformly taken up by the liver, reaching maximum uptake within 15 min after an intravenous injection of ^{131}I-MIBG, and is rapidly eliminated. Therefore, hepatic toxicity following ^{131}I-MIBG therapy has been closely monitored in neuroblastoma patients. Although symptomatic hepatic toxicity has not been reported in patients receiving single agent ^{131}I-MIBG dosing <12 mCi/kg, there is less information on the effect of ^{131}I-MIBG exposure to the liver for patients receiving ≥12 mCi/kg of ^{131}I-MIBG [32,38,39]. A recent dosimetry study supports the lack of toxicity seen in our study, as it showed that giving 18 mCi/kg of ^{131}I-MIBG results in <30 Gy of radiation to the liver, below liver toxicity range [39].

Liver function abnormalities following ^{131}I-MIBG therapy were more prevalent than thyroid function abnormalities, with 76 ± 4% of patients experiencing onset or worsening of hepatic toxicity of any grade. Of these patients, only 23 ± 5% experienced Grade 3 and/or 4 liver function abnormalities by 2 years after ^{131}I-MIBG therapy. However, 13 of 21 cases with onset or worsening of Grade 3 and/or 4 liver toxicity were deemed unlikely related to ^{131}I-MIBG therapy and attributed to another etiology. Therefore, <10% of patients with evaluable post-therapy liver data had Grade 3 and/or 4 liver toxicity that was possibly attributed to their ^{131}I-MIBG therapy.

Patients with Grade 3 and 4 liver toxicity who did not die shortly after due to progressive disease had their normalization of liver function after a median of 15 days. There were no cases of long-term hepatic complications related to liver function elevation after ^{131}I-MIBG therapy. Grade 1 and 2 liver toxicities attributable to ^{131}I-MIBG therapy were transient in patients with extended follow-up information and resolved without intervention.

Although age, gender, and the number of prior cancer treatments were not significantly associated with worsening of hepatic function, a strong correlation was seen between patient baseline liver function and the onset or worsening of any grade liver toxicity. In our analysis, the relative risk of onset of or worsening to Grade 3 or 4 hepatic toxicity after ^{131}I-MIBG therapy showed a non-significant but positive association with baseline grade, but the relative risk of *any* onset or worsening of hepatic toxicity was significantly and negatively associated with baseline grade. The latter result suggests that worsening of toxicity by 1 grade level is more likely in patients with normal liver function than for patients with Grade 1 or 2 toxicity at baseline. This apparent paradox may be a result of the fact that so many factors may cause mild elevation of transaminase levels, such as antibiotics and other medications or infections.

In conclusion, the prophylactic regimen of potassium iodide and potassium perchlorate with ^{131}I-MIBG therapy is an effective thyroid blocking regimen, with a relatively low incidence rate of symptomatic hypothyroidism when compared to prior studies. Liver abnormalities following ^{131}I-MIBG therapy are primarily transient and do not appear to pose a long-term threat to children who receive ^{131}I-MIBG therapy for neuroblastoma. Therefore, ^{131}I-MIBG therapy is a promising treatment for children with refractory or relapsed neuroblastoma with a relatively low rate of significant late thyroid or hepatic dysfunction.

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