A narrative review of 35 years of *meta*-[131I]iodobenzylguanidine therapy in neuroblastoma

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ABSTRACT

Neuroblastoma is the most common extracranial solid malignancy of childhood. Approximately half of the patients have high-risk neuroblastoma (HR-NBL), typically presenting as widespread metastatic disease at diagnosis. Despite aggressive multimodality treatment, patients with HR-NBL have a long-term survival rate of below 50%. This is primarily due to frequent progression and relapse, which often proves to be therapy resistant. To overcome therapy resistance in HR-NBL, researchers are exploring diverse treatment strategies, including radionuclide therapy. Radiolabelled meta-iodobenzylguanidine (mIBG) has served as a theranostic (therapeutic and diagnostic) radiopharmaceutical in the field of neuroblastoma for several decades. [123I]mIBG scintigraphy is recognized as the international standard to evaluate disease dissemination at diagnosis and to monitor treatment response. In contrast, the role of [131I]mIBG therapy in the management of neuroblastoma is less clear. Over the past 35 years, [131I]mIBG therapy has been studied in more than 1500 patients with neuroblastoma. In initial studies, [131I]mIBG monotherapy was applied as a second-line treatment in patients who failed first-line treatment. In current applications, [131I]mIBG therapy is combined with chemotherapy, radiosensitizers, and/or immunotherapy, and is increasingly integrated in the first-line treatment of HR-NBL. This narrative review provides an overview of the literature on [131I]mIBG therapy in HR-NBL. Studies show that [131I]mIBG therapy can be an effective treatment in one-third of patients with acceptable toxicity. Further investigations, particularly randomized controlled trials, are needed to determine the efficacy and optimal use of [131I]mIBG therapy in HR-NBL.

1. Introduction

Neuroblastoma is the most common extracranial solid malignancy of childhood [1]. Approximately half of patients have high-risk neuroblastoma (HR-NBL) at diagnosis. HR-NBL typically presents as widespread metastatic disease affecting bone (marrow) and lymph nodes [1]. First-line HR-NBL treatment involves three phases [2]. The *induction* phase consists of chemotherapy courses followed by surgical resection of the primary tumour. In the *consolidation* phase, any remaining tumour cells are targeted through high-dose chemotherapy (HDCT) along with autologous stem cell rescue (ASCR), and external beam radiotherapy. Lastly, in the *maintenance* phase, minimal residual disease is treated with anti-GD2 immunotherapy (dinutuximab bèta) and retinoic acid.

Despite this multimodality approach, long-term survival rates for patients with HR-NBL remain at only 40–50% [1,2]. The main challenge lies in the occurrence of progression or relapse during or after first-line treatment. When first-line treatment fails, treatment options are limited due to therapy resistance. New strategies are being explored to overcome therapy resistance in HR-NBL. Current second-line therapies consist of (immuno)chemotherapy (for example, irinotecan/topotecan, temozolomide, and dinutuximab bèta), as well as personalised targeted treatments based on molecular profiling [3]. Additionally, considering that neuroblastoma is a radiosensitive tumour, radionuclide therapy shows promise as a systemic treatment option.

For several decades, radiolabelled *meta*-iodobenzylguanidine (mIBG) has been used as a theranostic (therapeutic and diagnostic) radiopharmaceutical in neuroblastoma. As a norepinephrine analogue, mIBG shows a high affinity for neuroblastoma cells that overexpress the

norepinephrine transporter (NET). Radiolabelled mIBG with iodine-123 (^{123}I, half-life 13 hours) and iodine-131 (^{131}I, half-life eight days) offers excellent targeting of tumour cells for imaging and therapy, respectively (Fig. 1) [4]. [^{123}I]mIBG scintigraphy is the most established nuclear imaging technique used for disease staging and monitoring response in neuroblastoma patients. In contrast, the role of [^{131}I]mIBG therapy in neuroblastoma is less clear. By delivering high radiation doses directly to neuroblastoma cells, with activity lasting several weeks, [^{131}I]mIBG therapy holds the potential to induce an effective response or inhibit progression of both the primary tumour and metastatic sites.

Over the past 35 years, [^{131}I]mIBG therapy has been studied in more than 1500 patients with HR-NBL [5]. Following the introduction of [^{131}I]mIBG therapy in neuroblastoma in 1984, early trials focused on [^{131}I]mIBG monotherapy, establishing its feasibility, toxicity, and maximum tolerated activity [5]. It was discovered that an even higher ("myeloablative") activity (>444 MBq/kg) of [^{131}I]mIBG therapy could be administered when combined with ASCR [6]. Subsequent studies explored [^{131}I]mIBG combination treatments to enhance the therapeutic efficacy of [^{131}I]mIBG, involving various chemotherapeutic agents, radiosensitizers (Fig. 2), and immunotherapy [5]. Initially, research was focused on [^{131}I]mIBG therapy as a salvage option in patients who failed first-line treatment. However, recent research has shifted towards integrating [^{131}I]mIBG therapy into the first-line HR-NBL treatment, aiming to prevent the development of chemotherapy-resistant tumour cells.

This narrative review aims to increase our current understanding of the potential role of [^{131}I]mIBG therapy in the treatment of HR-NBL by providing an overview of key studies over the past 35 years.

2. First-line [^{131}I] mIBG therapy

2.1. Upfront

The approach of upfront [^{131}I]mIBG therapy in the treatment of HR-NBL was pioneered in the Netherlands [8]. In a prospective phase II trial,

Kraker *et al.* (2008) enrolled 44 patients with HR-NBL in the period 1989–1999 [9]. Patients received multiple cycles of [^{131}I]mIBG therapy, ranging from two to five cycles, with an average of three, at four-week intervals. The first cycle had a fixed activity of 7.4 GBq, with subsequent cycles of 3.7–5.6 GBq resulting in a median cumulative activity per patient of 18.5 GBq (range: 13–35). After two cycles of [^{131}I]mIBG therapy, 27 (66%) of the 41 evaluable patients demonstrated a complete/partial response. Patients were divided into two groups based on their induction treatment approach. Group 1 (n=24) continued with [^{131}I]mIBG cycles instead of induction chemotherapy. Group 2 (n=17) continued with induction chemotherapy, mainly due to stable disease. When evaluating the combined effect of both induction approaches, 73% of the 41 patients showed a (complete/partial) response at the end of induction. Another significant advantage of upfront [^{131}I]mIBG therapy was that it allowed for complete macroscopic resection of the primary tumour in 67% of cases. The cohort had remarkably low 5-year event-free survival (EFS) and overall survival (OS) rates: 12% and 15%, respectively. This is likely explained by the small number of patients (11/24 from group 1 and 6/17 from group 2) who underwent consolidation treatment (HDCT and ASCR), followed by maintenance therapy (retinoic acid).

Subsequently, Bleeker *et al.* (2013) conducted a retrospective analysis of acute toxicity in the same cohort of HR-NBL patients, as well as additional patients of all stages, who had undergone two cycles of upfront [^{131}I]mIBG therapy between 1992 and 2008 [10]. This cohort (*n*=66) is unique in investigating the toxicity of [^{131}I]mIBG therapy without prior treatment, specifically within the first month following [^{131}I]mIBG therapy. The median administered activity was 441 MBq/kg (range: 157–804) for the first cycle and 328 MBq/kg (range: 113–727) for the second cycle. The study concluded that upfront [^{131}I]mIBG therapy has an acceptable safety profile when considering the individual patient's condition. Details are summarized under the heading "Toxicity of [^{131}I]mIBG therapy."

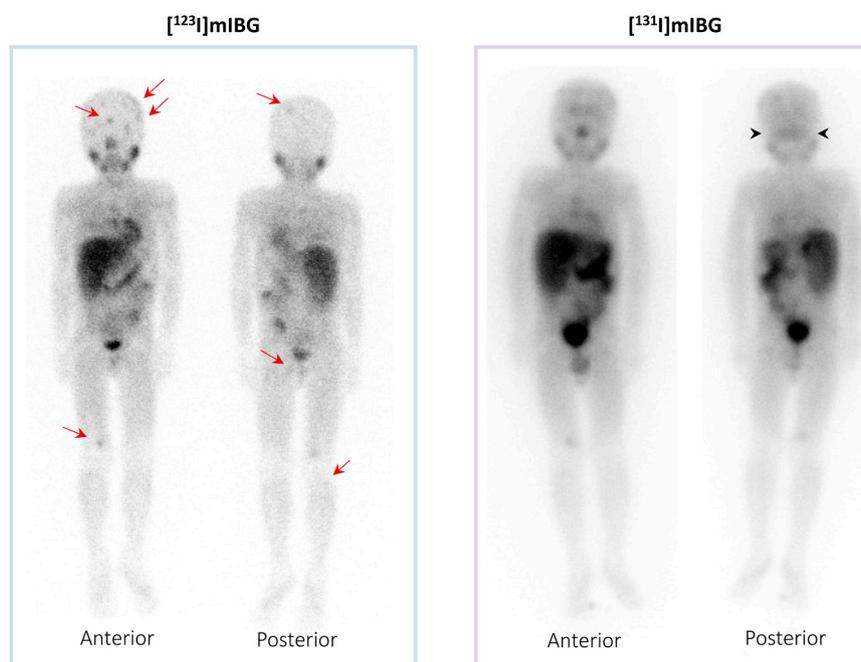As a result, two cycles of upfront [^{131}I]mIBG therapy was integrated

Fig. 1. Example of diagnostic [^{123}I]mIBG and post-therapeutic [^{131}I]mIBG scintigraphy in the same patient. The gamma radiation emitted by ^{131}I at 364 keV (abundance 81%) is higher compared to that of ^{123}I, which emits gamma radiation at 159 keV (abundance 83%). [^{131}I]mIBG scintigraphy utilizes high-energy general-purpose collimators, slightly compromising resolution compared to the medium-energy collimators used for [^{123}I]mIBG. Physiological mIBG uptake occurs in the salivary glands, heart, liver, thyroid (unless blocked), lacrimal glands, adrenal glands, nasal mucosa, myocardium, and to a lesser extent in the spleen, lungs, skeletal muscles, and brown adipose tissue. Excretion through urinary and gastrointestinal tracts results in activity in the bladder and intestines. Arrows indicate pathological uptake in skeletal lesions on [^{123}I]mIBG scintigraphy. Arrowheads indicate physiological cerebellum and basal ganglia uptake only seen on [^{131}I]mIBG scintigraphy.
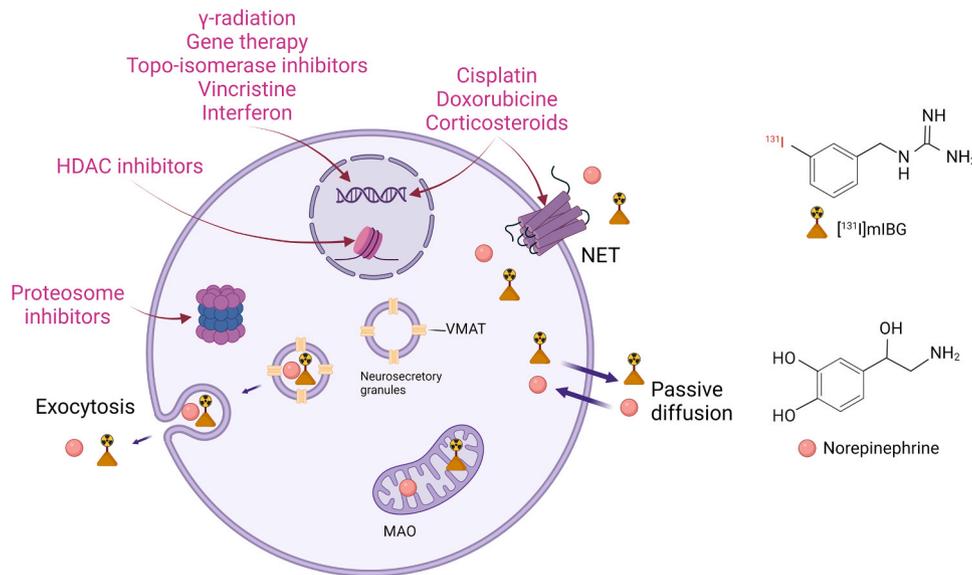
Fig. 2. Strategies to enhance [131I]mIBG efficacy in neuroblastoma cells. mIBG, similar to norepinephrine, is predominantly taken up by neuroblastoma cells through specific active uptake via the NET (previously known as the 'uptake-1' system) and to a lesser extent through non-specific passive diffusion. As neuroblastoma cells lack storage vesicles, the retention of mIBG primarily results from efficient re-uptake of accumulated mIBG [7]. Strategies to increase [131I]mIBG uptake, retention, and cytotoxicity of neuroblastoma cells include increasing neuroblastoma sensitivity to [131I]mIBG therapy (for instance, inhibiting DNA damage repair), upregulating NET mRNA expression, and enhancing NET function. Abbreviations: mIBG, *meta*-iodobenzylguanidine; NET, norepinephrine transporter; HDAC, histone deacetylase; VMAT, vesicular monoamine transporter; MAO, monoamine oxidase inhibitors; mRNA, messenger RNA; DNA, deoxyribonucleic acid.

into the national **Dutch NBL2009** treatment protocol for patients with HR-NBL. All patients were eligible to receive [131I]mIBG therapy, except for those with a poor clinical condition (including uncontrollable hypertension, orbital masses, and/or pleural effusion), or mIBG-negative disease. **Kraal et al. (2017)** retrospectively studied 21 patients with HR-NBL treated with this treatment regimen from 2005 to 2011 [11]. Within two weeks of diagnosis, two cycles of upfront [131I]mIBG therapy (450 and 370 MBq/kg) were administered at a four-week interval. Patients started induction chemotherapy three weeks after the second [131I]mIBG cycle. The complete/partial response rate after [131I]mIBG therapy was 38%, and none of the patients required ASCR after [131I]mIBG therapy. However, upfront [131I]mIBG therapy was removed from the Dutch treatment protocol in 2016, as it was frequently not feasible due to poor clinical condition of patients or logistic reasons.

2.2. Induction/consolidation

Mastrangelo et al. from Rome, Italy, were one of the first to incorporate [131I]mIBG therapy alongside induction chemotherapy for HR-NBL. In their initial pilot study (**Mastrangelo *et al.* 2011**) involving 13 patients, they used a median activity of 396 MBq/kg (range: 274–615) [12]. Subsequently, they modified their strategy to a higher dose of [131I]mIBG starting at 444 MBq/kg. In their latest study (**Mastrangelo *et al.* 2022**), they reported on 15 newly-diagnosed HR-NBL patients (including six patients from the previous study) receiving a single cycle of [131I]mIBG therapy (range: 444–677 MBq/kg) on the tenth day of a rapid 30-day induction regimen [13]. Approximately 50 days from the start of treatment, a complete/partial response rate of 87% was observed. There was no toxicity other than moderate haematological toxicity, as expected after administration of multiagent chemotherapy. Results were encouraging showing that chemotherapy combined with [131I]mIBG therapy followed by ASCR may achieve high tumour response.

In a prospective single-arm pilot study (**ANBL09P1, Weiss *et al.* 2021**), the Children's Oncology Group (COG) demonstrated the feasibility and tolerability of integrating [131I]mIBG therapy at the end of induction, followed by consolidation, in newly diagnosed HR-NBL patients [14]. Between 2011 and 2015 patients who had completed five

cycles of induction chemotherapy were eligible for one cycle of [131I]mIBG therapy (with ASCR) instead of the sixth chemotherapy cycle. The study employed a stepwise "activity" escalation approach (444, 555, and 666 MBq/kg), followed by a mandatory 10-week interval before proceeding with HDCT. Out of the 68 patients eligible for [131I]mIBG therapy at the end of induction chemotherapy, 59 (87%) received the treatment. Among the 45 patients evaluable for both [131I]mIBG therapy and HDCT, 37 (82%) received this combination. At the 555 MBq/kg activity level, the feasibility rate of [131I]mIBG therapy was 97% while the feasibility rate of [131I]mIBG therapy followed by HDCT after a 10-week gap was 81%. The complete/partial response rate was 72% (38/53) after [131I]mIBG therapy and 91% (31/34) after consolidation. The three-year EFS rate of [131I]mIBG therapy followed by consolidation and maintenance was 60% (95% CI: 44–76).

Building upon this pilot study, the COG designed the **ANBL1531** phase III trial (Table 1) to assess the role of [131I]mIBG therapy, double ASCR, and ALK-inhibitor crizotinib in 658 newly diagnosed patients with HR-NBL. Between 2018 and 2023, patients without ALK mutations and with [123I]mIBG-positive disease were randomized among three treatment arms. Unfortunately, the third arm trial was terminated early due to toxicity. In one out of the two remaining randomized arms, patients received [131I]mIBG therapy (555 MBq/kg) after three cycles of induction chemotherapy. The purpose of the randomization is to determine whether the addition of [131I]mIBG therapy during induction could improve EFS with acceptable long-term toxicity. Notable, this study represents the first randomized trial comparing the efficacy of [131I]mIBG therapy to no [131I]mIBG therapy. The trial has recently concluded, achieving the targeted number of inclusions.

Additionally, **NB-2009** (**Lee *et al.* 2017**) is a single-arm, phase I/II trial from Samsung Medical Centre, conducted between 2009 and 2013, where [131I]mIBG therapy was incorporated into consolidation [15]. Patients with newly-diagnosed HR-NBL were included after completing nine cycles of induction chemotherapy. In total, 47 patients received consolidation, involving tandem HDCT (with a 12-week interval in-between), ASCR, and radiotherapy; and continued with maintenance (retinoic acid, immunotherapy, and interleukin-2). Of these patients, 43 received one cycle of [131I]mIBG therapy (444 or 666 MBq/kg) between the first and second HDCT. The 5-year EFS and OS rates were 58% (95%

Table 1
Ongoing multicentre trials on [131I]mIBG therapy in patients with high-risk neuroblastoma.

Clinical trial name*	Centres (countries)	Clinical setting	Trial Description	Treatment arms	Primary endpoint
ANBL1531 †(NCT03126916)	160 (United States, Canada, Puerto Rico)	First-line	Phase III Randomized n=658	1) TC + CEM, tandem ASCR 2) [131I]mIBG, TC + CEM, tandem ASCR 3) [131I]mIBG, HD BuMel, single ASCR	3-year EFS
OPTIMUM(NCT03561259)	21 (United States)	Progression Relapse	Phase II n=60	1) [131I]mIBG monotherapy 2) [131I]mIBG, vorinostat	Overall response
NANT2017–01 (NCT03332667)	12 (United States)	Refractory disease Progression Relapse	Phase I n=45	1) [131I]mIBG, dinutuximab 2) [131I]mIBG, dinutuximab, vorinostat	Safety/ tolerability
MiNivAN(NCT02914405)	3 (United Kingdom and United States)	Refractory disease Progression Relapse	Phase I n=36	1) [131I]mIBG, nivolumab 2) [131I]mIBG, nivolumab, low dose dinutuximab 3) [131I]mIBG, nivolumab, full dose dinutuximab	Safety/ tolerability
VERITAS ‡(NCT03165292)	9 (France, Austria, Italy, Netherlands, Spain)	Refractory disease	Phase II Randomized n=150	1) TEMIRI, [131I]mIBG, topotecan, ASCR 2) TEMIRI, HD thiotepa, ASCR	3-year EFS

Abbreviations: TEMIRI, Temozolomide-Irinotecan; [131I]mIBG, meta-[131I]iodobenzylguanidine; TC, thiotepa cyclophosphamide; BuMel, busulfan melphalan; CEM, carboplatin etoposide melphalan; ASCR, autologous stem cell rescue, EFS, event-free survival.

* ClinicalTrials.gov Identifier

† The third arm of the ANBL1531 trial was discontinued earlier.

‡ The VERITAS trial was prematurely terminated before its scheduled completion.

CI: 44–72) and 72% (95% CI: 59–85), respectively. Survival rates were comparable but with lower toxicity compared to their previous protocol, which employed total body radiation instead of [131I]mIBG therapy [16].

3. Second-line [131I] mIBG therapy

Second-line [131I]mIBG therapy has been investigated in patients who experienced treatment failure during first-line treatment of neuroblastoma. Three types of treatment failure in neuroblastoma can be identified: **refractory disease** (non-progressive, residual disease after completing induction chemotherapy, requiring alternative therapy to improve remission status before proceeding to consolidation treatment); **progression** (disease progression after an incomplete/no response to therapy); and **relapse** (disease recurrence after a complete response to therapy). However, it is important to note that definitions of 'refractory', 'progression', and 'relapse' can vary between studies; and different types of treatment failure are often grouped and analysed together.

3.1. Meta-analysis

A meta-analysis by **Wilson et al. (2014)** analysed 27 studies including 1121 patients who experienced first-line treatment failure and underwent [131I]mIBG therapy as a second-line treatment between 1984 and 2005 [17]. In all studies, patients with mIBG-negative disease were not eligible for [131I]mIBG therapy. There were 20 studies on [131I]mIBG monotherapy and seven studies on [131I]mIBG therapy combined with chemotherapy. Only four studies were comparative, all non-randomized. Study populations were often small, ranging from 10 to 164 patients. Complete/partial response rates, reported in 25 studies (n=782), varied between 4–75%, with an overall mean response rate of 32% (95% CI: 29–36). In patients who received [131I]mIBG monotherapy, the response rate was 32% (199/629) compared to 39% (48/124) in patients who received concomitant chemotherapy. However, there was no evidence that response to [131I]mIBG therapy leads to a better EFS or OS rates.

In the largest comparative study, 111 patients from the German **NB97** trial (**Schmidt et al. 2006**) with stage 4 refractory HR-NBL between 1996 and 2003 were retrospectively identified [18]. Patients in the intervention arm (n=40) received one cycle of [131I]mIBG therapy (median: 444 MBq/kg, range: 141–1460). The control arm (n=71)

consisted of patients whose treating physicians decided against [131I]mIBG therapy. In the univariate analysis, there was a significant difference in 3-year EFS and OS rates between the two arms. However, this difference was confounded by the fact that the intervention arm more often received consolidation treatment afterward. In the subgroup analysis of patients who underwent consolidation therapy (n=66), outcomes for the [131I]mIBG arms versus the control arm were more similar: 3-year EFS rates 49% (95% CI: 31–67) versus 33% (95% CI: 15–51) respectively, and OS rates 59% (95% CI: 39–79) versus 59% (95% CI: 41–77), respectively. By multivariate analysis, [131I]mIBG therapy had no statistically significant impact on 3-year EFS (P=0.49) and OS (P=0.89). In conclusion, an independent advantage of [131I]mIBG therapy could not be proven, which emphasizes the importance of confounding factors (and other forms of bias) in non-randomized comparative studies. Results on [131I]mIBG therapy from the latest **NB2004** trial have not yet been reported.

In the largest single-arm (phase II) trial, **Matthay et al. (2007)** prospectively included 164 HR-NBL patients with any type of treatment failure between 1996 and 2005 [19]. Most patients (90%) received an administered activity of 666 MBq/kg [131I]mIBG therapy and 33% of patients were supported by ASCR. However, the overall (complete/partial) response rate was 36% and stable disease was observed in 34% of patients. The 1-year EFS and 2-year OS rates were 18% and 29%, respectively.

In another single-arm prospective trial from the University of Pennsylvania, **Johnson et al. (2011)** studied the safety and efficacy of tandem [131I]mIBG therapy (666 MBq/kg) in patients with any type of treatment failure [20]. In total, 76 patients received a first cycle of [131I]mIBG therapy: complete/partial response rate was 30% and stable disease rate was 49%. Patients were eligible for a second cycle 6–14 weeks after the initial cycle if they had available stem cell products. Forty-one patients followed with a second cycle: 29% showed a complete/partial response, and 37% had stable disease. The authors concluded that a second cycle of [131I]mIBG therapy safely reduces disease burden in patients with HR-NBL who experience first-line treatment failure. Interestingly, in five patients [123I]mIBG scintigraphy showed complete response, yet post-[131I]mIBG scintigraphy showed substantial disease burden. This supports the use of [131I]mIBG therapy in cases of apparent complete remission on [123I]mIBG scintigraphy.

3.2. UCSF and NANT trials

In a large retrospective cohort study, **Zhou et al. (2015)** studied HR-NBL patients with any type of treatment failure who were treated with [131I]mIBG therapy at UCSF Benioff Children's Hospital (**NCT01370330**); or New Approaches to Neuroblastoma Therapy (**NANT**) clinical trials, between 1996 and 2014 [21]. A total of 218 patients were analysed, out of which 102 (47%) were part of the meta-analysis by Wilson et al. (2014). Half of the patients were administered a [131I]mIBG activity of at least 666 MBq/kg. The complete/partial response rate after [131I]mIBG therapy was 27%; without a significant difference between patients with refractory disease and patients with progression/relapse. However, patients with relapse had a significantly lower 2-year OS rate compared to patients with refractory disease (38.7% versus 65.3%, respectively, P<0.01).

The **NANT2001–02 trial (Yanik et al. 2015)** was one of the included phase II trials and incorporated [131I]mIBG therapy before consolidation in patients who showed any type of treatment failure during induction therapy [22]. In the total study population (n=50), two cohorts could be identified: 1) a cohort of eight patients with a partial response at the end of induction chemotherapy; 2) a cohort of 42 patients with no response to induction therapy or progressive disease. Patients were administered [131I]mIBG therapy (444 MBq/kg) followed by consolidation treatment after 14–17 days. Response assessment was performed two months after the end of consolidation. The complete/partial response rate was only 10% in the evaluable 41 patients of second cohort. For this cohort, 3-year EFS and OS rates were 20% (95% CI: 6–34) and 62% (95% CI: 46–78), respectively. The addition of [131I]mIBG therapy before consolidation had similar toxicities when compared to consolidation treatment alone in these already highly pre-treated patients and did not affect hematologic recovery after ASCR. These results led to further studies on this combination.

3.3. Gaslini Institute

In a retrospective study, conducted by **Giardino et al. (2021),** the outcomes of 28 patients with refractory/relapsed HR-NBL treated with [131I]mIBG therapy and HDCT, at the Gaslini Institute, Genoa, Italy were reported [23]. Between 1996 and 2014, patients received one cycle of [131I]mIBG therapy (median: 315 MBq/kg, IQR: 241–444) and after a median interval of 17 days (IQR: 14–25) continued with HDCT and ASCR. This treatment approach proved feasible with acceptable toxicities, and a complete/partial response rate of 68%. Within this cohort, 39% of patients continued with maintenance.

3.4. NCT02258815 trial

The prospective **NCT02258815** trial (**Flaadt et al. 2023**) included 68 HR-NBL patients that presented with relapse (n=54) or refractory disease (n=3) after consolidation between 2010 and 2017 [24]. Patients received second-line treatment with haploidentical stem cell transplant followed by six cycles of dinutuximab bèta plus three cycles of interleukin-2. At the discretion of the treating centres, one cycle of [131I]mIBG therapy (444 MBq/kg) was administered to 43 (63%) patients at least two weeks before haploidentical stem cell transplant. The addition of [131I]mIBG therapy was associated with significantly improved OS and EFS rates. From the time of relapse, 5-year OS rate for [131I]mIBG therapy versus no [131I]mIBG therapy was 67 (95% CI: 51–79) versus 31% (95% CI: 14–50); and 5-year EFS rate was 55% (95% CI: 39–69) versus 23% (95% CI: 8–41), respectively. In the multivariate analysis, the hazard ratio of [131I]mIBG therapy versus no [131I]mIBG therapy was 0.3 for OS (P=0.02) and 0.3 for EFS (P=0.01).

3.5. Radiosensitizer studies

Researchers are also investigating the combination of [131I]mIBG

therapy with radiosensitizers that enhance the sensitivity of neuroblastoma cells to radiation therapy (Fig. 2) [5]. Phase I studies (**NANT2004–06, NCT01313936, NANT2007–03**), using vincristine and irinotecan together [25], or vorinostat [26] in combination with [131I]mIBG therapy showed promise in HR-NBL patients with any type of treatment failure.

In **NANT2011–01 (DuBois et al. 2021)**, a phase II randomized trial conducted between 2014 and 2019, these two regimens were compared to [131I]mIBG monotherapy [27]. Administered activity for [131I]mIBG therapy was 666 MBq/kg combined with ASCR. HR-NBL patients with all types of treatment failure with more than one [123I]mIBG-positive site (n=105) were randomly allocated to one of three treatment arms: **A.** [131I]mIBG and vorinostat (n=34); **B.** [131I]mIBG, vincristine, and irinotecan (n=35); **C.** [131I]mIBG monotherapy (n=36). Across the three study arms, 20% (21/105) had a complete/partial response to the treatment. For arms A, B, and C, complete/partial response rates after [131I]mIBG therapy were 32%, 14%, and 17%, respectively; rates of grade 4 neutropenia were 74%, 77%, 50%; and rates of any grade ≥3 non-hematologic toxicity after the [131I]mIBG therapy were 19%, 49%, and 35%, respectively. [131I]mIBG and vorinostat (arm A) is likely the arm with the highest true response rate with manageable toxicity when compared to the other two arms.

MIITOP is a French multicentre phase I/II trial **(Sevrin et al. 2023)**. Between 2008 and 2015, the combined use of tandem [131I]mIBG therapy and topotecan in 30 children with any type of treatment failure was investigated [28,29]. Following a three-week interval after the first [131I]mIBG cycle (444 MBq/kg), a second [131I]mIBG cycle was administered to obtain a cumulative total body irradiation of 4 Gy (based on personalized dosimetry), which was followed by ASCR. MIITOP was well tolerated with a complete/partial response rate after six weeks of 13% and 2-year EFS rate of 17% (95% CI: 6−32). Among the 16 patients with refractory disease: partial/complete response rate after MIITOP was 19%; 13 had at least stable disease; 11 continued with consolidation after two months; eight continued with maintenance; and four were alive at a follow-up of seven years.

3.6. Ongoing trials

Multiple ongoing trials are currently exploring the use of [131I]mIBG therapy as a second-line treatment, with a focus on combining [131I]mIBG with radiosensitizers and immunotherapy (Table 1). One of these trials is **OPTIMUM**, a two-arm phase II trial that combines [131I]mIBG therapy (666 MBq/kg) with the radiosensitizer vorinostat and compares it to [131I]mIBG monotherapy in patients with progression/relapse. The primary outcome of this trial is the overall response. Secondary outcomes include durability of effect at 12 weeks and two years, relative Curie score at six weeks, 12 weeks, and two years, as well as safety (including its correlation with whole-body radiation dose).

NANT2017–01 is another two-arm phase I trial, in which [131I]mIBG therapy with dinutuximab bèta is compared to [131I]mIBG therapy with dinutuximab bèta and vorinostat in patients with progression/relapse. The recommended activity of [131I]mIBG therapy to administer was 666 MBq/kg. The primary outcome is safety and tolerability, and the secondary outcome is the overall response. Preliminary results showed that the combination of [131I]mIBG therapy with standard doses of dinutuximab bèta and GM-CSF was well-tolerated without additional toxicity [30]. The promising preliminary efficacy data in this heavily pre-treated patient population led to the initiation of a phase II trial.

MiNivAN is a phase I trial, studying [131I]mIBG therapy (fixed dose of 2 Gy) in combination with immune checkpoint inhibitor nivolumab and two different doses of dinutuximab bèta. This trial follows a three-cohort treatment escalation design for dinutuximab bèta, with the primary outcome being safety and tolerability. Secondary outcomes include EFS, overall response, and associations between KIR/KIR-Ligand or FcγR genotype and response.

VERITAS in Europe was the only randomized phase II trial that

specifically focused on refractory patients. Unfortunately, this trial has recently been discontinued due to recruitment challenges. Patients with refractory disease after induction chemotherapy (SIOPEN score >3) were included and randomized into two treatment intensification strategies. All patients received three courses of temozolomide and irinotecan. In randomization arm A, patients received two cycles of [131I] mIBG therapy (total 4 Gy) combined with topotecan, followed by ASCR. Randomization arm B involved HDCT (thiotepa), followed by ASCR. Standard consolidation and maintenance treatment were continued after the treatment intensification. The primary outcome was EFS, and secondary outcomes were OS, safety, overall response, and feasibility of [131I]mIBG/topotecan in a multicentre setting.

4. Toxicity of [131I] mIBG therapy

Toxicities associated with [131I]mIBG therapy can be categorized into three groups: acute toxicity, early effects, and late effects. Determining the toxicity solely caused by [131I]mIBG alone is challenging as most patients undergo multiple other treatments before and after [131I] mIBG therapy.

Acute toxicity typically occurs within few hours or days after administration of [131I]mIBG and is primarily activity-dependent. During intravenous infusion of [131I]mIBG over 60–120 min, less than 10% of patients experience transient tachycardia or hypertension, as a result of increased sympathetic activity [5]. Within hours/days, nausea and vomiting occur in 21% of patients (max. grade II radiation gastritis [10]); and radiation sialadenitis in 50% of patients [31]. Symptoms are usually managed through supportive care [5].

Early effects occur within weeks after treatment, with the primary toxicity being haematological toxicity. Haematological toxicity is more prevalent in patients who receive a higher (cumulative) administered activity of [131I]mIBG therapy, those with massive bone marrow metastases, and those who have undergone extensive prior treatments [17]. The occurrence of haematological toxicity is activity-dependent, typically observed with an administered activity above 444 MBq/kg [6]. Activities exceeding 555 MBq/kg are considered myeloablative and require ASCR [5]. Patients with haematological toxicity usually present with signs of myelosuppression (anaemia, thrombocytopenia, and/or leukocytopenia), two to four weeks after [131I]mIBG infusion, which may persist for several months [5]. The previously mentioned study conducted by **Bleeker et al. (2013)** focusing on upfront [131I]mIBG therapy is unique in investigating the toxicity of [131I]mIBG alone in children that are naïve to chemotherapy [10]. With upfront [131I]mIBG therapy, thrombocytopenia, anaemia, or leukocytopenia were observed in up to 5% of patients after the first [131I]mIBG therapy and in 3% of patients after the second therapy; but no major bleeding occurred and ASCR was not necessary [10]. Non-hematologic grade 3–4 toxicities are rare when [131I]mIBG is administered as a single agent. However, when combined with myeloablative doses of chemotherapy, the rate of haematological and organ toxicities slightly increases, with hepatic toxicity rate reaching up to 15% [5].

Late effects can manifest months to years after [131I]mIBG therapy, with thyroid damage being the most common. Despite the use of thyroid-blocking agents, free 131I can accumulate in the thyroid gland. In a study by **Van Santen et al. (2002)**, 22 out of 42 patients with neuroblastoma presented with (subclinical) hypothyroidism after an average of 1.4 years following [131I]mIBG therapy, and eight of them required thyroxine replacement therapy [32]. In a subsequent study, eight (50%) out of sixteen survivors developed hypothyroidism and required thyroxine after a median of 15.5 years post-[131I]mIBG therapy [33]. Additionally, nine survivors were found to have thyroid nodules, and two of them were diagnosed with papillary thyroid carcinoma. Notably, these patients had received adequate thyroid protection, and no thyroidal [131I]mIBG uptake was seen on post-[131I]mIBG imaging. The study by **Giardino et al. (2021)** also found a high incidence hypothyroidism in one-third of patients [23].

Another important late effect could be primary ovarian insufficiency, documented in two patients who received [131I]mIBG therapy alone, suggesting that [131I]mIBG therapy may cause damage to the female gonads [34]. Furthermore, secondary malignancies, such as acute myelogenous leukaemia and myelodysplastic syndrome, have been reported in up to 5% of patients after [131I]mIBG therapy [5]. However, determining a causal relationship between [131I]mIBG therapy and the occurrence of late effects is challenging due to the confounding influence of multimodality treatment.

5. Discussion

Despite the challenges of performing [131I]mIBG therapy studies in children with neuroblastoma, this therapy has been studied in more than 1500 patients with HR-NBL. Thirty-five years of experience has proven that [131I]mIBG therapy can be an effective treatment to reduce tumour burden in approximately one-third of patients, either in first-line or second-line treatment. The independent contribution of [131I]mIBG therapy on long-term outcomes remains unclear. Up till recent years, no survival benefit for [131I]mIBG therapy could be proven. However, the introduction of [131I]mIBG combination therapies shows encouraging response rates with the promise for improving EFS and OS rates, with tolerable (haematological) toxicity. Nevertheless, caution is warranted because of potential long-term toxicity, such as thyroidal/gonadal dysfunction, and secondary malignancies.

The lack of comparative studies, the presence of confounding factors, and other biases make it difficult to assess the true effect of [131I]mIBG therapy. Despite more than fifty published studies, there is a lack of randomized trials that compare [131I]mIBG therapy to no [131I]mIBG therapy. Comparison between trials is difficult because of the large heterogeneity in factors such as patient population, treatment schedule (single/multiple cycles and timing of cycles), and the reporting of outcomes. A multi-institutional review focusing on patients treated with sequential [131I]mIBG therapy based on whole-body radiation-absorbed dose could be of interest [35]. Ultimately, randomized trials using standard operating procedures across multiple institutions are needed to reliably assess the efficacy and long-term safety of [131I]mIBG therapy. Given an objective tumour response rate of around 30%, it is evident that not all patients respond to [131I]mIBG therapy. Therefore, it is important to identify which patients are most likely to benefit from this therapy. To achieve this, the efficacy of [131I]mIBG therapy should be studied across various patient populations, considering distinct types of treatment failure.

Currently, the activity of [131I]mIBG to be administered is determined based on the patient's weight; and often used as a measure to correlate with response rates, survival, and toxicity. More preferable would be to select patients and determine the optimal activity to administer based on tumour dosimetry. A potential method for refined tumour dosimetry could be through the use of [124I]mIBG positron emission tomography (PET) [36]. The half-life of positron-emitting iodine-124 is 4.2 days, allowing for PET imaging multiple days following injection. PET imaging allows for accurate quantification of [124I]mIBG uptake, enabling the estimation of whole-body and tumour-absorbed doses [37]. With this information, it may be possible to better select patients who will likely respond to [131I]mIBG therapy. The adoption of [124I]mIBG PET holds promise to enhance patient selection and, consequently, improve outcomes for those undergoing [131I]mIBG therapy. To realize this potential, further research is necessary to establish activity thresholds for tumour sites, above which [131I] mIBG therapy will prove effective.

Often tumour lesions are missed on [123I]mIBG scintigraphy/SPECT because of its suboptimal resolution [20]. There is a need for better diagnostic imaging that can accurately detect the full extent of the disease, aid in the selection of patients for [131I]mIBG therapy, and assessment of post-[131I]mIBG response. Currently, PET radiopharmaceuticals are under investigation, such as [124I]mIBG and [18F]mFBG

[38].

In conclusion, [131I]mIBG therapy can be an effective agent against neuroblastoma. Especially combination treatments hold great promise for improving outcomes for patients with HR-NBL. However, [131I]mIBG therapy does not hold a standard position in the treatment of HR-NBL and continues to be studied in trials and off-protocol. Future studies, preferably in the form of randomized trials, will hopefully define the optimal use of [131I]mIBG therapy in the first-line and second-line treatment of HR-NBL.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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