[^{131}I]*m*IBG therapy in neuroblastoma – 35 Years of experience

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Abstract

Neuroblastoma is the most common extracranial solid malignancy of childhood. Approximately half of patients have high-risk neuroblastoma (HR-NBL), typically presenting with widespread metastatic disease at diagnosis. Despite aggressive multimodality treatment, patients with HR-NBL have a long-term survival of less than 50%, due to a high relapse/progression rate and therapy-resistant disease. To overcome therapy-resistance in neuroblastoma, researchers are exploring diverse treatment strategies including radionuclide therapy. For several decades now, radiolabelled meta-iodobenzylguanidine (*m*IBG) has been used as a theranostic (therapeutic and diagnostic) radiopharmaceutical in neuroblastoma. [^{123}I]*m*IBG imaging with scintigraphy/SPECT is the international standard to assess dissemination at diagnosis and to evaluate treatment response. In contrast, the role of [^{131}I]*m*IBG therapy is less clear. Over the past 35 years, [^{131}I]*m*IBG therapy has been studied in more than 1500 patients. In initial studies, [^{131}I]*m*IBG monotherapy was used as second-line treatment for patients with relapse/progression or refractory disease. In current applications, [^{131}I]*m*IBG therapy is combined with chemotherapy, radiosensitizers, and/or immunotherapy, also including front-line setting in patients with newly-diagnosed HR-NBL. This review provides an overview on contemporary literature regarding [^{131}I]*m*IBG therapy in HR-NBL.

Introduction

Neuroblastoma is the most common extracranial solid malignancy of childhood, with an incidence of 30 patients annually in the Netherlands (1). Patients are stratified into risk groups by age, stage, and tumour biology (figure 1) (2). Patients with low-risk neuroblastoma can show spontaneous regression, while patients with high-risk neuroblastoma (HR-NBL) frequently develop therapy-resistant tumour growth with fatal outcome. Approximately half of patients have HR-NBL at diagnosis, typically presenting as widespread metastatic disease affecting bone/bone marrow and lymph nodes (1). Standard HR-NBL treatment consists of three phases with both systemic and local therapies (2). "Induction" consists of several courses of chemotherapy, followed by primary tumour resection. During "consolidation", remaining tumour cells are eliminated by myeloablative high dose chemotherapy (HDCT), which is followed by reinfusion of hematopoietic stem cells that were harvested before (so called autologous stem cell transplantation, ASCT) and external beam radiotherapy. Lastly, any minimal residual disease is treated during "maintenance" with anti-GD2 immunotherapy (dinutuximab-beta) and isotretinoin.

Despite this aggressive multimodality treatment, long term survival of HR-NBL is only 40-50% (1,2). The most challenging problem of HR-NBL, is the high relapse/progression rate (40-50%) after initial (front-line) treatment. Relapsed/progressive disease has a dismal outcome with long term survival of less than 20% (3). Treatment options for those who fail front-line treatment are limited, mainly due to therapy-resistance. To overcome therapy-resistance in neuroblastoma, researchers are exploring new (combination) treatment strategies. Second-line treatments are based on a backbone of immunochemotherapy including irinotecan or topotecan, temozolomide, and dinutuximab-beta. In addition, individual tumours can be molecularly characterized for subsequent targeted treatment (4). Since neuroblastoma is a radiosensitive tumour, radionuclide therapy is one of the systemic treatment options.

For several decades, radiolabelled *meta*-iodobenzylguanidine (*m*IBG) has been used as theranostic (therapeutic

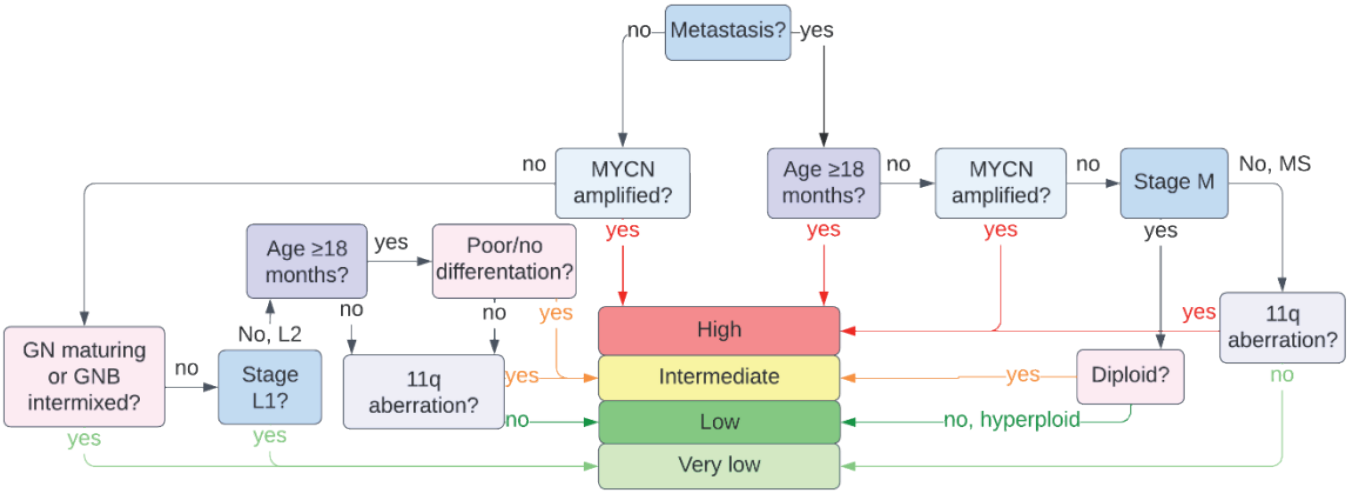

Figure 1. Neuroblastoma risk classification according to the International Neuroblastoma Risk Group.
Poor prognostic factors include age ≥18 months, more advanced disease stage, MYCN amplification, poorly differentiated or undifferentiated tumour histology, diploid DNA content, and the presence of segmental chromosome 11q aberrations.
Abbreviations: GN, ganglioneuroma; GNB, ganglioneuroblastoma.

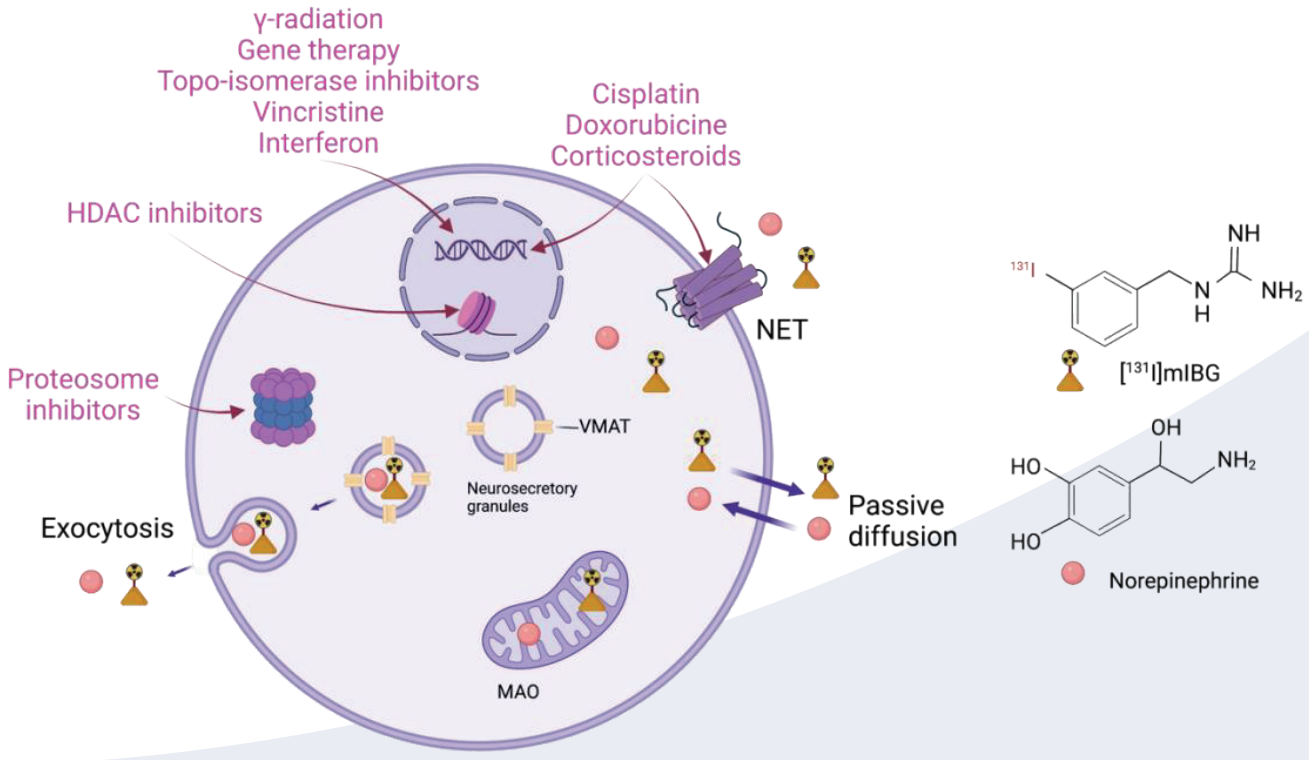

Figure 2. Mechanisms to enhance [^{131}I]*m*IBG efficacy in neuroblastoma cells. [^{131}I]*m*IBG uptake occurs mainly through (specific) active uptake via NET and to a lesser extent via (non-specific) passive diffusion. There are several strategies to increase [^{131}I]*m*IBG uptake, retention, and cytotoxicity of neuroblastoma cells. It is possible to increase the sensitivity of neuroblastomas to [^{131}I]*m*IBG therapy but also to directly increase NET mRNA expression or enhance NET function. Figure adapted from Schmidt *et al*. 2016 (4).
Abbreviations: *m*IBG, meta-iodobenzylguanidine; norepinephrine transporter, NET; HDAC, histone deacetylase; VMAT, vesicular monoamine transporter; MAO, monoamine oxidase inhibitors.

and diagnostic) radiopharmaceutical in neuroblastoma (figure 2: [^{123}I]/[^{131}I]*m*IBG scintigraphy). *m*IBG is a norepinephrine analogue that is taken up by cells via the norepinephrine transporter (NET). Neuroblastoma cells abundantly express NET and, therefore, radiolabelled *m*IBG offers excellent tumour cell targeting (5). [^{123}I]*m*IBG scintigraphy is currently the best-established and standard nuclear imaging technique to determine disease extent in patients with neuroblastoma; at initial staging and during therapeutic response monitoring. In contrast to [^{123}I]*m*IBG imaging, the role of [^{131}I]*m*IBG therapy in the management of neuroblastoma is less clear. In principle, [^{131}I]*m*IBG therapy can be an effective treatment to induce response of primary tumour and metastatic sites or to inhibit progression.

Over the past 35 years, [^{131}I]*m*IBG therapy has been studied in more than 1500 patients with HR-NBL (6). After the introduction of [^{131}I]*m*IBG therapy in neuroblastoma (1984), many trials were performed to establish the feasibility, toxicity, and maximum tolerated activity of [^{131}I]*m*IBG monotherapy (6). Matthay *et al*. (1998) showed that the maximum tolerated activity was 444 MBq/kg, however, a higher ("myeloablative") activity of [^{131}I]*m*IBG therapy can be administered if combined with ASCT (7). Later, combination treatments were investigated to increase the therapeutic effect of [^{131}I]*m*IBG with a variety of chemotherapeutic agents, radiosensitizers (figure 3), and immunotherapy (6).
In early studies, [^{131}I]*m*IBG therapy was mainly studied as second-line (salvage) treatment in HR-NBL patients who failed front-line treatment. In the past 10 years, studies have focused on integrating [^{131}I]*m*IBG therapy in front-line treatment of HR-NBL. It is hypothesized that early treatment with [^{131}I]*m*IBG therapy may prevent the development of therapy-resistant tumour cells.
The aim of this review was to provide an overview on [^{131}I]*m*IBG therapy in the treatment of HR-NBL over the past 35 years, by discussing several major studies and providing an update of contemporary literature and ongoing studies.

Front-line [^{131}I]*m*IBG therapy

Upfront

Upfront [^{131}I]*m*IBG therapy in the treatment of HR-NBL is an approach that was pioneered in the Netherlands. In a prospective (phase II) trial, de Kraker *et al*. (2008) included 44 patients with HR-NBL between 1989 and 1999 (8). Patients were treated with at least two cycles (median 3, maximum 5) of [^{131}I]*m*IBG therapy at four-week intervals (fixed activity of 7.4 GBq for first cycle, 3.7–5.6 GBq for further cycles). Cumulative activity per patient ranged from 13 to 35 GBq (median 18.5). Forty-one patients were evaluable after two courses of [^{131}I]*m*IBG therapy, 27 (66%) of whom had a partial or complete response. In 24 patients (group A), [^{131}I]*m*IBG cycles were continued as induction treatment, as replacement of induction chemotherapy. The other 17 patients (group B) continued with cycles of induction chemotherapy, the most frequent reason being stable disease. Use of these two induction regimens resulted in a (partial/complete) response rate of 73% in the 41 patients. Complete macroscopic resection of the primary tumour was possible in 67%, which is an important advantage of upfront [^{131}I]*m*IBG therapy. Only 11 patients from group A and 6 patients from group B continued with consolidation (HDCT and ASCT), and maintenance (isotretinoin). Five-year event-free survival (EFS) and overall survival (OS) in this cohort was remarkably poor: 12% and 15%, respectively.
Subsequently, Bleeker et al. (2013) retrospectively analysed acute toxicity in the same HR-NBL cohort, plus additional patients (of all stages) after two cycles of upfront [^{131}I]*m*IBG therapy (9). This cohort (n=66) was unique in investigating toxicity of [^{131}I]*m*IBG without prior treatment, in the first month following [^{131}I]*m*IBG therapy. The median first administered activity was 441 MBq/kg (range 157-804 MBq/kg) for the first cycle and 328 MBq/kg (range 113-727 MBq/kg) for the second cycle. Upfront [^{131}I]*m*IBG therapy had an acceptable safety profile if the condition of the patient was taken into consideration.

As a result of these studies, upfront [^{131}I]*m*IBG therapy was incorporated in the Dutch NBL2009 study for patients with HR-NBL. Within two weeks of diagnosis, two cycles of [^{131}I]*m*IBG therapy (7.4 and 5.5 GBq) were administered within a four-week interval. At a 21-day interval after the second cycle, patients started induction chemotherapy. Patients were excluded from [^{131}I]*m*IBG therapy if they were in poor clinical condition (uncontrollable hypertension, orbital masses, and/or pleural effusion) or in case of [^{131}I]*m*IBG negative disease. Kraal *et al*. (2017) conducted a retrospective multicentre study of this treatment regimen (2005-2011) in 32 HR-NBL patients (10). No stem cell rescue was needed after [^{131}I]*m*IBG therapy. The partial/complete response rates after [^{131}I]*m*IBG therapy was 38% and after consolidation 71% . However, upfront [^{131}I]*m*IBG therapy was removed from the Dutch treatment protocol in 2016, as it was frequently not feasible due to weak clinical condition of patients or logistical reasons.

Induction/consolidation

The Children's Oncology Group (COG) evaluated the safety and feasibility of [^{131}I]*m*IBG therapy at the end of induction in a (single-

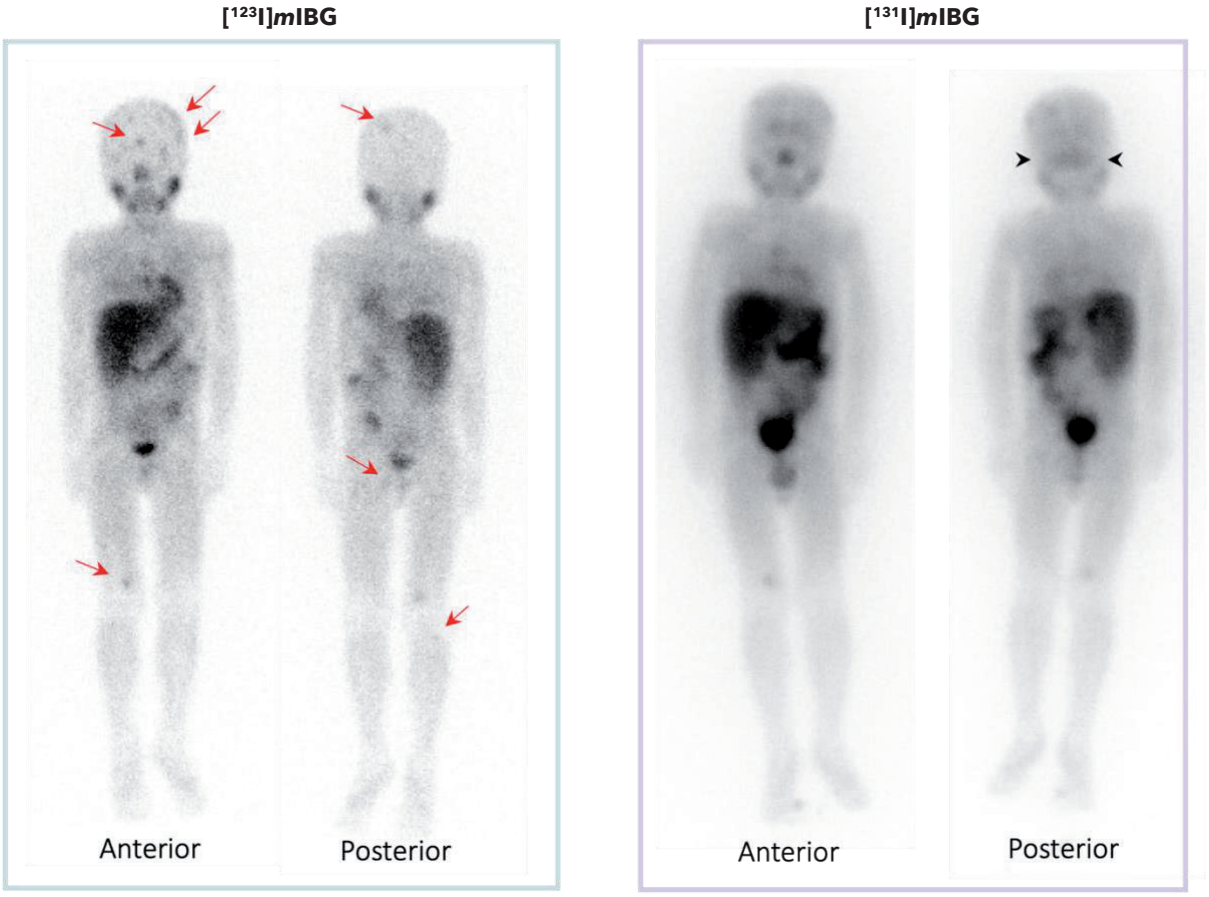

Figure 3. Distribution of meta-[^{123}I]/[^{131}I]iodobenzylguanidine on scintigraphy.
^{123}I is a principal γ emitter (T½ 13 hours), whereas ^{131}I emits both γ and β radiation (T½ 8 days). Because of the higher energy of ^{131}I γ radiation (364 keV, abundance 81%) compared to ^{123}I γ radiation (159 keV, abundance 83%), [^{131}I]*m*IBG scintigraphy is performed with high-energy-general-purpose collimators, which have a slightly lower resolution than the medium-energy-general-purpose collimators used for [^{123}I]*m*IBG scintigraphy. Physiological uptake of *m*IBG occurs in the salivary glands, heart, liver, thyroid (if not or inadequately blocked with thyroid prophylaxis), lacrimal glands, adrenal glands, nasal mucosa, myocardium; and in lesser extent in the spleen, lungs, skeletal muscles, and brown adipose tissue. As *m*IBG is excreted by the urinary tract and gastro-intestinal system, activity is seen in the bladder and intestines. Uptake in cerebellum and basal ganglia (black arrowheads) is only seen on post [^{131}I]*m*IBG therapy scintigraphy and not for diagnostic activities of [^{123}I]*m*IBG. Red arrows indicate pathological skeletal uptake on [^{123}I]*m*IBG scintigraphy. As a higher activity is used for [^{131}I]*m*IBG therapy compared to diagnostic [^{123}I]*m*IBG imaging, often more lesions are visible on post-[^{131}I]*m*IBG scintigraphy.

arm) pilot study (ANBL-09P1) (11). Patients who completed five cycles of induction chemotherapy were eligible to undergo [^{131}I]*m*IBG therapy instead of the sixth cycle of chemotherapy. The trial was designed to an "activity" escalation (444, 555, and 666 MBq/kg), with a required 10-week gap before continuing with HDCT of consolidation. Of the 68 eligible patients at the end of induction chemotherapy, 59 (86.8%) received [^{131}I]*m*IBG therapy. Of the 45 patients evaluable for [^{131}I]*m*IBG and HDCT, 37 (82.2%) received this combination. At a 555 MBq/kg activity level, the feasibility rate of [^{131}I]*m*IBG was 97% (95% CI: 83-99%) and the rate of [^{131}I]*m*IBG followed by HDCT after 10 weeks was 81% (95% CI: 60–92%). Three-year EFS of [^{131}I]*m*IBG and HDCT was 60% ± 8.3. This pilot study demonstrated the feasibility and tolerability of [^{131}I]*m*IBG therapy followed by consolidation in newly-diagnosed patients with HR-NBL. The study also laid the groundwork for the ongoing COG ANBL1531 trial (table 1). This large multicentre trial will study the role of [^{131}I]*m*IBG

Table 1. Ongoing multicentre trials on [^{131}I]*m*IBG therapy in patients with high-risk neuroblastoma.

Clinical trial name*	Centres (countries)	Clinical setting	Trial description	Treatment arms	Primary endpoint
OPTIMUM NCT03561259	21 (United States)	Relapse Progression	Phase II n=60	1) *m*IBG monotherapy 2) *m*IBG, vorinostat	Overall response
NANT2017-01 NCT03332667	12 (United States)	Relapse Progression Refractory disease	Phase I n=45	1) *m*IBG, dinutuximab 2) *m*IBG, dinutuximab, vorinostat	Safety/tolerability
MiNivAN NCT02914405	3 (United Kingdom and United States)	Relapse Progression Refractory disease	Phase I n=36	1) *m*IBG, nivolumab 2) *m*IBG, nivolumab, low dose dinutuximab 3) *m*IBG, nivolumab, full dose dinutuximab	Safety/tolerability
VERITAS NCT03165292	9 (France, Austria, Italy, Netherlands, Spain)	Refractory disease	Phase II RCT n=150	1) TEMIRI, *m*IBG, topotecan, ASCT 2) TEMIRI, HD thiotepa, ASCT	3-year EFS
ANBL1531 NCT03126916	160 (United States, Canada, Puerto Rico)	Front-line	Phase III RCT n=658	1) TC + CEM, tandem ASCT 2) *m*IBG, TC + CEM, tandem ASCT 3) *m*IBG, HD BuMel, single ASCT	3-year EFS

* ClinicalTrials.gov Identifier
Abbreviations: TEMIRI, Temozolomide-Irinotecan; *m*IBG, *meta*-[^{131}I]iodobenzylguanidine; RCT, randomized controlled trial; TC, thiotepa cyclophosphamide; BuMel, busulfan melphalan; CEM, carboplatin etoposide melphalan; ASCT, autologous stem cell transplantation, EFS, event-free survival.

therapy, double ASCT, and ALK-inhibitor crizotinib in 658 newly-diagnosed patients with HR-NBL. Patient with tumours harbouring ALK mutations are treated in the two non-randomized treatment arms. Patients without ALK mutations and [^{123}I]*m*IBG-positive disease are randomized among three other treatment arms. In two of the three arms patients are treated with [^{131}I]*m*IBG therapy after three cycles of induction chemotherapy. The aim of the randomization is to determine whether the addition of [^{131}I]*m*IBG during induction improves 3-year EFS with acceptable long-term toxicity. It should be mentioned that this study is the first randomized controlled trail (RCT) that will compare [^{131}I]*m*IBG therapy to no [^{131}I]*m*IBG therapy. Lee *et al*. (2017) performed a single arm, phase I/II trial (SMC NB-2009), in which [^{131}I]*m*IBG therapy (444 or 666 MBq/kg) was incorporated into consolidation (tandem HDCT, ASCT, and local radiotherapy) (12). Between 2009–2013, 54 patients with newly-diagnosed HR-NBL were included after 9 cycles of induction chemotherapy. Of these 54 patients, 47 received tandem HDCT (43 with [^{131}I]*m*IBG therapy), ASCT, and radiotherapy; and continued with maintenance (isotretinoin, immunotherapy, interleukin-2). The 5-year EFS rate and OS rate were 58 and 72%, respectively. Results were compared to the previous protocol (SMC NB-2004), in which HR-NBL patients were treated with total body irradiation instead of [^{131}I]*m*IBG therapy, with significant toxicity. [^{131}I]*m*IBG could achieve an equivalent survival rate (67.5 vs. 58%) with lower toxicity.

Second line [^{131}I]*m*IBG therapy

[^{131}I]*m*IBG therapy has also been studied in patients who failed front-line treatment. Three types of treatment failure in neuroblastoma can be recognized.
Recurrent disease after a complete response to therapy, often referred to as "relapse"; Progressive disease after an incomplete response to therapy; often referred to as "progression"; Residual (non-progressive)

disease after completing induction chemotherapy, requiring alternative therapy to improve remission status before proceeding to consolidation treatment; often referred to as "refractory".
Nevertheless, definitions of "relapse", "progression" and "refractory" often differ between studies; and different types of treatment failure are often pooled and studied together.

Meta-analysis

In a meta-analysis, Wilson *et al*. (2014) analysed 27 studies including 1121 patients who failed front-line treatment and underwent [^{131}I]*m*IBG therapy as second-line treatment between 1984-2005 (13). In all studies, patients with [^{123}I]*m*IBG-negative disease were not eligible for [^{131}I]*m*IBG therapy. There were 20 studies on [^{131}I]*m*IBG monotherapy and seven studies where [^{131}I]*m*IBG was combined with chemotherapy. Only four studies were comparative studies, all non-randomized. Study populations ranged from 10 to 164 patients. Mean (complete or partial) response rates, reported in 25 studies (782 patients), varied between 4-75%, with an overall mean response rate of 32% (95% CI 29-36%). In patients who received [^{131}I]*m*IBG monotherapy, response rate was 32% (199/629) compared to 39% in patients who received concomitant chemotherapy (48/124). However, there was no evidence that these responses lead to a better EFS or OS.

In the largest comparative study, 111 patients from the German NB97 Trial with stage 4 refractory HR-NBL after induction chemotherapy, were retrospectively identified (14). Patients in the intervention arm (n=40) received [^{131}I]*m*IBG therapy (444 MBq/kg). The control arm (n=71) consisted of patients whose treating physicians decided against [^{131}I]*m*IBG therapy. In the univariate analysis, there was a statistically significant difference in 3-year EFS and OS between the two arms. However, this difference was confounded as the intervention arm more often received consolidation treatment afterwards. In the subgroup analysis of patients who underwent consolidation therapy (n=66), outcomes for the [^{131}I]*m*IBG arms vs. control arm were more similar: 3-year EFS 49% vs. 33%, respectively (p=0.171) and OS 59% vs. 59%, respectively (p=0.285). By multivariate analysis, [^{131}I]*m*IBG therapy had no statistically significant impact on 3-year EFS (p=0.494) and OS (p=0.891). In conclusion, an independent advantage of [^{131}I]*m*IBG therapy could not be proven, which emphasises the importance of confounding factors (and other forms of bias) in non-randomized comparative studies. Results on [^{131}I]*m*IBG therapy of the latest German NB2004 Trial have not been reported yet (4).

In the largest single-arm (phase II) trial of Matthay et al. (2007), 164 HR-NBL patients with any type of treatment failure were prospectively included (15). Most patients (90%) received an administered activity of 666 MBq/kg and 33% of patients were supported by ASCT. Overall (complete or partial) response rate was 36% (95% CI 29-44%) and 34% of patients had stable disease. One-year EFS was 18% and the 2-year OS was 29%.
Another single-arm prospective trial (Johnson *et al*. 2011) studied the safety and efficacy of tandem [^{131}I]*m*IBG therapy (16). In total, 76 patients who failed to respond to standard induction therapy were included. After a first cycle of [^{131}I]*m*IBG therapy (666 MBq/kg), patients who had available hematopoietic stem-cells and showed either response or stable disease, followed with a second cycle (6–14 weeks after the initial cycle). After the first cycle, 30% of 76 patients showed a partial/complete response and 49% stable disease. After the second cycle (n=41), partial/complete response was seen in 29% and stable disease in 37%. Authors concluded that a second cycle of [^{131}I]*m*IBG therapy safely reduces disease burden in patients with HR-NBL that failed front-line treatment. Interestingly, in five patients [^{123}I]*m*IBG scintigraphy showed complete response but post-[^{131}I]*m*IBG scintigraphy showed substantial disease burden. This supports the potential use of [^{131}I]*m*IBG therapy in cases of apparent complete remission on [^{123}I]*m*IBG scintigraphy.

UCSF and NANT trials

Results of a large retrospective cohort study in patients with relapsed/progressive and refractory HR-NBL who were treated with [^{131}I]*m*IBG therapy at UCSF Benioff Children's Hospital (NCT01370330); or New Approaches to Neuroblastoma Therapy (NANT) clinical trials, between 1996 and 2014, was reported by Zhou et al. in 2015 (17). In total, 218 patients were analysed, 102 (47%) of whom were also included by the meta-analysis of Wilson et al. (2014). Half of patients received an activity of 666 MBq/kg [^{131}I]*m*IBG or higher. Complete or partial response rate after [^{131}I]*m*IBG therapy was 27%; without significant difference between relapse/progression vs. refractory disease. However, patients with relapse had a lower 2-year OS after [^{131}I]*m*IBG therapy compared to patients with refractory disease (38.7% vs. 65.3%, respectively, p<0.001).

In one of the included phase II trials (NANT2001-02), [^{131}I]*m*IBG therapy was incorporated before consolidation in patients who failed induction therapy (18). In the total study population (n=50), two cohorts could be identified: 1) efficacious cohort (n=8) with a partial response at the end of induction chemotherapy; 2) inefficacious cohort with no response to induction therapy (n=27) or progressive disease (n=15). Patients were treated with [^{131}I]*m*IBG therapy (444 MBq/kg), followed

by consolidation treatment after 14-17 days. Response assessment was performed two months after the end of consolidation. Complete or partial responses were seen in 10% of the evaluable 41 patients in the inefficacious cohort. For the inefficacious cohort, 3-year EFS and OS were 20% and 62%, respectively. The addition of [^{131}I]*m*IBG before consolidation had comparable toxicities to consolidation treatment alone in these already highly pre-treated patients and did not affect hematologic recovery after ASCT. These results led to further studies on this combination.

NCT02258815 trial

Recently, results of a phase I/II trial (NCT02258815) were published in which 68 patients that presented with relapse (n=54) or refractory (n=3) HR-NBL after consolidation between 2010 and 2017 were included (19). Patients received second-line treatment with haploidentical stem cell transplant (haplo-SCT) followed by six cycles of dinutuximab-beta plus three cycles of interleukin-2. At the discretion of the treating centres, [^{131}I]*m*IBG therapy (8-15.2 GBq) was given to 43 (63.2%) patients before haplo-SCT. [^{131}I]*m*IBG therapy was associated with a significant higher OS and EFS. From time of relapse, 5-year OS for [^{131}I]*m*IBG therapy yes vs. no was 67 (95% CI 51-79%) vs. 31% (95% CI 14-50); and 5-year EFS was 55% (95% CI 39-69) vs. 23% (95% CI 8–41), respectively. In the multivariate analysis, the hazard ratio of [^{131}I]*m*IBG therapy (compared to no [^{131}I]*m*IBG therapy) was 0.3 (95% CI 0.1-0.8) for OS and 0.3 (0.1-0.7) for EFS.

Radiosensitizer studies

Researchers are investigating the combination of [^{131}I]*m*IBG therapy with radiosensitizers that enhance the sensitivity of neuroblastoma cells to radiation therapy (figure 3) (6). Phase I studies (NANT2004-06, NCT01313936, NANT2007-03) in HR-NBL patients with any type of treatment failure, studied the combined use of vincristine and irinotecan together with [^{131}I]*m*IBG (666 MBq/kg) (20); or vorinostat, a histone deacetylase inhibitor, with [^{131}I]*m*IBG (666 MBq/kg) (21).
These studies were followed by a larger phase II randomized trial (NANT2011-01) in which these two regimens were compared to [^{131}I]*m*IBG monotherapy in 114 HR-NBL patients with all types of treatment failure with more than one [^{123}I]*m*IBG-positive site between 2014 and 2019 (22). Administered activity for [^{131}I]*m*IBG was 666 MBq/kg combined with ASCT. Included patients (n=105) were randomly allocated to one of three treatment arms: A. [^{131}I]*m*IBG and vorinostat (n=34); B. [^{131}I]*m*IBG, vincristine, and irinotecan (n=35); C. [^{131}I]*m*IBG monotherapy (n=36). Across the three study arms, 20% (21/105) had an objective response to the treatment. An improved response rate was observed in patients treated with arm A compared with arms B or C. Partial or complete response rates for arms A, B, and C, after [^{131}I]*m*IBG therapy were 32% (95% CI 18-51), 14% (5-31%) and 17% (5-30), respectively. Rates of any grade ≥3 non-hematologic toxicity after the [^{131}I]*m*IBG therapy were 19%, 49%, and 35%, respectively. [^{131}I]*m*IBG and vorinostat (arm A) is likely the arm with the highest true response rate with manageable toxicity. The combination of vincristine and irinotecan (arm B) does not appear to improve the response and was associated with increased toxicity.

Ongoing trials

There are several ongoing trials on [^{131}I]*m*IBG therapy in the second-line treatment, focusing on the combination of [^{131}I]*m*IBG with radiosensitizers and immunotherapy (table 1). OPTIMUM (NCT03561259) is a two-arm, phase II trial, in which [^{131}I]*m*IBG is combined with the radiosensitiser vorinostat and compared to [^{131}I]*m*IBG monotherapy in patients with relapse/progression. Primary outcome is overall response. Secondary outcomes are durability of effect (after 12 weeks, 2 years), relative Curie score (after 6 weeks, 12 weeks, and 2 years), and safety (including correlation with whole body radiation dose).
NANT2017-01 (NCT03332667) is a two-arm, phase I trial, in patients with relapse/progression, comparing [^{131}I]*m*IBG therapy with dinutuximab-beta to [^{131}I]*m*IBG therapy with dinutuximab-beta and vorinostat. The primary outcome is safety/tolerability and secondary outcome is overall response. Preliminary results on the combination of [^{131}I]*m*IBG therapy with standard doses of dinutuximab-beta and GM-CSF were presented in a conference abstract (23). This radioimmunotherapy regimen was well-tolerated without additive toxicity. A recommended activity of 666 MBq/kg [^{131}I]*m*IBG therapy was suggested. Preliminary efficacy data are encouraging in this heavily pre-treated patient population and a phase II trial is underway.
MiNivAN (NCT02914405) is a three-arm trial, in which [^{131}I]*m*IBG therapy is studied in combination with immune check-point inhibitor nivolumab and two different doses of dinutuximab-beta. The design is a treatment escalation study. Primary outcome is safety/tolerability. Secondary outcomes are EFS, overall response, and associations between KIR/KIR-Ligand or FcγR genotype and response.
The only randomized trial in refractory patients is VERITAS (NCT03165292), a European study. Patients with refractory disease after induction chemotherapy (SIOPEN score >3) are included and randomized into two treatment intensification strategies. All patients receive three courses of temozolomide and irinotecan. Then

randomization arm A receives two cycles of [^{131}I]*m*IBG therapy combined with topotecan and followed by ASCT; randomization arm B receives high dose thiotepa followed by ASCT. Afterwards, patients continue with standard consolidation and maintenance. Primary outcome is EFS. Secondary outcomes are OS, safety, overall response, and feasibility of [^{131}I]*m*IBG/topotecan in a multicentre setting. Unfortunately, this trial was recently discontinued, due to less than expected recruitment and limited availability of [^{131}I]*m*IBG in some centres.

Toxicity of [^{131}I]*m*IBG therapy

Toxicities associated with [^{131}I]*m*IBG therapy can be divided in three categories: acute events, early side effects, and late effects. As most patients are treated with several other therapies before/after [^{131}I]*m*IBG therapy, toxicity caused by [^{131}I]*m*IBG alone is difficult to determine.

Acute events occur within hours or days of [^{131}I]*m*IBG administration and are mostly activity-dependent. The cohort of Bleeker et al. (2013) studying upfront [^{131}I]*m*IBG therapy is unique in investigating toxicity of [^{131}I]*m*IBG alone. During intravenous infusion of [^{131}I]*m*IBG over 60-120 min, less than 10% of patients experience transient tachycardia or hypertension, due to increased sympathetic activity (6). Within hours/days, patients may experience nausea and vomiting (20%, max. grade II radiation gastritis (9)); and/or radiation sialadenitis (50%), all typically managed by supportive care (6).

Early side effects occur within weeks, with the primary toxicity being hematotoxicity. Hematotoxicity is more common in patients who receive higher activities of [^{131}I]*m*IBG therapy, those with bone marrow metastases, and those who are heavily pre-treated. Hematotoxicity is activity-dependent, often occurring in an administered activity > 444 MBq/kg (7). Activities > 555 MBq/kg are considered myeloablative and require stem cell rescue (6). Patients with hematotoxicity typically present with myelosuppression (anemia, thrombocytopenia, neutropenia, and/or lymphopenia), 2-4 weeks after [^{131}I]*m*IBG infusion, which may persist for several months (6). With upfront [^{131}I]*m*IBG therapy, thrombocytopenia, anemia or leukocytopenia occurred in up to 5% of patients after the first [^{131}I]*m*IBG therapy and in 3% of patients after the second; and did not result in episodes of major bleeding (9). No stem cell rescue was needed. Non-hematologic grade 3-4 toxicities are rare when [^{131}I]*m*IBG is administered as a single agent. Organ toxicities increase when [^{131}I]*m*IBG is used in combination with myeloablative doses of chemotherapy, with hepatic toxicities approaching 15% in this situation (6).

Late effects can occur months or years after [^{131}I]*m*IBG therapy, the most frequent being thyroid damage. Despite the use of thyroid blocking agents, free ^{131}I may accumulate in the thyroid gland. In a study by van Santen *et al*. (2002), 22 of 42 patients with neuroblastoma presented with (subclinical) hypothyroidism after a mean of 1.4 years after [^{131}I]*m*IBG therapy, eight of whom required thyroxine replacement therapy (24). In a follow-up study, eight (50%) of sixteen survivors developed hypothyroidism and required thyroxine after a median of 15.5 years post-[^{131}I]*m*IBG therapy (25). Thyroid nodules were found in nine survivors, two of whom were diagnosed with papillary thyroid carcinoma. In retrospect, these patients had received adequate thyroid protection, and no thyroidal [^{131}I]*m*IBG uptake was observed on post-[^{131}I]*m*IBG imaging. In addition, primary ovarian insufficiency has been documented in two patients who were treated with only [^{131}I]*m*IBG therapy suggesting that [^{131}I]*m*IBG therapy alone may damage the female gonads (26). Secondary malignancies, such as acute myelogenous leukaemia and myelodysplastic syndrome, have been reported in <5% of patients after [^{131}I]*m*IBG therapy (6). Nevertheless, the causal relation between [^{131}I]*m*IBG therapy and the occurrence of late effects is confounded by multimodality treatment.

Discussion

Despite the challenges of performing [^{131}I]*m*IBG studies in neuroblastoma, this form of therapy has been studied in more than 1500 children with HR-NBL. Thirty-five years of experience show that [^{131}I]*m*IBG therapy can be an effective treatment to reduce tumour burden in approximately one third of children. The independent effect of [^{131}I]*m*IBG therapy on long-term survival and side effects remain unclear. Up till recent years, no survival benefit for [^{131}I]*m*IBG therapy could be proven. However, the introduction of [^{131}I]*m*IBG combination therapies shows promise for improving EFS and OS, with tolerable (hemato) toxicity. Nevertheless, caution is warranted because of potential long-term toxicity, such as thyroidal/gonadal dysfunction, and secondary malignancies.

The lack of comparative studies, many confounding factors, and other forms of bias make it difficult to assess the true effect of [^{131}I]*m*IBG therapy. Despite more than 50 published studies, there are no RCTs that compare [^{131}I]*m*IBG therapy to no [^{131}I]*m*IBG therapy. RCTs are crucial to study the efficacy and (long-term) safety of [^{131}I]*m*IBG monotherapy and different combination therapies. Furthermore, comparison between trials is difficult because of large heterogeneity in patient population, treatment activity/schedule, and reporting of outcomes.

With an objective tumour response rate of approximately 30%, apparently not all patients respond well to

[^{131}I]*m*IBG therapy. It is important to identify which patients most likely benefit from [^{131}I]*m*IBG therapy. Therefore, efficacy of [^{131}I]*m*IBG therapy should be studied in different patient populations, for example for different types of treatment failure. Currently, the activity of [^{131}I]*m*IBG (MBq) to be administered is based on the patient's weight; and administered activity is often used as a measure to correlate with response rates and other outcomes. More preferable would be to determine the optimal activity with more standardized techniques such as [^{124}I]*m*IBG PET, which enables accurate quantification of *m*IBG uptake and anticipated whole-body/tumour absorbed doses, and to correlate personalized dosimetry with response.

Often, tumour lesions are missed on [^{123}I]*m*IBG scintigraphy/SPECT because of its suboptimal resolution (16). There is a need for better diagnostic imaging that can detect the full disease extent, aid in the selection of patients for [^{131}I]*m*IBG therapy, and assessment of post-[^{131}I]*m*IBG response. Currently, PET radiopharmaceuticals are under investigation, such as [^{124}I]*m*IBG and [^{18}F]mFBG (27).
In conclusion, [^{131}I]*m*IBG combination treatments hold great promise for improving outcomes for patients with HR-NBL. However, [^{131}I]*m*IBG therapy does not hold a standard position in treatment of HR-NBL and continues to be studied in trials and off-protocol. Future studies, preferably in the form of RCTs, will hopefully define the optimal use of [^{131}I]*m*IBG therapy in the front- or second-line treatment of HR-NBL.

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