

Granulocyte colony-stimulating factor combined regimen in cord blood transplantation for acute myeloid leukemia: a nationwide retrospective analysis in Japan

Cord blood transplantation (CBT) from an unrelated donor has been increasingly used as an alternative transplant method for adult patients without human leukocyte antigen (HLA)-compatible related or unrelated donors.¹⁻⁴ However, the main disadvantage of CBT is still the limited cell dose, especially in adults, and this might contribute to a higher incidence of graft failure and delayed hematopoietic recovery, leading to higher transplant-related mortality (TRM) or overall mortality after CBT.

The purpose of a conditioning regimen prior to allogeneic hematopoietic stem cell transplantation (allo-HSCT) for hematologic malignancies is disease eradication and

immunosuppression to overcome graft rejection. Although the standard myeloablative conditioning regimen prior to allo-HSCT has been total body irradiation (TBI) or busulfan combined with cyclophosphamide (CY) for patients with adult acute myeloid leukemia (AML), the role of an intensified conditioning regimen has been analyzed extensively in order to reduce the rate of post-transplant relapse and improve survival.⁵⁻⁷ However, the majority of these studies analyzed patients receiving allo-HSCT using bone marrow (BM) or mobilized peripheral blood (PB) as a stem cell source. Therefore, an optimal myeloablative conditioning regimen prior to CBT for adult AML still has to be determined.

Granulocyte colony-stimulating factor (G-CSF) stimulates proliferation, differentiation, and functional activation of neutrophils. In clinical use, G-CSF is most commonly used for reducing the duration of neutropenia after chemotherapy and HSCT, and for the mobilization of hematopoietic stem/progenitor cells from the BM into PB

Table 1. Characteristics of patients, cord blood units, and transplantation.

	Total	TBI \geq 10Gy+Ara-C +CY	TBI \geq 10Gy+Ara-C /G-CSF+CY	TBI \geq 10Gy+other	TBI<10Gy+other or non-TBI	P
Number of patients	438	163	80	156	39	
Age						0.61
16-39 years	226(52 %)	74(45 %)	40(50 %)	81(52 %)	17(44 %)	
40-55 years	212(48 %)	89(54 %)	40(50 %)	75(48 %)	22(56 %)	
Sex						0.82
Male	217(50 %)	83(50 %)	42(53 %)	73(47 %)	19(49 %)	
Female	221(50 %)	80(49 %)	38(48 %)	83(56 %)	20(51 %)	
Disease status at CBT *						0.32
Standard risk	214 (49 %)	74(45 %)	45(56 %)	79(51 %)	16(41 %)	
High risk	221(50 %)	87(53 %)	35(44 %)	76(49 %)	23(59 %)	
Unknown	3(<1 %)	2(1 %)	0	1(<1 %)	0	
GVHD prophylaxis						<0.001
Cyclosporine A+methotrexate	304(69 %)	107(66 %)	74(93 %)	100(64 %)	23(59 %)	
Tacrolimus+methotrexate	134(31 %)	56(34 %)	6(8 %)	56(39 %)	16(41 %)	
Number of nucleated cells						0.71
<2.5 \times 10 ⁷ /kg	204(47 %)	70(43 %)	40(50 %)	75(48 %)	19(49 %)	
\geq 2.5 \times 10 ⁷ /kg	200(46 %)	79(48 %)	33(41 %)	70(45 %)	18(37 %)	
Unknown	34(8 %)	14(9 %)	7(9 %)	11(7 %)	2(5 %)	
Number of CD34 ⁺ cells						0.23
<1 \times 10 ⁶ /kg	279(64 %)	110(67 %)	43(54 %)	101(64 %)	25(64 %)	
\geq 1 \times 10 ⁶ /kg	144(33 %)	52(32 %)	34(43 %)	46(29 %)	12(31 %)	
Unknown	15(3 %)	1(<1 %)	3(4 %)	9(6 %)	2(5 %)	
HLA disparities [†]						0.24
0	40(9 %)	9(6 %)	7(9 %)	19(1 %)	5(1 %)	
1	148(34 %)	64(39 %)	22(28 %)	50(1 %)	12(1 %)	
\geq 2	250(57 %)	90(55 %)	51(64 %)	87(1 %)	22(1 %)	
ABO incompatibility						0.11
Match	152(35 %)	67(41 %)	29(36 %)	42(27 %)	14(39 %)	
Major/bidirectional mismatch	175(25 %)	30(18 %)	22(28 %)	47(30 %)	11(28 %)	
Minor mismatch	110(40 %)	66(40 %)	29(36 %)	66(42 %)	14(39 %)	
Unknown	1(<1 %)	0	0	1(<1 %)	0	
Year of CBT						<0.001
1998-2002	56(13 %)	12(7 %)	16(20 %)	24(15 %)	4(10 %)	
2003-2005	158(36 %)	40(25 %)	32(40 %)	64(41 %)	22(56 %)	
2006-2008	224(51 %)	111(68 %)	32(40 %)	68(44 %)	13(33 %)	

*Disease status at CBT was classified as standard risk or high risk; complete remission without poor prognostic karyotype according to the MRC10 criteria was classified as standard risk, whereas patients in all other situations were classified as high risk. †The number of HLA disparities was defined as low resolution for HLA-A, -B, and -DR in graft-versus-host direction. Ara-C: cytosine arabinoside; CBT: cord blood transplantation; CY: cyclophosphamide; G-CSF: granulocyte colony-stimulating factor; GVHD: graft-versus-host disease; HLA: human leukocyte antigen; TBI: total body irradiation.

for HSCT. Furthermore, since administration of G-CSF increases the susceptibility to cytarabine arabinoside (Ara-C) through induction of cell cycle entry of dormant leukemia cells,^{8,9} the efficacy of concomitant use of G-CSF and chemotherapy has been analyzed.^{10,11} Several studies, as well as our own single institute studies, have demonstrated that G-CSF combined with myeloablative conditioning prior to allo-HSCT could be safely and effectively used for patients with myeloid malignancies in a single arm trial.^{9,12,13} However, there has been no comparative study of transplant outcomes for AML after allo-HSCT following a conditioning regimen with or without G-CSF. This retrospective study is the first to assess the effect of a G-CSF combination in a myeloablative conditioning regimen for CBT on the transplant outcome in adult AML patients in Japan. Patients and study methods are described in the *Online Supplementary Appendix*.

Characteristics of patients and cord blood units are shown in Table 1. There was a significant difference in cumulative incidence of neutrophil recovery among the four groups in univariate analysis ($P < 0.001$) (Figure 1A). In the multivariate analysis, the hazard risk of neutrophil engraftment was significantly higher in the TBI \geq 10Gy+Ara-C/G-CSF+CY group ($P < 0.001$) and lower in the TBI \geq 10Gy+other group ($P = 0.03$) and TBI $<$ 10Gy+other or non-TBI group ($P < 0.001$) compared with the TBI \geq 10Gy+Ara-C+CY group (Table 2). Among patients achieving neutrophil engraftment, neutrophil recovery times were significantly shorter in the TBI \geq 10Gy+Ara-C/G-CSF+CY group compared with the TBI \geq 10Gy+Ara-C+CY group ($P < 0.001$). There was a significant difference in cumulative incidence of platelet recovery among the four groups in univariate analysis ($P < 0.001$) (Figure 1B). Multivariate analysis showed no significant difference between the TBI \geq 10Gy+Ara-C+CY group and TBI \geq 10Gy+Ara-C/G-CSF+CY group ($P = 0.14$). However, the hazard risk of platelet engraftment was significantly lower in the TBI \geq 10Gy+other group ($P < 0.001$) and TBI $<$ 10Gy+other or non-TBI group ($P < 0.001$) compared with the TBI \geq 10Gy+Ara-C+CY group (Table 2). Among patients achieving platelet engraftment, there was no significant difference in platelet recovery times among the four groups ($P = 0.32$).

Among patients in the entire cohort, the cumulative incidence of TRM at 100 days and at one year was 17% (95%CI: 13%-20%) and 22% (95%CI: 18%-26%), respectively. There was no significant difference in cumulative incidence of TRM at one year among the four groups in univariate analysis ($P = 0.19$) (Figure 1C). Multivariate analysis of TRM, adjusting for other variables, showed no significant difference between the TBI \geq 10Gy+Ara-C+CY group and the TBI \geq 10Gy+Ara-C/G-CSF+CY group ($P = 0.67$), TBI \geq 10Gy+other group ($P = 0.25$), or TBI $<$ 10Gy+other or non-TBI group ($P = 0.95$) (Table 2). The cumulative incidence of relapse at three years was 30% (95%CI: 25%-35%) in the entire cohort. There was no significant difference in cumulative incidence of relapse at three years among the four groups ($P = 0.05$) (Figure 1D). In multivariate analysis, the hazard risk of relapse was lower in the TBI \geq 10Gy+Ara-C/G-CSF+CY group ($P = 0.03$), but not in the TBI \geq 10Gy+other group ($P = 0.94$) and TBI $<$ 10Gy+other or non-TBI group ($P = 0.73$) compared with the TBI \geq 10Gy+Ara-C+CY group (Table 2).

Among the entire cohort, the probability of disease-free survival (DFS) and overall survival (OS) at three years was 44% (95%CI: 39%-49%) and 52% (95%CI: 46%-57%), respectively. There was a significant difference in the probability of DFS at three years among the four groups in univariate analysis ($P = 0.001$) (Figure 1E). The probability of

Table 2. Multivariate analysis of transplant outcomes.

Outcomes	N. of patients	HR (95% CI)	P
Neutrophil engraftment			
Conditioning regimen			
TBI \geq 10Gy+Ara-C+CY	163	1	Reference
TBI \geq 10Gy+Ara-C/G-CSF+CY	80	1.57(1.17-2.11)	0.002
TBI \geq 10Gy+other	156	0.76(0.58-0.98)	0.03
TBI $<$ 10Gy+other or non-TBI	39	0.46(0.27-0.78)	0.004
Number of CD34 ⁺ cells			
$<1 \times 10^6$ /kg	279	1	Reference
$\geq 1 \times 10^6$ /kg	144	1.56(1.23-1.98)	<0.001
Platelet engraftment			
Conditioning regimen			
TBI \geq 10Gy+Ara-C+CY	163	1	Reference
TBI \geq 10Gy+Ara-C/G-CSF+CY	80	1.25(0.92-1.71)	0.14
TBI \geq 10Gy+other	156	0.54(0.39-0.73)	<0.001
TBI $<$ 10Gy+other or non-TBI	39	0.40(0.23-0.67)	<0.001
Number of CD34 ⁺ cells			
$<1 \times 10^6$ /kg	279	1	Reference
$\geq 1 \times 10^6$ /kg	144	1.58(1.22-2.06)	<0.001
Transplant-related mortality			
Conditioning regimen			
TBI \geq 10Gy+Ara-C+CY	163	1	Reference
TBI \geq 10Gy+Ara-C/G-CSF+CY	80	0.86(0.44-1.68)	0.67
TBI \geq 10Gy+other	156	1.31(0.82-2.10)	0.25
TBI $<$ 10Gy+other or non-TBI	39	1.02(0.46-2.25)	0.95
Age			
<40 years	226	1	Reference
≥ 40 years	212	1.64(1.08-2.49)	0.01
Disease status at CBT			
Standard risk	214	1	Reference
High risk	221	1.81(1.20-2.72)	0.004
Relapse			
Conditioning regimen			
TBI \geq 10Gy+Ara-C+CY	163	1	Reference
TBI \geq 10Gy+Ara-C/G-CSF+CY	80	0.45(0.21-0.95)	0.03
TBI \geq 10Gy+other	156	0.98(0.61-1.57)	0.94
TBI $<$ 10Gy+other or non-TBI	39	1.14(0.53-2.44)	0.73
Disease status at CBT			
Standard risk	214	1	Reference
High risk	221	3.28(2.16-4.98)	<0.001
Treatment failure			
Conditioning regimen			
TBI \geq 10Gy+Ara-C+CY	163	1	Reference
TBI \geq 10Gy+Ara-C/G-CSF+CY	80	0.57(0.36-0.91)	0.01
TBI \geq 10Gy+other	156	1.24(0.90-1.70)	0.17
TBI $<$ 10Gy+other or non-TBI	39	1.24(0.75-2.02)	0.39
Disease status at CBT			
Standard risk	214	1	Reference
High risk	221	3.10(2.29-4.19)	<0.001
Overall mortality			
Conditioning regimen			
TBI \geq 10Gy+Ara-C+CY	163	1	Reference
TBI \geq 10Gy+Ara-C/G-CSF+CY	80	0.52(0.31-0.87)	0.01
TBI \geq 10Gy+other	156	1.19(0.84-1.69)	0.31
TBI $<$ 10Gy+other or non-TBI	39	1.25(0.74-2.12)	0.39
Disease status at CBT			
Standard risk	214	1	Reference
High risk	221	2.68(1.93-3.71)	<0.001

The only significant variables other than conditioning regimen were described in each end point. Variables considered in multivariate analysis were conditioning regimen (TBI \geq 10Gy+Ara-C+CY vs. TBI \geq 10Gy+Ara-C/G-CSF+CY vs. TBI \geq 10Gy+other vs. TBI $<$ 10Gy+other or non-TBI), age (<40 vs. ≥ 40 years), patients' gender (male vs. female), disease status at CBT (standard risk vs. high risk), GVHD prophylaxis (cyclosporine A with methotrexate vs. tacrolimus with methotrexate), cord blood nucleated cell count ($<2.5 \times 10^6$ /kg vs. $\geq 2.5 \times 10^6$ /kg), cord blood CD34⁺ cell count ($<1 \times 10^6$ /kg vs. $\geq 1 \times 10^6$ /kg), HLA disparities (0 vs. 1 vs. ≥ 2), donor-recipient ABO compatibility (match vs. major/bidirectional mismatch vs. minor mismatch), and year of CBT (1998-2002 vs. 2003-2005 vs. 2006-2008). Ara-C: cytosine arabinoside; CBT: cord blood transplantation; CI: confidence interval; CY: cyclophosphamide; G-CSF: granulocyte colony-stimulating factor; HR: hazard ratio; TBI: total body irradiation.

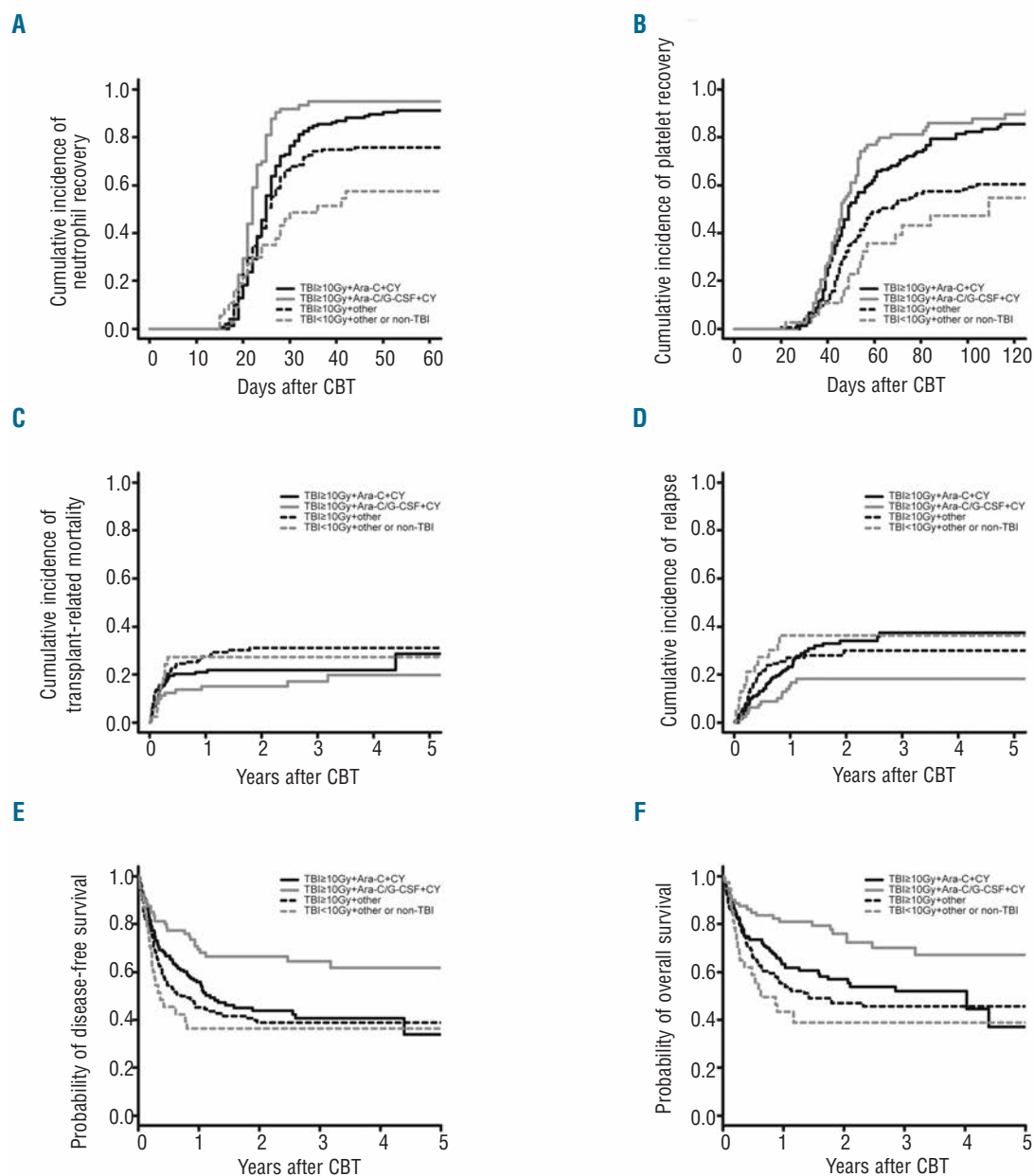


Figure 1. Cumulative incidences of neutrophil (A) and platelet (B) recovery, transplant-related mortality (TRM) (C) and relapse (D), probabilities of disease-free survival (E) and overall survival (F) after cord transplantation according to conditioning regimen. (A) Cumulative incidence of neutrophil recovery 42 days after CBT was 88% [95% confidence interval (CI): 81%-92%] in the TBI \geq 10Gy+Ara-C+CY group, 95% (95%CI: 85%-98%) in the TBI \geq 10Gy+Ara-C/G-CSF+CY group, 74% (95%CI: 66%-81%) in the TBI \geq 10Gy+other group, and 57% (95%CI: 37%-70%) in the TBI<10Gy+other or non-TBI group. Median times to neutrophil recovery were 24 days (range 17-53 days) in the TBI \geq 10Gy+Ara-C+CY group, 23 days (range 16-34 days) in the TBI \geq 10Gy+Ara-C/G-CSF+CY group, 23 days (range 15-65 days) in the TBI \geq 10Gy+other group, and 22 days (range 15-42 days) in the TBI<10Gy+other or non-TBI group. (B) Cumulative incidence of platelet recovery 100 days after CBT was 82% (95%CI: 74%-87%) in the TBI \geq 10Gy+Ara-C+CY group, 85% (95%CI: 74%-92%) in the TBI \geq 10Gy+Ara-C/G-CSF+CY group, 58% (95%CI: 48%-66%) in the TBI \geq 10Gy+other group, and 47% (95%CI: 25%-62%) in the TBI<10Gy+other or non-TBI group. Median times to platelet recovery were 46 days (range 28-168 days) in the TBI \geq 10Gy+Ara-C+CY group, 45.5 days (range 27-263 days) in the TBI \geq 10Gy+Ara-C/G-CSF+CY group, 48 days (range 20-249 days) in the TBI \geq 10Gy+other group, and 51 days (range 22-109 days) in the TBI<10Gy+other or non-TBI group. (C) Cumulative incidence of TRM at one year was 21% (95%CI: 15%-27%) in the TBI \geq 10Gy+Ara-C+CY group, 15% (95%CI: 8%-23%) in the TBI \geq 10Gy+Ara-C/G-CSF+CY group, 27% (95%CI: 20%-35%) in the TBI \geq 10Gy+other group, and 27% (95%CI: 14%-42%) in the TBI<10Gy+other or non-TBI group. (D) Cumulative incidence of relapse at three years was 37% (95%CI: 28%-46%) in the TBI \geq 10Gy+Ara-C+CY group, 18% (95%CI: 10%-27%) in the TBI \geq 10Gy+Ara-C/G-CSF+CY group, 30% (95%CI: 22%-37%) in the TBI \geq 10Gy+other group, and 36% (95%CI: 20%-52%) in the TBI<10Gy+other or non-TBI group. (E) Probability of disease-free survival at three years was 40% (95%CI: 31%-49%) for the TBI \geq 10Gy+Ara-C+CY group, 64% (95%CI: 52-74%) for the TBI \geq 10Gy+Ara-C/G-CSF+CY group, 38% (95%CI: 30%-47%) for the TBI \geq 10Gy+other group, and 36% (95%CI: 20%-51%) for the TBI<10Gy+other or non-TBI group. (F) Probability of overall survival was 52% (95%CI: 42%-60%) for the TBI \geq 10Gy+Ara-C+CY group, 70% (95%CI: 57%-79%) for the TBI \geq 10Gy+Ara-C/G-CSF+CY group, 45% (95%CI: 36%-54%) for the TBI \geq 10Gy+other group, and 39% (95%CI: 22%-55%) for the TBI<10Gy+other or non-TBI group. Median period of follow up for survivors (n=261) in the entire cohort was 24 months (range 1-122 months) after CBT.

DFS at three years was significantly better in the TBI \geq 10Gy+Ara-C/G-CSF+CY group compared with the TBI \geq 10Gy+Ara-C+CY group ($P=0.02$), the TBI \geq 10Gy+other group ($P=0.002$) and TBI $<$ 10Gy+other or non-TBI group ($P=0.006$). Multivariate analysis showed significantly decreased rates of treatment failure in the TBI \geq 10Gy+Ara-C/G-CSF+CY group compared with the TBI \geq 10Gy+Ara-C+CY group ($P=0.01$) (Table 2). In univariate analysis, there was a significant difference in the probability of OS at three years among the four groups ($P=0.001$) (Figure 1F). Multivariate analysis showed significantly decreased overall mortality in the TBI \geq 10Gy+Ara-C/G-CSF+CY group compared with the TBI \geq 10Gy+Ara-C+CY group ($P=0.01$) (Table 2). We also analyzed a subgroup of patients with standard risk ($n=214$) or high risk ($n=221$) at CBT. In standard-risk patients, the hazard risk of overall mortality ($P=0.04$), treatment failure ($P=0.01$) and relapse ($P=0.002$) was significantly lower in the TBI \geq 10Gy+Ara-C/G-CSF+CY group compared with the TBI \geq 10Gy+Ara-C+CY group, while that of high-risk patients was not (Online Supplementary Table S1 and Figures S1 and S2).

Anti-leukemia effects of allo-HSCT consist of leukemia eradication by both a conditioning regimen of chemotherapy with or without radiation and the graft-versus-leukemia (GvL) effect. Since relapse is the most common cause of death after allo-HSCT, an intensified conditioning regimen or enhancement of GvL effects is needed to reduce the incidence of relapse. Because of the difficulty in controlling the degree of GvL effects, an intensified conditioning regimen has been extensively analyzed. The several improvements to a typical conditioning regimen have included the addition of other agents to a standard myeloablative regimen, a dose escalation of drugs or TBI, or administration of drugs other than CY. Among these, the addition of other agents to a standard myeloablative regimen has been the most commonly used.^{5,6} In fact, several studies have reported a decrease in the incidence of relapse following intensified conditioning, but with a higher TRM, and no improvement in survival was achieved.^{5,7} Furthermore, the effect of adding high-dose Ara-C to a TBI/CY myeloablative conditioning regimen is controversial.⁷ However, all of these studies analyzed patients receiving BM or mobilized PB stem cell transplantation from related or unrelated donors. This finding was not confirmed in CBT. In our study, neutrophil and platelet engraftment was significantly higher in the TBI \geq 10Gy+Ara-C+CY group compared with the TBI \geq 10Gy+other group, suggesting that the addition of Ara-C to TBI/CY was beneficial in terms of stable engraftment, but not for survival in CBT for AML.

Granulocyte colony-stimulating factor was originally identified as an agent for stimulation of neutrophil production. Although G-CSF is most commonly used to reduce the duration of neutropenia after chemotherapy, it is also commonly used for hematopoietic stem cell (HSC) mobilization for HSCT. Although the mechanism of HSC mobilization is not clearly understood, G-CSF could disrupt the contact between HSC in a BM niche, leading to HSC migration. In a mouse bone marrow transplantation (BMT) model, G-CSF prior to low-dose irradiation enhanced donor HSC engraftment.¹⁴ This effect might be mainly due to the migration of recipient HSC from a BM niche by G-CSF treatment before transplantation. In fact, our data showed that neutrophil engraftment was significantly higher in the TBI \geq 10Gy+Ara-C/G-CSF+CY group compared with the TBI \geq 10Gy+Ara-C+CY group. These data

suggest that the effect of the addition of G-CSF to a conditioning regimen could enhance neutrophil engraftment after CBT.

It has been reported that the administration of G-CSF increased the susceptibility of the cell-cycle-specific agent Ara-C in leukemia cells *in vitro* and in a xenograft model.^{8,9,15} In clinical studies, several regimens have attempted to demonstrate the efficacy of concomitant use of G-CSF with chemotherapy for newly diagnosed AML.^{10,11} We hypothesized that the addition of G-CSF to a conditioning regimen might improve outcome in an allo-HSCT setting. In our study, relapse was significantly lower in the TBI \geq 10Gy+Ara-C/G-CSF+CY group compared with the TBI \geq 10Gy+Ara-C+CY group. In a subgroup analysis, the effect of a G-CSF combination regimen for reduced relapse was significant in standard-risk but not high-risk patients. This is similar to a previous prospective randomized study of concomitant use of G-CSF with chemotherapy by Löwenberg *et al.*¹¹ Further studies are required to confirm which subgroup of patients with AML could benefit from a G-CSF combination regimen in CBT to reduce the incidence of relapse.

In conclusion, our data show that the addition of G-CSF-combined Ara-C to a TBI+CY conditioning regimen resulted in a significantly higher incidence of neutrophil engraftment and significantly better DFS and OS, and a reduced relapse rate in CBT for AML. Although these findings should be confirmed in prospective studies, a G-CSF-combined myeloablative conditioning regimen promotes better engraftment and survival results in CBT for AML.

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