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·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

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·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

total whole-body absorbed dose of 4 Gy. The work by Gaze et al. (7) was extended by Buckley et al. (16), who used image-based dosimetry to determine the absorbed tumor dose to 3 patients treated using this protocol. Whole-body dosimetry has also been used for other radionuclide therapies. Wahl et al. (17) performed whole-body dosimetry for ^{131}I-anti B1 therapy for non-Hodgkin lymphoma, assuming a monoexponential decay.

At our center, most pediatric ^{131}I-MIBG therapy patients are administered an activity calculated to deliver a whole-body absorbed dose of 2 Gy, using either a pretherapy tracer study or a previous therapy to obtain pharmacokinetics for dosimetry. In some cases, the first therapy is given using a weight-based formula. In this work, we use a retrospective analysis of therapies to examine the relationship between whole-body absorbed dose and hematologic toxicity and the most accurate method of delivering a prescribed whole-body absorbed dose. Hematologic toxicity is dose-limiting in ^{131}I-MIBG therapy (18) (assuming stem cells are not available, which is often the case in salvage therapy). Evidence of a dose–response relationship, 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 ^{123}I-MIBG (185 MBq) as a tracer for the therapy. For 5 treatments, ^{131}I-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 overshoes but were otherwise separated from the child by a shielded wall, lead screens, or lead glass. Patients were hydrated to prevent an excessive bladder absorbed dose. Hydration commenced 4 h before the ^{131}I-MIBG infusion and continued for 24 h. Young patients were also catheterized. Potassium iodide capsules (60 mg daily) were administered from 1 d before until 14 d after therapy, to prevent thyroid uptake. A similar procedure was followed for the tracer study, both to acclimatize the child to the procedure and the surroundings and to ensure that data were acquired in the same way as for the therapy method. The main difference between the tracer and the therapy administrations was the volume of MIBG administered (3–5 mL for the tracer study and 20–30 mL for therapy study, depending on the activity prescribed). Both therapies were given intravenously, with the therapy administration infused over 30 min to 1 h, depending on the activity. Administered activities were calculated accurately by measuring residues in the syringe and tubing after administration. In most cases, it was possible to complete the administration without the patient voiding. Blood pressure and pulse were measured every 10 min during administration, and no adverse effects were seen.

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 ^{131}I-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 ^{131}I-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, Ã,
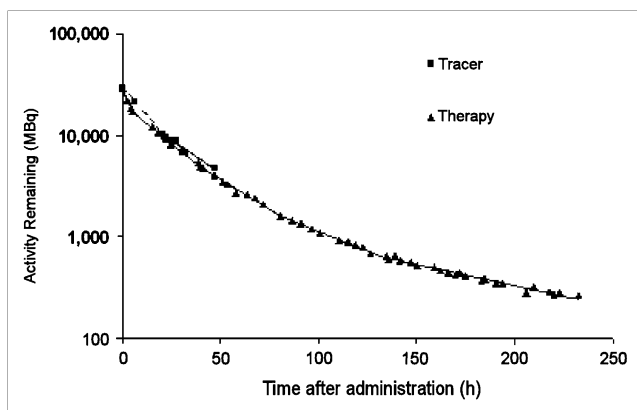
FIGURE 1. Example of time–activity curves for both ^{123}I-MIBG pretherapy tracer study (0–50 h) and therapy study (0–235 h) for patient 3's first treatment. Therapy activity of 29,378 MBq was administered.

$$\tilde{A} = \sum_{k=1}^{K} \frac{A_k - A_{k+1}}{\lambda_k}, \qquad \text{Eq.1}$$

where A_1 is the administered activity, A_k ($1 < k < K+1$) defines the activity level at the change from phase k-1 to phase k, λ_k is the effective decay constant of phase k, and K is the total number of exponential components. The mean absorbed dose, $\overline{D}$, was given by the product of the cumulated activity and the MIRD whole-body to whole-body S value, that is,

$$\overline{D}_{WB \leftarrow WB} = \tilde{A}_{WB} S_{(WB \leftarrow WB)}. \qquad \text{Eq. 2}$$

$S_{WB \leftarrow WB}$ values corrected for the weight of the child were obtained using the following equation:

$$S_{WB \leftarrow WB} = 1.34 \times 10^{-4} \, m_p^{-0.921} \, \text{Gy} \cdot \text{MBq}^{-1} \cdot \text{h}^{-1}, \qquad \text{Eq. 3}$$

where m_p is the patient's mass in kilograms. This equation was generated by interpolating the $S_{WB \leftarrow WB}$ values from the MIRD phantoms for a newborn; for 1-, 5-, 10-, and 15-y-old children; and for an adult, each of which has a specific mass (21).

Toxicity

For 30 administrations, sufficient blood data were available to calculate the post therapy platelet and leukocyte nadir. For 25 of these administrations, there were also sufficient data to determine the neutrophil nadir, and for 25 administrations there were sufficient data to calculate a recovery coefficient. This coefficient was defined as the increase in blood counts from nadir to normal divided by the time taken for this recovery. The grade of toxicity as defined by the Common Terminology Criteria for Adverse Events (CTCAE), version 3 (22), was also recorded after each administration.

Hematologic toxicity was analyzed for correlation with bone marrow involvement at therapy (positive bone marrow trephine biopsy), concomitant chemotherapy (OPEC/OJEC—vincristine [O], cisplatin [P]/carboplatin [J], etoposide [E] and cyclophosphamide [C]—topotecan, or melphalan), and relapsed or refractory

disease. 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 $10,302 \pm 7,402$ MBq (mean $\pm$ 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
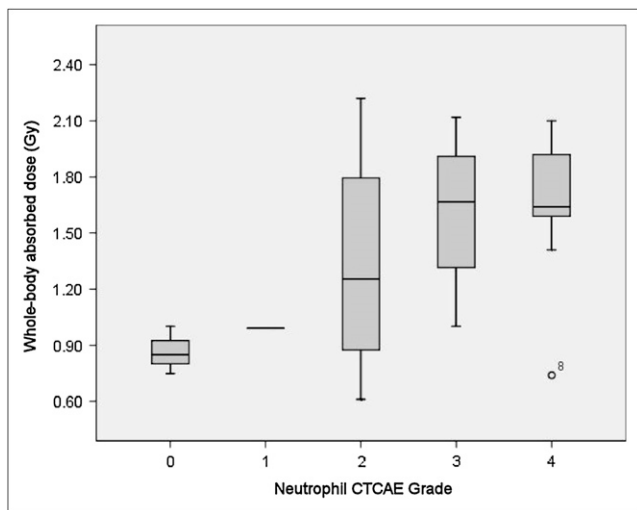
FIGURE 2. Correlation of CTCAE grade and whole-body absorbed dose. $P = 0.05$.

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 $46.1\% \pm 16.3\%$ for therapy 1 and $55.0\% \pm 23.8\%$ 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 (19×10^9/L and 70×10^9/L, $P = 0.008$). This trend was also seen in the leukocyte data (0.48×10^9/L and 2.3×10^9/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
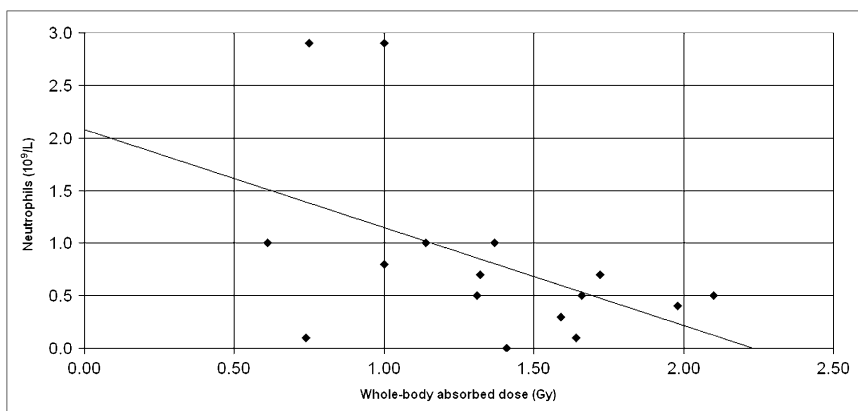
FIGURE 3. Correlation of neutrophils at nadir with measured whole-body absorbed dose ($r_p = -0.47$, $P = 0.064$). Data from 16 patients' first therapies were used to ensure independence of data points.

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).
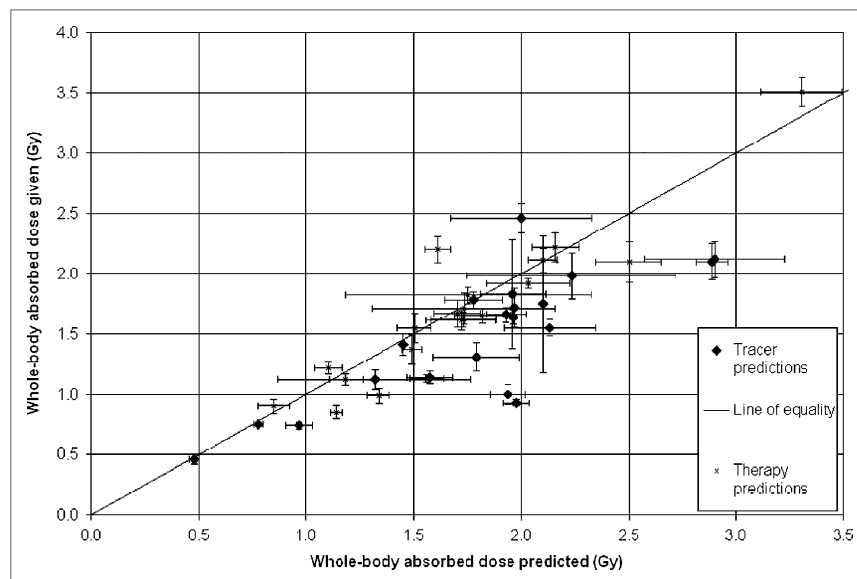
delivered dose ($P = 0.151$), thereby indicating that one therapy accurately predicts the next.

A total of 25% of the doses delivered were within ±10% using the weight-based formula. There was a wide range, with 10% of the predictions more than ±50% from the prescribed dose. The standard administration (7,400 MBq) had the largest range (0.3–3.11 Gy), with only 19% of the whole-body absorbed doses being within ±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}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}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
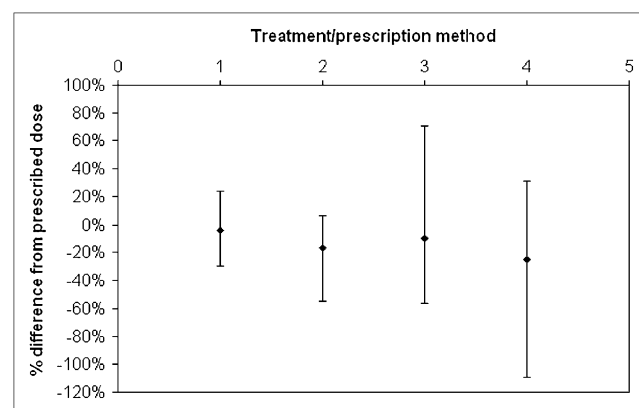
FIGURE 5. Range of doses delivered as percentage of prescribed dose for 4 prescription/treatment methods used (1 = previous therapy, 2 = tracer, 3 = weight-based, 4 = 7,400 MBq). The ♦ indicates median difference between delivered and prescribed dose, and error bars indicate range of these differences.

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 ^{131}I-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 ^{131}I-MIBG therapy. Because hematologic toxicity is dose-limiting in ^{131}I-MIBG therapy, calculating the dose from TRT to tumor and normal organs would also allow ^{131}I-MIBG to be combined with external-beam radiotherapy to boost primary tumor dose (*33*) above levels possible with ^{131}I-MIBG alone.

CONCLUSION

This study has demonstrated that for ^{131}I-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 ^{131}I-MIBG to be administered within the confines of bone marrow toxicity and thus enabled a personalization of therapy.

ACKNOWLEDGMENTS

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