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

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Supplementary methods

Study design and data collection

The clinical data were provided by the Japan Cord Blood Bank Network (JCBBN) through the Transplant Registry Unified Management Program (TRUMP) of the Japan Society of Hematopoietic Cell Transplantation (JSHCT).[1] This retrospective study included patients who were 16 to 55 years of age at the time of CBT, who had de novo AML, who received single-unit CBT without prior transplant history, who underwent a myeloablative conditioning regimen before CBT, and who received cyclosporine A or tacrolimus with methotrexate as graft-versus-host disease prophylaxis regimens, because a calcineurin inhibitor plus methotrexate is the most commonly used method for CBT in Japan. CBTs were performed between 1998 and 2008 in Japan. Finally, 438 patients were eligible for this study. The institutional review board of the Institute of Medical Science, The University of Tokyo approved this study. This study was conducted in accordance with the Declaration of Helsinki.

Definitions and end points

The study end points were neutrophil and platelet engraftment, transplant-related mortality (TRM), relapse, disease-free survival (DFS), and overall survival (OS). Neutrophil engraftment was defined as being achieved on the first of three consecutive days during which the absolute neutrophil count was at least 0.5×10^9/L. Platelet engraftment was defined as being achieved on the first of three consecutive days when the platelet count was higher than 50×10^9/L without transfusion support. TRM was defined as death during remission. Relapse was defined as morphologic evidence of disease in peripheral blood, bone marrow, or extramedullary sites. DFS (inverse of treatment failure) was defined as the time from the date of cord blood transplantation (CBT) to the data of relapse, death in

continuous complete remission or last contact. OS (inverse of overall mortality) was defined as the time from the date of CBT to the date of death or last contact. The myeloablative conditioning regimen was defined according to the Center for International Blood and Marrow Transplant Research (CIBMTR) criteria,[2] which included a regimen containing either total body irradiation (TBI) single doses of ≥5 Gy, or fractionated doses totaling ≥8 Gy, busulfan doses of >9 mg/kg, or melphalan doses of >150 mg/m^2 given either as single agents or in combination with other drugs. The conditioning regimen was categorized as follows: TBI≥10Gy+Ara-C+CY, TBI≥10Gy+Ara-C/G-CSF+CY, TBI≥10Gy+other, and TBI<10Gy+other or non-TBI. The conditioning regimen of TBI≥10Gy+Ara-C/G-CSF+CY consisted of TBI≥10Gy, Ara-C (total dose 12 g/m^2, and 3 g/m^2 every 12 h for 2 days) with 5 μg/kg G-CSF (Lenograstim) from 12 h before the first dose of cytarabine to the end of cytarabine dosing, and CY (total dose 120 mg/kg), which was originally described.[3-5] For disease status at CBT, patients in complete remission without poor prognostic karyotype were classified as standard risk,[6] 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 the graft-versus-host direction. 415 of 438 (94.7 %) patients were administered G-CSF after CBT to shorten the duration of neutropenia.

Statistical analysis

Baseline patient and transplant characteristics were compared using the chi-square test or Fischer's exact test for categorical variables and the Kruskal–Wallis test for continuous variables. The probability of DFS and OS was estimated according to the Kaplan–Meier method, and the groups were compared using the log-rank test. The probabilities of neutrophil and platelet engraftment, TRM, and relapse were estimated based on a cumulative incidence method to accommodate competing risks. Multivariate analysis was

performed with a Cox proportional hazard model adjusted for DFS and OS, and a Fine and Gray proportional hazards model was used for the other analyses. The following variables were considered: conditioning regimen, age (<40 vs. ≥40 years), patients' sex (male vs. female), disease status at CBT (standard risk vs. high risk), graft-versus-host disease (GVHD) prophylaxis (Cyclosporine A with Methotrexate vs. Tacrolimus with Methotrexate), cord blood nucleated cell count ($<2.5\times10^7$/kg vs. $\geq2.5\times10^7$/kg), cord blood CD34+ cell count ($<1\times10^5$/kg vs. $\geq1\times10^5$/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). In this study, the TBI≥10Gy+Ara-C+CY group was considered the reference group in the multivariate analyses, because the main purpose of this study was to evaluate the additional effects of G-CSF in a TBI≥10Gy+Ara-C+CY conditioning regimen. Final model variables were confirmed with a backward selection procedure at the level of significance of P = 0.05. All P-values were two-sided. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).[7]

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Supplementary Figure Legends

Supplementary Figure 1. Cumulative incidences of relapse (A), and probabilities of disease-free (B) and overall (C) survival after cord blood transplantation according to conditioning regimen in standard-risk patients.

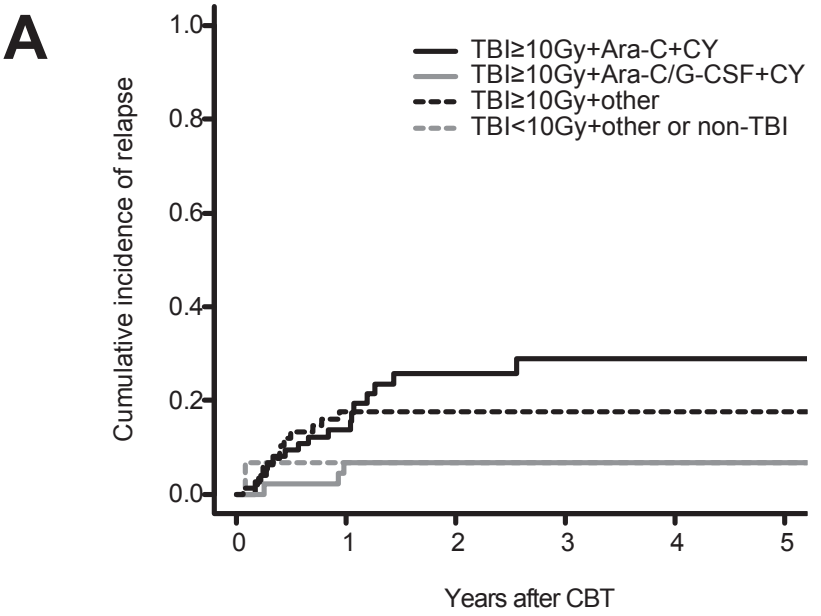
(A) The cumulative incidence of relapse at 3 years was 29 % (95 % CI, 17 % to 41 %) in the TBI≥10Gy+Ara-C+CY group, 6 % (95 % CI, 1 % to 16 %) in the TBI≥10Gy+Ara-C/G-CSF+CY group, 17 % (95 % CI, 9 % to 27 %) in the TBI≥10Gy+other group, and 6 % (95 % CI, 0 % to 26 %) in the TBI<10Gy+other or non-TBI group. (B) The probability of disease-free survival at 3 years was 54 % (95 % CI, 40 % to 66 %) for the TBI≥10Gy+Ara-C+CY group, 76 % (95 % CI, 60 % to 86 %) for the TBI≥10Gy+Ara-C/G-CSF+CY group, 55 % (95 % CI, 43 % to 66 %) for the TBI≥10Gy+other group, and 79 (95 % CI, 47 % to 92 %) for the TBI<10Gy+other or non-TBI group. (C) The probability of overall survival was 63 % (95 % CI, 48 % to 74 %) for the TBI≥10Gy+Ara-C+CY group, 81 % (95 % CI, 65 % to 90 %) for the TBI≥10Gy+Ara-C/G-CSF+CY group, 58 % (95 % CI, 45 % to 69 %) for the TBI≥10Gy+other group, and 77 % (95 % CI, 44 % to 92 %) for the TBI<10Gy+other or non-TBI group.

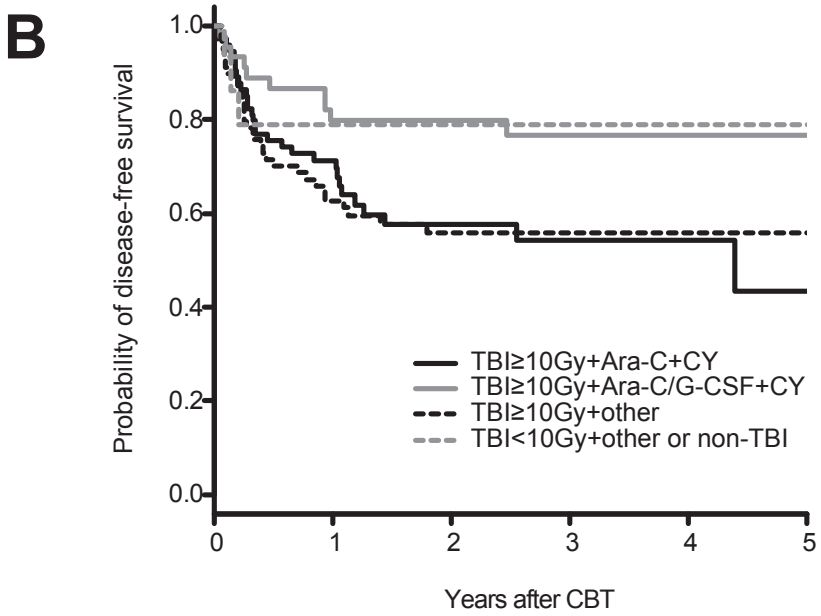
Supplementary Figure 2. Cumulative incidences of relapse (A), and probabilities of disease-free (B) and overall (C) survival after cord blood transplantation according to conditioning regimen in high-risk patients.

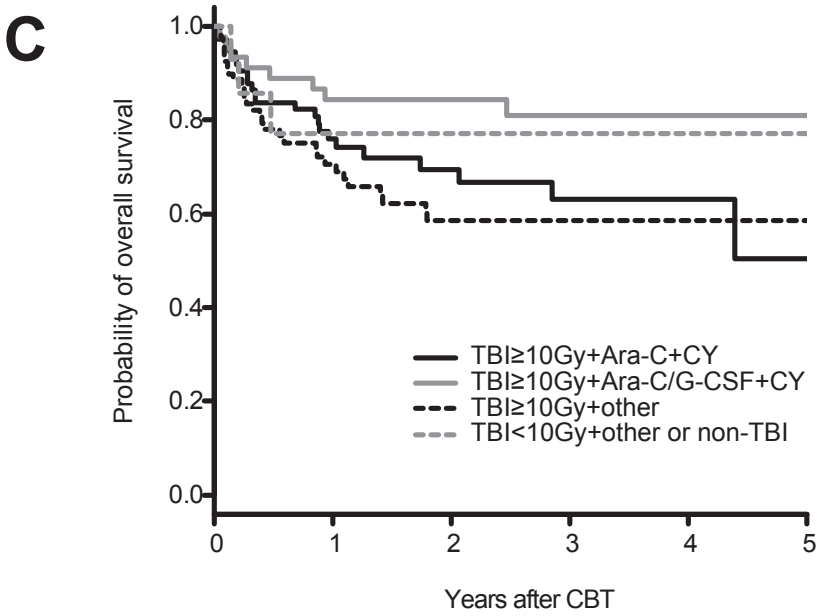
(A) The cumulative incidence of relapse at 3 years was 47 % (95 % CI, 33 % to 60 %) in the TBI≥10Gy+Ara-C+CY group, 34 % (95 % CI, 18 % to 51 %) in the TBI≥10Gy+Ara-C/G-CSF+CY group, 43 % (95 % CI, 31 % to 55 %) in the

TBI≥10Gy+other group, and 52 % (95 % CI, 29 % to 71 %) in the TBI<10Gy+other or non-TBI group. (B) The probability of disease-free survival at 3 years was 25 % (95 % CI, 14 % to 38 %) for the TBI≥10Gy+Ara-C+CY group, 48 % (95 % CI, 30 % to 64 %) for the TBI≥10Gy+Ara-C/G-CSF+CY group, 20 % (95 % CI, 11 % to 31 %) for the TBI≥10Gy+other group, and 13 (95 % CI, 3 % to 29 %) for the TBI<10Gy+other or non-TBI group. (C) The probability of overall survival was 40 % (95 % CI, 27 % to 53 %) for the TBI≥10Gy+Ara-C+CY group, 51 % (95 % CI, 29 % to 69 %) for the TBI≥10Gy+Ara-C/G-CSF+CY group, 31 % (95 % CI, 19 % to 43 %) for the TBI≥10Gy+other group, and 17 % (95 % CI, 5 % to 36 %) for the TBI<10Gy+other or non-TBI group.

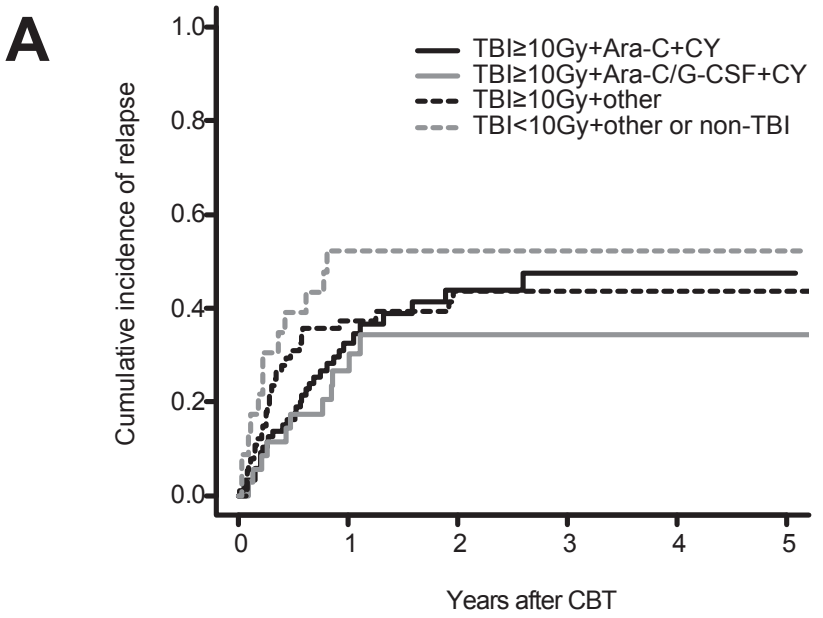
Supplementary Figure 1

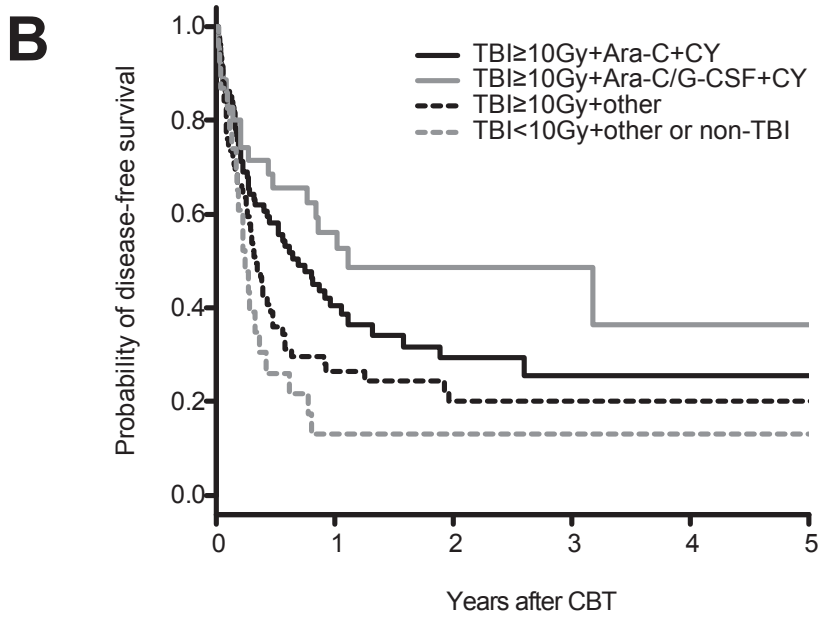


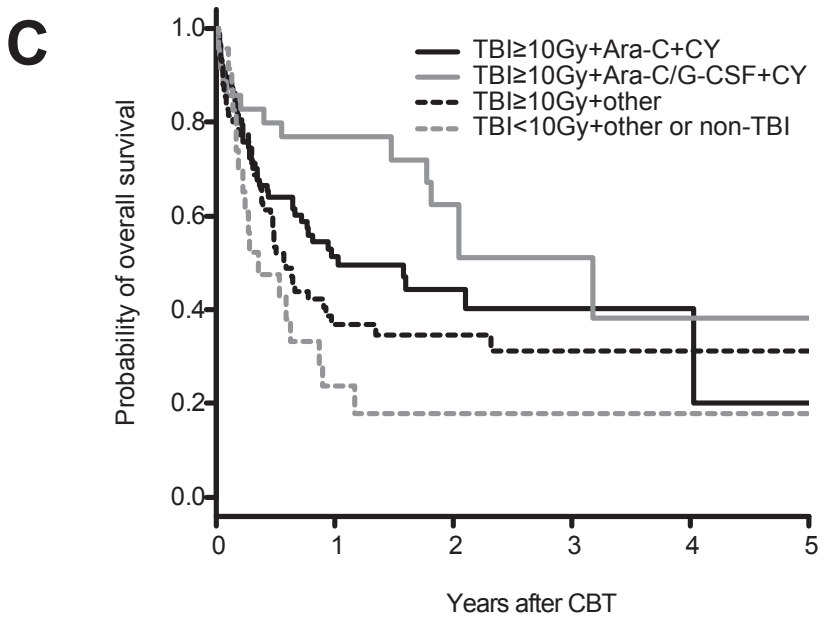




Supplementary Figure 2







Supplementary Table 1. Multivariate analysis of transplant outcomes according to the disease status at CBT

	Standard risk at CBT			High risk at CBT		
Outcome	Number of patients	HR (95 % CI)	*P-value*	Number of patients	HR (95 % CI)	*P-value*
Neutrophil engraftment						
TBI≥10Gy+Ara-C+CY	74	1	Reference	87	1	Reference
TBI≥10Gy+Ara-C/G-CSF+CY	45	1.52(1.01-2.29)	0.04	35	1.71(1.07-2.73)	0.02
TBI≥10Gy+other	79	0.69(0.49-1.01)	0.05	76	0.75(0.50-1.12)	0.17
TBI<10Gy+other or non-TBI	16	0.18(0.06-0.50)	0.001	23	0.69(0.34-1.37)	0.29
Platelet engraftment						
TBI≥10Gy+Ara-C+CY	74	1	Reference	87	1	Reference
TBI≥10Gy+Ara-C/G-CSF+CY	45	1.27(0.79-2.04)	0.32	35	1.68(0.93-2.76)	0.08
TBI≥10Gy+other	79	0.61(0.38-0.96)	0.03	76	0.37(0.23-0.61)	<0.001
TBI<10Gy+other or non-TBI	16	0.29(0.10-0.78)	0.01	23	0.43(0.22-0.85)	0.01
Transplant-related mortality						
TBI≥10Gy+Ara-C+CY	74	1	Reference	87	1	Reference
TBI≥10Gy+Ara-C/G-CSF+CY	45	0.88(0.35-2.22)	0.79	35	0.76(0.28-2.05)	0.59
TBI≥10Gy+other	79	1.46(0.64-3.29)	0.36	76	1.27(0.70-2.28)	0.42
TBI<10Gy+other or non-TBI	16	1.08(0.24-4.90)	0.92	23	0.91(0.36-2.29)	0.85
Relapse						
TBI≥10Gy+Ara-C+CY	74	1	Reference	87	1	Reference
TBI≥10Gy+Ara-C/G-CSF+CY	45	0.06(0.01-0.37)	0.002	35	0.87(0.38-1.98)	0.75
TBI≥10Gy+other	79	0.35(0.14-0.90)	0.02	76	1.27(0.72-2.24)	0.41
TBI<10Gy+other or non-TBI	16	NA	NA	23	2.01(0.88-4.57)	0.09
Treatment failure						
TBI≥10Gy+Ara-C+CY	74	1	Reference	87	1	Reference
TBI≥10Gy+Ara-C/G-CSF+CY	45	0.34(0.15-0.78)	0.01	35	0.69(0.38-1.23)	0.21
TBI≥10Gy+other	79	0.84(0.46-1.53)	0.57	76	1.45(0.97-2.16)	0.06
TBI<10Gy+other or non-TBI	16	0.37(0.08-1.63)	0.19	23	1.68(0.98-2.89)	0.05
Overall mortality						
TBI≥10Gy+Ara-C+CY	74	1	Reference	87	1	Reference

TBI≥10Gy+Ara-C/G-CSF+CY	45	0.41(0.17-0.99)	0.04	35	0.56(0.27-1.12)	0.10
TBI≥10Gy+other	79	1.08(0.57-2.05)	0.79	76	1.22(0.77-1.93)	0.39
TBI<10Gy+other or non-TBI	16	0.51(0.11-2.27)	0.38	23	1.55(0.83-2.88)	0.16

Variables considered in multivariate analysis were conditioning regimen, age, patients' sex, GVHD prophylaxis, cord blood nucleated cell count, cord blood CD34+ cell count, HLA disparities, donor–recipient ABO compatibility, and year of CBT. Ara-C: cytosine arabinoside; CBT: cord blood transplantation; CI: confidence interval; CY: cyclophosphamide; G-CSF: granulocyte colony-stimulating factor; HR: hazard ratio; NA: not applicable; TBI: total body irradiation.