Feasibility of sequential high-dose chemotherapy followed by autologous hematopoietic stem cell rescue in advanced pediatric solid tumors

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Feasibility of sequential high-dose chemotherapy followed by autologous hematopoietic stem cell rescue in advanced pediatric solid tumors

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Abbreviations

ANC: absolute neutrophil count

CT: chemotherapy

CR: complete response

G-CSF: granulocyte colony stimulating factor

HDCT: high-dose chemotherapy

HSC: hematopoietic stem cell

MR: minimal response

NR: no response

PBSC: peripheral blood stem cell

PD: progressive disease

PLT: platelet

PR: partial response

RHDCT: reduced conditioning high-dose chemotherapy

RT: radiation therapy

TBI: total body irradiation

TH RT PCR: tyrosine hydroxylase reverse transcriptase polymerase chain reaction

TRM: transplantation related mortality

VGPR: very good partial response

Abstract

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Background: Even though high-dose chemotherapy (HDCT) supported by autologous hematopoietic stem cell (HSC) infusion may improve the survival outcome in advanced pediatric solid tumors, most patients have had only brief response ending with early recurrence of primary tumor, which results in further need for maximum tolerated dose regimen with minimal toxicity.

Purpose: To evaluate the feasibility and early tumor response of 3 cycles of sequential HDCT which is consisted of two consequent cycles of reduced conditioning HDCT followed by final HDCT with autologous HSC infusion.

Patients and Methods: Medical records of 9 patients with advanced pediatric solid tumor diagnosed between June 2005 and December 2006 who

underwent 3 cycles of sequential HDCT followed by HSC infusion were reviewed in retrospective manner.

Results: Each median CD 34 positive HSC dose infused after 3 cycles of sequential HDCT were 3.4 x 10^6/kg, 3.2 x 10^6/kg and 4.4 x 10^6/kg. Each median time to an absolute neutrophil count > 0.5 x 10^9/L were 12, 13 and 12 days. Major toxic reactions after 3 cycles of HDCT included fever, microbiologically documented infection, stomatitis and vomiting. 7 out of 9 patients showed response (six complete responses and one partial response) to the therapy, 1 patient with no response showed progression of disease. 1 patient died of transplantation related mortality after 2nd cycle of reduced conditioning HDCT.

Conclusion: 3 cycles of sequential HDCT including 2 times of reduced conditioning HDCT supported by autologous HSC infusion seems to be feasible and effective in treating advanced childhood solid tumors, approaching and maintaining complete response status. Further studies with larger patient group and long term follow-up analysis are required.

Key words: high-dose, chemotherapy, childhood solid tumors

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I. INTRODUCTION

The prognosis for children with disseminated or recurrent solid tumors is poor. Few can be cured with conventional therapy, although many do show an initial, transient response to chemotherapy. It is postulated that dose intensification of cytotoxic agents followed by autologous hematopoietic stem cell (HSC) infusion may improve disease free survival in these patients, and the response rate of patients with advanced neuroblastoma, Ewing's sarcoma, or rhabdomyosarcoma to a single course of high-dose chemotherapy (HDCT) has been encouraging.[1-4] However, most patients have had only a brief response, ending with an

early recurrence of the primary tumor.[1] Over the last decade, a number of approaches have been tried to improve the result of HDCT. These approaches included increasing the number of agents in the myeloablative regimen and ‘double grafting’, ‘tandem transplantation’, ‘triple tandem transplantation’ and so on.[5] However, even though preliminary results of these trials suggested improvements in tumor response, significant obstacles such as extramedullary toxicities, cumulative toxicities with incomplete hematologic recovery, delay in treatment between courses were encountered.[6] With these factors in mind, we felt the need of developing a new HDCT strategy which can deliver maximum or near-maximum tolerated doses with minimal toxicities. In this study, we retrospectively investigated the feasibility and short term tumor response of sequential HDCT which consisted with 2 courses of reduced conditioning HDCT and final HDCT, each followed by autologous HSC infusion.

II. MATERIALS AND METHODS

1. Patients

Nine patients with advanced pediatric solid tumor who underwent sequential HDCT between June 2005 and December 2006 were enrolled to undergo retrospective chart review. All of the patients were considered as high risk solid tumors at the time of diagnosis which were felt to have less than a 20% chance of survival with conventional chemotherapy. The disease categories included in this study were stage IV neuroblastoma, stage IV rhabdomyosarcoma, stage IV nasopharyngeal cancer and stage IV yolk sac tumor. All nine patients fulfilled the requirements including age of 1-21 years, left ventriclular ejection fraction > 50%, normal serum creatinine and bilirubin levels, normal serum alkaline phosphate and alanine aminotrasnferase levels and Lansky's performance status > 70%. Characteristics of each patient are shown in Table 1.

Table 1. Patient characteristics

	Sex	Age (yr/mo)	Dx	Stage	Cycles of Prior Chemotherapy	Operation	Dz status at HDCT	Source of stem cell
1	M	5/7	NB	IV	5	Y	VGPR	auto PBSC
2	M	2/2	NB	IV	5	Y	VGPR	auto PBSC, auto CBSC
3	F	4/2	NB	IV	5	Y	PR	auto PBSC
4	F	9/5	NB	IV	3	N	PR	auto PBSC
5	F	5/5	NB	IV	4	Y	VGPR	auto PBSC
6	M	11/11	RMS	IV	6	Y	NR	auto PBSC
7	M	15/8	RMS	IV	3	N	PD	auto PBSC
8	M	8/7	NPC	IV	8	N	MR	auto PBSC
9	M	1/11	YST	IV	6	Y	PR	auto PBSC

yr: year, mo: month, Dx: diagnosis, Dz: disease, HDCT: high-dose chemotherapy, NB: neuroblastoma, RMS: rhabdomyosarcoma, NPC: nasopharyngeal cancer, YST: yolk sac tumor, Y: yes, N: no, VGPR: very good partial response, PR: partial response, NR: no response, PD: progressive disease, MR: minimal response, auto: autologous, PBSC: peripheral blood stem cell, CBSC: cord blood stem cell

2. Initial therapy and subsequent therapy

After evaluation of disease, all patients received initial therapy including induction chemotherapy, surgical resection of primary tumor if possible. Induction chemotherapy was performed according to their disease categories. After induction chemotherapy with or without surgical treatment, tumor response was evaluated.

Peripheral blood stem cell (PBSC) collection was recommended when bone marrow was clear of tumor cells (and negative findings of tyrosine hydroxylase reverse transcriptase polymerase chain reaction in case of neuroblastoma) and was done after third or fourth cycle of chemotherapy. PBSC were harvested and cryopreserved according to the standard technique after mobilization with granulocyte colony stimulating factor (G-CSF). Minimum 2 x 10^6 CD 34 positive stem cells per patient's body weight (kg) were recommended for one round of infusion, and if more than twice the targeted number of PBSC were collected, they were preserved in 2 bags. In one case, autologous cord blood stem cell was used after final HDCT.

After PBSC harvest, the patients underwent two consequent courses of reduced conditioning HDCT (etoposide 200mg/m^2 on day -3,-2,-1, cyclophophamide 2g/m^2 on day -3,-2, carboplatin 300mg/m^2 on day -3,-2) followed by autologous HSC infusion which were performed in four weeks of interval. After the two courses of reduced conditioning HDCT, patients underwent two or three cycles of conventional chemotherapy with or without local radiation therapy. Finally patients underwent HDCT (either with etoposide 150mg/m^2 on day -8,-7,-6,-5, carboplatin 200mg/m^2 on day -8,-7,-6,-5, melphalan

50mg/m^2 on day -8,-7,-6 with total body irradiation (TBI) 300cGy on day -3,-2,-1 or etoposide 200mg/m^2 on day -7,-6,-5,-4, carboplatin 300mg/m^2 on day -7,-6,-5,-4, melphalan 180mg/m^2 on day -2.) with autologous HSC infusion after completion of above treatment. The planned schema of therapy and conditioning regimens are shown in Figure 1. and Table 2.

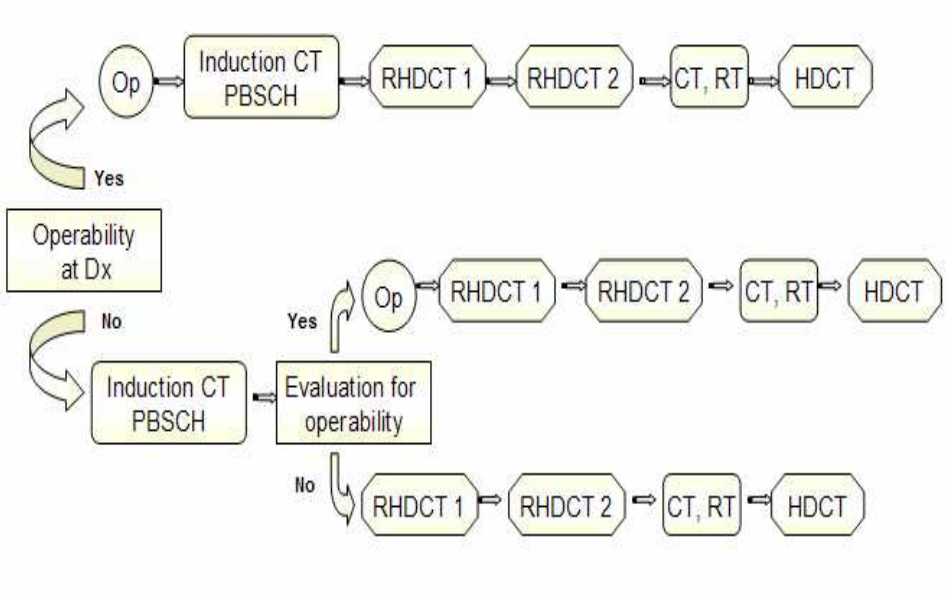

Figure 1. Planned schema of treatment

Dx: diagnosis, Op: operation, CT: chemotherapy, PBSCH: peripheral blood stem cell harvest, RHDCT: reduced conditioning high-dose chemotherapy, RT: radiation therapy, HDCT: high-dose chemotherapy.

Table 2. Regimens of high-dose chemotherapy

RHDCT			HDCT		
Etoposide	200mg/m^2	D-3,-2,-1	Etoposide	150mg/m^2	D-8,-7,-6,-5
Cyclophosphamide	2g/m^2	D-3, -2	Carboplatin	200mg/m^2	D-8,-7,-6,-5
Carboplatin	300mg/m^2	D-3,-2	Melphalan	50mg/m^2	D-8,-7,-6
			TBI	300cGy	D-3,-2,-1
				or	
			Etoposide	200mg/m^2	D-7,-6,-5,-4
			Carboplatin	300mg/m^2	D-7,-6,-5,-4
			Melphalan	180mg/m^2	D-2

RHDCT: reduced conditioning high-dose chemotherapy, HDCT: high-dose chemotherapy, TBI: total body irradiation

3. Supportive Care

After placement of double-lumen Hickman line, patients were admitted to the hospital for each course of high-dose chemotherapy. Continuous hydration was performed and mesna was administrated when cyclophosphamide was given. All patients received trimethoprim-sulfamethoxazole as prophylaxis against *Pneumocystis carinii* pneumonia.

Transfusion of platelets were administrated as necessary to maintain a platelet count greater than 30 x 10^9/L and transfusion of irradiated packed RBCs were administrated to maintain a hematocrit concentration of greater than 20% to 25%. If patients experienced

fever (body temperature of $\geq$ 38°C) and had an absolute neutrophil count (ANC) < 0.5 x 10^9/L, they were treated with broad-spectrum antibiotics and empirical antifungal agents. In addition, patients with a 10% weight loss from the time of starting therapy received nutritional support using total parenteral nutrition (TPN).

4. Analysis

Regimen related extramedullary toxicity was graded according to the national cancer institute (NCI) common toxicity criteria (CTC) version 2.0. Hematopoietic recovery was assessed by neutrophil engraftment time (the median time to absolute neutrophil count (ANC) > 0.5 x 10^9/L) and platelet recovery time (the median time to a sustained platelet count more than 50 x 10^9/L without transfusion). Tumor response was assessed after each course of HDCT and 2 months after completion of final HDCT. In case of Neuroblastoma, tumor response was evaluated by International neuroblastoma response criteria (INRC),[7] other solid tumors as following; complete response (CR) defined as disappearance of tumor judged by imaging studies and normalized biochemical levels, partial response (PR) defined as > 50% decrease of primary tumor with all measurable size

decrease by > 50% in metastatic lesions, minimal response (MR) as < 50% decrease of primary and metastatic tumor without any newly developed lesion, no response (NR) as < 50% decrease of primary lesion and < 25% increase of other existing lesion without any newly developed lesion, progressive disease (PD) as any measurable lesion with > 25% increase and any new lesion.

The over all survival from the time of diagnosis, follow up duration after completion of treatment and current survival status were also evaluated.

III. RESULTS

1. Patients

Nine patients aged 2-15 (median 5.5 years) were enrolled (Table 1). All patients had received a median of three cycles of previous chemotherapy (range 3-8 cycles) and were exposed to a median of five different cytotoxic agents (range 3-5 agents). All nine patients were diagnosed as stage IV disease. Five were neuroblastoma, two were rhabdomyosarcoma, and there were one nasopharyngeal cancer and one yolk sac tumor. Six patients received surgical resection of primary tumor before starting sequential HDCT, three were unresectable. The median time from primary treatment to sequential HDCT was 5 months (range 3-15 months). Disease status according to tumor response to their previous treatment showed three very good partial responses (VGPR), three partial responses (PR), one minimal response (MR), one stable disease (SD) and one progressive disease (PD).

2. Toxicities

Most common extramedullary toxicities after 1^{st} and 2^{nd} reduced

conditioning HDCT were fever (44.4% and 55.6%), nausea/vomiting (33.3% and 44.4%) and stomatitis (33.3% and 44.4%) (Table 3). Microbiologically documented infection were confirmed in two (22.2%) and three (33.3%) patients during 1st and 2nd reduced HDCT. Nausea/vomiting were well controlled with antiemetics, micro-biologically documented infection were controlled with broad spectrum antibiotics and antifungal agents. Diarrhea, liver enzyme elevation and coagulation disorder were developed in few patients, however they were also controlled with supportive treatment. There was one case of transplantation related mortality (TRM). The patient was 11 year old boy with stage IV rhabdomyosarcoma who experienced engraftment failure after 2nd round of reduced conditioning HDCT. Despite of reinfusion of PBSC after engraftment failure, the patient failed to recover which resulted in severe sepsis with multi-organ failure and major bleeding; pulmonary hemorrhage and gastrointestinal bleeding. Among nine patients who underwent 1st and 2nd reduced conditioning HDCT, two patients didn't go through the final HDCT. One was because of TRM who we explained just before, the other patient was because of disease progression in spite of 2nd course of reduced conditioning HDCT.

Table 3. Extramedullary toxicities after high-dose chemotherapy

	RHDCT (1) (n=9)	RHDCT(2) (n=9)	HDCT(3) (n=7)
Presence of high fever (≥ 38.5°C)	4/9 (44.4%)	5/9 (55.6%)	4/7 (57.1%)
Duration (days) of high fever	2.1 (0~5)	4.1 (0~13)	2.1 (0~6)
Microbiologically documented infection	2/9 (22.2%)	3/9 (33.3%)	2/7 (28.6%)
Nausea/vomiting	3/9 (33.3%)	4/9 (44.4%)	4/7 (57.1%)
Stomatitis	3/9 (33.3%)	4/9 (44,4%)	3/7 (42.9%)
Diarrhea	1/9 (11.1%)	2/9 (22,2%)	2/7 (28.6%)
Liver enzyme elevation	1/9 (11.1%)	1/9 (11.1%)	1/7 (14.3%)
Veno-occlusive disease	0/9 (0%)	0/9 (0%)	0/7 (0%)
Coagulation disorder	1/9 (11.1%)	2/9 (22.2%)	2/7 (28.6%)
Tx related mortality	0/9 (0%)	1/9 (11.1%)	0/7 (0%)

RHDCT: reduced conditioning high-dose chemotherapy, HDCT: high-dose chemotherapy

After final HDCT, which was 3rd round of sequential HDCT, the most common extramedullary toxicities were fever (57.1%), vomiting (57.1%), stomatitis (42.9%) and two patients were confirmed to have a microbiologically documented infection (28.6%). Those were also well controlled with antiemetics, broad spectrum antibiotics and antifungal agents. Diarrhea, liver enzyme elevation and coagulation disorder were developed in few patients which were well controlled with supportive treatment. There was no veno-occlussive disorder

during total three rounds of HDCT. None of the patients experienced toxic death after final HDCT.

3. Hematologic recovery

All nine patients had neutropenia after each cycle of HDCT. Platelet transfusion because of low platelet counts (< 30 x 10^9/L) was performed in most patients. Median number of platelet transfusion after each reduced conditioning HDCT was three (range 2~14) and four (range 3~7) after final HDCT. Median number of RBC transfusion was two (range 1~3) after each reduced conditioning HDCT and three (range 2~4) after final HDCT.

The number of PBSC infused per cycle ranged from 2.2 x 10^6 cells/kg to 8.3 x 10^6 cells/kg (median 3.4 x 10^6 cells/kg) at 1st reduced HDCT, 2.4 x 10^6 cells/kg to 7.0 x 10^6 cells/kg (median 3.2 x 10^6 cells/kg) at 2nd reduced conditioning HDCT and 3.2 x 10^6 cells/kg to 4.8 x 10^6 cells/kg (median 4.4 x 10^6 cells/kg) at final HDCT (Table 4). One patient used autologous cord blood stem cell (1.1 x 10^5 CD 34+ cells/kg, 3.4 x 10^7 total neucleated cells /kg) for his final HDCT. With the use of G-CSF and PBSC support, the resulting median engraftment time were 12 (range 9-22 days) and 13 (range 12-14 days,

except one case of engraftment failure) days after 1st and 2nd reduced conditioning HDCT, 12 (range 10-29 days, including case of cord blood stem cell infusion) days after final HDCT.

Median platelet engraftment time after 1st and 2nd reduced conditioning HDCT was 16 (range 10-26 days, except the case of engraftment failure) days, and after final HDCT, 14 (range 12-47 days, including the case of cord blood stem cell infusion) days were required.

Table 4. Infused cells and hematopoietic recovery time

	Infused CD34+ cell dose (x 10^6 cells/kg)	ANC engraftment (days)	PLT engraftment (days)
RHDCT(1)	3.4	12	16
RHDCT(2)	3.2	13	16
HDCT	4.4	12	14

ANC: absolute neutrophil count, PLT: platelet, RHDCT: reduced conditioning high-dose chemotherapy, HDCT: high-dose chemotherapy

4. Response and survival

Of the nine patients who underwent 1st and 2nd round of reduced conditioning HDCT, seven patients completed all three rounds of sequential HDCT (Table 5). One patient didn't undergo final HDCT because of disease progression in spite of two rounds of reduced

conditioning HDCT, the other patient experienced transplantation related death owing to engraftment failure during 2nd course reduced conditioning HDCT.

Three patients who showed VGPR after induction therapy had CR, another three patients who showed PR after induction therapy had CR, one patient with MR had PR and one patient with PD achieved PR after completion of sequential HDCT. In aspect of seven patients who completed total three courses of sequential HDCT, six patients achieved CR and one patient PR.

Median overall survival time from diagnosis was 18 months (range 9-24 months) and median follow up duration after completion of sequential HDCT was 9 months (range 4-11 months). Among seven patients who completed sequential HDCT, six patients are alive in CR status, one patient is alive in PR status without disease progression. One patient who completed only two rounds of reduced conditioning HDCT is alive with disease progression.

Table 5. Response and survival after sequential high-dose chemotherapy

No.	Dx	Dz status at HDCT	Response after completion of Tx	OS (mo)	F/U duration after HDCT (mo)	Current status
1	NB	VGPR	CR	18	11	alive, CR
2	NB	VGPR	CR	18	9	alive, CR
3	NB	PR	CR	19	9	alive, CR
4	NB	PR	CR	16	8	alive, CR
5	NB	VGPR	CR	12	4	alive, CR
6	RM	NR	NE	9	NE	TRM
7	RM	PD	PR	12	4	alive, PR
8	NPC	MR	NE	24	9	alive, PD
9	YST	PR	CR	23	9	alive, CR

yr: year, mo: month, Dx: diagnosis, Dz: disease, Tx: treatment, OS: overall survival, F/U: follow up, HDCT: high-dose chemotherapy, NB: neuroblastoma, RM: rhabdomyosarcoma, NPC: nasopharyngeal cancer, YST: yolk sac tumor, VGPR: very good partial response, PR: partial response, NR: no response, PD: progressive disease, MR: minimal response, NE: not evaluable, TRM: transplantation related mortality

IV. DISCUSSION

The dose-effect relationship in pediatric solid tumor chemotherapy has been emphasized during last few decades and the rationales for the use of megatherapy protocols with stem cell support and associated procedures are given. At first this approach was used in neuroblastoma, but it has subsequently been applied to most of advanced, common childhood solid tumors. The results of megatherapy followed by autologous stem cell reinfusion were encouraging in recurrent or refractory non-Hodgkin's lymphoma, advanced high risk neuroblastoma, Ewing's sarcoma, rhabdomyosarcoma, brain tumors and malignant germ cell tumor and so on.[2, 4, 8-15] However, most patients have had only brief response, ending with an early recurrence of the primary tumor. The overall long term survival rate was only 20-40%.[16, 17]

Since then, many approaches have been tried to improve the results of the megatherapy, and these approaches included increasing the number of agents in the myeloablative regimen and utilizing second course of HDCT with HSC infusion.[9, 12, 18] Over last decade, various methods of HDCT such as "tandem HDCT", "triple tandem HDCT", and some other forms of sequential HDCT with autologous HSC support have been tried in some disease entities of advanced high risk pediatric solid tumors.[5, 6, 12,

[18-22] However, despite of improving long-term survival rates seen in patients treated with these various HDCT, still considerable portion of patients are not cured, which encourage us to develop a near maximum tolerated dose of HDCT method with minimizing toxic effects.

Clinical use of high-dose alkylators and platinum compounds in high-risk solid tumors are limited by the acute and long term toxicities of these regimens.[20, 23, 24] Especially, myelosuppression and infections frequently necessitate dose reductions or prolonged delays between courses of therapy. One strategy to decrease myelosuppression and maintain dose intensity is to infuse autologous HSC after chemotherapy as hematopoietic support. Clinical trials using PBSC between submyeloablative chemotherapy courses have successfully increased dose intensity by delivering chemotherapy at shorter intervals in patients with breast cancer, lung cancer, adult sarcomas, germ cell tumors, pediatric brain tumors, and pediatric soft tissue sarcomas.[20, 25-27]

According to above backgrounds, protocol of this study had the following important characteristics: (1) collection of peripheral blood stem cells (PBSC) early in therapy, presumably before significant genetic damage in hematopoietic stem and progenitor cells had occurred from the induction chemotherapy cycles, (2) rapid progression from the first to the second

HDCT by decreasing the intensity of conditioning chemotherapy to submyeloablative level with autologous HSC support which prevented delay of treatment between two courses, (3) final HDCT for consolidation of residual disease in PR status patients and for consolidation of minimal residual disease in CR status patients. The intent of this study was to assess the feasibility of this approach and to evaluate the short term response rate to this intensive sequential HDCT regimen.

A response rate (CR/VGPR/PR) of 78% (7 out of 9) was documented, which is similar to other published reports using intensive therapy.[20, 24, 28, 29] Sequential PBSC mobilization and collection among young patients and even in the presence of bone marrow disease commonly seen in high risk neuroblastoma were feasible. The major toxicities of this regimen were hematologic and infectious complications. Other grade 3 and 4 toxicities (stomatitis, vomiting) were controllable with supportive treatments. There was one toxic death owing to engraftment failure which documents 11% of treatment mortality rate, however it was one engraftment failure out of 25 infusions.

There were no other serious organ toxicities observed during or after therapy with a median follow-up of 9 months. Overall, this study seems to be feasible with acceptable toxicities.

Mobilization and harvesting of PBSC was feasible even in youngest patient (13 months). Despite of presence of bone marrow involvement with neuroblastoma among 3 of the 5 patients at diagnosis, PBSC mobilization and harvest was feasible with every PBSC products testing free of tumor contamination by reverse transcriptase polymerase chain reaction for tyrosine hydroxylase. However, theoretical risk of tumor cell contamination which has the potentialities to contribute to disease recurrence still remains. Determining whether PBSC collection and reinfusion during induction significantly alters the event-free survival for children with high-risk neuroblastoma who ultimately proceed to consolidation using immunocytochemistry negative stem cell product would require a larger, prospective, randomized multi-institutional study.[20]

In aspect of hematologic recovery, there was no significant difference of engraftment duration of both neutrophil and platelet between three cycles of HDCT. The infectious complications encountered were manageable with broad spectrum antibiotics and empirical antifungal agents with intensive supportive care. However, both two patients who experienced microbiologically documented infection had another infectious event during next HDCT. Excluding one patient with engraftment failure all

infectious conditions were fully recovered.

Other grade 3 and 4 toxicities included nausea, vomiting and stomatitis with small portion of liver enzyme elevation and coagulation disorder. All of these toxic effects were well controlled with supportive treatment and was completely recovered after hematologic engraftment. For painful stomatitis, oral or intravenous analgesics were used according to pain scale. Gastrointestinal discomfort was managed with antiemetics, in case of weight loss because of poor oral intake, nutritional support was provided by total parenteral nutrition.

The response rate (CR/VGPR/PR) of this study was 78%, which was comparable to most published reports for high-risk neuroblastoma.[20, 28, 30] Kushner et al. have reported a CR/VGPR of 79% and a PR of 16% using the MSKCC N6 protocol using five cycles of intensive chemotherapy instead of seven to reduce toxicities.[31] Pradhan et al. have reported response rate (CR/VGPR/PR) of 78% using sequential intensive induction chemotherapy (etoposide, carbopatin and intensive cyclophosphamide) with sequential PBSC infusion.[20] Other disease entities included in this study such as rhabdomyosarcoma, nasopharyngeal cancer and yolk sac tumor do not have comparable response data since sequential HDCT method yet. However, in case of

those advanced high-risk solid tumors with poor prognosis with conventional chemotherapy, it seems to be feasible to applicate this method for an option of treatment according to its acceptable toxicity.

The results of this study demonstrate that it is feasible to treat advanced pediatric solid tumor patients with sequential HDCT including 2 cycles of reduced conditioning HDCT supported by autologous HSC. We found that it was possible to collect a sufficient number of PBSCs to support children through total 3 cycles of HDCT and rescue. The rate of death because of toxicities was within the range observed with other stem-cell approaches. The response rate following sequential HDCT is comparable with published reports with acceptable hematologic toxicities and engraftment time. In view of the small number of evaluable patients, this result should be considered as preliminary. The antitumor effects of this regimen need to be further evaluated with a larger group of pediatric patients.

V. CONCLUSION

3 cycles of sequential HDCT including 2 courses of reduced conditioning HDCT supported by autologous HSC seems to be feasible in advanced childhood solid tumors. It was feasible to collect sufficient PBSCs for 3 courses of HDCT and the hematologic recovery of patients were achieved within 2 weeks except one case of engraftment failure which is one engraftment failure of out of 25 HSC infusions. Extramedullary toxicities were controllable with supportive treatment, and no serious organ toxicities were found during median follow-up period of 9 months. Tumor response rate of this sequential HDCT was 78% which is comparable with previous HDCT regimens. It seems that sequential HDCT including 2 times of reduced conditioning HDCT seems to be effective in treating advanced childhood solid tumors, approaching and maintaining CR status. Since the follow-up period is short, these results should be considered as preliminary findings which requires long-term follow up about adverse effects and survival. In addition, the antitumor effect of this regimen needs to be further evaluated with a larger group of patients.

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요약

진행된 소아 고형 종양에서 조혈모세포 구제를 동반한 sequential high-dose chemotherapy 의 시행 가능성

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배경: 파종성 혹은 재발성 소아 고형 종양은 고식적인 항암치료로는 그 예후가 매우 불량하여 다양한 방법의 고용량 항암 치료 방법이 시도되어 왔으나, 독성을 최소화하면서 충분히 강력한 발전적인 고용량 항암 치료 방법의 개발이 필요한 실정이다.

목적: 본 연구에서는 2회의 reduced conditioning high-dose chemotherapy (HDCT) 후 최종 고용량 항암치료를 시행하는 총 3회의 sequential HDCT 의 시행 가능성과 치료 반응에 대하여 알아보고자 하였다.

방법: Sequential HDCT를 시행 받은 9명의 환자들의 특성, 진단 후 진행된 초기 치료와 고용량 항암 치료의 치료 과정에 대해 후향적으로 조사하였으며, 주입된 조혈모세포의 양과 조혈기능 회복 기간 및 독성 효과와 합병증에 대해 분석하였다. 또한 치료 종료 후의 치

료 반응과 생존에 대하여 분석하였다.

결과: 9명중 7명에서 부분 반응 및 완전 반응을 보여 78%의 반응율을 보였다. 1명에서 이식 관련 사망이 발생하였으며 1명이 치료 중 병의 진행으로 인해 최종 HDCT 를 시행하지 않았다. 이외의 독성 합병증들은 보조적인 치료로 모두 회복되었다.

결론: 2회의 reduced conditioning HDCT를 포함한 총 3회의 sequential HDCT 는 진행된 소아 고형 종양 환자에서 적용 가능할 것으로 생각되며, 완전 반응에 도달하고 이를 유지하는데 효과를 기대할 수 있으리라 사료되나, 더 많은 수의 환자에서의 시도와 장기 추적 관찰의 결과가 필요하다.

핵심되는 말: 고용량 항암 치료, 소아, 고형 종양