Whole-Body Dosimetry for Individualized Treatment Planning of $^{131}$I-MIBG Radionuclide Therapy for Neuroblastoma

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The aims of this study were to examine the relationship between whole-body absorbed dose and hematologic toxicity and to assess the most accurate method of delivering a prescribed whole-body absorbed dose in $^{131}$I-metaiodobenzylguanidine ($^{131}$I-MIBG) therapy for neuroblastoma. **Methods:** A total of 20 children (1–12 y), 5 adolescents (13–17 y), and 1 adult (20 y) with stage 3 or 4 neuroblastoma were treated to a prescribed whole-body absorbed dose, which in most cases was 2 Gy. Forty-eight administrations of $^{131}$I-MIBG were given to the 26 patients, ranging in activity from 1,759 to 32,871 MBq. For 30 administrations, sufficient data were available to assess the effect of whole-body absorbed dose on hematologic toxicity. Comparisons were made between the accuracy with which a whole-body absorbed dose could be predicted using a pretherapy tracer study and the patient's most recent previous therapy. The whole-body absorbed dose that would have been delivered if the administered activity was fixed ($7,400$ MBq) or determined using a weight-based formula ($444$ MBq $\cdot$ kg$^{-1}$) was also estimated. **Results:** The mean whole-body absorbed dose for patients with grade 4 Common Terminology Criteria for Adverse Events (CTCAE) neutropenia after therapy was significantly higher than for those with grade 1 CTCAE neutropenia (1.63 vs. 0.90 Gy; $P = 0.05$). There was no correlation between administered activity and hematologic toxicity. Absorbed whole-body doses predicted from previous therapies were within ±10% for 70% of the cases. Fixed-activity administrations gave the largest range in whole-body absorbed dose (0.30–3.11 Gy). **Conclusion:** The results indicate that even in a highly heterogeneous and heavily pretreated patient population, a whole-body absorbed dose can be prescribed accurately and is a more accurate predictor of hematologic toxicity than is administered activity. Therefore, a whole-body absorbed dose can be used to deliver accurate and reproducible $^{131}$I-MIBG therapy on a patient-specific basis.

**Key Words:** dosimetry; $^{131}$I MIBG therapy; neuroblastoma; treatment planning

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At present, few targeted radionuclide therapies (TRT) are administered with the aid of dosimetry-based prospective treatment planning. Instead, standardized treatment regimens usually involve the administration of a fixed level of radioactivity or an activity based on patient weight or body surface area (1–3). However, European regulations now stipulate the need to perform individual patient treatment planning for TRT (4). To date, there have been few studies whereby the feasibility or potential benefit of dosimetry-based treatment planning has been examined (5–8).

Neuroblastoma is a pediatric neuroendocrine solid tumor that accounts for 7% of all childhood cancers (9). In the last 15 y, $^{131}$I-metaiodobenzylguanidine ($^{131}$I-MIBG) has been increasingly used in a multimodality approach to improve palliation and progression-free survival rates, predominantly in relapsed and refractory patients who have undergone a wide range of prior chemotherapy. $^{131}$I-MIBG is largely given as a salvage therapy, and patients present with a wide range of tumor burdens and disease sites. MIBG is taken up by an active transport mechanism into the neurosecretory granules of catecholamine-producing neuroblastoma cells, thus allowing radiation to be selectively targeted to these cells (10). Treatments vary widely. Administered activities can be fixed, based on patient weight, or prescribed according to a whole-body absorbed dose and are sometimes given with concomitant chemotherapy. The outcome of these treatments is variable, with reported partial responses ranging from 15% to 65% (11–13).

Matthay et al. (14) and Monsieurs et al. (15) determined the whole-body absorbed doses resulting from $^{131}$I-MIBG therapy for neuroblastoma; the administered activity was determined from a weight-based formula, and a fixed number of decay phases was assumed. Gaze et al. (7) gave 2 fractions of $^{131}$I-MIBG therapy to neuroblastoma patients for whom the first fraction was prescribed according to activity per body weight (444 MBq $\cdot$ kg$^{-1}$). The whole-body absorbed dose calculated from whole-body retention measurements made during the first fraction was then used to prescribe the second therapy administration, to deliver a...
based on weight (444 MBq from the first therapy. The initial therapies for 5 patients were administered, the first therapy was used to deter-

At our center, most pediatric 131I-MIBG therapy patients are administered an activity calculated to deliver a whole-

in combination with an accurate prescription method, would allow treatment to a maximally tolerated dose, as is normally the case in chemotherapy. We report the correlation of whole-body absorbed dose and administered activity with hematologic toxicity and examine whether concomitant chemotherapy, bone marrow involvement, and refractory or relapsed disease affect these correlations. The accuracy of delivering a prescribed whole-body absorbed dose using 4 different methods (previous therapy, tracer, weight-based, and fixed activity) is also reported.

**MATERIALS AND METHODS**

**Patient Population and Administrations**

Twenty-six patients (age range, 1–23 y) with recurrent and advanced neuroblastoma (stage 3 or 4) undergoing 48 administrations were considered. Most treatments were given according to a predicted whole-body absorbed dose of 2 Gy. For 16 treatments, the prediction was obtained from an administration of 123I-MIBG (185 MBq) as a tracer for the therapy. For 5 treatments, 131I-MIBG was administered as a tracer. In 20 cases in which additional therapies were administered, the first therapy was used to determine the administered activity for the subsequent therapy. The mean length of time between therapy administrations was 7.5 wk, with a range of 2–22 wk. Patients were treated on an individual basis, with the duration between treatments based on response from the first therapy. The initial therapies for 5 patients were based on weight (444 MBq kg⁻¹ (7)). Two patients were given a fixed-activity administration. The study was approved by the local ethics committee, and informed consent was obtained for all patients. A summary of patient details is given in Supplemental Table 1 (supplemental materials are available online only at http://jnm.snmjournals.org).

**Therapy Procedure**

For therapy, patients were isolated within a purpose-built room with adjacent toilet facilities (19). Parents and caretakers were allowed limited access to the patient when suitably protected against contamination with a gown, an apron, gloves, and over-

**Data Acquisition**

Whole-body measurements were acquired with the patient lying supine in a reproducible position. For the tracer study, measurements were obtained using a shielded (3 cm of lead; diameter, 5 cm; thickness, 5 cm) NaI detector fixed into the ceiling space 2 m directly above the patient’s bed (19). Sufficient counts were acquired to ensure that the Poisson noise was below 5%. For 131I-MIBG therapy measurements, data were acquired using a shielded (2 cm of lead) compensated Geiger counter, which was positioned in the ceiling next to the NaI detector. Care was taken to reproduce the patient–counter geometry as closely as possible for each reading by always having the bed at its lowest level. At this bed position, the size of the detector field of view was a circle 2 m in diameter for the NaI detector and a rectangle 2 m long by 1 m wide for the Geiger counter (i.e., large enough to include the whole bed). The 2 detectors were specifically chosen to cover a large range of dose rates (1E-04 to 1 mSv/h) as estimated from phantom and patient measurements using a range of radionuclides and activity levels. The first measurement was acquired immediately after administration and before the first bladder void, to obtain the reading corresponding to 100% activity. Subsequent readings were taken consistently after the child’s natural void and were not performed overnight, unless the child woke naturally. Usually 40–60 readings were taken per administration. An example of a typical postinjection time–activity curve for both tracer and therapy is shown in Figure 1. Blood samples were acquired from which the platelet, leukocyte, and neutrophil concentrations were determined. On average, 16 blood samples were taken at a frequency of 1 every 6 d after therapy, with the first sample taken 1 d before 131I-MIBG was administered.

**Whole-Body Dosimetry**

Whole-body absorbed doses were calculated according to the standard MIRD schema. Between 3 and 5 exponential effective decay phases were user-defined, and errors were calculated using a method detailed previously (20) (Fig. 1). The resulting time–activity curve was integrated using multiple exponential lines of best fit to determine the cumulated activity, Å.
The mean values of the hematologic variables were compared for each clinical variable using the t test for parametric data and the Mann–Whitney test for nonparametric data. Associations between sets of continuous variables were analyzed using the Pearson correlation ($r_p$). Data from only the first therapy of 16 patients were used for these tests to ensure that all measurements were independent. For 10 patients, who received 2 therapies, the differences in the hematologic data acquired after therapy 1 and therapy 2 were compared using a paired t test. All the statistical analyses were performed using SPSS 14.0 (SPSS Inc.).

**Predictions of Whole-Body Absorbed Dose Delivered During Therapy**

Four methods were used to predict the whole-body absorbed dose that would be delivered from the therapy administration of $^{131}$I-MIBG.

An $^{123}$I- or $^{131}$I-MIBG Tracer Study. For the 21 tracer studies, the methodology used to calculate the whole-body absorbed dose was the same as that used after therapy, and linear extrapolation of the whole-body absorbed dose as a function of administered activity for the patient was assumed. Where $^{123}$I-MIBG was given as a tracer, the biokinetics were assumed to be identical to those for the therapy, and a conversion was made to allow for the different physical half-lives of the $^{123}$I- and $^{131}$I-MIBG (13.27 h and 8.02 d, respectively).

Previous Therapy Studies. In 20 cases in which a previous therapy had been given before the administration, the results from this therapy were used to predict the whole-body absorbed dose.

**Standard Administration.** Retrospective analysis was performed to determine the whole-body absorbed dose that would have been delivered had an activity of 7,400 MBq been administered in each of the 48 therapies. This is a standard protocol for many treatments for both pediatric and adult neuroendocrine tumors (1). As with the administration of a tracer study, linear extrapolation of the whole-body absorbed dose as a function of administered activity for the patient was assumed.

**Weight-Based Formula.** A simple weight-based formula was used, corresponding to 444 MBq kg$^{-1}$ (7). Linear extrapolation of the whole-body absorbed dose as a function of administered activity for the patient was assumed, and the whole-body absorbed dose that would have been delivered if 444 MBq kg$^{-1}$ of $^{131}$I-MIBG had been administered was calculated for all 48 therapies.

**RESULTS**

For the 48 therapy administrations, a mean activity of 10,302 ± 7,402 MBq (mean ± SD) was administered (range, 1,759–32,871 MBq), equating to a mean of 385 ± 161 MBq kg$^{-1}$ (range, 60–809 MBq kg$^{-1}$). A mean whole-body absorbed dose of 1.58 ± 0.62 Gy was delivered (range, 0.46–3.51 Gy).

**Toxicity**

The hematologic data for the therapy patients are shown in Supplemental Table 2. Toxicities for CTCAE thrombocytopenia, leukopenia, and neutropenia ranged from grade 0 to grade 4 (Supplemental Table 3). A statistically significant difference for the mean whole-body absorbed dose between patients with grade 1 and patients with grade 4 neutropenia was seen (1.63 ± 0.40 Gy and 0.90 ± 0.12 Gy, respectively) ($P = 0.05$) (Fig. 2). A negative correlation
was found between the neutrophils at nadir and the whole-body absorbed dose ($r_p = -0.47$, $P = 0.064$) (Fig. 3). Although this $P$ value fell slightly outside 5% significance, it was considered important because it mirrored the statistically significant relationship already seen between the mean whole-body absorbed dose and the grade of CTCAE neutropenia observed after therapy. No significant difference was observed in the mean whole-body absorbed dose in patients with grades 1 and 4 thrombocytopenia or leukopenia. No correlation was found between the administered activity and any of the blood counts at nadir.

For the 10 cases in which data were available for 2 therapies in the same patient, a paired $t$ test was used to evaluate whether there was any significant difference between the measured parameters for the 2 therapies. For therapy 1, the platelet nadir occurred at 25 ± 14 d. There was a wide range of 8–62 d. For therapy 2, the nadir was at 27 ± 15 d, again with a wide range. No significant difference was found between the means of these 2 groups ($P = 0.74$). In addition, no significant difference was found between the means of the therapy 1 and therapy 2 groups for the leukocyte and neutrophil data. No significant difference was found between the recovery coefficients of the platelets, leukocytes, or neutrophils for the 2 therapies. The percentage drop in platelets at nadir per unit change in whole-body absorbed dose was 46.1% ± 16.3% for therapy 1 and 55.0% ± 23.8% for therapy 2. There was no statistically significant difference between the 2 therapies in this case. The leukocyte and neutrophil data showed similar results.

The platelets at nadir were found to be significantly lower for those patients who underwent concomitant chemotherapy than for those who underwent $^{131}$I-MIBG therapy alone ($19 \times 10^9/L$ and $70 \times 10^9/L$, $P = 0.008$). This trend was also seen in the leukocyte data ($0.48 \times 10^9/L$ and $2.3 \times 10^9/L$, $P < 0.001$). This difference may be explained by the lower levels of blood counts before therapy in the chemotherapy group, although this difference is less pronounced than at nadir. The time to platelet nadir was also significantly shorter for those undergoing chemotherapy, taking 23 d to reach nadir, compared with 32 d for those who did not receive concurrent therapy ($P = 0.025$). This effect was also noticed in the neutrophils, in which the time to nadir was 20 d for the chemotherapy group and 35 d for the $^{131}$I-MIBG–only group ($P = 0.029$). None of the hematologic outcome variables was found to be significantly different for patients with and without bone marrow involvement. This was also true for patients with relapsed versus refractory disease.

**Prediction of Whole-Body Absorbed Dose**

The prescribed whole-body absorbed dose was predicted by a previous therapy to within ±10% in 70% of cases. All predictions were within ±30%. For the tracer dosimetry, 24% of the predictions were within ±10% of the prescribed dose, and all the predictions were within ±50%. Figure 4 shows a plot of predicted versus received whole-body absorbed dose for the patients. In general, the whole-body absorbed dose delivered during therapy was lower than predicted. A paired $t$ test confirmed that the mean predicted dose from tracer studies is significantly higher than the mean delivered dose ($P < 0.001$), with the mean difference equal to 0.42 Gy. There was no significant difference between the predictions from a previous therapy and the
delivered dose \((P = 0.151)\), thereby indicating that one therapy accurately predicts the next.

A total of 25% of the doses delivered were within \( \pm 10\% \) using the weight-based formula. There was a wide range, with 10% of the predictions more than \( \pm 50\% \) from the prescribed dose. The standard administration \((7,400 \text{ MBq})\) had the largest range \((0.3–3.11 \text{ Gy})\), with only 19% of the whole-body absorbed doses being within \( \pm 10\% \) of the prescribed dose (Fig. 5).

**DISCUSSION**

This study has demonstrated an inverse correlation between whole-body absorbed dose and the grade of CTCAE neutropenia observed after \(^{131}\text{I-MIBG}\) therapy. Because no correlation was observed between any of the hematologic parameters studied and the administered activity, the prescription of therapies based on the whole-body absorbed dose would allow personalized treatment according to an individual’s toxicity. Whole-body absorbed dose was used in this study because it could be calculated for all patients, unlike red marrow dose, which can be derived from blood doses using standard models only if there is no marrow involvement \((23)\).

The strong correlation of prior chemotherapy with increased hematologic toxicity suggests that if the patient cohort was large enough to analyze the toxicities of these 2 groups separately (and therefore remove this confounding factor), a more pronounced correlation would be found between whole-body absorbed dose and hematologic toxicity, with the relationship being different for the chemotherapy and the no-chemotherapy groups. In practice, having a large enough cohort to analyze the 2 groups would require a multicenter trial and may provide another method of optimizing therapy, with some treatment fractions given with and some without chemotherapy, based on the blood status of the individual.

The results from this study justify the use of a fractionated treatment regimen for \(^{131}\text{I-MIBG}\) therapy, which has previously been advocated by Gaze et al. \((7)\). The use of fractionation enables the most accurate method of dose prescription (previous therapy) to be used, with the first therapy being based on weight or a tracer measurement (Fig. 5). The study showed that in general the whole-body absorbed dose delivered was lower than tracer measurements predicted. The greater predictive accuracy of a previous therapy suggests that this could be due to the different tracer and therapy volumes administered. It would be possible to incorporate this underestimation into the therapy prescription method, although this has not been done at present to keep the number of patients given more than 2 Gy to a minimum. It may also be feasible to determine a more accurate formula, taking into account the individual’s hematologic status.

**FIGURE 4.** Whole-body absorbed dose delivered as function of whole-body absorbed dose predicted from either previous tracer study or from prior therapy. Line of equality is also shown. Error bars indicate uncertainty in absorbed dose due to random errors generated during data acquisition and were calculated using method described by Chittenden et al. \((19)\).

**FIGURE 5.** Range of doses delivered as percentage of prescribed dose for 4 prescription/treatment methods used \((1 = \text{previous therapy}, 2 = \text{tracer}, 3 = \text{weight-based}, 4 = 7,400 \text{ MBq})\). The \(\bullet\) indicates median difference between delivered and prescribed dose, and error bars indicate range of these differences.
into account other patient-specific factors, such as kidney function (24). Because the study results indicate that time to hematologic nadir is patient-dependent and specifically affected by concomitant chemotherapy, the frequency and number of treatments in the fractionation schedule could also be tailored to the individual.

The levels of leukopenia and thrombocytopenia are greater after therapy 2 than after therapy 1. The percentage decrease as a function of dose at nadir, however, was consistent for the 2 therapies. Both the whole-body absorbed dose and the fall in platelets and leukocytes for a second therapy can be predicted using data from the first therapy, enabling patient-specific treatment planning (which aims to treat to an individual’s hematologic toxicity, thus optimizing therapy).

Despite only a few studies, initial research has provided some evidence that absorbed radiation dose to tumor will be maximized by the administration of higher activities of 131I-MIBG (25). Increasing the absorbed radiation dose to the tumor is important, because for many tumor types there are established dose–response relationships reported in external-beam therapy (26–29). There is some evidence that this holds true for brachytherapy and TRT, despite the lower dose rate (30,14). The ability to predict hematologic toxicity from an accurately delivered prescribed whole-body absorbed dose will allow the safe escalation of administered activity to further test this hypothesis. Initial research has shown no relationship between whole-body and tumor absorbed dose (16), nor is this expected because tumor burden varies significantly and whole-body absorbed dose is largely determined by kidney function. Image-based tumor dosimetry and whole-body dosimetry are therefore both required to evaluate combination treatment strategies, such as the addition of the radiosensitizing agents cisplatin (31) and topotecan (32) to 131I-MIBG therapy. Because hematologic toxicity is dose-limiting in 131I-MIBG therapy, calculating the dose from TRT to tumor and normal organs would also allow 131I-MIBG to be combined with external-beam radiotherapy to boost primary tumor dose (33) above levels possible with 131I-MIBG alone.

CONCLUSION

This study has demonstrated that for 131I-MIBG therapy in relapsed or refractory neuroblastoma, the whole-body absorbed dose can be prescribed accurately and is a good predictor of hematologic toxicity. Compared with a fixed or weight-based radioactivity administration, the whole-body absorbed dose allowed higher activities of 131I-MIBG to be administered within the confines of bone marrow toxicity and thus enabled a personalization of therapy.

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REFERENCES


