Allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia with t(6;9)(p23;q34) dramatically improves the patient prognosis: A matched-pair analysis

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Allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia with t(6;9)(p23;q34) dramatically improves the patient prognosis: A matched-pair analysis

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Abstract

Acute myeloid leukemia (AML) with t(6;9)(p23;q34) is well known to have a poor prognosis treated with chemotherapy and autotransplantation. The presence of this karyotype is an indicator for allogeneic hematopoietic stem cell transplantation (HSCT); however, the impact of t(6;9)(p23;q34) on the HSCT outcome remains unclear. We conducted a matched-pair analysis of *de novo* AML patients with and without t(6;9)(p23;q34) using data obtained from the Japanese HSCT data registry. Fifty-seven patients with t(6;9)(p23;q34) received transplants between 1996 and 2007, and 171 of 2056 normal karyotype patients matched for age, disease status at HSCT and graft source were selected. The overall survival, disease-free survival, cumulative incidence of relapse and the non-relapse mortality in t(6;9)(p23;q34) patients were comparable to those for normal karyotype patients. A univariate analysis showed that t(6;9)(p23;q34) had no significant impact on the overall survival. These findings suggest that allogeneic HSCT may overcome the unfavorable impact of t(6;9)(p23;q34) as an independent prognostic factor.

Introduction

Acute myeloid leukemia (AML) is a hematological malignancy resulting from the proliferation of leukemic stem cells. Because of the resistance of leukemic stem cells to chemotherapy,(1) long-term survival is generally seen in only 50% of patients treated with chemotherapy alone. Therefore, allogeneic stem cell transplantation (HSCT) is often considered as a curative treatment option.(2) AML is the most common indication for HSCT in North America and in Japan, but fatal transplant-related adverse events are difficult to avoid, despite the improvements in supportive treatment in recent years. Therefore, treatment of AML is hard to standardize, and the attending physician must make a decision on a case-by-case basis, weighing the advantages and disadvantage of HSCT.

The results of past large clinical trials have indicated that abnormalities of the chromosomal karyotype are considered to be one of the most powerful factors to predict the patient prognosis.(3, 4) AML with unfavorable cytogenetic risk group, such as a partial deletion of the long arm of chromosome 7 (del (7q)), monosomy of chromosome 7 (-7) or with a complex karyotype is considered to be a good indication for HSCT, even during the first remission, because of the high cytogenetic risk associated with chemotherapy and the beneficial outcome that can be achieved by HSCT.(5-8)

The translocation of chromosome (6;9)(p23;q34) forming the *DEK/NUP214* fusion mRNA is observed in approximately 1% of AML cases.(9) The characteristics of AML with t(6;9)(p23;q34) are known to include development at a younger age,(10) resistance to chemotherapy, and a very poor prognosis.(9) Therefore, the presence of this karyotype in AML patients is an indication for HSCT; however, the impact of t(6;9)(p23;q34) on the outcome of HSCT remains unclear because of the rarity of this

entity. We conducted a retrospective study to examine the outcomes of HSCT in AML patients with t(6;9)(p23;q34) using the data from the Japan Society for Hematopoietic Cell Transplantation Data Registry.

Patients and methods

Study population

Clinical data were collected from the databases of the Japan Society for Hematopoietic Cell Transplantation (JSHCT) and the Japan Cord Blood Bank Network (JCBBN) using a standardized report form. Follow-up reports were submitted at 100 days, 1 year and annually after HSCT. Patients with *de novo* AML aged 15 years or older at the time of first HSCT and who received the transplant between January 1996 and December 2007 were extracted from the databases. We compared the clinical features and the outcomes among the patients with t(6;9)(p23;q34) and the patients with a normal karyotype in G-band staining. Cytogenetic data were analyzed according to the Southwestern Oncology Group (SWOG) criteria in each institution(7) instead of by central review. We selected patient pairs with t(6;9)(p23;q34) and the normal karyotype using an optimal matching method with the following 3 matching factors: recipient age, disease status at HSCT and graft source. This study was approved by the Committee for Nationwide Survey Data Management of the Japan Society for Hematopoietic Cell Transplantation. Written informed consent was obtained in accordance with the Declaration of Helsinki.

Statistical analysis

The overall survival (OS) was defined as the number of days from HSCT until death from any cause. Disease relapse was defined as the number of days from HSCT to relapse of the underlying disease. Non-relapse mortality (NRM) was defined as death without relapse. Any patients who were alive at the last-follow-up date were censored. All statistical analyses were performed using the R version 2.13.0 software program (R Foundation for Statistical Computing; www.r-project.org). Probabilities and times-to-events were compared between the two groups using the Mantel-Haenszel method and stratified Cox proportional hazard modeling, respectively. The cumulative incidences of NRM and relapse were calculated considering each other event as a competing risk, and were compared using the stratified Grey test.(11) P values were two sided, and outcomes were considered to be significant when $P \leq 0.05$.

Results

Patient characteristics

A total of 2577 AML cases met the inclusion criteria. The number of cases with t(6;9)(p23;q34) and a normal karyotype was 57 and 2,056, respectively; and 171 patients with the normal karyotype were selected for matched-pair analysis by a 1:3 matching ratio. The characteristics of the patients are shown in Table 1; there were no statistically significant differences between the t(6;9)(p23;q34) patients and the normal karyotype patients except the use of total body irradiation (TBI) as a preconditioning regimen.

Survival, relapse and non-relapse mortality

The probability of OS in the patients with t(6;9)(p23;q34) was as good as that for patients with a normal karyotype (the probability of 5-year OS in t(6;9)(p23;q34) and normal karyotype patients was 45% and 40%, respectively; Figure 1A). When the t(6;9)(p23;q34) patients and the normal karyotype patients were further categorized according to the disease status at HSCT, the OS of the t(6;9)(p23;q34) patients and the normal karyotype patients were comparable in both the CR at HSCT patients, and the non-CR at HSCT patients (Figure 1B). The probability of DFS in these patients was also not significantly different (the probability of 5-year DFS in patients with t(6;9)(p23;q34) and the normal karyotype was 42% and 33%, respectively; Figure 1C). The cumulative incidence of relapse (Figure 2A) and the NRM (Figure 2B) in t(6;9)(p23;q34) patients were also comparable to those for normal karyotype patients (the 5-year cumulative incidence was 42% in t(6;9)(p23;q34) patients and 45% in normal karyotype patients for relapse (P=0.34) and 16% and 22% (P=0.85) for NRM). The prognostic factors affecting OS revealed that there were no significant differences related to karyotype, gender, gender mismatch between donor and recipient, HLA disparity, recipient cytomegalovirus serostatus and use of TBI for the preconditioning regimen by the univariate analyses (Table 2A).

Discussion

Previous reports have confirmed the negative impact of t(6;9)(p23;q34) on the outcome after standard-dose chemotherapy and high-dose therapy with autologous stem cell transplantation in patients with AML.(9, 10) The current matched-pair analysis of the nationwide survey demonstrated that the OS and the TRM, as well as the relapse rate, were independent of the presence of t(6;9)(p23;q34) in allogeneic HSCT recipients, thus

suggesting that allogeneic HSCT may be able to overcome the unfavorable effect of t(6;9)(p23;q34) in AML patients.

However, it is difficult to draw any firm conclusions regarding the results of the present analysis owing to the small numbers of patients in the matched-pairs subsets. These findings require confirmation in larger studies specifically examining the impact of t(6;9)(p23;q34) status. Nevertheless, the suggestion that allogeneic HSCT appears to overcome the adverse survival impact of t(6;9)(p23;q34) is supported by other studies.(12, 13) In a EBMT study of AML patients with t(6;9)(p23;q34), allogeneic HSCT produced responses that were independent of t(6;9)(p23;q34), and the 3-year OS of patients with t(6;9)(p23;q34) was as high as 51±7%, comparable to AML patients with the normal karyotype.(13) Also, the incidence of relapse following allogeneic HSCT appeared to be similar in patients with t(6;9)(p23;q34) compared to those without t(6;9)(p23;q34). However, the EBMT study made it somewhat difficult to determine whether HSCT would lead to a good outcome, because 87% of the patients were transplanted while in CR, while only 29 of 57 (51%) patients in our study received HSCT in CR, which is a more clinically relevant expectation, as a CR is difficult to achieve in these patients.

In conclusion, the current study showed that AML patients with t(6;9)(p23;q34) can be expected to have a post-transplant survival comparable to patients with a normal karyotype, thereby supporting the opinion that they are good candidates for HSCT.

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Conflict of Interest

The authors declare no competing financial interests.

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Figure legends

Figure 1. Survival of the patients. A. The overall survival (OS) of the patients stratified by cytogenetics. B. The OS of the patients grouped according to their disease status at transplantation. C. The disease-free survival of the patients.

Figure 2. Cumulative incidence of events after transplantation stratified by cytogenetics. A. The cumulative incidence of relapse of the patients. B. The cumulative incidence of non-relapse mortality of the patients.

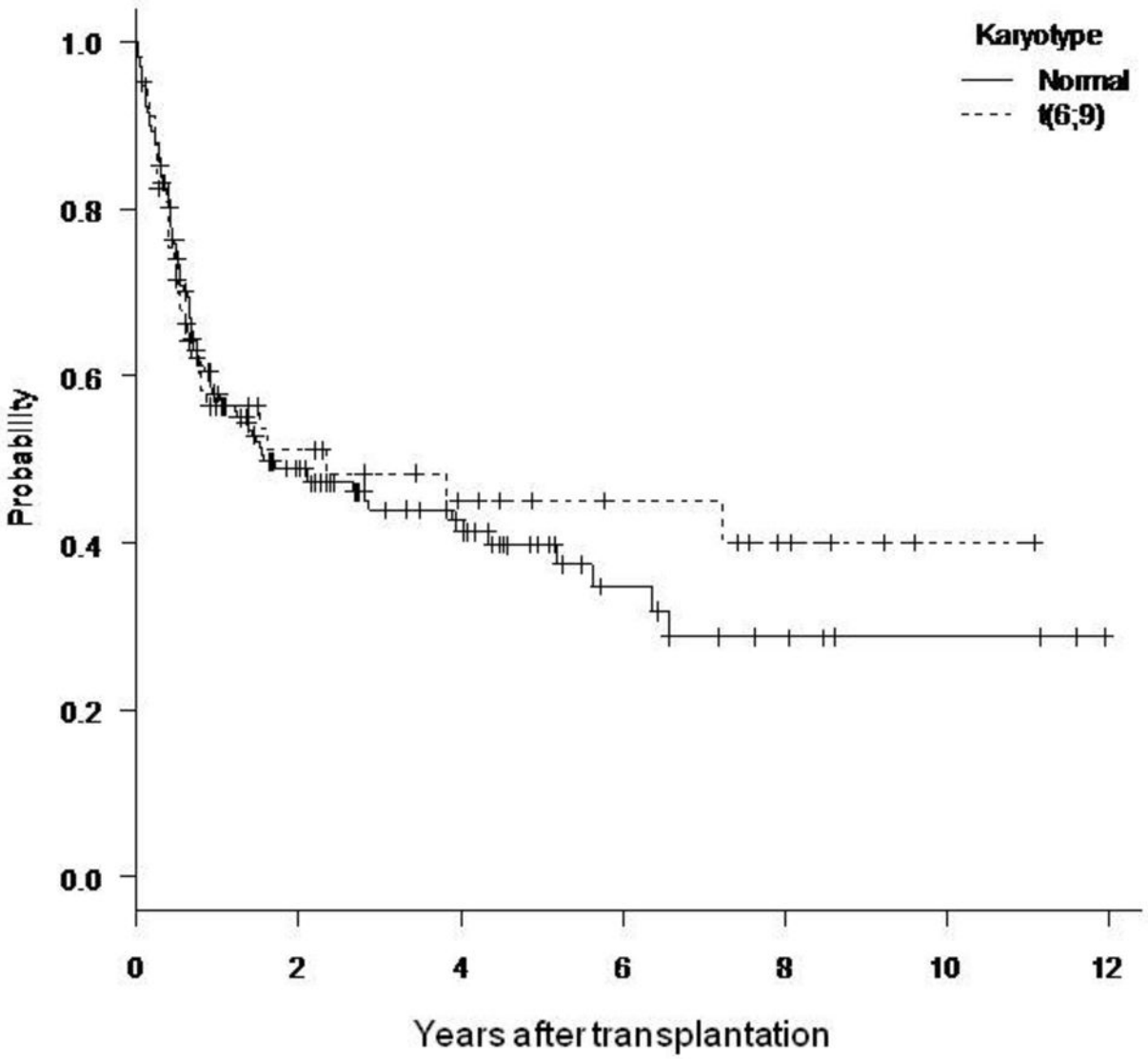

Figure 1

A. Overall survival.

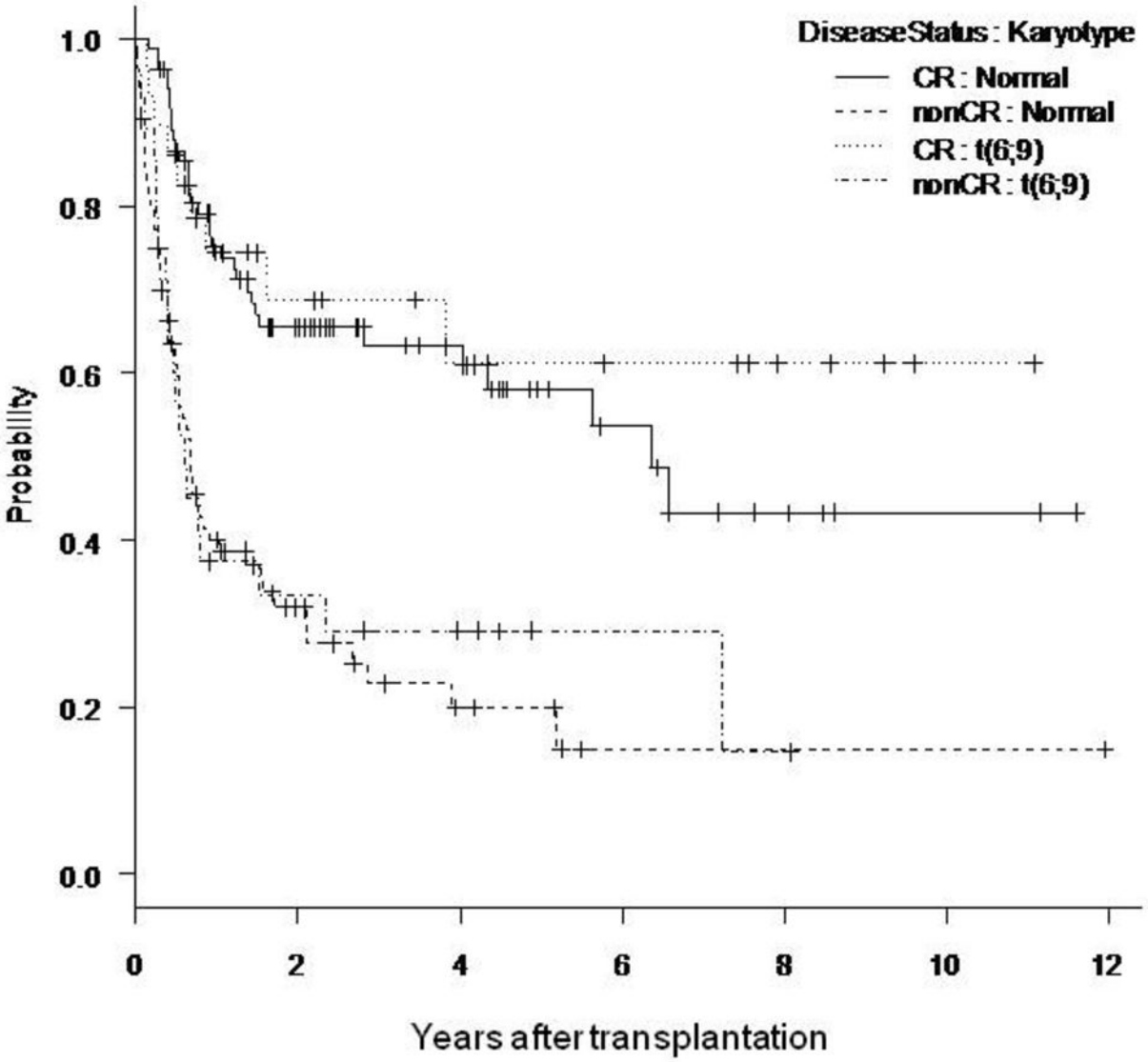

Figure 1

B. Overall survival, grouped according to the disease status at transplantation.

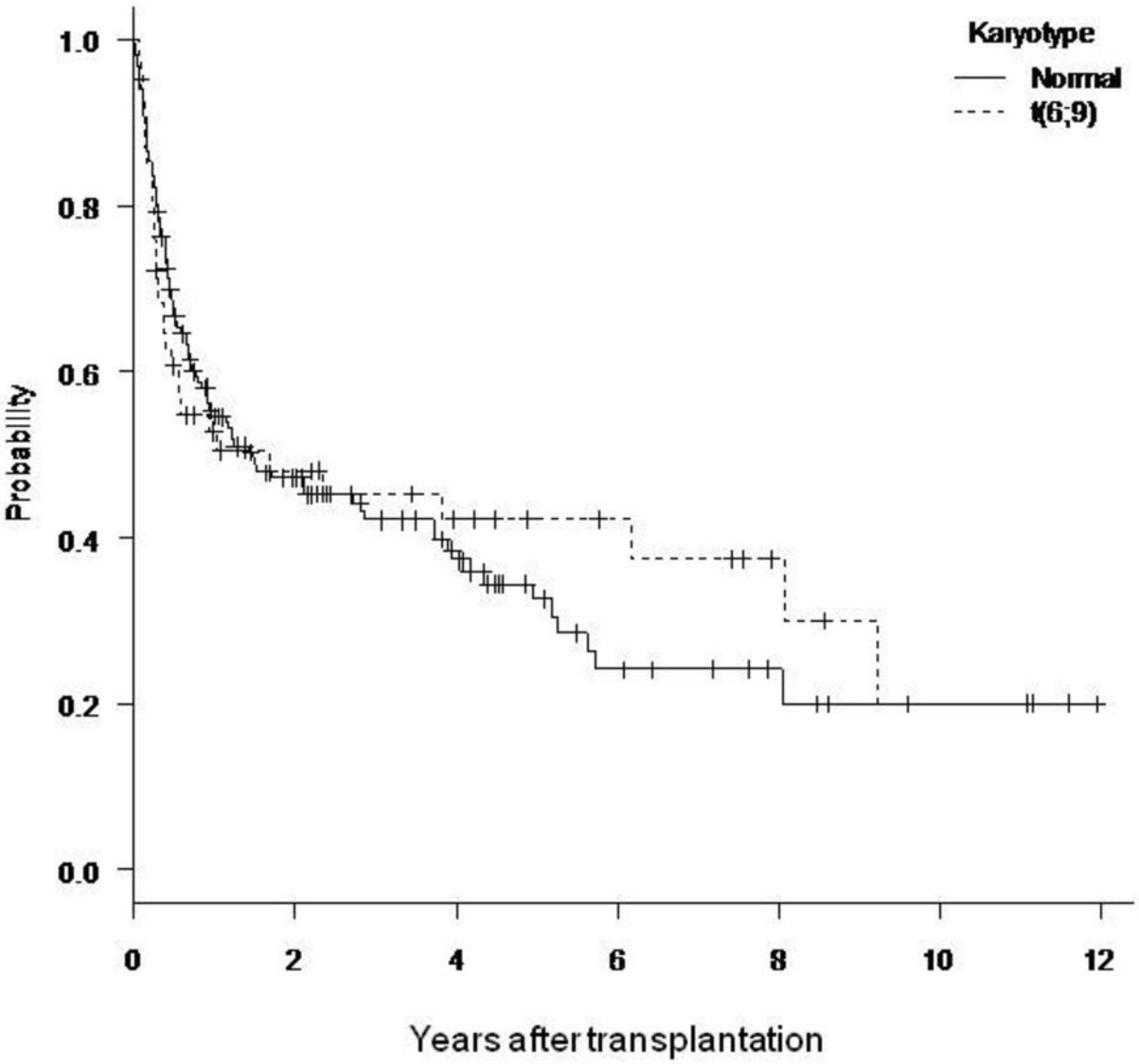

Figure 1

C. Disease-free survival.

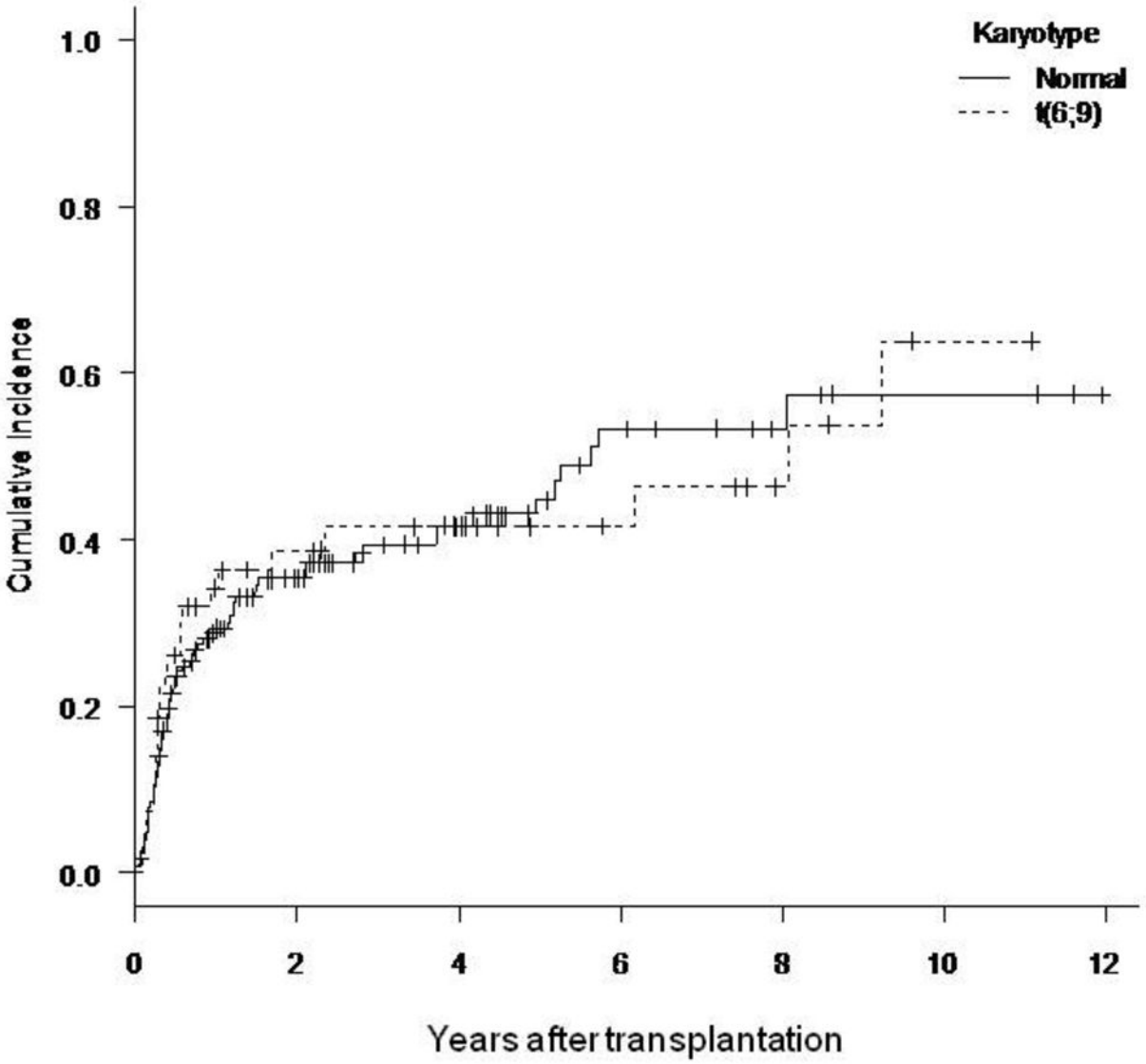

Figure 2

A. Relapse.

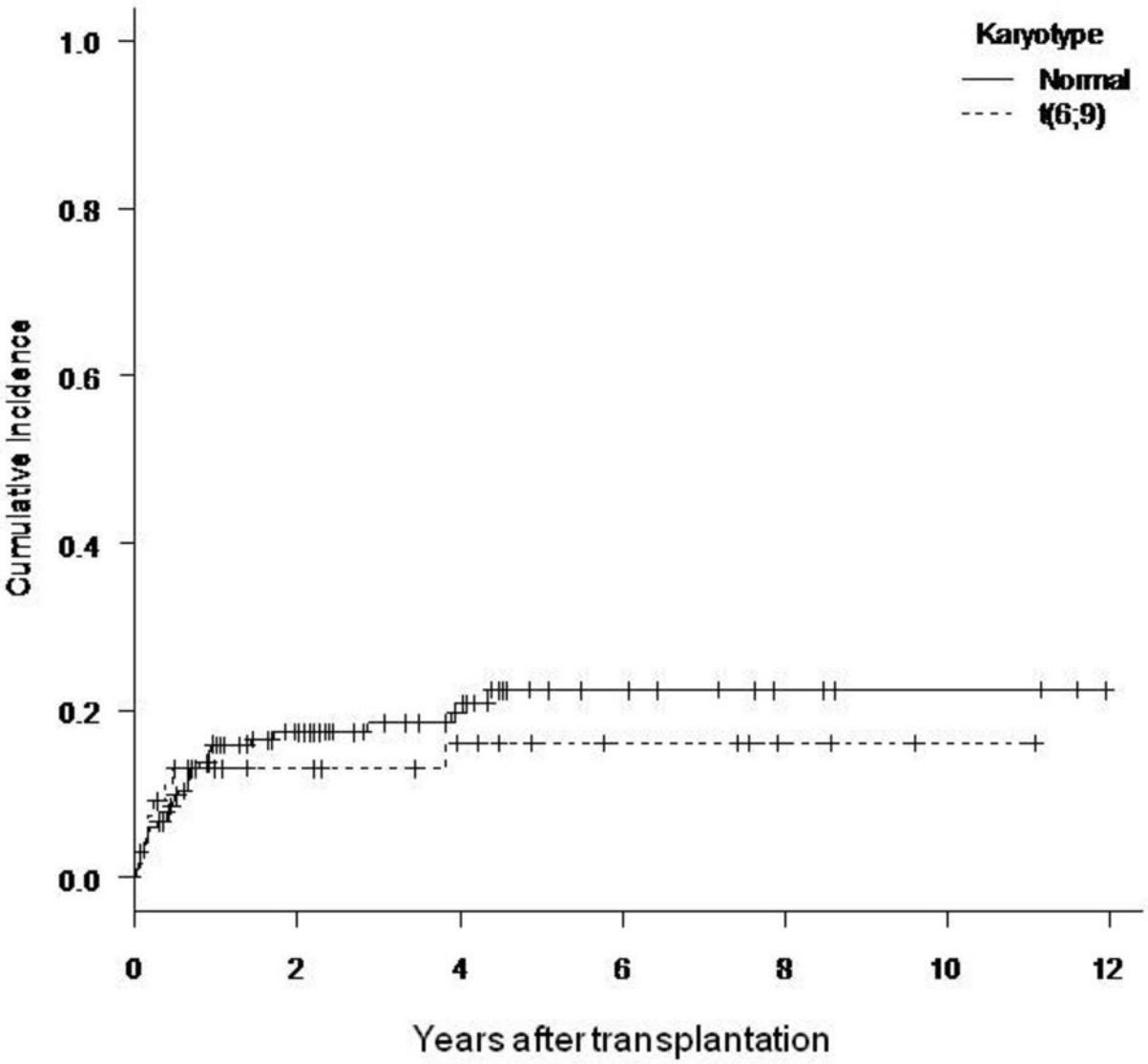

Figure 2

B. Non-relapse mortality.

Table 1. Patient characteristics

		t(6;9)(p23;q34)	Normal karyotype	p value
Age				
	15-24	14	42	0.999
	25-34	14	45	
	35-44	20	58	
	45-54	7	20	
	55-64	2	6	
Gender				
	Male	34	97	0.758
	Female	23	74	
Disease status at HSCT				
	CR1 or CR2	29	87	1.0
	Not in remission	28	84	
Preconditioning regimen, TBI				
	No	21	33	0.0102
	Yes	33	131	
Donor				
	Related	26	78	1.0
	Unrelated bone marrow	18	54	
	Unrelated cord blood	13	39	
Number of HLA mismatch				
	0	24	47	0.379
	1	5	23	
	2	10	27	
	3	0	2	

Abbreviations: CR, complete remission; HSCT, hematopoietic stem cell transplantation; TBI, total body irradiation.

Table 2. Prognostic factors affecting overall survival

	Risk factor	Hazard ratio	95%CI	p value
Karyotype	t(6;9)	1.07	0.66-1.74	0.79
Gender	Male	1.06	0.64-1.73	0.83
Gender mismatch	Female to Male	1.41	0.74-2.68	0.29
HLA compatibility	mismatch	0.98	0.57-1.75	0.94
Recipient CMV	Positive	0.27	0.028-2.70	0.27
Donor CMV	Positive	1.51	0.61-3.78	0.37
TBI	Yes	1.47	0.75-2.90	0.26

Abbreviations: CMV, cytomegalovirus; TBI, total body irradiation.