Toxicity of upfront $^{131}$I-metaiodobenzylguanidine ($^{131}$I-MIBG) therapy in newly diagnosed neuroblastoma patients: a retrospective analysis

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Abstract

Purpose In the treatment of patients with high-risk neuroblastoma, different doses of $^{131}$I-metaiodobenzylguanidine ($^{131}$I-MIBG) are administered at different time points during treatment. Toxicity, mainly haematological (thrombocytopenia), from $^{131}$I-MIBG therapy is known to occur in extensively chemotherapy pretreated neuroblastoma patients. Up to now, acute toxicity from $^{131}$I-MIBG as initial treatment has never been studied in a large cohort. The aim of this retrospective study was to document acute toxicity related to upfront $^{131}$I-MIBG.

Methods All neuroblastoma patients (stages 1–4 and 4S) treated upfront with $^{131}$I-MIBG at the Emma Children’s Hospital, Academic Medical Centre (1992–2008) were included in this retrospective analysis. The acute toxicity (during therapy) and short-term toxicity (1st month following therapy) of the first two $^{131}$I-MIBG therapies were studied.

Results Of 66 patients (34 boys, 32 girls; median age 2.2 years, range 0.1–9.4 years), 49 had stage 4 disease, 5 stage 4S, 6 stage 3, 1 stage 2 and 5 stage 1. The median first dose was 441 MBq/kg (range 157–804 MBq/kg). The median second dose was 328 MBq/kg (range 113–727 MBq/kg). The most frequently observed symptoms were nausea and vomiting (21%, maximum grade II). The main toxicity was grade IV haematological, occurring only in stage 4 patients, after the first and second $^{131}$I-MIBG therapies: anaemia (5% and 4%, respectively), leucocytopenia (3% and 4%) and thrombocytopenia (2% and 4%). No stem cell rescue was needed.

Conclusion The main acute toxicity observed was haematological followed by nausea and vomiting. One patient developed posterior reversible encephalopathy syndrome during $^{131}$I-MIBG therapy, possibly related to $^{131}$I-MIBG. We consider $^{131}$I-MIBG therapy to be a safe treatment modality.

Keywords Neuroblastoma · $^{131}$I-MIBG therapy · Acute toxicity

Introduction

Despite intense multimodality treatment, 5-year overall survival of patients with stage 4 neuroblastoma is only 30% to 40%. This poor prognosis has improved with the addition of immune therapy with anti-GD2 antibody [1]. Current induction protocols for patients with high-risk neuroblastoma consist of intensive chemotherapy regimens. However, if a partial response is not achieved or residual bone marrow disease persists, survival rates are below 10%. This is probably due to early drug resistance.

An alternative treatment modality for this patient population is $^{131}$I-metaiodobenzylguanidine ($^{131}$I-MIBG), a norepinephrine analogue with specific affinity for neural crest cells.
Phase II studies investigating $^{131}$I-MIBG in patients with refractory or relapsed neuroblastoma have shown response rates in the range 0 – 56% [2]. In the Emma Children’s Hospital, Academic Medical Centre (EKZ-AMC) patients with high-risk neuroblastoma receive initial $^{131}$I-MIBG prior to induction chemotherapy (upfront) to reduce tumour load, while avoiding the induction of early drug resistance. This targeted treatment is most effective in those with a moderate to large tumour burden because the radiation from the beta-emitter $^{131}$I-MIBG to the individual cell can penetrate neighbouring cells with a mean radius in tissue of about 0.5 mm (crossfire effect). De Kraker et al. were the first to report that $^{131}$I-MIBG therapy is effective in patients with newly diagnosed high-risk neuroblastoma with a large tumour mass and high uptake of the radiopharmaceutical [3]. In the current protocol of the Dutch Childhood Oncology Group (DCOG NB2009) patients with high-risk neuroblastoma are being treated with two courses of upfront $^{131}$I-MIBG therapy, followed by chemotherapy according to the high-risk protocol of the Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH NB 2004).

Over the past 20 years, preceding the DCOG NB 2009 study, in our hospital neuroblastoma patients have been treated with upfront $^{131}$I-MIBG, while other study groups have predominantly used $^{131}$I-MIBG in patients with refractory and relapsed disease. Therefore, our cohort is unique to study toxicity of $^{131}$I-MIBG only. Up to now, toxicity of $^{131}$I-MIBG has mainly been reported in extensively pretreated patients. From these studies it is known that $^{131}$I-MIBG can cause haematological toxicity with severe and prolonged thrombocytopenia. Toxicity of $^{131}$I-MIBG as first-line single therapeutic agent has never been reported before in a large cohort of patients. The aim of this retrospective study was to investigate acute toxicity of upfront $^{131}$I-MIBG therapy in a large cohort of neuroblastoma patients (stages 1–4 and 4S).

Materials and methods

Patients

All patients (0 – 18 years old) with histologically proven (ganglio)neuroblastoma of any stage (International Neuroblastoma Staging System) treated with upfront $^{131}$I-MIBG between January 1992 and April 2008 at the EKZ-AMC or the Netherlands Cancer Institute-Antonie van Leeuwenhoek Hospital (NKI-AVL) were eligible for this retrospective analysis. Patients with stage 4 disease were treated with upfront $^{131}$I-MIBG, followed by induction chemotherapy and autologous stem cell transplantation according to the consecutive high risk protocols. In earlier days, patients with stage 1 to 3 and stage 4S were treated with $^{131}$I-MIBG if they had inoperable MIBG-positive lesions that were causing or were in danger of causing organ dysfunction.

Study design

Clinical data concerning acute toxicity were retrospectively collected from medical and nursing records of the first two $^{131}$I-MIBG therapies. $^{131}$I-MIBG was given according to the protocol previously described by de Kraker et al. [3]. Fixed doses were given; the first dose was generally 7,400 or 5,550 MBq and the second 5,550 or 3,700 MBq. Dose modifications were made based on age and stage. For the purpose of this study we calculated dose per kilogram body weight. Patients younger than 1 year were not sedated. Patients involved in the care of their child and therefore were required to take potassium iodide 200 mg daily for 2 weeks, beginning the day prior to their child’s $^{131}$I-MIBG therapy. Patients remained in radiation protective isolation until the exposure rate was less than 20 μSv/h, measured with a counter at a distance of 1 m from the patient [3]. Whole-body exposure dose was not measured. The parents were extensively informed about the nature and precise elements of the treatment and the differences from other strategies, and consent was obtained prior to treatment.

Data collection

As well as general patient characteristics, we documented tumour-related features and data regarding $^{131}$I-MIBG therapy. In brief, the total number of $^{131}$I-MIBG therapies per patient, dose (megabecquerels and millicuries), infusion duration, medication (analgesics, sedatives, antiemetics and thyroid protection), tube-feeding and the duration of radiation protective isolation were recorded.

To assess acute toxicity caused by $^{131}$I-MIBG, we searched for: symptoms during infusion and during radiation protective isolation (catecholamine-induced, cardiovascular, pulmonary, gastrointestinal, neurological, blood and lymphatic system and general symptoms), hepatic and renal toxicity, haematological toxicity, red blood cell and platelet transfusions, paediatric consultations during radiation protective isolation and reasons for premature discharge from radiation protective isolation. Toxicity was scored according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. We report the highest toxicity grade observed.

Statistical analysis

Correlations were tested with the Mann-Whitney $U$ test (presence of grade IV haematological toxicity versus $^{131}$I-MIBG dose), and Fisher’s exact test (presence of grade IV haematological toxicity versus bone marrow involvement at diagnosis).
Results

Patients

We identified 121 neuroblastoma patients of any stage (Supplementary Fig. 1). Of these patients, 13 were excluded because of missing data and 42 because of pretreatment. The characteristics of the remaining 66 patients are presented in Table 1. Their median age was 2.2 years (range 0.1 – 9.4 years).

Most patients presented with symptoms typical of neuroblastoma such as abdominal distension, fever, fatigue, painful limbs and/or hypertension. At diagnosis, 36 of the 66 patients had hypertension (grade 2), which improved after the first $^{131}$I-MIBG therapy (data not shown).

$^{131}$I-MIBG therapy

Administered $^{131}$I-MIBG doses are shown in Table 2 (fixed doses are shown in Supplementary Table 1). The median first $^{131}$I-MIBG dose was 430 MBq/kg in children younger than 12 months and 447 MBq/kg in children aged 12 months and older, with a median of 441 MBq/kg (range 157 – 804 MBq/kg) in all patients. The median second dose was 430 MBq and 314 MBq, respectively, with a median of 328 MBq/kg (range 113 – 727 MBq/kg) in all patients.

During the first $^{131}$I-MIBG therapy, the median periods of radiation protective isolation were 3 days in children younger than 12 months and 4 days in children aged 12 months and older, with a median of 4 days (range 1 – 8 days). During second therapy, the median periods were 4 and 4 days, respectively, with a median of 4 days (range 2 – 7 days) in all patients. Two patients were prematurely discharged from radiation protective isolation on the day of $^{131}$I-MIBG infusion because of serious adverse events (SAEs; see Table 7).

Toxicity during infusion

Because uptake of $^{131}$I-MIBG in the tumour can give symptoms of catecholamine excretion, both during infusion and during radiation protective isolation symptoms related to catecholamine excretion were scored. No symptoms related to catecholamine excretion were reported in medical or nursing files, not even when the infusion duration was reduced from 240 to 120 min in 1997 (data not shown). The only symptom reported was grade II vomiting in one patient after the first $^{131}$I-MIBG infusion (data not shown).

Table 1 Patient characteristics

| Characteristic                          | Valuea |
|----------------------------------------|--------|
| Sex, n (%)                             |        |
| Male                                    | 34/66 (52) |
| Female                                  | 32/66 (48) |
| Age at diagnosis (years), median (range)| 2.2 (0.1 – 9.4) |
| Age at diagnosis <1 year, n (%)         | 15 (23) |
| Stage, n (%)b                          |        |
| 1                                      | 5/66 (8) |
| 2                                      | 1/66 (1) |
| 3                                      | 6/66 (9) |
| 4                                      | 49/66 (74) |
| 4S                                     | 5/66 (8) |
| Genetic aberrations, n (%)             |        |
| MYCN amplification                     | 17/63 (27) |
| Chromosome 1p loss of heterozygosity    | 18/53 (34) |
| Urinary catecholamines elevated, n (%)  | 61/64 (95) |
| Lactate dehydrogenase >1,500 U/l, n (%) | 13/64 (20) |
| Ferritin ≥143 ng/ml, n (%)             | 32/63 (51) |

aBecause of missing data, the total number of patients can vary; reported are the actual number of patients with positive findings/total number of patients with data

bInternational Neuroblastoma Staging System

Fever was reported in five patients (grade I or II) during radiation protective isolation. The origin of the fever was unknown (tumour fever) in three patients (two stage 4, one stage 4S). Sepsis was reported in two patients (stage 4). These two patients were treated during radiation protective isolation, without the need for intensive treatment.

Toxicity during radiation protective isolation

Pain medication (acetaminophen) was prescribed in 38 of 66 patients and in 16 of 52 patients before the start of the first and second therapies, respectively (Supplementary Table 2). Patients with neuroblastoma frequently suffer from Hutchinson syndrome with limping and irritability due to skeletal metastases from the neuroblastoma. In our population pain did not exceed grade 3 (data not shown). Sedative medication (chloral hydrate, histamine-blocking agents or benzodiazepines) was given to 41 of 66 patients during the first $^{131}$I-MIBG therapy and 26 of 52 patient during second therapy (Supplementary Table 2).
Respiratory symptoms due to abdominal masses improved during and after the first $^{131}$I-MIBG therapy in most patients. Three patients (stage 4) developed respiratory symptoms during the first $^{131}$I-MIBG therapy, caused by ascites, primary varicella infection and fever (one patient each). Two of these patients (stage 4 and 4S) developed respiratory failure. Further details of these SAEs are presented in Table 7 (patients 41 and 74). No renal toxicity was observed in 39 patients after the first $^{131}$I-MIBG therapy (27 patients missing data) and in 40 patients after the second therapy (12 patients missing data). Hepatic toxicity after the first $^{131}$I-MIBG therapy was observed in 11 patients (seven grade I, one grade II and three grade III; 38 patients missing data). After the second $^{131}$I-MIBG therapy eight patients showed grade I hepatic toxicity (28 patients missing data).

Haematological toxicity

Grade IV anaemia was seen in three patients after the first $^{131}$I-MIBG therapy and in two other patients after the second therapy (Table 4). Two patients developed grade IV leucocyte toxicity after the first $^{131}$I-MIBG therapy and two after the second therapy. Two of these patient had a neutropenia, one after the first and second and one only after the second therapy (for the time lines of neutrophil counts of these patients, see Supplementary Fig. 2a).

One patient developed grade IV thrombocytopenia after the first $^{131}$I-MIBG therapy and two after the second (for the time lines of platelet counts of these patients, see Supplementary Fig. 2b). All patients had their next treatment modality within 5 weeks of the $^{131}$I-MIBG therapy. Haematological toxicity was

### Table 3 Clinical symptoms of toxicity mentioned in medical and nursing records during radiation protective isolation and after discharge (first 4 weeks after $^{131}$I-MIBG therapy). Toxicity was scored according to CTCAE version 4.0; the highest toxicity grade was reported.

| Symptom                          | Grades reported | First therapy $(n = 66), n (%)$ | Second therapy $(n = 52), n (%)$ |
|----------------------------------|-----------------|---------------------------------|----------------------------------|
| During isolation                 |                 |                                 |                                  |
| Catecholamine-induced Flushes    | –               | 0 (0)                           | 0 (0)                            |
| Sweating                         | I               | 4 (6)                           | 0 (0)                            |
| Pallor                           | I               | 3 (5)                           | 0 (0)                            |
| Cardiovascular                   |                 |                                 |                                  |
| Circulatory failure IV           | IV              | 1 (2)                           | 0 (0)                            |
| Gastrointestinal                 |                 |                                 |                                  |
| Vomiting I, II                   | 14 (21)         | 5 (10)                          |                                  |
| Nausea I, II                    | 7 (11)          | 3 (6)                           |                                  |
| General                          |                 |                                 |                                  |
| Tumour fever I, II              | 3 (5)           | 0 (0)                           |                                  |
| Infection I, III                | 2 (3)           | 0 (0)                           |                                  |
| Neurological                     |                 |                                 |                                  |
| Seizures III                    | 1 (2)           | 0 (0)                           |                                  |
| Pulmonary                        |                 |                                 |                                  |
| Dyspnoea III                    | 1 (2)           | 0 (0)                           |                                  |
| Respiratory failure IV          | 2 (3)           | 0 (0)                           |                                  |
| After discharge                  |                 |                                 |                                  |
| Blood and lymphatic system       |                 |                                 |                                  |
| Epistaxis I                     | 0 (0)           | 1 (2)                           |                                  |
| General                          |                 |                                 |                                  |
| Tumour fever I, II              | 1 (2)           | 0 (0)                           |                                  |
| Infection I, II, III            | 4 (6)           | 2 (4)                           |                                  |
| Pulmonary                        |                 |                                 |                                  |
| Dyspnoea I, II                  | 2 (3)           | 0 (0)                           |                                  |
only present in patients with bone marrow involvement at diagnosis (7 of 49 patients). Patients without bone marrow involvement did not have any grade IV haematological toxicity (Table 5). There was no significant difference in the administered first $^{131}$I-MIBG dose between patients with and without haematological toxicity ($P=0.269$). Five patients were not included in the analysis because of missing data.

At diagnosis (before the first $^{131}$I-MIBG therapy), 58% of patients (38/66) needed a red blood cell transfusion (Table 6). After the first therapy, only 23% (15/66) needed a red blood cell transfusion and 23% (12/52) after the second. One of the patients who needed a red blood cell transfusion had stage 1 disease and two had stage 4S disease; all others had stage 4 disease. The need for a platelet transfusion increased slightly after $^{131}$I-MIBG therapy. One patient needed a platelet transfusion at diagnosis, and four after the first and two after the second therapy (all stage 4). One of these patients had grade IV leucocytopenia. Two patients (stage 4) developed a gastrointestinal infection without fever caused by rotavirus and Clostridium difficile (not shown in Table 3, because they did not meet the CTCAE criteria). Respiratory distress (grades I and II) was reported in two patients (one stage 4, one stage 4S) and was caused by sepsis and oedema. Epistaxis (grade I) was reported by one patient and was caused by thrombocytopenia.

**Table 4** Number (percentage) of patients with haematological toxicity scored according to CTCAE version 4.0; the highest toxicity grade was reported

| Toxicity   | First therapy ($n = 66$) | Second therapy ($n = 52$) |
|------------|--------------------------|---------------------------|
|            | CTCAE grade | Total | Missing | CTCAE grade | Total | Missing |
|            | I   | II   | III  | IV   | I   | II   | III  | IV   | I   | II   | III  | IV   |
| Haemoglobin| 4 (6) | 23 (35) | 14 (21) | 3 (5) | 44 (67) | 8 (12) | 4 (6) | 22 (42) | 5 (10) | 2 (4) | 38 (73) | 5 (10) |
| Leucocytes | 14 (21) | 15 (23) | 4 (6) | 2 (3) | 35 (53) | 8 (12) | 9 (17) | 16 (31) | 11 (21) | 2 (4) | 36 (69) | 5 (10) |
| Platelets  | 16 (24) | 3 (5) | 6 (9) | 1 (2) | 15 (23) | 10 (15) | 13 (25) | 6 (12) | 4 (8) | 2 (4) | 19 (37) | 7 (13) |

4 and two stage 3): pneumonia, Staphylococcus aureus sepsis, S. epidermidis sepsis, infection of the catheter entry point, urinary tract infection and a common cold (one patient each). One of these six patients had grade IV leucocytopenia. Two patients (stage 4) developed a gastrointestinal infection without fever caused by rotavirus and Clostridium difficile (not shown in Table 3, because they did not meet the CTCAE criteria). Respiratory distress (grades I and II) was reported in two patients (one stage 4, one stage 4S) and was caused by sepsis and oedema. Epistaxis (grade I) was reported by one patient and was caused by thrombocytopenia.

**Table 5** Grade IV haematological toxicity according to CTCAE criteria vs. bone marrow involvement at diagnosis as evaluated by trephine biopsy or MIBG scan

| Grade IV haematological toxicity | Bone marrow involvement at diagnosis |
|----------------------------------|-------------------------------------|
|                                 | Present | Absent | Total |
| Present                          | 7       | 0      | 7     |
| Absent                           | 42      | 17     | 59    |
| Total                            | 49      | 17     | 66    |

**Table 6** Number (percentage) of patients who needed a red blood cell or platelet transfusion

| Transfusion | At diagnosis ($n = 66$) | First therapy ($n = 66$) | Second therapy ($n = 52$) |
|-------------|-------------------------|--------------------------|---------------------------|
| Red blood cells | 38 (58) | 15 (23) | 12 (23) |
| Platelets    | 1 (2)    | 4 (6)    | 2 (4)    |

**Serious adverse events**

SAEs observed during radiation protective isolation or within 4 weeks of $^{131}$I-MIBG therapy are shown in Table 7. All four patients had disseminated disease (one stage 4S) with MYCN amplification; two patients also had chromosome 1p loss of heterozygosity. Two patients were prematurely discharged from radiation protective isolation. Patient 41 was an infant at the start of therapy. Although under the age of 1 year, she had high-risk disease (MYCN amplification). During the first day of radiation protective isolation, emergency treatment was indicated because the abdominal tumour mass was causing respiratory distress. This patient experienced respiratory failure and needed mechanical ventilation, so she was transported from the radiation protective isolation unit to the paediatric intensive care unit (PICU). Subsequently she had circulatory collapse. Resuscitation was ineffective and post mortem examination was refused by the parents. Patient 74 suffered from hypertensive encephalopathy causing seizures on the first day of radiation protective isolation. These seizures were treated...
with diazepam (benzodiazepine). Consequently, she experienced respiratory failure and was admitted to the PICU. After recovery, the hypertension remained difficult to control with medication. She was treated within the standard arm of the GPOH NB2004. Within 1 year of $^{131}$I-MIBG therapy she died of progressive disease.

Despite $^{131}$I-MIBG therapy, disease progressed in two other patients. At diagnosis tumour invasion caused major bleeding in the thorax of patient 29. After stabilization of vital functions, the first $^{131}$I-MIBG therapy was tolerated well. However, this patient died 1 day after discharge from radiation protective isolation because of uncontrollable arterial lung bleeding caused by progressive disease. The thrombocyte count was within the normal range. Patient 53 had an uneventful first and second $^{131}$I-MIBG course. One week after the second course she developed progressive disease with severe inferior vena cava syndrome, respiratory distress, restlessness and opisthotonus. Despite acute chemotherapy treatment, she died due to tumour progression 2 weeks after her second $^{131}$I-MIBG therapy.

### Discussion

In newly diagnosed neuroblastoma patients, the most frequently encountered toxicity of $^{131}$I-MIBG was haematological, followed by nausea and vomiting. Although this was a retrospective study, we believe that from this large cohort, conclusions can be drawn.

#### Haematological toxicity

Until now, $^{131}$I-MIBG toxicity has predominantly been documented in patients with refractory or relapsed neuroblastoma who have received extensive chemotherapy treatment before $^{131}$I-MIBG therapy. Toxicity of $^{131}$I-MIBG only has therefore been difficult to determine. Haematological toxicity, the main toxicity observed in this pretreated population, was mostly severe and persistent thrombocytopenia [4, 5]. In our cohort of neuroblastoma patients treated with upfront $^{131}$I-MIBG only, grade IV thrombocytopenia occurred in only 1% of patients after the first therapy and in 3% of patients after the second. These percentages are lower than would be expected with induction chemotherapy [6]. Besides, no episodes of major bleeding due to thrombocytopenia were observed. Nowadays, toxicity of $^{131}$I-MIBG is often related to the delivered whole-body dose. Due to the nature of this retrospective cohort, whole-body doses were not available for this study. However, we did not find a correlation between administered $^{131}$I-MIBG dose and grade IV haematological toxicity. Mastrangelo et al. also recently investigated the toxicity of upfront $^{131}$I-MIBG delivered in combination with chemotherapy (cisplatin, cyclophosphamide, etoposide, vincristine, and doxorubicin) in 13 newly diagnosed neuroblastoma patients. Toxicity was only haematological and considered acceptable [7].

Previous studies have suggested a correlation between bone marrow invasion and $^{131}$I-MIBG-induced myelosuppression [4]. In our cohort we also found a correlation between these two factors, and patients with grade IV anaemia, leucocytopenia or thrombocytopenia all had disseminated disease. Matthay et al. demonstrated the feasibility without significant toxicity of high-dose (up to a cumulative dose of 36 mCi/kg), rapid-sequence, double-infusion $^{131}$I-MIBG with stem cell support in patients with refractory or relapsed disease [8]. Although not the focus of this study, we can report that in our study population no stem cell rescue was required during or after the first two $^{131}$I-MIBG therapies in these newly diagnosed patients, even after doses up to 814 MBq/kg. Induction chemotherapy, surgery, dose-intense chemotherapy and autologous stem cell rescue were feasible after $^{131}$I-MIBG therapy. Furthermore, $^{131}$I-MIBG therapy early in induction did not affect the yield of stem cell or bone marrow harvest (data not shown).

#### Nonhaematological toxicity

As has been found in previous studies, nausea and vomiting were the symptoms most often observed during radiation protective isolation, without exceeding grade II, possibly due to tube feeding and medication (potassium iodide) [9]. Infections occur frequently after induction chemotherapy due to myelosuppression, and contribute significantly to

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**Table 7** Serious adverse events

| Patient | Stage | Age (years) | Biological markers | Events |
|---------|-------|-------------|--------------------|--------|
| 29      | 4     | 3.7         | MYCN amplification | Sepsis during isolation. After the first treatment arterial bleeding in the thorax due to tumour invasion of blood vessels |
| 41      | 4S    | 0.1         | MYCN amplification | Respiratory and circulatory insufficiency and subsequently died |
| 53      | 4     | 2.3         | MYCN amplification, chromosome 1p loss of heterozygosity | Severe inferior vena cava syndrome, respiratory distress, restlessness and opisthotonus |
| 74      | 4     | 6.1         | MYCN amplification, chromosome 1p loss of heterozygosity | Respiratory insufficiency due to convulsions (caused by posterior reversible encephalopathy syndrome) and anticonvulsive medication |
morbidity and mortality in neuroblastoma patients. Infections have also been reported during and after 131I-MIBG therapy in heavily pretreated patients and in patients treated with myeloablative 131I-MIBG therapy [8]. Matthay et al. found infectious events (grade 3 or 4) in 10.9% of patients with refractory neuroblastoma [9]. In contrast, only a few patients in our cohort were diagnosed with infections not exceeding grade II in severity. As patients in our study were chemotherapy-naive, they might have had better bone marrow reserve. Patients with infections were not neutropenic and could be treated during radiation protective isolation without the need for intensive treatment. The need for pain medication decreases immediately after the first 131I-MIBG therapy. Therefore, 131I-MIBG is often used in palliative care for pain reduction or relief of other tumour-related symptoms [10]. During radiation protective isolation, blood pressure was not frequently monitored. However, when it became apparent that hypertensive episodes can occur many hours after 131I-MIBG infusion this policy was changed in our hospital. Currently blood pressure is monitored for at least 48 h after administration of 131I-MIBG [10]. Foley catheters are standard of care in some centres. We did not use Foley catheters, and no renal or urinary toxicity was observed [8, 9].

Serious adverse events

Four SAEs occurred during or directly after 131I-MIBG therapy. In one patient posterior reversible encephalopathy syndrome (PRES), a rare complication in paediatric oncology patients, caused seizures. The PRES was presumably caused by preexisting hypertension, but toxicity of 131I-MIBG cannot be excluded. Kosmin et al. found a significant association between adverse events during and 20 to 25 h after 131I-MIBG infusion and a systolic blood pressure above the 90th centile before 131I-MIBG infusion. One of the four adverse events they describe was severe with seizures [11]. In the literature only two other cases of PRES have been described in neuroblastoma patients, and none of these patients were treated with 131I-MIBG [12].

In conclusion, 131I-MIBG therapy has an acceptable safety profile if the seriously ill condition of this patient population is taken into consideration. The main toxicity observed in this cohort was haematological (grade IV) and nausea and vomiting (maximum grade II). Thrombocytopenia occurred in a few patients but did not result in episodes of major bleeding.

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Conflicts of interest None.

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