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

Acute myeloid leukemia (AML) with chromosomal translocation between 7p15 and 11p15 [t(7;11)(p15;p15)], resulting in a fusion between the nucleoporin 98 and homeobox A9 genes (*NUP98-HOXA9*),[1] is rare and has been reported sporadically in Asian countries.[2-5] The *NUP98-HOXA9* fusion gene can dysregulate hematopoietic precursor transcription, disrupt cell differentiation, enhance cell proliferation, and contribute to leukemogenesis.[6-8] Although AML with t(7;11)(p15;p15) as the sole abnormality is classified as an intermediate-risk condition in recent cytogenetic stratifications,[9-10] previous studies reported dismal outcomes, with a median survival of 8–13 months.[2-3] Most patients in these studies underwent chemotherapy rather than allogeneic hematopoietic stem cell transplantation (HSCT). Moreover, the number of patients in each study was small. To date, no study has directly compared transplant outcomes between patients with AML harboring t(7;11)(p15;p15) and those with other AML variants. In this study, using nationwide registration data in Japan, we compared transplant outcomes of patients with AML harboring t(7;11)(p15;p15) with those of patients with intermediate- or poor-risk AML variants. We also evaluated the risk factors for survival in patients with AML harboring t(7;11)(p15;p15) who underwent allogeneic HSCT.

Clinical data were collected through the Transplant Registry Unified Management Program, which is the nationwide data registry of the Japan Society for Hematopoietic Cell Transplantation and the Japanese Data Center for Hematopoietic Cell Transplantation.[11] The study endpoints were overall survival (OS), disease-free survival (DFS), relapse rate, and transplant-related mortality. Definitions of each endpoint, covariates considered in the univariate models for each analysis, and statistical methods are described in the *Online Supplement*.

From 1986 through 2014, we identified 91 patients with AML harboring t(7;11)(p15;p15), 7,308 with intermediate-risk AML, and 2,406 with poor-risk AML with chromosomal changes other than t(7;11)(p15;p15). Among the survivors (n=4,278), the median follow-up period was 1,124 days. Patient and transplant characteristics are summarized in *Online Supplementary Tables S1* and *S2*.

At 3 years after allogeneic HSCT, OS and DFS probabilities were 40.1% and 37.8% in the t(7;11)(p15;p15) group; 48.0% and 44.8% in the intermediate-risk group; and 28.5% and 25.1% in the poor-risk group, respectively (Figure 1A,B). Patients in the poor-risk group exhibited significantly lower survival probabilities than those in the t(7;11)(p15;p15) group (OS, *P*=0.008; DFS, *P*=0.006),

Table 1. Multivariate analysis for transplant outcomes in patients with t(7;11)(p15;p15).

	OS		DFS		Relapse		TRM	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Ages, years								
<55	1							
≥55	1.52 (0.78–2.95)	0.22						
Type of donor								
Related					1		1	
Unrelated					0.87 (0.22–3.47)	0.84	2.56 (0.76–8.58)	0.13
Source of stem cells								
Bone marrow			1		1			
Peripheral blood			1.60 (0.75–3.40)	0.22	1.95 (0.70–5.44)	0.2		
Cord blood			0.72 (0.36–1.44)	0.35	0.97 (0.20–4.66)	0.97		
HLA disparity								
Matched					1		1	
Mismatched					0.58 (0.18–1.89)	0.37	1.09 (0.40–2.99)	0.87
Disease status at transplantation								
CR1	1		1		1			
CR2	1.92 (0.70–5.25)	0.21	2.90 (1.12–7.53)	0.028	2.20 (0.58–8.38)	0.25		
High risk	1.84 (0.96–3.51)	0.067	2.61 (1.39–4.91)	0.003	2.77 (1.28–6.01)	0.009		
Performance status								
0-1	1		1				1	
≥2	1.93 (0.81–4.62)	0.14	1.32 (0.57–3.05)	0.52			4.98 (1.62–15.3)	0.005
GvHD prophylaxis								
CyA-based	1		1		1			
Tac-based	0.59 (0.33–1.05)	0.07	0.67 (0.37–1.20)	0.18	0.57 (0.18–1.83)	0.35		

OS, overall survival; DFS, disease-free survival; TRM, transplant-related mortality; HR, hazard ratio; CI, confidence interval; HLA, human leukocyte antigen; CR1, first complete remission; CR2, second complete remission; GvHD, graft-*versus*-host disease; CyA, cyclosporine A; Tac, tacrolimus. *Patients in third or more complete remission and those not in complete remission were defined as high-risk patients.

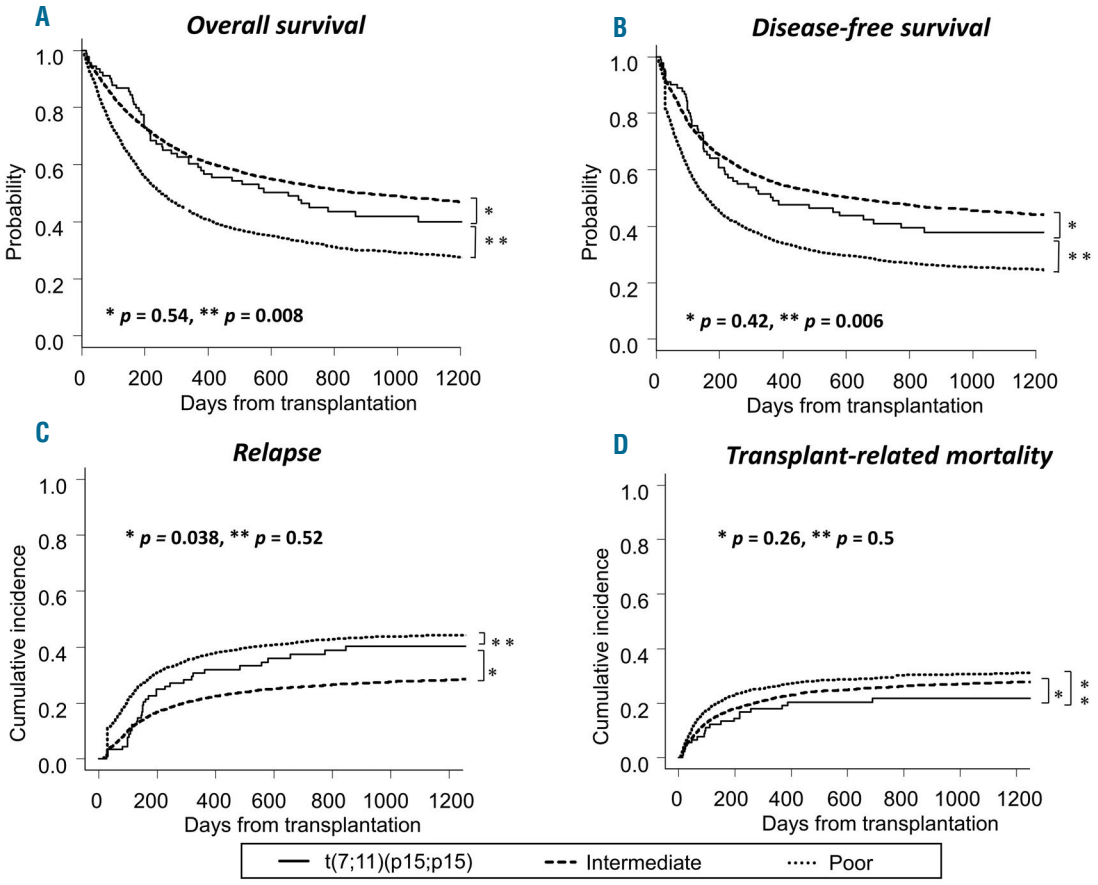

Figure 1. Transplant outcomes in each cytogenetic group. (A) Overall survival and (B) disease-free survival rates in the t(7;11)(p15;p15) group were significantly lower than those in the poor-risk group. (C) Relapse rate in the t(7;11)(p15;p15) group was higher than that in the intermediate-risk group. (D) Transplant-related mortality in the t(7;11)(p15;p15) group was similar to those in the intermediate- and poor-risk groups.

although the differences between the t(7;11)(p15;p15) and intermediate-risk groups were not statistically significant (OS, *P*=0.54; DFS, *P*=0.42). After adjusting for covariates, OS and DFS in the poor-risk group were comparable with those in the t(7;11)(p15;p15) group [OS: hazard ratio (HR), 1.16; 95% confidence interval (95% CI), 0.83–1.61; *P*=0.38 and DFS: HR, 1.16; 95% CI: 0.84–1.60; *P*=0.37]. In contrast, OS and DFS in the intermediate-risk group were higher than those in the t(7;11)(p15;p15) group (OS: HR, 0.77; 95% CI: 0.56–1.07; *P*=0.12 and DFS: HR, 0.77; 95% CI: 0.56–1.06; *P*=0.11), although the differences were not statistically significant (*Online Supplementary Table S3*). Adjusted OS and DFS for each cytogenetic group after adjusting for covariates are shown in *Online Supplementary Figure S1*. The estimated cumulative incidence of relapse at 3 years was 40.3% in the t(7;11)(p15;p15) group, which was higher than that in the intermediate-risk group (27.9%; *P*=0.038), and similar to that in the poor-risk group (44.0%; *P*=0.52) (Figure 1C). In contrast, the 3-year transplant-related mortality rate in the t(7;11)(p15;p15) group (21.8%) was similar to those in the intermediate-risk (27.3%; *P*=0.26) and poor-risk groups (30.7%; *P*=0.5) (Figure 1D). Multivariate analysis revealed a significant difference in the cumulative incidence of relapse between patients with t(7;11)(p15;p15) and those with intermediate-risk AML (HR, 0.62; 95% CI: 0.43–0.89; *P*=0.01), although the difference between patients with t(7;11)(p15;p15) and those with poor-risk AML was not statistically significant (HR, 1.02; 95% CI: 0.71–1.47; *P*=0.92). Regarding transplant-related mortality, no significant differences were found between patients with t(7;11)(p15;p15) and those with intermediate-risk AML (HR, 1.09; 95% CI: 0.62–1.89; *P*=0.77) or poor-risk AML (HR, 1.11; 95% CI: 0.63–1.94; *P*=0.72) after adjusting for covariates (*Online Supplementary Table S3*).

We performed univariate and multivariate analyses of patients with t(7;11)(p15;p15). The 2-year OS and DFS rates in the patients who underwent allogeneic HSCT in first complete remission (CR1; n=44) were 60.6% and 56.1%, respectively, which were higher than the rates in patients in second complete remission (CR2; n=10; OS: 37.3%; *P*=0.3 and DFS: 25.0%; *P*=0.056) and in the high-risk group (n=37; OS: 29.7%; *P*=0.005 and DFS: 27.1%; *P*=0.001) (Figure 2A,B). In multivariate analysis, the only factor influencing DFS was disease status at allogeneic HSCT (CR2: HR, 2.90; 95% CI: 1.12–7.53; *P*=0.028 and high risk: HR, 2.61; 95% CI: 1.39–4.91; *P*=0.003) (Table 1). A lower relapse rate at 2 years was observed for patients in CR1 (25.5%) than for those in CR2 (45.0%; *P*=0.32) or in the high-risk group (50.5%; *P*=0.054) (Figure 2C), confirmed by multivariate analysis (CR2: HR, 2.20; 95% CI: 0.58–8.38; *P*=0.25 and high risk: HR, 2.77; 95% CI: 1.28–

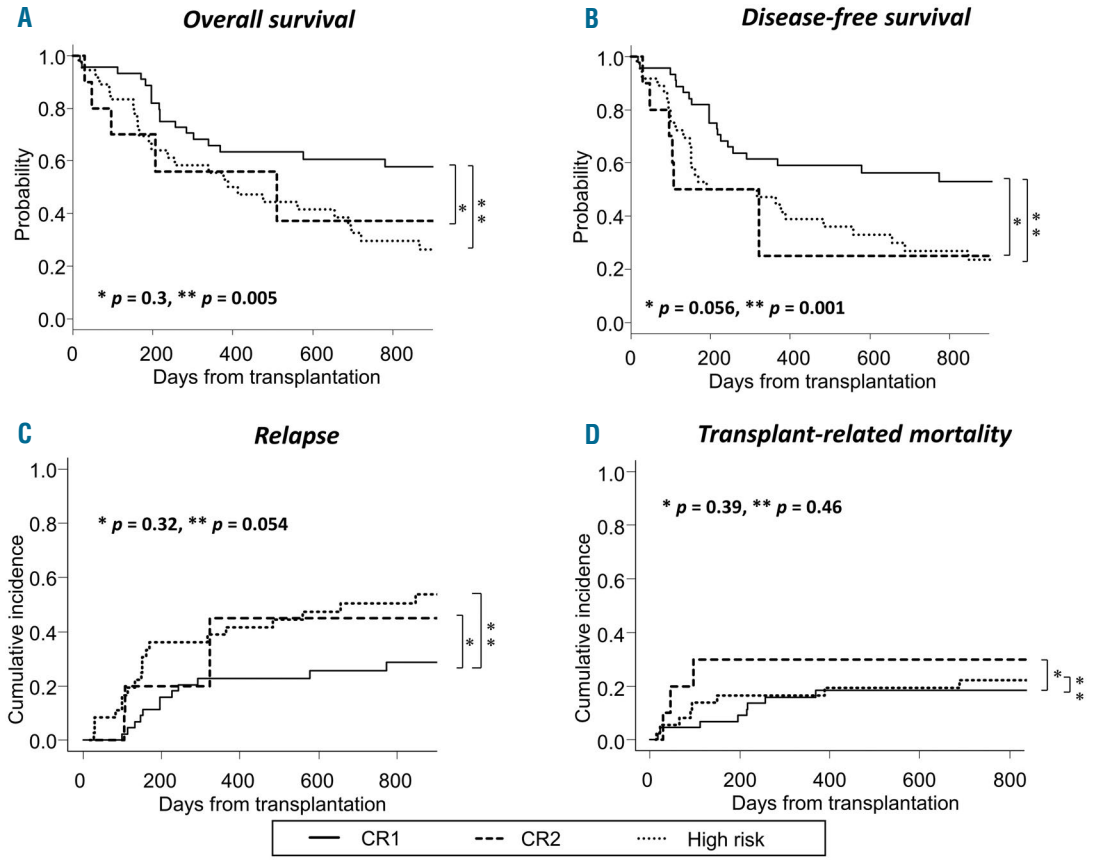

Figure 2. Transplant outcomes in the t(7;11)(p15;p15) group stratified by disease status at transplantation. (A) Overall survival and (B) disease-free survival rates in the patients who underwent allogeneic HSCT in CR1 were higher than those in high-risk patients. (C) Relapse rate for patients in CR1 was lower than those in CR2 or high-risk patients, without the difference being statistically significant. (d) Transplant-related mortality for patients in CR1 was similar to those in CR2 or high-risk patients.

6.01; *P*=0.009) (Table 1). In these statistical analyses, the presence of additional chromosomal abnormalities was included as a covariate. However, in univariate analysis, additional chromosomal abnormalities (n=9) were not a significant risk factor for DFS (2-year DFS: 33.3% in patients with additional chromosomal abnormalities *versus* 38.3% in those without; *P*=0.92) (*Online Supplementary Table S4*).

Among the patients with t(7;11)(p15;p15), the cumulative incidences of grade II–IV acute graft-*versus*-host disease (GvHD) and limited chronic GvHD were 39.8% and 45.1%, respectively (*Online Supplementary Figure S2A,C*). To clarify the effect of GvHD on survival, we used Cox-proportional regression models with acute or chronic GvHD as the time-dependent covariate. Both the development of grade I–II acute GvHD (HR, 0.51; 95% CI: 0.28–0.95; *P*=0.033) and limited chronic GvHD (HR, 0.11; 95% CI: 0.01–0.83; *P*=0.032) significantly improved DFS (*Online Supplementary Table S5*).

At the time of analysis, 54 patients with t(7;11)(p15;p15) had died and 37 were alive. The leading cause of death was disease relapse (n=18; 33.3%), followed by infection (n=10; 18.5%) and multiple-organ failure (n=6; 11.1%). Only four patients (7.4%) died from GvHD (*Online Supplementary Table S6*).

To date, no studies have compared transplant outcomes between patients with t(7;11)(p15;p15) and those with other AML variants because of the rarity of the former disease. While its actual prognostic relevance remains unclear, extremely high incidences of relapse in patients with t(7;11)(p15;p15) have been reported.[2-5] Although the cumulative incidence of relapse in the t(7;11)(p15;p15) group was significantly higher than that in the intermediate-risk group, there were no significant differences in survival between the two groups. Although these results suggest that allogeneic HSCT might overcome or at least ameliorate the poor prognosis of AML with t(7;11)(p15;p15), the present study is retrospective, and further prospective studies comparing allogeneic HSCT and chemotherapies are warranted to determine the prognostic relevance of AML harboring t(7;11)(p15;p15).

Our results showed that patients who underwent allogeneic HSCT in CR2 or were at high risk were more likely to relapse than those in CR1. In general, the survival of patients with AML after first relapse was approximately 30% at 12 months;[1,2] however, only 8% of the patients harboring t(7;11)(p15;p15) were still alive 12 months after first relapse, if previous results were considered together and were estimated by the Kaplan–Meier method.[1,2] This highlights the dismal outcomes of AML with t(7;11)(p15;p15) after the first relapse. Thus, allogeneic HSCT in CR1 for patients with t(7;11)(p15;p15) appears to be reasonable,

with a 2-year survival rate of 56%. However, our results should be interpreted carefully. Because our study only included patients who underwent allogeneic HSCT, it would have the limitation of biased selection of patients.

Although a previous study[2] documented minimal residual disease in most patients with t(7;11)(p15;p15), even after conditioning regimens, our results demonstrated that allogeneic HSCT is a potentially curative therapy for a substantial number of patients with t(7;11)(p15;p15), at least in part, through graft-*versus*-leukemia effects. The development of grade I-II acute GvHD or limited chronic GvHD had positive effects on DFS in the analysis that included these factors as time-independent variables. As regards allogeneic HSCT, the prognostic effects on survival that result from graft-*versus*-leukemia effects could be counterbalanced by those complications. However, only 7.4% of patients succumbed to GvHD in our study, and the beneficial graft-*versus*-leukemia effects on survival outweighed the deleterious effects of GvHD.

In conclusion, our study demonstrated the transplant outcomes of patients with (7;11)(p15;p15) compared with those with intermediate-risk or poor-risk AML. Among patients with t(7;11)(p15;p15), allogeneic HSCT in CR1 produced superior outcomes to those in CR2 or high risk. There are few data available regarding treatment options for patients with AML harboring t(7;11)(p15;p15). This study, for the first time, examines the therapeutic use of allogeneic HSCT for patients with AML harboring t(7;11)(p15;p15). We believe that our study could be a milestone in managing patients with AML harboring t(7;11)(p15;p15), until prospective studies clarify the role of allogeneic HSCT in the treatment of this disease.

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