Pediatr Transplantation 2014: 18: 510–517

Pediatric Transplantation
DOI: 10.1111/petr.12271

The potential role of pretransplant MIBG diagnostic scintigraphy in targeted administration of ^{131}I-MIBG accompanied by ASCT for high-risk and relapsed neuroblastoma: A pilot study

Hamidieh AA, Beiki D, Paragomi P, Fallahi B, Behfar M, Fard-Esfahani A, Hosseini AS, Shamshiri A, Eftekhari M, Ghavamzadeh A. The potential role of pretransplant MIBG diagnostic scintigraphy in targeted administration of ^{131}I-MIBG accompanied by ASCT for high-risk and relapsed neuroblastoma: A pilot study.

Abstract: MIBG is an effective component in treatment of neuroblastoma. Furthermore, MIBG scintigraphy is an imaging modality in primary assessments. None of the previous studies have evaluated the role of pretransplant MIBG scintigraphy in decision making for neuroblastoma treatment. We selected therapeutic regimen based on pretransplant ^{131}I-MIBG scintigraphy. Twenty high-risk patients were enrolled. On day −30, patients underwent diagnostic MIBG scintigraphy. Patients were then subdivided into two groups (10 cases in each arm). MIBG-avid subgroup received MIBG (12 mCi/kg), etoposide (1200 mg/m^2), carboplatin (1500 mg/m^2), and melphalan (210 mg/m^2). Non-MIBG-avid subgroup received etoposide (600 mg/m^2), carboplatin (1200 mg/m^2), and melphalan (150 mg/m^2). Patients received CRA after ASCT. Mean age at diagnosis was 42.5 months (range, 17–65) in MIBG-avid and 38.9 months (range, 18–65) in non-MIBG-avid patients. Mean age at diagnosis and transplantation did not reveal significant difference between two subgroups. In MIBG-avid patients, the three-yr OS was 66 ± 21%. In MIBG-non-avid subgroup, the three-yr OS was 53 ± 20%. In MIBG-avid and non-MIBG-avid subgroups, the three-yr EFS were 66 ± 21% and 47 ± 19%, respectively. These findings may suggest an effective role in selecting the therapeutic strategy for pre-ASCT MIBG scintigraphy in high-risk neuroblastoma. MIBG-avid subset may benefit from the combination of therapeutic MIBG and high dose of chemotherapy.

Amir Ali Hamidieh[1], Davood Beiki[2], Pedram Paragomi[1], Babak Fallahi[2], Maryam Behfar[1], Armaghan Fard-Esfahani[2], Ashraf Sadat Hosseini[1], Ahmadreza Shamshiri[1], Mohammad Eftekhari[2] and Ardeshir Ghavamzadeh[1]

[1]Hematology-Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Shariati Hospital, Tehran, Iran, [2]Research Center for Nuclear Medicine, Tehran University of Medical Sciences, Tehran, Iran

Key words: metaiodobenzylguanidine – autologous stem cell transplantation – neuroblastoma – transplant – pediatrics

Amir Ali Hamidieh, Hematology, Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Shariati Hospital, North Kargar Ave., 14114 Tehran, Iran
Tel.: +98 21 84902645
Fax: +98 21 88004140
E-mail: aahamidieh@tums.ac.ir

Accepted for publication 11 March 2014

Neuroblastoma is the most common solid extracranial tumor in children. Majority of patients assign to high-risk or relapsed neuroblastoma with unsatisfactory prognosis. This subset of neuroblastoma still poorly responds to different amalgamated modalities (1, 2).

Neuroblastoma is presumed to originate from neural crest tissue. As a property of sympathetic

Abbreviations: ANC, absolute neutrophil count; ASCT, autologous stem cell transplantation; BMA/B, bone marrow aspiration/biopsy; CRA, 13-cis retinoic acid; CR, complete response; CTCAE, common toxicity terminology criteria for adverse effects; EFS, event-free survival; G-CSF, granulocyte colony-stimulating factor; GFR, glomerular filtration rate; HEPA, high-efficiency particulate air; HORCSCT, Hematology-Oncology Research Center and Stem Cell Transplantation; HVA, homovanillic acid; INSS, International Neuroblastoma Staging System; IRB, institutional review board; MIBG, metaiodobenzylguanidine; OPEC, vincristine, prednisolone, etoposide, chlorambucil; OS, overall survival; PBSC, peripheral blood stem cell; PR, partial response; RCNM, Research Center for Nuclear Medicine; VGPR, very good partial response; VMA, vanillylmandelic acid.

nervous system, neuroblastoma cells express the norepinephrine transporter, which mediates active intracellular uptake of radiolabeled MIBG in about 90% of patients (3, 4). Since early introduction of this radiopharmaceutical in 1981, it has been widely utilized in diagnosis of neural crest tumors. Specifically, MIBG scintigraphy is instrumental in detection of bone and bone marrow involvement (5) and plays invaluable role in staging of patients with neuroblastoma according to INSS (6). Furthermore, Matthay et al. introduced the therapeutic role of MIBG in management of neuroblastoma (7).

The abundance of MIBG-avid subgroup of tumors supports the rationale for implication of ^{131}I-MIBG as a targeted therapeutic agent. A number of studies have underlined therapeutic role of ^{131}I-MIBG monotherapy in children with refractory or relapsed neuroblastoma. PR rates between 30 and 35% have been reported by these studies (8–11). The combination of ^{131}I-MIBG with various therapeutic regimens has led to favorable results. Based on the previous studies, high-dose MIBG therapy may lead to a cure, but it can result in severe adverse effects (12–16). Myelosuppression is considered as the main toxicity caused by therapeutic ^{131}I-MIBG (12). Moreover, the combination of MIBG with high-dose chemotherapy induces non-hematologic toxicities such as oral mucositis, hemorrhage, or hepatic veno-occlusive disease (7). Dubois et al. revealed 36% of neuroblastoma cohort receiving high dosage of ^{131}I-MIBG eventually demanded stem cell support (17).

Therefore, to avoid the long-term myelosuppression specifically in patients receiving higher doses of radiolabeled agents, supportive treatment with autologous hematopoietic stem cells is demanded (12, 18–20). During the last decade, improved outcome in high-risk patients with neuroblastoma was induced by conditioning regimen consisting of myeloablative chemotherapy with or without MIBG therapy prior to ASCT and administration of CRA after ASCT (1, 2, 7, 12, 18, 20–22).

Previously, a number of studies have underlined the significance of MIBG scintigraphy at the time of disease diagnosis, and therapeutic decisions were made mostly based on this early assessment (5, 23, 24). However, in a considerable proportion of patients, MIBG-avid lesions subside after induction therapy. The efficacy of therapeutic MIBG in these patients is questionable. In many countries, especially developing regions of the world due to absence of nuclear medicine facilities (25), MIBG scintigraphy at disease onset might not be available and treatment needs to begin as soon as possible. Thus, a majority of patients with neuroblastoma who are referred for ASCT have received some kind of preliminary treatments, which would potentially lead to negative MIBG scintigraphy results in later course of disease. However, in a number of neuroblastoma cases, MIBG-avid lesions are still present after receiving different modalities such as chemotherapy, surgery, or radiotherapy. A number of studies have revealed these patients with higher pre-ASCT MIBG scores have poorer prognosis and shorter event-free and OS (26, 27). The more complicated course of neuroblastoma in this subgroup supports the rationale for application of intensified chemotherapy regimen along with MIBG-targeted therapy.

In the present study, we applied MIBG scintigraphy immediately before ASCT in high-risk patients with neuroblastoma and used therapeutic strategies based on this imaging. We studied two distinctive therapeutic modalities in MIBG-avid and non-MIBG-avid patients.

Materials and methods

Patients enrollment

This prospective study included high-risk or relapsed patients with neuroblastoma (aged 1–14) who were referred to Hematology-Oncology and Stem Cell Transplantation Research Center from May 2007 to December 2012. The diagnosis of neuroblastoma was made at their original centers where they received initial treatments such as chemotherapy, radiotherapy, or surgery. The preliminary chemotherapy modality applied for all patients was OPEC (vincristine, prednisolone, etoposide, and chlorambucil). All relapsed cases received ICE chemotherapy (ifosfamide, carboplatin, and etoposide). Our study design including chemotherapy regimens was approved by the IRB and Ethical Committee. Patients' parents were required to sign informed consent form prior to enrollment. The study included patients who achieved a good partial remission or favorable status according to standard criteria (6, 28). Furthermore, the patient's bone marrow should be in remission prior to inclusion in the study. Remission was confirmed via bilateral BMA/B two wk prior to PBSC collection. The collection targets for $CD34^+$ cells and MNCs were at least 1×10^6 cell/kg and $2–4 \times 10^8$ cell/kg, respectively. Any remnants of tumor detected in immunocytologic study or BM routine morphology before PBSC collection would lead to exclusion of patients from the study.

To clarify the capacity to radioactive iodine uptake, 30 days before initiation of our treatment protocol, diagnostic ^{131}I-MIBG (37 MBq, 1 mCi) was carried out in all registered patients. All patients were referred for diagnostic ^{131}I-MIBG scintigraphy at the RCNM. Both Hematology-Oncology and Stem Cell Transplantation Research Center and RCNM are located in the same university hospital. According to MIBG scintigraphy results, patients were divided into two subgroups: MIBG-avid and non-MIBG-avid. The latter subgroup of patients received the IRB-approved protocol that was generally applied in our center at the time of study. On the other hand, in MIBG-avid

patients a different protocol consisting higher dose of chemotherapy and MIBG-targeted therapy was applied.

Conditioning regimen in MIBG-avid group

All MIBG-positive patients were required to meet the inclusion criteria in order to pursue the study. Adequate renal function indicated by GFR or 24-h creatinine clearance higher than 60 mL/min per 1.73 m^2 was required. Prior to ^{131}I-MIBG therapy, on day −26, G-CSF was administered with dosage of 5 μg/kg for three consecutive days, and on day −23, the dosage was increased to 10 μg/kg. On day −22, stem cells from peripheral blood were harvested and cryopreserved. Prior to study enrollment, thyroid function was assessed in all patients. In order to protect the patient's thyroid function, Lugol's solution was administered two days before the planned radiopharmaceutical administration and continued for up to 10 days post-therapy. The Foley catheter was fixed to protect the bladder and to avoid staff exposure to radiation emission. The registered patients were then transferred to RCNM, where they received slow infusion of ^{131}I-MIBG (12 mCi/kg) within two h. Patients stayed in the isolation zone for seven days. When the radiation dose fell within standard limits, patients were transferred to pediatric stem cell transplantation unit in HORCSCT. Two wk after ^{131}I-MIBG infusion, on day −7, the myeloablative chemotherapy regimen commenced. The patients received continuous infusion of etoposide 1200 mg/m^2 and carboplatin 1500 mg/m^2 for five days on days −7 to −3. Melphalan was administered via IV bolus on days −7, −6, and −5 with total dosage of 210 mg/m^2. On day 0, PBSCs were infused. From day +1, subcutaneous G-CSF with dosage of 5 μg/kg was started and continued till the ANC count reached higher than 1000/mm^3 for three consecutive days. From day +60, CRA was administered with dosage of 120–160 mg/m^2/day for 14 consecutive days in a 28-day cycle for a period of 12 months.

Conditioning regimen in non-MIBG-avid subgroup

Patients of MIBG-non-avid subgroup received lower chemotherapeutic dose for a shorter duration. On days −8, −7, and −6, G-CSF was administered with dosage of 5 μg/kg. On day −5, the G-CSF dose escalated to 10 μg/kg, and on day −4, stem cells were collected from peripheral blood, while cryopreservation was not performed in this subgroup. Conventional conditioning regimen comprised of carboplatin 1200 mg/m^2 and etoposide 600 mg/m^2 dosed over 72 h on days −3, −2, and −1, and melphalan 150 mg/m^2 was administered on days −2 and −1. Like MIBG-avid patients, on day 0, PBSCs were infused. In addition, G-CSF was administered on day +1 with dosage of 5 μg/kg and continued till ANC count reached 1000/mm^3 for three consecutive days. From day +60, CRA was administered with dosage of 120–160 mg/m^2/day for 14 consecutive days in a 28-day cycle for a period of 12 months.

Post-transplant supportive care

During admission in pediatric transplant unit, each subgroup of patients received similar supportive care. All patients were cared for in identical isolation rooms with HEPA filter. Acyclovir and fluconazole were administered on day −8. Acyclovir dosage switched to oral form on day +10 and continued till day +180, while fluconazole treatment ended on day +58. In order to prevent *Pneumocystis jirovecii* infection, trimethoprim–sulfamethoxazole was administered on day +36 and continued for six months. During admission, all patients were screened for CMV infection twice weekly. This test was based on quantitative CMV/DNA by PCR or CMV PP 65 Ag.

Semiquantitative MIBG scoring

The Curie scoring was carried out in accordance with the method described in literature (26, 29). MIBG positivity was evaluated in 10 anatomic sectors including osteomedullary and extraosseous sites. The observed osteomedullary sites comprised of skull, upper arms, lower arms, chest, upper spine, lower spine, pelvis, upper legs, and lower legs. Based on the number of active sites, each individual sector was scored 0–3. If there was no MIBG-positive lesion in a sector, score zero would be assigned. If one active site presented score 1 and if more than one lesion was detected in each site, score 2 was registered. Score 3 introduced massive involvements (more than 50% of the segment). The cumulative score for each patient was reported as the absolute MIBG score. Two nuclear medicine physicians reviewed MIBG scans collaboratively and processed MIBG scores. If there were three discordant opinions on MIBG scoring, a third nuclear medicine physician was invited to consult for the case.

Follow-up

All patients underwent BMA/B on day +30 in order to assess their bone marrow status. Response to therapy was evaluated by MIBG, CT scan, urine HVA, and VMA every three months in first year, every four months in second year and every six months in third year of follow-up. Response in measurable soft tissue lesions was assessed in accordance with Response Evaluation in Solid Tumors Group criteria (30). Furthermore, in MIBG-avid subgroup, relative MIBG score was calculated as the ratio between MIBG scores on days −30 and +90. According to guidelines for MIBG scoring application, MIBG relative score below 0.5 was indicative of response to treatment (29, 31).

Toxicity evaluation

Non-hematologic toxicities were categorized in accordance with National Cancer Institute Common Toxicity Criteria. CTCAE version 4.0 was applied to address toxicities (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Major categories of adverse events comprised of infection/febrile neutropenia, cardiovascular, hemorrhage, gastrointestinal, pulmonary, hepatic, renal, metabolic, and neurologic adverse events.

Definitions

The high-risk neuroblastoma was defined based on the Children's Oncology Group definition (1). In order to determine EFS and OS, the date of stem cell injection was established as the starting point. EFS was the time span extended to progressive disease, death, or last contact. OS was defined as the time extent between ASCT and death or last recorded follow-up. Patients who were alive and did not experience relapse were censored by the date of last visit. Neutrophil engraftment was set as the first of three consecutive days of an ANC ≥500/μL, and platelet engraftment was assigned as the first of three consecutive days of platelet count ≥20 000/

μL unsupported by platelet transfusion. Response to treatment was classified as previously established in the literature (6, 28).

Statistical analysis

Mann–Whitney *U*-test was applied to compare patients' characteristics and the percentage of toxicities in two subgroups. Kaplan–Meier method was used to analyze OS and EFS in two subsets. When p-Values were <0.05, the results were considered statistically significant. All of the analyses were performed via SPSS software version 19 (SPSS, Chicago, IL, USA).

Results

Patients' characteristics

Of 28 patients with neuroblastoma referred to our center, 20 high-risk cases fulfilled inclusion criteria and were consecutively enrolled in the study. Based on preliminary MIBG investigation on day −30, patients were subdivided into two subgroups of MIBG-avid and non-MIBG-avid, each containing 10 patients.

Mean age at diagnosis was 42.5 ± 17.2 months (range, 17–65) in MIBG-avid subgroup and 38.9 ± 16.5 months (range, 18–65) in non-MIBG-avid patients (p = 0.639). Mean age at transplantation was 60.2 ± 21.3 (range, 34–92) months in MIBG-avid and 56.6 ± 23.9 (range, 24–92) months in non-MIBG-avid patients (p = 0.726).

Patients showed various responses to previous treatments. In MIBG-avid subgroup, eight patients achieved a VGPR, and two patients had a PR to previous treatments. In non-MIBG-avid subgroup, eight patients were in CR and two patients achieved a VGPR. Overall, MIBG-avid subgroup had poorer response to previous treatments.

Rate of N-MYC amplification, bone marrow, and bone metastasis at presentation did not reveal significant difference between MIBG-avid and non-MIBG-avid subgroups. On the contrary, Shimada unfavorable pathology was more frequently detected in MIBG-avid patients (Tables 1 and 2).

Time to engraftment (days after ASCT)

The median time to neutrophil engraftment after ASCT was 10 days (range, 9–13 days) in MIBG-avid and 11 days (range, 9–13 days) in MIBG-non-avid subgroups. The median time to platelet engraftment was 13 days (range: 10–20 days) in MIBG-avid cases and 12 days (range: 9–13 days) in non-MIBG-avid patients. None of the patients studied in both arms failed to engraft after transplant.

Table 1. MIBG-non-avid patients' characteristics

Patient no.	Sex	Age at diagnosis*	Age at transplant*	N-MYC amplification	Shimada classification	Pre-ASCT status	High risk/ relapsed	Time to relapse*	Site of relapse	Patients' previous treatment	Follow-up period*	ASCT response	Status
1	M	40	92	–	Favorable	CR	Relapsed	15	Bone	Chemotherapy	19	MR	Expired
2	M	60	76	–	Unfavorable	VGPR	High risk	–	–	Chemotherapy, surgery	21	NR	Expired
3	F	45	60	+	Favorable	CR	Relapsed	9	Adrenal	Chemotherapy, surgery	50	CR	Alive
4	M	48	84	+	Unfavorable	VGPR	Relapsed	14	Lymph node, Adrenal	Chemotherapy, surgery	3	MR	Expired
5	M	65	72	+	Favorable	CR	High risk	–	–	Chemotherapy, surgery	17	MR	Expired
6	F	20	37	+	Favorable	CR	*De novo*	–	–	Chemotherapy, surgery	31	CR	Alive
7	F	43	53	–	Unfavorable	CR	High risk	–	–	Chemotherapy	9	MR	Expired
8	F	28	37	+	Favorable	CR	High risk	–	–	Chemotherapy, surgery	23	CR	Alive
9	M	18	24	+	Favorable	CR	Relapsed	5	Bone	Chemotherapy	7	CR	Alive
10	M	22	31	+	Favorable	CR	High risk	–	–	Chemotherapy, surgery	7	CR	Alive

M, male; F, female; MR, mixed response; NR, no response.
*Follow-up period, time to relapse, and age at diagnosis and transplantation are reported in months.

Table 2. MIBG-avid patients' characteristics

Patient No.	Sex	Age at diagnosis*	Age at transplant*	N-MYC amplification	Shimada classification	Pre-ASCT MIBG score	Post-ASCT MIBG score	Pre-ASCT status	High risk/ relapsed	Time to relapse*	Site of relapse	Patients' previous treatment	Follow-up period*	ASCT response	Status
1	M	56	77	–	Unfavorable	12	0	VGPR	Relapsed	8	Bone	Chemotherapy	13	PR	Expired
2	F	17	34	+	Unfavorable	4	0	VGPR	Relapsed	10	Liver	Chemotherapy, surgery	40	CR	Alive
3	F	65	88	–	Unfavorable	4	0	VGPR	Relapsed	7	Paraspinal ganglion	Chemotherapy	38	CR	Alive
4	M	31	43	+	Unfavorable	4	0	VGPR	Relapsed	6	Bone	Chemotherapy, surgery	7	NR	Expired
5	M	60	92	+	Favorable	4	2	VGPR	Relapsed	13	Adrenal, Bone	Chemotherapy, surgery	16	VGPR	Alive
6	F	31	48	+	Unfavorable	2	0	VGPR	High risk	–	–	Chemotherapy, surgery	13	CR	Alive
7	F	48	61	+	Unfavorable	4	0	PR	Relapsed	7	Bone	Chemotherapy	10	CR	Alive
8	F	25	43	+	Unfavorable	6	0	VGPR	High risk	–	–	Chemotherapy	8	CR	Alive
9	F	60	75	+	Unfavorable	2	0	VGPR	Relapsed	13	Adrenal	Chemotherapy, radiotherapy	9	CR	Alive
10	M	32	41	–	Unfavorable	4	2	PR	High risk	–	–	Chemotherapy, radiotherapy	3	CR	Alive

M, male; F, female; MR, mixed response; NR, no response.
*follow-up period, time to relapse, age at diagnosis and transplantation are reported in months.

Non-hematologic toxicity

The most common non-hematologic toxicity was GI adverse reactions, mostly due to oral mucositis. All 20 patients developed oral mucositis. However, MIBG-avid cases tended to develop more severe oral mucositis (five patients had grade 3, and five cases had grade 4 mucositis). Non-MIBG-avid patients all had oral mucositis of grade 1 or 2. All detected grade 3 and 4 non-hematologic toxicities are tabulated in Table 3.

MIBG scores in MIBG-avid patients

In MIBG-avid subgroup, the median Curie score on day −30 was four (range, 2–12), while median Curie score on day +90 was 0 (range, 0–2). On post-transplant day 90, only two patients had MIBG-avid foci. All reported MIBG-avid sites were correlated with CT scan findings.

OS and EFS

The three-yr-event-free survival (three-yr EFS) of all 20 patients was 55 ± 14%, and the three-yr overall survival (three-yr OS) was 59 ± 15%. During follow-up period, seven patients (35%) experienced relapse. The relapsed cases included two MIBG-avid (20%) and five non-MIBG-avid (50%) patients. The mean time to disease progression was 5.5 ± 2.1 months in MIBG-avid subgroup (median: five and a half months) and 7.4 ± 3.4 months in non-MIBG-avid subgroup (median: nine months). None of the variables including gender, N-MYC amplification, pre-ASCT MIBG scores, and Shimada classification had significantly influenced EFS or OS (Table 4).

In MIBG-avid and non-MIBG-avid subgroups, the three-yr EFS was 66 ± 21% and 47 ± 19%, respectively (log-rank p = 0.650). In MIBG-avid patients, the three-yr OS was 66 ± 21%, while in non-MIBG-avid subgroup, the three-yr OS was 53 ± 20% (log-rank p = 0.972) (Figs. 1 and 2).

Table 3. Grade 3–4 non-hematologic toxicities

Non-hematologic toxicity	MIBG-avid n (%)	MIBG-non-avid n (%)	p-Value
Constitutional symptoms/pain	1 (10)	2 (20)	0.531
Infection/febrile neutropenia	4 (40)	2 (20)	0.639
Renal/genitourinary	1 (10)	0	0.305
Gastrointestinal	10 (100)	10 (100)	0.068
Hemorrhage	1 (10)	2 (20)	0.531
Skin	0	2 (20)	0.305

Table 4. Influence of different features on three-yr OS and three-yr EFS

Variable	Odds ratio	95% CI	p-Value
Overall survival			
Gender	6.35	0.95–149.72	0.055
Age at diagnosis	1.08	0.89–1.14	0.90
Age at transplant	0.97	0.88–1.00	0.065
Diagnosis to transplant interval	0.83	0.78–1.01	0.84
Pre-ASCT MIBG score	1.13	0.80–1.32	0.889
Shimada classification	4.22	0.001–9.575	0.33
N-MYC amplification	3.80	0.38–14.84	0.36
Event-free survival			
Gender	5.65	0.68–102.03	0.08
Age at diagnosis	1.91	0.71–1.06	0.82
Age at transplant	0.83	0.83–0.98	0.09
Diagnosis to transplant interval	0.93	0.73–1.09	0.93
Pre-ASCT MIBG	1.73	0.82–1.36	0.70
Shimada classification	5.52	0.02–8.32	0.39
N-MYC amplification	3.24	0.62–17.65	0.49

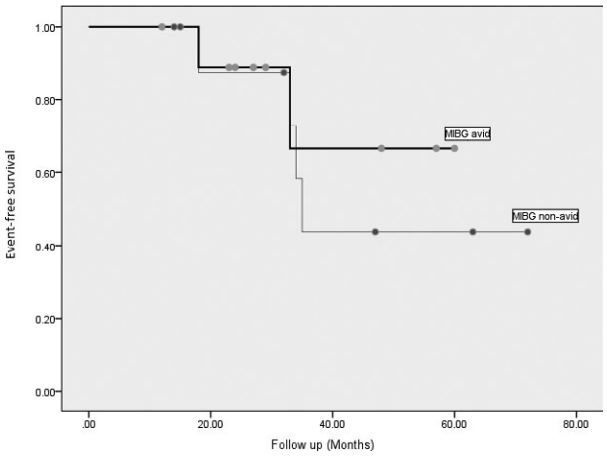

Fig. 1. Three-yr event-free survival (three-yr EFS).

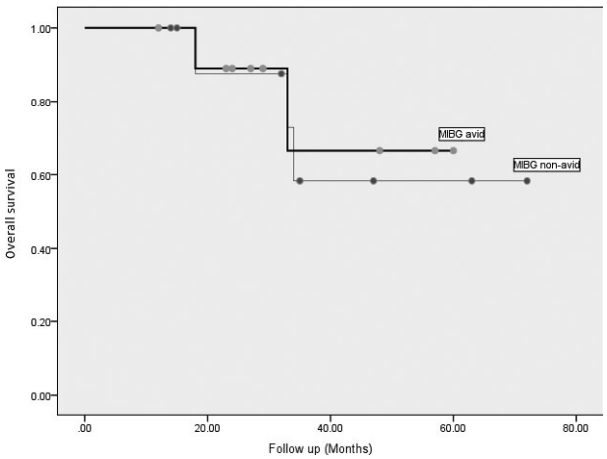

Fig. 2. Three-yr overall survival (three-yr OS).

Discussion

The poor prognosis of high-risk patients with neuroblastoma supports the rationale for implementing multimodality treatment (7). During the recent two decades, the application of ASCT has emerged as a consistent part of treatment in high-risk or relapsed neuroblastoma (1, 21, 32–34). While ASCT improved the outcome, more scrutinized studies recommended the combination of ASCT with other modalities including MIBG therapy in order to reach optimum outcome (12, 13, 21, 35).

Also, MIBG scan is considered a decisive tool in evaluation of tumor extent and response to treatments. Previous studies have mainly decided their therapeutic plan based on MIBG scintigraphy results at the presentation of disease (36). In approximately 90% of neuroblastoma cases, MIBG-avid lesions are detectable at the time of diagnosis (29). However, in a considerable proportion of patients with neuroblastoma, MIBG-avid lesions subside after induction therapy. Thus, administration of therapeutic MIBG may not play the beneficial role in cases with MIBG-non-avid pre-ASCT scintigraphy.

Semiquantitative scoring system has been applied to assess MBG-avid lesions at different phases of disease including post-induction tumors (29, 31, 37). Previous studies have outlined controversial results about the advantage of pre-ASCT MIBG scintigraphy scoring in decision making for treatment of neuroblastoma (38, 39). A body of evidence has outlined the correlation between pre-ASCTMIBG and prognosis of disease (39, 40). Post-induction MIBG-avid lesions indicate more aggressive behavior of neuroblastoma. Yanik et al. have unraveled the correlation between post-induction Curie score >2 and extremely poor prognosis of neuroblastoma (26). Furthermore, this study has suggested these poor prognosis patients are candidates for alternative therapeutic regimens (26).

Due to poor prognostic profile, we applied a more intensified chemotherapy regimen coupled with MIBG-targeted therapy in patients who had MIBG-avid lesions in pre-ASCT scans. Meanwhile, in order to avoid side effects of therapeutic MIBG or high-dose chemotherapy, non-MIBG-avid subgroup received conventional chemotherapy regimen without MIBG-targeted therapy.

In the current pilot study, we applied pre-ASCT MIBG scintigraphy to stratify high-risk or relapsed patients with neuroblastoma into an intensive vs. less intensive conditioning regimen. To our knowledge, none of the previous studies

have exclusively addressed the neuroblastoma patients with negative MIBG scintigraphy immediately prior to ASCT. The treatment protocol applied in non-MIBG-avid subgroup has some key advantages such as shorter time frame, lower dose of chemotherapy, independence of nuclear medicine facility, and cryopreservation process. Furthermore, serious side effects of MIBG therapy such as bone marrow suppression (41, 42) are avoided in this trend.

On the other hand, in MIBG-avid subgroup, which demonstrated resistance to previous treatments and featured poor prognosis, our applied therapeutic modality led to acceptable outcome (three-yr EFS of 66 ± 21% and three-yr OS was 66 ± 21%).

The results of the present study may underline the significance of pre-ASCT MIBG scintigraphy in stratification of high-risk patients with neuroblastoma. Pre-ASCT MIBG scintigraphy may lead to optimized decision making in conditioning regimen of patients with neuroblastoma. The applied strategy demanded higher dose of chemotherapy in MIBG-avid patients, while MIBG-non-avid subgroup underwent conventional chemotherapy regimen. Our findings may suggest that therapeutic MIBG administration might be unnecessary in non-MIBG-avid subgroup of neuroblastoma. However, larger randomized studies are warranted to confirm the advantage of applied approach in our study.

Acknowledgments

The authors thank children, parents, and nursing staff who participated in this study. The authors also thank Nooshin Naeimi for editing the English manuscript.

References

1. Matthay KK, Villablanca JG, Seeger RC, et al. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. Children's Cancer Group. N Engl J Med 1999: 341: 1165–1173.
2. Matthay KK, Reynolds CP, Seeger RC, et al. Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: A Children's Oncology Group study. J Clin Oncol 2009: 27: 1007–1013.
3. Carlin S, Mairs RJ, McCluskey AG, et al. Development of a real-time polymerase chain reaction assay for prediction of the uptake of meta-[(131)I]iodobenzylguanidine by neuroblastoma tumors. Clin Cancer Res 2003: 9: 3338–3344.
4. Treuner J, Feine U, Niethammer D, et al. Scintigraphic imaging of neuroblastoma with [131-I]iodobenzylguanidine. Lancet 1984: 1: 333–334.
5. Howman-Giles R, Shaw PJ, Uren RF, Chung DK. Neuroblastoma and other neuroendocrine tumors. Semin Nucl Med 2007: 37: 286–302.
6. Brodeur GM, Pritchard J, Berthold F, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. J Clin Oncol 1993: 11: 1466–1477.
7. Matthay KK, Tan JC, Villablanca JG, et al. Phase I dose escalation of iodine-131-metaiodobenzylguanidine with myeloablative chemotherapy and autologous stem-cell transplantation in refractory neuroblastoma: A new approaches to Neuroblastoma Therapy Consortium Study. J Clin Oncol 2006: 24: 500–506.
8. Castellani MR, Chiti A, Seregni E, Bombardieri E. Role of ^{131}I-metaiodobenzylguanidine (MIBG) in the treatment of neuroendocrine tumours. Experience of the National Cancer Institute of Milan. Q J Nucl Med 2000: 44: 77–87.
9. Kang TI, Brophy P, Hickeson M, et al. Targeted radiotherapy with submyeloablative doses of ^{131}I-MIBG is effective for disease palliation in highly refractory neuroblastoma. J Pediatr Hematol Oncol 2003: 25: 769–773.
10. Garaventa A, Bellagamba O, Lo Piccolo MS, et al. ^{131}I-metaiodobenzylguanidine (131I-MIBG) therapy for residual neuroblastoma: A mono-institutional experience with 43 patients. Br J Cancer 1999: 81: 1378–1384.
11. Garaventa A, Guerra P, Arrighini A, et al. Treatment of advanced neuroblastoma with I-131 meta-iodobenzylguanidine. Cancer 1991: 67: 922–928.
12. Matthay KK, Yanik G, Messina J, et al. Phase II study on the effect of disease sites, age, and prior therapy on response to iodine-131-metaiodobenzylguanidine therapy in refractory neuroblastoma. J Clin Oncol 2007: 25: 1054–1060.
13. Matthay KK, Panina C, Huberty J, et al. Correlation of tumor and whole-body dosimetry with tumor response and toxicity in refractory neuroblastoma treated with (131)I-MIBG. J Nucl Med 2001: 42: 1713–1721.
14. Modak S, Pandit-Taskar N, Kushner BH, et al. Transient sialoadenitis: A complication of ^{131}I-metaiodobenzylguanidine therapy. Pediatr Blood Cancer 2008: 50: 1271–1273.
15. Weiss B, Vora A, Huberty J, Hawkins RA, Matthay KK. Secondary myelodysplastic syndrome and leukemia following ^{131}I-metaiodobenzylguanidine therapy for relapsed neuroblastoma. J Pediatr Hematol Oncol 2003: 25: 543–547.
16. Garaventa A, Gambini C, Villavecchia G, et al. Second malignancies in children with neuroblastoma after combined treatment with ^{131}I-metaiodobenzylguanidine. Cancer 2003: 97: 1332–1338.
17. DuBois SG, Messina J, Maris JM, et al. Hematologic toxicity of high-dose iodine-131-metaiodobenzylguanidine therapy for advanced neuroblastoma. J Clin Oncol 2004: 22: 2452–2460.
18. Matthay KK, DeSantes K, Hasegawa B, et al. Phase I dose escalation of ^{131}I-metaiodobenzylguanidine with autologous bone marrow support in refractory neuroblastoma. J Clin Oncol 1998: 16: 229–236.
19. Voute PA, Hoefnagel CA, de Kraker J, Valdes Olmos R, Bakker DJ, van de Kleij AJ. Results of treatment with 131 I-metaiodobenzylguanidine (131 I-MIBG) in patients with neuroblastoma. Future prospects of zetotherapy. Prog Clin Biol Res 1991: 366: 439–445.
20. Goldberg SS, DeSantes K, Huberty JP, et al. Engraftment after myeloablative doses of ^{131}I-metaiodobenzylguanidine followed by autologous bone marrow transplantation for treatment of refractory neuroblastoma. Med Pediatr Oncol 1998: 30: 339–346.
21. Yanik GA, Levine JE, Matthay KK, et al. Pilot study of iodine-131-metaiodobenzylguanidine in combination with myeloablative chemotherapy and autologous stem-cell support for the treatment of neuroblastoma. J Clin Oncol 2002: 20: 2142–2149.
22. Schmidt M, Simon T, Hero B, et al. Is there a benefit of 131 I-MIBG therapy in the treatment of children with stage 4

neuroblastoma? A retrospective evaluation of The German Neuroblastoma Trial NB97 and implications for The German Neuroblastoma Trial NB2004. Nuklearmedizin 2006: 45: 145–151; quiz N39-40.
23. Kushner BH. Neuroblastoma: A disease requiring a multitude of imaging studies. J Nucl Med 2004: 45: 1172–1188.
24. Boubaker A, Bischof Delaloye A. MIBG scintigraphy for the diagnosis and follow-up of children with neuroblastoma. Q J Nucl Med Mol Imaging 2008: 52: 388–402.
25. Dondi M, Kashyap R, Paez D, et al. Trends in nuclear medicine in developing countries. J Nucl Med 2011: 52(Suppl 2): 16S–23S.
26. Yanik GA, Parisi MT, Shulkin BL, et al. Semiquantitative mIBG scoring as a prognostic indicator in patients with stage 4 neuroblastoma: A report from the Children's Oncology Group. J Nucl Med 2013: 54: 541–548.
27. Ladenstein R, Philip T, Lasset C, et al. Multivariate analysis of risk factors in stage 4 neuroblastoma patients over the age of one year treated with megatherapy and stem-cell transplantation: A report from the European Bone Marrow Transplantation Solid Tumor Registry. J Clin Oncol 1998: 16: 953–965.
28. Pizzo P, Poplack D. Principles and Practice of Pediatric Oncology, 4th edn. Philadelphia: Lippincott Williams & Wilkins, 2002.
29. Matthay KK, Edeline V, Lumbroso J, et al. Correlation of early metastatic response by ^{123}I-metaiodobenzylguanidine scintigraphy with overall response and event-free survival in stage IV neuroblastoma. J Clin Oncol 2003: 21: 2486–2491.
30. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000: 92: 205–216.
31. Ady N, Zucker JM, Asselain B, et al. A new ^{123}I-MIBG whole body scan scoring method–application to the prediction of the response of metastases to induction chemotherapy in stage IV neuroblastoma. Eur J Cancer 1995: 31A: 256–261.
32. Grupp SA, Stern JW, Bunin N, et al. Tandem high-dose therapy in rapid sequence for children with high-risk neuroblastoma. J Clin Oncol 2000: 18: 2567–2575.
33. Philip T, Ladenstein R, Lasset C, et al. 1070 myeloablative megatherapy procedures followed by stem cell rescue for neuroblastoma: 17 years of European experience and conclusions. European Group for Blood and Marrow Transplant Registry Solid Tumour Working Party. Eur J Cancer 1997: 33: 2130–2135.
34. Kletzel M, Katzenstein HM, Haut PR, et al. Treatment of high-risk neuroblastoma with triple-tandem high-dose therapy and stem-cell rescue: Results of the Chicago Pilot II Study. J Clin Oncol 2002: 20: 2284–2292.
35. de Kraker J, Hoefnagel KA, Verschuur AC, van Eck B, van Santen HM, Caron HN. Iodine-131-metaiodobenzylguanidine as initial induction therapy in stage 4 neuroblastoma patients over 1 year of age. Eur J Cancer 2008: 44: 551–556.
36. Suc A, Lumbroso J, Rubie H, et al. Metastatic neuroblastoma in children older than one year: Prognostic significance of the initial metaiodobenzylguanidine scan and proposal for a scoring system. Cancer 1996: 77: 805–811.
37. Messina JA, Cheng SC, Franc BL, et al. Evaluation of semiquantitative scoring system for metaiodobenzylguanidine (mIBG) scans in patients with relapsed neuroblastoma. Pediatr Blood Cancer 2006: 47: 865–874.
38. Englaro EE, Gelfand MJ, Harris RE, Smith HS. I-131 MIBG imaging after bone marrow transplantation for neuroblastoma. Radiology 1992: 182: 515–520.
39. Grupp SA, Asgharzadeh S, Yanik GA. Neuroblastoma: Issues in transplantation. Biol Blood Marrow Transplant 2012: 18(1 Suppl): S92–S100.
40. Katzenstein HM, Cohn SL, Shore RM, et al. Scintigraphic response by ^{123}I-metaiodobenzylguanidine scan correlates with event-free survival in high-risk neuroblastoma. J Clin Oncol 2004: 22: 3909–3915.
41. Hutchinson RJ, Sisson JC, Miser JS, et al. Long-term results of [131I]metaiodobenzylguanidine treatment of refractory advanced neuroblastoma. J Nucl Biol Med 1991: 35: 237–240.
42. Hutchinson RJ, Sisson JC, Shapiro B, et al. 131-I-metaiodobenzylguanidine treatment in patients with refractory advanced neuroblastoma. Am J Clin Oncol 1992: 15: 226–232.