Feasibility of allogeneic hematopoietic stem cell transplantation using reduced-intensity conditioning with fludarabine and melphalan in patients relapsed after autologous hematopoietic stem cell transplantation

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Feasibility of allogeneic hematopoietic stem cell transplantation using reduced-intensity conditioning with fludarabine and melphalan in patients relapsed after autologous hematopoietic stem cell transplantation

Directed by Professor Yoo Hong Min

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Abstract

Feasibility of allogeneic hematopoietic stem cell transplantation using reduced-intensity conditioning with fludarabine and melphalan in patients relapsed after autologous hematopoietic stem cell transplantation

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The current study was performed to determine the feasibility of allogeneic hematopoietic stem cell transplantation (HSCT) using reduced-intensity conditioning (RIC) with fludarabine and melphalan in patients relapsed after autologous HSCT. Twelve patients (multiple myeloma n=7, non-Hodgkin's lymphoma n=3, acute myeloid leukemia n=2) received allogeneic HSCT using the RIC with fludarabine (25mg/m^2 for 5days) and melphalan (140mg/m^2 for 1day) for relapsed disease after a prior autologous HSCT. The graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine plus a mini-dose of methotrexate. All patients achieved a neutrophil or platelet engraftment in a median of 13.5 days and 17.5 days, respectively. The transplant-related mortality was 2 patients (16.7%). Grade II~IV acute GVHD and chronic extensive GVHD was noted in 4 (33.3%) and 1

patient (11.1%), respectively. Over a median follow-up duration of 12.5 months, 5 patients are currently alive without evidence of disease. The estimated non-relapse mortality (NRM) at 1 year was 28.4%. The estimated overall survival (OS) rate at 1 year 2was 58.3% and the estimated event-free survival (EFS) rate at 1 year was 41.7%. Allogeneic HSCT using RIC with fludarabine and melphalan appears to be feasible for a second HSCT in patients relapsed after autologous HSCT.

Key words : second HSCT, reduced intensity conditioing, fludarabine and melphalan

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I. INTRODUCTION

The conventional myeloablative conditioning (MAC) regimen for allogeneic hematopoietic stem cell transplantation (HSCT) has been extensively used in patients with advanced hematologic malignancies; it has resulted in a significantly higher remission rate compared to chemotherapy or autologous HSCT. However, the use of the MAC regimen has been limited to young patients without major co morbidities because of the increased risk of treatment-related morbidity and mortality and the relatively high risk of graft-versus-host disease (GVHD).[1,2]

During the last decade, the introduction of reduced-intensity conditioning (RIC) regimens has enabled the use of allogeneic HSCT to the elderly patients, patients with co-morbidity and patients who have already received significant treatment previously. Previous investigators have suggested comparable outcomes between allogeneic HSCT using RIC and MAC for the treatment of patients with hematological malignancies in diverse disease status.[3-5] Several groups have investigated the use of the combination of fludarabine and

melphalan for a appropriate RIC regimen and have shown a high rate of remission and engraftment with acceptable toxicities.[6-8]

Another issue to consider is the salvage treatment of relapsed hematologic malignant disease, especially after a prior HSCT. Patients with relapsed acute myeloid leukemia (AML), non-Hodgkin lymphoma (NHL), and multiple myeloma (MM) after prior HSCT have a very grim prognosis and generally cannot not be salvaged with standard or high dose chemotherapy. Currently, there is no standard treatment strategy exists for patients with relapsed disease after a prior HSCT. Moreover, since these patients have already received a HSCT, they are not generally considered eligible for another course of MAC based allogenic HSCT, due to the risk of cumulative organ toxicity and non-relapse mortality (NRM).

Herein, we attempted to determine the feasibility and tolerability of a RIC regimen based on fludarabine and melphalan for a second HSCT as salvage treatment for patients with relapsed hematological malignancies after failure of a previous autologous HSCT.

II. MATERIALS AND METHODS

1. Patient eligibility

The patients with relapsed disease after a prior HSCT, who had a second HSCT using a RIC with fludarabine and melphalan as salvage treatment, were included retrospectively in this study. The following disease entities were included: MM (n=7), NHL (n=3), and AML (n=2) from January 2004 untill November 2007. This study was approved by the Institutional Review Board of the Samsung Medical Center and confidentiality of all patients was protected.

2. Preparative regimen

The conditioning regimen consisted of fludarabine 25mg/m^2 for 5 days and

melphalan 140mg/m^2 for 1 day. Patients required either a full human leukocyte antigen (HLA)-matched unrelated donor (serologic match for class I antigens and high resolution molecular matching for class II antigens) or a fully matched or one-antigen mismatched related donor. GVHD prophylaxis consisted of cyclosporine (5 mg/kg/day continuous intravenous infusion on day -1 and 3 mg/kg/day continuous intravenous infusion from transplant day 0) and methotrexate (5 mg/kg/day bolus intravenous infusion on transplant day 1, 3, 6, and 11).

3. Supportive management

Antiviral and antifungal prophylaxis was provided according to the institutional protocol, including acyclovir for herpes virus and nystatin for *Candida* infection. Patients on steroids received trimethoprim/sulfamethoxazole for *Pneumocystis jiroveci* prophylaxis. Patients were screened weekly for cytomegalovirus antigenemia, preemptive intravenous gancyclovir was given once positive results were documented (5mg/kg IV twice daily for 2 weeks).

All patients received filgrastim 5 μg/kg/day from transplant day 7 until an absolute neutrophil count of more than 1.5 x 10^9 /L for 3 consecutive days was achieved. Patients with neutropenic fever were treated with broad spectrum antibiotics according to the institutional protocol. The blood products were transfused after irradiation and leukocyte filtration.

4. Clinical endpoints

Neutrophil engraftment was defined as an absolute neutrophil count of more than 0.5 x 10^9/L for 3 consecutive days. Platelet engraftment was defined as a platelet count more than 20.0 x 10^9/L independent of platelet transfusions at least 3 consecutive days. Acute and chronic GVHD were graded as previously described.[9] Toxicity profiles were recorded according to the Seattle criteria.[10] The evaluation for chimerism evaluation was performed 30 days

post-transplantation and every 3 months thereafter.

5. Statistical analysis

The overall survival, event free survival and non-relapse mortality were plotted using the Kaplan-Meier method. The overall survival was calculated from the date of the HSCT to date of death from any cause. The non-relapse mortality was calculated from the date of the HSCT until death without evidence of progression. Statistical analyses were carried out using SAS Enterprise Guide 3.0 (SAS Institute, Inc., Cary, NC, USA).

III. RESULTS

1. Patient and disease characteristics

The patient and donor characteristics are summarized in Table 1. A total of 12 patients were included. The median age was 39.5 years (range, 26~50 years); 6 patients were women and 6 patients were men. Seven patients had MM, 3 patients had NHL, and 2 patients had AML. The disease characteristics are summarized in Table 2.

Table 1. Patients, disease and donor characteristics

Variable		Number	%
No. of patients		12	
Median age, years (range)		39.5 (26~50)	
Age	≥ 50 years	1	8.3
	< 50 years	11	91.7
Gender	Female	6	50.0
	Male	6	50.0
Diagnosis	Multiple myeloma	7	58.3
	Non-Hodgkin's lymphoma	3	25.0
	Acute myeloid leukemia	2	16.7
Median time from 1st to 2nd HSCT, months (range)		9.0 (2.9~30.6)	
HLA typing	Matched	12	100.0
	Mismatched	0	0.0
Donor type	Unrelated	4	33.3
	Related	8	66.7
Stem cell source	Peripheral blood	11	91.7
	Bone marrow	1	8.3
Infused CD34+ cell dose (x 10^6/kg)		6.99 (0.65~9.48)	

HSCT : hematopoietic stem cell transplantation, HLA : human leukocyte antigen

Table 2. Disease characteristics in patients

Diagnosis		Number
Multiple myeloma		7
Disease status at transplant	sCR/CR/VGPR	0
	Partial response	2
	Stable disease	1
	Progressive disease	4
Non-Hodgkin's lymphoma		3
Disease status at transplant	CR/CRu	0
	Partial response	1
	Relapse	2
	Refractory	0
Diagnosis	Peripheral T cell lymphoma	2
	NK-T cell lymphoma	1
Acute myeloid leukemia		2
Disease status at transplant	Complete remission	1
	Relapse	1
	Refractory	0
Karyotype group	Unfavorable risk	0
	Intermediate risk	2
	Favorable risk	0

sCR : stringent complete response, CR : complete response,

VGPR : very good partial response, CRu : complete response, undetermined

2. Engraftment and chimerism

All 12 patients achieved neutrophil and platelet engraftment successfully. The median time to a neutrophil and platelet engraftment was 13.5 days (range, 11~22 days) and 17.5 days (range, 15~110 days), respectively. There was no primary graft failure. Post-transplantation chimerism results were available in 11 patients, 1 patient was too frail for further bone marrow evaluation. Nine patients among the 11 patients (81.8%) showed 100% donor chimerism 30 days post-transplantation. Two patients (16.7%) showed mixed chimerism with 1.1% and 0.5% of the recipient's cells, respectively. Among them, one patient converted to complete donor chimerism 100 days post-transplantation and 1 patient remained a mixed chimera with 1.2% of recipient' cells and was in complete remission.

3. Complications and toxicity

Grade II to IV acute GVHD was observed in 4 patients (33.3%) with a median onset of 20 days (range, 11~90 days) after the HSCT. Chronic extensive GVHD was documented in 1 of 9 patients (11.1%), that survived over 100 days after HSCT and could be evaluated for chronic GVHD.

Febrile neutropenia was noted in 11 out of 12 patients (91.7%), documented bacteremia in 2 patients (16.7%) and an invasive fungal infection in 1 patient (6.7%). No hepatic veno-occlusive disease was noted. Cytomegalovirus reactivation was noted in 3 patients (25.0%) with successful treatment using preemptive gancyclovir. The complication and toxicity profiles are summarized in Table 3 and Table 4 respectively.

Table 3. Complication profile of the patients

Complication	Number (%)
Acute GVHD (Grade II~IV)	4/12 (33.3)
Chronic GVHD	1/9 (11.1)
Febrile neutropenia	11/12 (91.7)
Bacteremia	2/12 (16.7)
Fungal infection	1/12 (6.7)
CMV antigenemia	3/12 (25.0)
CMV disease	0/12 (0.0)
Hepatic VOD	0/12 (0.0)

GVHD : graft-versus-host disease, CMV : cytomegalovirus,
VOD : veno-occlusive disease

Table 4. Toxicity profile using Seattle criteria in 12 patients

Involved organ	Grade I No. (%)	Grade II No. (%)	Grade III No. (%)	Grade IV No. (%)
Gut	6 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stomatitis	6 (50.0)	4 (33.3)	0 (0.0)	0 (0.0)
CNS	0 (0.0)	2 (16.7)	0 (0.0)	0 (0.0)
Liver	3 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
Lung	1 (8.3)	0 (0.0)	0 (0.0)	1 (8.3)
Kidney	2 (16.7)	1 (8.3)	0 (0.0)	0 (0.0)
Bladder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Heart	0 (0.0)	2 (16.7)	0 (0.0)	0 (0.0)

CNS : central nervous system

4. Mortality and survival

Transplantation related mortality within 100 days was observed in 2 patients (16.7%). (1 case of acute GVHD with septic shock and 1 case of pneumonia).

Responses and treatment outcomes after allogeneic HSCT using RIC with fludarabine and melphalan are summarized in Table 5. With the median follow-up duration of 12.5 months (range, 10.3~41.4 months). Five patients are currently alive in complete remission, including 2 patients with MM, 2 patients with NHL and 1 patient with AML. The median duration of overall survival was 15.2 months (95% CI, 1.4~30.0) and the event-free survival was 5.9 months (95% CI, 0.0~12.8). At 1 year, the estimated overall survival for all patients was 58.3% (95% CI, 30.5~86.1) and the estimated event-free survival was 41.7% (95% CI, 13.9~69.5). (Figure 1 and Figure 2) The estimated non-relapse mortality at 1 year was 28.4% (95% CI, 1.0~55.8). (Figure 3)

Table 5. Patients characteristics and treatment results.

Patient	Age /Sex	Diagnosis	Previous chemotherapy	Disease at RIC TPL	Donor	GVHD (Grade II~IV)	Response	Current status	Survival (months)
1	41/M	MM	VAD#3 →auto-HSCT →VAD#2 →bortezomib#4	PD	MRD	Grade IV	PR	Dead	5.9
2	45/M	MM	VAD#3 →auto-HSCT →bortezomib#2	PD	MRD	None	CR	Dead	15.2
3	32/F	MM	Fludarabine#3 →TD#3 →auto-HSCT →VD#2	PD	MRD	None	CR	Alive in CR	12.5+
4	46/F	MM	TD#4 →PAD#3 →auto-HSCT →DCEP#1	PD	MRD	None	N/A	Dead	1.2
5	40/M	MM	VAD#3 →auto-HSCT →PAD#3 →MPT#3 →DCEP#5	SD	MRD	None	N/A	Dead	4.9
6	39/F	MM	VAD#3 →auto-HSCT	PR	MRD	Grade II /Ext.chronic	CR	Alive in CR	41.4+
7	38/F	MM	VAD#3 →auto-HSCT	PR	MRD	None	CR	Dead	28.0
8	38/M	NHL (NK-T)	VIPD#3 →auto-HSCT → CHOP#2	Relapse	MUD	Grade III	PR	Dead	9.0
9	31/F	NHL (PTCL)	CHOP#6 →IMVP16/PD#5 →auto-HSCT	Relapse	MUD	None	CR	Alive in CR	29.3+
10	46/F	NHL (PTCL)	CHOP#6 →auto-HSCT →A-DHAP#3 →IMVP16/PD#4	PR	MRD	None	CR	Alive in CR	11.8+
11	39/F	AML	IA →HiDAC/Id#2 →auto-HSCT	Relapse	MUD	Grade II	CR	Dead	6.0
12	24/M	AML	IA →HiDAC/Id#2 → auto-HSCT → MA	CR	MUD	None	CR	Alive in CR	10.4+

GVHD : graft-versus-host disease, MM : multiple myeloma, AML : acute myeloid leukemia, NHL : non-Hodgkin lymphoma, NK-T : natural killer-T cell lymphoma, PTCL : peripheral T cell lymphoma, VAD : vincristine/doxorubicin/dexamethasone, TD : thalidomide/dexamethasone, VD : bortezomib/ dexamethasone, PAD :bortezomib/doxorubicin/dexamethasone, DCEP :dexamethasone/cyclophosphamide/ etoposide/cisplatin, MPT : melphalan/prednisone/thalidomide, IA : idarubicin/cytarabine, HiDAC/Id : high dose cytarabine/idarubicin, MA :mitoxantrone/cytarabine, VIPD:etoposide/ifosfamide/mesna/cisplatin /dexamethasone, CHOP :cyclophosphamide/doxorubicin/vincristine/prednisone, IMVP16/PD : ifosfamide/ mesna/methotrexate/etoposide/prednisone, A-DHAP : Alemtuzumab/cisplatin/cytarabine/dexamethasone, CR : complete remission, PR : partial remission, SD : stable disease, N/A : not available, MRD : matched related donor, MUD : matched unrelated donor, RIC TPL : reduced intensity conditioning transplantation

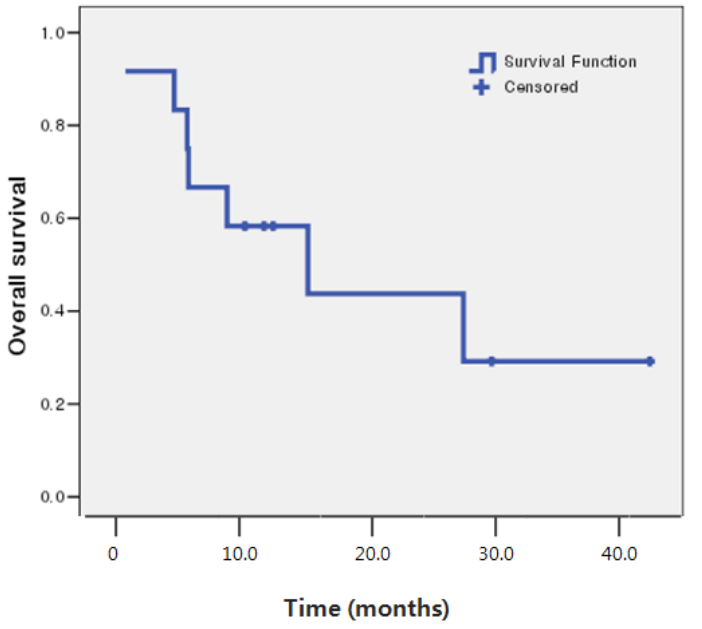

Figure 1. Overall survival.

The median overall survival was 15.2 months (95% CI, 1.4~30.0).

At 1 year, the estimated survival for all patients was 58.3% (95% CI, 30.5~86.1)

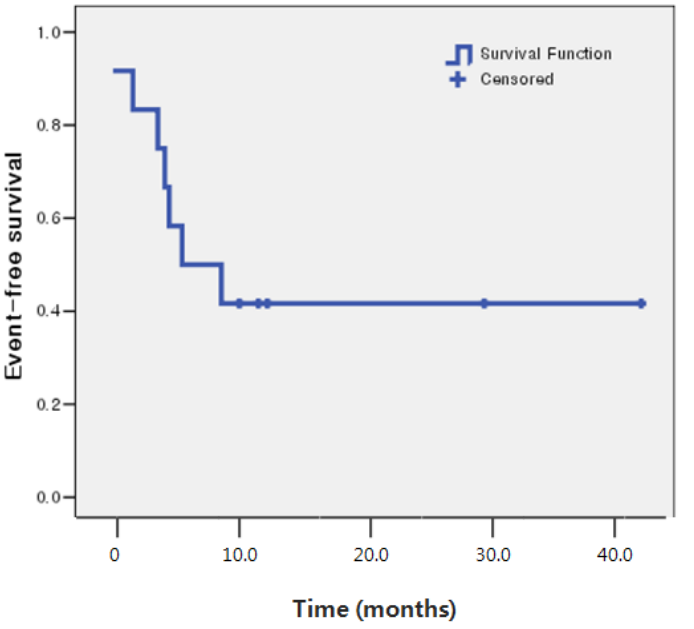

Figure 2. Event-free survival.

The median event free survival was 5.9 months (95% CI, 0.0~12.8)

At 1 year, the estimated survival for all patients was 41.7% (95% CI, 13.9~69.5)

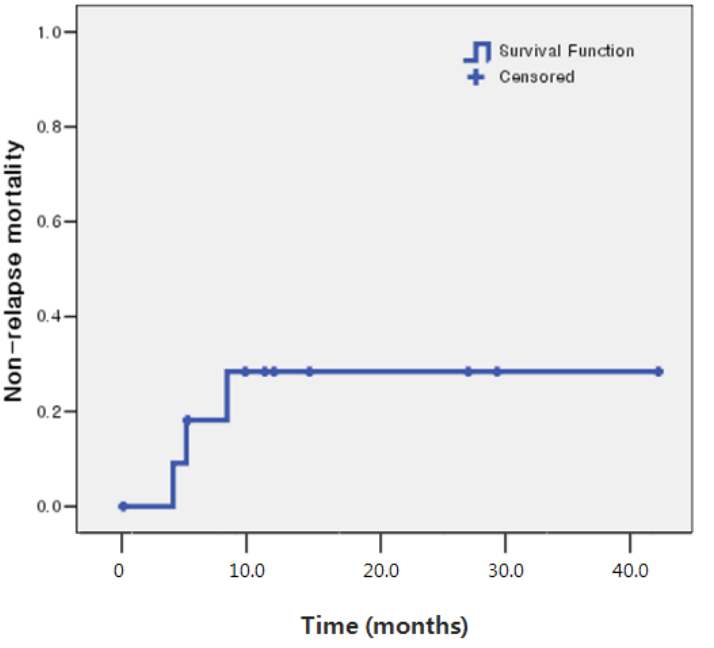

Figure 3. Non-relapse mortality.

The estimated non relapse mortality at 1 year was 28.4% (95% CI, 1.0~55.8)

IV. DISCUSSION

The major disadvantages of allogeneic HSCT using the MAC regimen are increasing toxicity from the intensive regimen together with the risk of treatment related morbidity and mortality.[1,2] Thus, the use of the MAC regimen has been limited to patients who can tolerate the toxicity of the preparative regimen; this has generally restricted the MAC regimen to young patients without major co morbidities. Accordingly, patients with advanced age, co-morbidity or a previous history of intensive treatment are not candidates for allogeneic HSCT using the MAC regimen.

To date, allogeneic HSCT using the RIC regimen has been studied mainly for older aged patients. Several groups have reported on a series of patients in the 6th decade of life and have shown the feasibility and efficacy of RIC regimens in elderly patients.[11,12] Recently, salvage treatment for patients with relapsing hematological malignancies, after prior HSCT, has become an intriguing issue; investigators are evaluating the feasibility of allogeneic HSCT using the RIC regimen for a second HSCT as a salvage treatment option for relapsed disease after a prior HSCT.[13-15] However, there is very limited clinical data on the feasibility and efficacy of a second allogeneic HSCT, using RIC regimen. Therefore, in this study, we focused on the population of patients with relapsing hematologic malignancies, after autologous HSCT, and investigated the feasibility of allogeneic HSCT using RIC with fludarabine and melphalan as an option for allogenic second HSCT.

For patients with MM, the use of high dose chemo-radiotherapy with or without autologous stem cell support has resulted in a higher incidence of complete remission and improved treatment outcomes.[16,17] However, disease recurrence usually occurs and only a minority patients remain disease free after autologous HSCT.[18] One study reported discouraging results of a 25% of disease-free survival at 5 years with allogenic HSCT using the MAC regimen in MM patients, primarily due to the high treatment related mortality of 40~50%.[19] While, a promising study reported encouraging results of consistent engraftment, manageable toxicity and a

low rate of non-relapse mortality (19% at 100 days) with RIC, using fludarabine and melphalan in patients with MM.[8] In this study, 9 out of 22 patients received allogenic HSCT with the RIC regimen as a salvage treatment after failure of a prior autologous HSCT.

For AML, the donor lymphocyte infusion (DLI) was introduced for treatment of leukemic relapses after allogeneic HSCT; however only a few remissions were reported in selected cases.[20,21] Accordingly, the role of DLI for relapsed AML, after an allogenic HSCT, needs to be refined further. Moreover, there is no consensus on the treatment of relapsing AML or NHL after autologous HSCT.[22,23] Recently, Thomson et al suggested that allogeneic HSCT procedures with RIC were superior to conventional salvage chemotherapy for relapsed Hodgkin's lymphoma, after failure of autologous HSCT.[13] Grullich et al also suggested that a RIC regimen, using fludarabine and thiotepa, was feasible and well tolerated for second allergeneic HSCT, in patients with relapsed hematological malignancies after a prior HSCT.[14]

We recently adopted a RIC protocol with fludarabine and melphalan as salvage treatment, mainly for patients with relapsed hematological malignancies after a prior autologous HSCT. We evaluated the feasibility and tolerability of this treatment approach. In the present study, all 12 patients achieved successful neutrophil and platelet engraftment. In addition, full donor chimerism was achieved in 10 out of 11 patients (90.9%). A treatment-related mortality within 100 days was observed only in 2 patients (16.7%) and the occurrence of acute GVHD and toxicities were mostly manageable, as shown in Table 3 and Table 4. The estimated non-relapse mortality at 1 year was 28.4% (95% CI, 1.0~55.8) With a median follow up duration of 12.5 months after transplant, 5 patients (2 MM patients, 1 AML patient and 2 NHL patients) are currently alive without evidence of disease. The current study results showed an estimated overall and event-free survival of 58.3% (95% CI, 30.5~86.1%) and 41.7% (95% CI, 13.9~69.5%) at 1 year, respectively; relatively improved outcomes compared to a previous report.[14] This

result might have been due to the the relatively high proportion of patients with MM and the reasons that all patients received a prior autologous HSCT in this study. The major limitation of the present study was the small numbers of patients. However, only a few studies were reported so far, adopting a homogenous RIC regimen for second HSCT after failure of prior autologous HSCT, especially from a single institution.

V. CONCLUSION

In conclusion, allogeneic HSCT using a RIC with fludarabine and melphalan for a second HSCT was safe and tolarable for the salvage treatment of patients with relapsed hematological malignancies after a prior autologous HSCT. Further studies with a larger number of patients are warranted for confirmation of the efficacy of a RIC regimen using fludarabine and melphalan for a allogeneic second HSCT in patients with relapsed hematological malignancies after a prior autologous HSCT.

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ABSTRACT (IN KOREAN)

자가 조혈모세포이식 이후 재발한 환자에서의 fludarabine과 melphan을 사용한 저강도 전처치 동종 조혈모세포이식

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이 연구는 자가 조혈모세포이식 이후 재발한 다양한 혈액암 환자에게 있어 이 연구는 자가 조혈모세포이식 이후 재발한 다양한 혈액암 환자에게 있어 fludarabine과 melphalan을 사용한 저강도 전처치 후 동종 조혈모세포이식의 효과를 알아보고자 하였다. 자가 조혈모세포이식 이후 재발한 12명(다발성골수종 7명, 비호지킨림프종 3명, 급성골수성백혈병 2명)의 환자에서 fludarabine (25mg/m^2 for 5days)과 melphalan (140mg/m^2 for 1day)을 이용한 저강도 전처치 동종 조혈모세포 이식술을 시행하였다. 이식편대 숙주반응 예방을 위해서 cyclosporin과 methotrexate를 투여하였다. 12명 모든 환자에서 호중구와 혈소판은 각각 중앙값 13.5일, 17.5일에 생착되었다. 이식관련 사망은 2명(16.7%)의 환자에서 발생하였다. 급성 이식편대 숙주반응(Grade II~IV)과 만성 확장성 이식편대 숙주반응은 각각 4명(33.3%)과 1명(11.1%)의 환자에서 발생하였다. 중앙값 추적관찰기간 12.5월에 5명의 환자가 현재 완전관해 상태로 추적관찰중에 있다. 1년 추정 무재발 사망률은 28.4% 였다. 1년 추정 전체생존률과 무사건생존률은 각각 58.3%, 41.7% 였다. 자가 조혈모세포이식 이후 재발한 환자를 대상으로 fludarabine과 melphalan을 사용한 저강도 전처치 동종 조혈모세포이식이 시행

가능할 것으로 생각되며, 향후 장기 생존률의 관점에서 추가적인 연구가 필요할 것이다.

핵심되는 말: 2차 조혈모세포이식, 저강도전처치, fludarabine과 melphalan

PUBLICATION LIST

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