의학석사 학위논문

고위험 신경모세포종 연속적 고용량 화학요법 및 자가조혈모세포 이식치료에서 ^{131}I 표지 메타요오도벤질구아니딘의 병합 효과

The impact of ^{131}I-metaiodobenzylguanidine as conditioning regimen of tandem high dose chemotherapy and autologous stem cell transplantation for high-risk neuroblastoma

2021년 2월

서울대학교 대학원

의학과 중개의학 전공

박 현 진

고위험 신경모세포종 연속적 고용량 화학요법 및 자가조혈모세포 이식치료에서 ^{131}I 표지 메타요오도벤질구아니딘의 병합 효과

The impact of ^{131}I-metaiodobenzylguanidineasconditioningregimenoftandemhigh-dosechemotherapy and autologous stem cell transplantation for high-risk neuroblastoma

지도교수 강 형 진

이 논문을 의학석사학위논문으로 제출함

2020년 10월

서울대학교 대학원

의학과 중개의학 전공

박 현 진

박현진의 석사 학위논문을 인준함

2021년 1월

위 원 장 신 희 영 (인)

부 위 원 장 강 형 진 (인)

위 원 최 기 정 (인)

ABSTRACT

The impact of ^{131}I-metaiodobenzylguanidine as conditioning regimen of tandem high-dose chemotherapy and autologous stem cell transplantation for high-risk neuroblastoma

Hyun Jin Park
Medicine, Translational research
The Graduate School
Seoul National University

Neuroblastoma (NBL) is originated from neural crest cell, and therefore, shows high avidity of metaiodobenzylguanidine (MIBG), an analog of the catecholamine norepinephrine. Based on this, the MIBG radiolabeled with ^{131}iodine (^{131}I-MIBG) is one of most commonly used targeted therapy for refractory and relapse neuroblastoma. But, the feasibility as first-line therapy for high-risk (HR) NBL, especially as

conditioning regimen for tandem high dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT), has not been established. Therefore, we performed this study to analyze the outcome of tandem HDC/ASCT in HR NBL and evaluate the effectiveness of ^{131}I-MIBG incorporation.

We retrospectively analyzed the clinical data of 33 HR NBL patients who underwent tandem HDC/ASCT from 2007 to 2019 at the Seoul National University Children's Hospital. The indications for tandem HDC/ASCT were as followings; 1) aged ≥1 year at diagnosis and INSS stage IV tumor, 2) stage III with suspected residual tumor after induction therapy or *MYCN*-amplified tumor, 3) aged <1 year at diagnosis and *MYCN*-amplified stage IV tumor.

The median age at diagnosis was 3.6-year-old (range 4-month-old to 13.6-year-old). The ^{131}I-MIBG was administered to 13 (39.4%) of the 33 patients. Local radiation therapy was applied in 26 (78.8%) patients. Thirty patients (90.9%) had maintenance therapy after tandem HDC/ASCT, consisting of 22 patients (66.7%) with isotretinoin ± interleukin-2 and 8 patients (24.2%) of salvage chemotherapy. There were 2 treatment-related-mortalities, renal failure and viral pneumonia after second HDC/ASCT. The 5-year overall survival (OS) and EFS rates of all patients were 74.1% and 59.6%, respectively. Comparing ^{131}I-MIBG combined group and the other, the OS rates were 79.1%/73.4% (p-value 0.845) and the EFS rates were 68.4%/58.3% (p-value 0.939), respectively. Among grade 3 or 4 adverse effects, the incidence of liver enzyme elevation was only significantly higher in non-^{131}I-MIBG group. There was no significant

difference in long term toxicity between two groups.

Although tandem HDC/ASCT with TTC/MEC regimen showed promising outcome for HR NBL, ^{131}I-MIBG combination did not improve survival rates or complications. As production of ^{131}I-MIBG has declined in Korea, we should evaluate the efficacy of ^{131}I-MIBG as conditioning regimen and try to figure out the optimum use of ^{131}I-MIBG.

.....

Keywords: Neuroblastoma, High dose chemotherapy, Autologous stem cell transplantation, ^{131}I-metaiodobenzylguanidine, Pediatrics

Student Number: 2018-29230

CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

HR NBL	High risk neuroblastoma
HDC	High dose chemohterapy
ASCT	Autologous stem cell transplantation
OS	Overall survival
EFS	Event-free survival
MIBG	Meta-iodobenzylguanidine
CR	Complete response
PR	Partial response
SD	Stable disease
PD	Progressive disease
TMA	Thrombotic microangiopathy
VOD	Veno-occlusive disease
TRM	Therapy-related
ITT	Isotretinoin
IL-2	Interleukin-2

INTRODUCTION

Neuroblastoma (NBL) is the most common extra-cranial solid tumor of childhood. It has been classified into low-risk, intermediate-risk, and high-risk group based on diagnostic age, histology, stage, and molecular marker. Pediatric oncologist groups including the International Neuroblastoma Risk Group (INRG) have updated the classification regularly. Because the prognosis and treatment response are markedly different by risk-groups, risk-adjusted therapy are applied. [1, 2] Though the treatment outcome of NBL has improved due to multimodal and intensive treatment, high-risk (HR) NBL has still known for poor prognosis. The 5-year overall survival (OS) in HR NBL is around 50% in latest reports. [3-5]

High dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT) is a standard treatment in HR NBL and to enhance the effect, diverse studies about HDC/ASCT in HR NBL are ongoing. [3, 6, 7] In terms of intensification, Park JR et al. reported that tandem HDC/ASCT was superior to single HDC/ASCT in 3-year event-free survival (EFS) especially combined with immunotherapy. [8] In addition, a phase III clinical trial was done to optimize the regimen for HDC/ASCT, comparing busulfan and melphalan (BuMel) with carboplatin, etoposide, and melphalan (MEC). The results showed that BuMel prolonged 3-year EFS comparing with MEC and caused fewer grade 3-4 adverse events, but more frequent veno-occlusive disease (VOD). [9] However, there is no

consensus for tandem HDC regimen. Park JR et al. used thiotepa/cyclophosphamide (ThioCy) and MEC for each first and second HDC. [8] Pasqualini C et al. used high dose thiotepa and BuMel for tandem HDC regimen in very high risk NBL. [10]

Meanwhile, with the conception that most NBL accumulates the meta-iodobenzylguanidine (MIBG), the MIBG radiolabeled with ^{131}iodine (^{131}I-MIBG) has been used as targeted radiotherapy. [11] The ^{131}I-MIBG was initially used in relapsed/refractory NBL, and on the strength of antitumor effects, there have been attempts to apply ^{131}I-MIBG to newly diagnosed HR NBL and combine ^{131}I-MIBG with other conventional chemotherapy. [11, 12] Hamidieh et al. selectively added ^{131}I-MIBG in HDC/ASCT with MEC according to patient's MIBG-avidity. The 3-year EFS were not significantly different between groups. [13] In several reports, ^{131}I-MIBG combination was successfully performed without marked increase in toxicity, but the efficacy and the optimal timing, dosage, and indication for ^{131}I-MIBG administration have not been determined. [11, 12] Furthermore, as the production ^{131}I-MIBG has been reduced in Korea, the use of ^{131}I-MIBG is becoming increasingly difficult.

In this context, we retrospectively analyzed the outcome of ^{131}I-MIBG combination in tandem HDC/ASCT of HR NBL patients. We performed tandem HDC/ASCT with uniform conditioning regimen, topotecan-thiotepa-carboplatin (TTC) for the first HDC/ASCT and MEC for the second HDC/ASCT, and added ^{131}I-MIBG a month before the second HDC/ASCT from 2013, when ^{131}I-MIBG therapy was introduced in our center. After tandem HDC/ASCT, we

implemented radiation therapy, and selectively administered maintenance therapy according to treatment response. Through this retrospective analysis, we evaluated the efficacy and feasibility of ^{131}I-MIBG as conditioning regimen of tandem HDC/ASCT for HR NBL.

MATERIALS AND METHODS

Patients

We reviewed the clinical data of 33 patients diagnosed with HR NBL and underwent tandem HDC/ASCT, from 2007 to 2019. We included patients who had completed both first and second HDC/ASCT with TTC/MEC regimen, and excluded patients who did not received planned second HDC/ASCT due to disease progression or complications. The indication for tandem HDC/ASCT was comprised of patients over the age of one year at diagnosis with International Neuroblastoma Stating System (INSS) stage 4, patients under the age of one year at diagnosis with INSS stage 4 and with amplified MYCN proto-oncogene, bHLH transcription factor (*MYCN*), and patients with INSS stage 3 at any age and with *MYCN* amplification. [14]

Assessment of disease extent and response criteria

Tumor extent was evaluated using computed tomography (CT) or magnetic resonance imaging (MRI), technetium-99m bone scintigraphy, 18F-fluoro-deoxy-D-glucose positron emission tomography (FDG-PET)/CT, and bilateral bone marrow examination. ^{123}I-MIBG scan was performed to check the uptake of MIBG in tumor. *MYCN* amplification was identified by fluorescence in situ hybridization on tumor tissues.

Response was evaluated every three cycles of induction chemotherapy, after surgical resection, before the first and second HDC/ASCT, every 3 months for the first four years after the second HDC/ASCT, every 6 months thereafter. Treatment response was assessed based on the International Neuroblastoma Response Criteria (INRC). [15]

Pre-transplant treatment

Induction chemotherapy consists of 60 mg/m^2 of cisplatin, 200mg/m^2 of etoposide, 30 mg/m^2 of adriamycin and 60 mg/kg of cyclophosphamide (CPM), based on CCG 321-P2. [16] When treatment response of CCG 321-P2 was poorer than partial response (PR), than we changed regimens, modified CCG-ICE (6000 mg/m2 of ifosfamide, 700 mg/m2 of carboplatin, and 400 mg/m2 of etoposide) or TCE (1250 mg/m2 of CPM, 5 mg/m2 of topotecan, and 300 mg/m2 of etoposide). [17, 18] At least 6 cycles of pre-transplant chemotherapy were done before the first HDC/ASCT and if possible, surgical resection was performed. After confirming no involvement of bone marrow, 3000 mg/m^2 of CPM and 450 mg/m^2 of etoposide were administered for peripheral stem cell mobilization. (Table 1) G-CSF was administered from day 7 of CPM/etoposide chemotherapy.

Tandem HDC/ASCT

The regimen for the first HDC consists of 10 mg/m^2 of topotecan,

900 mg/m^2 of thiotepa and 1500 mg/m^2 of carboplatin (TTC). The regimen for the second HDC consists of 210 mg/m^2 of melphalan, 800 mg/m^2 of etoposide and 1400 mg/m^2 of carboplatin (MEC). Carboplatin dose was reduced in ^{131}I-MIBG combined group to 1200 mg/m^2 (mMEC + ^{131}I-MIBG). (Table 1) We added ^{131}I-MIBG for the second HDC from 2013. In mMEC + ^{131}I-MIBG protocol, ^{131}I-MIBG was administered in day -21 of the second ASCT and the dose of MIBG treatment was 12 mCi/kg, except one patient with 17 mCi/kg. The minimal interval between each ASCT was 12 weeks and if the patient had complication following the first HDC/ASCT, we performed the second HDC/ASCT after the complication completely resolved. All patients were supported with G-CSF from day 1 of autologous peripheral stem cell infusion to recovery of neutrophil above 3000/μL or 1000/μL for 3 consecutive days.

Post-HDC/ASCT

After 1 month from the second HDC/ASCT, patients received radiation therapy to the primary tumor beds. If a residual tumor was suspicious in the first image evaluation, 3 months from the second HDC/ASCT, second-look surgery was performed to determine whether tumor cells remain indeed. In case of complete response (CR), we administered immunotherapy with IL-2 and isotretinoin (ITT) for 2 years as maintenance therapy. On the other hand, we applied salvage intensification chemotherapy, cyclophosphamide and topotecan.

Evaluation of adverse effects

We monitored acute toxicities during HDC/ASCT based on the common Terminology Criteria for Adverse Events (version 4.0) of the US National Cancer institute. VOD was evaluated by modified Seattle Criteria and thrombotic microangiopathy (TMA) was assessed with criteria by the International Working Group. [19]

Survival analysis and statistics

Differences in continuous variables were measured by the student's t-test or Mann-Whitney test. Differences in categorical variables were measured by the chi-square test or Fisher's exact test. EFS was calculated from the date of the second ASCT until the date of relapse, progression, secondary malignancy, or death, whichever occurred first. OS was calculated from the date of the second ASCT until death from any cause. Survival rates and standard errors were estimated using the Kaplan-Meier method. Differences in survival rates between the two groups were compared using the log-rank test. P-values <0.05 were considered significant.

RESULTS

Patient characteristics

Total 33 patients with HR NBL were analyzed retrospectively and the patients' characteristics are summarized in table 2. The median age at diagnosis was 3.6-year-old (range 4-month-old to 13.6-year-old) and the median follow-up duration from diagnosis was 6.3 years (range 1.1-12.5). The youngest patient was 4-month-old at diagnosis and classified as INSS stage 4S, but had *MYCN*-amplified tumor. The most frequent primary site was retroperitoneum including adrenal gland (29/33, 87.9%) and other primary lesions were pelvic cavity, paraspinal area, posterior mediastinum, and left upper abdominal cavity. All the patients had metastatic tumor and most common metastatic sites were lymph node (27/33, 81.8%), bone marrow (21/33, 63.6%), and bone (21/33, 63.6%). We classified cases with extensive necrosis or taken initial biopsy after chemotherapy as 'unknown' histology.

Pre-transplant chemotherapy

The median number of pre-transplant chemotherapy cycles was 7 (range 5-15) and the median duration for pre-transplant chemotherapy was 6 months (range 3-14). Seven patients (21.2%) changed regimen during induction. Six of them changed regimen due to residual or progressive disease, and the other one patient changed drug-related

toxicity, cardiomyopathy. The patient with cardiomyopathy completed treatment without aggravation after excluding cardiotoxic drug, adriamycin. All patients experienced neutropenic fever, and other toxicities occurring in pre-transplant chemotherapy were manageable. Patients achieved complete response (CR) (4/33, 12.1%) or partial response (29/33, 87.9%) before first HDC/ASCT.

Tandem HDC/ASCT

For the first and second HDC/ASCT, the median infused $CD34^+$ dose was 5.28 (range 0.99-12.92) × 10^6 cells/kg and 4.96 (range 1.175-12.92) × 10^6 cells/kg, respectively. The mean infused $CD34^+$ dose in the second HDC/ASCT of MEC and mMEC + ^{131}I-MIBG groups were 6.54 ± 3.20 × 10^6 cells/kg and 4.25 ± 2.34 × 10^6 cells/kg (p = 0.034), respectively. Except one case with therapy-related mortality during the second ASCT, all patients had engraftment for both neutrophil and platelet. For the first ASCT, all patients had neutrophil and platelet engraftment on the median of day 10 (range 9-13) and day 13 (range 10-18), respectively. After the second ASCT, the median time to neutrophil and platelet engraftment was 10 days (range 8-13) and 14 days (range 9-27), respectively. Comparing engraftment time between MEC and mMEC + ^{131}I-MIBG groups, the mean neutrophil engraftment duration for each group was 10.42 ± 1.17 and 9.69 ± 0.48 (p = 0.022). The median interval between first and second ASCT was 98 days (range 82-275). One patient delayed the second HDC/ASCT for 275 days due to cytomegalovirus retinitis.

In mMEC+^{131}I-MIBG group, a median dose of ^{131}I-MIBG was 12.2 mCi/kg (range 10.9-17.6). One patient received 17.6 mCi/kg of ^{131}I-MIBG as an myeloablative dose, and dose for other patients were targeted 12 mCi/kg.

Post-consolidation therapy

After the second HDC/ASCT, 26 patients (78.8%) received radiation therapy to primary tumor bed incompletely resected by surgery. The median interval between second ASCT and radiation therapy was 46.5 days (range 31-73 days). A median dose of radiotherapy to tumor bed was 16.5 Gy (range 12-27). Second-look surgery was performed in 8 patients and CT-guided biopsy was done in one patient. Seven of them were confirmed with residual tumor pathologically.

Among 30 patients excluding 3 patients of therapy-related mortality (TRM) or lost to follow-up right after the second ASCT, eight patients (8/30, 26.7%), pathologically confirmed residual tumor or radiologically progressive disease, received salvage chemotherapy as maintenance therapy and the median number of chemotherapy cycle was 22 (range 3-50). Of the remaining 22 patients (22/30, 73.3%), 3 patients (10%) were administered ITT and 19 patients (63.3%) were administered both ITT and IL-2. Between MEC and mMEC + ^{131}I-MIBG group, the ratio of maintenance therapy type was not significantly different. (Table 2)

Toxicity and complications

The table 3 lists acute and chronic complications during the first and second HDC/ASCT. The most common adverse effect was febrile neutropenia in both first and second HDC/ASCT, but except one patient with respiratory syncytial virus (RSV) associated pneumonia, there was no documented bacterial, fungal and viral infection. Between two groups, grade 3 or 4 liver enzyme elevation was significantly more frequent in MEC group. (p-value <0.001)

There were 2 TRMs during the second HDC/ASCT. One case in MEC group was caused by acute renal failure and sudden cardiac arrest. There was no evidence of VOD. The other case in mMEC+^{131}I-MIBG group was caused by RSV associated pneumonia, identified with bronchoalveolar lavage specimen. Though ribavirin was administered, the progressive pneumonitis with fever was not controlled. One patient was treated for VOD during the second HDC and it was manageable. Two patients were diagnosed with TMA after the second HDC and received plasmapheresis.

Among 26 patients monitored more than one year after completing treatment, hypothyroidism and growth failure occurred in each 4 and 8 patients, respectively. There was no significant difference of hypothyroidism and growth failure incidence between MEC and mMEC + ^{131}I-MIBG groups. (p-value 0.591, 0.667)

Relapse/progression and secondary malignancy

Relapse or progression occurred in 9 patients (27.3%) at a median 11 months (range 2-74) after the second ASCT.
Three patients were lost to follow-up, five patients were expired, and one patient was alive without disease after salvage chemotherapy. Six patients were in MEC group (6/20, 30.0%) and 3 patients were in mMEC + ^{131}I-MIBG group (3/13, 23.1%). (p-value 1.00)

One patient was diagnosed with therapy-related myelodysplastic syndrome (t-MDS) in 6.8 years after the second HDC/ASCT. Two patients were diagnosed with each renal cell carcinoma and squamous cell carcinoma occurred after 7.1 and 3.8 years, respectively. All three patients belonged to MEC group.

Tumor response and survival

The overall treatment course and response to each treatment are organized in figure 1. Four patients with complete response (CR) after induction chemotherapy continued CR after tandem HDC/ASCT. One of them recurred disease and was deceased due to complication after chemotherapy. Twenty-nine patients in PR from induction chemotherapy became 18 CR, 3 PR, 4 stable disease (SD), 2 progressive disease (PD), 2 TRMs after tandem HDC/ASCT. Among patients administered salvage chemotherapy, 6 patients were alive without disease.

Figure 2 shows the OS and EFS in each group. Overall 26 of 33

patients (78.8%) survived. The OS and EFS rates of all patients were 74.1% and 59.6%, respectively. Comparing ^{131}I-MIBG combined group and the other, the OS rates were 79.1%/73.4% (p-value 0.845) and the EFS rates were 68.4%/58.3% (p-value 0.939), respectively (Figure 2-c, 2-d). Reanalyzing the survival rates by risk factors, the OS rates of *MYCN*-positive/-negative patients were 55.6%/81.8% (p-value 0.065), and the EFS rates of *MYCN*-positive/-negative patients were 29.6%/74.8% (p-value 0.038), respectively. The OS rate of stage 3/stage 4 were 71.4%/76.3% (p-value 0.278), and the EFS rate were 71.4%/57.7% (p-value 0.941), respectively.

Table 1. Chemotherapy regimens

Regimen	Drug	Dose	Schedule	Total dose
Pre-transplant chemotherapy				
CCG 321P2	Cisplatin	60mg/m^2/day	Day 0	60mg/m^2
	Etoposide	100mg/m^2/day	Day 2, 5	200mg/m^2
	Adriamycin	30mg/m^2/day	Day 2	30mg/m^2
	CPM	30mg/kg/day	Day 3, 4	60mg/kg
Modified CCG-ICE	Ifosfamide	1200mg/m^2/day	Day 0 to 4	6000mg/m^2
	Carboplatin	350mg/m^2/day	Day 0, 1	700mg/m^2
	Etoposide	100mg/m^2/day	Day 0 to 3	400mg/m^2
TCE	Topotecan	1mg/m^2/day	Day 0 to 4	5mg/m^2
	CPM	250mg/m^2/day	Day 0 to 4	1250mg/m^2
	Etoposide	100mg/m^2/day	Day 0, 1, 2	300mg/m^2
PBSCM				
CPM+ VP	CPM	1000mg/m^2/day	Day 0, 1, 2	3000mg/m^2
	Etoposide	150mg/m^2/day	Day 0, 1, 2	450mg/m^2
	G-CSF	10μg/kg	Day 7 to end of PBSCM	
1st HDC				
TTC	Topotecan	2mg/m^2/day	Day -8 to -4	10mg/m^2
	Thiotepa	300mg/m^2/day	Day -8, -7, -6	900mg/m^2
	Carboplatin	500mg/m^2/day	Day -5, -4, -3	1500mg/m^2
2nd HDC				
MEC	Melphalan	140mg/m^2/day (d-7) 70mg/m^2/day (d-6)	Day -7, -6	210mg/m^2
	Etoposide	200mg/m^2/day	Day -8 to -5	800mg/m^2
	Carboplatin	350mg/m^2/day	Day -8 to -5	1400mg/m^2
mMEC+ ^{131}I-MIBG	^{131}I-MIBG	12 or 17 mCi/kg (10.9-17.6 mCi/kg)	Day -21	
	Melphalan	140mg/m^2/day (d-7) 70mg/m^2/day (d-6)	Day -7, -6	210mg/m^2
	Etoposide	200mg/m^2/day	Day -8 to -5	800mg/m^2
	Carboplatin	300mg/m^2/day	Day -8 to -5	1200mg/m^2

PBSCM, peripheral stem cell transplantation; HDC, high dose chemotherapy; CPM, cyclophosphamide

cf. The chemotherapy dose was reduced for patients younger than 1-year-old or less than 10 kg of body weight. Weight-based dose for <1 year-old and <10 kg of body weight, median value of weight-based dose and body-surface-area based dose for >1 year-old and <10kg of body weight.

Table 2. Patient characteristics

Characteristics	MEC (n=20)	mMEC+MIBG (n=13)	*p*-value	Total (n=33)
Sex, n (%)				
Male	11 (55.0)	9 (69.2)	0.485	20 (60.6)
Female	9 (45.0)	4 (30.8)		13 (39.4)
Age at diagnosis, months, median (range)	38 (4-129)	43 (16-163)	0.984	43 (4-163)
INSS stage, n (%)				
Stage 3	5 (25.0)	2 (15.4)		7 (21.2)
Stage 4	14 (70.0)	11 (84.6)	0.676	25 (75.8)
Stage 4S*	1 (5.0)	0 (0.0)		1 (3.0)
MYCN amplification, n (%)	6 (30.0)	3 (23.1)	1.000	9 (29.0)
INPC, n (%)				
Unfavorable	7 (35.0)	9 (69.2)		16 (48.5)
favorable	7 (35.0)	2 (15.4)	0.156	9 (27.3)
Unknown	6 (30.0)	2 (15.4)		8 (24.2)
^{123}I-MIBG avidity, n (%)				
Yes	5 (25.0)	11 (84.6)		16 (48.5)
No	1 (5.0)	0 (0.0)	0.004	1 (3.0)
Unknown	14 (70.0)	2 (15.4)		16 (48.5)
Primary site, n (%)				
Retroperitoneum	16 (80.0)	13 (100.0)	0.136	29 (87.9)
Others	4 (20.0)	0 (0.0)		4 (12.1)
Disease status before ASCT, n (%)				
CR	3 (15.0)	1 (7.7)	1.000	4 (12.1)
PR	17 (85.0)	12 (92.3)		29 (87.9)
Local RTx, n (%)	17 (85.0)	9 (69.2)	0.393	26 (78.8)
Second look Op, n (%)	0 (0.0)	8 (57.1)	<0.001	8 (23.5)
Maintenance Tx total, n (%)	19 (95.0)	11 (78.6)	0.283	30 (90.9)
Salvage chemoTx, n (%)	3 (15.0)	5 (38.5)	0.522	8 (24.2)
ITT, n (%)	2 (10)	1 (7.7)	1.000	3 (9.1)
IL-2 + ITT, n (%)	14 (70.0)	5 (38.5)	0.073	19 (57.6)
Follow-up duration, months, median (range)	114 (18-150)	61 (13-83)	0.001	76 (13-150)

n, number; CR, complete response; PR, partial response; RTx, radiation therapy; Op, operation; Tx, therapy; ITT, isotretinoin; IL-2, interleukin-2

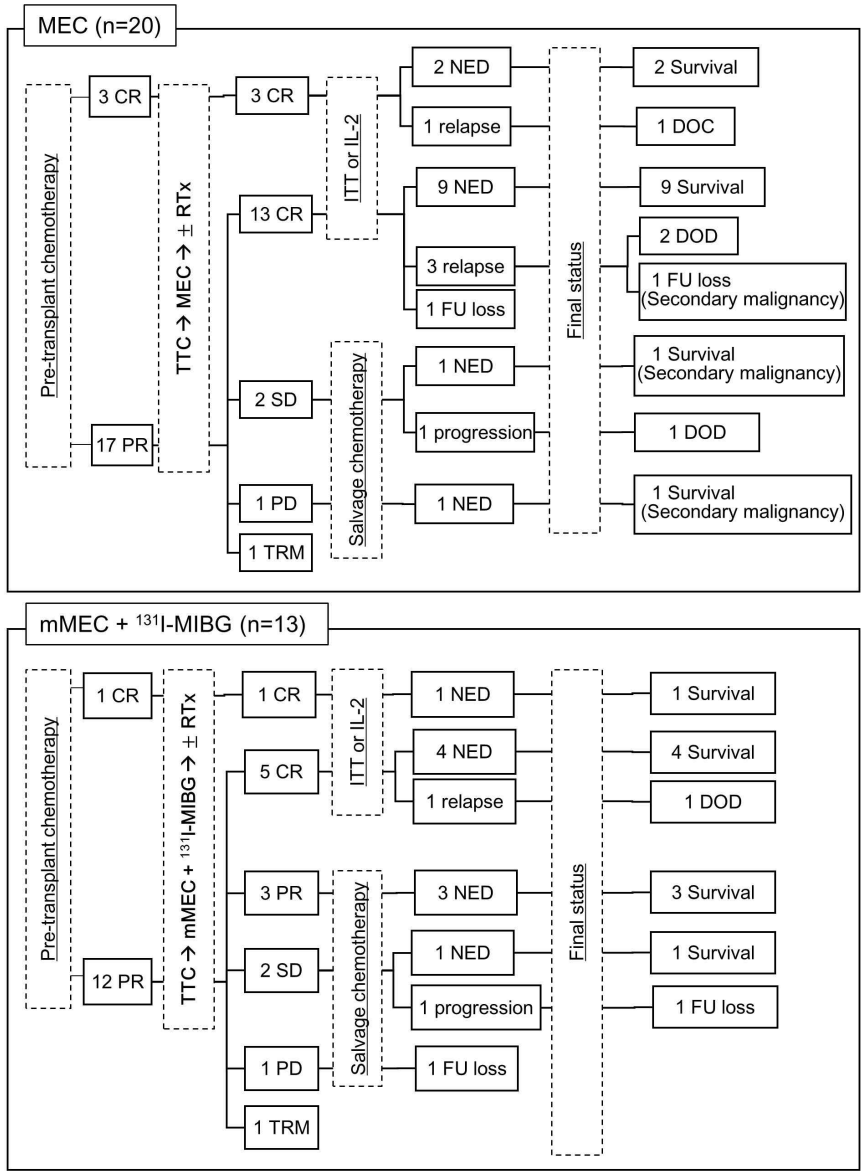
*One patient diagnosed with Stage 4S was reported *MYCN* amplication positive

Table 3. Acute and late complications after first and second HDC/ASCT

Complication n, (%)	1st HDC/ASCT	2nd HDC/ASCT			
	TTC (n=33)	MEC (n=20)	mMEC+MIBG (n=13)	*p*-value	Total (n=33)
TRM	-	1 (5.0)	1 (7.7)	1.00	2 (6.1)
VOD	0 (0.0)	1 (5.0)	0 (0.0)	1.00	1 (3.0)
TMA	0 (0.0)	1 (5.0)	1 (7.7)	1.00	2 (6.1)
Acute toxicity, CTCAE Grade 3/4					
Febrile neutropenia	33 (100)	19 (95.0)	13 (100)	1.00	33 (97.0)
Pericardial effusion	0 (0.0)	1 (5.0)	0 (0.0)	1.00	1 (3.0)
Diarrhea	13 (39.4)	3 (15.0)	1 (7.7)	1.00	4 (12.1)
Vomiting	10 (30.3)	3 (15.0)	1 (7.7)	1.00	4 (12.1)
Oral mucositis	22 (66.7)	8 (40.0)	7 (53.8)	0.435	15 (45.5)
Total bilirubin	0 (0.0)	1 (5.0)	1 (7.7)	1.00	2 (6.1)
LFT elevation	15 (45.5)	19 (95.0)	1 (7.7)	<0.001	20 (60.6)
AKI	0 (0.0)	1 (5.0)	1 (7.7)	1.00	2 (6.1)
Creatinine	0 (0.0)	2 (10.0)	1 (7.7)	1.00	3 (9.1)
Proteinuria	0 (0.0)	3 (15.0)	1 (7.7)	1.00	4 (12.1)
Hematuria	2 (6.1)	0 (0.0)	1 (7.7)	0.394	1 (3.0)
Long-term toxicity	(n=26)	(n=17)	(n=9)		(n=26)
Secondary malignancy		3 (15.0)	0 (0.0)	0.261	3 (9.1)
Hypothyroidism		2 (11.8)	2 (22.2)	0.591	4 (15.4)
Growth failure		6 (35.3)	2 (22.2)	0.667	8 (30.8)

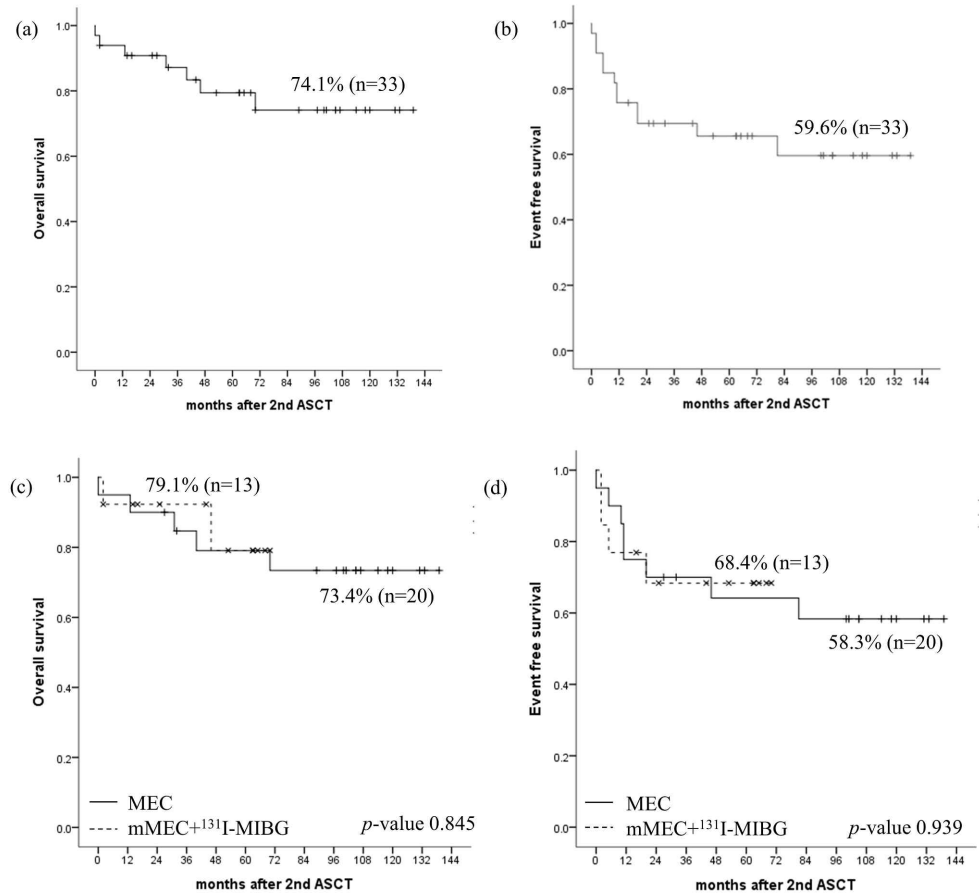
HDC, high dose chemohterpay; ASCT, autologous stem cell transplantation; TRM, therapy-related mortality; VOD, Veno-occlusive disease; TMA, Thrombotic microangiopathy; LFT, Liver function test; AKI, Acute kidney injury

Figure 1. Treatment response of all involved patients



CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; FU, follow-up; TRM, therapy-related mortality; NED, no evidence of disease; DOC, died of complication; DOD, died of disease; TTC, Topotecan/Thiotepa/Carboplatin; MEC, Melphalan/Etoposide/Carboplatin ^{131}I-MIBG, ^{131}Iodine-metaiodobenzylguanidin; RTx, radiation therapy; ITT, isotretinoin; IL-2, Interleukin-2

Figure 2. Overall survival and event-free survival



(a) Overall survival (OS) of all the patients

(b) Event-free survival (EFS) of all the patients

(c) OS in MEC and mMEC+^{131}I-MIBG groups

(d) EFS in MEC and mMEC+^{131}I-MIBG groups

Discussion

In this report, we evaluated the treatment outcome of tandem HDC/ASCT with uniform conditioning regimen, TTC/MEC, and the efficacy of ^{131}I-MIBG combination as conditioning regimen. After completing consolidation therapy, we administered maintenance therapy and stratified the intensity based on treatment response. The results were favorable, the 5-year OS of 79.4% and the 5-year EFS of 65.6%. Overall, there were 2 TRMs during the second HDC/ASCT and other acute toxicities were manageable. Combination of ^{131}I-MIBG did not make significant difference in survival rates and major toxicities.

In spite of intensive multimodal therapy, HR NBL is known for poor prognosis. About half of HR NBL is refractory or relapse for the first-line therapy. [3, 4] HDC/ASCT has proved to improve the survival rate without significant increase of TRM or secondary malignancy. [6, 7, 20, 21] Moreover, recent randomized trial showed that tandem HDC/ASCT combined with post-consolidative immunotherapy improved 3-year EFS, while cumulative toxicities seemed similar. [8] Still, attempts continue to find optimal regimen for HDC/ASCT. At the same time, studies for target therapy, multi-modal combination and treatment-intensification are ongoing.

Most neuroblastoma features MIBG uptake and radiolabeled MIBG has been used as diagnostic and therapeutic tools for a long time. [11] At first, the radioactive target therapeutics, ^{131}I-MIBG, was

evaluated as monotherapy in relapsed/refractory neuroblastoma. The objective response rate ranged from 0% to 66% and even there was no objective response, it showed definite pain relief. [12] Based on this success, current studies try to administer ^{131}I-MIBG to newly diagnosed patients. There has been no randomized trial, but according to currently reported evidence, the benefit of ^{131}I-MIBG combination is unclear. [11, 12, 17] Hamidieh et al. reported the result of prospective pilot study, comparing ^{131}I-MIBG-combined group and chemotherapy only group. Though ^{131}I-MIBG was administered to patients with positive MIBG-avidity, the 3-year EFS and OS were not statistically different. [13] Besides, reports from Lee JW et al., Suh JK et al. showed that tandem HDC/ASCT concomitant with ^{131}I-MIBG did not improve survival rates but only reduced several toxicities. [22, 23]

In our study, some patients were not initially evaluated for MIBG avidity because the ^{123}I-MIBG scan was not possible at the time of diagnosis. Johnson et al. reported that some patients identified CR in ^{123}I-MIBG scan had residual MIBG-avid lesions in ^{131}I-MIBG scan. [24] Based on this, after 2013, when ^{131}I-MIBG therapy became available in our institution, we applied ^{131}I-MIBG combined conditioning regimen to all HRNBL patients subject to tandem HDC/ASCT, including patients negative in ^{123}I-MIBG scan before HDC/ASCT. As a result, the only significant difference in patients' characteristics between two groups was not MIBG avidity but treatment points. Although the group with ^{131}I-MIBG was treated with advanced supportive care, the survival rates did not improve. In ^{131}I-MIBG-combined group, there were two patients with unknown ^{123}I-MIBG avidity, and eventually, no ^{131}I-MIBG avid lesion was

found in post-therapy ^{131}I-MIBG scan.

For toxicity and complications, TRM rate (2/33, 5.8%) of the study was similar to previous reports, 0-9.3%. [8, 22, 23, 25] One of TRMs, who died of renal failure, was delayed with the second HDC/ASCT due to CMV retinitis, but the second HDC/ASCT was forced to be performed due to definite residual disease after the first HDC/ASCT. We used MEC for second HDC/ASCT, which was identified as a risk factor of TMA. [26, 27] There was no case of TMA after the first HDC/ASCT, but 2 cases of TMA occurred after the second HDC/ASCT. In light of engraftment, the infused cell dose was significantly higher in MEC group than ^{131}I-MIBG combination group, but neutrophil engraftment time was significantly longer in MEC group. However, there was no case of engraftment failure in both groups and the difference of mean engraftment time was only about 1 day. Even though liver enzyme elevation was significantly more common in MEC group, all cases were manageable and there was neither irreversible hepatic failure nor significant difference in VOD incidence. All three cases of secondary malignancy occurred in MEC group. However, since follow-up duration was significantly shorter in ^{131}I-MIBG group, long term follow-up is necessary for evaluation.

As regulations were tightened to reduce the risk of radiation exposure, production of radioactive ^{131}I-MIBG has declined in Korea and ^{131}I-MIBG became difficult to get for the past 5 years. Given the current situation, it has become important to evaluate the efficacy of ^{131}I-MIBG combination for HDC/ASCT and to establish the optimal indication for ^{131}I-MIBG administration. In addition, there has been

controversy in the dose of ^{131}I-MIBG. It seemed that dose escalation improved the response rate through phase I/II studies. [28] Most studies has used 12 mCi/kg of ^{131}I-MIBG based on phase I study, but dose escalation to 18 mCi/kg combined with myeloablative therapy (BuMel) was tolerable in refractory neuroblastoma patients. [29, 30] In this study, the only one patient who received 17.6 mCi/kg was alive without disease. However, we can not evaluate the effectiveness of dose escalation due to a small number of cases. Further study for dose escalation of ^{131}I-MIBG is needed.

On the other hand, besides the combination of ^{131}I-MIBG, the conditioning regimen of HDC/ASCT for NBL is also controversial. For a single HDC/ASCT, the institutions in the United States use MEC widely, while BuMel is used in Europe and Middle East. [9] There are several reports comparing MEC and BuMel, and in a recent randomized/phase III trial, BuMel showed better 3-year EFS with fewer complications. [9, 31, 32] For the tandem HDC/ASCT, the conditioning regimen is much varied. Park et al. reported that the 3-year EFS after tandem HDC/ASCT with thiotepa-cyclophosphamide (ThioCy) and MEC was 61.6%. [8] Suh JK et al. used BuMel or MEC for the first HDC and ThioCy + ^{131}I-MIBG for the second HDC, and the 5-year OS and EFS were 79% and 61%, respectively. [23] Lee JW et al. used MEC and thiotepa-melphalan + ^{131}I-MIBG for each first and second HDC, and the 5-year OS and EFS were 72.4 and 58.3%, respectively. [22] Comparing with these previous results, our study with TTC/MEC showed comparable outcome.

To sum up, this study had several differences compared to prior

reports. First, we used uniform conditioning chemotherapy regimen, TTC and MEC, for both first and second HDC/ASCT. It can reduce the effect caused by differences of chemotherapy regimen. Second, we administered same dose of MIBG, except one patient with 17.6 mCi/kg, at the same time point. Third, we did not divide 2 groups according to MIBG avidity. Therefore, bias arising from difference of MIBG avidity could be reduced.

In conclusion, ^{131}I-MIBG combination did not improve the outcome of tandem HDC/ASCT for HRNBL, but tandem HDC/ASCT with TTC/MEC regimens still showed promising results. Considering recent limitation of ^{131}I-MIBG use in Korea, we should find out optimal indication and usage of ^{131}I-MIBG in HRNBL. One possibility to increase efficacy of ^{131}I-MIBG combination is administering ^{131}I-MIBG only to patients with high avidity. To this end, a comparative analysis is needed to determine if there is any difference in treatment outcome by dividing subgroups according to the degree of MIBG avidity. Prospective randomized study for ^{131}I-MIBG combination in tandem HDC/ASCT will be also necessary, and the efforts to optimize regimen for tandem HDC/ASCT should continue. As the tandem HDC/ASCT showed stronger effect especially with anti-GD2 antibody, the direction of further study would be focus on the feasibility of combination with newly developed targeted agents.

REFERENCES

1. Sokol E, Desai A. The Evolution of Risk Classification for Neuroblastoma. Children. 2019;6(2):27.

2. Maris JM, Hogarty MD, Bagatell R, Cohn SL. Neuroblastoma. The Lancet. 2007;369(9579):2106-20.

3. Smith V, Foster J. High-Risk Neuroblastoma Treatment Review. Children (Basel). 2018;5(9).

4. Colon NC, Chung DH. Neuroblastoma. Adv Pediatr. 2011;58(1):297-311.

5. Whittle SB, Smith V, Doherty E, Zhao S, McCarty S, Zage PE. Overview and recent advances in the treatment of neuroblastoma. Expert Review of Anticancer Therapy. 2017;17(4):369-86.

6. Yalçin B, Kremer LC, Van Dalen EC. High-dose chemotherapy and autologous haematopoietic stem cell rescue for children with high-risk neuroblastoma. Cochrane Database of Systematic Reviews. 2015.

7. Berthold F, Boos J, Burdach S, Erttmann R, Henze G, Hermann J, et al. Myeloablative megatherapy with autologous stem-cell rescue versus oral maintenance chemotherapy as consolidation treatment in patients with high-risk neuroblastoma: a randomised controlled trial. Lancet Oncol. 2005;6(9):649-58.

8. Park JR, Kreissman SG, London WB, Naranjo A, Cohn SL,

Hogarty MD, et al. Effect of Tandem Autologous Stem Cell Transplant vs Single Transplant on Event-Free Survival in Patients With High-Risk Neuroblastoma: A Randomized Clinical Trial. JAMA. 2019;322(8):746-55.

9. Ladenstein R, Potschger U, Pearson ADJ, Brock P, Luksch R, Castel V, et al. Busulfan and melphalan versus carboplatin, etoposide, and melphalan as high-dose chemotherapy for high-risk neuroblastoma (HR-NBL1/SIOPEN): an international, randomised, multi-arm, open-label, phase 3 trial. Lancet Oncol. 2017;18(4):500-14.

10. Pasqualini C, Dufour C, Goma G, Raquin MA, Lapierre V, Valteau-Couanet D. Tandem high-dose chemotherapy with thiotepa and busulfan-melphalan and autologous stem cell transplantation in very high-risk neuroblastoma patients. Bone Marrow Transplant. 2016;51(2):227-31.

11. Kraal KC, Van Dalen EC, Tytgat GA, Van Eck-Smit BL. Iodine-131-meta-iodobenzylguanidine therapy for patients with newly diagnosed high-risk neuroblastoma. Cochrane Database of Systematic Reviews. 2017.

12. Schmidt M, Hero B, Simon T. I-131-mIBG therapy in neuroblastoma: established role and prospective applications. Clinical and Translational Imaging. 2016;4(2):87-101.

13. Hamidieh AA, Beiki D, Paragomi P, Fallahi B, Behfar M, Fard-Esfahani A, et al. The potential role of pretransplant MIBG diagnostic scintigraphy in targeted administration of131I-MIBG accompanied by ASCT for high-risk and relapsed neuroblastoma: A

pilot study. Pediatric Transplantation. 2014;18(5):510-7.

14. Castel V, Garcia-Miguel P, Canete A, Melero C, Navajas A, Ruiz-Jimenez JI, et al. Prospective evaluation of the International Neuroblastoma Staging System (INSS) and the International Neuroblastoma Response Criteria (INRC) in a multicentre setting. Eur J Cancer. 1999;35(4):606-11.

15. Park JR, Bagatell R, Cohn SL, Pearson AD, Villablanca JG, Berthold F, et al. Revisions to the International Neuroblastoma Response Criteria: A Consensus Statement From the National Cancer Institute Clinical Trials Planning Meeting. Journal of Clinical Oncology. 2017;35(22):2580-7.

16. Stram DO, Matthay KK, O'Leary M, Reynolds CP, Haase GM, Atkinson JB, et al. Consolidation chemoradiotherapy and autologous bone marrow transplantation versus continued chemotherapy for metastatic neuroblastoma: a report of two concurrent Children's Cancer Group studies. Journal of Clinical Oncology. 1996;14(9):2417-26.

17. Yi ES, Son MH, Hyun JK, Cho HW, Ju HY, Lee JW, et al. Predictors of survival in patients with high risk neuroblastoma who failed tandem high dose chemotherapy and autologous stem cell transplantation. Pediatric Blood & Cancer. 2020;67(2).

18. Simon T, Langler A, Harnischmacher U, Fruhwald MC, Jorch N, Claviez A, et al. Topotecan, cyclophosphamide, and etoposide (TCE) in the treatment of high-risk neuroblastoma. Results of a phase-II trial. J Cancer Res Clin Oncol. 2007;133(9):653-61.

19. Miano M, Faraci M, Dini G, Bordigoni P. Early complications following haematopoietic SCT in children. Bone Marrow Transplantation. 2008;41(S2):S39-S42.

20. Matthay KK, Reynolds CP, Seeger RC, Shimada H, Adkins ES, Haas-Kogan D, 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(7):1007-13.

21. Pritchard J, Cotterill SJ, Germond SM, Imeson J, de Kraker J, Jones DR. High dose melphalan in the treatment of advanced neuroblastoma: results of a randomised trial (ENSG-1) by the European Neuroblastoma Study Group. Pediatr Blood Cancer. 2005;44(4):348-57.

22. Lee JW, Lee S, Cho HW, Ma Y, Yoo KH, Sung KW, et al. Incorporation of high-dose (131)I-metaiodobenzylguanidine treatment into tandem high-dose chemotherapy and autologous stem cell transplantation for high-risk neuroblastoma: results of the SMC NB-2009 study. J Hematol Oncol. 2017;10(1):108.

23. Suh JK, Koh KN, Min SY, Kim YS, Kim H, Im HJ, et al. Feasibility and effectiveness of treatment strategy of tandem high dose chemotherapy and autologous stem cell transplantation in combination with 131 I MIBG therapy for high risk neuroblastoma. Pediatric Transplantation. 2020;24(2).

24. Johnson K, McGlynn B, Saggio J, Baniewicz D, Zhuang H, Maris JM, et al. Safety and efficacy of tandem 131

I-metaiodobenzylguanidine infusions in relapsed/refractory neuroblastoma. Pediatric Blood & Cancer. 2011;57(7):1124-9.

25. Sung KW, Son MH, Lee SH, Yoo KH, Koo HH, Kim JY, et al. Tandem high-dose chemotherapy and autologous stem cell transplantation in patients with high-risk neuroblastoma: results of SMC NB-2004 study. Bone Marrow Transplant. 2013;48(1):68-73.

26. Tolbert VP, Dvorak CC, Golden C, Vissa M, El-Haj N, Perwad F, et al. Risk Factors for Transplant-Associated Thrombotic Microangiopathy after Autologous Hematopoietic Cell Transplant in High-Risk Neuroblastoma. Biology of Blood and Marrow Transplantation. 2019;25(10):2031-9.

27. Jodele S, Dandoy CE, Myers K, Wallace G, Lane A, Teusink-Cross A, et al. High-dose Carboplatin/Etoposide/Melphalan increases risk of thrombotic microangiopathy and organ injury after autologous stem cell transplantation in patients with neuroblastoma. Bone Marrow Transplantation. 2018;53(10):1311-8.

28. Kayano D, Kinuya S. Iodine-131 metaiodobenzylguanidine therapy for neuroblastoma: reports so far and future perspective. ScientificWorldJournal. 2015;2015:189135.

29. French S, Dubois SG, Horn B, Granger M, Hawkins R, Pass A, et al. 131I-MIBG followed by consolidation with busulfan, melphalan and autologous stem cell transplantation for refractory neuroblastoma. Pediatric Blood & Cancer. 2013;60(5):879-84.

30. Matthay KK, Tan JC, Villablanca JG, Yanik GA, Veatch J, Franc B, et al. Phase I dose escalation of iodine-131-metaiodobenzyl-

guanidine with myeloablative chemotherapy and autologous stem-cell transplantation in refractory neuroblastoma: a new approaches to Neuroblastoma Therapy Consortium Study. J Clin Oncol. 2006;24(3):500-6.

31. Desai AV, Heneghan MB, Li Y, Bunin NJ, Grupp SA, Bagatell R, et al. Toxicities of busulfan/melphalan versus carboplatin/etoposide/melphalan for high-dose chemotherapy with stem cell rescue for high-risk neuroblastoma. Bone Marrow Transplant. 2016;51(9):1204-10.

32. Desai AV, Seif AE, Li Y, Getz K, Fisher BT, Huang V, et al. Resource Utilization and Toxicities After Carboplatin/Etoposide/Mel-

alan and Busulfan/Melphalan for Autologous Stem Cell Rescue in High-Risk Neuroblastoma Using a National Administrative Database. Pediatr Blood Cancer. 2016;63(5):901-7.

국문초록

신경모세포종은 신경능선세포에서 기원하는 종양으로 노르아드레날린 유사물인 메타아이오도벤질구아니딘 (MIBG) 의 높은 흡취성을 보인다. 이를 이용하여 요오드-131 표지 MIBG는 재발성 불응성 신경모세포종의 가장 널리 사용되는 표적 치료제 중에 하나이다. 하지만 고위험 신경모세포종의 일차 치료제로서의 효용성은 확립되지 않았고, 특히 고위험 신경모세포종의 공고 요법인 고용량 화학요법 및 자가조혈모세포이식치료의 전처치 제제로 활용될 가능성은 아직 평가되지 않았다. 이에 본 연구에서는 고위험 신경모세포종의 연속적 고용량 화학요법 및 자가조혈모세포이식치료에서 ^{131}I-MIBG 병합 요법의 효용성을 평가해보고자 한다.

서울대학교 어린이병원에서 2007년부터 2019년까지 연속적 고용량 화학요법 및 자가조혈모세포이식치료를 받은 33명의 고위험 신경모세포종 환자의 임상 기록을 후향적으로 분석하였다. 치료의 대상으로는 INSS 4기 종양을 진단받은 1세 이상의 환자와 INSS 3기 종양 중 관해 요법 치료 후 잔존암이 남은 경우 혹은 MYCN 증폭이 확인된 경우와, 1세 미만 INSS 4기 종양 중 MYCN 증폭이 확인된 환자를 포함하였다.

진단 연령의 중간값은 3.6세였다. (범위, 4개월 - 13.6세) ^{131}I-MIBG이 적용된 환자는 13명 (39.4%) 이었고, 2차 이식치료 후 방사선치료는 26명 (78.8%)에서 시행되었다. 30명의 환자가 (90.9%) 공고요법 후 유지치료를 받았으며, 그중 22명의 (66.7%) 환자가 아이소트레티노인 혹은 인터류킨-2를 투약하였으며, 구제 화학요법은 8명에서 (24.2%) 시행되었다. 치료 관련 사망은 2례 있었고 각각 신부전과 이차 이식치료 중 발생한 바이러스성 폐렴에 의한 것이었다. 전체 환자군에서 5년 생존율은 74.1%였고 4년 무사건 생존율은 59.6%였다. ^{131}I-MIBG 병합요법군과 비

병합요법군을 비교했을 때, 전체생존율은 각각 79.1%와 73.4%였다. (p-value 0.845) ^{131}I-MIBG 병합요법군과 비병합요법군의 무사건생존율은 각각 68.4%와 58.3%였다. (p-value 0.939) 3단계 이상의 약물 관련 부작용 중 간효소 수치 상승만이 유의미하게 ^{131}I-MIBG 비병합요법군에서 더 많이 발생하였다. 그 외의 급성기 부작용과 장기 부작용 중 두 군 간의 발생율의 차이를 보이는 것은 없었다.

본 연구에서 고위험 신경모세포종 환자를 대상으로 TTC/MEC 제제를 사용한 연속적 고용량 화학요법 및 자가조혈모세포이식치료는 유망한 결과를 보였으나, ^{131}I-MIBG 병합요법은 생존율이나 합병증을 개선하지 못했다. 방사선 노출에 대한 우려로 방사선의약품 생산 관련한 규제가 강화되면서 한국에서 ^{131}I-MIBG 생산은 감소하였다. 현 상황에서 ^{131}I-MIBG 의 전처치 제제로서의 효용성을 밝히는 것은 중요하며, 최적의 사용법을 찾기 위한 후속 연구가 앞으로 더 진행되어야 할 것이다.

.....

주요어: 신경모세포종, 고용량 화학요법, 자가조혈모세포이식, 소아, 요오드-131 표지 메타아이오도벤질구아니딘

학 번: 2018-29230