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Iodine-131-metaiodobenzylguanidine as initial induction therapy in stage 4 neuroblastoma patients over 1 year of age

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ABSTRACT

Purpose: To determine the response to radionuclide targeted therapy with I-131-metaiodobenzylguanidine (^{131}I-MIBG) as induction therapy in high-risk neuroblastoma patients.
Patients and methods: The protocol dictated at least two cycles of ^{131}I-MIBG with a fixed dose of 7.4 and 3.7 GBq, respectively, followed by surgery, if feasible, or followed by neoadjuvant chemotherapy and surgery. This was followed by consolidation with four courses of chemotherapy myeloablative chemotherapy and autologous stem-cell transplantation (ASCT). Consolidation therapy with 13-cis-retinoic acid was given for 6 months.
Results: Of 44 consecutive patients, 41 were evaluable after two courses of ^{131}I-MIBG. The objective response rate at this point was 66%. In 24 patients, ^{131}I-MIBG was continued as pre-operative induction treatment. Seventeen patients required additional chemotherapy before surgery. After pre-operative therapy and surgery, the overall response rate was 73%.
Conclusion: First line ^{131}I-MIBG-targeted therapy is a valuable tool in the treatment of MIBG-positive high-risk neuroblastoma patients.

1. Introduction

Neuroblastoma, a tumour of the autonomic nervous system, is the most frequent extra cranial solid tumour in children. Over the age of 1 year, the disease most commonly presents with metastases. There has been substantial progress in the understanding of the disease, but the treatment results of advanced neuroblastoma after infancy are still poor. Intensive multi-agent chemotherapy and consolidation therapy with myeloablative chemotherapy, with or without total-body irradiation, followed by autologous bone marrow transplantation or peripheral stem-cell re-infusion has contributed to an improvement in cure rates.[1–3] The observed response to ^{131}I-MIBG therapy in recurrent neuroblastoma, the non-invasiveness of the procedure, and the decreased risk of developing resistance to chemotherapy led to new approaches in these patients.[4] One of these was to combine ^{131}I-MIBG therapy with high dose chemotherapy (HDCT) with or without total body irradiation, or with HDCT and immunotherapy for consolidation, with the aim of ablating minimal residual disease.[5–7] We chose to use ^{131}I-MIBG therapy as induction therapy with the aim of reducing the volume of the primary tumour and the number of malignant cells at metastatic sites, enabling adequate surgical resection and avoiding the toxicity of chemotherapy and the induction of early drug resistance. Surgery was then followed by chemotherapy to eliminate

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residual disease. We present an analysis of 44 consecutively registered patients to investigate the feasibility and response to MIBG when used as induction treatment.

2. Patients and methods

Patients between 1 and 18 years of age at diagnosis who had high-risk, MIBG positive neuroblastoma were eligible for the study. The parents were extensively informed about the nature and precise elements of the treatment and the differences with other strategies and consent was obtained prior to inclusion. Previous chemotherapy was an exclusion criterion, but initial surgery as the only treatment modality was not. Initial staging evaluation included computed tomography imaging of the primary tumour, ^{123}I-MIBG diagnostic scintigraphy, bone marrow aspirates, and biopsies of both sides of the iliac crest. The two most frequent genetic alterations, MYCN amplification and deletion of the chromosomal 1p region, were analysed. Lactate dehydrogenase (LDH) and ferritin were documented at diagnosis, and later at specific time points. All patients were staged according to the revised International Neuroblastoma Staging System (INSS) and assessment of response was according to the International Neuroblastoma Response Criteria (INRC).[8] Survival distributions were calculated using the Kaplan–Meier life table method and differences in survival between groups were compared using Log rank and Breslow tests.

2.1. Study design

The first objective of the study was to document response after two infusions of MIBG as a single agent given after diagnosis in high-risk patients. The second objective was to find the rate of resectability of >95% of the primary tumour together with a significant reduction in tumour mass at the metastatic sites in patients with an objective response to MIBG single agent therapy. In case of an ongoing response, more than two MIBG infusions were allowed to achieve this goal (Group A). Progressive disease or stable disease after two or more infusions of MIBG was considered as a failure of MIBG therapy. These patients were switched to pre-operative chemotherapy as induction therapy (Group B). All eligible patients had an initial infusion of ^{131}I-MIBG at fixed doses of 200 mCi (7.4 GBq) for the first infusion and 100–150 mCi (3.7–5.6 GBq) for the second and all subsequent infusions. The interval between MIBG infusions was 4 weeks. Group B patients were switched to induction chemotherapy comprised of vincristin 1.5 mg. /m^2 i.v. on day 1, ifosfamide 3000 mg/m^2 i.v. over 1 h on days 1 and 2, carboplatin 400 mg/m^2 i.v. in a 24-h infusion on day 3, and etoposide 150 mg/m^2 i.v. over 4 h on day 4 (VECI). These courses were given at 4 week intervals. After MIBG therapy or MIBG plus chemotherapy, surgery was performed as soon as the surgeon felt that a greater than 95% resection was feasible. After surgery, four courses of chemotherapy (VECI) were given independent of the preoperative therapy. This was followed by consolidation therapy 4 weeks after the last VECI course with carboplatin 800 mg/m^2 i.v. over 6 h on day 1, followed by melphalan 180 mg/m^2 i.v. on day 3, and re-infusion of bone marrow or peripheral blood stem cells on day 5. The harvest of stem cells took place during the post-operative VECI courses as soon as the patient was in VGPR or CR with a clean bone marrow. After stem cell re-infusion, 13-*cis*-retinoic acid, in a dose of 160 mg per square meter per day administered orally in two divided doses for 14 consecutive days in a 28-day cycle, was given for 6 months, beginning 4 weeks after stem-cell re-infusion, in 14-day cycles (Fig. 1).

2.2. MIBG treatment

^{131}I-MIBG with a specific activity of 1.48 GBq/mg was administered intravenously over 4 h through a lead-shielded infusion line equipped with a pump and a dose meter. Immediately before administering a therapeutic dose, a quality control check of the radionuclide and radiochemical purity was carried out and less than 5% free ^{131}I was allowed in the formulation. There was no follow up done on whole body dosimetry and estimated tumour dose because of the many inaccuracies associated with these observations. The patients were isolated until they had reached the radiation emitting threshold of 20 μSv/h measured at a distance of one metre. The scheduled interval between the two infusions was 4 weeks. The thyroid was protected against 131-iodine uptake by the administration of 100 mg potassium iodide (KI) for 14 days, beginning one day before the MIBG infusion. Plasma thyrotropin (TSH) and thyroxine (T4) values were measured before and after each ^{131}I-MIBG infusion. Thyroid dysfunction was defined as a plasma TSH level of >4.5 mU/L. Also, parents who were involved in the care of their child were required to take potassium iodide 200 mg daily for 2 weeks, beginning the day prior to their child's ^{131}I-MIBG therapy.

3. Results

From April 1989 to October 1999, 44 consecutive children diagnosed with high-risk, MIBG positive neuroblastoma were in-

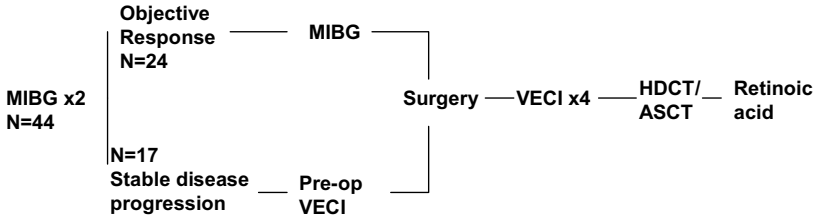

Fig. 1 – Outline of the study.

Table 1 – Characteristics of patients at diagnosis (Δ), patients treated with MIBG only (Group A) and patient's who needed additional chemotherapy as induction treatment (Group B)

Characteristic	At Δ No. (%)	Group A No. (%)	Group B No. (%)
Patients (number)	44[a]	24	17
Age, years (median)	2.6	2.9	2.7
Age, years (range)	1.0–15.4	1.2–15.5	1.2–9.4
Males	23[a]	13	8
Females	21[a]	11	9
Bone marrow tumour positive	44/44[a] (100)	24	17
Ferritin (>2× upper limit)	12/ 41[b] (29)	7 (29)	5 (29)
LDH (>2× upper limit)	30 / 41[b] (73)	14 (58)	16 (94)
MYCN amplification	10 / 44 (23)	4 (16)	6 (35)
1-p deletion	20 / 43[b] (47)	12 (50)	8 (47)
Add 17q	26 / 41[b] (63)	15 (63)	11 (64)

a Three patients (two males, one female) were excluded for further evaluation (see text).
b Values not available for all patients.

cluded in the study. Thirty three of these 44 children were included in a preliminary report.[9] On-study characteristics are listed in Table 1. In two patients, it was not feasible to start MIBG-treatment. One patient had an early progression requiring immediate treatment, and the other patient had sepsis and was too unstable for MIBG-treatment. In three patients, only one infusion of ^{131}I-MIBG was given. One patient progressed very rapidly after the first MIBG-infusion and died; another patient responded poorly and was switched to chemotherapy. Both of these patients were kept in the cohort for evaluation. A third patient was diagnosed at a highly progressed stage of the disease and the parents refused any further therapy after one MIBG infusion. This patient was not evaluable for response. The remaining patients (39) had at least two infusions (range 2–5, median 3) of MIBG. They received a cumulative dose of 350–950 mCi (13–35GBq) ^{131}I-MIBG (median 500 miC) as induction therapy. It was feasible to have an interval of 4 weeks between the first and the second course of ^{131}I-MIBG in 34 of 39 patients. In five patients, the interval was slightly longer because the isolation facility was not available. In all patients who had three or more infusions the third infusion was administered exactly 4 weeks after the second.

3.1. *Response after two ^{131}I-MIBG infusions*

The MIBG-scans at the time of the third infusion or a 123I-MIBG scan 4 weeks after the second infusion if no third infusion was given were compared with the scintigrams of the first MIBG infusion to evaluate response on MIBG imaging. Partial response was documented in case the primary tumour appeared smaller with a decrease in measured tumour uptake, and a decrease in uptake of all metastatic sites, and no new lesions appeared. After two infusions 30/41 patients showed a partial response on MIBG imaging. After two MIBG infusions, the primary tumour decreased by > 50% in volume in 27/41 patients (66%). Twenty out of 34 evaluable patients (58%) cleared their bone marrow at this point. According to INRC criteria this means an objective response rate of 66% (1 CR, 0 VGPR, and 26 PR) (n = 41) (Table 2). Four additional patients had mixed responses (MR). Five patients had stable disease (SD) and four had disease progression after two courses of MIBG infusions. One patient was not evaluable, but later received chemotherapy in his home country and had disease progression. The four patients with MR, five patients with SD, four patients with PD, and the non evaluable patient were all placed in group B. Three patients who met the criteria for PR were also classified in group B, because the investigators felt that the response in these patients with MIBG alone was insufficient, and that they would derive greater benefit from preoperative chemotherapy.

Twenty four patients with CR or PR (group A) continued therapy solely with MIBG-infusions, and the response rate of this group before surgery was 79% (19/24). After surgery, the response-rate in this group increased to 91% (22/24) (Table 2). Fourteen of 20 evaluable patients (70%) from group A

Table 2 – Detailed response to MIBG, MIBG and surgery, or MIBG, chemotherapy, and surgery at different time points during the treatment

Evaluation	After MIBG × 2	MIBG-only Before S[a]	MIBG-only + S[a]	MIBG + CT Before S[b]	MIBG + CT + S	Overall after S
CR	1	2	14	–	2	16
VGPR	–	1	1	1	0	1
PR	26	16	7	5	6	13
MR	4	2	2	–	0	2
SD	5	3	0	2	0	0
PD	4	0	0	9	9	9
NE	1	–	–	–	–	
Total	41	24	24[c]	17	17[d]	41
OR (%)	66	79	91	35	47	73

Abbreviations: MIBG, metaiodobenzylguanidine; CR,complete remission; VGPR very good partial response; PR partial response; MR mixed response; SD stable disease; PD progressive disease; NE not evaluable; OR overall response; S surgery; CT chemotherapy.
a Group A.
b Group B.
c Eighteen of these had a complete resection of the primary tumour.
d Eight of these had a complete resection of the primary tumour.

cleared their bone marrow. A change to pre-operative chemotherapy was necessary for the 17 patients placed in group B. For these patients, the response rate before surgery was 35% (6/17). Response after surgery in this group was 47% (8/17) (Table 2). In Group B, 6 of 14 evaluable patients (43%) cleared their marrow. The overall response rate after surgery for Group A and Group B combined was 73% (30/41). The characteristics of patients who had MIBG only (group A) and those who needed additional chemotherapy before surgery (group B) were only slightly different (Table 1).

3.2. *Resectability after induction with ^{131}I-MIBG*

Fourteen patients did not receive surgery. Three patients had no primary tumour because they were registered with recurrent disease after surgery for what was presumed at that time to be a localised tumour. Two patients had multiple inoperable primary tumours. Nine patients had no surgery because their tumour progressed despite additional chemotherapy. Complete local control of the primary tumour was possible in 26 of 39 (67%) patients who had at least two ^{131}I-MIBG infusions. In 18 of 24 patients, the primary tumour was resected after 'MIBG-only' as preoperative therapy. In patients requiring additional chemotherapy as induction therapy, complete local control was feasible in eight of 17 patients. From 41 evaluable patients, nine progressed before surgery. One patient died due to a surgical complication.

3.3. *Clinical course after surgery*

After surgery, during postoperative chemotherapy, seven patients had a progression of there disease and another seven patients never got into VGPR or CR and are considered as refractory disease. Stem cell harvest was only performed in patients if in CR or VGPR. None of these patients reached this state of response long enough to allow for stem cell harvest.

In 17 patients, stem cells were harvested after 1–5 (median 3) infusions of MIBG. The median yield in the first eight patients was 11.6×10^4/kg CFU-C colonies (range 2.9–31.6), and was a median of 4.9×10^6/kg CD34 + cells (range 1.2–17.0) in nine patients. The other patients progressed before stem cells could be harvested. Eleven patients from group A and six from group B had high dose chemotherapy (HDCT) and autologous stem-cell transplant. The median time to neutrophil ($> 1.0 \times 10^3$/μl) and platelet ($> 50 \times 10^3$/μl) engraftment was 23 and 47 days, respectively. Four patients from Group A and one patient from Group B are long-term disease free survivors (Figs. 2,3). The median EFS for all 41 patients was 10 months (95% CI, 7–13 months). The median OS was 15 months (95% CI, 7–23 months). The 5-year EFS in the study was 12.2% with an OS at 5 years of 14.6%.

3.4. *Side-effects*

Both the ^{131}I-MIBG therapy and the isolation were well tolerated by all patients. Neither renal nor hepatic toxicity greater than grade one were observed in these patients during, or within 4 weeks following the last ^{131}I-MIBG-treatment. Haematological side-effects were limited to thrombocytopenia. At the first course of ^{131}I-MIBG, the median platelet count

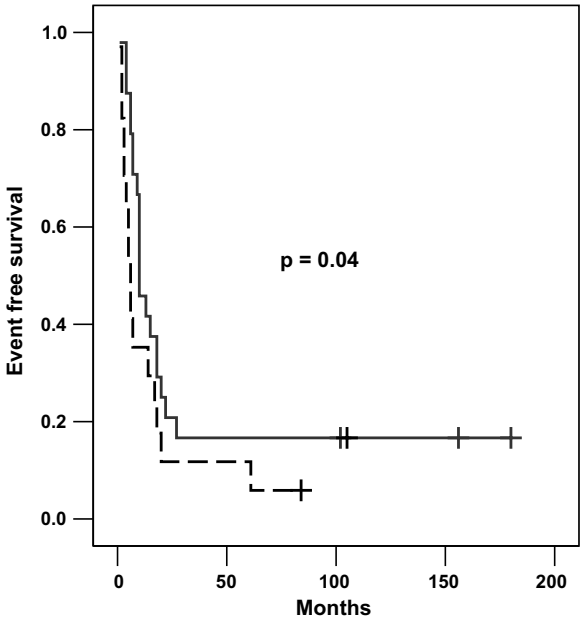

Fig. 2 – Kaplan–Meier curves of EFS for patients treated with MIBG only (solid line) and MIBG + chemotherapy (dashed line) as pre-operative therapy. The difference between the curves was not significant by the log rank method; it was statistically significant by the Breslow method ($p = 0.04$) which emphasises differences in the beginning of the survival curve.

was 167 (range 10–434). Just before the second, third, and fourth infusion of ^{131}I-MIBG, these values were 157 (range 11–302), 156 (range 10–304), and 131 (range 5–323), respectively. Seventeen patients underwent autologous bone-marrow transplantation. Four deaths occurred. One patient died 43 days after stem cell reinfusion of a cerebral bleeding while still thrombocytopenic. This patient had a cumulative dose of 800 mCi of MIBG. A toxic myelosuppression is highly suspicious for the death. Three patients died due to multifocal infections, 8, 9, and 16 days after rein fusion. They were still neutropenic at the time of their death. They had two, three, and three MIBG infusions respectively (Table 3). In 22 patients (48.9%), plasma thyrotropin and thyroxine values were measured before and after ^{131}I-MIBG treatment. After a mean follow-up of 19 months (range 0.7–129 months), 10 of 22 patients (45.5%) developed elevated plasma TSH, which was transient in three patients. Free T4 levels were all within the age related normal range. TSH levels in seven patients remained elevated and five of these patients were subsequently prescribed thyroxine.[10]

4. Discussion

It is feasible to obtain a remission rate of 70% or more in advanced neuroblastoma patients with intensive chemotherapy and surgery. However, the relapse rate is still high and the recurrent tumour is usually resistant to chemotherapy. The excellent tumour targeting, rapid clearance by the kidneys and metabolic stability of ^{131}I-MIBG makes it an ideal agent for systemic radiotherapy. The first reports using

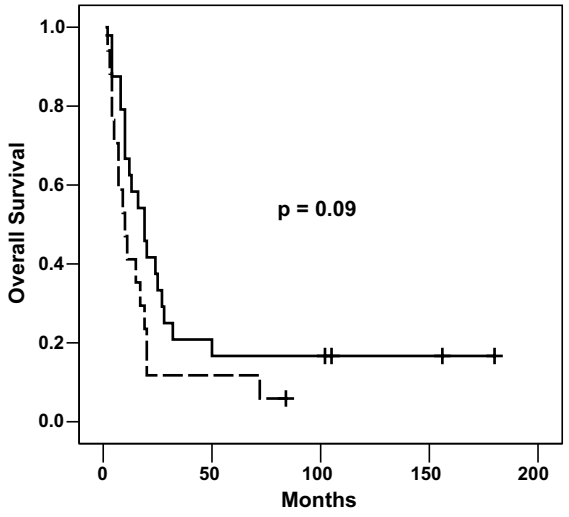

Fig. 3 – Kaplan–Meier curves of overall survival of patients treated with MIBG only (solid line) and MIBG + chemotherapy (dashed line) as pre-operative therapy. No statistical difference was observed using log rank test or Breslow test.

^{131}I-MIBG as a therapeutic agent showed objective response rates in patients with recurrent disease. MIBG-therapy in combination with myeloablative chemotherapy and autologous stem-cell support was shown to be feasible with acceptable toxicity in the treatment of neuroblastoma.[11] The idea of using radionuclide therapy as first line treatment is based on the hypothesis that the radiation dose to the individual cell can also penetrate neighbouring cells within a radius of 800 μm (the crossfire effect). On the basis of our experience in previous patients, we chose for a fixed dose of MIBG, accepting the fact that in a minority of the patients a total body dose of > 2 Gy might appear. At diagnosis, there is a large volume of metabolically viable tumour, and optimal effects can be obtained from the crossfire effect. To compensate for less viable cells at the second infusion which could increase the total body exposure we decreased the dose after the first infusion. We did not measure whole body dose exposure because of lack of evidence for a good correlation between the ^{131}I-MIBG activity administered and the resulting exposure at the beginning of our study. The interval between the MIBG infusions is based on our experience with tumour regrowth and bone marrow recovery in a previous study of recurrent patients. Among the included patients two had multiple primary tumours and three were included in the study at the time of relapse after surgery for a localised tumour, but were actually patients with recurrent disease. Three patients were 11, 13, and 15 years old at diagnosis. Because they all fulfilled the entry criteria, they were consequently included but may have affected the overall outcome. After induction therapy, 65% of the primary tumours were completely resected. Taking into account the small number of patients and the single institution experience, this is comparable with three consecutive Italian studies, using the same definition for a complete resection, and utilising multi-agent chemotherapy for induction with resection rates of 59.0%, 50.8%, and 57.9%.[12] After two infusions of ^{131}I-MIBG, the therapy was switched to chemotherapy if no objective response was documented at the primary site or the metastatic sites. After this switch, nine of 17 patients still failed to become resectable. A high number of patients progressed before (nine) and shortly after surgery (seven). Another seven patients had refractory disease. This is explained by an ineffective chemotherapy. The combination of vincristin, etoposide, carboplatin, and ifosfamide at the dosages used at that time was probably not intense enough to prevent tumour regrowth. As a consequence of early progression only 17/41 patients arrived at a clinical stage where harvest of stem cells was indicated. Since there is evidence that myeloablative therapy improves outcome, the low number of transplanted patients also explains the poor survival and gives cause for concern. After induction chemotherapy, surgery and high dose chemotherapy with autologous stem cell rescue, no additional local treatment was given. Radiotherapy was not considered as evidence for its role in neuroblastoma was established after the design of our study. Among the transplanted patients we observed 4/17 treatment related deaths. In one patient MIBG related myelosuppression is a reasonable explanation. In three other patients who died of septicaemia the role of MIBG is less clear. In the context of the era in which these patients were treated, and the fact that none of these patients had colony stimulating factors after stem cell reinfusion, it is not surprising to find a higher toxic death rate than expected. The small number of patients makes it impossible to find a relation with the number of MIBG courses given and the toxic complications, but in combination with the observed time to engraftment

Table 3 – Characteristics of the patients who died transplant related

Characteristic	Patient number			
	1	2	3	4
Age at Δ (yrs)	16	2.5	3.4	1.2
Bone marrow at Δ	pos	pos	pos	pos
Cumulative dose MIBG (mCi)	800	350	500	500
Yield results cfu-c/10^4/kg	2.9	31.6	12.2	1.23 (CD-34/10^6/kg)
Days between reinfusion and death	43	9	16	8
Cause of death	intra cerebral bleeding	sepsis/streptococ.	sepsis/MOF	overwhelming infection

Abbreviation: MOF, multi organ failure.

for platelets and neutrophils for the whole population there is an issue for limiting the number of MIBG infusions. In our current study with two ^{131}I-MIBG infusions followed by more usual induction chemotherapy, only two out of fourteen patients progressed before ASCT. Ten patients responded well, were successfully harvested, transplanted and are without evidence of disease.

At the start of the treatment myelosuppression was limited to reversible thrombocytopenia in this cohort of patients. This is in contrast to the common observation in patients who had ^{131}I-MIBG therapy after being heavily pre-treated with chemotherapy, surgery, and radiation therapy.[13–15] However, a high cumulative radiation dose in patients with more than two infusions might contribute to a delayed engraftment and toxic deaths. This is probably due to damage to the haematopoietic stem cells and the stroma of the bone marrow caused by the radioisotope. Secondary malignancies, as documented in the literature, were not seen.[16] However, in this population with only five patients surviving for more than 4 years, this finding is questionable.

In conclusion, ^{131}I-MIBG-therapy is effective in newly diagnosed, high risk neuroblastoma patients with a large tumour mass and a high uptake and storage of the radio-pharmaceutical. After an initially favourable response, a further response after two 131I-MIBG infusions does not seem to outweigh the risk for disease progression with the used chemotherapy. Disease progression, refractory disease due to ineffective chemotherapy and bone marrow related toxicity in patients with a high cumulative radiation dose resulted in inferior survival rates. This suggests that MIBG-therapy is mainly effective in the first few weeks of treatment. The optimal response to this single agent therapy appears to occur after two infusions. Further intensive chemotherapy should be implemented on a short term basis to consolidate and improve the response before additional local therapy. These findings have been implemented in our ongoing study.

Conflict of interest statement

None declared.

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