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MINGUEZ GABINA, PABLO; Flux, Glenn; Genolla, Jose; Guayambuco, Sonia; Delgado, Alejandro; Fombellida, Jose Cruz; Sjögreen Gleisner, Katarina

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PO Box 117
221 00 Lund
+46 46-222 00 00

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Dosimetric results in treatments of neuroblastoma and neuroendocrine tumors with ^{131}I-metaiodobenzylguanidine with implications for the activity to administer

Pablo Mínguez[a)]
Department of Medical Radiation Physics, Lund University, Lund, Sweden
Department of Medical Physics, Gurutzeta/Cruces University Hospital, Barakaldo, Spain

Glenn Flux
Joint Department of Physics, Royal Marsden NHS Foundation Trust & Institute of Cancer Research, Sutton, UK

José Genollá
Department of Nuclear Medicine, Gurutzeta/Cruces University Hospital, Barakaldo, Spain

Sonía Guayambuco
Department of Nuclear Medicine, Gurutzeta/Cruces University Hospital, Barakaldo, Spain

Alejandro Delgado
Department of Nuclear Medicine, Gurutzeta/Cruces University Hospital, Barakaldo, Spain

José Cruz Fombellida
Department of Nuclear Medicine, Gurutzeta/Cruces University Hospital, Barakaldo, Spain

Katarina Sjögreen Gleisner
Department of Medical Radiation Physics, Lund University, Lund, Sweden

Purpose: The aim was to investigate whole-body and red-marrow absorbed doses in treatments of neuroblastoma (NB) and adult neuroendocrine tumors (NET) with ^{131}I-metaiodobenzylguanidine (mIBG), and to propose a simple method for determining the activity to administer when dosimetric data for the individual patient are not available.

Methods: Nine NB patients and six NET patients were included, giving in total 19 treatments as four patients were treated twice. Whole-body absorbed doses were determined from dose-rate measurements and planar gamma-camera imaging. For six NB and five NET treatments, red-marrow absorbed doses were also determined using the blood-based method.

Results: Dosimetric data from repeated administrations in the same patient were consistent. In groups of NB and NET patients, similar whole-body residence times were obtained, implying that whole-body absorbed dose per unit of administered activity could be reasonably well described as a power function of the patient mass. For NB, this functional form was found to be consistent with dosimetric data from previously published studies. The whole-

body to red-marrow absorbed dose ratio was similar among patients, with values of 1.4±0.6 to 1.7±0.7 (1 standard deviation) in NB treatments, and between 1.5±0.6 and 1.7±0.7 (1 standard deviation) in NET treatments.

Conclusions: The consistency of dosimetric results between administrations for the same patient supports prescription of the activity based on dosimetry performed in pre-treatment studies, or during the first administration in a fractionated schedule. The expressions obtained for whole-body absorbed doses per unit of administered activity as a function of patient mass for NB and NET treatments are believed to be a useful tool to estimate the activity to administer at the stage when the individual patient biokinetics has not yet been measured.

Key words: Neuroblastoma, Neuroendocrine tumors, Treatment schedule, ^{131}I-mIBG.

1. INTRODUCTION

In treatments of neuroblastoma (NB) and adult neuroendocrine tumors (NET), surgery is the first-line therapy with the aim of achieving a complete cure[1,2]. If radical surgery is not feasible, multimodal treatment options include surgery, chemotherapy, external beam radiotherapy (EBRT) and molecular radiotherapy (MRT)[3]. ^{131}I-mIBG therapy is administered for inoperable pheocromocytomas, paragangliomas, carcinoid tumors, stage III or IV relapsed or primary refractory NBs and metastatic or recurrent medullary thyroid cancers[4]. The number of patients treated with ^{131}I-mIBG is usually limited compared to the total number of NB and NET patients as ^{131}I-mIBG therapy is frequently considered only when other treatment modalities have been exhausted.

During the last two decades several studies have been published on the use of ^{131}I-mIBG for NB and NET treatments[5-12], and guidelines have been provided by the European Association of Nuclear Medicine (EANM)[4]. The administered activity is most commonly prescribed using

fixed activities[13,14] or a specified activity per patient mass[15-18] or per body surface[19]. Some studies have shown an improved treatment outcome with increased administered activities[20,21]. In NB treatments, the most established schedule is given by Gaze *et al.*[17]. In this protocol, two treatment administrations separated by a fortnight are given where the first is prescribed as activity per body mass (444 MBq/kg), and the second is tailored to deliver a whole-body absorbed dose of 4 Gy in total for the two administrations. In NET treatments, where dosimetric data are still limited[22], established schedules are currently lacking, although in principle a similar dosimetry-based approach could be adopted. In both NB and NET treatments, there is a need to compile experience and working knowledge of clinically obtained whole-body absorbed doses per unit of administered activity. Such information can be used to improve estimates of the activity to administer at the stage when dosimetric data are lacking, such as for the first activity administration in a fractionated schedule.

Hematologic toxicity is dose limiting in ^{131}I-mIBG therapy[23-25]. When activities above 444 MBq/kg are administered, harvesting of autologous tumor-free, hematopoietic stem cells must be performed before treatment[26]. In the schedule by Gaze *et al.*[17], stem-cell rescue is performed after approximately four weeks from the first administration, when the activity in the body has decreased below 30 MBq. When stem cells are not available, it must be ensured that the administered activity does not exceed levels that may induce non-tolerable red-marrow absorbed doses. Here, the use of whole-body dosimetry as a surrogate for red-marrow dosimetry has been established[27]. This obviates the need for repeated blood sampling, which is considered invasive, particularly in children. However, as pointed out in a recent review[12], no study has yet focused on the difference between whole-body and red-marrow absorbed doses.

This study reports on dosimetric results from ^{131}I-mIBG NB and NET treatments in the Gurutzeta-Cruces University Hospital during the last six years. The aim is to investigate

absorbed doses for whole body and red marrow. A further aim is to propose a simple method for determining the activity to administer at the stage when dosimetric data are not available for the individual patient, based on data acquired in this study and in the context of other published studies. The recommendations of the EANM[28] have been taken into account in the composition of the paper.

2. METHODS

2.A. Patient population and administrations

NB treatments

Nine patients (six male and three female, age 3y–22y) with relapsed stage-4 NB were included. Three patients were given two treatments separated by more than one year, with the result that twelve treatments were considered in total. Further on, NB treatments are denoted $T_{NB}1$—$T_{NB}9$, with postscripts *a* and *b* to indicate repeated treatment of the same patient. A summary of treatment data including patient mass, m_p, administered activity, A_{adm}, and performed measurements is given in Table 1. Treatments $T_{NB}1a$, $T_{NB}2$, $T_{NB}3$, $T_{NB}4$, $T_{NB}6a$, $T_{NB}7$ and $T_{NB}8$ were performed following the schedule by Gaze *et al.*[17]. Treatments $T_{NB}1b$, $T_{NB}5$, $T_{NB}6b$, $T_{NB}4$ and $T_{NB}9b$ were performed without concomitant chemotherapy and stem cell support in one or two fractions (see Table 1) aiming at giving a whole-body absorbed dose, D_{wb}, of 2 Gy. Treatment $T_{NB}9a$ was performed with concomitant chemotherapy and stem cell support but did not follow the schedule by Gaze *et al.*[17] to avoid exceeding A_{adm} of 37 GBq. The timing of stem cell support was approximately 4 weeks post-^{131}I-mIBG administration, as determined using dose-rate measurements.

Treatment	m_p (kg)	A_{adm} (GBq)			Performed measurements	
		Adm 1	Adm 2	Total	Adm 1	Adm 2
$T_{NB}1a$	11	5.0	5.5	10.5	DR/BD	DR
$T_{NB}1b$ (+13 months)*	13	5.5	N/A	5.5	DR	*N/A*
$T_{NB}2$	13	5.7	13.7	19.4	DR/BD	DR
$T_{NB}3$	14	6.3	6.7	13.0	DR/BD/PL	DR/BD/PL
$T_{NB}4$	17	7.7	6.5	14.2	DR	DR
$T_{NB}5$	18	4.2	3.7	7.9	DR	DR
$T_{NB}6a$	20	9.0	8.3	17.3	DR/BD	DR
$T_{NB}6b$ (+35 months)*	24	10.8	N/A	10.8	DR	*N/A*
$T_{NB}7$	22	9.8	9.8	19.6	DR	DR
$T_{NB}8$	32	13.0	14.4	27.4	DR	DR
$T_{NB}9a$	63	11.1	22.2	33.3	DR/BD	DR
$T_{NB}9b$ (+16 months)*	63	10.5	10.4	20.9	DR/BD/PL	DR/BD/PL

Table 1. Data of NB treatments. DR=Dose-rate measurement. BD=Blood dosimetry. PL=Planar imaging. Adm=Administration. *Time between repeated treatments.

NET treatments

Six NET patients were included (five female and one male, age 21y−80y). One patient was treated twice, so in total seven treatments were considered. Further on, NET treatments are denoted $T_{NET}1$—$T_{NET}6$, with postscripts *a* and *b* to indicate repeated treatment. A summary of treatment data is given in Table 2. For $T_{NET}2$, $T_{NET}3$, $T_{NET}5$, $T_{NET}6a$ and $T_{NET}6b$, a pre-treatment dosimetry study was also performed approximately one month before treatment.

Treatment	m_p (kg)	A_{adm} (GBq)				Performed measurements		
		Pre-Tr Adm	Adm 1	Adm 2	Total (Adm 1 + Adm 2)	Pre-Tr Adm	Adm 1	Adm 2
$T_{NET}1$ (paraganglioma)	58	N/A	16.2	N/A	16.2	N/A	DR	N/A
$T_{NET}2$ (carcinoid tumor)	44	0.44	21.2	N/A	21.2	PL/BD	DR	N/A
$T_{NET}3$ (pheochromocytoma)	66	0.071	14.4	N/A	14.4	PL/BD	DR	N/A
$T_{NET}4$ (pheochromocytoma)	49	N/A	5.6	7.8	13.4	N/A	DR	DR
$T_{NET}5$ (carcinoid tumor)	80	0.23	9.0	8.6	17.6	PL/BD	DR/BD	DR
$T_{NET}6a$ (pheochromocytoma)	49	0.19	7.8	N/A	7.8	PL/BD	DR	N/A
$T_{NET}6b$ (pheochromocytoma) (+1 year)*	49	0.20	8.4	9.6	18.0	PL/BD	DR	DR

Table 2. Data of NET treatments, including diagnosis. DR=Dose-rate measurement. BD=Blood dosimetry. PL=Planar imaging. Pre-Tr Adm=Pre-treatment administration. Adm=Administration. *Time between repeated treatments.

Specific activity of the administered ^{131}I-mIBG was 1110 MBq/mg. In both NB and NET treatments, the average time as inpatients was five days in each administration (range four−six days) and patients were released according to Spanish national regulations, in agreement with recommendations of the IAEA[29]. The therapeutic use of ^{131}I-mIBG is approved by the Spanish Agency of Medicines and Medical Devices and informed consent from all patients, or from their parents in the case of children, was obtained.

2.B. Data acquisition and activity quantification

Dose-rate measurements were performed during the time as inpatients for estimation of the whole-body time-activity curve (see Tables 1 and 2). Measurements were performed using a handheld, pressurized ion-chamber survey-meter, Inovision Model 451P, Fluke Biomedical (Eindhoven, The Netherlands). Acquisitions were made at distances of 1 m and 2 m from standing patients at marked positions on the floor, in both anterior and posterior directions. The height of the detector in relation to the floor was held constant with reference to an external mark, and all measurements were made by trained staff. The first measurement was performed immediately after the administration to obtain a reading corresponding to the total A_{adm}. Remaining measurements were made approximately every two hours during the first day, every four hours during the second day and every six hours during the remaining days, aiming at performing acquisitions after bladder voids. In total this yielded approximately 20 time points for each treatment. The signal-to-noise ratio, estimated by dividing the patient readings with the variability in background readings, was above 20 in all measurements, and dead-time effects were negligible. A sequence of whole-body time-activity values, $A_{wb}(t)$, was determined from the anterior and posterior readings, $R_A(t)$ and $R_P(t)$, for each patient-detector distance according to

$$A_{wb}(t) = A_{adm}\frac{\sqrt{R_A(t)R_P(t)}}{\sqrt{R_A(0)R_P(0)}} = A_{adm}\, r(t) \qquad (1)$$

where $r(t)$ were the relative values obtained from measurement, with $r(0)$ =1. The $A_{wb}(t)$ values from measurements at 1 m and 2 m differed less than 5%, and the average value was therefore used. A dose calibrator, Capintec CRC®-15R, (Capintec, Inc Ramsey, NJ, USA), was used for measurements of A_{adm}.

Planar imaging using a gamma camera was employed to estimate the whole-body time-activity curve in NET pre-treatment dosimetric studies, and also in two NB treatments for comparison to dose-rate meter derived values (Tables 1 and 2). Acquisitions were made employing a dual-head General Electric (GE, Fairfield, CT, USA) Infinia Hawkeye gamma camera, with a crystal thickness of 9.5 mm and equipped with High-Energy General-Purpose collimators. A scan speed of 12 cm/min, a matrix size of 256×1024, and an energy window of 20% centered at 364 keV were used. For the NET pre-treatment dosimetric studies, in which acquisitions were performed a few minutes, 24 h, 48 h and 120 h after the administration, the administered activity was low and dead-time effects were thus negligible. To avoid dead-time effects for NB patients, where pre-treatment imaging was not performed, the first therapy administration was separated into two fractions. Approximately 370 MBq was injected and a whole-body scan was performed. Immediately after this acquisition, the rest of the activity was injected. The remaining acquisitions were performed approximately at 48 h and 115 h. In all the acquisitions performed, the count rate was below 10000 counts per second. The whole-body activity was determined using Eq. (1), where $R_A(t)$ and $R_P(t)$ were then the net count rates in regions of interest (ROIs) encompassing the body in anterior and posterior images, subtracted by the count rate in background ROIs rescaled to the area of the whole-body ROI, to partly compensate for septal penetration and scatter.

Blood sampling was performed in six NB treatments, five NET pre-treatment studies, and one NET treatment, for the purpose of red-marrow dosimetry (see Tables 1 and 2). For NB patients blood sampling was performed at a few minutes, 6 h, 24 h, 48 h, 72 h, and 96 h or

115 h after injection, whereas for NET patients, blood sampling was made at a few minutes, 6 h, 24 h, 48 h, and 120 h. Blood samples of 1 ml or 2 ml volume were prepared using a pipette, and were then allowed to decay to avoid dead-time effects. Measurements were performed using a calibrated γ-well counter 1282 Compugamma CS LKB Wallac (Melbourne, Australia). The activity concentration was determined by dividing the obtained count rate by a pre-determined calibration factor and the sample volume.

2.C. Dosimetric calculations

D_{wb} were calculated following the standard MIRD methodology[30], as described in Appendix A. Blood-based calculation of red-marrow absorbed dose, D_{rm}, was carried out according to procedures in the EANM guidelines[26] and to the MIRD formalism, including source terms from activity in the red marrow and in the remainder of the body for the self- and cross-absorbed dose, respectively, as described in Appendix B. Additionally, the method described by Traino *et al.*[31] was used.

The standard deviations in D_{wb} and D_{rm} were estimated by uncertainty propagation[32], as described in Appendix C. For both D_{wb} and the whole-body residence time, τ_{wb}, the relative standard deviation was estimated to be 20%. The main contribution to D_{rm} was the cross-absorbed dose from the remainder of the body, and the relative standard deviation for D_{rm} was thus also estimated to be 20%. These uncertainties are in line with values suggested by others[33,34].

2.D. Hematologic toxicities

The post-therapy platelet, neutrophil and leukocyte nadir was obtained in NET treatments in order to study hematologic toxicity. The grade of toxicity was analyzed according to the Common Terminology Criteria of Adverse Events (CTCAE), version 3[35] (available at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). In

NB treatments the grade of hematologic toxicity was not quantified, since in the majority of treatments the intent was aplasia.

3. RESULTS

3.A. NB treatments

Table 3 summarizes values obtained for τ_{wb} and D_{wb}/A_{adm}. The mean value of D_{wb}/A_{adm} was 0.22 ±0.04 (1 standard deviation) Gy/GBq (median 0.22 Gy/GBq). For all treatments except $T_{NB}2$, where the patient suffered from nephropathy and thus had a shorter τ_{wb}, values of τ_{wb} were within 25.1 h - 29.3 h (mean 27.1 ±5.4 h, median 26.7 h). For the patients that followed the schedule by Gaze *et al.*[17], that is, those who were prescribed a D_{wb} of 4 Gy in two administrations, the prescription was followed to within 0.1 Gy.

Treatment	τ_{wb} (h)		D_{wb}/A_{adm} (Gy/GBq)			D_{wb} (Gy)		
	Adm 1	Adm 2	Adm 1	Adm 2	Total	Adm 1	Adm 2	Total
$T_{NB}1a$	26.5±5.3	25.5±5.1	0.38±0.08	0.36±0.07	0.37±0.07	1.9±0.4	2.0±0.4	3.9±0.8
$T_{NB}1b$	25.1±5.0	N/A	0.33±0.07	N/A	0.33±0.07	1.8±0.4	N/A	1.8±0.4
$T_{NB}2$	15.9±3.2	16.0±3.2	0.21±0.04	0.20±0.04	0.21±0.04	1.2±0.2	2.8±0.6	4.0±0.8
$T_{NB}3$	26.7±5.3	28.2±5.6	0.30±0.06	0.33±0.07	0.32±0.06	1.9±0.4	2.2±0.4	4.1±0.8
$T_{NB}4$	28.6±5.7	28.3±5.7	0.29±0.06	0.28±0.06	0.28±0.06	2.2±0.4	1.8±0.4	4.0±0.8
$T_{NB}5$	25.5±5.1	25.2±5.0	0.24±0.05	0.22±0.04	0.23±0.05	1.0±0.2	0.8±0.2	1.8±0.4
$T_{NB}6a$	27.3±5.5	27.9±5.6	0.23±0.05	0.24±0.05	0.24±0.05	2.1±0.4	2.0±0.4	4.1±0.8
$T_{NB}6b$	26.3±5.3	N/A	0.19±0.04	N/A	0.19±0.04	2.0±0.4	N/A	2.0±0.4
$T_{NB}7$	26.0±5.2	26.2±5.2	0.19±0.04	0.20±0.04	0.20±0.04	1.9±0.4	2.0±0.4	3.9±0.8
$T_{NB}8$	26.6±5.3	26.1±5.2	0.15±0.03	0.15±0.03	0.15±0.03	1.9±0.4	2.1±0.4	4.0±0.8
$T_{NB}9a$	29.3±5.9	28.9±5.8	0.09±0.02	0.09±0.02	0.09±0.02	1.0±0.2	1.9±0.4	2.9±0.6
$T_{NB}9b$	28.8±5.8	28.9±5.8	0.09±0.02	0.09±0.02	0.09±0.02	0.9±0.2	0.9±0.2	1.8±0.4

Table 3. Results for τ_{wb}, D_{wb}/A_{adm} and D_{wb} in NB treatments

Data in Table 3 are based on probe-based dose-rate measurements. Figure 1 shows a comparison between A_{wb} (t) derived from dose-rate measurements and gamma camera images for $T_{NB}3$. Differences between values obtained from imaging and dose-rate measurements were within 10% for both $T_{NB}3$ and $T_{NB}9b$.

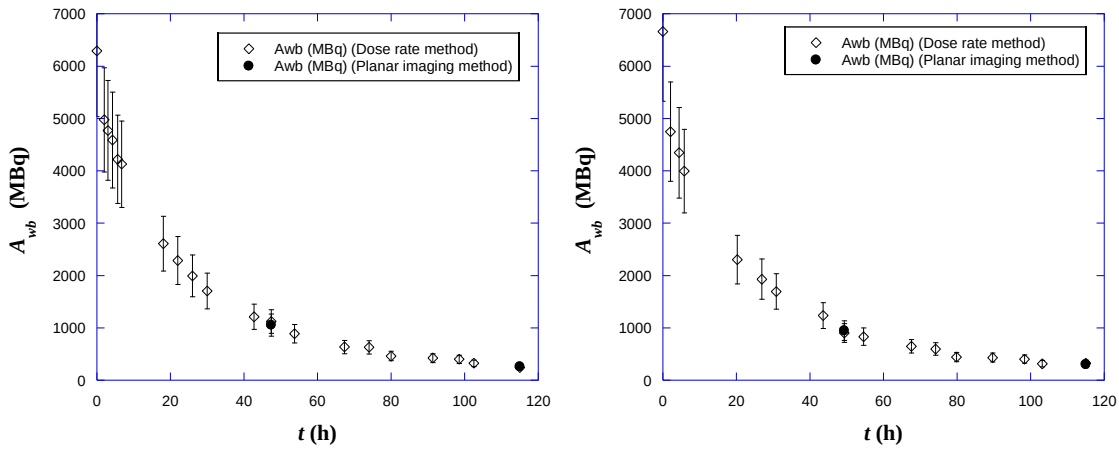

Figure 1. Results for $A_{wb}(t)$, for the first (left panel), and second administration (right panel), in $T_{NB}3$. Open symbols are from dose-rate measurements, and closed symbols are from whole-body planar images acquired at 48h and 115h.

Table 4 shows the results of D_{rm} and D_{rm}/A_{adm}. For $T_{NB}1b$, $T_{NB}4$, $T_{NB}5$, $T_{NB}6b$, $T_{NB}7$ and $T_{NB}8$ red-marrow dosimetry could not be performed due to lack of blood samples. Following the procedure by Traino *et al.*[31] values obtained for D_{rm} were lower, but within 10 % of values of D_{rm} in Table 4. The self-absorbed dose was between 9% and 11% of the total D_{rm}. For the two treatments where measurements were made in both administrations ($T_{NB}3$ and $T_{NB}9b$), the ratio D_{rm}/A_{adm} was approximately equal. For the other treatments, D_{rm} for the second administration was thus estimated by assuming an equal D_{rm}/A_{adm} between administrations. Table 4 also shows the ratio D_{wb}/D_{rm}, which ranged from 1.4 to 1.7 (mean 1.5±0.6, median 1.5).

Treatment	Adm 1		Adm 2		Both Adm	
	D_{rm} (Gy)	D_{rm}/A_{adm} (Gy/GBq)	D_{rm} (Gy)	D_{rm}/A_{adm} (Gy/GBq)	D_{rm} (Gy)	D_{wb}/D_{rm}
$T_{NB}1a$	1.4±0.3	0.27±0.05	1.5±0.3*	N/A	2.9±0.6	1.4±0.6
$T_{NB}2$	0.8±0.2	0.15±0.03	2.0±0.4*	N/A	2.9±0.6	1.4±0.6
$T_{NB}3$	1.1±0.2	0.18±0.04	1.3±0.3	0.19±0.04	2.4±0.5	1.7±0.7
$T_{NB}6a$	1.0±0.3	0.14±0.03	1.2±0.2*	N/A	2.5±0.5	1.6±0.6
$T_{NB}9a$	0.6±0.1	0.06±0.01	1.3±0.3*	N/A	1.9±0.4	1.5±0.6
$T_{NB}9b$	0.6±0.1	0.05±0.01	0.6±0.1	0.06±0.01	1.2±0.2	1.5±0.6

Table 4. Results for D_{rm} and D_{rm}/A_{adm}, in administrations 1 and 2, in NB treatments. For both administrations, the values of the total D_{rm} and D_{wb}/D_{rm} are shown. * Extrapolated values obtained by assuming the value of D_{rm}/A_{adm} obtained for the first administration.

3.B. NET treatments

Table 5 summarizes the values obtained for τ_{wb} and D_{wb}/A_{adm}. The mean value of D_{wb}/A_{adm} was 0.16±0.03 Gy/GBq (median 0.13 Gy/GBq). With the exception of $T_{NET}4$ and $T_{NET}5$, who suffered from a large tumor burden and thus had notably longer τ_{wb}, values of τ_{wb} were within the range 31.0 h — 35.2 h (mean 33.1 ±6.6 h, median 33.3 h).

Treatment	τ_{wb} (h)		D_{wb}/A_{adm} (Gy/GBq)			D_{wb} (Gy)		
	Adm 1	Adm 2	Adm 1	Adm 2	Total	Adm 1	Adm 2	Total
$T_{NET}1$	32.1±6.4	N/A	0.10±0.02	N/A	0.10±0.02	1.7±0.3	N/A	1.7±0.3
$T_{NET}2$	35.2±7.0	N/A	0.15±0.03	N/A	0.15±0.03	3.1±0.6	N/A	3.1±0.6
$T_{NET}3$	31.0±6.2	N/A	0.09±0.02	N/A	0.09±0.02	1.3±0.3	N/A	1.3±0.3
$T_{NET}4$	82.2±16.4	82.6±16.5	0.30±0.06	0.31±0.06	0.31±0.06	1.7±0.3	2.4±0.5	4.1±0.8
$T_{NET}5$	69.5±13.9	58.2±11.6	0.17±0.03	0.14±0.03	0.15±0.03	1.5±0.3	1.2±0.2	2.7±0.5
$T_{NET}6a$	33.1±6.6	N/A	0.13±0.03	N/A	0.13±0.03	1.0±0.2	N/A	1.0±0.2
$T_{NET}6b$	33.7±6.7	33.5±6.7	0.13±0.03	0.14±0.03	0.13±0.03	1.1±0.2	1.3±0.3	2.4±0.5

Table 5. Results for τ_{wb}, D_{wb}/A_{adm} and D_{wb} in NET treatments.

Table 6 shows D_{rm}/A_{adm} obtained for pre-treatment dosimetric studies. In $T_{NET}1$ and $T_{NET}4$ blood samples could not be obtained. Following the procedure by Traino *et al.*[31] lower values for D_{rm} were obtained, but within 10% of values of D_{rm} in Table 6. The self-absorbed dose was between 14% and 18% of the total D_{rm}. For $T_{NET}5$, D_{rm} was also calculated during the first treatment administration. The value of D_{rm}/A_{adm} obtained was 0.10±0.02 Gy/GBq, which was thus in agreement with that of the pre-treatment study. Table 6 also shows the ratio D_{wb}/D_{rm}, which ranged between 1.5 and 1.7 (mean 1.6±0.6, median 1.7).

Pre-treatment study	D_{rm}/A_{adm} (Gy/GBq)	D_{wb}/D_{rm}
$T_{NET}2$	0.08±0.02	1.7±0.7
$T_{NET}3$	0.06±0.01	1.5±0.6
$T_{NET}5$	0.09±0.02	1.7±0.7
$T_{NET}6a$	0.07±0.01	1.7±0.7
$T_{NET}6b$	0.08±0.02	1.6±0.6

Table 6. Results for D_{rm}/A_{adm}, and D_{wb}/D_{rm} in pre-treatment dosimetric studies in NET patients.

The grade of toxicity in NET treatments is shown in Table 7. No correlation between the grade of toxicity in platelets, leukocytes and neutrophils and D_{wb} or D_{rm} was found. However, there was a tendency that toxicity was more pronounced for elderly patients than for younger ones.

Treatment	Grade of toxicity			Patients' age
	Platelets	Leukocytes	Neutrophils	(y)
$T_{NET}1$	None	None	None	24
$T_{NET}2$	3	4	4	73
$T_{NET}3$	4	4	4	62
$T_{NET}4$	3	3	2	60
$T_{NET}5$	3	3	2	80
$T_{NET}6a$	None	None	None	27
$T_{NET}6b$	None	None	None	28

Table 7. Grade of toxicity in NET treatments.

3.C. Analysis of dosimetric results for NBs and NETs

Figure 2 shows the ratio D_{wb}/A_{adm} for both NB and NET treatments, and a large variability between patients can be observed. Values of D_{wb}/A_{adm} for repeated administrations (including treatments and pre-treatment dosimetric studies) in the same patient were consistent, thus supporting the concept of performing absorbed dose planning for subsequent administrations.

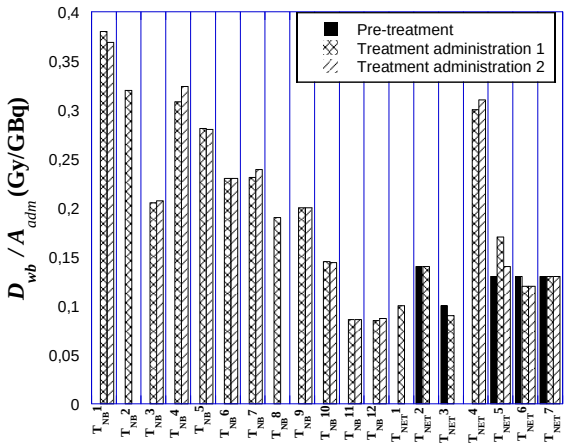

Figure 2. Results obtained for D_{wb}/A_{adm} in NB treatments and in NET pre-treatment and treatment studies.

As seen in Table 3, a similar τ_{wb} was obtained in NB treatments, except for $T_{NB}2$. If inserting one single value of τ_{wb} into Eq. (A1), the ratio D_{wb}/A_{adm} follows a power dependence with m_p. Using the mean value of τ_{wb} obtained in this study, the following Equation was obtained:

$$(D_{wb}/A_{adm})_{NB} = 3.63\, m_p^{-0.921} \qquad (2)$$

in unit of Gy/GBq. Results of Eq. (2) were compared to results from previously published studies, using data of D_{wb}/A_{adm} for NB treatments as retrieved from the study by Toporski *et al.*[11] performed at Lund University Hospital, Sweden, and from the study by Buckley *et al.*[25] performed at Royal Marsden Hospital, UK. To rule out inconsistencies in calculation methods among centers, a small comparison exercise was undertaken sharing three sets of acquired time-dose rate data. D_{wb} were calculated at each of the three centers, with results obtained of within ±10% from the mean value, thus supporting a combined data analysis. Figure 3 shows Eq. (2) in relation to data acquired in this study, and combined with data from Toporski *et al.*[11] and Buckley *et al.*[25].

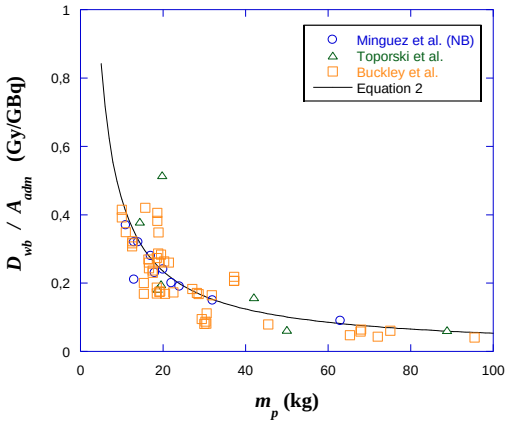

Figure 3. Results for D_{wb}/A_{adm} as function of m_p from Toporski *et al.*[11], Buckley *et al.*[25], and data obtained in this study. The solid line shows the curve obtained from Eq. (2).

Regarding NET (Table 5), similar values of τ_{wb} were obtained for the five treatments with modest tumor burden. Inserting the mean value obtained into Eq. (A1), the following Equation was obtained:

$$(D_{wb}/A_{adm})_{NET} = 4.44\, m_p^{-0.921} \qquad (3)$$

Figure 4 shows D_{wb}/A_{adm} as a function of m_p using Eq. (3). Comparing the graphs for NB and NET treatments (Figure 4, right panel), differences in D_{wb}/A_{adm} values were small for adult masses but increased slightly for pediatric masses.

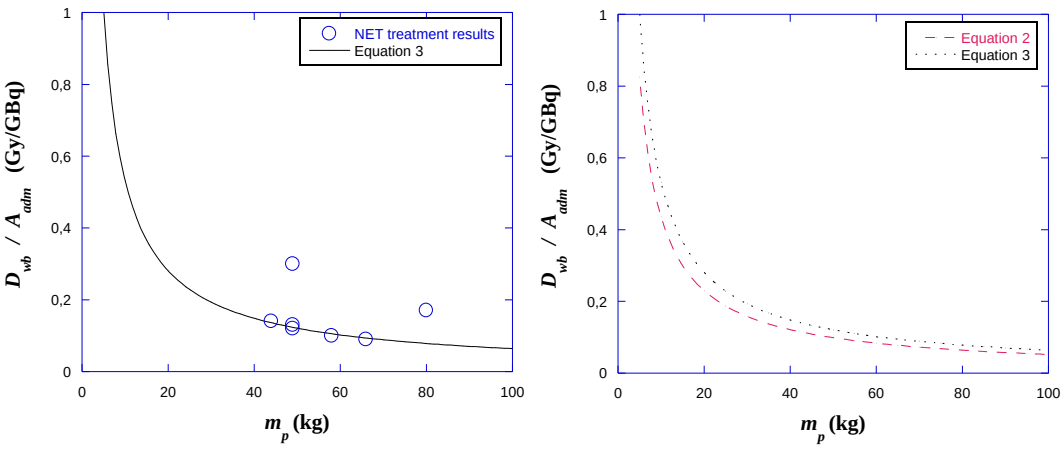

Figure 4. Results for D_{wb}/A_{adm} as a function of m_p in NET patients (left), and (right) comparison of Eqs. (2) and (3), representing D_{wb}/A_{adm} as a function of m_p for NB and NET patients, respectively.

4. DISCUSSION

In NB and NET treatments with ^{131}I-mIBG, very different schedules have been reported[13-19], often using prescriptions in terms of a fixed activity or a predetermined activity per body mass. For treatment of NB, the most widely used dose scheduling approach is that of Gaze *et al.*[17] and is based on planning of D_{wb} using two treatment fractions. In NET treatments, such established schedules are still lacking, although a similar approach could be adopted to tailor D_{wb} with regard to the risk of inducing hematologic and non-hematologic toxicities.

The analysis of patient data by Eqs. (2) and (3) for NB and NET treatments, respectively, was motivated by a practical need for activity prescriptions in situations when τ_{wb} for an individual patient has not yet been measured, such as for the first activity administration in a dosimetry-based schedule. Eqs. (2) and (3) should be thus regarded as an alternative to prescribing a fixed activity or activity per body mass. For comparison with the schedule given by Gaze *et al.*[17], Eq. (2) was reformulated in terms of D_{wb} as a function of A_{adm}/m_p (Figure 5). Eq. (2) has the advantage of taking the decreasing values of $S_{wb\leftarrow wb}$ into account, which implies that for the heavier patients, a lower activity can be administered. For instance, for a 70 kg patient the activity to administer is decreased by approximately 12% as compared to using 444 MBq/kg[17]. Comparison was also made to the work by Matthay *et al.*[22], where a linearly increasing D_{wb} was obtained when presented as a function of A_{adm}/m_p, with a considerably larger variability in D_{wb} for higher values of A_{adm}/m_p. Their results thus agree with Eq. (2), both concerning the linear increase and the larger variability in D_{wb} for higher values of A_{adm}/m_p. Due to the limited amount of data for NET patients (Figure 4), Eq. (3) should be treated with caution and regarded as preliminary. Comparison studies with results from other centers would be desirable, especially for m_p values outside the included range. However, in the literature, reported dosimetry values for ^{131}I-mIBG treatment of NET patients are still few. In this study, D_{wb}/A_{adm} values are higher and show a wider range for NB than for NET

treatments consistent with those reported in Sudbrock *et al.*[9] and Hindorf *et al.*[27]. Figures 3 and 4, based on Eqs. (2) and (3), respectively, provide an explanation for those results based on the dependence of D_{wb}/A_{adm} on m_p. It is important to note that Eqs. (2) and (3) are not intended as replacement for dosimetry-based schedules, since τ_{wb} of individual patients may vary to a high degree. For instance, in $T_{NB}2$, the patient (m_p=13kg) suffered from a nephropathy and the obtained D_{wb}/A_{adm} value was lower that the value obtained by Eq. (2), as seen in Figure 3 and Table 3. In $T_{NET}4$ and $T_{NET}5$ (m_p=49 kg and 80 kg, respectively), patients had an extensive tumor burden and their D_{wb}/A_{adm} values were notably higher than the value obtained from Eq. (3), as seen in Figure 4 (left) and Table 5. Thus, whole-body dosimetry measurements during the first administration would still be necessary in order to calculate the activity to deliver in the second administration.

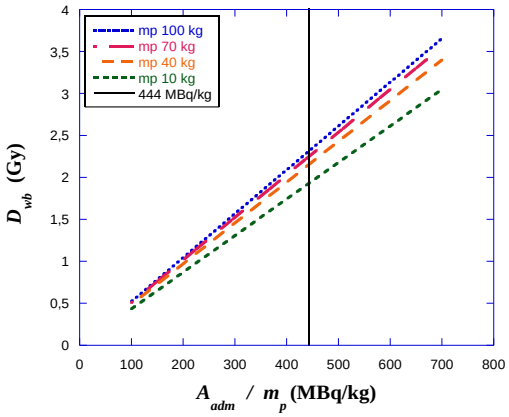

Figure 5. Representation of Eq. (2) in terms of D_{wb} as a function of A_{adm}/m_p. The vertical line represents the activity of 444MBq/kg given in the schedule by Gaze *et al.*[17].

D_{wb} is generally used as a surrogate for D_{rm} in ^{131}I-mIBG therapy. In this study, values of D_{rm} were found to be between 60% and 70% of D_{wb}, which is reasonable considering the modest contribution of the self-absorbed dose and the values for the $S_{wb\leftarrow wb}/S_{rm\leftarrow wb}$ ratio. In patients in whom there is red-marrow and/or bone uptake, it is generally recommended to use imaging-based estimates of D_{rm}[26,36,37], as blood-based values may underestimate the real value. However, results from the blood-based method may be a good approximation when red-

marrow or bone uptake is localized to small regions[36]. For the patients in this study where red-marrow dosimetry was performed, in five patients ($T_{NB}9a$, $T_{NB}9b$, $T_{NET}2$, $T_{NET}6a$ and $T_{NET}6b$) uptake in red marrow or bone was seen in separate SPECT-CT studies, but involved less than 5% of the total marrow volume, thus justifying the use of the blood-based dosimetry method.

A further analysis was performed by comparison to the results from Matthay *et al.*[22], who studied dose escalation of ^{131}I-mIBG in treatment of NB with autologous stem-cell rescue. In their work, none of the 18 patients who were given activities < 555 MBq/kg required stem cell infusion, whereas two of seven patients given 555 MBq/kg and nine of 17 patients given 666 MBq/kg required stem-cell support. Using Eq. (2) and the obtained mean value of D_{wb}/D_{rm} for NB of 1.5, an estimation of D_{rm} for values of A_{adm}/m_p of 444, 555 and 666 MBq/kg was made (Figure 6). Activities of 666 MBq/kg resulted in a D_{rm} which for most m_p exceeded the tolerance dose of approximately 1.6—2 Gy[25]. Giving 555 MBq/kg, D_{rm} close to 2 Gy were obtained, whereas for 444 MBq/kg, D_{rm} were well below 2 Gy. Figure 6 also shows the D_{wb} as estimated from Eq. (2), indicating that on average 444 MBq/kg[17] results in D_{wb} above 2 Gy for patients above approximately 15 kg.

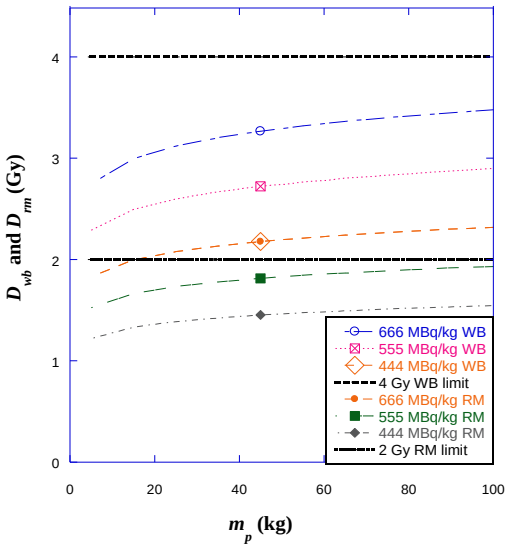

Figure 6. Representation of D_{wb} and D_{rm} as function of m_p for NB patients, for A_{adm} of 444, 555 and 666 MBq/kg. Values have been derived from Eq. (2) and a value of D_{wb}/D_{rm} of 1.5.

The grade of hematologic toxicity (Table 7) shows that caution must be exercised for high-activity treatments. Unlike that of Buckley *et al.*[25], this study found no correlation between the grade of hematologic toxicity and D_{wb}. Notably, in $T_{NET}3$, a D_{wb} of 1.3 Gy was delivered but the patient suffered grade-4 toxicity (platelets, leukocytes and neutrophils) and in $T_{NET}4$, the patient with multiple bone metastases received a D_{wb} of 4.1 Gy but did not exceed grade-3 toxicity. As with D_{wb}, no correlation was found between the grade of hematologic toxicity and D_{rm}. There are several possible reasons for the lack of correlation found between D_{rm} and D_{wb} with hematologic toxicity. Among those are the low number of patients included, the different ages of patients, the diversity of NETs (pheochromocytoma, carcinoid tumor and paraganglioma), prior hematotoxic treatments, and the way the cross-absorbed dose to the red marrow is calculated in Eq. (B1). Regarding the latter point, if the activity in the remainder of the body is mainly localized in tumors, then its contribution to D_{rm} is likely to be heterogeneous with an important proportion of the red marrow receiving absorbed doses below tolerance values. In a study of hematological toxicity in EBRT performed by Petersson *et al.*[38], it was shown that the severity of toxicity correlated with the volume fraction of red marrow that was irradiated. In this study the volume distribution of D_{rm} was not addressed, and so, depending on the tumor burden, two treatments with the same value of D_{rm} obtained from Eq. (B1) may show different hematologic toxicity. These results indicate the need to improve currently used methods for red-marrow dosimetry in MRT, taking the heterogeneous distribution of internal absorbed doses into account.

5. CONCLUSIONS

In treatments with ^{131}I-mIBG, the activity to administer in order to give a prescribed D_{wb} varies from patient to patient. In this study, consistent values of D_{wb}/A_{adm} were obtained when

determined for different administrations in the same patient, whereas a considerable variation was seen among patients. These results thus support the use of absorbed-dose planning for multiple-fraction treatment. Moreover, an expression was proposed for prescription of the activity for the first administration, which takes into account the dependence of D_{wb}/A_{adm} on m_p, to be used at the stage when dosimetric data for the individual patient have not yet been measured. For red marrow, D_{rm} was found to be between 60% and 70% of D_{wb}.

Competing interests

The authors declare that they have no competing interests.

APPENDIX A: WHOLE-BODY ABSORBED DOSE (D_{wb})

D_{wb} is given by:

$$D_{wb} = \tilde{A}_{wb} S_{wb \leftarrow wb} = A_{adm}\, \tau_{wb}\, S_{wb \leftarrow wb} \tag{A1}$$

where $\tilde{A}_{wb}$ is the cumulated activity in the whole body (wb) and $S_{wb \leftarrow wb}$ is the whole-body absorbed dose per cumulated activity in wb, calculated according to Cristy *et al.*[39]:

$$S_{wb \leftarrow wb} = 1.34 \times 10^{-4}\, m_p^{-0.921} \tag{A2}$$

in Gy MBq^{-1} h^{-1}, and m_p is the patient mass (kg). The residence time τ_{wb} is determined from the values $r(t)$ obtained from measurement (Eq. (1)), by fitting one exponential function for each of the n components and performing integration, according to:

$$\tau_{wb} = \sum_{i=1}^{n} \frac{a_i - a_{i+1}}{\lambda_i} \tag{A3}$$

where coefficient a_i is the initial value for component i and λ_i is the effective half-life, in unit h^{-1}, for the respective component[25]. The value of n was set to 3 and 2, for dose-rate measurements and gamma-camera imaging, respectively.

APPENDIX B: RED-MARROW ABSORBED DOSE (D_{rm})

D_{rm} is given by:

$$D_{rm} = \tilde{A}_{rm} S_{rm \leftarrow rm} + \tilde{A}_{rb} S_{rm \leftarrow rb} \tag{B1}$$

where $\tilde{A}_{rm}$ and $\tilde{A}_{rb} = \tilde{A}_{wb} - \tilde{A}_{rm}$ are the cumulated activities in the red marrow (*rm*) and the remainder of the body (*rb*), respectively, $S_{rm \leftarrow rm}$ is the factor describing the self-absorbed dose from activity residing in *rm*, and $S_{rm \leftarrow rb}$ is the factor describing the cross-absorbed dose from activity residing in *rb* and is given by the expression:

$$S_{rm \leftarrow rb} = S_{rm \leftarrow wb} \frac{m_{wb}}{m_{rb}} - S_{rm \leftarrow rm} \frac{m_{rm}}{m_{rb}} \tag{B2}$$

where $S_{rm \leftarrow wb}$ is the factor describing the cross-absorbed dose from activity residing in *wb*, and m_{wb}, m_{rb} , and m_{rm}, are the masses of *wb*, *rb* and *rm*, respectively. *S*-values and values of m_{wb}, m_{rb} and m_{rm} were obtained for the male and female reference phantoms in OLINDA/EXM[40], and were scaled to the mass of the individual patient.

$\tilde{A}_{rm}$ was obtained following:

$$\tilde{A}_{rm} = [\tilde{A}]_{blood} \, RMBLR \cdot m_{rm} \tag{B3}$$

where $[\tilde{A}]_{blood}$ is the cumulated activity in blood per unit of volume, and *RMBLR* is the red marrow-to-blood activity concentration ratio, which was set to 1[41,42].

APPENDIX C: ESTIMATION OF UNCERTAINTIES

The standard deviation in D_{wb} was determined by uncertainty propagation through Eq. (A1), considering only the uncertainty in $\tilde{A}_{wb}$ as determined from standard deviations of A_{adm} and τ_{wb}. The relative standard deviation of A_{adm} was estimated to be 5%. The uncertainty in τ_{wb} (Eq. (A3)) depended on the uncertainty in the parameters a_i and λ_i, which in turn depended on the uncertainty of $r(t)$ in Eq. (1), and the number of data points used for curve fitting. The standard deviation in $r(t)$, σ_r, was calculated by uncertainty propagation through the expression for $r(t)$. For dose rate measurements, uncertainties in $R_A(t)$ and $R_P(t)$ were primarily related to measurements of patient-detector distance and fluctuations in the measured value, for which the relative standard deviations were estimated to be 5% in both cases. For gamma camera measurements, the major sources of uncertainty in $R_A(t)$ and $R_P(t)$ were assumed to be operator dependency in delineation of the whole-body ROI, and a variability in the accuracy of Eq. (1) due to different attenuation and scatter conditions for different times after administration. The relative standard deviations of these effects were estimated to be 7% and 10%, respectively. The uncertainty contribution to τ_{wb} from curve fitting was determined from simulated, typical time-retention curves, consisting of three components. This simulation was performed by generating time-series of values $r(t)$ using an analytical expression, and then replacing each data point with a value which was sampled from a normal distribution with standard deviation σ_r. One hundred simulations were performed, giving a relative standard deviation for τ_{wb} of approximately 19% for both measurement techniques. The relative standard deviations in $\tilde{A}_{wb}$ and thus in D_{wb}, were approximately 20%. Because the main contribution to D_{rm} was the cross-absorbed dose, the uncertainty in D_{rm} was estimated to be approximately equal to the uncertainty in D_{wb}.

[a] Author to whom correspondence should be addressed. Electronic mail: pablo.minguezgabina@osakidetza.net. Telephone: +34 94 600 61 73

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