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ORIGINAL ARTICLE

Dosimetry-based high-activity therapy with ^{131}I-metaiodobenzylguanidine (^{131}I-mIBG) and topotecan for the treatment of high-risk refractory neuroblastoma

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Abstract

Purpose Patients with high-risk neuroblastoma have an increased risk of recurrence and relapse of disease and a very poor prognosis. ^{131}I-metaiodobenzylguanidine (^{131}I-mIBG) in combination with topotecan as a radiosensitizer can be an effective and relatively well-tolerated agent for the treatment of refractory neuroblastoma. The aim of this retrospective study was to evaluate response and outcome of combined therapy with ^{131}I-mIBG and topotecan.

Methods Ten patients, between 3 and 20 years of age, were included. Nine patients had been refractory to several lines of chemotherapy and radiotherapy. One patient with a very high-risk neuroblastoma had received only induction therapy. Response was graded according to the International Neuroblastoma Staging System.

Results Regarding treatment response, two patients achieved complete remission, one with relapse at 16 months, five achieved a partial remission, four showed progression at between 1 and 18 months; two showed stable disease with progression at between 1 and 5 months, and one showed progressive disease. Eight of the ten patients died with overall survival between 4 and 63 months, and two patients were still alive without disease at the time of this report: 52 and 32 months (patient had received only induction therapy). Acute and subacute adverse effects were mainly haematological, and one patient developed a differentiated thyroid cancer.

Conclusion In patients with high-risk refractory neuroblastoma, administration of high activities of ^{131}I-mIBG in combination with topotecan was found to be an effective therapy, increasing overall survival and progression-free survival. Further studies including a larger number of patients and using ^{131}I-mIBG for first-line up-front therapy are warranted.

Keywords High-risk neuroblastoma · ^{131}I-mIBG therapy · Topotecan · Dosimetry

Introduction

Neuroblastoma is the most common extracranial malignant solid tumour of childhood. There is a marked variability in its clinical behaviour, that ranges from spontaneous regression or differentiation, to rapid and progressive fatal disease. Prognosis is highly variable [1], and the two most important clinical prognostic factors are patient age and stage. Patients younger than 18 months at initial diagnosis have a lower risk of developing recurrent disease [2]. MYCN oncogene amplification (the most important independent factor) [3] and tumour histopathological grade are biological prognostic factors [4, 5].

Treatment of neuroblastoma depends upon the estimated relapse risk that is based on clinical and biological prognostic features. Components of therapy in high-risk disease are: induction with intensive multimodal chemotherapy and surgical resection, consolidation with radiation therapy, and high-dose chemotherapy combined with autologous stem cell transplantation (ASCT). These patients also benefit from maintenance therapy for minimal residual disease. Although this intensive approach has been shown to improve outcomes, 15–20% of

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patients who present with metastatic disease are refractory to induction chemotherapy, and patients with high-risk disease frequently relapse and fewer than 50% of these patients will be long-term survivors [6, 7]. The poor outcomes in patients with high-risk disease and the fact that 90% of tumours show metaiodobenzylguanidine (mIBG) avidity [8] provide the rationale for the use of ^{131}I-mIBG therapy.

mIBG is a norepinephrine analogue with high affinity and specificity for the norepinephrine transporter (NET). NET actively transports norepinephrine primarily by a saturable specific process known as the Uptake-1 mechanism. Norepinephrine is also brought into cells by passive, nonspecific diffusion, a process known as the Uptake-2 mechanism [9]. Intracellularly, mIBG may be transported to secretory granules via vesicular monoamine transporters [10] or may remain in the cytoplasm [11].

The use of mIBG therapy was first reported in 1983 [12, 13]. When ^{131}I-mIBG was first introduced into clinical practice for neuroblastoma therapy, it was reserved for heavily pretreated patients with relapsed disease [14]. Different therapeutic protocols in the treatment of these relapsed or refractory tumours, including ^{131}I-mIBG, have been used. These range from palliative treatment for end-stage disease, to becoming part of a potentially curative strategy with ^{131}I-mIBG monotherapy, in combination with other treatments such as chemotherapy [15], chemotherapy and conventional ^{131}I-mIBG therapy [16], and ^{131}I-mIBG with ASCT both with and without myeloablative chemotherapy [17] and in conjunction with various radiosensitizers [18, 19]. Currently, its use as a "front-line" therapeutic agent is being investigated in those without relapsed or recurrent disease as well at the end of induction [20].

A treatment strategy with radiosensitizers uses a combination of high activities of ^{131}I-mIBG plus topotecan [19]. Topotecan is a cytotoxic drug that can be used in combination with other chemotherapeutic agents [21] or as a single agent against neuroblastoma [22]. It interferes with DNA repair, inhibiting the enzyme topoisomerase I [23], and also acts as a radiosensitizer [24], and thus improves the efficacy of ^{131}I-mIBG therapy by inhibiting DNA repair. In addition to these effects, administration of topotecan could enhance the uptake of ^{131}I-mIBG by neuroblastoma tumours due to the increased expression of the NET by the tumour leading to increased efficacy [25]. Experimental models have shown that the combined treatment is synergistic in relation to single-modality therapy. There is evidence from studies in neuroblastoma xenografts that topotecan is synergistic with ^{131}I-mIBG if it is given simultaneously or after ^{131}I-mIBG, but not if it is given before ^{131}I-mIBG [26]. Therefore, it is possible to enhance the effectiveness of ^{131}I-mIBG treatment by incorporating topotecan into the treatment schedule. This therapeutic strategy could be improved by carrying out a dosimetry study aiming to achieve a whole-body absorbed dose of 4 Gy in combination with ASCT to increase the therapeutic efficacy [18].

We summarize here our experience in using high-activity ^{131}I-mIBG as a therapeutic agent for resistant high-risk neuroblastoma in combination with topotecan supported by autologous stem cell rescue using a dosimetry study to guide delivery to achieve a total whole-body absorbed dose of 4 Gy accurately from two administrations of ^{131}I-mIBG according to the protocol followed by Gaze et al. [18].

Materials and methods

Patients

We included ten patients with refractory neuroblastoma, seven boys and three girls, with ages ranging from 13 to 197 months at the time of diagnosis (only one patient was younger than 18 months). All of them were treated with a combination of high-activity ^{131}I-mIBG and topotecan supported by ASCT according to the protocol followed by Gaze et al. [18]. In one patient, treatment was repeated within 15 months of the first treatment. In nine patients ^{131}I-mIBG was used as a palliative treatment. In one patient the treatment was administered after induction therapy with curative intent. The following haematological values were required in all patients: neutrophils >750/ml, platelets >20.000/ml, creatinine <2 mg/dl and bilirubin <2 mg/dl. All patients or their guardians signed informed consent to the treatment according to the ^{131}I-mIBG compassionate use protocol.

Therapy procedure and response evaluation

All patients showed ^{123}I-mIBG uptake. The first procedure was to harvest peripheral blood stem cells. Thyroid protection with potassium iodide was performed from 3 days before to 9 days after treatment. Patients were premedicated prior to treatment in the Department of Pediatric Oncology twice daily with ondansetron 20 μg/kg, and were hydrated with 0.9% saline 2.0 l per 1.73 m^2/24 h for 4 h before treatment to ensure adequate diuresis. Topotecan 0.7 mg/m^2 was then infused over 30 min before administration of ^{131}I-mIBG (GE Healthcare Bio-Sciences). Topotecan was administered daily for the subsequent 4 days. After the first topotecan administration, patients were transferred to a shielded room for ^{131}I-mIBG therapy. An activity of 444 MBq/kg (12 mCi/kg) measured in a dose calibrator was diluted with normal saline to 50 ml, and then infused as soon as possible over 30 min. Patients remained in the isolation room until the exposure rate was lower than 40 μSv/h at 1 m. The second therapeutic administration, on day 15, followed the same procedure. The activity of ^{131}I-mIBG for the second administration was calculated based on the measured whole-body absorbed dose from the

first administration, with the aim of giving a total whole-body absorbed dose of 4 Gy. Stem cells were reinfused when the whole-body residual activity was lower than 30 MBq, approximately 25–29 days after the first treatment (Fig. 1). Details of the method followed to obtain the whole-body absorbed doses from the treatments are provided in the Appendix. The specific activity of the ^{131}I-mIBG and the amount of ^{131}I-iobenguane in 6.5 GBq (175 mCi; considered a standard activity) were calculated.

Response to treatment was assessed by comparing the CT and ^{123}I-mIBG-SPECT/CT scans obtained before therapy with those obtained between 8 and 10 weeks after ^{123}I-mIBG plus topotecan administration. The response criteria used were those approved by the International Neuroblastoma Response Criteria, RECIST, the semiquantitative SIOPEN mIBG score and bone marrow biopsy. All patients were evaluated for haematological and nonhaematological toxicities.

Results

Table 1 shows the clinical characteristics of the patients at diagnosis, their clinical responses to ^{131}I-mIBG plus topotecan therapy, and their status at the time of this report. Table 2 shows patient therapy prior to ^{131}I-mIBG and topotecan administration. Primary tumours were in the adrenal glands in three patients, the abdomen in five, the cervical region in one and a cervicothoracoabdominal location in one. At diagnosis, one patient had localized disease, another had lymph node involvement, and the remainder (eight) had distant metastases. Nine patients underwent surgical resection, which was complete in four. One patient had unresectable disease. Nine patients had received several lines of chemotherapy (induction, consolidation, rescue) and differentiating therapy with 13-*cis*-retinoic acid. Four patients received anti-GD2 antibody maintenance therapy. One patient (patient 10) had received only induction therapy. Six patients received radiotherapy to the primary tumour.

The treatment received by patient 10 after ^{131}I-mIBG plus topotecan therapy consisted of: rescue with haematopoietic ASCT, local radiotherapy, retinoic acid differentiation therapy and immunotherapy in the "long term continuous infusion ch14.18 plus subcutaneous IL-2" assay.

The administered activities of ^{131}I-mIBG (Table 3) ranged from 5.0 to 22.2 GBq. Patient 4 was over 60 kg in weight, so standard dose calculation would have given a corresponding activity of 27 GBq at the first treatment. As far as we knew there was no bibliography including patients treated with such high activities, so a more conservative approach was followed: a first fraction of 11.1 GBq (176 MBq/kg) and a second of 22.2 GBq (352 MBq/kg) were administrated. Treatment was repeated 15 months later in this patient without ASCT with a first fraction of 10.5 GBq (167 MBq/kg) and a second fraction of 10.4 GBq (167 MBq/kg). Whole-body absorbed doses per administered activity ranged from 0.09 Gy/GBq to 0.37 Gy/GBq.

The tumour absorbed dose was calculated by MIRD methodology [27, 28] in only two patients: for the first fraction in patient 3, and for both fractions of the second treatment in patient 4. The tumour absorbed doses were 7.6 Gy in patient 3 and 15.4 Gy/15.4 Gy in patient 4. Tumour dosimetry was challenging from the radiation protection point of view because of the potential for radiation exposure from the high activities handled. This prevented the calculation of tumour absorbed

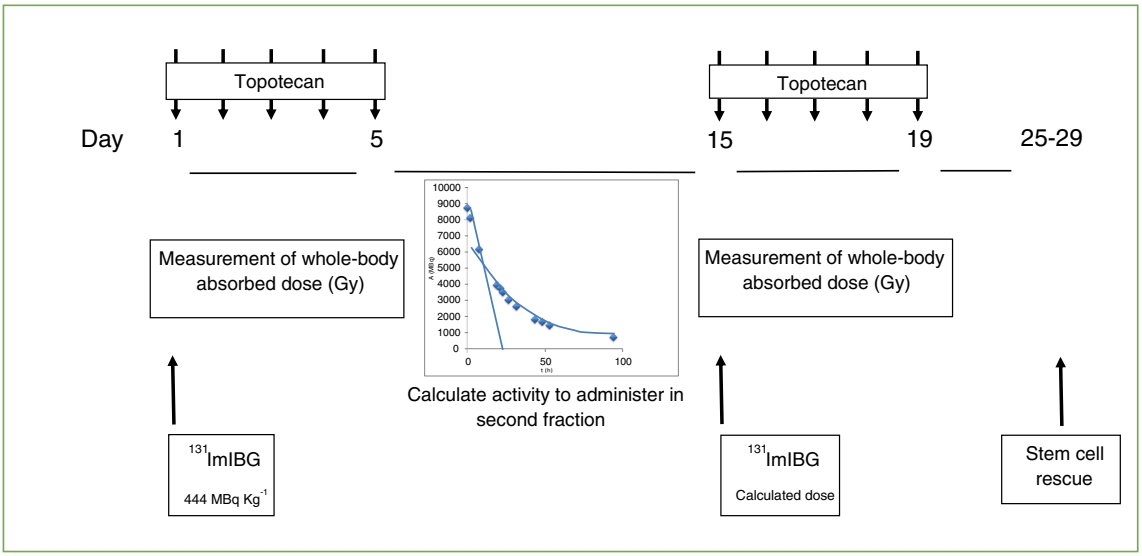

Fig. 1 Treatment schedule. Therapy with ^{131}I-mIBG combined with topotecan in two fractions separated by 2 weeks. Haematological stem cell reinfusion was performed on days 25–29 when the whole-body residual activity was lower than 30 MBq

Table 1 Clinical characteristics of the patients at diagnosis, their clinical responses to ^{131}I-mIBG plus topotecan therapy and their status at the time of this report

Patient	Sex	Age at diagnosis (months)	Location of primary tumour	MYCN status	INSS stage	Response to ^{131}I-mIBG + topotecan	Relapse/progression (months)	Outcome (months after mIBG therapy)
1	M	95	Abdominal	Not amplified	4	PD	1	Dead (4)
2	F	35	Cervicothoracoabdomen	Not amplified	3	PR	4	Dead (61)
3	M	27	Abdominal	Amplified	4	SD	1	Dead (13)
4	M	197	Abdominal	Not amplified	4	SD	5	Dead (63)
5	M	22	Cervical	Amplified	2	PR	4	Dead (15)
6	M	45	Adrenal gland	Unknown	4	PR	18	Dead (42)
7	M	35	Adrenal gland	Unknown	4	CR	16	Dead (22)
8	F	13	Abdominal	Not amplified	4	PR (minimal disease)	No	Alive without disease (52)
9	M	49	Abdominal	Not amplified	4	PR	1	Dead (23)
10	F	52	Adrenal gland	Not amplified	4	CR	No	Alive without disease (32)

INSS International Neuroblastoma Staging System, *CR* complete remission, *PR* partial remission, *SD* stable disease, *PD* progressive disease

Table 2 Previous therapy to ^{131}I-mIBG plus topotecan administration

Patient	Age at ^{131}I-mIBG plus topotecan therapy (years)	Induction chemotherapy	Extent of resection of the primary	Rescue chemotherapy	Radiotherapy	13-*cis*-Retinoic acid	Anti-GD2 antibody	ASCT
1	16	Carbo-eto	Partial	No	Yes	Yes	Yes	Yes
2	5	CADO, Carbo-eto	Partial	Carbo-eto	No	Yes	No	Yes
3	5	Rapid COJEC	Partial	No	Yes	Yes	Yes	Yes
4	20	Rapid COJEC, TVD, TOTEM, bevacizumab	Complete	No	Yes	Yes	No	Yes
5	3	Rapid COJEC	Partial	TVD	Yes	Yes	Yes	Yes
6	4	Rapid COJEC	Complete	TEMIRI and TOTEM	Yes	Yes	No	Yes
7	6	Rapid COJEC	Complete	No	No	Yes	No	Yes
8	4	Rapid COJEC	Unresectable	Dox-CF	No	Yes	No	Yes
9	7	Rapid COJEC, TVD	Partial	TEMIRI	Yes	Yes	Yes	Yes
10	5	TEMIRI, TVD, Carbo-eto	Complete	No	No	No	No	No

ASCT autologous stem cell transplantation, *Rapid COJEC* cisplatin, vincristine, carboplatin, etoposide and cyclophosphamide, *Carbo-eto* carboplatin and etoposide; *TEMIRI* temozolamide and irinotecan, *TVD* topotecan, vincristine and doxorrubicin, *TOTEM* topotecan and temozolomide, *CADO* cyclophosphamide and doxorrubicin, *Dox-CF* doxorrubicin and cyclophosphamide

Table 3 Administered activities of ^{131}I-mIBG in each patient

Patient	Administered activity (GBq)		Whole-body dose (Gy)
	First	Second	
1	13.0	14.4	4.0
2	9.0	8.3	4.1
3	6.3	6.7	4.1
4	11.1/10.5	22.2/10.4	2.9/1.8
5	5.0	5.6	3.9
6	7.7	6.5	4.0
7	5.8	3.5	4.46
8	5.7	13.7	4.0
9	9.8	9.8	3.9
10	9.1	8.7	3.9

doses in the remaining patients. The specific activity of ^{131}I-mIBG and the amount of ^{131}I-iobenguane existing in 6.5 GBq (175 mCi) were, respectively, 0.0511% and 3.0083 μg.

Clinical responses to ^{131}I-mIBG plus topotecan and the status of the patients at the time of this report are shown in Table 1. After ^{131}I-mIBG-topotecan therapy, five patients achieved partial remission (one with residual minimal disease), two showed stable disease, two showed complete remission, and one had progressive disease since there was no treatment response. At the end of the study, eight patients had died from the disease at 4–63 months of treatment. Two patients were alive without disease: patient 8 at 52 months, and patient 10 (who had received only induction therapy) at 32 months (Fig. 2).

After the first ^{131}I-mIBG therapy, clinical improvement (reduction/disappearance of disease) was achieved in all patients with pretreatment bone pain or pain localized to soft tissue. No symptoms related to catecholamine excretion were observed during the infusion. Nonhaematological adverse events were seen, and consisted of fever (four patients), post-irradiation mumps and submaxillitis (one patient), acute thyroiditis (one patient) and oral mucositis (one patient); none of these patients required parenteral nutrition. Among haematological toxicity symptoms, neutropenia was seen in seven patients (all grade 4) with no severe infections, and anaemia in ten patients (grade 4 in one, grade 3 in six and grade 2 in three). All patients showed grade 4 thrombocytopenia (without haemorrhagic complications). One patient developed a differentiated thyroid cancer at 15 months. No patient showed an adverse effect on bone marrow reconstitution after ASCT.

Discussion

Our results indicate that high-activity ^{131}I-mIBG combined with topotecan and ASCT is a feasible and well tolerated therapeutic protocol in patients with high-risk refractory neuroblastoma. The good disease response to this therapy suggests that this strategy may improve outcomes in patients with refractory disease. In agreement with the findings of previous studies [17], this study has proven the safety of incorporating ^{131}I-mIBG in therapeutic regimens, and the use ^{131}I-mIBG did not adversely affect bone marrow reconstitution after ASCT.

It has been shown that a tumour absorbed dose–response relationship exists [29]. This indicates that delivery of higher administered activities of ^{131}I-mIBG might result in better responses to treatment than the use of standard activities, assuming that the radiobiological relationship between absorbed dose and cell kill demonstrated in laboratory studies also occurs in patients [17]. Although in our study we were able to calculate the tumour absorbed dose in only two patients, we believe that it should be performed in all patients, if possible, to assess this relationship.

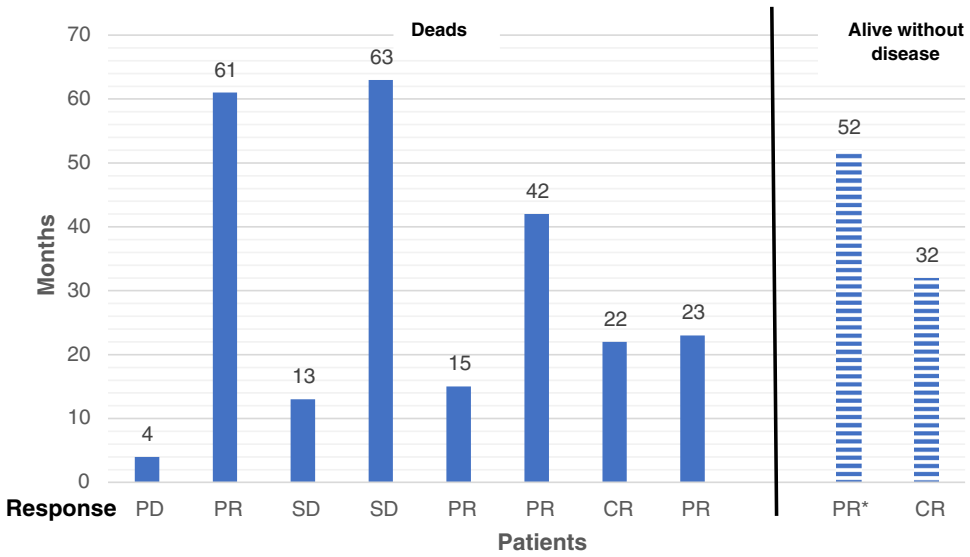

Fig. 2 Response to ^{131}I-mIBG-topotecan therapy in each patient, and each patient's survival status at the time of this report. *CR* complete Remission, *PR* partial remission, *PR** partial remission – minimal disease, *SD* stable disease, *PD* progressive disease

^{131}I-mIBG activity escalation treatment using whole-body dosimetry combined with topotecan as a radiosensitizer with ASCT support to overcome myelosuppression has been devised. Gaze et al. [18] reported a protocol in which an initial mass-based activity of 444 MBq/kg was administered to give a whole-body absorbed dose of about 2 Gy, followed by a second administration 2 weeks later, with the aim of giving a total whole-body dose of 4 Gy. Our results have proven that this protocol is reliable and reproducible. We highly recommend that sufficient measurements be obtained for the dosimetry procedure.

The range of total whole-body absorbed doses found in this study seems to be high, with values between 1.70 and 4.46 Gy. According to Buckley et al. [30] and Sudbrock et al. [31] whole-body absorbed dose is an important indicator of impending adverse events after ^{131}I-mIBG therapy. In relation to the whole-body absorbed doses found by these authors, the whole-body absorbed doses were high (1.70–4.46 Gy vs. 0.5–3.5 Gy and 1.56–2.87, respectively [30, 31]). This is probably because our aim was to deliver a whole-body absorbed dose of 4 Gy in combination with ASCT.

The specific activity of ^{131}I-mIBG is of major importance, as it has been demonstrated that no-carrier-added ^{131}I-mIBG provides a significantly higher accumulation in target tissues [32]. As uptake of mIBG in tumour cells is possibly saturable, the nonradiolabelled mIBG and the total amount of biogenic amines may have a critical effect. It has been observed that in tissues that express NETs, the higher the specific activity of the preparation, the greater will be the uptake of the radiopharmaceutical [33]. Commercial preparations of ^{131}I-mIBG are based on an isotope exchange reaction and contain large mass amounts of unlabelled mIBG, or “cold carrier”, molecules. Studies have shown that >99% of mIBG molecules in commercial formulations are not radiolabelled [34]. Thus, the percentage specific activity of our commercial formulation was very low, about 0.0511%. The amount of ^{131}I-iobenguane existing in 6.5 GBq (175 mCi) was 3.0083 μg. We believe, therefore, that because of their high specific activity, the use of no-carrier-added ^{131}I-mIBG preparations may improve both diagnostic and therapeutic studies.

DuBois et al. [35] demonstrated that NET expression of neuroblastoma tumour cells correlates with their clinical avidity for mIBG and also with the status of the tumour MYCN oncogene. Thus, we believe that it would be important to study the degree of tumour NET expression to assess its correlation with response to treatments including high ^{131}I-mIBG activities.

Nonhaematological toxicity was minimal. After the first administration of ^{131}I-mIBG it mainly consisted of fever (four patients), without the need for intensive treatment. After the second treatment, one patient developed postirradiation mumps and submaxillitis, one acute thyroiditis and four mucositis. No patient showed nausea or vomiting, contrary to the findings of Bleeker et al. [36], who found that these were the most frequent symptoms. The haematological complications did not imply haemorrhagic alterations or infections, and only one patient showed grade 4 anaemia. One patient developed a differentiated thyroid cancer, as reported by Polishchuk et al. [37], at 15 months. No patient showed an adverse effect on bone marrow reconstitution after ASCT.

The totality of patients in our study with bone pain or localized pain in soft tissues before therapy showed improvement after treatment with ^{131}I-mIBG. This finding coincides with those of Ben-Arush et al. [38] and Troncone et al. [39], although they administered lower ^{131}I activities.

Responses to ^{131}I-mIBG therapy have been found to be heterogeneous in previous studies which have used ^{131}I-mIBG as a single agent or in combination with chemotherapeutic agents [40]. In our study, we obtained a response in seven of ten patients (70%). Two patients had a complete response and one had progressive disease. Three patients showed long survival (42, 61 and 63 months, respectively). At the time of this report, two patients were still alive without disease at 52 and 32 months. However, it is not possible to draw strong conclusions on overall survival from our study due to the small number of patients included.

One of the patients with a metastatic very high-risk neuroblastoma showed a poor response to induction chemotherapy, and intensified consolidation therapy was performed with ^{131}I-mIBG and topotecan. At the time of this report, this patient was in complete remission 32 months after the treatment. Although our patient group included only one of this kind of patients, we believe that this treatment can be used safely after induction/consolidation therapy, as also concluded by the authors of a French study reviewing their experience with the use of busulfan/melphalan and stem cell rescue after ^{131}I-mIBG plus topotecan therapy [20]. Therefore, it would be of interest to carry out studies such as the International SIOPEN study (VERITAS) [41], which proposes the same treatment schedule. This would allow us to increase the global and disease-free survival in these patients.

In conclusion, therapy with high activities of ^{131}I-mIBG (preferably no-carrier-added), performing whole-body dosimetry, in combination with topotecan is well tolerated and effective in patients with high-risk recurrent neuroblastoma. We observed benefits in the treatment of relapse/progression, improving survival rates without severe toxicities, with a high response rate. We consider that this therapy should be used as consolidation therapy or for induction in this risk group. The overall response to this therapy and survival in a larger group of patients remain to be assessed to confirm our results.

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Authors' contributions J.G., T.R. and R.L. designed the study. V.L. and A.E. collected the data and created the tables. P.M. performed the dosimetric study. J.G., T.R. and V.L. drafted the manuscript, to which all the authors contributed with revisions and approved the final version.

Data availability The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional (CEIC Cruces University Hospital) and/or national research committee and with the principles of the 381 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent for publication This article does not describe any individual patient's data or identifiable information.

Conflicts of interest None.

Appendix

To obtain the whole-body absorbed dose in the treatments, dose-rate measurements were performed with a pressurized μR ion chamber survey meter (Inovision Model 451P) at 1 and 2 m from the standing patient. At both distances, measurements were acquired with the patients facing and turning their back to the meter, and the geometrical mean of the two measurements was calculated. All measurements were taken by trained staff, taking care to reproduce the same geometry each time. A background measurement was taken prior to treatment. The first measurement was taken immediately after the administration of the ^{131}I-mIBG to obtain the reading corresponding to the whole activity administered, and before the patient emptied the bladder, at a precisely recorded time. The rest of the measurements were taken approximately every 2 h during the first day, every 4 h during the second day and every 6 h during the remaining days, trying to acquire them after a bladder void.

Whole-body absorbed dose was calculated according to standard MIRD methodology, in which D_{wb} is given by the expression:

$$D_{\mathrm{wb}} = A_{c,\mathrm{wb}} S_{\mathrm{wb}\leftarrow\mathrm{wb}}$$

where $A_{\mathrm{c,wb}}$ is the cumulated activity in the whole-body, and $S_{\mathrm{wb}\leftarrow\mathrm{wb}}$ is the S factor for the whole body.

The cumulated activity in the whole body, $A_{\mathrm{c,wb}}$, was calculated by integrating the activity–time curve. The curve fitting was performed considering three exponential decay phases of the activity in the whole body, obtaining the next expression for $A_{\mathrm{c,wb}}$ [30]:

$$A_{c,\mathrm{wb}} = \sum_{i=1}^{3} \frac{A_i - A_{i+1}}{\lambda_i}$$

where A_1 is the administered activity. A_i is the activity value at the change from phase $i-1$ to phase i, and λ_i is the effective decay constant of phase i.

The S factor, $S_{\mathrm{wb}\leftarrow\mathrm{wb}}$, was calculated using the expression:

$$S_{\mathrm{wb}\leftarrow\mathrm{wb}} = 1.34 \times 10^{-4} m_p^{-0.921}\,\mathrm{GyMBq^{-1}h^{-1}}$$

where m_{p} is the patient's weight in kilograms. This expression was obtained by interpolating data from new-born, one-year-old, five-year-old and adult phantoms [42].

The accuracy of the absorbed dose estimate will depend largely on the accuracy of the measurements. A gross estimation gave an uncertainty value for our absorbed dose of ±20% [43].

The activity to administer in the second therapy was obtained by performing a straightforward calculation from the whole-body absorbed dose in the first therapy.

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