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Impact of Whole-Body Radiation Dose on Response and Toxicity in Patients With Neuroblastoma After Therapy With ^{131}I-Metaiodobenzylguanidine (MIBG)

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Abstract

Background.—^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) is a targeted radiopharmaceutical for patients with neuroblastoma. Despite its tumor-specific uptake, the treatment with ^{131}I-MIBG results in whole-body radiation exposure. Our aim was to correlate whole-body radiation dose (WBD) from ^{131}I-MIBG with tumor response, toxicities, and other clinical factors.

Methods.—This retrospective cohort analysis included 213 patients with high-risk neuroblastoma treated with ^{131}I-MIBG at UCSF Benioff Children's Hospital between 1996 and 2015. WBD was determined from radiation exposure rate measurements. The relationship between WBD ordered tertiles and variables were analyzed using Cochran–Mantel–Haenszel test of trend, Kruskal–Wallis test, and one-way analysis of variance. Correlation between WBD and continuous variables was analyzed using Pearson correlation and Spearman rank correlation.

Results.—WBD correlated with ^{131}I-MIBG administered activity, particularly with ^{131}I-MIBG per kilogram ($P < 0.001$). Overall response rate did not differ significantly among the three tertiles of WBD. Correlation between response by relative Curie score and WBD was of borderline significance, with patients receiving a lower WBD showing greater reduction in osteomedullary metastases by Curie score ($r_s = 0.16$, $P = 0.049$). There were no significant ordered trends among

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Additional Supporting Information may be found in the online version of this article.

Conflict of interest: Nothing to declare.

tertiles in any toxicity measures (grade 4 neutropenia, thrombocytopenia $<20{,}000/\mu l$, and grade $>$ 1 hypothyroidism).

Conclusions.—This study showed that ^{131}I-MIBG activity per kilogram correlates with WBD and suggests that activity per kilogram will predictWBD in most patients. Within the range of activities prescribed, there was no correlation between WBD and either response or toxicity. Future studies should evaluate tumor dosimetry, rather than just WBD, as a tool for predicting response following therapy with ^{131}I-MIBG. Pediatr Blood Cancer 2016;63:436–442.

Keywords

dosimetry; ^{131}I-metaiodobenzylguanidine (MIBG); neuroblastoma; whole-body radiation dose (WBD)

INTRODUCTION

Neuroblastoma, a malignancy arising from neural crest cells of the sympathetic nervous system, is the most common extracranial solid cancer in children. At diagnosis, approximately half of pediatric neuroblastoma patients will present with metastatic disease. Although outcomes for children with advanced disease have improved with intensive multimodal treatment, survival rates are still less than 50%.[1]

Neuroblastoma cells often express the human norepinephrine transporter that facilitates avid uptake of metaiodobenzylguanidine (MIBG), an arylalkylguanidine norepinephrine analog.[2] This proclivity of greater than 90% of neuroblastomas to accumulate MIBG allows for the use of radiolabeled MIBG for targeted imaging (^{123}I-MIBG) and therapy (^{131}I-MIBG).[3] The use of ^{131}I-MIBG as targeted radiotherapy has been successful with >30% response rates in patients with refractory or relapsed neuroblastoma.[4] ^{131}I-MIBG is now increasingly being used as a part of induction and consolidation frontline therapy.[5]

Despite its tumor-specific uptake, the treatment with ^{131}I-MIBG results in whole-body exposure to a significant radiation doserangingfrom50to600cGy,whichcanleadtovariousacute andlatetoxicities.Phase1andotherpilotstudieshaveshownthe primary dose-limiting toxicity to be myelosuppression, though this toxicity can be alleviated through autologous hematopoietic stem cell support.[6,7] Possible nonhematological toxicities include transient nausea and vomiting, sialoadenitis, hypertensive episodes, hepatic dysfunction, hypothyroidism, infertility, and secondary cancers.[8–11]

A prior pilot study from our group showed that the whole-body radiation dose (WBD) received from ^{131}I-MIBG therapy correlated with the activity of ^{131}I-MIBG administered per kilogram and with hematological toxicity.[12] In the current retrospective cohort study, we aimed to analyze WBD from ^{131}I-MIBG therapy in relation to tumor response, toxicities, and other clinical factors, including age, ^{131}I-MIBG activity, ^{131}I-MIBG activity per kilogram of body weight, disease extent and sites, and Curie score.

METHODS

Study Subjects

Patients of more than 1-year of age with high-risk neuroblastoma treated with ^{131}I-MIBG at UCSF Benioff Children's Hospital on three local and six New Approaches to Neuroblastoma Therapy (NANT) clinical trials between August 30, 1996 and May 15, 2015 were evaluated for this retrospective cohort analysis. For patients that received multiple courses of ^{131}I-MIBG therapy, only the first treatment course was included in this analysis. Results were obtained by chart review and data abstraction. Eligibility for inclusion in this study included calculation of WBD. Of the 224 patients evaluated, 11 patients were excluded for unavailable (n=10) or incomplete (n=1) radiation exposure rate measurements. Whole-body dosimetry doses on 62 the 213 patients eligible for this study were reported in primary trial publications.[12–15]

Informed consent was obtained for all patients for each ^{131}I-MIBG treatment protocol. This retrospective analysis was approved by the UCSF institutional review board.

Treatment

Patients were treated on the following nine clinical trials using ^{131}I-MIBG therapy: an ongoing UCSF compassionate use study of ^{131}I-MIBG; a Phase II study of MIBG monotherapy;[16] NANT 99–01;[17] NANT 2000–01[18], NANT 2001–02;[19] NANT 2004–06;[13] NANT 2007–01;[20] NANT 2007–03;[15] and UCSF ^{131}I-MIBG vincristine/irinotecan [14] (Supplementary Table SI). Patients treated on NANT 2000–01, a double-infusion protocol, received 19.9–50.7 mCi/kg of ^{131}I-MIBG over two treatments at a 2-week interval. Patients treated on the remaining clinical trials received 4.1–20.9 mCi/kg of ^{131}I-MIBG. ^{131}I-MIBG was given intravenously over 1–2 hr, with KI used for thyroid protection and Foley catheters were used for bladder protection. All patients were isolated for 5–7 days until radiation emissions met institutional regulations (<2 mr/hr at 1 m).

Calculation of WBD

The WBD from ^{131}I-MIBG was calculated for every patient using radiation exposure rate measurements following the method described previously.[12] Measurements after 2001 were obtained by a ceiling-mounted ionization chamber every 3 min for 5–7 days following infusion. Measurements for patients treated before 2001 were obtained by a handheld ionization chamber, held 1 m from the patient's body surface, taken at 4-hrtimepointsonday1aftertheinfusionandthendailyfor5–7 days following infusion. All data points within 24 hr of washout and hourly data points thereafter were used to graph a whole-body time–exposure curve, with which a three-compartment double-exponential curve was fit for most patients. Two-phase exponential decay was used with 12 patients for whom the three-compartment curve did not fit. Nonlinear regression analysis was performed using GraphPad Prism to obtain exponential time constants and coefficients, with which the whole-body cumulated activity, $\tilde{A}_{wb}$, was derived. WBD was then calculated according to medical internal radiation dose methodology:

$$D_{wb} = \widetilde{A}_{wb} S_{wb \leftarrow wb}(^{131}I),$$

where $\tilde{A}_{wb}$ is the whole-body cumulated activity and $S_{wb \leftarrow wb}$ (^{131}I) is the weight-specific interpolated *S*-factor for ^{131}I.[21,22]

Assessment of Overall Response and Relative Curie Score

For patients treated on NANT studies and the UCSF ^{131}I-MIBG vincristine/irinotecan protocol, overall response to ^{131}I-MIBG therapy was assessed by blinded central review according to modified International Neuroblastoma Response Criteria as utilized by NANT.[23] These criteria use Response Evaluation Criteria in Solid Tumors, Curie score, and bone marrow morphology to grade responses as complete response, partial response, mixed response, stable disease, or progressive disease.[24,25] Mixed response designates patients who achieved partial response in at least one site and stable disease in another site.[23] For patients treated on UCSF institutional studies, response was evaluated using similar criteria by UCSF radiologists and oncologists by comparison of ^{123}I-MIBG scans, CT scans, and bone marrow biopsies obtained before and approximately 6–8 weeks following ^{131}I-MIBG therapy.

Curie scores were determined centrally for patients on NANT protocols and for patients on UCSF institutional protocols by consensus of two nuclear medicine physicians (R.A.H. and L.N.).[26] Pretherapy extension scores were utilized to evaluate tumor burden at treatment entry. Relative extension scores, calculated by dividing posttherapy extension score by pretherapy extension score, were used to assess response to ^{131}I-MIBG therapy, with values >1 indicating greater disease burden posttreatment and values <1 indicating lower disease burden posttreatment.

Evaluation of Hematologic and Thyroid Toxicity

Laboratory data (CBC and thyroid function) were reviewed for each patient. Myelosuppression was categorized by occurrence of grade 4 neutropenia per CTCv4.0 (ANC<500 cells/μl) or thrombocytopenia defined as platelets <20,000/μl. Pre- and posttherapy TSH and T4 values were obtained for the assessment of posttherapy thyroid dysfunction and recorded as normal or outside normal range.

Statistical Methods

This was a retrospective analysis of the impact of WBD on response and toxicity. We also tested correlation with ^{131}I-MIBG infused activity, and clinical factors including disease sites, Curie score, age, and *MYCN* status. WBD was divided into tertiles for the majority of analyses, though WBD as a continuous variable was evaluated in a subset of analyses.

The Cochran–Mantel–Haenszel test of trend was used to test the relationship between WBD ordered tertiles and categorical variables. Kruskal–Wallis test and one-way analysis of variance were used to test the relationship between tertiles of WBD and patient age and ^{131}I-MIBG activity, respectively. Mean WBD was compared between responders (partial response or better) and nonresponders (all other patients) and between patients treated with

and without concomitant radiation sensitizer (irinotecan or vorinostat) using a *t*-test. Correlations between WBD and ^{131}I-MIBG infused activity were assessed using Pearson correlation (r). Correlations between WBD and Curie score and relative Curie score were assessed using Spearman rank correlation (r_s). Kaplan–Meier methods were used to estimate overall survival from date of ^{131}I-MIBG administration and compared between groups with the log-rank test. All analyses were performed in Stata v12.

RESULTS

Patient Characteristics

A total of 213 patients were eligible for inclusion in this analysis, with the characteristics shown in Table I. The median WBD for the entire group was 217 cGy and for WBD Tertiles 1, 2, and 3 were 160 cGy (62–195 cGy), 217 cGy (196–253 cGy), and 314 cGy (254–659 cGy), respectively. The proportion of patients treated with ^{131}I-MIBG alone, rather than with concomitant administration of other antitumor agents or radiosensitizers, increased with increasing WBD tertile ($P = 0.002$). Comparing patients who received ^{131}I-MIBG monotherapy at 18 mCi/kg (n = 62; actual range 17–19 mCi/kg to account for rounding) with patients who received this dose of ^{131}I-MIBG therapy with concomitant radiosensitizer (n = 26), we found no significant trend across WBD tertiles ($P = 0.68$). Similarly, no statistically significant difference was found between these two cohorts in evaluation of WBD as a continuous variable (mean WBD with monotherapy = 251 cGy vs. 251 cGy with concomitant radiation sensitizer; $P = 0.96$).

The proportion of patients with *MYCN* amplification increased with increasing WBD tertile ($P = 0.051$). Males predominated in all tertiles, showing no correlation between sex and WBD. Median age at diagnosis and treatment entry did not differ across tertiles. As expected, there was no significant correlation between stage at diagnosis and WBD, with stage 4 neuroblastoma patients making up greater than 80% of all tertiles. The proportion of patients with prior autologous stem cell transplant did not demonstrate a significant ordered trend across the three WBD tertiles. Only four patients in our study had received prior whole-body radiation as a part of their conditioning.

Administered ^{131}I-MIBG

Total ^{131}I-MIBG administered (mCi) correlated positively with WBD, as shown in Figure 1A (r = 0.3574, $P < 0.001$). The median WBD was 176, 213, and 250 cGy at 12, 15, and 18 mCi/kg, respectively. There was a stronger positive correlation between ^{131}I-MIBG administered per kilogram of body weight and WBD, as shown in Figure 1B(r=0.6485, $P<0.001$).

Lack of Effect of Disease Burden on WBD

Sites of disease involvement at treatment entry did not correlate significantly with tertiles of WBD (Table I). For Tertiles 1 and 2, the majority of patients (51% and 54%, respectively) had bone or bone marrow involvement only. For Tertile 3, the patients predominantly had disease involvement in both soft tissue and bone/bone marrow compartments (49%). We

tested Curie score at entry as a measure of disease burden and observed no significant correlation with WBD (r_s = 0.07, P = 0.35; Fig. 2A).

Overall Response

Overall response rate did not differ significantly among the three tertiles of WBD (Table II). By examination of WBD as a continuous variable, the mean WBD for patients with an objective response (partial response or better) was 227 cGy (95% CI 206–249 cGy), while the mean WBD for patients without an objective response was 246 cGy (95% CI 229–262 cGy), which was not significantly different (P = 0.23). In sensitivity analyses restricted to patients who received ^{131}I-MIBG at 18 mCi/kg (actual range 17–19 mCi/kg to account for rounding) and no associated myeloablative chemotherapy, we also did not see statistically significant difference analyzing the data across WBD tertiles (P = 0.14) or as a continuous variable (mean WBD for responders = 231 vs. 258 cGy for nonresponders; P = 0.10).

In evaluation of the specific response categories (complete response, partial response, mixed response, stable disease, and progressive disease), there was no correlation among the three tertiles of WBD (P = 0.08). However, correlation between response, as assessed by relative Curie score, and WBD was of borderline significance, with patients receiving a lower WBD paradoxically showing a greater reduction in osteomedullary metastases by Curie score (r_s = 0.16, P = 0.049; Fig. 2B).

Toxicities

Of the patients with available CBC values, 115 of 160 (72%) and 115 of 157 (73%) experienced grade 4 neutropenia and thrombocytopenia (< 20,000/μl), respectively. Of the patients with available baseline and posttherapy TSH and/or T4 lab values (n = 134), 17% experienced posttreatment grade ≥ 1 hypothyroidism. Comparable results were found in the subanalysis of patients treated with ^{131}I-MIBG monotherapy. Details of toxicities by tertiles of WBD are presented in Table III. There were no significant ordered trends among tertiles in any of the measures of toxicity.

Overall Survival

The 24-month overall survival was lowest for Tertile 3 patients at 37.8% (95% CI 26.0–49.5%), compared to 54.5% (95% CI 41.6–65.7%) for Tertile 1 patients and 57.4% (95% CI 44.1– 68.1%) for Tertile 2 patients, although there was not a significant difference (P = 0.22; Fig. 3).

DISCUSSION

In this study, we found that WBD correlated with ^{131}I-MIBG activity, particularly with ^{131}I-MIBG administered per kilogram. This finding serves to validate the results of our previous study, suggesting that activity administered per kilogram can be used as a measure of expected whole-body radiation exposure.[12] As expected, ^{131}I-MIBG protocol correlated significantly with WBD, because the MIBG monotherapy cohort included patients treated on the double-infusion protocol (NANT 2000–01) and administered ^{131}I-MIBG activity was decreased in myeloablative protocols for toxicity. Furthermore, we found trends to suggest

correlations between both *MYCN* amplification and relative Curie score. In contrast to our hypothesis and results of previous studies, we did not find a significant correlation between WBD and response or toxicity.[6,12,13,27–32]

Our findings regarding the correlation between WBD and ^{131}I-MIBG activity support the results of previous studies.[12, 17,20,31,33] The strong positive correlation of WBD to ^{131}I-MIBG activity per kilogram suggests that activity prescriptions for^{131}I-MIBGtherapiesshouldbemadebasedonpatientweight as opposed to a predetermined total activity dose in order to achieve a targeted WBD. A recent study by Minguez et al. proposed an equation, which describes whole-body absorbed dose per unit of administered activity as a function of patient mass, as an alternative for prescriptions of activity on first administration when dosimetry data for the individual patient are unknown.[31]

The lack of correlation of disease sites and baseline Curie score to WBD suggests that tumor burden does not impact WBD. Although this association has not previously been investigated in ^{131}I-MIBG therapy, prior studies have assessed the effect of tumor burden on the biodistribution of different radiopharmaceuticals and its subsequent impact on WBD. These studies on non-Hodgkin lymphoma patients treated with ^{131}I-rituximab (anti-CD20 antibody) and ^{131}I-tositumomab (anti-B1 antibody) and patients with gastrointestinal malignancies treated with ^{131}I-COL-1 suggest the dependence of clearance kinetics on tumor burden.[34–36] The studies independently proposed that patients with larger tumor burden might bind a greater fraction of the administered radiopharmaceutical, yielding a decreased concentration in serum and, therefore, an increased clearance of the serum radioactivity. We expected that increased neuroblastoma burden would similarly increase uptake and retention of ^{131}I-MIBG, effectively increasing WBD. While Tertile 3 had the greatest proportion of patients with disease involvement in all compartments, we found no significant correlation between tumor burden and WBD, perhaps due to the more rapid plasma clearance of ^{131}I-MIBG compared to radiolabeled antibodies.

Our previous pilot study found that tumor self-absorbed radiation dose (TSARD) predicted tumor volume decrease and also correlated with both WBD and overall tumor response.[12] Therefore, we hypothesized that WBD might correlate with overall response. However, similar to other previous studies, we found no relationship between WBD and overall response.[12, 30] Although not statistically significant, our results suggest that responders received a lower mean WBD (227 cGy) compared to nonresponders (246 cGy), similar to the results of DuBois et al.[13] These findings were also reflected in our comparison of relative Curie score and WBD, in which patients, who received lower WBD, showed the greatest reduction in Curie score. This unexpected finding could be explained if overall response is described as a function of a therapeutic ratio (TSARD/WBD), wherein response is not so much dependent on the value of WBD, but rather the fraction of WBD localized in the tumor. Because TSARD was not calculated in our study, this relationship could not be evaluated. Future studies including more accurate tumor dosimetry such as ^{124}I-MIBG with PET-CT technology will improve our assessment of this ratio.[37]

Many past studies have found a significant association between WBD and hematologic toxicity.[6,12,13,27–30,32] However, in our study, we were unable to establish any

relationship between hematologic or thyroid toxicity and WBD. Inclusion of patients treated on myeloablative protocols may have confounded our analysis by increasing the hematologic toxicity at lower WBD. To account for this, we conducted a subanalysis of MIBG monotherapy protocols and again no significant association was observed. A recent study also found no correlation between grade of hematologic toxicity and WBD, but they suggested that the lack of correlation might be attributed to small sample size, wide age variance, or prior hematotoxic treatments.[31] One possible explanation for the low correlation in our study is the narrow range of WBD. In a study by Lashford et al., 31% of patients developed grade 3 or 4 thrombocytopenia at WBD of 2.0 Gy and 40% of patients developed grade 3 or 4 neutropenia at WBD of 2.5 Gy.[30] In our Phase I dose escalation study, grade 4 hematologic toxicity occurred in 80% of patients receiving >12 mCi/kg. Because it has been previously established that 18 mCi/kg is the maximal dose of ^{131}I-MIBG, the majority of the patients in our study received WBD levels above the toxicity threshold, so no significant association could be assessed. Variable receipt of hematopoietic stem cell support after ^{131}I-MIBG therapy may have also impacted our ability to detect a difference in hematologic toxicity according to WBD. Whether WBD may correlate with other late toxicities, such as second malignancy or reduced fertility, will require further study.

Although there was no significant difference in the 24-month OS among the three tertiles of WBD, 24-month OS was lowest for Tertile 3 patients at 37.8%. As shown in Table I, lack of difference in 24-month OS among the three tertiles does not appear to be due to a higher proportion of relapsed patients compared to refractory patients.[38] Instead, it may be due to the increased proportion of Tertile 3 patients with disease involvement in all three compartments, previously shown to be a higher risk group.[16] The low 24-month OS may also be due to decreased response rate, as assessed by relative Curie score.

Limitations of our study may include (i) inter patient variability, such as differing rates of renal excretion, (ii) comparison of different ^{131}I-MIBG protocols, some of which include concomitant administration of different agents and radiosensitizers that may have confounded response or toxicity results, (iii) lack of tumor dosimetry for most patients because of the requirement for pretreatment serial imaging, and (iv) a narrow range of WBD, which may have limited the evaluation of toxicity.

CONCLUSIONS

This study has shown that ^{131}I-MIBG activity per kilogram correlates with WBD and suggests that ^{131}I-MIBG activity per kilogram will predict WBD in most patients. Despite lack of correlation to response and toxicity, WBD correlated inversely with relative Curie score. This unexpected finding prompts future studies to evaluate tumor dosimetry, rather than just WBD, as a tool for predicting response following therapy with ^{131}I-MIBG.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

MIBG	metaiodobenzylguanidine
NANT	New Approaches to Neuroblastoma Therapy
TSARD	tumor self-absorbed radiation dose
WBD	whole-body radiation dose

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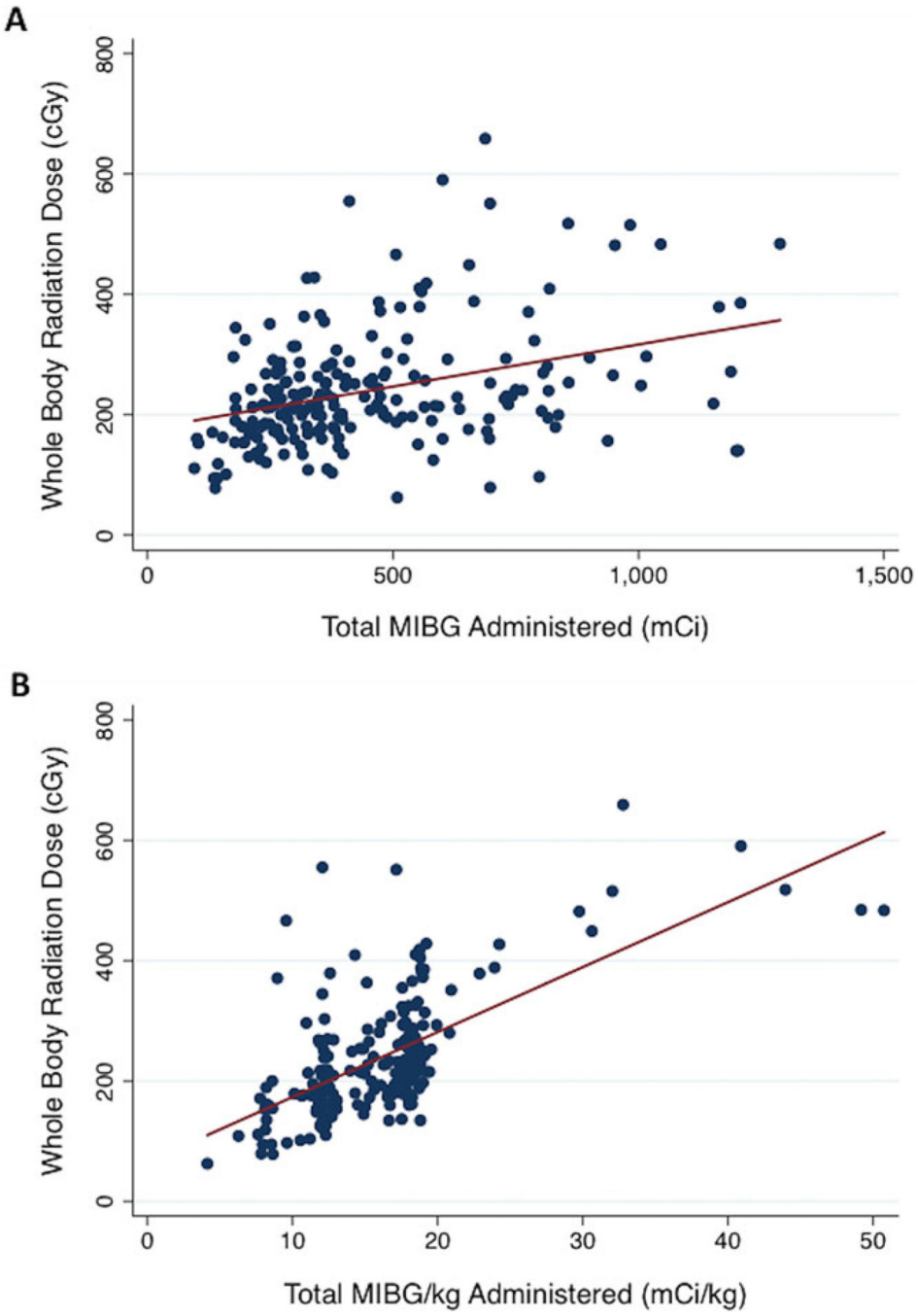

Fig. 1.

(**A**) Total ^{131}I-MIBG administered (mCi) correlates positively with whole-body radiation dose (cGy) (r = 0.36, $P < 0.001$). (**B**) ^{131}I-MIBG administered per kilogram body weight (mCi/kg) correlates positively with whole-body radiation dose (cGy) (r=0.65, $P < 0.001$).

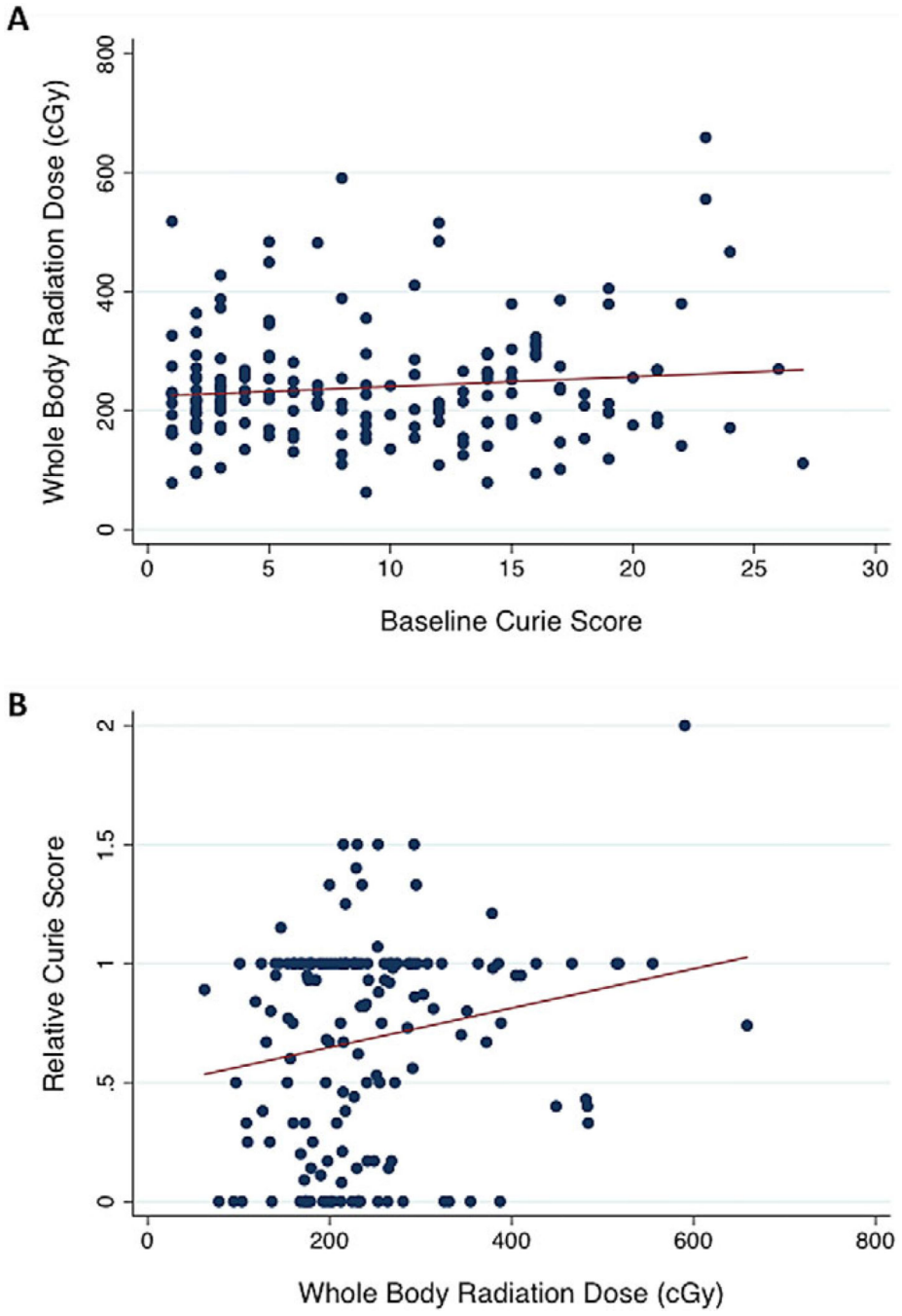

Fig. 2.

(**A**) Correlation of whole-body radiation dose with baseline Curie score (n =179, r_s = 0.07, *P* = 0.35). (**B**) Correlation of relative Curie score with whole-body radiation dose (n =160, r_s = 0.16, *P* = 0.049).

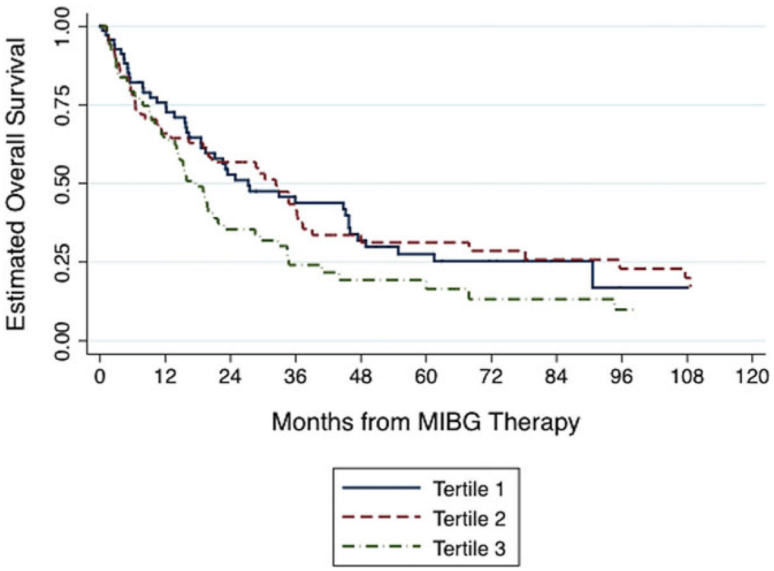

Fig. 3.

Estimated overall survival according to tertiles of whole-body radiation dose ($P = 0.22$).

TABLE I.

Characteristics of 213 Patients Treated with ^{131}I-MIBG

Characteristic	All patients	Tertile 1 62–195 cGy	Tertile 2 196–253 cGy	Tertile 3 254–659 cGy	P-value
No. of patients	213	71	71	71	-
Sex					
Male	136 (64%)	45 (63%)	42 (59%)	49 (69%)	0.49[a]
Female	77 (36%)	26 (37%)	29 (41%)	22 (31%)	
Age at diagnosis (years)					
Median	4.68	4.42	4.59	4.95	0.54[b]
Range	0.33–50.79	0.33–29.22	0.38–26.18	0.83–50.79	
Age at entry (years)					
Median	7.14	6.19	7.41	8.14	0.30[b]
Range	1.87–51.20	2.59–30.22	1.87–26.84	2.16–51.20	
Stage at diagnosis					
1,2,3	35 (16%)	13 (18%)	12(17%)	10 (14%)	0.50[a]
4	178 (84%)	58 (82%)	59 (83%)	61 (86%)	
MYCN amplification[d]					
Yes	40 (24%)	8 (15%)	14 (25%)	18 (31%)	0.05[a]
No	127 (76%)	45 (85%)	42 (75%)	40 (69%)	
Prior ASCT					
Yes	120 (56%)	35 (49%)	43 (61%)	42 (59%)	0.24[a]
No	93 (44%)	36 (51%)	28 (39%)	29 (41%)	
Disease status prior to ^{131}I MIBG therapy					
Relapse	141 (66%)	43 (61%)	50 (70%)	48 (68%)	0.38[a]
Refractory	72 (34%)	28 (39%)	21 (30%)	23 (32%)	
Sites of disease involvement at entry					
ST + B/BM	88 (41%)	25 (35%)	28 (39%)	35 (49%)	0.09[a]
ST only	24(11%)	10 (14%)	5 (7%)	9 (13%)	

Characteristic	All patients	Tertile 1 62–195 cGy	Tertile 2 196–253 cGy	Tertile 3 254–659 cGy	P-value
B/BM only	101 (48%)	36 (51%)	38 (54%)	27 (38%)	
Type of ^{131}I-MIBG protocol					
MIBG alone[e]	129 (61%)	33 (46%)	45 (63%)	51 (72%)	0.002[a]
Combination	84 (39%)	38 (54%)	26 (37%)	20 (28%)	
Total dose of ^{131}I-MIBG administered (mCi)					
Mean	455.23	372.28	439.34	554.07	0.0001[c]
Standard deviation	253.12	242.74	206.33	274.60	
Dose of ^{131}I-MIBG per kilogram of body weight (mCi/kg)					
Mean	16.25	12.68	16.52	19.54	<0.0001[c]
Standard deviation	5.94	3.56	2.62	7.97	

[a]Cochran–Mantel–Haenszel test;

[b]Kruskal–Wallis test;

[c]One-way analysis of variance;

[d]*MYCN* amplification status unknown for 46 patients (18 Tertile 1, 15 Tertile 2, and 13 Tertile 3);

[e]MIBG alone = any patient without concomitant administration of other antitumor agents or radiosensitizers. ASCT, autologous stem cell transplant; ST, soft tissue; B, bone; BM, bone marrow.

TABLE II.

Response to ^{131}I-MIBG by Tertiles of Whole-Body Radiation Dose

	All[a]	Tertile 1	Tertile 2	Tertile 3	*P*-value[b]
Response	57 (27%)	21 (30%)	19 (27%)	17 (24%)	0.45
No response	156 (73%)	50 (70%)	52 (73%)	54 (76%)	
CR	16 (8%)	9 (13%)	4 (6%)	3 (4%)	
PR	42 (20%)	13 (18%)	15 (22%)	14 (20%)	
SD	96 (46%)	33 (47%)	32 (46%)	31 (44%)	0.08
PD	38 (18%)	9 (13%)	14 (20%)	15 (21%)	
MR	18 (8%)	6 (9%)	4 (6%)	8 (11%)	

[a]Response for three patients was not evaluable;

[b]Cochran–Mantel–Haenszel test. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; MR, mixed response; ASCT, autologous stem cell transplant.

TABLE III.

Toxicities by Tertiles of Whole-Body Radiation Dose

	AH ^{131}I-MIBG Protocols[a]				
Toxicity	**All**	**Tertile 1**	**Tertile 2**	**Tertile 3**	**P-value[c]**
Grade 4 neutropenia					
Yes	115 (72%)	32 (67%)	37 (67%)	46 (81%)	0.10
No	45 (28%)	16(33%)	18 (33%)	11 (19%)	
Thrombocytopenia[b]					
Yes	115 (73%)	29 (64%)	44 (83%)	42 (71%)	0.54
No	42 (27%)	16(36%)	9 (17%)	17 (29%)	
Posttreatment hypothyroidism					
Yes	23 (17%)	8 (18%)	10 (23%)	5(11%)	0.35
No	111 (83%)	36 (82%)	34 (77%)	41 (89%)	
	^{131}I-MIBG Monotherapy Protocols[d]				
Grade 4 neutropenia					
Yes	80 (71%)	19 (63%)	27 (71%)	34 (77%)	0.19
No	32 (29%)	11 (37%)	11 (29%)	10 (23%)	
Thrombocytopenia[b]					
Yes	91 (76%)	22 (71%)	35 (88%)	34 (71%)	0.79
No	28 (24%)	9 (29%)	5 (12%)	14 (29%)	
Posttreatment hypothyroidism					
Yes	16(16%)	4(16%)	7 (21%)	5 (12%)	0.62
No	82 (84%)	21 (84%)	26 (79%)	35 (88%)	

[a] Lab values unavailable for 53 patients (ANC), 56 patients (platelet count), and 79 patients (TSH/T4);

[b] Assessed using a platelet count threshold of 20,000/μl;

[c] Cochran–Mantel–Haenszel test;

[d] Lab values unavailable for 17 patients (ANC), 10 patients (platelet count), and 31 patients (TSH/T4).