Prognostic factors for acute myeloid leukemia patients with t(6;9)(p23;q34) who underwent an allogeneic hematopoietic stem cell transplant

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Ken Ishiyama[1,2], Akiyoshi Takami[1], Yoshinobu Kanda[3], Shinji Nakao[1], Michihiro Hidaka[4], Tetsuo Maeda[5], Tomoki Naoe[6], Shuichi Taniguchi[7], Keisei Kawa[8], Tokiko Nagamura[9], Ken Tabuchi[10], Yoshiko Atsuta[11] and Hisashi Sakamaki[12].

A. Takami and Y. Kanda were equally contributed to the study.

1: Department of Cellular Transplantation Biology, Kanazawa University Graduate School of Medical Sciences, Kanazawa, Ishikawa; 2: Department of Hematology, Tokyo Metropolitan Ohtsuka Hospital, Toshima, Tokyo; 3: Division of Hematology, Saitama Medical Center, Jichi Medical University, Saitama; 4: Department of Hematology, National Hospital Organization Kumamoto Medical Center, Kumamoto; 5: Department of Hematology and Oncology, Osaka University Hospital, Suita, Osaka; 6: Department of Hematology and Oncology, Nagoya University Graduate School of Medicine, Nagoya, Aichi; 7: Department of Hematology, Toranomon Hospital, Minato, Tokyo; 8: Department of Hematology/Oncology, Osaka Medical Center and Research Institute for Maternal and Child Health, Izumi, Osaka; 9: Department of Cell Processing and Transfusion, The Institute of Medical Science, The University of Tokyo, Minato, Tokyo; 10: Department of Pediatrics, Hematology/Oncology , Kanagawa Children's Medical Center, Yokohama, Kanagawa; 11: Department of Hematopoietic Stem Cell Transplantation Data Management/Biostatistics, Nagoya University School of Medicine, Nagoya, Aichi; 12: Department of Hematology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Bunkyo, Tokyo, Japan.

Correspondence: Ken Ishiyama, Department of Hematology, Tokyo Metropolitan Ohtsuka Hospital, 2-8-1 Minami-Ohtsuka, Toshima, Tokyo 170-8476, Japan. Phone: +81 3 3941 3211, Fax: +81 3 3941 7267, E-mail: ishiyama-knz@umin.ac.jp

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Abstract

We have recently reported that the outcome of acute myeloid leukemia (AML) patients with t(6;9)(p23;q34) who underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) was comparable to that of patients with a normal karyotype. We performed a further analysis regarding the prognostic factors for t(6;9)(p23;q34) AML patients who underwent a HSCT. Seven pediatric patients and 57 adult patients, transplanted between 1996 and 2007, were assessed in this study. The overall survival (OS) of the pediatric patients tended to be better than the OS of the adults, although there were no statistically significant differences. The present study focused on the adult patients revealed that the disease status at HSCT was the sole prognostic factor affecting the OS identified in the univariate analysis. A multivariate analysis showed that the disease status at HSCT and M2 in the FAB classification were extracted as the significant variables affecting the OS. The patients who were not in remission at HSCT and had non-FAB-M2 showed a poorer outcome; 6 deaths in the 9 patients were due to a relapse of the AML. These findings suggest that novel therapeutic approaches might be needed for patients with these poor prognostic factors.

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is often selected as a curative treatment strategy for acute myeloid leukemia (AML). In particular, AML patients with poor cytogenetics at diagnosis are considered for allo-HSCT as the first-line therapy.(1-4) Recently, we have reported that AML with the t(6;9)(p23;q34) abnormality, which predicts a very poor prognosis in patients treated with chemotherapy,(5) is associated with an outcome in patients receiving allo-HSCT that is comparable to that in patients with a normal karyotype.(6) However, 55% of the AML patients with t(6;9)(p23;q34) eventually had a negative outcome. We herein performed a further analysis for AML patients with t(6;9)(p23;q34) who received allo-HSCT to identify the prognostic factors affecting their overall survival (OS).

Materials and Methods

Study population and data management

A total of 64 *de novo* AML patients with t(6;9)(p23;q34) detected in G-band staining at diagnosis, who received their first allo-HSCT between January 1996 and December 2007, were extracted from the databases of the Japan Society for Hematopoietic Cell Transplantation (JSHCT) and the Japan Cord Blood Bank Network. The cytogenetic data were analyzed according to the Southwestern Oncology Group (SWOG) criteria for each institution, instead of by central review.(3) The clinical data were collected using a standardized report form, which was submitted at 100 days, 1 year and annually after HSCT. This study was approved by the Committee for Nationwide Survey Data Management of the JSHCT. Written informed consent was obtained in accordance with the Declaration of Helsinki.

Statistical analysis

The OS was defined as the number of days from HSCT until death from any cause. Non-relapse mortality (NRM) was defined as death without relapse. Any patients who were alive at the last-follow-up date were censored. The analysis was performed using the R version 2.13.0 software program (R Foundation for Statistical Computing; www.r-project.org).(7) The probability of OS was calculated using the Kaplan-Meier method and compared using the log-rank test. The probabilities of TRM and disease relapse were compared using the Grey test(8) and were analyzed using the cumulative incidence analysis,(7) while considering relapse and death without disease relapse as respective competing risks.

The following variables related to the survival of the adult patients older than 15 years and their clinical data were compared in a univariate analysis: recipient characteristics (age; younger than 35 vs. older than 35, gender, performance status at diagnosis; 0 to 2 vs. 3 or 4, FAB classification; M2 or others, positivity for peroxidase in leukemic blasts at diagnosis; less than 50% vs. greater than 50%, cytogenetic abnormality), donor characteristics (age; younger than 35 vs. older than 35, gender, sex compatibility, compatibility of cytomegalovirus antibody serostatus, relationship; related vs. unrelated, and ABO compatibility), transplant characteristics (disease status at HSCT; CR vs. non-CR, use of total body irradiation as a preconditioning regimen, source of the graft; bone marrow (BM), peripheral blood stem cell (PBSC), cord blood (CB)), GVHD prophylaxis; cyclosporine vs. tacrolimus and the use of methotrexate. Multivariate Cox models were used to evaluate the hazard ratios associated with the prognosis. Covariates found to be significant in the univariate analyses ($P \leq 0.10$) were

included in the models. For both the univariate and the multivariate analyses, P values were two sided, and outcomes were considered to be significant for $P \leq 0.05$.

Results

Survival of the pediatric patients

A total of 64 AML patients with t(6;9)(p23;q34) patients were analyzed (Table 1). The OS of the 7 pediatric patients younger than 14 years old seemed to be better than the OS of the 57 adult patients older than 15 years, although there were no statistically signficant differences between the groups (Figure 1A, the probability of 3-year OS in pediatric patients and adult patients was 83% and 48%, respectively (P=0.12)).

OS, relapse and NRM of the adult patients

We performed a further analysis in the 57 adult patients older than 15 years. The univariate analysis showed that the disease status at HSCT was the sole significant prognostic factor affecting the OS (Figure 1B, the probability of 3-year OS in patients with CR and with non-CR at HSCT was 69% and 29%, respectively (P<0.003)), and the number of HLA disparities, M2 in the FAB classification, and CB as the source of the graft were calculated to have a P-value < 0.1 (Table 2). No statistically significant tendencies related to gender, gender mismatch between the donor and recipient, recipient cytomegalovirus serostatus or the use of total body irradiation for the preconditioning regimen were observed. The cumulative incidence of relapse and of NRM are shown in Figure 2; the cumulative incidence of relapse was significantly lower in patients with a CR at HSCT than in patients without CR (Figure 2A, the 3-year cumulative incidence was 25% in CR patients and 58% in non-CR patients (P=0.005)),

although such differences were not seen in the cumulative incidence of NRM between these 2 groups (Figure 2B, the 3-year cumulative incidence was 10% in CR patients and 16% in non-CR patients (P=0.85)).

In the multivariate analysis, the disease status at HSCT and FAB-M2 remained the significant variables associated with the OS (Table 2). The OS of the patients categorized by the combination of the disease status at HSCT and FAB-M2 showed a favorable outcome in FAB-M2 patients with a CR at HSCT (Figure 3, the probability of 3-year OS in patients with CR/FAB-M2, CR/non-FAB-M2, non-CR/FAB-M2 and non-CR/non-FAB-M2 was 76%, 60%, 43% and not reached, respectively (P<0.001)). In contrast, the patients who were not in remission at the time of HSCT and had non-FAB-M2 showed a poorer outcome; the cause of death in 6 out of the 9 patients was due to a relapse of the AML.

Discussion

The characteristics of the patients with the t(6;9)(p23;q34) subtype of AML were known to have a poor prognosis and to be associated with development at a younger age, frequent M2 in the FAB classification, and achievement of a morphological 1st CR not predicting a favorable outcome.(9) In this study, we distinguished the 7 pediatric patients who seemed to have a superior OS from the adult patients, because the better prognosis in the children might reflect differences in the pathogenesis of the disease, consistent with the better OS in the previous report.(5)

The current study revealed that the cumulative incidence of relapse was significantly worse in patients without CR than in patients with CR, although the cumulative incidence of NRM was comparable between these two groups. These results

suggest that it is important to have an appropriate treatment strategy, ie, allo-HSCT for the patients who achieved 1st CR is imperative, while the development of an effective treatment for the refractory/relapsed AML patients is critical.

The presence of FLT3-ITD is recognized as a poor prognostic factor in AML patients.(10-12) Since FLT3-ITD was frequently detected in patients with t(6;9)(p23;q34),(5) it has been suggested that the presence of FLT3-ITD might contribute to the poor prognosis of the t(6;9)(p23;q34) patients.(13) With regard to the rate of FLT3-ITD positive disease, there were no apparent between-group differences in the FAB classification,(14) however, the expression levels of FLT3 were higher in patients with monocytic AML (M4 and M5 in the FAB classification) than in the other patients,(15) and were associated with an unfavorable prognosis.(16) The current study has distinguished FAB-M2 from non-M2, and two-thirds of the non-M2 cases (n=23) in the present study consisted of monocytic AML (the number of M4 patients and M5 patients was 13 and 2, respectively). Therefore, the poor prognosis of the non-FAB-M2 patients might be due to the presence of FLT3-ITD. Unfortunately, we could not confirm this hypothesis because this retrospective analysis did not examine the presence of FLT3-ITD. Future studies will be needed to determine whether the FLT3-ITD status was responsible for the poor prognosis in these patients.

In conclusion, the current study showed that a CR at the time of HSCT and M2 in the FAB classification are favorable prognostic factors in AML patients with t(6;9)(p23;q34). However, refractoriness to chemotherapy remains an obstacle to a favorable allo-HSCT outcome, especially in non-M2 patients. Novel therapeutic approaches, such as immunotherapy using anti-FLT antibodies combined with HSCT, may also be required for patients expected to have a poor prognosis.(17, 18)

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Conflict of Interest

The authors declare no competing financial interests.

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Figure legends

Figure 1. The probabilities of OS in the patients with the t(6;9)(p23;q34) abnormality. A. The OS of the patients stratified by age at HSCT. Solid line, pediatric patients younger that 14 years; dotted line, adult patients older than 15 years. B. The OS of the patients stratified by the disease status at HSCT. Bold line, all patients; Solid line, patients in CR; dotted line, patients in non-CR.

Figure 2. The cumulative incidence of events after allo-HSCT stratified by the disease status at the time of HSCT. A. The cumulative incidence of relapse of the patients. B. The cumulative incidence of NRM of the patients. Solid line, patients in CR; dotted line, patients in non-CR.

Figure 3. The probability of OS of the patients grouped according to the FAB classification and the disease status at HSCT. Solid line, FAB-M2 patients in CR; dashed line, non-FAB-M2 patients in CR; dotted line, FAB-M2 patients in non-CR; chain line, non-FAB-M2 in non-CR.

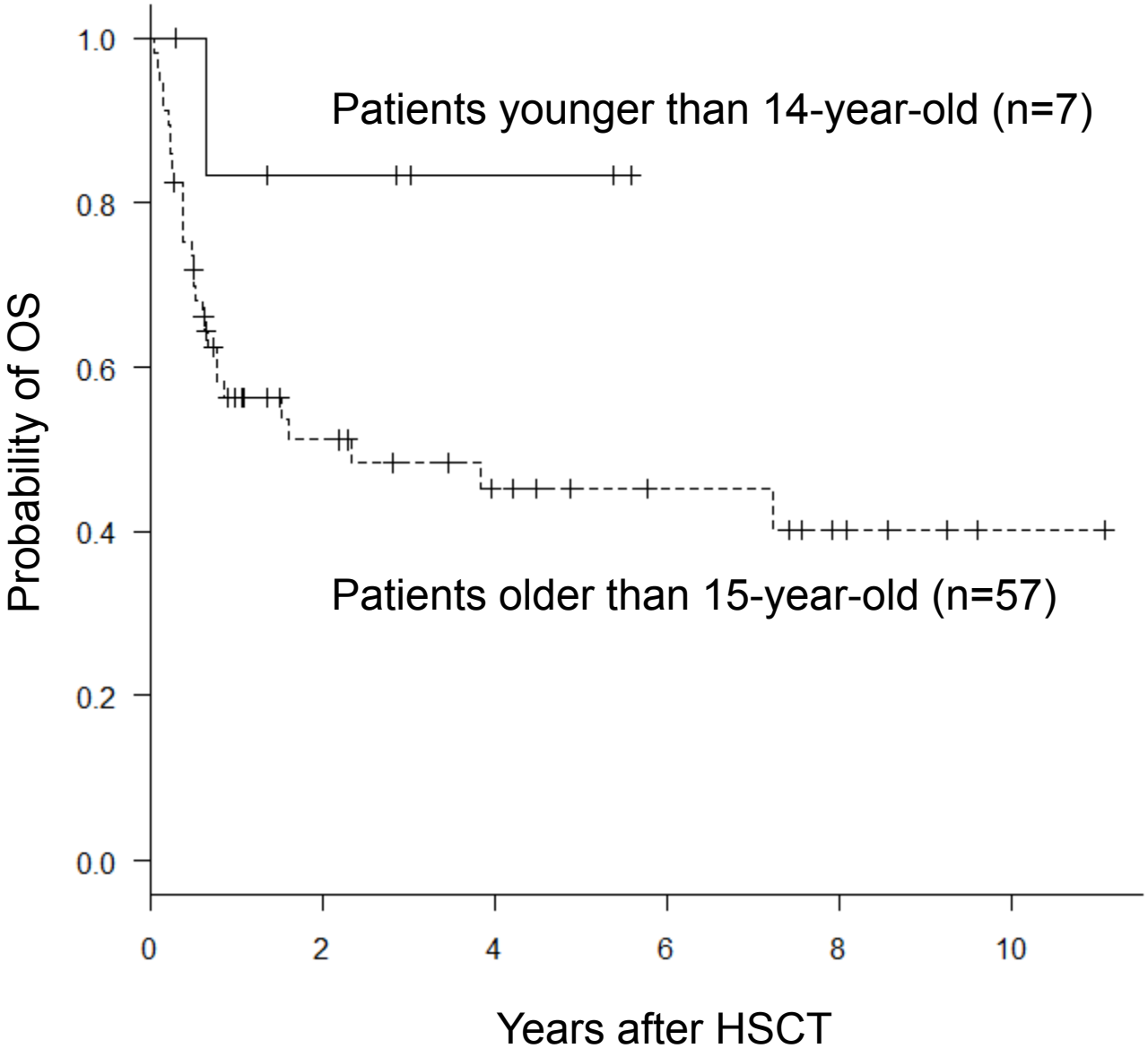
Patients younger than 14-year-old (n=7)
Patients older than 15-year-old (n=57)
Probability of OS
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
Years after HSCT

Figure 1A.

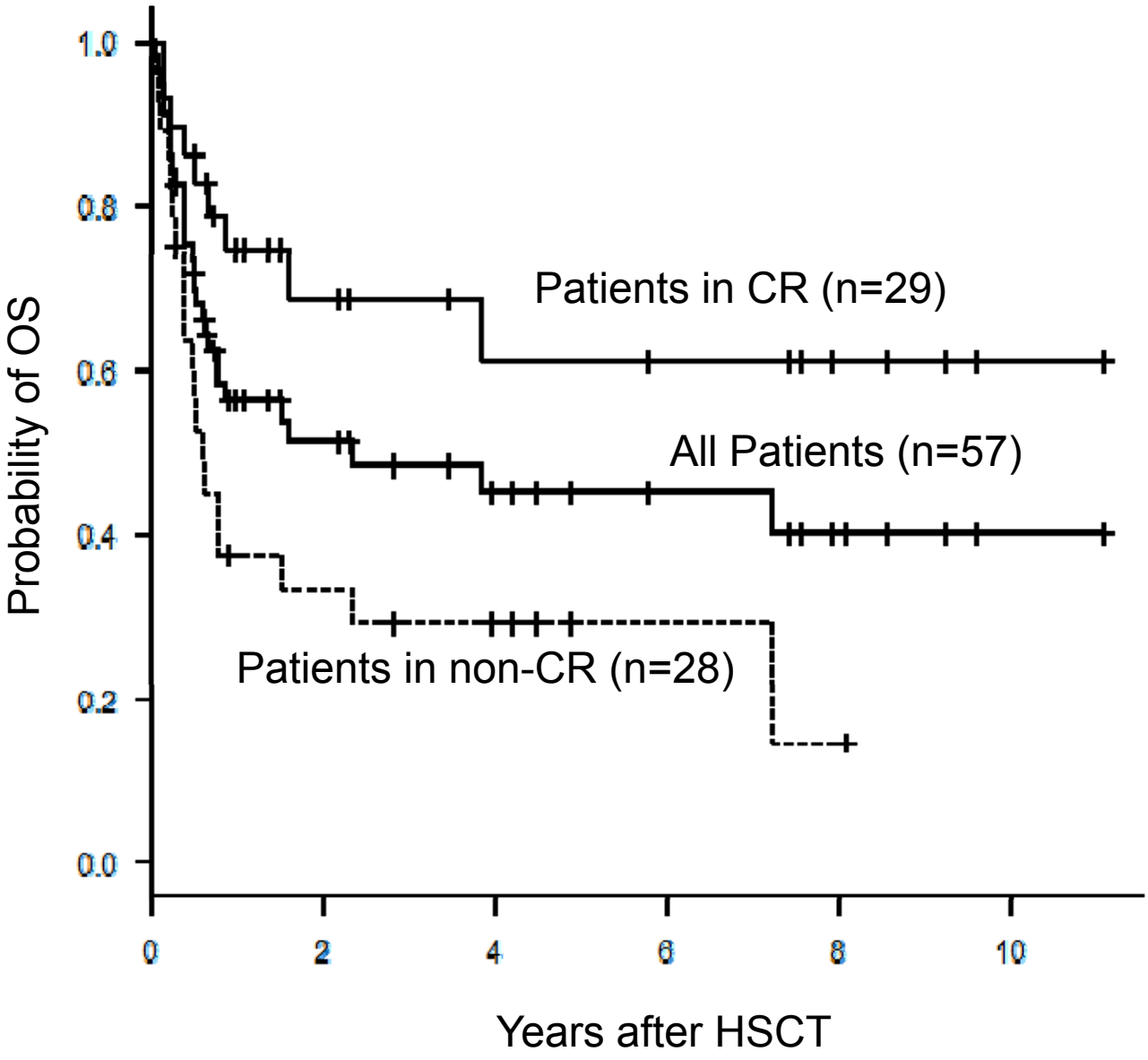
1.0
0.8
0.6
0.4
0.2
0.0
Probability of OS
Patients in CR (n=29)
All Patients (n=57)
Patients in non-CR (n=28)
0
2
4
6
8
10
Years after HSCT

Figure 1B.

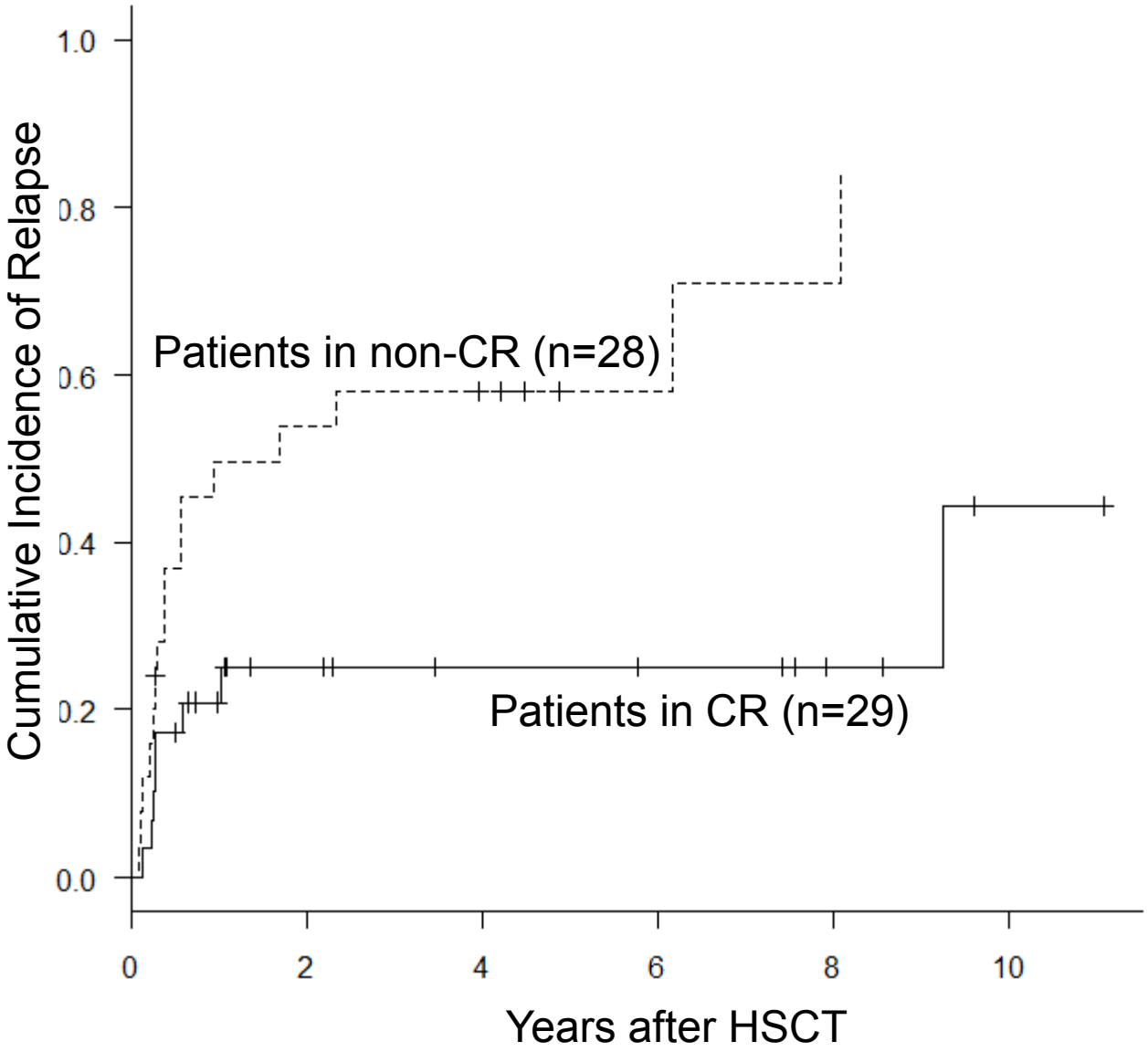
Cumulative Incidence of Relapse
1.0
0.8
0.6
0.4
0.2
0.0
Patients in non-CR (n=28)
Patients in CR (n=29)
0
2
4
6
8
10
Years after HSCT

Figure 2A.

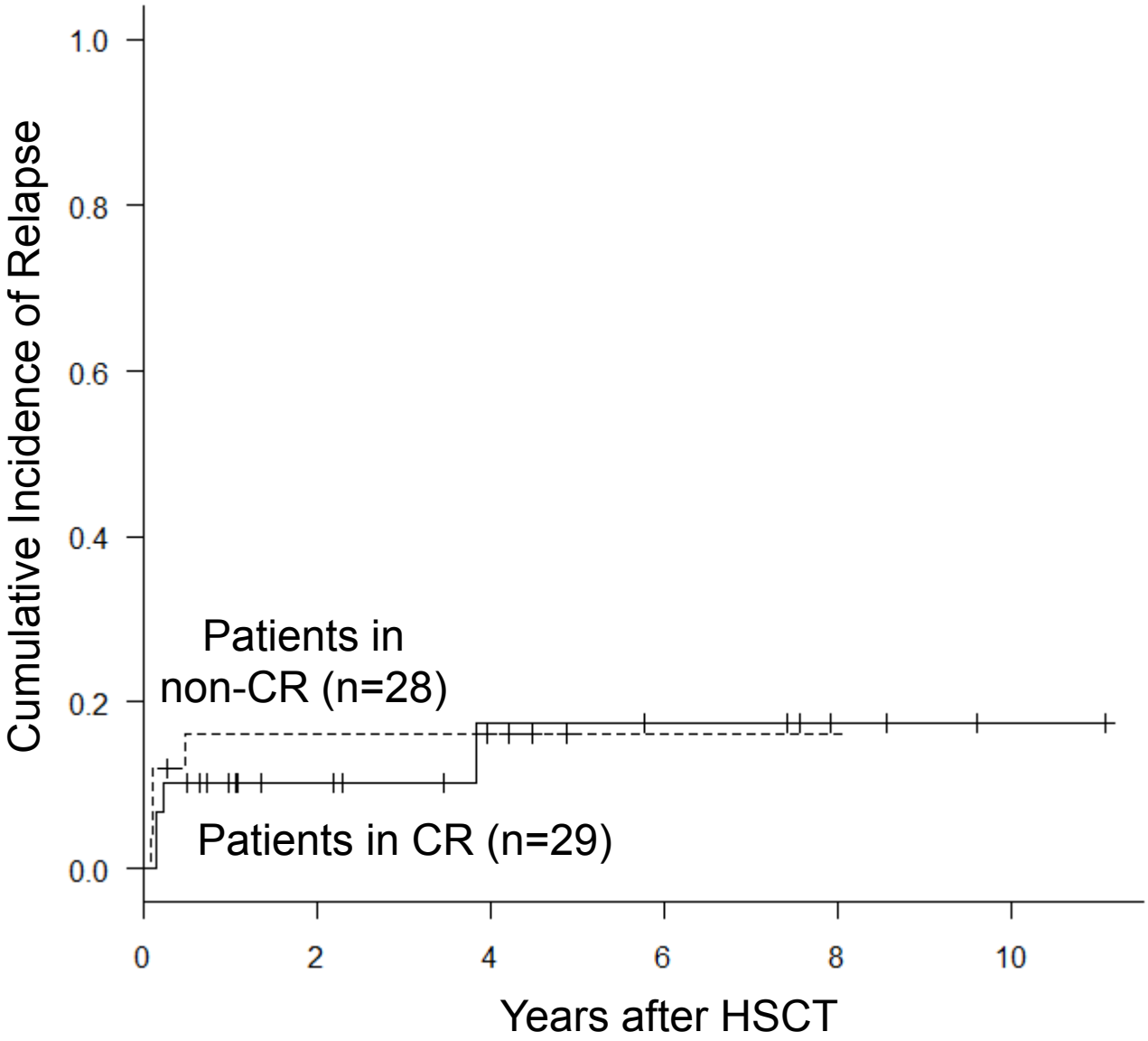
Cumulative Incidence of Relapse
1.0
0.8
0.6
0.4
0.2
0.0
Patients in
non-CR (n=28)
Patients in CR (n=29)
0
2
4
6
8
10
Years after HSCT

Figure 2B.

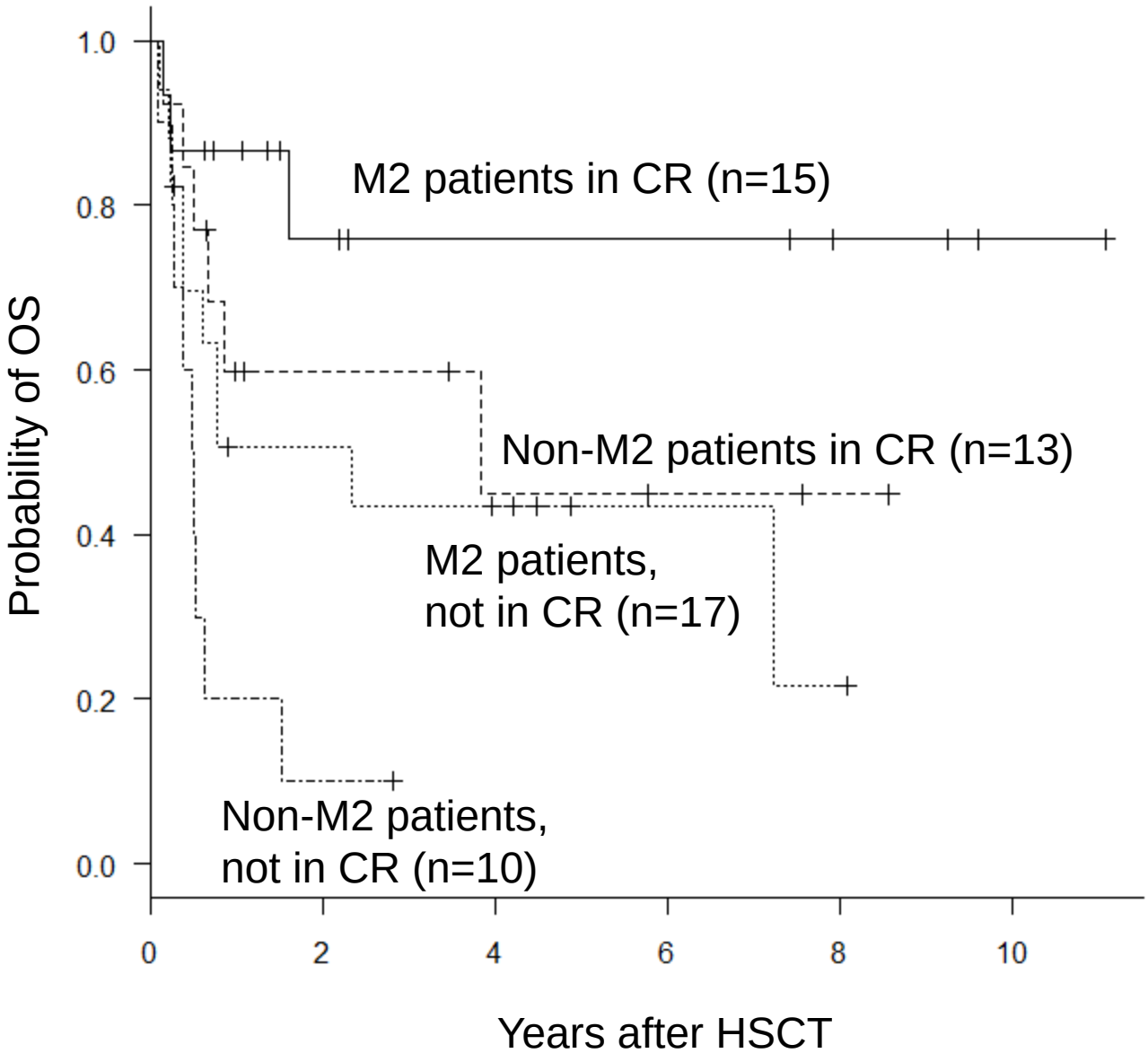
1.0
0.8
0.6
0.4
0.2
0.0
Probability of OS
M2 patients in CR (n=15)
Non-M2 patients in CR (n=13)
M2 patients,
not in CR (n=17)
Non-M2 patients,
not in CR (n=10)
0
2
4
6
8
10
Years after HSCT

Figure 3.

Table 1. Characteristics of patients with t(6;9)(p23;q34).

		Children (n=7)	Adult (n=57)
Age, median (range)		9 (6-14)	35 (17-58)
Gender, male / female		1 / 6	34 / 23
FAB classification*	M0	0	1
	M1	0	7
	M2	5	32
	M4	1	13
	M5	1	2
Status at HSCT, CR / non-CR		5 / 2	29 / 28
HLA disparity**	0	2	24
	1	2	5
	2	0	10
Graft source	BM	3	32
	PBSC	2	12
	CB	2	13

*: Data not available in 2 adult patients.

**: Data not available in 3 pediatric patients and 18 adult patients.

Abbreviations: BM, bone marrow; CB, cord blood; CR, complete remission; HSCT, hematopoietic stem cell transplantation; PBSC, peripheral blood stem cells.

Table 2. Prognostic factors affecting overall survival of adult patients with t(6;9)(p23;q34).

Variables	**Risk factors**	**univariate**	**multivariate**		
			HR	**95% CI**	**P**
Disease status at HSCT	CR	*<0.003*	1		
	non-CR		2.54	1.17-5.51	*<0.02*
FAB classification	M2	0.075	1		
	Other than M2		3.61	1.59-8.21	*<0.003*
Number of HLA disparity	0	0.061	NA		
	1				
	2				
Source of the graft	BM or PBSC	0.076	NA		
	CB				

Abbreviations: BM, bone marrow; CB, cord blood; CI, confidence interval; CR, complete remission; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; NA, not assessed; PBSC, peripheral blood stem cells.