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ORIGINAL ARTICLE

^{131}I-mIBG therapy in relapsed/refractory neuroblastoma: an old bridge to the future

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Available online 4 April 2025

Background: The prognosis of relapsed/refractory (R/R) neuroblastoma (NB) is still dismal. The role of iodine-131 meta-iodobenzylguanidine (^{131}I-mIBG) treatment as a tool to reduce tumour burden before novel immunotherapies is not defined.

Patients and methods: Patients with R/R NB were included in a prospective observational study based on two infusions of ^{131}I-mIBG plus melphalan (110 mg/m^2), supported by autologous haematopoietic stem cell rescue. The activity of the first administration was 444 MBq (12 mCi/kg), while the second dose was modulated to reach a whole-body absorbed dose of 4 Gy. The International Neuroblastoma Response Criteria (INRC) were used for response.

Results: Twenty-six patients with a median age of 5.9 years (range 2.5-17.2 years) were treated. Twenty-three patients presented a bone/bone marrow involvement, and 21 patients presented an uptake at primary site or at soft-tissue sites. The median International Society of Paediatric Oncology Europe Neuroblastoma Group (SIOPEN) skeletal score was 10 (range 1-70). The main recorded toxicities were haematological, with no toxic deaths and only one grade 4 mucositis. Hypothyroidism was reported in 6 patients of the 14 alive patients. The overall response rate was 48% [95% confidence interval (CI) 28% to 69%] with only one progression; after treatment the median SIOPEN skeletal score was 6 (range 0-70) with a median reduction of 35% (range 4.3%-100%). Overall, 52% (95% CI 32% to 73%) of patients achieved/maintained a SIOPEN skeletal score <7 and a soft-tissue lesion <5 cm was seen in 67% (95% CI 43% to 91%). After this treatment, 65% of patients underwent GD2-targeting chimeric antigen receptor (CAR)-T-cell therapy and 50%, high-dose chemotherapy with busulfan and melphalan. The 3-year overall survival was 55% (95% CI 33% to 73%) and event-free survival was 42% (95% CI 23% to 60%).

Conclusion: The ^{131}I-mIBG therapy plus melphalan is confirmed to be effective to reduce/control tumour burden. Further studies are needed to clarify the role and timing of this treatment and to integrate its role in the strategy of CAR-T cells.

Key words: paediatric oncology, neuroblastoma, ^{131}I-mIBG therapy, theranostics

INTRODUCTION

Neuroblastoma (NB) is the most common extracranial solid tumour of childhood, with a heterogeneous clinical behaviour, spanning from localized disease that spontaneously resolves to high-risk (HR) disease that can often be lethal.[1] About half of the patients present with a HR NB, namely a metastatic disease in children older than 18 months or tumour carrying an MycN amplification[1] with an event-free survival (EFS) not exceeding 50% despite intensive, multimodal treatment[2]; for relapsed/refractory (R/R) NB, the prognosis is grim, with the long-term survival being $<$10%-20%.[3]

NB cells express the norepinephrine transporter (NET).[4] Meta-iodobenzylguanidine (mIBG) is a norepinephrine analogue that can be labelled with a radioactive isotope, namely ^{123}I or ^{131}I, and used clinically for imaging and for treatment. Since the 1990s, many studies have been conducted to explore the role of ^{131}I-mIBG as molecular radiotherapy on patients with R/R NB; more recently, other

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studies have investigated its use also in front-line treatment, both in the induction and consolidation setting. The combination of ^{131}I-mIBG with myeloablative chemotherapy followed by haematopoietic stem cell rescue was also investigated to minimize the risk of resistance using two treatment modalities.[5-7] In particular, melphalan is used within myeloablative regimens by both the International Society of Paediatric Oncology Europe Neuroblastoma Group (SIOPEN) and Children's Oncology Group (COG) trials,[1] and its combination with molecular radiotherapy has been tested in phase I and II studies.[8,9] However, the role of ^{131}I-mIBG treatment remains disputed both in the first-line and in the R/R setting.

In recent years, the efforts of the NB scientific community have been mainly focused on immunotherapy as salvage treatment for R/R NB, with promising results obtained both in terms of response rate[10] and in terms of long-term survival.[11,12] The immunotherapy approach seems to be more effective in patients with low disease burden; in particular, according to the SIOPEN MIBG skeletal score,[13] the cut-off of 7 has a prognostic value in patients treated with GD2-directed chimeric antigen receptor (CAR)-T cells.[11] In this scenario, strategies to reduce the disease burden become crucial and the role of ^{131}I-mIBG may be reconsidered along this new prospective.

At Bambino Gesù Children Hospital, Rome, Italy, a prospective study (1247_OPBG_2016) has been set up to collect real-world data on safety, efficacy and long-term outcomes associated with ^{131}I-mIBG treatment. Two preliminary reports[14,15] were focused on feasibility and dosimetry. In this article, we report on a cohort of R/R NB children given this therapy, focusing on response and considering ^{131}I-mIBG as a treatment before a consolidation phase.

PATIENTS AND METHODS

The ^{131}I-mIBG therapy is considered in the institutional guideline for relapsed HR NB, refractory HR NB who were not included in VERITAS protocol (NCT03165292), and for relapsed low/intermediate NB who failed an initial salvage treatment with standard chemotherapy. This report includes patients enrolled in a prospective observational study (1247_OPBG_2016) approved by the Ethical Committee of Bambino Gesù Children's Hospital. Patients' guardians signed informed consent forms for the treatment with ^{131}I-mIBG. All investigations were conducted in accordance with the principles expressed in the Declaration of Helsinki.

The ^{131}I-mIBG therapy was proposed only to patients with mIBG-avid NB with persistent uptake at enrolment and was considered after a re-induction treatment in relapsed HR NB, after second relapse in low/intermediate NB and after a second line of treatment after rapid COJEC in refractory patients. We considered refractory the HR patients who did not achieve a SIOPEN skeletal score <3 and and/or a bone marrow involvement $<5\%$ at the end of the induction phase (COJEC). The treatment consisted of two infusions of ^{131}I-mIBG administered with a 2-week interval; thyroid protection with Lugol's solution and triiodothyronine was started 72 h before the first ^{131}I-mIBG administration and continued for 15 days after the second administration, as previously reported.[14] A single dose of melphalan 110 mg/m^2 was administered 72-96 h after the second ^{131}I-mIBG infusion followed after 48-72 h by autologous haematopoietic stem cell transplantation (auto-HSCT). An antiemetic—ondansetron—was administered 30 min before the ^{131}I-mIBG infusion and later in case of nausea or vomit. The first ^{131}I-mIBG administration was carried out in a protected regimen; patients were discharged after 4-5 days according to caregivers and population dose constraints established by law after the first administration, while after the second, they were managed as inpatient until haematological recovery.

The dose of the first administration of ^{131}I-mIBG was 444 MBq/kg (12 mCi/kg), except for patients over 50 kg, who received no >17 GBq (460 mCi), as previously described by Matthay and colleagues.[16] The whole-body (WB) absorbed dose, resulting from the first administration, was used to determine the second amount of activity to be injected to reach ideally a WB absorbed dose of 4 Gy. Absorbed dose to WB was calculated according to the medical internal radiation dose [17] and European Association of Nuclear Medicine (EANM) guidelines[18] using the following formula: $D_{WB} = S_{WB \leftarrow WB}\, \tilde{A}_{WB}$, where S is called S-Factor and depends on the radioisotope, the height and the weight of the patient whose value is reported in OLINDA/EXM Software® (Hermes Medical Solutions, Stockholm, Sweden) for different phantoms ages; $\tilde{A}$ is the cumulated activity and it is related to the radiopharmaceutical biokinetic.

The absorbed dose to red marrow (RM) was estimated through blood samples as reported in the EANM guidelines,[18] considering blood as a surrogate of RM and applying the red marrow—blood ratio (RMBLR) correction factor.

The mean absorbed dose to RM is the sum of the contributions from RM auto-irradiation and the remainder of body (RoB) irradiation. Similarly to WB case, its expression can be reported as follows: $D_{RM} = \tilde{A}_{RM}\, S_{RM \leftarrow RM} + (\tilde{A}_{WB} - \tilde{A}_{RM})\, S_{RM \leftarrow RoB}$ where $S_{RM \leftarrow RM}$ is the S-factor of the RM auto-irradiation for ^{131}I, calculated and reported by OLINDA/EXM; $S_{RM \leftarrow RoB}$ is the S-factor of the RoB irradiation on RM for ^{131}I and it can be calculated as reported in the EANM guidelines[18]; $\tilde{A}_{WB}$ and $\tilde{A}_{RM}$ are the WB and RM cumulated activities, respectively. $\tilde{A}_{RM}$ is calculated plotting the blood activity concentration in time and selecting the best fitting model. For the activity concentration estimation, a precision balance and a home-calibrated well counter (NaI: Tl scintillation detector) were used.

To assess the cumulated activity, WB residual activity was measured with an external probe (a plastic scintillator detector) with the following time samples: 0.5 h, 24-30 h, 48 h, 72 h and 144-168 h after the administration. To reduce the

error in the WB absorbed dose calculation, each measurement was acquired in anterior—posterior (AP) and posterior—anterior (PA) views at 2 m from the patient's surface.

Data on demographics, disease status, previous treatment, ^{131}I-mIBG treatment, antitumour activity, toxicity and safety of each patient treated were collected prospectively. A full disease evaluation was requested before treatment and after 30-60 days from the end of treatment and before any other treatments with magnetic resonance imaging (MRI)/computed tomography (CT) scan, mIBG scan and bone marrow evaluation. Response was assessed according to the modified International Neuroblastoma Response Criteria (INRC).[19] Bone response was monitored by mIBG scintigraphy and SIOPEN scoring[13]; bone marrow biopsies and aspirates were routinely carried out. The overall response rate (ORR) was defined as the sum of complete (CR) or partial response (PR) or minor response (MR) according to the INRC.[20] The MIBG scintigraphy for this report were reviewed by three senior nuclear medicine experts (MCG, MFV, CA), while CT/MRI scan were reviewed by two senior radiologists (PT, MLD). Clinical and laboratory adverse events during treatment are reported according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0)[21] for this report. Overall survival (OS) was defined as the time from study entry until death, and EFS was defined as the time from study entry until death, progression or relapse of any type, whichever occurred first. The Kaplan—Meier method was used to calculate both OS and EFS. Statistical analysis was carried out using EZR (Easy R) software.[22]

RESULTS

Patients

From October 2017 to February 2022, a total of 26 patients with R/R NB received tandem ^{131}I-mIBG with melphalan and auto-HSCT. The median age at study inclusion was 5.9 years (range 2.5-17.2 years); 14 patients were male and 12 females. All patients had previously received $\geq$2 lines of treatment; in detail, 14/26 (54%) had received 2 previous lines and 12 (46%) >2 lines of treatment; no patient had received chemoimmunotherapy before ^{131}I-mIBG treatment. Out of 26 patients, 10 (38%) presented a primary refractory disease. Patients' characteristics are summarized in Table 1 while details about previous treatment are summarized in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.104541. At diagnosis, 21 patients were stage M, 4 stage L2 and only one L1 according to International Neuroblastoma Risk Group (INRG). All patients presented a metastatic dissemination at the time of treatment with an mIBG-avid disease. Overall, 22 patients presented a bone involvement, 10 patients a bone marrow involvement (isolated in one), 3 patients an isolated lymph node involvement, while combined metastasis was reported in 12 cases. The median SIOPEN skeletal score was 10 (range 1-70). Before enrolment, 12 patients (46%) had a stable disease (SD), 7 (27%) a progressive disease (PD), 6 (23%) a PR and 1 (4%) an MR.

Table 1. Patient characteristics

Patients, *n*	26
Median age, years (range)	5.9 (2.5-17.2)
Sex ratio (male/female)	14/12
Disease status at mIBG treatment, *n* (%)	
- Refractory	10 (38)
o PD	2 (8)
o SD	7 (27)
o MR	0
o PR	1 (4)
- Relapsed	16 (62)
o PD	5 (19)
o SD	5 (19)
o MR	1 (4)
o PR	4 (15)
Disease present at study entry, *n* (%)	
- Primary tumour	18 (69)
- Bone	22 (85)
- Bone marrow	10 (38)
- Soft tissue	15 (58)
Initial INRG stage at diagnosis, *n* (%)	
- L1	1 (4)
- L2	4 (15)
- M	21 (81)
MycN status, *n* (%)	
- Amplification	7 (27)
- Gain	3 (12)
- No amplification	16 (51)
Prior treatment, *n* (%)	
- HR-NBL1/SIOPEN protocol or according to HR-NBL1/SIOPEN	21 (81)
- LINES protocol	5 (19)
Previous line of chemotherapy, *n* (%)	
- 2	14 (54)
- >2	12 (46)

mIBG, meta-iodobenzylguanidine; INRG, International Neuroblastoma Risk Group; MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease; SIOPEN, International Society of Paediatric Oncology Europe Neuroblastoma Group.

Treatment

A total of 48 ^{131}I-mIBG infusions were administered in 26 patients for 26 planned tandem treatments; in 4 patients, the targeted WB absorbed dose of 4 Gy was already reached after the first infusion. The median cumulative WB absorbed dose was 3.69 Gy ranging from 1.61 Gy to 5.62 Gy, while the median cumulative dose on bone marrow was 2.13 Gy ranging from 1.01 Gy to 4.28 Gy; 18/26 (69%) received a WB absorbed dose >3.5 Gy and 23/26 (88%) received a WB absorbed dose >3 Gy.

Toxicity

The ^{131}I-mIBG infusion was well tolerated in all patients, the main extramedullary toxicity being represented by nausea and/or vomiting grade $\leq$ 2 controlled by administration of antiemetic drugs (ondansetron). No hypertension crisis occurred. After the first infusion, patients were discharged according to dosimetry; as mentioned, in four patients, the maximum WB absorbed dose of 4 Gy was already reached with the first administration, and, thus, they remained in the ward, while the other 22 patients were discharged without any further admission before the second infusion. After the second infusion, all patients were managed in the ward until haematological recovery. The main toxicities observed were haematological and are summarized in Table 2. The median

Table 2. Haematological toxicity according to CTCAE version 5, considering after each infusion for a total of 48 infusions

Toxicity	Grade 4	Grade 3	Grade 2	Grade 1	Grade 0	Overall
Neutropenia	31	11	3	1	2	46 (95%)
Leukopenia	26	11	4	2	4	43 (91%)
Thrombocytopenia	26	1	0	10	11	37 (77%)

CTCAE, Common Terminology Criteria for Adverse Events.

time to neutrophil engraftment (namely the first of 2 consecutive days with neutrophil $>500/mm^3$) was 11 days (range 0-27 days). The median time to platelet engraftment (namely the first of 2 consecutive days with platelets $>20\,000/mm^3$without transfusion support) was 16 days (range 0-46 days); one patient never achieved platelet engraftment due to a rapidly progressive disease. There were no toxic deaths and only one grade 4 mucositis with no other extra-haematological toxicity > grade 3. Grade 2/3 mucositis was reported in seven patients (grade 2 in two and grade 3 in five patients) and grade 4 in one, neutropenic fever in three patients, grade 2 liver toxicity in one patient and viral lung infections in two patients.

Hypothyroidism after ^{131}I-mIBG therapy was the most frequent long-term toxicity, reported in 6 of the 14 patients (43%) who are currently alive.

Response and survival

At the last follow-up on 1 May 2024, 14 patients were alive and 12 died (all because of disease progression), with a median follow-up of 4.9 years (range 0.9-11 years) from diagnosis and 2.8 years (range 0.3-6.6 years) from mIBG therapy. The 3-year OS was 55% [95% confidence interval (CI) 33% to 73%] and the 3-year EFS was 42% (95% CI 23% to 60%) (Figure 1).

One patient with only soft-tissue involvement refused the evaluation after treatment and was excluded from response analysis and considered only for survival. The ORR was 48% (95% CI 28% to 69%) (12 MR according to INRC), with only one patient with a metastatic progression soon after treatment (see Table 3 and Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.esmoop.2025.104541, for details).

In details according to INRC, considering the primary tumour CR/PR was reported in 3/19 patients (16%, 95% CI 3% to 40%), considering bone involvement CR/PR was reported in 3/21 (14%, 95% CI 3% to 36%), considering soft-tissue/lymph node CR/PR was achieved in 8/15 (53%, 95% CI 27% to 79%), while CR/minimal disease on bone marrow evaluation was achieved in 9/13 patients (69%, 95% CI 39% to 91%) (resumed in Table 3 and Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.104541).

The median SIOPEN skeletal score decreased to 6 (range 0-70); in 10 out of 23 (43%) the score had a median reduction of 35% (range 4.3%-100%). Complete metabolic remission was achieved in 2 out of 23 (9%, 95% CI 1% to 28%) with positive mIBG on bone and in 3 out of 20 (15%, 95% CI 3% to 38%) with positive mIBG on soft tissue. To note, all primary (or residual primary) lesions remained mIBG avid with a median tumour reduction of 18% (range 5%-51%), while the soft-tissue/lymph nodes presented a median size reduction of 36% (range 1%-100%) reported in 13 out of 15 patients.

Considering the cut-off of 7 for the SIOPEN skeletal score that we identified in our trial as predictive of an improved long-term outcome after treatment with GD2-CART01, 15 patients had >7 at enrolment and 5/15 (33%, 95% CI 12% to 61%) had a reduction to a value <7 after treatment. Overall, at the end of treatment 12/23 (52%, 95% CI 32% to 73%) patients had a SIOPEN skeletal score <7. For primary tumours and soft-tissue lesions, we had identified a cut-off <5 cm of the longest diameter as predictive of improved survival and this goal was achieved on primary tumour in 9/21, (43%, 95% CI 22% to 66%) and on soft tissue in 10/15 patients (67%, 95% CI 43% to 91%).

The patient with PD presented a body weight >70 kg and the WB absorbed dose was 1.61 Gy. Evaluating the response according to the median cumulative WB absorbed >3.69 Gy, the absorbed dose did not influence ORR according to INRC or skeletal disease response (data not shown). Considering only the response of soft tissues, the ORR disease was 2/7 (26%) in patients with a WB <3.69 Gy and 6/9 (67%) in those with a WB >3.69 Gy ($P = 0.3147$). Moreover, all PR and CR considering both skeletal and soft-tissue diseases were observed in patients who received a WB absorbed dose >3 Gy (dose achieved in 88% of patients). To note, the three patients who received WB absorbed dose <3 Gy died of PD. Out of four patients who received a single mIBG infusion (see Table 3 and Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.104541, for details), three patients presented a SD, while one patient with only soft-tissue metastatic disease achieved a CR. The WB absorbed dose for each patient is reported in Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.esmoop.2025.104541, together with response data.

After mIBG therapy, 7 patients received high-dose chemotherapy with melphalan plus busulfan, 10 underwent CAR-T-cell therapy (GD2-CART01) according to our institutional study protocol NCT03373097[11] and 6 received high-dose chemotherapy with melphalan plus busulfan and subsequent GD2-CART01. Nine patients were non-eligible for GD2-CART01 for the following reasons: (i) type of relapse (i.e. first metastatic relapse of a low/intermediate NB at diagnosis); (ii) parental refusal; (iii) disease progression; and (iv) high disease burden. A standard maintenance with CRA

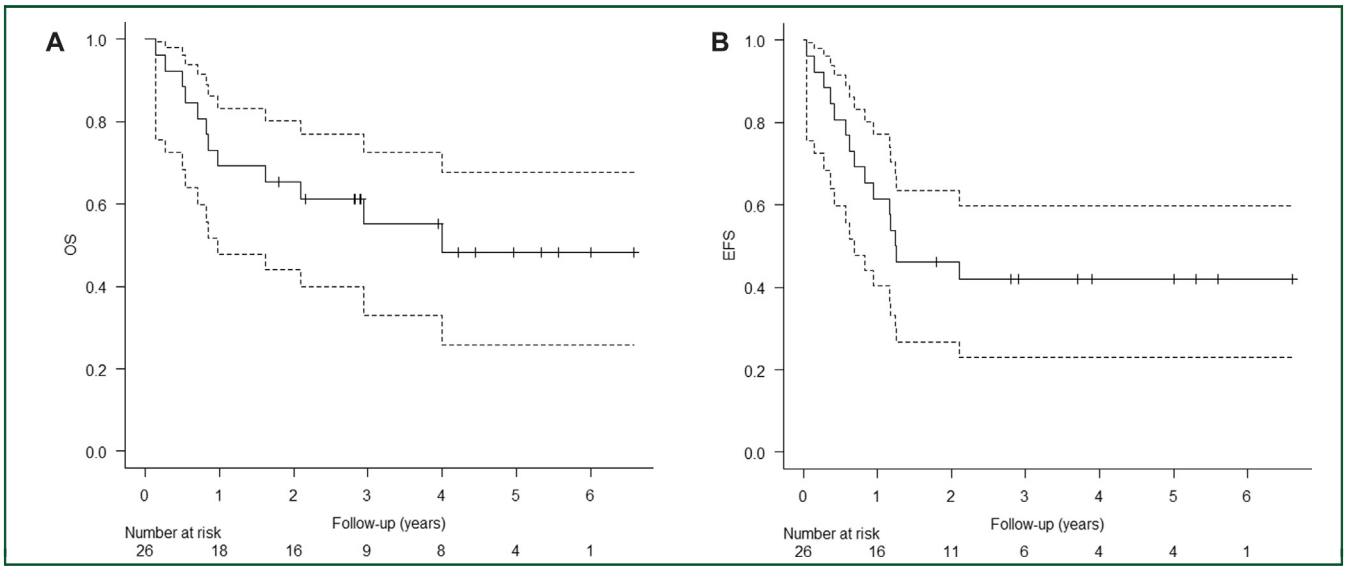

Figure 1. Kaplan–Meier curves for 3-year OS (A) and 5-year EFS (B). Dashed lines enclose the 95% confidence interval.
EFS, event-free survival; OS, overall survival.

(13-cis retinoic acid) plus dinutuximab beta was proposed in patients not eligible for GD2-CART01. Whenever possible, local control of the primary tumour with surgery and radiotherapy completed the strategy for refractory patients.

DISCUSSION

Since the end of the 1980s, ^{131}I-mIBG has been explored as a therapeutic strategy in NB.[23] Many studies have been conducted on patients with R/R disease, although there was no wide international consensus on the role and positioning of this treatment option on the whole therapeutic plan of R/R NB. These studies differ significantly in terms of administered dose, use or non-use of concomitant chemotherapy and response rate obtained.[5-7,24,25] Moreover, although the ability of radiotherapy to stimulate tumour immunogenicity has long been known,[26] the role of molecular radiotherapy in combination with immunotherapy needs to be further investigated.

R/R NB remains an unmet medical need with poor long-term outcomes; the 5-year OS is below 20% for children with refractory NB and $<$10% for relapsed disease.[19] During the last decade, different second-line strategies have been proposed with an impressive effort consisting of $>$150 phase I and II trials from 2011 to 2020.[27] Currently, the 'standard' backbone therapy in R/R NB developed by international cooperative groups is represented by temozolomide-based regimens, such as temozolomide/irinotecan (TEMIRI) and topotecan/temozolomide (TOTEM) with similar outcomes[28,29] and topotecan/cyclophosphamide.[30] The BEACON-Neuroblastoma randomized trial investigated the role of the addition of bevacizumab to backbone chemotherapy regimens (temozolomide, TEMIRI or TOTEM); the ORR was 26% in the bevacizumab arms, and 18% in the non-bevacizumab arms, respectively.[31] More recently, the addition of immunotherapy (i.e. use of anti-GD2 monoclonal antibodies) to chemotherapy seems to improve the therapeutic effect of standard backbone treatments, inducing an ORR of 40%-50%,[10,32,33] whereas only molecularly targeted treatment on ALK have a major role in the NB setting.[34] Overall, ^{131}I-mIBG proved to be a suitable option in R/R NB.[5] Interestingly, the COG group reported that mIBG therapy may wield more favourable effect for refractory NB than for relapsed disease, based on a retrospective analysis of 218 patients included in three local and six NANT clinical trials.[35]

In this study, we confirm that the tandem mIBG therapy combined with melphalan followed by auto-HSCT is a well-tolerated treatment, with the major toxicity being a haematological one with non-impact in the following treatment in patients who received melphalan plus busulfan. Hypothyroidism represents the major long-term toxicity reported in 43% of patients and being suitable to be corrected by hormonal replacement therapy. The ORR was 48% with only one progression (5%); a metabolic CR was achieved in 2 (9%) out of the 23 patients with positive mIBG on bone/bone marrow sites and in 3 (15%) out of the 20 children with positive mIBG on soft tissue. Interestingly, patients

Table 3. Response according to INRC

	Primary tumour	Bone	Soft-tissue/lymph node	Bone marrow
CR/PR (MD for bone marrow)	16%	14%	53%	69%
95% CI	3%-40%	3%-36%	27%-79%	39%-91%

I, confidence interval; CR, complete response; INRC, International Neuroblastoma Response Criteria; MD, minimal disease; PR, partial response.

with disease under control seem to benefit most from treatment with molecular radiotherapy: only one out of seven patients with PD achieved a response (MR), confirming the results of the COG group analysis showing a better response for patients with refractory NB compared with relapsed disease.[35] A dosimetry approach to reach a WB absorbed dose of 4 Gy was safe and effective; a WB absorbed dose >3.5 Gy was reached in 69% of patients and >3 Gy in 88% of patients. To note, all response were observed in patients who reached a WB absorbed dose >3 Gy and the only progression was recorded in a patient with a WB absorbed dose <2 Gy.

Achieving a WB absorbed dose of 4 Gy is subject to several limitations The first limitation is related to (i) inter-patient variability in the biodistribution of ^{131}I-mIBG influenced by individual metabolism, (ii) tumour uptake and (iii) body weight. To note in patients with a body weight >50 kg, the maximum administrable activity was limited to 17 GBq for safety reasons. Finally, the last limitation concerns the WB dose calculation methodology: the activity of the second ^{131}I-mIBG administration was adjusted on first dosimetry. However, an accurate prediction is challenging due to the intrapatient variability in the clearance curve between the two administrations.

The combination of ^{131}I-mIBG with melphalan seems safe but according to more recent evidence different combinations may be considered and further studies are needed to clarify the benefit in terms of response of the ^{131}I-mIBG combination with vorinostat or topotecan.[5,6,14,21,22]

These results are consistent in terms of both response and toxicities with the recent prospective French study[25] and the COG experience.[24] The NANT consortium conducted a pick-the-winner study to compare the combination of ^{131}I-mIBG plus different radiosensitizer agents with ^{131}I-mIBG alone; the ORR after one course of ^{131}I-mIBG alone or with vincristine and irinotecan was 14%, while that with ^{131}I-mIBG and vorinostat was 31%, this suggesting that the combination with vorinostat is likely more effective. However, the estimated progression-free survival and OS were comparable in all groups.[24] A French phase II study evaluated tandem infusions of ^{131}I-mIBG and topotecan; the ORR was 13% and the 2-year EFS was 17%. The treatment was overall well tolerated, and haematological toxicity was the major side-effect of the study. Moreover, a favourable outcome was confirmed in patients who subsequently received busulfan and melphalan, as confirmed in our series.[25]

Although the efficacy and safety of ^{131}I-mIBG in the NB treatment have been tested for decades in different settings, a consensus has not yet been achieved and it is unclear as to which is the ideal scenario to maximize its potential. In particular, it seems very intriguing to combine the molecular radiotherapy with immunotherapeutic strategies that in recent years have emerged as the most attractive option for patients with R/R NB, namely the use of CAR-T cells against GD2[11] and HLA-haploidentical HSCT followed by the anti-GD2 antibody dinutuximab beta.[12] A more favourable outcome was observed in patients with a low disease burden achieved before treatment in both these immunotherapy strategies. Our group has previously identified a cut-off of 7 for the SIOPEN skeletal score and a cut-off of 5 cm for major diameter for bulky disease (considering both primary tumour or soft-tissue metastasis) as variables predictive of a better outcome.[11] Both CAR-T cells and HLA-haploidentical HSCT may be considered as 'consolidation' treatment after an 'induction' phase, as in the first-line approach. In this scenario, our data indicate that mIBG therapy may be considered a suitable bridge option to reduce the tumour burden with an ORR of 48%, and 33% of patients achieved a SIOPEN skeletal score <7 while soft-tissue bulky lesions <5 cm were achieved/maintained in >60% of patients before the administration of other consolidative treatments, including CAR-T cells. Remarkably, a low incidence (5%) of early progression was observed. These promising results must be confirmed by further studies including more patients to clarify the usefulness and the timing of molecular radiotherapy with ^{131}I-mIBG in the new era of immunotherapies.

DISCLOSURE

The authors have declared no conflicts of interest.

FUNDING

This work was supported by the Italian Ministry of Health with current research funds (no grant number).

DATA SHARING

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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