Outcomes after allogeneic hematopoietic stem cell transplantation in patients with acute myeloid leukemia harboring t(7;11)(p15;p15)

Kaito Harada,[1,2] Noriko Doki,[1] Jun Aoki,[3] Jinichi Mori,[4] Shinichiro Machida,[2] Masayoshi Masuko,[5] Naoyuki Uchida,[6] Yuho Najima,[1] Takahiro Fukuda,[7] Heiwa Kanamori,[3] Hiroyasu Ogawa,[8] Shuichi Ota,[9] Kazuei Ogawa,[10] Satoshi Takahashi,[11] Masanobu Kasai,[12] Akio Maeda,[13] Koji Nagafuji,[14] Toshiro Kawakita,[15] Tatsuo Ichinohe[16] and Yoshiko Atsuta[17,18]

[1]Division of Hematology, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo; [2]Department of Hematology and Oncology, Tokai University School of Medicine, Isehara; [3]Department of Hematology, Kanagawa Cancer Center, Yokohama; [4]Department of Hematology, Jyoban Hospital, Tokiwakai, Fukushima; [5]Department of Stem Cell Transplantation, Niigata University Hospital; [6]Department of Hematology, Federation of National Public Service Personnel Mutual Aid Associations Toranomon Hospital, Tokyo; [7]Department of Hematopoietic Stem Cell Transplantation, National Cancer Center Hospital, Tokyo; [8]Division of Hematology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya; [9]Department of Hematology, Sapporo Hokuyu Hospital; [10]Department of Hematology, Fukushima Medical University Hospital; [11]Division of Molecular Therapy, The Advanced Clinical Research Center, The Institute of Medical Science, University of Tokyo; [12]Department of Hematology and Oncology, Nagoya Daini Red Cross Hospital; [13]Department of Hematology, Hyogo Cancer Center; [14]Division of Hematology and Oncology, Department of Medicine, Kurume University Hospital; [15]Department of Hematology, National Hospital Organization Kumamoto Medical Center; [16]Department of Hematology and Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University; [17]Japanese Data Center for Hematopoietic Cell Transplantation and [18]Department of Healthcare Administration, Nagoya University Graduate School of Medicine, Japan

Correspondence: k.harada@fuji.tokai-u.jp
doi:10.3324/haematol.2017.179804

Supplementary Methods

Patients

The inclusion criteria were patients aged ≥18 years with acute myeloid leukemia (AML) and who underwent an initial allogeneic hematopoietic stem cell transplantation (allo-HSCT) from 1986 through 2014. Patients without available cytogenetic data at diagnosis were excluded. Finally, 9,805 patients were eligible. The data management committees of the Transplant Registry Unified Management Program[1-2] and the Institutional Review Board of Cancer and Infectious diseases Center, Tokyo Metropolitan Komagome Hospital approved this retrospective study.

Definition

Cytogenetic risk stratification was performed using the karyotype at diagnosis, according to the criteria provided by National Comprehensive Cancer Network Guidelines for AML version 1. 2016 (ref. 3). Molecular abnormalities were not considered, because of the lack of data. Additional chromosomal abnormalities (ACAs) were defined as at least one chromosomal change other than t(7;11)(p15;p15). Overall survival was defined as the time between transplantation and death owing to any cause or last visit. Disease-free survival was defined as the time interval from allo-HSCT to a first event, either relapse or death. Transplant-related mortality was defined as death without relapse. Regarding the disease status, patients in third or more complete remission (CR) or those with non-CR were defined as high-risk patients. Conditioning intensity was classified as myeloablative or reduced-intensity conditioning according to the Center and

International Blood and Marrow Transplant Research Classification.[4] Acute and chronic graft-versus-host disease was diagnosed and graded at each center according to previously reported criteria.[5-6] Human leukocyte antigen (HLA) disparity was defined as HLA mismatched when at least a 1-antigen mismatch between the recipient and donor was detected at the serological HLA–A or –B level or at the allele HLA–DR level.

Statistical analysis

We compared patient-specific characteristics and transplant outcomes using Fisher's exact test for categorical variables and the Kruskal–Wallis test for continuous variables. Overall survival and disease-free survival probabilities were estimated using the Kaplan–Meier method. Univariate analysis for survival was performed using log-rank test. Cumulative incidences of relapse and transplant-related mortality were evaluated using Gray's method by considering each risk as a competing risk. Multivariate analysis, including significant variables from univariate analysis was performed using Cox-proportional hazard tests for survival and Fine-gray's methods for cumulative incidence of relapse and transplant-related mortality. Covariates considered in the univariate models for each analysis included age at allo-HSCT (<55 vs. ≥55 years), sex (male vs. female), performance status (0–1 vs. 2–4), disease status at allo-HSCT (first CR vs. second CR or high risk), conditioning regimen (myeloablative vs. reduced intensity), donor relation (related vs. unrelated donor), stem cell source (bone marrow vs. peripheral blood or cord blood), HLA disparity (HLA-matched vs. HLA-mismatched donor), hematopoietic cell transplantation-specific comorbidity index (0–2 vs. ≥3), ABO incompatibility (ABO-

matched vs. ABO-mismatched donor), graft-versus-host disease prophylaxis (cyclosporine- vs. tacrolimus-based), and year at transplantation (early, 1986–2008; n = 4,899 vs. later, 2009–2014; n = 4,906). In the analysis of patients with t(7;11)(p15;p15), we included the presence of ACAs (presence vs. absence) to the variables. Factors associated with at least a borderline significance ($P < 0.20$) on univariate analyses were subjected to multivariate analyses, and both hazard ratios and 95% confidence intervals were calculated. For multiple comparisons, P values were corrected using Dunnet test. Two-tailed P values of <0.05 were considered to be significant. All statistical analyses were performed using EZR, a graphical user interface for R software (The R Foundation for Statistical Computing, version 2.13.0, Vienna, Austria).[7]

References for supplementary Methods

1. Atsuta Y. Introduction of Transplant Registry Unified Management Program 2 (TRUMP2): scripts for TRUMP data analyses, part I (variables other than HLA-related data). Int J Hematol. 2016;103(1):3-10.
2. Kanda J. Scripts for TRUMP data analyses. Part II (HLA-related data): statistical analyses specific for hematopoietic stem cell transplantation. Int J Hematol. 2016;103(1):11-19.
3. nccn.org [internet]. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. Version 1. 2016. Available from: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp
4. Giralt S, Ballen K, Rizzo D, et al. Reduced-intensity conditioning regimen workshop: defining the dose spectrum. Report of a workshop convened by the center for international blood and marrow transplant research. Biol Blood Marrow Transplant. 2009;15(3):367-369.
5. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant. 1995;15(6):825-828.
6. Sullivan KM, Agura E, Anasetti C, et al. Chronic graft-versus-host disease and other late complications of bone marrow transplantation. Semin Hematol. 1991;28(3):250-259.
7. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48(3):452-458.

Supplementary Table 1. Patient characteristics stratified by cytogenetic risk.

Variables	t(7;11)(p15;p15) n = 91	Intermediate n = 7,308	Poor n = 2,406	P value
Age, median (range)	45 (19–72)	48 (18–80)	50 (18–85)	<0.001
Sex (%)				
Male	46 (50.5)	4,195 (57.4)	1,535 (63.8)	<0.001
Female	45 (49.5)	3,113 (42.6)	871 (36.2)	
PS (%)				
0 or 1	75 (82.4)	5,860 (80.2)	1,836 (76.3)	<0.001
≥2	9 (9.9)	662 (9.1)	405 (16.8)	
Missing	7 (7.7)	786 (10.8)	165 (6.9)	
Disease status at transplantation (%)				
CR1	44 (48.4)	2,881 (39.4)	733 (30.5)	<0.001
CR2	10 (11.0)	1,133 (15.5)	111 (4.6)	
High risk	37 (40.7)	3,189 (43.6)	1,532 (63.7)	
Missing	0 (0)	105 (1.4)	30 (1.2)	
Conditioning Intensity (%)				
MAC	71 (78.0)	4,730 (64.7)	1,495 (62.1)	<0.001
RIC	13 (14.2)	1,994 (27.2)	758 (31.5)	
Missing	7 (7.6)	584 (7.9)	153 (6.3)	
Donor relation (%)				
Related	31 (34.1)	2,692 (36.8)	871 (36.2)	0.75
Unrelated	60 (65.9)	4,616 (63.2)	1,535 (63.8)	
Stem cell source (%)				
BM	53 (58.2)	3,971 (54.3)	1,143 (47.5)	<0.001
PB	15 (16.5)	1,519 (20.8)	544 (22.6)	
CB	23 (25.3)	1,818 (24.9)	719 (29.9)	
HLA disparity (%)				
Match	58 (63.7)	4,204 (57.5)	1,274 (53.0)	<0.001
Missmatch	31 (34.1)	2,803 (38.4)	1,049 (43.6)	
Missing	2 (2.1)	301 (4.1)	83 (3.4)	
HCT-CI (%)				
0 to 2	61 (67.0)	3,972 (54.4)	1,282 (53.3)	<0.001
≥3	7 (7.7)	608 (8.3)	395 (16.4)	
Missing	23 (25.3)	2,728 (37.3)	729 (30.3)	
ABO incompatibility (%)				
Match	37 (40.7)	3,241 (44.3)	1,060 (44.1)	0.53
Mismatch	45 (49.5)	3,338 (45.7)	1,138 (47.3)	
missing	9 (9.9)	729 (10.0)	208 (8.6)	
GVHD prophylaxis (%)				
CyA-based	41 (45.6)	3,365 (46.5)	1,107 (42.4)	0.001
Tac-based	49 (54.4)	3,868 (53.5)	1,504 (57.6)	
Other	1 (1.1)	149 (2.0)	51 (2.1)	
Year at transplantation (%)				

Early	37 (40.7)	3,760 (51.5)	1,102 (45.8)	<0.001
Later	54 (59.3)	3,548 (48.5)	1,304 (54.2)	

Abbreviations: MAC, myeloablative conditioning; RIC, reduced intensity conditioning; BM, bone marrow; PB, peripheral blood; CB, cord blood; HLA, human leukocyte antigen; CR1, first complete remission; CR2, second complete remission; PS, performance status; HCT-CI, hematopoietic stem cell transplantation-specific comorbidity index; FAB, French-American-British; GVHD, graft-versus-host disease; CyA, cyclosporine A; Tac, tacrolimus.

Supplementary Table 2. Details of additional chromosomal abnormalities and FAB classification in patients with t(7;11)(p15;p15).

	n (%)
Chromosomal change	
t(7;11)(p15;p15)	82 (90.1)
t(7;11)(p15;p15), +8	3 (3.3)
t(7;11)(p15;p15), +8, 3q-	1 (1.1)
t(7;11)(p15;p15), +8, del(17)(p11), t(1;3)(p36;q21)	1 (1.1)
t(7;11)(p15;p15), del(9)(q?)	2 (2.2)
t(7;11)(p15;p15), inv(8)(q12q24)	1 (1.1)
der(7)t(7;11)(p15;p15)inv(7)(p15q11), der(11)t(7;11)	1 (1.1)
FAB classification	
M1	6 (6.6)
M2	64 (70.3)
M4	14 (15.4)
Missing	7 (7.7)

Abbreviation: FAB, French-American-British.

Supplementary Table 3. Multivariate analysis for transplant outcomes in a whole cohort.

	OS		DFS		Relapse		TRM	
Variables	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Cytogenetics								
t(7;11)(p15;p15)	1		1		1		1	
Intermediate	0.77 (0.56–1.07)	0.12	0.77 (0.56–1.06)	0.11	0.62 (0.43–0.89)	0.01	1.09 (0.62–1.89)	0.77
Poor	1.16 (0.83–1.61)	0.38	1.16 (0.84–1.60)	0.37	1.02 (0.71–1.47)	0.92	1.11 (0.63–1.94)	0.72
Age								
<55	1		1		1		1	
≥55	1.39 (1.29–1.51)	<0.001	1.27 (1.18–1.37)	<0.001	0.94 (0.85–1.05)	0.27	1.50 (1.33–1.69)	<0.001
Sex								
Female	1		1				1	
Male	1.22 (1.14–1.32)	<0.001	1.16 (1.08–1.24)	<0.001			1.29 (1.16–1.43)	<0.001
Conditioning Intensity								
MAC	1		1		1		1	
RIC	0.98 (0.90–1.06)	0.54	1.01 (0.93–1.09)	0.78	1.03 (0.92–1.15)	0.57	1.01 (0.90–1.14)	0.85
Related donor								
Related	1				1		1	
Unrelated	1.17 (1.03–1.34)	0.019	1.05 (0.92–1.19)	0.49	0.83 (0.71–0.96)	0.015	1.31 (1.08–1.60)	0.007
Source								
BM	1		1		1		1	
PB	1.14 (1.00–1.31)	0.05	1.05 (0.93–1.19)	0.43	0.99 (0.84–1.16)	0.89	1.12 (0.91–1.37)	0.28
CB	0.96 (0.85–1.07)	0.43	0.96 (0.86–1.07)	0.42	1.00 (0.86–1.16)	0.98	0.95 (0.81–1.11)	0.53

HLA disparity								
Match	1		1		1		1	
Missmatch	1.23 (1.11–1.35)	<0.001	1.16 (1.05–1.27)	0.003	0.80 (0.70–0.91)	<0.001	1.55 (1.35–1.78)	<0.001
Disease status at transplantation								
CR1	1		1		1		1	
CR2	1.08 (0.94–1.24)	0.28	1.08 (0.95–1.24)	0.23	1.08 (0.90–1.29)	0.4	1.07 (0.90–1.28)	0.43
High risk	2.40 (2.20–2.61)	<0.001	2.27 (2.10–2.47)	<0.001	2.42 (2.17–2.70)	<0.001	1.40 (1.24–1.57)	<0.001
PS								
0 to 1	1		1		1		1	
≥2	1.90 (1.73–2.09)	<0.001	1.83 (1.67–2.01)	<0.001	1.13 (0.98–1.30)	0.091	1.75 (1.52–2.02)	<0.001
HCT-CI								
0 to 2	1		1		1		1	
≥3	1.24 (1.13–1.35)	<0.001	1.23 (1.13–1.35)	<0.001	0.91 (0.80–1.04)	0.16	1.39 (1.22–1.57)	<0.001
GVHD prophylaxis								
CyA-based	1		1				1	
Tac-based	0.90 (0.82–0.98)	0.012	0.91 (0.83–0.98)	0.019			0.88 (0.77–0.99)	0.036
Year at transplantation								
Early					1		1	
Later					1.00 (0.90–1.12)	0.98	0.81 (0.72–0.91)	<0.001

Abbreviations: OS, overall survival; DFS, disease-free survival; TRM, transplant-related mortality; HR, hazard-ratio; CI, confidence interval; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; BM, bone marrow; PB, peripheral blood; CB, cord blood; HLA, human leukocyte antigen; CR1, first complete remission; CR2, second complete remission; PS, performance status; HCT-CI, hematopoietic stem cell transplantation-specific comorbidity index; GVHD, graft-versus-host disease; CyA, cyclosporine A; Tac, tacrolimus.

Supplementary Table 4. Univariate analysis for survivals in patients with t(7;11)(p15;p15).

Variables (n)	OS		DFS	
	Survival rate at 2 years (95% CI)	P value	Survival rate at 2 years (95% CI)	P value
Age				
<55 (69)	0.49 (0.36-0.60)	0.14	0.45 (0.32-0.56)	0.25
≥55 (22)	0.34 (0.15-0.54)		0.30 (0.12-0.49)	
Sex				
Female (45)	0.48 (0.32-0.62)	0.85	0.44 (0.28-0.58)	0.97
Male (46)	0.43 (0.28-0.57)		0.38 (0.24-0.52)	
Conditioning Intensity				
MAC (71)	0.42 (0.30-0.54)	0.95	0.37 (0.250-0.48)	0.61
RIC (13)	0.46 (0.19-0.69)		0.46 (0.19-0.70)	
Related donor				
Related (31)	0.49 (0.30-0.66)	0.89	0.39 (0.22-0.56)	0.44
Unrelated (60)	0.43 (0.29-0.55)		0.42 (0.29-0.54)	
Source				
BM (53)	0.44 (0.30-0.58)	0.31	0.43 (0.29-0.56)	0.14
PB (15)	0.34 (0.12-0.59)		0.21 (0.05-0.45)	
CB (23)	0.53 (0.30-0.72)		0.49 (0.28-0.69)	
HLA disparity				
Match (58)	0.43 (0.30-0.56)	0.81	0.39 (0.26-0.51)	0.89
Missmatch (31)	0.46 (0.27-0.63)		0.43 (0.25-0.60)	
Disease status at transplantation				
CR1 (44)	0.61 (0.44-0.74)	0.009	0.56 (0.40-0.69)	0.002
CR2 (10)	0.37 (0.07-0.69)		0.25 (0.02-0.63)	
High risk (37)	0.30 (0.16-0.45)		0.27 (0.14-0.42)	
PS				
0 to 1 (75)	0.44 (0.32-0.56)	0.047	0.39 (0.28-0.51)	0.093
≥2 (9)	0.28 (0.04-0.59)		0.28 (0.04-0.59)	
HCT-CI				
0 to 2 (61)	0.45 (0.31-0.58)	0.23	0.39 (0.26-0.52)	0.21
≥3 (7)	0.29 (0.04-0.61)		0.29 (0.04-0.61)	
GVHD prophylaxis				
CyA-based (41)	0.41 (0.25-0.55)	0.14	0.36 (0.22-0.51)	0.091
Tac-based (49)	0.48 (0.32-0.62)		0.43 (0.28-0.58)	
Year at transplantation				
Early (37)	0.51 (0.34-0.66)	0.49	0.43 (0.27-0.58)	0.93
Later (54)	0.39 (0.25-0.53)		0.39 (0.25-0.53)	
ACAs				
Absence (82)	0.47 (0.35-0.57)	0.95	0.42 (0.31-0.53)	0.88
Presence (9)	0.33 (0.08-0.62)		0.33 (0.08-0.62)	

Abbreviations: OS, overall survival; DFS, disease-free survival; CI, confidence interval; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; BM, bone marrow; PB, peripheral blood; CB, cord blood; HLA, human leukocyte antigen; CR1, first complete remission; CR2, second complete remission; PS, performance status; HCT-CI, hematopoietic stem cell transplantation-specific comorbidity index; GVHD, graft-versus-host disease; CyA, cyclosporine A; Tac, tacrolimus; ACAs, additional chromosomal abnormalities.

Supplementary Table 5. Multivariate analysis for DFS with GVHD as the time-dependent variable.

Variables	HR (95% CI)	P value
Grade I–II acute GVHD*		
Absence	1	
Presence	0.51 (0.28–0.95)	0.033
Source		
BM	1	
PB	1.48 (0.70–3.16)	0.31
CB	0.75 (0.37–1.51)	0.42
Disease status at transplantaion		
CR1	1	
CR2	2.51 (0.95–6.62)	0.062
High risk	2.88 (1.52–5.46)	0.001
PS		
0 to 1	1	
≥2	1.40 (0.60–3.27)	0.44
GVHD prophylaxis		
CyA-based	1	
Tac-based	0.59 (0.32–1.07)	0.081
Chronic GVHD (limited)**		
Absence	1	
Presence	0.11 (0.01–0.83)	0.032
Source		
BM	1	
PB	1.66 (0.78–3.51)	0.19
CB	0.82 (0.41–1.63)	0.57
Disease status at transplantaion		
CR1	1	
CR2	4.14 (1.55–11.0)	0.005
High risk	2.33 (1.24–4.37)	0.008
PS		
0 to 1	1	
≥2	1.28 (0.55–2.96)	0.57
GVHD prophylaxis		
CyA-based	1	
Tac-based	0.61 (0.34–1.11)	0.1

Abbreviations: DFS, disease-free survival; GVHD, graft-versus-host disease; HR, hazard-ratio; CI, confidence interval; BM, bone marrow; PB, peripheral blood; CB, cord blood; CR1, first complete remission; CR2, second complete remission; PS, performance status; CyA, cyclosporine A; Tac, tacrolimus.

* Patients who survived without relapse at 30 days were included in the analysis.

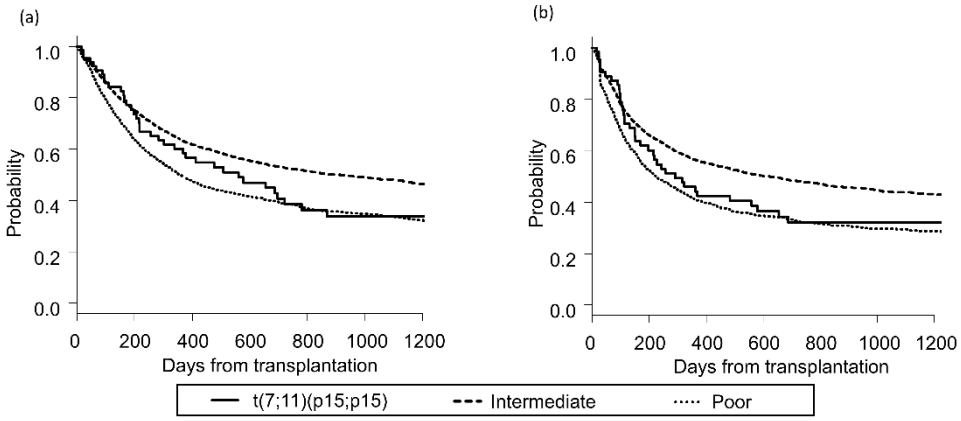
** Patients who survived without relapse at 100 days were included in the analysis.

Supplementary Table 6. Cause of death in patients with t(7;11)(p15;p15).

	n = 54
Relapse	18 (33.3)
Infection	10 (18.5)
MOF	6 (11.1)
Hemorrhage	5 (9.3)
GVHD	4 (7.4)
VOD	3 (5.6)
IP	2 (3.7)
Trauma	2 (3.7)
HPS	1 (1.9)
PTLD	1 (1.9)
Engraftment failure	1 (1.9)
Sudden death	1 (1.9)

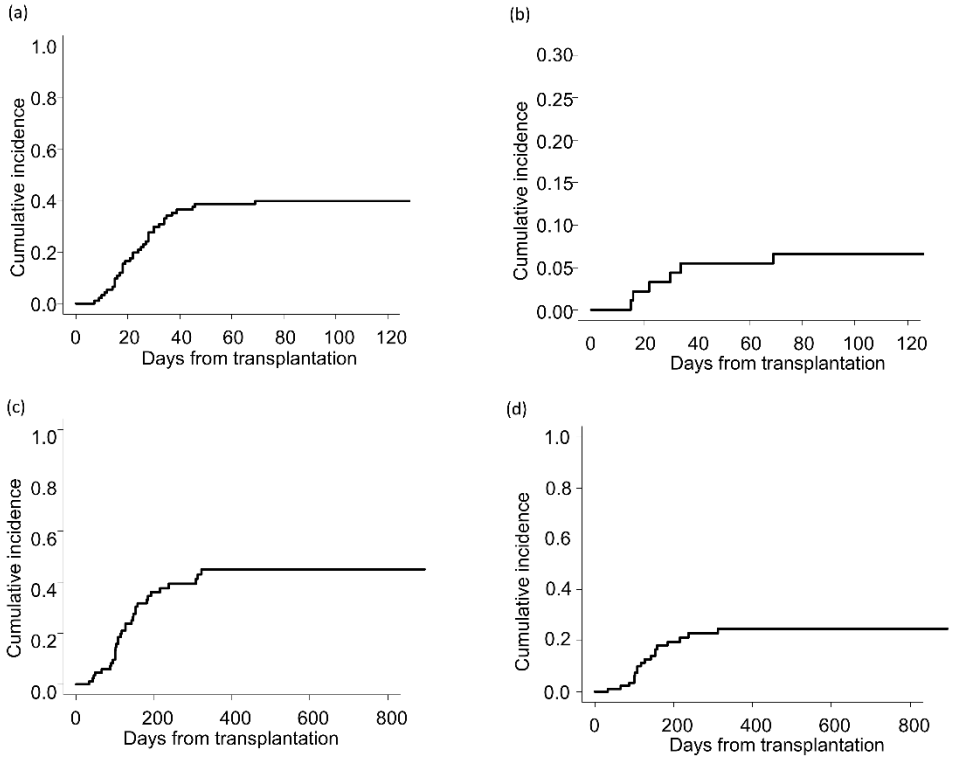
Abbreviations: MOF, multiple-organ failure; GVHD graft-versus-host disease; VOD, Vono-occulusive disease; IP, interstitial pneumonia; HPS, hemophagocytic syndrome; PTLD, Post-transplant lymphoproliferative disorder.

Supplementary Figure 1.



Supplementary Figure 1. The adjusted overall survival (a) and disease-free survival (b) in each cytogenetic group. The 3-year overall and disease-free survival rates were 33.8% and 32.2%, respectively, in the t(7;11)(p15;p15) group; 48.0% and 43.6%, respectively, in the intermediate-risk group; and 33.7% and 29.2%, respectively, in the poor-risk group.

Supplementary Figure 2.



Supplementary Figure 2. Cumulative incidence of grade II–IV (a), III–IV (b) acute GVHD, limited (c), and extensive (d) chronic GVHD in patients with t(7;11)(p15;p15). The cumulative incidences of grade II–IV and III–IV acute GVHD were 39.8% and 6.6%, respectively. In contrast, cumulative incidences of limited and extensive chronic GVHD were 45.1% and 24.6%, respectively.