의학석사 학위 논문

High dose chemotherapy and autologous stem cell transplantation with melphalan, etoposide and carboplatin for high risk osteosarcoma

소아 골육종 고위험군의 고용량 항암치료와 자가 조혈모세포 이식

2013 년 10 월

서울대학교 대학원

임상의과학과 석사 과정

홍 채 리

A thesis of the Degree of Master

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by

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이 논문을 임상의과학 석사 학위논문으로 제출함

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ABSTRACT

Introduction: Despite the greatly improved overall survival of high risk osteosarcoma, treatment outcomes remain poor for patients with poor response to neo-adjuvant chemotherapy or metastatic disease, and those who progress during treatment or relapse after completion of conventional therapy. Patients with these risk factors were treated with high dose chemotherapy and autologous stem cell transplantation (HDCT & ASCT) to overcome their poor survival. We herein analyzed the treatment outcome of these patients, and evaluated the feasibility of HDCT & ASCT for high risk osteosarcoma.

Methods: Medical record review was done on children with high risk osteosarcoma who underwent HDCT & ASCT with melphalan, etoposide and carboplatin at Seoul National University Children's Hospital between March 2006 and March 2013. High risk osteosarcoma was defined as those with tumor necrosis below 90% after neo-adjuvant chemotherapy, metastasis at diagnosis, progression during treatment or relapse after completion of conventional therapy.

Results: HDCT & ASCT was performed in 19 patients at median age of 12.4 years old (range, 6.1 to 19.7 years old), at median 9 months (range, 6 to 51 months) from diagnosis. They underwent HDCT & ASCT for tumor necrosis below 90% after neo-adjuvant chemotherapy only (n=8, Group I), for initial lung metastasis, with or without poor response to neo-adjuvant chemotherapy (n=5, Group II), for progression during treatment, regardless of presence of

initial lung metastasis or poor response to neo-adjuvant chemotherapy (n=3, Group III), and for relapse after completion of conventional therapy (n=3, Group IV). Median 6.1 × 10^6/kg CD34 cells were infused, and neutrophils engrafted at median 10 days from infusion. Grade 4 adverse events occurred in 3 patients, and these resolved in 2 patients. Transient veno-occlusive disease occurred in 4 patients. One patient died of transplantation-related mortality. The event-free survival was 67.4% at median 31 months (range, 0 to 91 months) from HDCT & ASCT. Five patients (26%) relapsed; 2 patients achieved remission with further chemotherapy, 1 patient is currently on chemotherapy, and 2 patients refused further treatment and died of disease. The overall survival was 78.3% at median 31 months (range, 0 to 91 months) from ASCT.

Conclusions: HDCT & ASCT with melphalan, etoposide and carboplatin may be a promising treatment option for high risk osteosarcoma. Further strategies are needed to overcome relapses after HDCT & ASCT.

Keywords osteosarcoma, high dose chemotherapy, autologous stem cell transplantation, metastasis, necrosis, progression, relapse

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LIST OF ABBREVIATIONS

HDCT & ASCT : high dose chemotherapy and autologous stem cell transplantation

OS : overall survival

IRB : institutional review boards

MRI : magnetic resonance imaging

PET : positron emission tomography

IV CDDP/ADR/HDMTX : intravenous cisplatin, adriamycin and high dose methotrexate

IA CDDP/ADR : intra-arterial cisplatin and adriamycin

PBSC : peripheral blood stem cell

G-CSF : granulocyte colony-stimulating factor

HDCT : high dose chemotherapy

CTCAE v4.03 : National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03

VOD : veno-occlusive disease

EFS : event-free survival

ASCT : autologous stem cell transplantation

TRM : transplantation-related mortality

AST, ALT : aspartate aminotransferase and alanine aminotransferase

AKI : acute kidney injury

GENERAL INTRODUCTION

Osteosarcoma is the most common bone tumor in children, with peak incidence in adolescence. From when surgery was the sole treatment option, the introduction of adjuvant chemotherapy, neo-adjuvant chemotherapy, and multi-agent aggressive chemotherapy has greatly improved the overall survival, from 15% to 70% (1-5). Current 5- and 10-year overall survival for localized osteosarcoma is approximately 70% and 65% respectively (6-8). Nonetheless, treatment outcomes remain poor for high risk osteosarcoma, such as those with poor response to neo-adjuvant chemotherapy, those with metastasis at presentation, and those who relapse (9-11). The reported overall survival of metastatic osteosarcoma is 25%, and that of relapsed osteosarcoma is less than 20% (12, 13).

We have previously analyzed the entire cohort of children with osteosarcoma treated at our institute (14). In this analysis, children with tumor necrosis below 90% after neo-adjuvant chemotherapy, metastasis at diagnosis, progression during treatment, and relapse after completion of conventional therapy were found to be associated with significantly worse survival. Fortunately, our preliminary results with high dose chemotherapy and autologous stem cell transplantation had been promising.

CHAPTER 1

High dose chemotherapy and autologous stem cell transplantation with melphalan, etoposide and carboplatin for high risk osteosarcoma

INTRODUCTION

Osteosarcoma is the most common bone tumor in children, with peak incidence in adolescence. From when surgery was the sole treatment option, the introduction of adjuvant chemotherapy, neo-adjuvant chemotherapy, and multi-agent aggressive chemotherapy has greatly improved the overall survival (OS), from 15% to 70% (1-5). Current 5- and 10-year OS for localized osteosarcoma is approximately 70% and 65% respectively (6-8). Nonetheless, treatment outcomes remain poor for high risk osteosarcoma, such as those with poor response to neo-adjuvant chemotherapy, those with metastasis at presentation, and those who relapse (9-11). The reported OS of metastatic osteosarcoma is 25%, and that of relapsed osteosarcoma is less than 20% (12, 13).

In attempt to evaluate the potential role of high dose chemotherapy and autologous stem cell transplantation (HDCT & ASCT) in improving the outcome of high risk osteosarcoma, we have previously analyzed the entire cohort of children treated for osteosarcoma at our institute between January 2000 and December 2007. In this analysis, children with tumor necrosis below 90% after neo-adjuvant chemotherapy, metastasis at diagnosis, progression during treatment, and relapse after completion of conventional therapy were found to be associated with significantly worse survival. With the promising preliminary results of high dose chemotherapy and autologous stem cell transplantation, we have previously suggested that HDCT & ASCT may be an alternative treatment option for these patients (14).

Thereafter, osteosarcoma patients with tumor necrosis below 90% after neo-adjuvant chemotherapy, metastasis at diagnosis, progression during

treatment, and relapse after completion of conventional therapy, underwent HDCT & ASCT at our institute. We herein report the treatment outcome of these patients. We thus aim to evaluate the feasibility of HDCT & ASCT with melphalan, etoposide and carboplatin for high risk osteosarcoma.

MATERIALS AND METHODS

1. Patient selection

A retrospective medical record review was done on 19 children with high risk osteosarcoma who underwent HDCT & ASCT with melphalan, etoposide and carboplatin at Seoul National University Children's Hospital between March 2006 and March 2013.

High risk osteosarcoma was defined as those with one or more of the following risk factors: poor response to neo-adjuvant chemotherapy, metastasis at diagnosis, progression during treatment, or relapse after completion of conventional therapy. Poor response to neo-adjuvant chemotherapy was defined as those with tumor necrosis below 90% after neo-adjuvant chemotherapy. Lung metastases were those that were radiologically evident on computed tomography (CT) of the chest. Both progression and relapse were those that were radiologically evident.

Of the osteosarcoma patients with 1 or more of the above risk factors, those who achieved complete remission with conventional therapy underwent HDCT & ASCT, with informed consent of all patients and/or their legal guardians. Patients were classified into 4 groups according to the indications for HDCT & ASCT. Patients with poor response to neo-adjuvant chemotherapy only were classified as Group I, and patients with metastasis at diagnosis, with or without poor response to neo-adjuvant chemotherapy, were classified as Group II. Patients who progressed during treatment, regardless of the presence of metastasis or poor response to neo-adjuvant chemotherapy, were classified as Group III, and patients who relapsed after completion of conventional therapy were classified as Group IV.

The institutional review boards (IRB) at Seoul National University Hospital approved this retrospective medical record review (IRB number: H-1308-081-513).

2. Conventional therapy

Biopsied specimens were histopathologically confirmed as osteosarcomas by the institutional pathologist. Initial evaluation consisted of magnetic resonance imaging (MRI) of the primary site, computed tomography (CT) of the chest, and bone scan and positron emission tomography (PET) of the whole body.

All patients underwent neo-adjuvant chemotherapy, which consisted either of intravenous cisplatin, adriamycin and high dose methotrexate (IV CDDP/ADR/HDMTX) or of intra-arterial cisplatin and adriamycin (IA CDDP/ADR). Intra-arterial neo-adjuvant chemotherapy was chosen in all technically feasible cases. Tumor response to neo-adjuvant chemotherapy was assessed by the institutional pathologist, based on the degree of necrosis of the resected primary tumor after neo-adjuvant chemotherapy.

Definitive surgery was performed either after 2 cycles of IV CDDP/ADR/HDMTX or after 4 cycles of IA CDDP/ADR. The institutional orthopedic surgeon decided on the procedure of surgery; wide excision and limb salvage operation was strongly encouraged whenever possible. Availability of allo-bones determined the choice for limb reconstruction. Allo-bones or synthetic prostheses were preferred to pasteurized autologous bones. All radiologically evident metastatic lesions were resected. For lung metastases, all resectable lesions were resected.

3. HDCT & ASCT

Autologous peripheral blood stem cell (PBSC) mobilization was performed with cyclophosphamide 1,000 mg/m^2 (day 0, 1, and 2) and etoposide 150 mg/m^2 (day 0, 1, and 2). Granulocyte colony-stimulating factor (G-CSF) 10 ug/kg/day was started 120 hours after chemotherapy. Those who failed chemo-mobilization underwent plerixafor-based mobilization; G-CSF 10 ug/kg/day for 4 days without prior chemotherapy, then plerixafor 240 ug/kg/day and G-CSF 10 ug/kg/day before each apheresis (15).

High dose chemotherapy consisted of melphalan 140 mg/m^2 (day -7), 70 mg/m^2 (day -6), etoposide 200 mg/m^2 (day -8, -7, -6, and -5) and carboplatin 400 mg/m^2 (day -8, -7, -6, and -5). Autologous PBSCs were infused 120 hours after the end of high dose chemotherapy (HDCT).

G-CSF 300 ug/m^2/day was administered from day +1 until the neutrophil count was more than 1 $\times$ 10^9/L for 3 consecutive days. Achieving neutrophil count of 1 $\times$ 10^9/L or greater was defined as neutrophil engraftment.

4. Complications

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03). Hepatic veno-occlusive disease (VOD) was diagnosed according to the Baltimore criteria (16).

5. Statistical analysis

The probability of survival was calculated using the Kaplan-Meier method, and subgroup comparisons were done with the log-rank test. Event-free survival (EFS) was defined as the time from autologous stem cell transplantation (ASCT) to relapse or any other cause of death such as transplantation-related mortality (TRM). OS was defined as the time from diagnosis of osteosarcoma to death or last follow-up. The analysis was performed with the IBM SPSS Statistics version 19. *P*-values lower than 0.05 were considered statistically significant.

RESULTS

Clinical characteristics

Nineteen patients (13 boys, 6 girls) underwent HDCT & ASCT at median age of 12.4 years old (range, 6.1 to 19.7 years old), at median 9 months (range, 6 to 51 months) from diagnosis (Table 1). According to the indications for HDCT & ASCT, 8 patients were classified as Group I, 5 patients as Group II, 3 patients as Group III, and 3 patients as Group IV.

Distal femur was the most common site of primary tumor (n=13, 68%), followed by proximal humerus, proximal tibia and distal tibia. Osteoblastic type was the most frequent histologic type (n=15, 79%), followed by chondroblastic, fibroblastic and giant cell-rich osteosarcoma. Six patients (32%) had metastasis at diagnosis; lung was the sole site of metastasis for all of them (Table 1).

Conventional therapy

All 19 patients underwent neo-adjuvant chemotherapy; 12 patients (63%) received IV CDDP/ADR/HDMTX, and 7 patients (37%) received IA CDDP/ADR. Fourteen patients (74%) showed poor response to neo-adjuvant chemotherapy, with less than 90% of tumor necrosis (Table 1).

The entire study population managed to undergo wide excision and limb salvage operations after neo-adjuvant chemotherapy. Synthetic prostheses were most frequently used for limb salvage operations (n=8, 42%), followed by allo-bones (n=5, 26%), and autologous bones (n=4, 21%). A combination of allo-bone and autologous bone was used in 1 patient (5%), and

a combination of prosthesis, allo-bone, and autolgous bone was used in another patient (5%) (Table 1). The patient (No. 5) who used a combination of synthetic prosthesis, allo-bone, and autologous bone experienced local relapse, and thus underwent above knee amputation thereafter (Table 2).

Three patients (16%) progressed during conventional therapy, and 3 patients (16%) relapsed after completion of conventional therapy.

Table 1-1. Patient characteristics

	Group I (n=8)	Group II (n=5)	Group III (n=3)	Group IV (n=3)	Total (N=19)
Median age at diagnosis (years)	12.3 (8.8-15.4)	10.2 (5.4-15.7)	13.6 (8.7-13.9)	10.6 (6.6-15.4)	11.8 (5.4-15.7)
Median age at HDCT & ASCT (years)	13.1 (9.6-16.1)	10.8 (6.1-16.4)	14.7 (10.2-16.8)	12.4 (9.7-19.7)	12.4 (6.1-19.7)
Sex (%)					
Male	6 (75)	4 (80)	1 (33)	2 (67)	13 (68)
Female	2 (25)	1 (20)	2 (67)	1 (33)	6 (32)
Primary site (%)					
Distal femur	4 (50)	4 (80)	3 (100)	2 (67)	13 (68)
Proximal humerus	2 (25)	1 (20)	-	-	3 (16)
Proximal tibia	1 (13)	-	-	1 (33)	2 (11)
Distal tibia	1 (13)	-	-	-	1 (5)
Histologic type (%)					
Osteoblastic	6 (75)	5 (100)	2 (67)	2 (67)	15 (79)
Chondroblastic	1 (13)	-	1 (33)	-	2 (11)
Fibroblastic	-	-	-	1 (33)	1 (5)
Giant cell-rich	1 (13)	-	-	-	1 (5)
Metastasis at diagnosis (%)					
Lung metastasis	-	5 (100)	1 (33)	-	6 (32)
Neoadjuvant chemotherapy (%)					
IV CDDP/ADR/HDMTX	6 (75)	4 (80)	2 (67)	-	12 (63)
IA CDDP/ADR	2 (25)	1 (20)	1 (33)	3 (100)	7 (37)
Surgery (%)					
Wide excision & limb salvage	8 (100)	5 (100)	3 (100)	3 (100)	19 (100)
AK amputation after local relapse	-	-	-	1 (33)	1 (5)
Type used for limb salvage operation (%)					
Synthetic prosthesis	6 (75)	-	1 (33)	1 (33)	8 (42)
Allo-bone	1 (13)	2 (40)	1 (33)	1 (33)	5 (26)
Autologous bone	1 (13)	2 (40)	1 (33)	-	4 (21)
Allo-bone + Autologous bone	-	1 (20)	-	-	1 (5)
Synthetic prosthesis + Allo-bone + Autologous bone	-	-	-	1 (33)	1 (5)
Necrosis (%)					
Necrosis ≥ 90%	-	1 (20)	-	3 (100)	4 (21)
50% ≤ Necrosis < 90%	4 (50)	2 (40)	1 (33)	-	7 (37)
10% ≤ Necrosis < 50%	3 (38)	-	1 (33)	-	4 (21)
Necrosis < 10%	1 (13)	1 (20)	1 (33)	-	3 (16)
Not evaluable	-	1 (20)	-	-	1 (5)

HDCT & ASCT, high dose chemotherapy and autologous stem cell transplantation; IV CDDP/ADR/HDMTX, intravenous cisplatin, adriamycin and high dose methotrexate; IA CDDP/ADR, intra-arterial cisplatin and adriamycin; AK, above knee

Table 1-2. Clinical characteristics and treatment outcome of the entire cohort

No.	Sex	Age at ASCT (yr)	1° site	Histology	NeoadjC Tx	Surgery	Prosth/ bone	Group	Poor necr (%)	Initial meta	Progression	Relapse	Complication	Events (relapse site)	Status (mo from ASCT)
1	F	16.8	dF	Ob	IA	WE/LS	prosth	III	Y (60%)	–	Y (Local, RLg)	–	Gr 4 Cr	–	NED (91)
2	M	13.7	dF	Ob	IA	WE/LS	auto	II	Y (50%)	Y (BLg)	–	–	Gr 4 LFT, VOD	Relapse (BLg, T4 VB, skin)	DOD (5)
3	M	9.7	dF	Ob	IA	WE/LS	prosth	IV	–	–	–	Y (Frontal bone)	–	–	NED (67)
4	F	13.7	pH	Ob	IV	WE/LS	prosth	I	Y (<10%)	–	–	–	–	–	NED (60)
5	F	12.4	pT	Ob	IA	WE/LS, AK ampt	p-allo-auto	IV	–	–	–	Y (Local)	–	–	NED (55)
6	M	9.6	pH	Ob	IV	WE/LS	prosth	I	Y (50%)	–	–	–	–	–	NED (51)
7	M	16.4	pH	Ob	IV	WE/LS	allo	II	Y (80%)	Y (BLg)	–	–	–	Relapse (RLg, 8th rib)	DOD (38)
8	M	14.7	dF	Ob	IV	WE/LS	allo	III	Y (20%)	–	Y (Local, LLg)	–	–	Relapse (Local)	NED (46)
9	M	16.1	dF	Ob	IA	WE/LS	prosth	I	Y (30%)	–	–	–	–	Relapse (LLg)	NED (40)
10	M	6.1	dF	Ob	IV	WE/LS	auto	II	–	Y (RLg)	–	–	VOD	–	NED (33)
11	M	10.8	dF	Ob	IV	WE/LS	allo	II	Y (<10%)	Y (LLg)	–	–		–	NED (31)
12	M	9.7	dF	Ob	IV	WE/LS	prosth	I	Y (10%)	–	–	–	–	–	NED (27)
13	M	12.4	dT	Cb	IV	WE/LS	allo	I	Y (40%)	–	–	–	VOD	–	NED (26)
14	F	10.2	dF	Cb	IV	WE/LS	auto	III	Y (<10%)	Y (BLg)	Y (BLg)	–	VOD	TRM (SCA)	TRM (0)
15	M	10.2	pT	Ob	IV	WE/LS	auto	I	Y (80%)	–	–	–	–	–	NED (19)
16	F	8.5	dF	Ob	IV	WE/LS	allo-auto	II	N/E	Y (BLg)	–	–	–	Relapse (Local)	On CTx (19)
17	M	19.7	dF	Fb	IA	WE/LS	allo	IV	–	–	–	Y (BLg)	Gr 4 AKI	–	NED (19)
18	M	14.5	dF	Gc	IA	WE/LS	prosth	I	Y (85%)	–	–	–	–	–	NED (16)
19	F	14.6	dF	Ob	IV	WE/LS	prosth	I	Y (80%)	–	–	–	–	–	NED (8)

ASCT, autologous stem cell transplantation; yr, years; 1°, primary; Neoadj, Neo-adjuvant; CTx, Chemotherapy; prosth, synthetic prosthesis; necr, necrosis; meta, metastasis; mo, months; F, female; M, male; dF, distal femur; pT, proximal tibia; pH, proximal humerus; dT, distal tibia; Ob, osteoblastic; Fb, fibroblastic; Cb, condroblastic; Gc, Giant cell-rich; IA, intra-arterial cisplatin and adriamycin; IV, intravenous cisplatin, adriamycin, and high dose methotrexate; WE/LS, wide excision and limb salvage; AK ampt, above knee amputation; auto, autologous bone; allo, allo-bone; Y, yes; N/E, not evaluable; BLg, bilateral lung; RLg, right lung; LLg, left lung; Gr 4, Grade 4 adverse event by Common Terminology Criteria for Adverse Events version 4.03; Cr, creatinine elevation; LFT, aspartate aminotransferase and alanine aminotransferase elevation; AKI, acute kidney injury; VOD, veno-occlusive disease; T4 VB, T4 vertebral body; TRM, transplantation-related mortality; SCA, sudden cardiac arrest; NED, no evidence of disease; DOD, died of disease

HDCT & ASCT

For autologous PBSC infusion, median 6.1 × 10^6/kg (range, 1.6−15.7 × 10^6/kg) CD34 cells were infused on day 0. Except for the 1 patient who died 4 days after infusion, before engraftment, all 18 patients achieved neutrophil engraftment at median 10 days (range, 8−11 days) from infusion (Table 3).

Table 1−3. Outcome of HDCT & ASCT

	Group I (n=8)	Group II (n=5)	Group III (n=3)	Group IV (n=3)	Total (N=19)
Infused cell dose					
MNC, ×10^8/kg (range)	10.3 (4.4−30.1)	7.6 (5.8−18.3)	15.1 (2.9−15.9)	16.5 (4.6−17.4)	10.8 (2.9−30.1)
CD34, ×10^6/kg (range)	6.3 (2.5−14.5)	4.4 (4.0−15.7)	6.3 (4.3−12.0)	3.3 (1.6−13.9)	6.1 (1.6−15.7)
Neutrophil engraftment					
Day from infusion	10 (8−11)	10 (9−11)	10 (9−11)	10 (10−11)	10 (8−11)
Complications (%)					
Gr 4 AST, ALT elevation	−	1 (20)	−	−	1 (5)
Gr 4 Creatinine elevation	−	−	1 (33)	−	1 (5)
Gr 4 Acute kidney injury	−	−	−	1 (33%)	1 (5)
Veno−occlusive disease	1 (13)	2 (40)	1 (33)	−	4 (21)
Events					
Relapse	1 (13)	3 (60)	1 (33)	−	5 (26)
Tpl−related mortality	−	−	1 (33)	−	1 (5)
FU duration from ASCT, mo (range)	27 (8−60)	31 (5−38)	46 (0−91)	55 (19−67)	31 (0−91)
Current status					
No evidence of disease	8 (100)	2 (40)	2 (67)	3 (100%)	15 (79)
On CTx after relapse	−	1 (20)	−	−	1 (5)
Tpl−related mortality	−	−	1 (33)	−	1 (5)
Died of disease	−	2 (40)	−	−	2 (11)

MNC, mononuclear cells; Gr 4, Grade 4 adverse event; AST, ALT, aspartate aminotransferase and alanine aminotransferase; Tpl, transplantation; FU, follow−up; ASCT, autologous stem cell transplantation; CTx, Chemotherapy

Complications

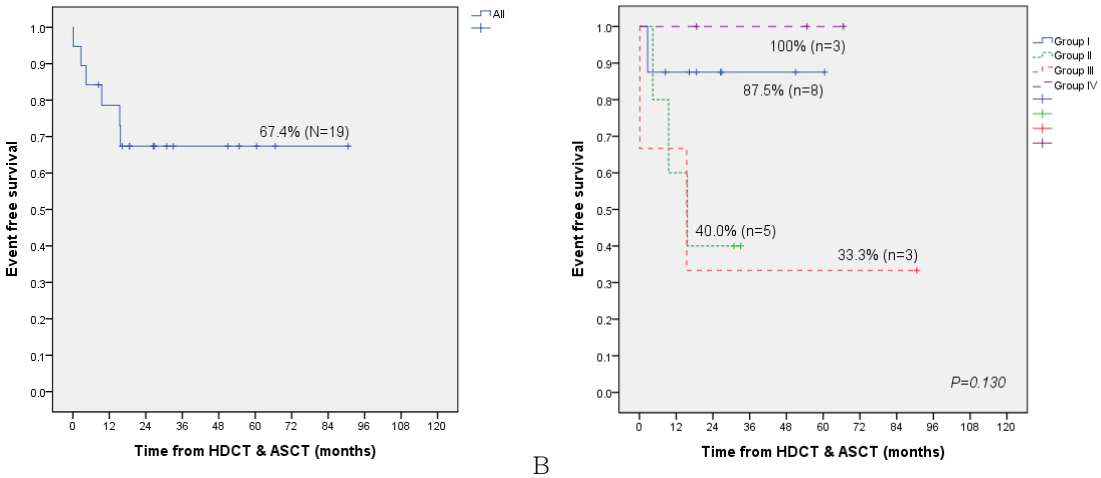
Three patients (16%) experienced grade 4 adverse events. One patient had transient grade 4 aspartate aminotransferase and alanine aminotransferase (AST, ALT) elevation. Another patient had transient grade 4

creatinine elevation. But another patient (No. 17) had grade 4 acute kidney injury (AKI) which progressed to borderline chronic kidney disease. Four patients (21%) experienced VOD, but all of them resolved (Table 2, 3).

Transplantation-related mortality occurred in 1 patient (5%). She (No. 14) died of sudden cardiac arrest on day +4 (Table 2, 3).

Events

At median 31 months (range, 0 to 91 months) from ASCT, the EFS was 67.4% (Table 3) (Figure 1-1A). The EFS of Group I, Group II, Group III, and Group IV were 87.5%, 40.0%, 33.3% and 100% respectively (Figure 1-1B).



A B

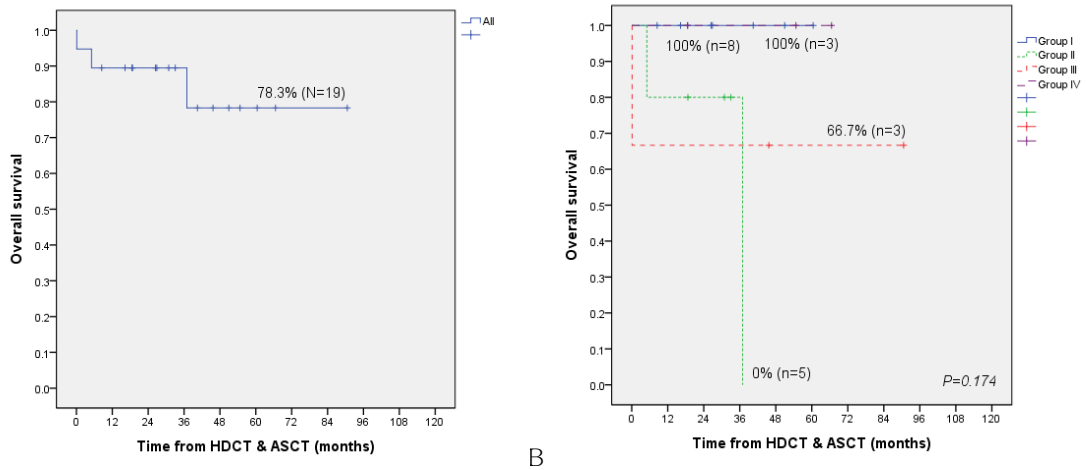
Figure 1-1. Event-free survival (A) of the total study population, and (B) of the different indication groups (Group I, poor response to neo-adjuvant chemotherapy only; Group II, lung metastasis with or without poor response to neo-adjuvant chemotherapy; Group III, progression during treatment, regardless of the presence of lung metastasis or poor response to neo-adjuvant chemotherapy; Group IV, relapse after completion of conventional therapy).

Five patients (26%) relapsed at median 9 months (range, 3 to 15 months) from HDCT & ASCT (Table 3). Two patients (11%) refused further treatment, 2 patients (11%) received further surgery and chemotherapy, and

1 patient (5%) is currently undergoing chemotherapy. The 2 patients who refused further treatment died of disease at median 16 months (range, 2 to 29 months) from relapse. The 2 patients who underwent further surgery and chemotherapy are both alive with no evidence of disease at 37 months (range, 30 to 43 months) from relapse; patient No. 8 received 13 cycles chemotherapy with ifosfamide, carboplatin, etoposide and cyclophosphamide, and patient No. 9 recieved 8 cycles of chemotherapy with gemcitabine and docetaxel (Table 2). The patient who is currently on chemotherapy, patient No. 16, is on chemotherapy with ifosfamide, carboplatin and etoposide.

Outcome

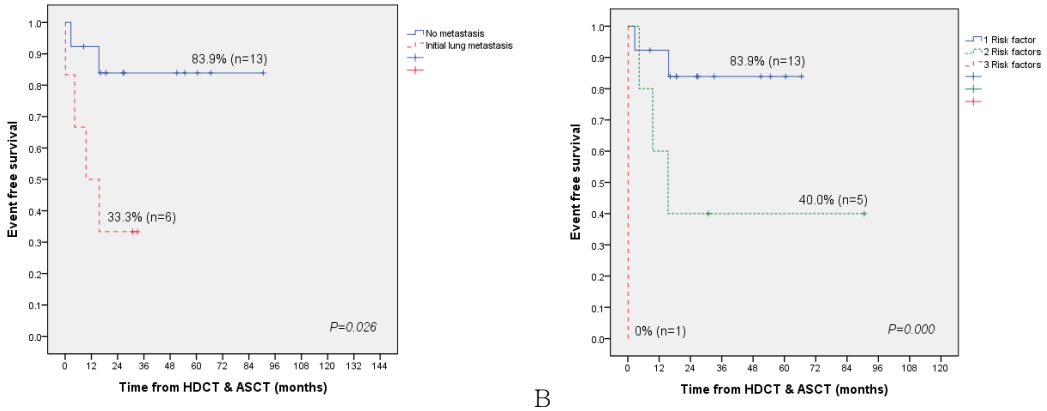
At median 31 months (range, 0 to 91 months) from ASCT, the OS was 78.3% (Table 3) (Figure 1-2A). The OS of Group I, Group II, Group III, and Group IV were 100%, 0%, 66.7% and 100% respectively (Figure 1-2B).



A B

Figure 1-2. Overall survival (A) of the total study population, and (B) of the different indication groups (Group I, poor response to neo-adjuvant chemotherapy only; Group II, lung metastasis with or without poor response to neo-adjuvant chemotherapy; Group III, progression during treatment, regardless of the presence of lung metastasis or poor response to neo-adjuvant chemotherapy; Group IV, relapse after completion of conventional therapy).

Regardless of the presence of other indications for HDCT & ASCT, patients with lung metastases at diagnosis had significantly worse EFS compared to those without lung metastases. Patients with lung metastases had EFS of 33.3%, whereas those without had EFS of 83.9% (Figure 1-3A). In particular, patients with bilateral lung metastases at presentation relapsed more often after HDCT & ASCT. Of the 6 patients with initial lung metastases, all 4 patients with bilateral lung metastases relapsed, whereas both of the 2 patients with unilateral lung metastases did not (Table 2). Also, patients with 2 or more risk factors had significantly worse EFS compared to those with only 1 risk factor. The patient with 3 risk factors had EFS of 0%, the patients with 2 risk factors had EFS of 40.0%, and the patients with 1 risk factor had EFS of 83.9% (Figure 1-3B).



A B

Figure 1-3. Event-free survival (A) depending on the presence of lung metastasis at diagnosis, and (B) depending on the number of risk factors (risk factors: poor response to neo-adjuvant chemotherapy, metastasis at diagnosis, progression during treatment, or relapse after completion of conventional therapy).

Overall, there were 3 mortalities (16%) (Table 3). One patient (5%) died of transplantation-related mortality, and 2 patients (11%) died of disease after relapse. Currently, 15 patients (79%) are disease-free at 32 months

(range, 8 to 91 months) from ASCT, and 1 patient (5%) is on chemotherapy after relapse (Table 2).

DISCUSSION

Current study population of high risk osteosarcoma showed improved survival compared to previous literatures; EFS was 67.4% and OS was 78.3%, at median 31 months (range, 0 to 91 months) from ASCT. HDCT & ASCT with melphalan, etoposide and carboplatin may thus be a promising treatment option for high risk osteosarcoma.

Patients with tumor necrosis below 90% had poor survival in our previous study; they had 5-year EFS of 29.2% and OS of 51.6% with conventional therapy (14). With HDCT & ASCT, survival of Group I patients improved; their EFS was 87.5% and their OS was 100%, at median 27 months (range, 8 to 60 months) from ASCT. Patients who progress during conventional treatment are known to have poor survival. The EFS of 33.3% and OS of 66.7% of Group III patients, at median 46 months (range, 0 to 91 months) from ASCT, are promising results. The OS following relapse is reported to be between 20 to 24% (11, 13). Previous studies with HDCT & ASCT for relapsed patients were not promising; their EFS ranged between 12 to 32%, and OS ranged between 20 to 41% (17, 18). In current study, HDCT & ASCT was successful in improving the outcome of patients in Group IV; their EFS was 100% and OS was 100%, at median 55 months (range, 19 to 67 months).

Patients with clinically detectable metastases are reported to have survival between 10 to 30% (10, 12, 19-21). Likewise, in our previous study, patients with metastases had poor survival; their 5-year EFS was 11.1% and their OS was 43.8% with conventional therapy (14). In current study, 3 of the 5 patients in Group II relapsed after HDCT & ASCT, and 2 of the 3 patients

refused further treatment and died of disease. Thus the OS of HDCT & ASCT for patients with relapses should be interpreted with caution. Also, although their EFS of 40.0%, at median 31 months (range, 5 to 38 months) from ASCT, may be improvements from former reports, further improvements are still needed.

Current HDCT & ASCT regimen was relatively well tolerated. Few patients experienced grade 4 adverse events, and most of them resolved completely. Also, all of the few veno-occlusive diseases resolved. However, 1 patient experienced transplantation-related mortality, which necessitates refinements in current practice.

The portion of patients who relapsed after HDCT & ASCT suggests that single HDCT & ASCT with melphalan, etoposide and carboplatin may not be sufficient for certain groups of high risk osteosarcoma. It has previously been shown that although HDCT & ASCT was effective in inducing complete remission in a large group of patients, the length of remission was short, and a large portion, 84.4%, relapsed or progressed after HDCT & ASCT (18). In our study, 5 patients (26%) relapsed after HDCT & ASCT. Further treatment strategy is thus needed to overcome these relapses after HDCT & ASCT, especially for patients with initial lung metastasis, and those with 2 or more risk factors (Figure 1-3A, 1-3B). Considering the successes of tandem HDCT & ASCT in high risk neuroblastoma, this may be a possible option for overcoming relapses after HDCT & ASCT (22-24).

Although HDCT & ASCT with melphalan, etoposide, and carboplatin is a promising treatment option for high risk osteosarcoma, current data should be interpreted with caution. For one, a large percentage of the study

population had poor response to neo-adjuvant chemotherapy as the sole factor that designated them as high risk osteosarcoma. For another, patients were followed-up for only a median period of 31 months (range, 0 to 91 months) from ASCT and long term follow-up data should thus be waited for. Also, current study evaluated a small number of patients treated in a single institute and multicenter collaboration study is thus warranted.

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국문 초록

서론: 신보강화학요법와 다중약제등의 치료를 도입한 후 소아 골육종의 성적이 많이 향상되었다. 그럼에도 불구하고 진단 당시 전이가 있거나, 신보강화학요법에 반응이 좋지 않았거나, 치료 중 진행을 하였거나, 치료 종결 후 재발을 한 경우에는 예후가 좋지 않다. 이에 골육종의 고위험군에 있어서 고용량 항암치료와 자가 조혈모세포 이식에 대한 후향적 연구를 통해 이의 효용성과 대해 알아보고자 하였다.

방법: 서울대학교 어린이병원 소아청소년과에서 2006 년 3 월과 2013 년 3 월 사이에 골육종의 고위험군 환아들에서 고용량 항암치료와 자가 조혈모세포 이식을 시행한 의무기록을 후향적으로 분석하였다. 본 연구에서 골육종 고위험군은 신보강화학요법 후 종양의 괴사가 90% 미만이었던 경우, 진단시 폐전이가 있는 경우, 치료 중 진행하였던 경우, 그리고 치료 종결 후 재발 하였던 경우로 정의하였다.

결과: 총 19 명의 환아는 정중 나이 12.4 세에 고용량 항암치료와 자가 조혈모세포 이식을 받았다. 이식된 정중 CD34+ 세포는 6.1 × 10^6/kg 개였고, 정중 day10 에 생착되었다 (day 4 에 사망한 환아 제외). 4 명의 환아에서 정맥 폐쇄성 질환이 있었고 3 명에서 이상반응이 있었지만 급성 신장 손상이 있었던 1 명을 제외하고는 호전되었다. 이식관련사망은 1 명에서 있었다. 자가 조혈모세포 이식으로부터 정중 관찰기간 31 개월에 (범위: 0 개월~ 91 개월) 환아들의 무병 생존률은 67.4%이었다. 재발한 5 명(26%)의 환아 중, 2 명의 환아는 추가적인 항암치료 후 관해되었고, 1 명의 환아는 현재 항암치료 중이며, 2 명의 환아는 추가적인 치료를 거부하고 사망하였다.

결론: Melphalan, etoposide, carboplatin 을 사용한 고용량 항암치료와 자가 조혈모세포 이식은 골육종 고위험군의 치료 전략이 될 수 있겠다. 그러나 아직 조혈모세포이식후 재발에 대해서는 더 나은 대안이 필요한 실정이다.

주요어 : 골육종, 고용량 항암치료, 자가 조혈모세포 이식, 전이, 괴사, 진행, 재발
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의학석사 학위 논문

High dose chemotherapy and autologous stem cell transplantation with melphalan, etoposide and carboplatin for high risk osteosarcoma

소아 골육종 고위험군의 고용량 항암치료와 자가 조혈모세포 이식

2013 년 10 월

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임상의과학과 석사 과정

홍 채 리

A thesis of the Degree of Master

소아 골육종 고위험군의 고용량 항암치료와 자가 조혈모세포 이식

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October, 2013

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A thesis submitted to the Department of Clinical Medical Sciences, in partial fulfillment of the requirements for the Degree of Master in Clinical Medical Sciences at Seoul National University College of Medicine

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지도 교수 강형진

이 논문을 임상의과학 석사 학위논문으로 제출함

2013 년 10 월

서울대학교 대학원

임상의과학과

홍채리

홍채리의 임상의과학석사 학위논문을 인준함

2013 년 12 월

위 원 장 신희영 (인)

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ABSTRACT

Introduction: Despite the greatly improved overall survival of high risk osteosarcoma, treatment outcomes remain poor for patients with poor response to neo-adjuvant chemotherapy or metastatic disease, and those who progress during treatment or relapse after completion of conventional therapy. Patients with these risk factors were treated with high dose chemotherapy and autologous stem cell transplantation (HDCT & ASCT) to overcome their poor survival. We herein analyzed the treatment outcome of these patients, and evaluated the feasibility of HDCT & ASCT for high risk osteosarcoma.

Methods: Medical record review was done on children with high risk osteosarcoma who underwent HDCT & ASCT with melphalan, etoposide and carboplatin at Seoul National University Children's Hospital between March 2006 and March 2013. High risk osteosarcoma was defined as those with tumor necrosis below 90% after neo-adjuvant chemotherapy, metastasis at diagnosis, progression during treatment or relapse after completion of conventional therapy.

Results: HDCT & ASCT was performed in 19 patients at median age of 12.4 years old (range, 6.1 to 19.7 years old), at median 9 months (range, 6 to 51 months) from diagnosis. They underwent HDCT & ASCT for tumor necrosis below 90% after neo-adjuvant chemotherapy only (n=8, Group I), for initial lung metastasis, with or without poor response to neo-adjuvant chemotherapy (n=5, Group II), for progression during treatment, regardless of presence of

initial lung metastasis or poor response to neo-adjuvant chemotherapy (n=3, Group III), and for relapse after completion of conventional therapy (n=3, Group IV). Median 6.1 × 10^6/kg CD34 cells were infused, and neutrophils engrafted at median 10 days from infusion. Grade 4 adverse events occurred in 3 patients, and these resolved in 2 patients. Transient veno-occlusive disease occurred in 4 patients. One patient died of transplantation-related mortality. The event-free survival was 67.4% at median 31 months (range, 0 to 91 months) from HDCT & ASCT. Five patients (26%) relapsed; 2 patients achieved remission with further chemotherapy, 1 patient is currently on chemotherapy, and 2 patients refused further treatment and died of disease. The overall survival was 78.3% at median 31 months (range, 0 to 91 months) from ASCT.

Conclusions: HDCT & ASCT with melphalan, etoposide and carboplatin may be a promising treatment option for high risk osteosarcoma. Further strategies are needed to overcome relapses after HDCT & ASCT.

Keywords osteosarcoma, high dose chemotherapy, autologous stem cell transplantation, metastasis, necrosis, progression, relapse

CONTENTS

LIST OF TABLES AND FIGURES

Chapter 1

LIST OF ABBREVIATIONS

HDCT & ASCT : high dose chemotherapy and autologous stem cell transplantation

OS : overall survival

IRB : institutional review boards

MRI : magnetic resonance imaging

PET : positron emission tomography

IV CDDP/ADR/HDMTX : intravenous cisplatin, adriamycin and high dose methotrexate

IA CDDP/ADR : intra-arterial cisplatin and adriamycin

PBSC : peripheral blood stem cell

G-CSF : granulocyte colony-stimulating factor

HDCT : high dose chemotherapy

CTCAE v4.03 : National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03

VOD : veno-occlusive disease

EFS : event-free survival

ASCT : autologous stem cell transplantation

TRM : transplantation-related mortality

AST, ALT : aspartate aminotransferase and alanine aminotransferase

AKI : acute kidney injury

GENERAL INTRODUCTION

Osteosarcoma is the most common bone tumor in children, with peak incidence in adolescence. From when surgery was the sole treatment option, the introduction of adjuvant chemotherapy, neo-adjuvant chemotherapy, and multi-agent aggressive chemotherapy has greatly improved the overall survival, from 15% to 70% (1-5). Current 5- and 10-year overall survival for localized osteosarcoma is approximately 70% and 65% respectively (6-8). Nonetheless, treatment outcomes remain poor for high risk osteosarcoma, such as those with poor response to neo-adjuvant chemotherapy, those with metastasis at presentation, and those who relapse (9-11). The reported overall survival of metastatic osteosarcoma is 25%, and that of relapsed osteosarcoma is less than 20% (12, 13).

We have previously analyzed the entire cohort of children with osteosarcoma treated at our institute (14). In this analysis, children with tumor necrosis below 90% after neo-adjuvant chemotherapy, metastasis at diagnosis, progression during treatment, and relapse after completion of conventional therapy were found to be associated with significantly worse survival. Fortunately, our preliminary results with high dose chemotherapy and autologous stem cell transplantation had been promising.

CHAPTER 1

High dose chemotherapy and autologous stem cell transplantation with melphalan, etoposide and carboplatin for high risk osteosarcoma

INTRODUCTION

Osteosarcoma is the most common bone tumor in children, with peak incidence in adolescence. From when surgery was the sole treatment option, the introduction of adjuvant chemotherapy, neo-adjuvant chemotherapy, and multi-agent aggressive chemotherapy has greatly improved the overall survival (OS), from 15% to 70% (1-5). Current 5- and 10-year OS for localized osteosarcoma is approximately 70% and 65% respectively (6-8). Nonetheless, treatment outcomes remain poor for high risk osteosarcoma, such as those with poor response to neo-adjuvant chemotherapy, those with metastasis at presentation, and those who relapse (9-11). The reported OS of metastatic osteosarcoma is 25%, and that of relapsed osteosarcoma is less than 20% (12, 13).

In attempt to evaluate the potential role of high dose chemotherapy and autologous stem cell transplantation (HDCT & ASCT) in improving the outcome of high risk osteosarcoma, we have previously analyzed the entire cohort of children treated for osteosarcoma at our institute between January 2000 and December 2007. In this analysis, children with tumor necrosis below 90% after neo-adjuvant chemotherapy, metastasis at diagnosis, progression during treatment, and relapse after completion of conventional therapy were found to be associated with significantly worse survival. With the promising preliminary results of high dose chemotherapy and autologous stem cell transplantation, we have previously suggested that HDCT & ASCT may be an alternative treatment option for these patients (14).

Thereafter, osteosarcoma patients with tumor necrosis below 90% after neo-adjuvant chemotherapy, metastasis at diagnosis, progression during

treatment, and relapse after completion of conventional therapy, underwent HDCT & ASCT at our institute. We herein report the treatment outcome of these patients. We thus aim to evaluate the feasibility of HDCT & ASCT with melphalan, etoposide and carboplatin for high risk osteosarcoma.

MATERIALS AND METHODS

1. Patient selection

A retrospective medical record review was done on 19 children with high risk osteosarcoma who underwent HDCT & ASCT with melphalan, etoposide and carboplatin at Seoul National University Children's Hospital between March 2006 and March 2013.

High risk osteosarcoma was defined as those with one or more of the following risk factors: poor response to neo-adjuvant chemotherapy, metastasis at diagnosis, progression during treatment, or relapse after completion of conventional therapy. Poor response to neo-adjuvant chemotherapy was defined as those with tumor necrosis below 90% after neo-adjuvant chemotherapy. Lung metastases were those that were radiologically evident on computed tomography (CT) of the chest. Both progression and relapse were those that were radiologically evident.

Of the osteosarcoma patients with 1 or more of the above risk factors, those who achieved complete remission with conventional therapy underwent HDCT & ASCT, with informed consent of all patients and/or their legal guardians. Patients were classified into 4 groups according to the indications for HDCT & ASCT. Patients with poor response to neo-adjuvant chemotherapy only were classified as Group I, and patients with metastasis at diagnosis, with or without poor response to neo-adjuvant chemotherapy, were classified as Group II. Patients who progressed during treatment, regardless of the presence of metastasis or poor response to neo-adjuvant chemotherapy, were classified as Group III, and patients who relapsed after completion of conventional therapy were classified as Group IV.

The institutional review boards (IRB) at Seoul National University Hospital approved this retrospective medical record review (IRB number: H-1308-081-513).

2. Conventional therapy

Biopsied specimens were histopathologically confirmed as osteosarcomas by the institutional pathologist. Initial evaluation consisted of magnetic resonance imaging (MRI) of the primary site, computed tomography (CT) of the chest, and bone scan and positron emission tomography (PET) of the whole body.

All patients underwent neo-adjuvant chemotherapy, which consisted either of intravenous cisplatin, adriamycin and high dose methotrexate (IV CDDP/ADR/HDMTX) or of intra-arterial cisplatin and adriamycin (IA CDDP/ADR). Intra-arterial neo-adjuvant chemotherapy was chosen in all technically feasible cases. Tumor response to neo-adjuvant chemotherapy was assessed by the institutional pathologist, based on the degree of necrosis of the resected primary tumor after neo-adjuvant chemotherapy.

Definitive surgery was performed either after 2 cycles of IV CDDP/ADR/HDMTX or after 4 cycles of IA CDDP/ADR. The institutional orthopedic surgeon decided on the procedure of surgery; wide excision and limb salvage operation was strongly encouraged whenever possible. Availability of allo-bones determined the choice for limb reconstruction. Allo-bones or synthetic prostheses were preferred to pasteurized autologous bones. All radiologically evident metastatic lesions were resected. For lung metastases, all resectable lesions were resected.

3. HDCT & ASCT

Autologous peripheral blood stem cell (PBSC) mobilization was performed with cyclophosphamide 1,000 mg/m^2 (day 0, 1, and 2) and etoposide 150 mg/m^2 (day 0, 1, and 2). Granulocyte colony-stimulating factor (G-CSF) 10 ug/kg/day was started 120 hours after chemotherapy. Those who failed chemo-mobilization underwent plerixafor-based mobilization; G-CSF 10 ug/kg/day for 4 days without prior chemotherapy, then plerixafor 240 ug/kg/day and G-CSF 10 ug/kg/day before each apheresis (15).

High dose chemotherapy consisted of melphalan 140 mg/m^2 (day -7), 70 mg/m^2 (day -6), etoposide 200 mg/m^2 (day -8, -7, -6, and -5) and carboplatin 400 mg/m^2 (day -8, -7, -6, and -5). Autologous PBSCs were infused 120 hours after the end of high dose chemotherapy (HDCT).

G-CSF 300 ug/m^2/day was administered from day +1 until the neutrophil count was more than 1 $\times$ 10^9/L for 3 consecutive days. Achieving neutrophil count of 1 $\times$ 10^9/L or greater was defined as neutrophil engraftment.

4. Complications

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03). Hepatic veno-occlusive disease (VOD) was diagnosed according to the Baltimore criteria (16).

5. Statistical analysis

The probability of survival was calculated using the Kaplan-Meier method, and subgroup comparisons were done with the log-rank test. Event-free survival (EFS) was defined as the time from autologous stem cell transplantation (ASCT) to relapse or any other cause of death such as transplantation-related mortality (TRM). OS was defined as the time from diagnosis of osteosarcoma to death or last follow-up. The analysis was performed with the IBM SPSS Statistics version 19. *P*-values lower than 0.05 were considered statistically significant.

RESULTS

Clinical characteristics

Nineteen patients (13 boys, 6 girls) underwent HDCT & ASCT at median age of 12.4 years old (range, 6.1 to 19.7 years old), at median 9 months (range, 6 to 51 months) from diagnosis (Table 1). According to the indications for HDCT & ASCT, 8 patients were classified as Group I, 5 patients as Group II, 3 patients as Group III, and 3 patients as Group IV.

Distal femur was the most common site of primary tumor (n=13, 68%), followed by proximal humerus, proximal tibia and distal tibia. Osteoblastic type was the most frequent histologic type (n=15, 79%), followed by chondroblastic, fibroblastic and giant cell-rich osteosarcoma. Six patients (32%) had metastasis at diagnosis; lung was the sole site of metastasis for all of them (Table 1).

Conventional therapy

All 19 patients underwent neo-adjuvant chemotherapy; 12 patients (63%) received IV CDDP/ADR/HDMTX, and 7 patients (37%) received IA CDDP/ADR. Fourteen patients (74%) showed poor response to neo-adjuvant chemotherapy, with less than 90% of tumor necrosis (Table 1).

The entire study population managed to undergo wide excision and limb salvage operations after neo-adjuvant chemotherapy. Synthetic prostheses were most frequently used for limb salvage operations (n=8, 42%), followed by allo-bones (n=5, 26%), and autologous bones (n=4, 21%). A combination of allo-bone and autologous bone was used in 1 patient (5%), and

a combination of prosthesis, allo-bone, and autolgous bone was used in another patient (5%) (Table 1). The patient (No. 5) who used a combination of synthetic prosthesis, allo-bone, and autologous bone experienced local relapse, and thus underwent above knee amputation thereafter (Table 2).

Three patients (16%) progressed during conventional therapy, and 3 patients (16%) relapsed after completion of conventional therapy.

Table 1-1. Patient characteristics

	Group I (n=8)	Group II (n=5)	Group III (n=3)	Group IV (n=3)	Total (N=19)
Median age at diagnosis (years)	12.3 (8.8-15.4)	10.2 (5.4-15.7)	13.6 (8.7-13.9)	10.6 (6.6-15.4)	11.8 (5.4-15.7)
Median age at HDCT & ASCT (years)	13.1 (9.6-16.1)	10.8 (6.1-16.4)	14.7 (10.2-16.8)	12.4 (9.7-19.7)	12.4 (6.1-19.7)
Sex (%)					
Male	6 (75)	4 (80)	1 (33)	2 (67)	13 (68)
Female	2 (25)	1 (20)	2 (67)	1 (33)	6 (32)
Primary site (%)					
Distal femur	4 (50)	4 (80)	3 (100)	2 (67)	13 (68)
Proximal humerus	2 (25)	1 (20)	-	-	3 (16)
Proximal tibia	1 (13)	-	-	1 (33)	2 (11)
Distal tibia	1 (13)	-	-	-	1 (5)
Histologic type (%)					
Osteoblastic	6 (75)	5 (100)	2 (67)	2 (67)	15 (79)
Chondroblastic	1 (13)	-	1 (33)	-	2 (11)
Fibroblastic	-	-	-	1 (33)	1 (5)
Giant cell-rich	1 (13)	-	-	-	1 (5)
Metastasis at diagnosis (%)					
Lung metastasis	-	5 (100)	1 (33)	-	6 (32)
Neoadjuvant chemotherapy (%)					
IV CDDP/ADR/HDMTX	6 (75)	4 (80)	2 (67)	-	12 (63)
IA CDDP/ADR	2 (25)	1 (20)	1 (33)	3 (100)	7 (37)
Surgery (%)					
Wide excision & limb salvage	8 (100)	5 (100)	3 (100)	3 (100)	19 (100)
AK amputation after local relapse	-	-	-	1 (33)	1 (5)
Type used for limb salvage operation (%)					
Synthetic prosthesis	6 (75)	-	1 (33)	1 (33)	8 (42)
Allo-bone	1 (13)	2 (40)	1 (33)	1 (33)	5 (26)
Autologous bone	1 (13)	2 (40)	1 (33)	-	4 (21)
Allo-bone + Autologous bone	-	1 (20)	-	-	1 (5)
Synthetic prosthesis + Allo-bone + Autologous bone	-	-	-	1 (33)	1 (5)
Necrosis (%)					
Necrosis ≥ 90%	-	1 (20)	-	3 (100)	4 (21)
50% ≤ Necrosis < 90%	4 (50)	2 (40)	1 (33)	-	7 (37)
10% ≤ Necrosis < 50%	3 (38)	-	1 (33)	-	4 (21)
Necrosis < 10%	1 (13)	1 (20)	1 (33)	-	3 (16)
Not evaluable	-	1 (20)	-	-	1 (5)

HDCT & ASCT, high dose chemotherapy and autologous stem cell transplantation; IV CDDP/ADR/HDMTX, intravenous cisplatin, adriamycin and high dose methotrexate; IA CDDP/ADR, intra-arterial cisplatin and adriamycin; AK, above knee

Table 1-2. Clinical characteristics and treatment outcome of the entire cohort

No.	Sex	Age at ASCT (yr)	1° site	Histology	NeoadjC Tx	Surgery	Prosth/ bone	Group	Poor necr (%)	Initial meta	Progression	Relapse	Complication	Events (relapse site)	Status (mo from ASCT)
1	F	16.8	dF	Ob	IA	WE/LS	prosth	III	Y (60%)	–	Y (Local, RLg)	–	Gr 4 Cr	–	NED (91)
2	M	13.7	dF	Ob	IA	WE/LS	auto	II	Y (50%)	Y (BLg)	–	–	Gr 4 LFT, VOD	Relapse (BLg, T4 VB, skin)	DOD (5)
3	M	9.7	dF	Ob	IA	WE/LS	prosth	IV	–	–	–	Y (Frontal bone)	–	–	NED (67)
4	F	13.7	pH	Ob	IV	WE/LS	prosth	I	Y (<10%)	–	–	–	–	–	NED (60)
5	F	12.4	pT	Ob	IA	WE/LS, AK ampt	p-allo-auto	IV	–	–	–	Y (Local)	–	–	NED (55)
6	M	9.6	pH	Ob	IV	WE/LS	prosth	I	Y (50%)	–	–	–	–	–	NED (51)
7	M	16.4	pH	Ob	IV	WE/LS	allo	II	Y (80%)	Y (BLg)	–	–	–	Relapse (RLg, 8th rib)	DOD (38)
8	M	14.7	dF	Ob	IV	WE/LS	allo	III	Y (20%)	–	Y (Local, LLg)	–	–	Relapse (Local)	NED (46)
9	M	16.1	dF	Ob	IA	WE/LS	prosth	I	Y (30%)	–	–	–	–	Relapse (LLg)	NED (40)
10	M	6.1	dF	Ob	IV	WE/LS	auto	II	–	Y (RLg)	–	–	VOD	–	NED (33)
11	M	10.8	dF	Ob	IV	WE/LS	allo	II	Y (<10%)	Y (LLg)	–	–		–	NED (31)
12	M	9.7	dF	Ob	IV	WE/LS	prosth	I	Y (10%)	–	–	–	–	–	NED (27)
13	M	12.4	dT	Cb	IV	WE/LS	allo	I	Y (40%)	–	–	–	VOD	–	NED (26)
14	F	10.2	dF	Cb	IV	WE/LS	auto	III	Y (<10%)	Y (BLg)	Y (BLg)	–	VOD	TRM (SCA)	TRM (0)
15	M	10.2	pT	Ob	IV	WE/LS	auto	I	Y (80%)	–	–	–	–	–	NED (19)
16	F	8.5	dF	Ob	IV	WE/LS	allo-auto	II	N/E	Y (BLg)	–	–	–	Relapse (Local)	On CTx (19)
17	M	19.7	dF	Fb	IA	WE/LS	allo	IV	–	–	–	Y (BLg)	Gr 4 AKI	–	NED (19)
18	M	14.5	dF	Gc	IA	WE/LS	prosth	I	Y (85%)	–	–	–	–	–	NED (16)
19	F	14.6	dF	Ob	IV	WE/LS	prosth	I	Y (80%)	–	–	–	–	–	NED (8)

ASCT, autologous stem cell transplantation; yr, years; 1°, primary; Neoadj, Neo-adjuvant; CTx, Chemotherapy; prosth, synthetic prosthesis; necr, necrosis; meta, metastasis; mo, months; F, female; M, male; dF, distal femur; pT, proximal tibia; pH, proximal humerus; dT, distal tibia; Ob, osteoblastic; Fb, fibroblastic; Cb, condroblastic; Gc, Giant cell-rich; IA, intra-arterial cisplatin and adriamycin; IV, intravenous cisplatin, adriamycin, and high dose methotrexate; WE/LS, wide excision and limb salvage; AK ampt, above knee amputation; auto, autologous bone; allo, allo-bone; Y, yes; N/E, not evaluable; BLg, bilateral lung; RLg, right lung; LLg, left lung; Gr 4, Grade 4 adverse event by Common Terminology Criteria for Adverse Events version 4.03; Cr, creatinine elevation; LFT, aspartate aminotransferase and alanine aminotransferase elevation; AKI, acute kidney injury; VOD, veno-occlusive disease; T4 VB, T4 vertebral body; TRM, transplantation-related mortality; SCA, sudden cardiac arrest; NED, no evidence of disease; DOD, died of disease

HDCT & ASCT

For autologous PBSC infusion, median 6.1 × 10^6/kg (range, 1.6−15.7 × 10^6/kg) CD34 cells were infused on day 0. Except for the 1 patient who died 4 days after infusion, before engraftment, all 18 patients achieved neutrophil engraftment at median 10 days (range, 8−11 days) from infusion (Table 3).

Table 1−3. Outcome of HDCT & ASCT

	Group I (n=8)	Group II (n=5)	Group III (n=3)	Group IV (n=3)	Total (N=19)
Infused cell dose					
MNC, ×10^8/kg (range)	10.3 (4.4−30.1)	7.6 (5.8−18.3)	15.1 (2.9−15.9)	16.5 (4.6−17.4)	10.8 (2.9−30.1)
CD34, ×10^6/kg (range)	6.3 (2.5−14.5)	4.4 (4.0−15.7)	6.3 (4.3−12.0)	3.3 (1.6−13.9)	6.1 (1.6−15.7)
Neutrophil engraftment					
Day from infusion	10 (8−11)	10 (9−11)	10 (9−11)	10 (10−11)	10 (8−11)
Complications (%)					
Gr 4 AST, ALT elevation	−	1 (20)	−	−	1 (5)
Gr 4 Creatinine elevation	−	−	1 (33)	−	1 (5)
Gr 4 Acute kidney injury	−	−	−	1 (33%)	1 (5)
Veno−occlusive disease	1 (13)	2 (40)	1 (33)	−	4 (21)
Events					
Relapse	1 (13)	3 (60)	1 (33)	−	5 (26)
Tpl−related mortality	−	−	1 (33)	−	1 (5)
FU duration from ASCT, mo (range)	27 (8−60)	31 (5−38)	46 (0−91)	55 (19−67)	31 (0−91)
Current status					
No evidence of disease	8 (100)	2 (40)	2 (67)	3 (100%)	15 (79)
On CTx after relapse	−	1 (20)	−	−	1 (5)
Tpl−related mortality	−	−	1 (33)	−	1 (5)
Died of disease	−	2 (40)	−	−	2 (11)

MNC, mononuclear cells; Gr 4, Grade 4 adverse event; AST, ALT, aspartate aminotransferase and alanine aminotransferase; Tpl, transplantation; FU, follow−up; ASCT, autologous stem cell transplantation; CTx, Chemotherapy

Complications

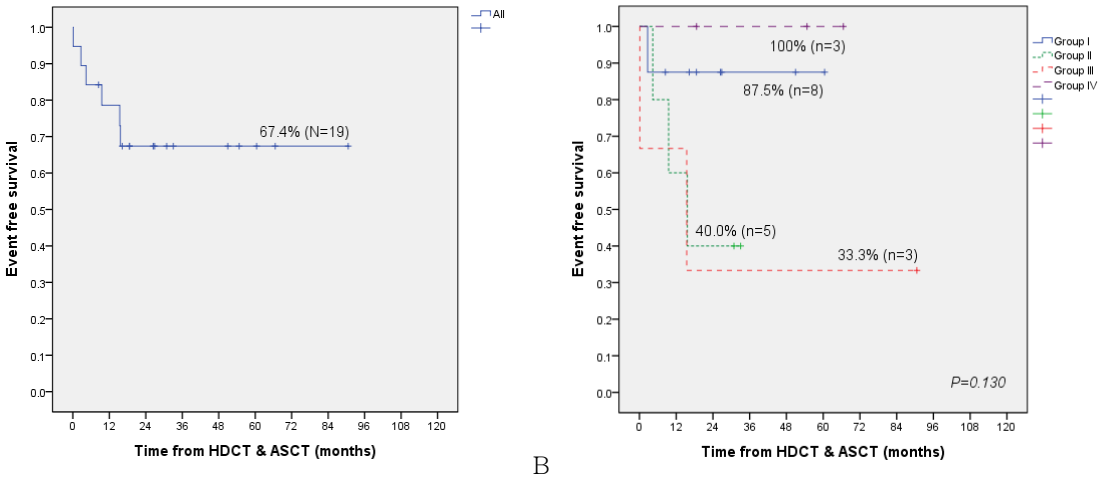
Three patients (16%) experienced grade 4 adverse events. One patient had transient grade 4 aspartate aminotransferase and alanine aminotransferase (AST, ALT) elevation. Another patient had transient grade 4

creatinine elevation. But another patient (No. 17) had grade 4 acute kidney injury (AKI) which progressed to borderline chronic kidney disease. Four patients (21%) experienced VOD, but all of them resolved (Table 2, 3).

Transplantation-related mortality occurred in 1 patient (5%). She (No. 14) died of sudden cardiac arrest on day +4 (Table 2, 3).

Events

At median 31 months (range, 0 to 91 months) from ASCT, the EFS was 67.4% (Table 3) (Figure 1-1A). The EFS of Group I, Group II, Group III, and Group IV were 87.5%, 40.0%, 33.3% and 100% respectively (Figure 1-1B).



A B

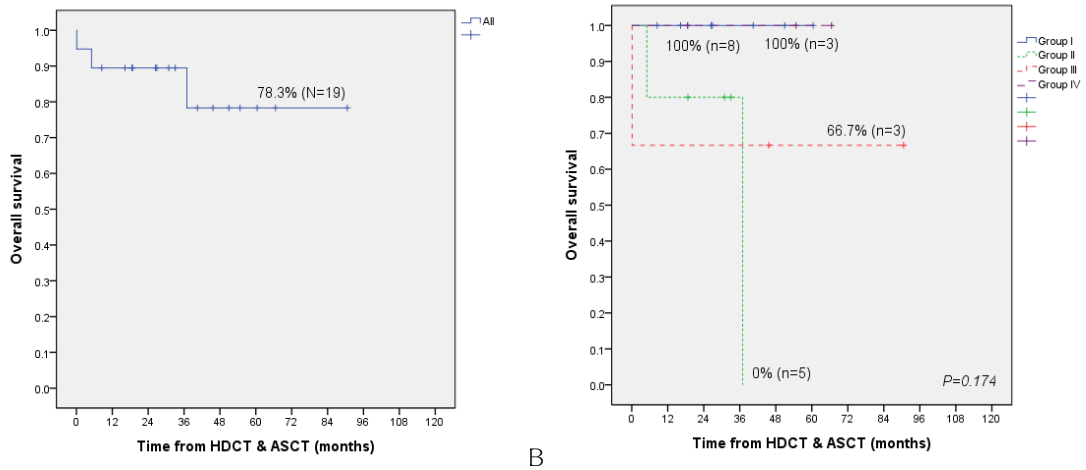
Figure 1-1. Event-free survival (A) of the total study population, and (B) of the different indication groups (Group I, poor response to neo-adjuvant chemotherapy only; Group II, lung metastasis with or without poor response to neo-adjuvant chemotherapy; Group III, progression during treatment, regardless of the presence of lung metastasis or poor response to neo-adjuvant chemotherapy; Group IV, relapse after completion of conventional therapy).

Five patients (26%) relapsed at median 9 months (range, 3 to 15 months) from HDCT & ASCT (Table 3). Two patients (11%) refused further treatment, 2 patients (11%) received further surgery and chemotherapy, and

1 patient (5%) is currently undergoing chemotherapy. The 2 patients who refused further treatment died of disease at median 16 months (range, 2 to 29 months) from relapse. The 2 patients who underwent further surgery and chemotherapy are both alive with no evidence of disease at 37 months (range, 30 to 43 months) from relapse; patient No. 8 received 13 cycles chemotherapy with ifosfamide, carboplatin, etoposide and cyclophosphamide, and patient No. 9 recieved 8 cycles of chemotherapy with gemcitabine and docetaxel (Table 2). The patient who is currently on chemotherapy, patient No. 16, is on chemotherapy with ifosfamide, carboplatin and etoposide.

Outcome

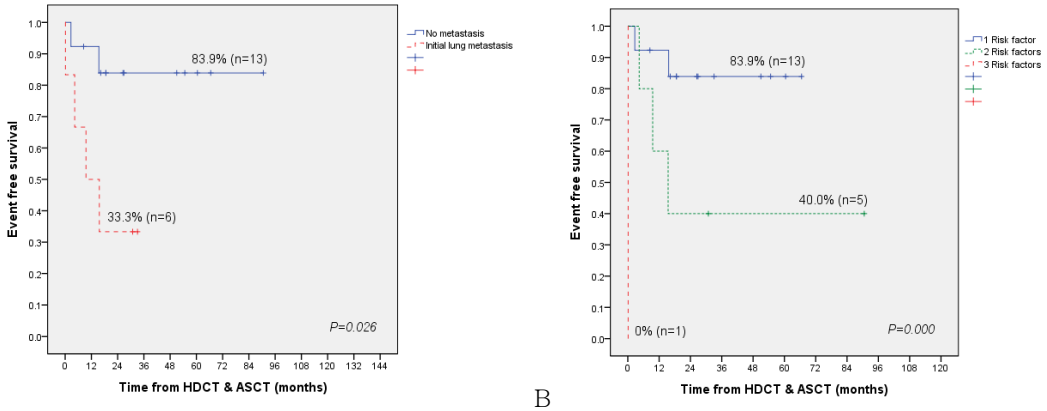
At median 31 months (range, 0 to 91 months) from ASCT, the OS was 78.3% (Table 3) (Figure 1-2A). The OS of Group I, Group II, Group III, and Group IV were 100%, 0%, 66.7% and 100% respectively (Figure 1-2B).



A B

Figure 1-2. Overall survival (A) of the total study population, and (B) of the different indication groups (Group I, poor response to neo-adjuvant chemotherapy only; Group II, lung metastasis with or without poor response to neo-adjuvant chemotherapy; Group III, progression during treatment, regardless of the presence of lung metastasis or poor response to neo-adjuvant chemotherapy; Group IV, relapse after completion of conventional therapy).

Regardless of the presence of other indications for HDCT & ASCT, patients with lung metastases at diagnosis had significantly worse EFS compared to those without lung metastases. Patients with lung metastases had EFS of 33.3%, whereas those without had EFS of 83.9% (Figure 1-3A). In particular, patients with bilateral lung metastases at presentation relapsed more often after HDCT & ASCT. Of the 6 patients with initial lung metastases, all 4 patients with bilateral lung metastases relapsed, whereas both of the 2 patients with unilateral lung metastases did not (Table 2). Also, patients with 2 or more risk factors had significantly worse EFS compared to those with only 1 risk factor. The patient with 3 risk factors had EFS of 0%, the patients with 2 risk factors had EFS of 40.0%, and the patients with 1 risk factor had EFS of 83.9% (Figure 1-3B).



A B

Figure 1-3. Event-free survival (A) depending on the presence of lung metastasis at diagnosis, and (B) depending on the number of risk factors (risk factors: poor response to neo-adjuvant chemotherapy, metastasis at diagnosis, progression during treatment, or relapse after completion of conventional therapy).

Overall, there were 3 mortalities (16%) (Table 3). One patient (5%) died of transplantation-related mortality, and 2 patients (11%) died of disease after relapse. Currently, 15 patients (79%) are disease-free at 32 months

(range, 8 to 91 months) from ASCT, and 1 patient (5%) is on chemotherapy after relapse (Table 2).

DISCUSSION

Current study population of high risk osteosarcoma showed improved survival compared to previous literatures; EFS was 67.4% and OS was 78.3%, at median 31 months (range, 0 to 91 months) from ASCT. HDCT & ASCT with melphalan, etoposide and carboplatin may thus be a promising treatment option for high risk osteosarcoma.

Patients with tumor necrosis below 90% had poor survival in our previous study; they had 5-year EFS of 29.2% and OS of 51.6% with conventional therapy (14). With HDCT & ASCT, survival of Group I patients improved; their EFS was 87.5% and their OS was 100%, at median 27 months (range, 8 to 60 months) from ASCT. Patients who progress during conventional treatment are known to have poor survival. The EFS of 33.3% and OS of 66.7% of Group III patients, at median 46 months (range, 0 to 91 months) from ASCT, are promising results. The OS following relapse is reported to be between 20 to 24% (11, 13). Previous studies with HDCT & ASCT for relapsed patients were not promising; their EFS ranged between 12 to 32%, and OS ranged between 20 to 41% (17, 18). In current study, HDCT & ASCT was successful in improving the outcome of patients in Group IV; their EFS was 100% and OS was 100%, at median 55 months (range, 19 to 67 months).

Patients with clinically detectable metastases are reported to have survival between 10 to 30% (10, 12, 19-21). Likewise, in our previous study, patients with metastases had poor survival; their 5-year EFS was 11.1% and their OS was 43.8% with conventional therapy (14). In current study, 3 of the 5 patients in Group II relapsed after HDCT & ASCT, and 2 of the 3 patients

refused further treatment and died of disease. Thus the OS of HDCT & ASCT for patients with relapses should be interpreted with caution. Also, although their EFS of 40.0%, at median 31 months (range, 5 to 38 months) from ASCT, may be improvements from former reports, further improvements are still needed.

Current HDCT & ASCT regimen was relatively well tolerated. Few patients experienced grade 4 adverse events, and most of them resolved completely. Also, all of the few veno-occlusive diseases resolved. However, 1 patient experienced transplantation-related mortality, which necessitates refinements in current practice.

The portion of patients who relapsed after HDCT & ASCT suggests that single HDCT & ASCT with melphalan, etoposide and carboplatin may not be sufficient for certain groups of high risk osteosarcoma. It has previously been shown that although HDCT & ASCT was effective in inducing complete remission in a large group of patients, the length of remission was short, and a large portion, 84.4%, relapsed or progressed after HDCT & ASCT (18). In our study, 5 patients (26%) relapsed after HDCT & ASCT. Further treatment strategy is thus needed to overcome these relapses after HDCT & ASCT, especially for patients with initial lung metastasis, and those with 2 or more risk factors (Figure 1-3A, 1-3B). Considering the successes of tandem HDCT & ASCT in high risk neuroblastoma, this may be a possible option for overcoming relapses after HDCT & ASCT (22-24).

Although HDCT & ASCT with melphalan, etoposide, and carboplatin is a promising treatment option for high risk osteosarcoma, current data should be interpreted with caution. For one, a large percentage of the study

population had poor response to neo-adjuvant chemotherapy as the sole factor that designated them as high risk osteosarcoma. For another, patients were followed-up for only a median period of 31 months (range, 0 to 91 months) from ASCT and long term follow-up data should thus be waited for. Also, current study evaluated a small number of patients treated in a single institute and multicenter collaboration study is thus warranted.

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국문 초록

서론: 신보강화학요법와 다중약제등의 치료를 도입한 후 소아 골육종의 성적이 많이 향상되었다. 그럼에도 불구하고 진단 당시 전이가 있거나, 신보강화학요법에 반응이 좋지 않았거나, 치료 중 진행을 하였거나, 치료 종결 후 재발을 한 경우에는 예후가 좋지 않다. 이에 골육종의 고위험군에 있어서 고용량 항암치료와 자가 조혈모세포 이식에 대한 후향적 연구를 통해 이의 효용성과 대해 알아보고자 하였다.

방법: 서울대학교 어린이병원 소아청소년과에서 2006 년 3 월과 2013 년 3 월 사이에 골육종의 고위험군 환아들에서 고용량 항암치료와 자가 조혈모세포 이식을 시행한 의무기록을 후향적으로 분석하였다. 본 연구에서 골육종 고위험군은 신보강화학요법 후 종양의 괴사가 90% 미만이었던 경우, 진단시 폐전이가 있는 경우, 치료 중 진행하였던 경우, 그리고 치료 종결 후 재발 하였던 경우로 정의하였다.

결과: 총 19 명의 환아는 정중 나이 12.4 세에 고용량 항암치료와 자가 조혈모세포 이식을 받았다. 이식된 정중 CD34+ 세포는 6.1 × 10^6/kg 개였고, 정중 day10 에 생착되었다 (day 4 에 사망한 환아 제외). 4 명의 환아에서 정맥 폐쇄성 질환이 있었고 3 명에서 이상반응이 있었지만 급성 신장 손상이 있었던 1 명을 제외하고는 호전되었다. 이식관련사망은 1 명에서 있었다. 자가 조혈모세포 이식으로부터 정중 관찰기간 31 개월에 (범위: 0 개월~ 91 개월) 환아들의 무병 생존률은 67.4%이었다. 재발한 5 명(26%)의 환아 중, 2 명의 환아는 추가적인 항암치료 후 관해되었고, 1 명의 환아는 현재 항암치료 중이며, 2 명의 환아는 추가적인 치료를 거부하고 사망하였다.

결론: Melphalan, etoposide, carboplatin 을 사용한 고용량 항암치료와 자가 조혈모세포 이식은 골육종 고위험군의 치료 전략이 될 수 있겠다. 그러나 아직 조혈모세포이식후 재발에 대해서는 더 나은 대안이 필요한 실정이다.

주요어 : 골육종, 고용량 항암치료, 자가 조혈모세포 이식, 전이, 괴사, 진행, 재발
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