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Upfront consolidation treatment with ^{131}I-mIBG followed by myeloablative chemotherapy and hematopoietic stem cell transplantation in high-risk neuroblastoma

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ABSTRACT

Importance: ^{131}I-metaiodobenzylguanidine (^{131}I-mIBG) has a significant targeted antitumor effect for neuroblastoma. However, currently there is a paucity of data for the use of ^{131}I-mIBG as a "front-line" therapeutic agent in those patients with newly diagnosed high-risk neuroblastoma as part of the conditioning regimen for myeloablative chemotherapy (MAC).

Objective: To evaluate the feasibility of upfront consolidation treatment with ^{131}I-mIBG plus MAC and hematopoietic stem cell transplantation (HSCT) in high-risk neuroblastoma patients.

Methods: A retrospective, single-center study was conducted from 2003–2019 on newly diagnosed high-risk neuroblastoma patients without progressive disease (PD) after the completion of induction therapy. They received ^{131}I-mIBG infusion and MAC followed by HSCT.

Results: A total of 24 high-risk neuroblastoma patients were enrolled with a median age of 3.0 years at diagnosis. After receiving this sequential consolidation treatment, 3 of 13 patients who were in partial response (PR) before ^{131}I-mIBG treatment achieved either complete response (CR) (n = 1) or very good partial response (VGPR) (n = 2) after HSCT. With a median follow-up duration of 13.0 months after ^{131}I-mIBG therapy, the 5-year event-free survival and overall survival rates estimated were 29% and 38% for the entire cohort, and 53% and 67% for the patients who were in CR/VGPR at the time of ^{131}I-mIBG treatment.

Interpretation: Upfront consolidation treatment with ^{131}I-mIBG plus MAC and HSCT is feasible and tolerable in high-risk neuroblastoma patients, however the survival benefit of this ^{131}I-mIBG regimen is only observed in the patients who were in CR/VGPR at the time of ^{131}I-mIBG treatment.

KEYWORDS
Neuroblastoma, ^{131}I-mIBG, Transplantation

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INTRODUCTION

Neuroblastoma, a tumor derived from neural crest progenitor cells, is the most common extracranial solid tumor of childhood.[1] Despite the use of an intensive multimodal approach, combining induction with multi-agent chemotherapy and surgical resection of primary disease, consolidation with radiation therapy, and myeloablative chemotherapy (MAC) followed by autologous hematopoietic stem cell transplant (auto-HSCT), maintenance with isotretinoin and immunotherapy using a tumor-specific anti-disialoganglioside (GD2) antibody, about 50%–60% 5-year event-free survival (EFS) rates are reported for high-risk neuroblastoma patients.[2-6] In addition, while many patients have good initial tumor response to intensive induction, still 15%–20% develop refractory and early progressive disease (PD).[7-10] Further dose escalation of induction chemotherapy and MAC consolidation followed by auto-HSCT will be limited by toxicity, especially cumulative visceral toxic effects of alkylating drugs.[11] Therefore, it is important to evaluate the efficacy and toxicity of the addition of new tumor-targeted or non-cross-resistant agents to multimodal treatment for high-risk neuroblastoma.

Metaiodobenzylguanidine (mIBG) is an analogue of norepinephrine, with specific affinity for neural crest cells.[12] Iodine-131 labeled mIBG (^{131}I-mIBG) has been proven to be effective for targeted therapy of neuroblastoma in both newly diagnosed patients and in patients who experienced relapse.[13-15] In the upfront treatment of high-risk neuroblastoma, ^{131}I-mIBG therapy has produced a 66% objective response rate and a mild toxicity profile.[16,17] Different therapeutic protocols, including ^{131}I-mIBG, in the treatment for patients with relapsed or refractory neuroblastomas have been reported. These range from ^{131}I-mIBG monotherapy,[18] to the combination with other treatments such as chemotherapy,[19] HSCT with and without MAC of carboplatin, etoposide, and melphalan (CEM),[20] and various radiosensitizers.[21-23] However, currently there is a paucity of data for the use of ^{131}I-mIBG as a "front-line" therapeutic agent in those patients with newly diagnosed high-risk neuroblastoma as part of the conditioning regimen for MAC. Over the past 16 years, in Prince of Wales Hospital in Hong Kong, upfront consolidation treatment with ^{131}I-mIBG plus MAC and HSCT has been used for treatment of high-risk neuroblastoma patients without PD after the completion of induction therapy. Here we present an analysis of 24 consecutively treated high-risk neuroblastoma patients to investigate the feasibility of this sequential consolidation treatment.

METHODS

Ethical approval

The study was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee. Written informed consent was obtained from parents or legal guardians.

Patients

We performed a retrospective single-center analysis of pilot cohort (2003–2019), including consecutive newly diagnosed pediatric patients with International Neuroblastoma Staging System (INSS) stage 4 neuroblastoma (≥ 18 months at diagnosis) or *MYCN*-amplified neuroblastoma regardless of stage. All patients must have completed intensive induction chemotherapy based on N7 protocol[24] or rapid COJEC protocol,[25] and met the International Neuroblastoma Response Criteria (INRC) for complete response (CR), very good partial response (VGPR), partial response (PR) or minor response (MR) before the ^{131}I-mIBG therapy at study entry. Patients were excluded from ^{131}I-mIBG therapy if ^{131}I-mIBG uptake at diagnosis was negative. Prior mIBG therapy and prior total-body radiation (TBI) were also excluded.

After induction chemotherapy and surgical resection, autologous stem cell harvest was performed in patients without gross residual disease. Patients were primed with 16 $\mu g \cdot kg^{-1} \cdot d^{-1}$ granulocyte colony-stimulating factor (G-CSF) for 3–4 days before the harvest. The targeted number of $CD34^+$ cells was 2×10^6/kg.

Patients received high-activity (12 mCi/kg) ^{131}I-mIBG infusion before MAC which was supported by hematopoietic stem cell transplantation (HSCT). The following laboratory values were required in all patients at the time of ^{131}I-mIBG treatment: absolute neutrophil count (ANC) $\geq 0.5 \times 10^9$/L, platelets $\geq 20 \times 10^9$/L, glomerular filtration rate (GFR) or creatinine clearance of > 60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ and bilirubin less than 2 times upper limit of normal, alanine aminotransferase (ALT) less than 10 times upper limit of normal, and no evidence of clinically significant cardiac dysfunction.

Therapy procedure

Patients were nursed in a radiation-protected isolation room and then received an intravenous infusion of ^{131}I-mIBG over 2 hours with hydration, thyroid protection with potassium iodide and potassium perchlorate, and a Foley catheter for bladder protection. Patients remained in the isolation room until radiation emissions met institutional regulations,[26] typically 3 to 7 days after ^{131}I-mIBG infusion. Subsequently, MAC followed by hematopoietic stem-cell rescue was delivered within 1 month after ^{131}I-mIBG administrations. Before year 2012, all patients received CEM MAC regimen (carboplatin 300 $mg \cdot m^{-2} \cdot d^{-1}$ on days −6 to −3; etoposide 160 $mg \cdot m^{-2} \cdot d^{-1}$ on days −6 to −3; melphalan 140 $mg \cdot m^{-2} \cdot d^{-1}$ on day −5 and 70 $mg \cdot m^{-2} \cdot d^{-1}$ on day −4) with the exception of 1 patient who received melphalan only (140 mg/m^2 as a

bolus dose on day −1). After release of results of the HR-NBL1/SIOPEN trial showing improved EFS using a BuMel MAC regimen compared with a CEM regimen for newly diagnosed neuroblastoma,[27] BuMel MAC regimen (intravenous busulfan, 0.8–1.2 mg/kg per dose for 16 doses over 5 days with dose adjustment according to busulphan plasma level; melphalan, 4 mg/kg as a bolus dose on day −1) was adopted for all patients since year 2012, with the exception of 1 patient received CEM regimen.

Stem cells were infused 24 hours after the completion of BuMel or melphalan regimen, or 72 hours after the completion of CEM regimen. Patients received G-CSF from day 5 post-HSCT until neutrophil engraftment. All patients also received ursodiol for hepatic veno-occlusive disease (VOD) prophylaxis for BuMel regimen. Empiric antibiotic treatment was initiated as soon as fever occurred. After HSCT, patients received further treatment with isotretinoin (160 $mg \cdot m^{-2} \cdot d^{-1}$ administered for 2 weeks on and 2 weeks off) +/− anti-GD2 antibody (8 courses [6 before HSCT and 2 after megatherapy] of murine IgG3 anti-GD2 antibody m3F8 [10 $mg \cdot m^{-2} \cdot d^{-1}$] for 5 consecutive days every 4 weeks, or 5 courses of dinutuximab [20 $mg \cdot m^{-2} \cdot d^{-1}$] for 5 consecutive days every 4 weeks at around 3 months after HSCT). Cytokines (granulocyte-macrophage colony-stimulating factor [GM-CSF] and/or interleukin-2) were not administered during the anti-GD2 antibody treatment.

Before year 2014, external-beam radiotherapy to primary tumor site was given at 1 month before HSCT. In order to reduce the treatment-related hepatotoxicity due to the short interval between the administration of external-beam radiotherapy and ^{131}I-mIBG therapy, external-beam radiotherapy to primary tumor site was later changed to be given at around 6 weeks after HSCT. The dose of radiation administered was 21 Gy in 14 fractions.

Toxicity and response evaluation

Neutrophil recovery was defined as the first of three consecutive days of an ANC > 0.5×10^9/L, and platelet recovery was defined as the first day of seven consecutive days of a platelet count > 20×10^9/L independent of platelet transfusion support. Hematological and nonhematological toxicity were graded according to National Cancer Institute Common Toxicity Criteria, version 4.0.

Responses were determined by ^{131}I-mIBG scintigraphy, CT scans, and bone marrow aspirate and trephine biopsy pre-mIBG therapy, at 1–3 months after HSCT, and subsequently every 6–12 months up to 3 years. The ^{131}I-mIBG scans were reviewed by blinded radiologists and qualitatively analyzed. Response of soft tissue lesions was evaluated according to Response Evaluation Criteria in Solid Tumors, if a measurable lesion was present on CT. Overall, response for all patients was defined using response criteria developed by the International Neuroblastoma Response Criteria group.

Statistical analysis

Categorical variables were compared with Fisher's exact test or chi-square test. The Wilcoxon rank-sum test was used to compare continuous variables. A two-tailed *P*-value of < 0.05 was considered statistically significant. However, since this was not a randomized study, all comparisons should be considered with caution. EFS was defined as the time from the initiation of ^{131}I-mIBG therapy to the date of first event (progression, relapse or death). Overall survival (OS) was measured from the initiation of ^{131}I-mIBG therapy to the date of death by any cause or the last follow-up. The probabilities of EFS and OS were calculated using the Kaplan-Meier method and compared using the log-rank test. All statistical analyses were performed using the Stata version 12 software (StataCorp LP, College Station, TX, USA).

RESULTS

Patients

A total of 24 patients with newly diagnosed high-risk neuroblastoma were enrolled between August 2003 and April 2019; including 20 (83.3%) patients aged 18 months or order with stage 4 neuroblastoma and 4 (16.7%) patients younger than 18 months with *MYCN*-amplified neuroblastoma (Table 1). In all patients ^{131}I-mIBG was administered after intensive induction chemotherapy with curative intent. For the entire study population, the median age at diagnosis was 3.0 years (range, 0.8 to 15.4 years), with patients treated a median of 7.5 months from initial diagnosis. The majority of patients (n = 16; 66.7%) received only 1 line of chemotherapy. Eight patients who did not achieve treatment response to the first-line chemotherapy were given the second- or third-line chemotherapy (topotecan, temozolamide and irinotecan) to achieve better remission before ^{131}I-mIBG therapy. Nine (37.5%) patients exhibited CR (n = 6; 25.0%) or VGPR (n = 3; 12.5%) at study entry, whereas 15 (62.5%) patients exhibited PR (n = 14; 58.3%) or MR (n = 1; 4.2%). The median time between the end of induction therapy and start of ^{131}I-mIBG therapy was 3.9 (range 0.6–15.2) months. Twenty-three (95.8%) patients underwent autologous peripheral blood stem cell transplantation (PBSCT) after MAC, while one (4.2%) patient failed stem cell mobilization and received HLA-identical sibling allogeneic PBSCT. Overall response was evaluated a median of 3.0 months post-HSCT (range, 0.9 to 6.2 months). Post-HSCT maintenance therapy consisted of retinoids in 23 (95.8%) patients; 17 (70.8%) concurrently with anti-GD2 immunotherapy (including 3F8 in 10 [41.7%] patients, and dinutuximab in 7 [29.2%] patients). One (4.2%) patient could not receive maintenance treatment due to severe VOD occurred post HSCT and the patient died of VOD at 5.5 months after HSCT.

TABLE 1 Demographic and clinical characteristics of patients with neuroblastoma

Variables	CR/VGPR group (n = 9)	PR/MR group (n = 15)	P
Age at diagnosis (years)	2.6 (1.3–15.4)	3.2 (0.8–10.6)	0.65
Gender			
Boy	4 (44.4)	10 (66.7)	0.29
Girl	5 (55.6)	5 (33.3)	
Primary tumor			
Abdominal	7 (77.8)	12 (80.0)	0.90
Thoracic	2 (22.2)	3 (20.0)	
Metastases			
Bone marrow	7 (77.8)	15 (100)	0.06
Bone	7 (77.8)	13 (86.7)	0.57
MYCN status			
Amplified	5 (55.6)	3 (20.0)	0.20
Non-amplified	2 (22.2)	7 (46.7)	
Unknown	2 (22.2)	5 (33.3)	
No. of prior regimens			
One	6 (66.7)	10 (66.7)	0.24
Two	3 (33.3)	2 (13.3)	
Three	0	3 (20.0)	
Extent of resection of the primary			
Complete	4 (44.4)	10 (66.7)	0.31
Partial	5 (55.6)	4 (26.7)	
Unresectable	0	1 (6.7)	
Prior external-beam radiotherapy to the primary tumor bed	7 (77.8)	8 (53.3)	0.23
Pre-^{131}I-mIBG disease status			
CR	6 (66.7)	0	<0.01
VGPR	3 (33.3)	0	
PR	0	14 (93.3)	
MR	0	1 (6.7)	
^{131}I-mIBG (mCi/kg)	11.9 (5.8–12.8)	12 (9.8–12.9)	0.40
Myeloablative regimen			
CEM	5 (55.6)	6 (40.0)	0.61
BuMel	4 (44.4)	8 (53.3)	
Melphalan	0	1 (6.7)	
Post-HSCT maintenance†			
Retinoids + anti-GD2 therapy	6 (66.7)	11 (73.3)	0.53
Retinoids, no anti-GD2 therapy	3 (33.3)	3 (20.0)	

Data were shown as n (%) or median (range). †One patient interrupted maintenance treatment due to severe hepatic veno-occlusive disease occurred post-transplant. ^{131}I-mIBG,^{131}I-metaiodobenzylguanidine; CR, complete response; VGPR, very good partial response; PR, partial response; MR, minor response; CEM, carboplatin, etoposide, and melphalan; BuMel, busulfan and melphalan; HSCT, hematopoietic stem cell transplant.

Response

Twenty-three of 24 patients were evaluable for primary response assessment. One patient died from VOD before post-HSCT response assessment. Among 6 patients with CR at the time of ^{131}I-mIBG treatment, 5 maintained stable CR post-HSCT, while 1 developed PD. Among 3 patients with VGPR at the time of ^{131}I-mIBG treatment, 1 achieved CR post-HSCT, 2 maintained stable VGPR. Among 13 patients with PR at the time of ^{131}I-mIBG treatment, 1 achieved CR, 2 achieved VGPR, while 1 developed PD post-HSCT. As for the patient with MR at the time of ^{131}I-mIBG treatment, stable disease (SD) was achieved post-HSCT (Table 2).

Hematologic toxicity

The median time to neutrophil (ANC > 0.5 × 10^9/L) and platelet (> 20 × 10^9/L) engraftment of the entire cohort was 13 days (range, 9 to 54 days) and 36 days (range, 9 to 180 days), respectively. More rapid neutrophil engraftment was noted in these patients receiving MAC with CEM when compared with those receiving BuMel (P < 0.05). The detailed results are listed in Table 3. One patient was diagnosed with acute mixed lymphoblastic-myelomonoblastic leukemia 3 years after HSCT.

Nonhematologic toxicity

Grade 3 to 4 nonhematologic toxicities after HSCT are summarized in Table 3. Overall, hepatic VOD developed in 4 (16.7%) patients, with no significant difference in the incidence of between CEM and BuMel MAC regimens (P = 0.32). Among the 4 cases with VOD, one showed a severe form (maximum total bilirubin of 743 μmol/L and died of VOD), which occurred at 65 days after HSCT. The other three patients developed a mild VOD (maximum total bilirubin < 50 μmol/L and resolved within 1 week). Nineteen (79.2%) patients developed febrile neutropenia. Sepsis was reported in 1 patient with Pseudomonas putida. No patients died of sepsis in this study.

EFS and OS

Overall, 11 patients died with a median survival of 12.6 months (range, 5.4 to 55.8 months) after beginning ^{131}I-mIBG therapy. The causes of death included post-transplant VOD in 1 patient, and disease progression in 9 patients. One patient developed disease relapse 26 months after HSCT and received irinotecan and temozolamide as salvage therapy. Unfortunately, this patient developed secondary acute leukemia 37 months after HSCT and received one course of anti-leukemia treatment but

TABLE 2 Patient responses after transplantation

Pre-^{131}I-mIBG disease status	No.†	Patient responses evaluated post-HSCT				
		CR	VGPR	PR	PD	SD
CR/VGPR	9	6	2	0	1	0
PR/MR	14	1	2	9	1	1

†Twenty-three of 24 patients were evaluable for response. ^{131}I-mIBG,^{131}I-metaiodobenzylguanidine; HSCT, hematopoietic stem cell transplant; CR, complete response; VGPR, very good partial response; PR, partial response; MR, minor response; PD, progressive disease; SD, stable disease.

TABLE 3 Engraftment and complications after transplantation

Items	All (n = 24)	CEM group (n = 11)	BuMel group (n = 12)	P
Dose of ^{131}I-mIBG (mCi/kg)	12.0 (5.8–12.9)	12.0 (9.8–12.9)	11.8 (5.8–12.5)	0.04
^{131}I-mIBG to MAC (days)	13 (5–29)	11 (5–18)	18.5 (9–29)	<0.01
CD34$^+$ cells ($\times 10^6$/kg)	3.18 (1.04–18.20)	3.28 (2.47–18.20)	3.53 (1.04–14.80)	0.33
Engraftment (days)				
ANC > 0.5 × 10^9/L	13 (9–54)	12 (9–32)	14 (11–18)	<0.05
PLT > 20 × 10^9/L	36 (9–180)	26 (9–88)	41 (9–79)	0.24
Grade 3 to 4 adverse events				
Mucositis	12 (50.0)	6 (54.5)	6 (50.0)	0.83
Febrile neutropenia	19 (79.2)	9 (81.8)	9 (75.0)	0.69
Sepsis	1 (4.2)	0	1 (8.3)	0.33
VOD	4 (16.7)	1 (9.1)	3 (25.0)	0.32

CEM, carboplatin, etoposide, and melphalan; BuMel, busulfan and melphalan; ^{131}I-mIBG, ^{131}I-metaiodobenzylguanidine; MAC, myeloablative chemotherapy; ANC, absolute neutrophil count; PLT, platelet; VOD, veno-occlusive disease.

stopped due to excessive toxicity, then ultimately died from pseudomonas aeruginosa septicemia during the palliative treatment.

With a median follow-up duration of 13.0 months (range: 4.6–188.7 months) after beginning ^{131}I-mIBG therapy, the 5-year EFS and OS rates estimated for the entire cohort were 29% ± 11% and 38% ± 12%, respectively (Figure 1). Thirteen patients are alive at a median of 20.7 months post-HSCT (range: 3.6–188.3 months). Eight patients are in continuous CR (6.8–188.3 months post-HSCT) and two patients were alive with residual disease (3.6–5.0 months post-HSCT). Three patients developed relapse/progressive disease, one of whom became CR after the treatment with re-induction chemotherapy and the second ^{131}I-mIBG therapy (11.8 mCi/kg) followed by fludarabine, melphalan, thiotepa and antithymocyte globulin conditioning, and haploidentical allo-HSCT.

Association between disease status at the time of ^{131}I-mIBG therapy and survival

In order to evaluate the prognostic effect of the disease status at the time of ^{131}I-mIBG therapy in high-risk neuroblastoma patients receiving ^{131}I-mIBG therapy followed by MAC and HSCT, the patients were stratified into 2 groups based upon the disease status at the time of ^{131}I-mIBG therapy. CR/VGPR group included the patients who were in CR/VGPR at the time of ^{131}I-mIBG therapy. PR/MR group included the patients who were in PR/MR at the time of ^{131}I-mIBG therapy. Patient characteristics of the 2 groups are presented in Table 1. The EFS and OS for the 2 groups are shown in Figure 2. The better outcome was observed for the patients who were in CR/VGPR at the time of ^{131}I-mIBG therapy (5-year EFS: 53% ± 17%; 5-year OS: 67% ± 16%). Furthermore, when the patients were stratified based upon the combination of anti-GD2 immunotherapy post HSCT and the disease status at the time of ^{131}I-mIBG therapy, the best outcome was observed for the patients who were in CR/VGPR at the time of ^{131}I-mIBG therapy as well as received anti-GD2 immunotherapy post HSCT (5-year EFS: 67% ± 19%; 5-year OS: 67% ± 19%).

DISCUSSION

From the year 2003, we began to use the targeted radiotherapy agent (^{131}I-mIBG) plus MAC and HSCT for clearance of minimal residual disease in high-risk neuroblastoma patients who have achieved CR/VGPR

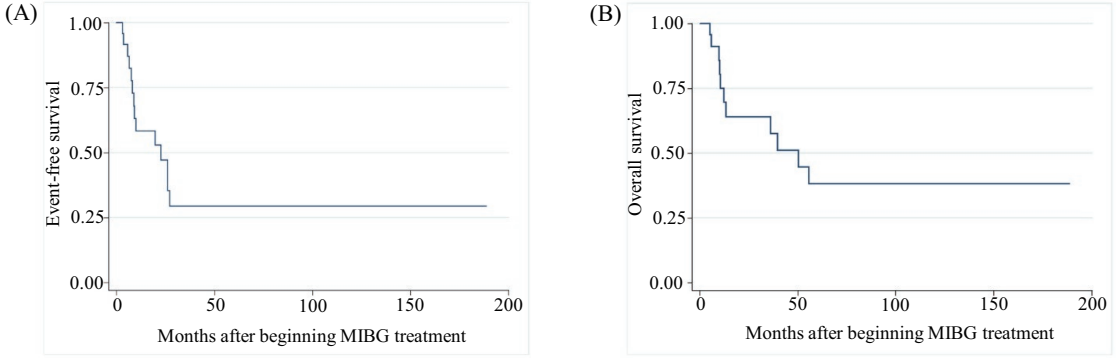

FIGURE 1 Kaplan–Meier curves for event-free survival (A) and overall survival (B) for the whole cohort, with 5-year event-free survival of 29% ± 11%, and 5-year overall survival of 38% ± 12%. MIBG, metaiodobenzylguanidine.

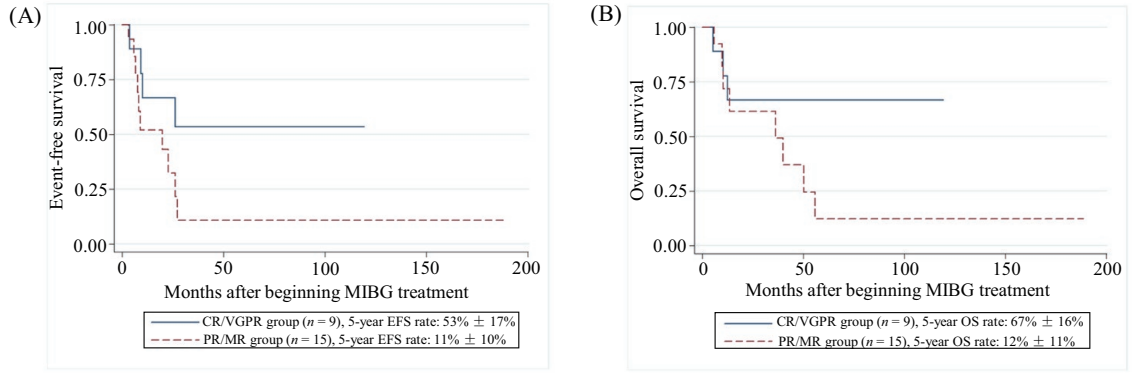

FIGURE 2 Kaplan–Meier curves for event-free survival (A) and overall survival (B) for 24 high-risk neuroblastoma patients according to the disease status at the time of MIBG therapy. MIBG, metaiodobenzylguanidine; CR, complete response; VGPR, very good partial response; PR, partial response; MR, minor response.

after the completion of induction therapy. In addition, considering that those high-risk neuroblastoma patients with a PR to initial induction therapy had a less than 30% 5-year EFS rate at the initiation of the study in the year 2003,[9] we also used ^{131}I-mIBG preceding MAC and HSCT to intensify this therapy and improve prognosis in high-risk neuroblastoma patients with a PR/MR at end of induction therapy. This pilot study confirmed the activity and tolerability of this regimen. Three of 13 patients who were in PR after the completion of induction therapy achieved either CR (n = 1) or VGPR (n = 2). Although the long term survival (5-year EFS: 29% ± 11%; 5-year OS: 38% ± 12%) for the entire cohort is unsatisfactory when compared with a recent upfront ^{131}I-mIBG therapy followed by the GPOH 2004 NBL protocol for newly diagnosed stage 4 neuroblastoma patients,[28] the 5-year EFS (53% ± 17%) and 5-year OS (67% ± 16%) observed in the patients who were in CR/VGPR at the time of ^{131}I-mIBG treatment are encouraging for this high-risk neuroblastoma patient population.

Previous studies have demonstrated the safety of the combination of ^{131}I-mIBG therapy and MAC. Gaze et al[29] identified that the use of ^{131}I-mIBG therapy combined with high-dose melphalan and TBI was well tolerated and feasible. In a pilot study, the combination of ^{131}I-mIBG therapy and high-dose chemotherapy with PBSC support was also tolerable in 11 patients with disseminated neuroblastoma.[30] More recently, Yanik et al[31] reported that the use of ^{131}I-mIBG therapy combined with CEM regimen produced a similar toxicity profile when compared with the use of the CEM regimen only. In the present study, the administration of ^{131}I-mIBG with a median dose of 12 mCi/kg on a median of day −11 before CEM did not affect neutrophil recovery post-HSCT, with a median engraftment time of 12 days (range: 9–32 days), similar to non-^{131}I-mIBG neuroblastoma transplantation regimen.[4,9] In addition, the use of ^{131}I-mIBG therapy preceding BuMel did not appear to affect the time to neutrophil engraftment. The median neutrophil engraftment appeared to be comparable to previous studies of high-dose BuMel with HSCT for high-risk neuroblastoma.[32,33] Moreover, French's study of ^{131}I-mIBG therapy followed by consolidation with BuMel and auto-HSCT showed a similar time to neutrophil engraftment.[34] In our study, the median time to platelet engraftment after CEM was 26 days (range, 9 to 88 days), which is shorter than that observed in Desai's study of children with high-risk neuroblastoma who received CEM (alone or in combination with ^{131}I-mIBG) preparative regimens.[35] Meantime, the present study showed that the median time to platelet engraftment after BuMel was 41 days (range, 9 to 79 days), which is similar to that observed in Desai's study of children with high-risk neuroblastoma who received BuMel (alone or in combination with ^{131}I-mIBG) preparative regimens.[35] However, it should be noted that one patient developed secondary leukemia following ^{131}I-mIBG/MAC therapy. The risk of secondary leukemia following ^{131}I-mIBG therapy in patients with neuroblastoma who have received intensive chemotherapy has also been reported in other series.[36,37] Therefore, this potential complication of ^{131}I-mIBG therapy should be carefully monitored in further studies.

Likewise, treatment with a median dose of 12 mCi/kg ^{131}I-mIBG within 1 month prior to the MAC regimen did not appear to add significant non-hematologic toxicity. In the present study, 54.5% of patients after ^{131}I-mIBG + CEM and 50.0% of patients after ^{131}I-mIBG + BuMel developed mucositis of grade 3 or more, which is lower than that was observed in the previous studies with 64% rate of stomatitis/mucositis reported for ^{131}I-mIBG + CEM[31] and 77.8% rate of mucositis reported for ^{131}I-mIBG + BuMel.[38] In the phase I trial of the combination of ^{131}I-mIBG with CEM, 3 (18.8%) of 16 patients with normal-GFR experienced VOD post-HSCT.[20] The rate of VOD in patients treated with IV BuMel followed by HSCT is reported to be 18%.[27] In our study, the development of VOD in 1 (9.1%) of 11

patients after CEM and 3 (25.0%) of 12 patients after IV BuMel is comparable to these previous studies. Although 3 of the 4 patients with VOD were mild cases and had no delay of post-HSCT maintenance therapy, however, considering the only case of treatment-related death due to VOD in the present study, this adverse effect remains a significant risk that should be monitored in future studies using the combination of ^{131}I-mIBG with MAC.

Improved end-induction response in high-risk neuroblastoma has been reported to be associated with superior EFS and OS.[39] In the present pilot study, compared with the patients who were in PR/MR at the time of ^{131}I-mIBG therapy, those patients who were in CR/VGPR at the time of ^{131}I-mIBG therapy showed a better clinical outcome (5-year EFS: 53% ± 17% versus 11% ± 10%; 5-year OS: 67% ± 16% versus 12% ± 11%). In addition to the survival benefit associated with improved end-induction response, following high-dose chemotherapy, surgical resection, auto-HSCT and radiation therapy, anti-GD2 immunotherapy was shown in several studies to have superior survival when compared with standard therapy with isotretinoin alone in high-risk neuroblastoma patients.[6,40,41] Recently, a phase I trial is ongoing to assess the efficacy and tolerability of chimeric anti-GD2 monoclonal antibody 14.18 in combination with ^{131}I-mIBG and anti-PD1 immune checkpoint inhibition.[42] In the present pilot study, when we further analyzed the results of EFS and OS for the different patient groups according to the combination of anti-GD2 immunotherapy and the diseases status at the time of ^{131}I-mIBG therapy, we observed a group of patients with a clearly better prognosis, corresponding to the patients who were in CR/VGPR at the time of ^{131}I-mIBG therapy and received anti-GD2 immunotherapy (5-year EFS: 67% ± 19%; 5-year OS: 67% ± 19%). Though the number of patients was small to make any definite conclusions, the initial positive survival benefit to this combination therapy (^{131}I-mIBG + MAC + HSCT + anti-GD2 antibody) support for a larger prospective trial of this approach for high-risk neuroblastoma patients with CR/VGPR after the completion of induction therapy. However, it should be noted that the efficacy of the combination therapy (^{131}I-mIBG + MAC + HSCT + anti-GD2 antibody) might be attributed to anti-GD2 antibody.[43] Therefore, a prospective randomized, controlled trial is required to verify the benefit of adding ^{131}I-mIBG to MAC and immunotherapy in high-risk neuroblastoma patients with CR/VGPR after the completion of induction therapy.

One disappointing result of the present study is that a dismal prognosis was observed in patients who were in PR/MR at the time of ^{131}I-mIBG therapy (5-year EFS: 11% ± 10%; 5-year OS: 12% ± 11%). Previous studies evaluating a median dose of 7–12 mCi/kg ^{131}I-mIBG in combination with MAC in patients with high-risk or refractory neuroblastoma showed that the combination was tolerable.[31,44] In the present study, the median dose of 12 mCi/kg ^{131}I-mIBG followed by MAC appears safe and tolerable. However, adopting a higher dose of up to 18 mCi/kg, as reported by other studies,[34] may be considered in future study for a better control in high risk patients with PR/MR or even CR/VGPR to induction treatment. In addition, a recent phase 1 clinical trial found that humanized 3F8 anti-GD2 antibody hu3F8 was associated with low immunogenicity and substantial antineuroblastoma activity, and the substantially better response rate was noted with higher hu3F8 dosages (≥ 162 mg/m^2 per course).[45] Considering that m3F8 and dinutuximab were tolerated only at a dosage of 100 mg/m^2 per course, therefore, further research is need on whether high risk patients with PR/MR to induction treatment would benefit from the combination therapy with ^{131}I-mIBG + MAC + hu3F8.

The limitations of this pilot study include the small sample size and patient selection bias. For example, during the study period, there were 5 patients with stage 4 neuroblastoma who could not receive ^{131}I-mIBG therapy because they all had PD before the consolidation treatment. The primary tumor recurred rapidly before or after surgery, and one with brain metastasis. These patients were not eligible for MAC and HSCT, thus ^{131}I-mIBG therapy was also not given. In addition, in the present study, ^{131}I-mIBG scintigraphy was qualitatively analyzed. Therefore, the disease burden semiquantified by mIBG scoring system (such as Curie score or the SIOPEN score[46-48]) was not available. However, for patients treated in COG A3973, a post-induction Curie score of more than 2 (versus 2 or less) was associated with an inferior outcome in patients with stage 4 neuroblastoma.[47] Therefore, the efficacy of consolidation treatment with ^{131}I-mIBG plus MAC and HSCT should be further evaluated in high-risk neuroblastoma patients with different disease burden semiquantified by mIBG scoring system.

In conclusion, upfront consolidation treatment with ^{131}I-mIBG plus MAC and HSCT is feasible and tolerable in high-risk neuroblastoma patients, and the better survival benefit of this ^{131}I-mIBG regimen is observed in the patients who were in CR/VGPR at the time of ^{131}I-mIBG treatment. However, the benefit of the combination therapy (^{131}I-mIBG + MAC + HSCT + anti-GD2 antibody) for high-risk neuroblastoma patients with CR/VGPR after the completion of induction therapy should be further validated in larger series.

CONFLICT OF INTEREST

No financial or nonfinancial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

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