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Individualized ^{131}I-mIBG therapy in the management of refractory and relapsed neuroblastoma

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Objective **Iodine-131-labelled meta-iodobenzylguanidine (^{131}I-mIBG) therapy is an established treatment modality for relapsed/refractory neuroblastoma, most frequently administered according to fixed or weight-based criteria. We evaluate response and toxicity following a dosimetry-based, individualized approach.**

Materials and methods **A review of 44 treatments in 25 patients treated with ^{131}I-mIBG therapy was performed. Patients received ^{131}I-mIBG therapy following relapse ($n = 9$), in refractory disease ($n = 12$), or with surgically unresectable disease despite conventional treatment ($n = 4$). Treatment schedule (including mIBG dose and number of administrations) was individualized according to the clinical status of the patient and dosimetry data from either a tracer study or previous administrations. Three-dimensional tumour dosimetry was also performed for eight patients.**

Results **The mean administered activity was 11089 ± 7222 MBq and the mean whole-body dose for a single administration was 1.79 ± 0.57 Gy. Tumour-absorbed doses varied considerably (3.70 ± 3.37 mGy/MBq). CTCAE grade 3/4 neutropenia was documented following 82% treatments and grade 3/4 thrombocytopenia following 71% treatments. Further acute toxicity was found in 49% of patients. All acute toxicities resolved with appropriate therapy. The overall response rate was 58% (complete or partial response), with a further 29% of patients having stable disease.**

Conclusion **A highly personalized approach combining patient-specific dosimetry and clinical judgement enables delivery of high activities that can be tolerated by patients, particularly with stem cell support. We report excellent response rates and acceptable toxicity following individualized ^{131}I-mIBG therapy.** ***Nucl Med Commun*** **37:466–472**

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Introduction

Neuroblastoma is an embryonal tumour of childhood arising from the neural crest. The majority of patients have high-risk disease at presentation, which is associated with a poor outcome despite intensive multimodal therapy. Targeted molecular radiotherapy with iodine-131-labelled meta-iodobenzylguanidine (^{131}I-mIBG) has been used for patients with relapsed and refractory disease and as an induction and consolidation therapy for over 20 years [1–7], although reported treatment schedules vary widely and are difficult to standardize because of the wide range of presentations, including disease status, patient age and treatment history. An individualized approach to treatment is therefore required to maximize therapeutic potential.

Although ^{131}I-mIBG is usually administered either as a fixed activity [8] or according to patient weight [9–11], an alternative approach is to modify the administration according to a prescribed whole-body absorbed dose (WBD), which offers the possibility to deliver large activities and to maximize the absorbed doses delivered to disease sites without unnecessary toxicity [12,13]. Administrations can be further increased with stem cell support. It has been shown previously that the prescribed WBD can be delivered accurately and correlates closely with haematological toxicity, thereby acting as a surrogate biomarker for red marrow absorbed dose [14].

Data presented previously at the Annual Congress of the EANM, October 2013; Lyon, France, and published as an abstract in EANM abstract book.

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The aim of this study was to evaluate the response, toxicity and long-term outcome of ^{131}I-mIBG therapy in the treatment of refractory and relapsed neuroblastoma on the basis of an individualized approach: administrations were tailored to patients according to their biokinetics in addition to their clinical status at the time of ^{131}I-mIBG therapy including age, stage, previous therapies, site(s) of disease and response to previous therapies.

Materials and methods

Ethical considerations

^{131}I-mIBG therapy is considered a standard treatment option in patients with relapsed and refractory neuroblastoma. For all patients who received ^{131}I-mIBG therapy, clinical details were examined in an institutional multidisciplinary meeting and consensus on treatment was reached. Informed written consent was obtained before therapy from all patients. Institutional review board approval was obtained for the retrospective collection of clinical data throughout follow-up at our institution.

Patients

A review was performed of 44 ^{131}I-mIBG treatments administered between 1994 and 2013 in 25 patients with a histologically proven diagnosis of neuroblastoma. Patients were considered eligible for ^{131}I-mIBG therapy if there was greater tumour uptake than in normal liver, following relapse ($n=9$), in refractory disease ($n=12$) or with surgically unresectable disease despite conventional treatment ($n=4$).

A median of two different chemotherapy regimens was administered before ^{131}I-mIBG therapy (range 1–5). In addition, 8/25 patients had previously received high-dose chemotherapy with autologous stem cell rescue and six patients had previously received external beam radiotherapy. Patient characteristics are shown in Table 1.

^{131}I-mIBG therapy

Patients were treated in a room specially designed for radioisotope therapy within the children's ward. ^{131}I-mIBG was administered intravenously over 2 h with hydration. Thyroid protection was provided with potassium iodide.

Table 1 Patient characteristics

Characteristics	Value
Sex [*n*/*N* (%)]	
Male	15/25 (60)
Female	10/25 (40)
Median age at diagnosis (range) (months)	53 (5–229)
Median age at first ^{131}I-mIBG therapy (range) (months)	72 (17–241)
Stage at diagnosis[a] [*n*/*N* (%)]	
2	3/25 (12)
3	4/25 (16)
4	18/25 (72)

^{131}I-mIBG, ^{131}iodine-labelled meta-iodobenzylguanidine.
[a]Stage according to the International Neuroblastoma Staging System.

Blood pressure and heart rate were monitored during the procedure and for 24 h after treatment. For the first treatment, 15 patients received a tracer study from which the activity required to deliver a WBD of 2 Gy was calculated. The initial administered activity for the remaining 10 patients was calculated from a simple weight-based formula of 444 MBq/kg, followed by an adjustment to the administered activity according to a measured WBD for subsequent therapies.

The methodology for whole-body dosimetry has been described previously [14,15]. Briefly, lead-shielded ceiling-mounted counters (a NaI detector for ^{123}I tracer studies and a compensated Geiger counter for ^{131}I-mIBG therapies) were used to acquire whole-body counts. 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. Between 40 and 60 readings were acquired to define multiexponential effective decay phases. The cumulated activity was determined from the integral of the curve, extrapolated to infinity. The absorbed dose was calculated according to the medical internal radiation dose schema [16] using an S-factor modified according to patient weight.

Tumour dosimetry

Image data were obtained to calculate tumour-absorbed doses for eight of the 25 patients. Between three and eight SPECT acquisitions were performed on consecutive days following the treatment depending on patient availability and remaining activity. Scans were acquired on a Philips Forte (Philips Medical Systems, Milpitas, California, USA) or a GE Millennium VG gamma camera (GE Healthcare, Waukesha, Wisconsin, USA) using high-energy general-purpose collimators and a 128×128 matrix. The same camera was used for all scans for any given patient. Image processing and reconstruction were performed with triple energy window scatter correction (20% photopeak energy window centred on 364 keV, with a 6% window of the peak on either side), a uniform attenuation correction (Chang) and deadtime corrections determined experimentally for each camera [17]. Reconstructed scans for each patient were sequentially coregistered to allow 3D voxelized dosimetry to be performed using an in-house dosimetry software package (Qrius) [18]. This software is based on patient-specific convolution dosimetry calculations at the voxel level, with ^{131}I absorbed dose voxel kernels generated using the general-purpose Monte Carlo code EGSnrc/EGS++ [19]. The radiation spectra of ^{131}I used to calculate dose voxel kernels were obtained from the medical internal radiation dose decay scheme [20]. The image-based 3D dosimetry application provides an

absorbed dose map of consecutive therapies from which dose volume histograms (DVH) were derived.

Toxicity

Acute toxicity was defined as any consequence arising from the point of administration until neutrophil count recovery to greater than 1. Acute and long-term treatment toxicity was assessed in all patients by electronic record and case note review. In patients for whom data were available (those whose blood counts were monitored at our institution after ^{131}I-mIBG therapy), haematological toxicity was graded according to common terminology for adverse events criteria version 4.0.

Response assessment, follow-up and survival analysis

Following ^{131}I-mIBG therapy, response was assessed by a combination of diagnostic ^{131}I-mIBG scanning and cross-sectional imaging (computed tomography or MRI), which was chosen in accordance with the baseline imaging modality to enable a direct comparison. Imaging was reviewed by at least two radiologists and consensus response was classified according to the International Neuroblastoma Risk Classification definition of response.

Overall survival (OS) analysis was carried out using the Kaplan–Meier method and 1-year OS and median OS calculated. Any further therapy administered to consolidate ^{131}I-mIBG response was also recorded.

Statistical analysis

Statistical analysis was carried out with GraphPad Prism software (version 6.00; GraphPad Software Inc., La Jolla, California, USA) using a two-tailed *t*-test for paired data (Wilcoxon matched-pairs signed rank test in the case of nonparametric data). A double-sided *P* value of less than 0.05 was considered significant.

Results

Whole-body dosimetry

The ^{131}I-mIBG activity administered and WBD for each patient are shown in Table 2. The mean administered activity was 11089 MBq (range 3539–32871 MBq, SD 7222). The mean ^{131}I-mIBG WBD was 1.79 Gy (range 0.93–3.51, SD 0.57). The median interval between treatments was 67 days (range 15–1134 days, interquartile range 45–94). The use of tracer-based and weight-based methods to prescribe a therapeutic administration enabled considerably higher activities to be delivered than is standardly the case with fixed activity administrations, although as reported previously, both methods slightly overestimated the absorbed whole-body dose delivered during therapy [15]. There was no difference between WBD predicted from a previous therapy and the WBD delivered ($P = 0.28$), thus indicating the predictive power of consecutive therapies.

Table 2 Administered activities and whole-body absorbed dose

Study number	AA (MBq)	Weight (MBq/kg)	WBD (Gy)
1a	6611	398	1.70
1b	6605	398	1.61
2a	10 524	357.9	1.00
2b	15 673	517.2	1.37
2c	19 811	649.5	1.62
2d	19 723	644.5	2.2
2e	13 988	466.3	1.13
3a	29 378	391.2	1.78
3b	32 710	352.5	1.12
4	9834	480	1.66
5	3539	281	1.14
6	20 823	458	1.64
7	5559	505	1.94
8a	8243	292.3	1.41
8b	9961	348.3	1.67
9a	6893	393.8	1.59
9b	9363	535	2.22
10a	4775	477.5	1.98
10b	4900	490	1.92
11a	8797	472.95	3.36
11b	8652	465.7	3.51
12a	6889	551.4	2.11
12b	4892	391.4	1.55
13a	6400	345.9	1.75
13b	6417	329.1	1.82
14a	21 066	322.6	1.00
14b	32 871	483.4	2.12
15	13 457	497	2.46
16a	5321	273.8	0.93
16b	15 733	815.2	2.11
17a	6941	341.9	1.83
17b	6572	315.5	1.71
18	11 652	433	2.28
19	9358	307	1.45
20a	7766	413.1	1.35
20b	11 227	578.7	1.83
20c	9270	501	1.47
21a	6701	446.7	1.76
21b	6397	412.7	1.62
22	6144	361	1.11
23	14 538	434	1.62
24a	7636	406.2	3.25
24b	5271	289.1	2.26
25	9060	458	1.96

AA, administered activities; WBD, whole-body absorbed dose.

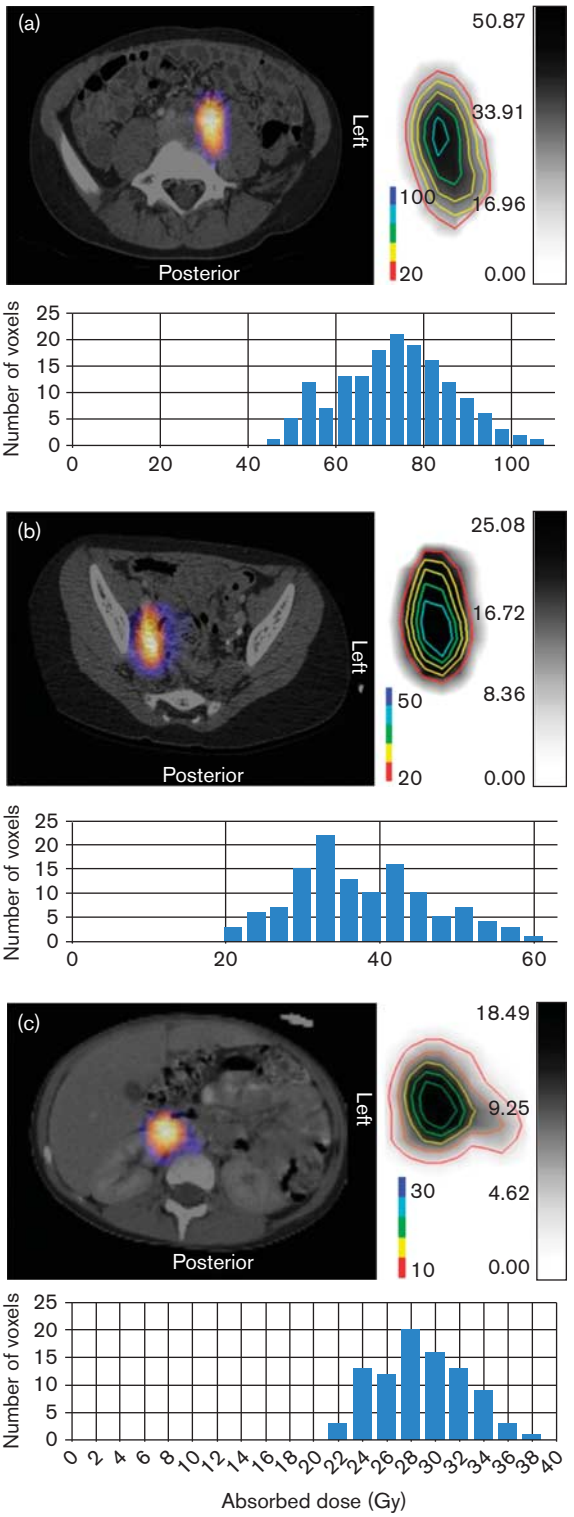
Tumour dosimetry

A representation (studies no. 2, 20 and 25) of patient tumour dosimetry utilizing the 3D dosimetry tool is shown in Fig. 1. The generated 3D absorbed dose maps with isodose curves enable DVH to be produced to evaluate the spatial heterogeneity of absorbed dose following therapy.

Tumour-absorbed doses were calculated for eight patients and are summarized in Fig. 2. The mean tumour-absorbed dose delivered was 43.7 ± 27.5 Gy, whereas the mean liver and kidney doses were 5.7 ± 1.4 and 2.5 ± 0.4 Gy, respectively. Allowing for the uncertainty in the dosimetry, the absorbed doses delivered were consistent. Absorbed dose ratios between consecutive therapies are summarized in Table 3.

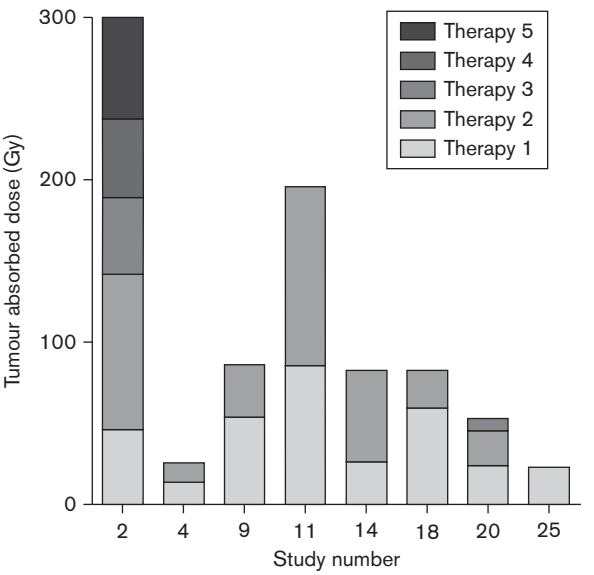
One patient received three (study no. 20) and one received five (study no. 2) treatments. For the first patient, tumour uptake decreased with consecutive

Fig. 1



Representation of 3D tumour dosimetry in three patients. The maximum absorbed doses received were (a) 51 Gy, (b) 25 Gy, and (c) 18 Gy. For each patient the top left image in each panel shows the absorbed dose map overlaid onto the corresponding CT slice, the top right image shows the iodose contours, and the bottom image shows the cumulative dose volume histogram of the number of voxels receiving a given absorbed dose.

Fig. 2



Tumour-absorbed doses.

Table 3 Absorbed tumour dose ratios for consecutive therapies (T)

	T2/T1			T3/T2		
Study number	AA ratio	Tumour uptake ratio	Tumour dose ratio	AA ratio	Tumour uptake ratio	Tumour dose ratio
2	1.5	1.0	1.5±0.9	1.3	0.5	0.6±0.4
4	1.1	0.8	0.9±0.4	–	–	–
9	1.4	0.4	0.6±0.2	–	–	–
11	1.0	1.3	1.3±0.2	–	–	–
14	1.6	1.3	2.1±0.9	–	–	–
18	1.4	0.3	0.4±0.2	–	–	–
20	1.4	0.6	0.9±0.3	0.8	0.4	0.4±0.1

AA, administered activity.

therapies, with the final therapy receiving three times less than the initial therapy, while absorbed tumour dose ratios also decreased (Table 3). The second patient showed very similar tumour-absorbed dose ratios for all therapies, showing that tumour uptake per cumulated activity for all therapies was very similar [Table 3, missing data for study no. 2: AA ratio (T4/T3) 1.0; (T5/T4) 0.8; and tumour dose ratio (T4/T3) 1.2±0.6; (T5/T4) 1.6±1.0].

Toxicity

Common terminology for adverse events grade 3/4 neutropenia was observed following 18/22 (82%) treatments and grade 3/4 thrombocytopenia was observed following 19/24 (71%) treatments. Autologous stem cell transplant was administered following ^{131}I-mIBG therapy in 14/24 patients. In addition to the haematological toxicity, further acute toxicity was documented following 21/43 (49%) treatments. With the exception of four treatments,

all acute toxicity involved either culture negative fever or documented infection. Of the four patients who had nonfever/infection-related complications, two patients experienced parotitis, one patient had a hypertensive episode and one patient complained of back pain. All acute toxicities resolved with appropriate therapy. With respect to potentially vulnerable target organs such as the liver, kidneys and thyroid gland, one patient with a transient fever had an associated transaminitis, although no long-term target organ toxicity was observed in any patient. Only one patient, who did not receive stem cell rescue, experienced prolonged thrombocytopenia.

Response

Data were available on response in 24/25 patients (Table 4). Two patients achieved complete remission (CR) after ^{131}I-mIBG therapy. The first patient remained in CR for 11 months before relapse (is alive at the time of writing with disease 16 months after ^{131}I-mIBG therapy). The second patient developed a relapse 6 months after ^{131}I-mIBG therapy and subsequently died of disease.

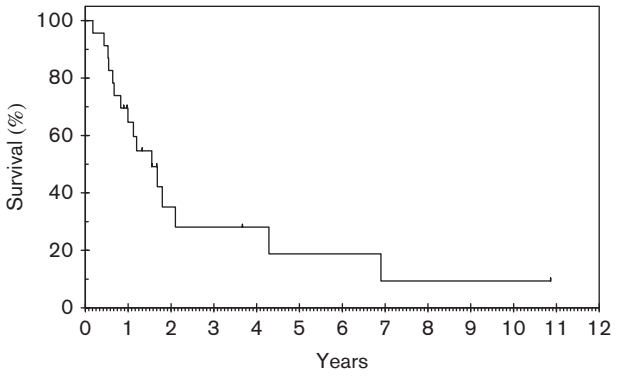
Two patients with partial response (PR) following ^{131}I-mIBG therapy subsequently achieved CR after further consolidation therapy. One patient who had previously received multiple lines of chemotherapy, surgery and high-dose therapy for metastatic neuroblastoma developed a localized recurrence that was surgically unresectable. She received five cycles of ^{131}I-mIBG therapy with a continued PR after each cycle, and then further treatment with surgical resection, radiotherapy and cis-retinoic acid treatment. She remains alive and disease free after 6 years of follow-up. The second patient had a surgically unresectable localized disease despite multiple previous lines of chemotherapy. PR following ^{131}I-mIBG therapy enabled surgical resection. This was consolidated with radiotherapy and she remains alive and disease free 12 years since the diagnosis. The median OS was 18.6 months (95% confidence interval 10.4–26.9), with a 1-year OS of 65% (95% confidence interval 48–88%). The median follow-up was 44 months (Fig. 3). Six patients were alive with disease at last follow-up (median follow-up from ^{131}I-mIBG therapy 12 months, range 4–32 months), whereas 16 patients are known to have died from disease. The median time from the last ^{131}I-mIBG therapy to death was 12 months (range 2–82 months).

Table 4 INRC response

INRC response	*n* (%)
Complete remission	2 (8.3)
Partial response	12 (50)
Stable disease	7 (29.2)
Progressive disease	2 (8.3)
Mixed response	1 (4.2)

INRC, international neuroblastoma risk classification.

Fig. 3



Kaplan–Meier plot of overall survival.

Discussion

Cumulative evidence from institutional reports and some early phase trials has established ^{131}I-mIBG therapy as a standard treatment option in patients with relapsed and refractory neuroblastoma [2,8,9,13]. There has also been limited use of ^{131}I-mIBG as part of first-line treatment [4, 7]. However, to date, there are currently no published randomized-controlled trials of ^{131}I-mIBG therapy for neuroblastoma at any stage of treatment [21]. To maximize the therapeutic potential of ^{131}I-mIBG therapy, well-designed clinical trials incorporating dosimetry are needed. A WBD approach for ^{131}I-mIBG therapy as followed here enables safe delivery of considerably higher activities than are standardly provided with fixed administrations and can be used to deliver reproducible therapy results on a patient-specific basis [14,22]. Patients with stage III or stage IV neuroblastoma present with tumours of varying sizes and uptake distributions. There is a wide interpatient variation in the absorbed doses delivered to tumours, although these are consistent between consecutive therapies. As yet, there is no clearly defined methodology to incorporate DVHs in patient specific planning or to compare DVHs for individual therapies or to relate to outcome. However, it is clear that dose heterogeneity could affect the outcome of subsequent therapies and may partially explain the variation in responses. In light of this, a 3D dosimetry approach where DVHs are taken together with tumour-absorbed dose as well as dose-limiting criteria provides a reasonable method to help plan patient-specific treatment and should be used as a guideline to inform subsequent therapies.

It is difficult to make direct comparisons of trials of ^{131}I-mIBG therapy in neuroblastoma as the study groups are very heterogeneous and treatment protocols, including administration and concomitant therapy, are highly variable. ^{131}I-mIBG therapy is often administered with a fixed or weight-based activity and with these techniques,

response rates (PR and CR) vary between 30 and 56% [1, 8,23]. Within this context, our response rate of 58%, with 88% of patients having stable disease or better following ^{131}I-mIBG therapy, is noteworthy. Our data also support a previous study showing that a dosimetry-based approach to augment mIBG intensity may improve response rates [13]. It is also noteworthy that in our series, in two cases, a CR was achieved following either surgery or radiotherapy consolidation after mIBG therapy and that in several cases, the duration of response was long.

Administrations based on fixed activities must inevitably be limited according to the most vulnerable of patients. This can lead to undertreatment of the majority. As found in this study, an individualized approach, on the basis of patient pharmacokinetics, will often result in the administration of higher activities. The capacity to include stem cell support and concomitant chemotherapy necessitates a multidisciplinary approach and specialized care as detailed in the European Association of Nuclear Medicine guidelines [24].

As this report is a retrospective collation of data from patients who received individualized ^{131}I-mIBG therapy schedules on the basis of their clinical features and dosimetry, there are a number of inherent limitations. Our patient group was heterogeneous in many ways; they had different disease stages and tumour burdens, had received various different previous chemotherapy regimens and ^{131}I-mIBG therapy was used under several different clinical scenarios. However, although the heterogeneity in our patient group makes drawing direct comparisons with other series difficult, this is a true reflection of the diverse nature of the clinical situations where ^{131}I-mIBG therapy is applied in standard clinical practice.

Neuroblastoma has an extremely variable clinical picture with respect to site(s) of presentation, tumour biology and disease aggressiveness. In infants with metastatic disease, their disease may spontaneously regress. However, metastatic disease in older patients is associated with rapid progression and a poor prognosis. Other patients may have surgically unresectable localized disease compressing vital structures, but with differentiated histology and little propensity to metastasize. In such a heterogeneous group of patients, an adaptive approach that incorporates adjustment of dose and schedule, according to clinical judgement, on the basis of a patient's individual needs and dosimetry may maximize the potential benefit to the patient.

A limitation of our study is that there is a significant amount of missing data specifically on haematological toxicity. This is because patients are referred for ^{131}I-mIBG therapy from a wide geographical area and blood counts following therapy are monitored at the patients' local institution. This is a common situation with this relatively rare and highly specialized treatment and indicates the need for a Europe-wide initiative to ensure data collection. Nevertheless, our reported haematological toxicity is as expected following ^{131}I-mIBG therapy and previous work from our institution has shown a clear correlation between the absorbed whole-body dose and haematological toxicity [14]. Data on non-haematological toxicity are more complete because of a 'shared care' system, whereby the treating centre is notified by local hospitals of any admission or problems requiring intervention. Further nonhaematological toxicities observed in our patients were all resolved with appropriate treatment and no long-term effects were found.

In summary, excellent response rates have been obtained in our institution following individualized ^{131}I-mIBG therapy while keeping toxicity within acceptable limits. Our data support the use of patient-specific dosimetry in future clinical trials to maximize the efficacy of ^{131}I-mIBG therapy.

Conclusion

^{131}I-mIBG therapy is a safe and effective treatment for relapsed or refractory neuroblastoma. A highly personalized approach, combining clinical judgment with patient-specific dosimetry, can be used to safely maximize therapeutic efficacy. Further multicentre clinical trials are essential to optimize the treatment and to determine its place within the patient pathway.

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Conflicts of interest

There are no conflicts of interest.

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