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なし

Ⅲ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

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Ⅳ. 研究成果の刊行物・別刷

Allogeneic hematopoietic stem cell transplantation from family members other than HLA-identical siblings over the last decade (1991-2000)

Yoshinobu Kanda, Shigeru Chiba, Hisamaru Hirai, Hisashi Sakamaki, Tohru Iseki, Yoshihisa Kodera, Takahiro Karasuno, Shinichiro Okamoto, Noriyuki Hirabayashi, Koji Iwato, Atsuo Maruta, Yoshihiro Fujimori, Tatsuo Furukawa, Shin Mineishi, Keitaro Matsuo, Nobuyuki Hamajima, and Masahiro Imamura

The reported outcome of hematopoietic stem cell transplantation (HSCT) from HLA-mismatched family members has been inconsistent. The object of this study was to evaluate the true impact of HLA-mismatch by using recent data from a homogenous population, excluding HSCT procedures that used graft manipulations, and by considering genotypic matching. Clinical data of 2947 patients who underwent allogeneic HSCT for leukemia or myelodysplastic syndrome were extracted from the database of the Japan Society for Hematopoietic Cell Transplantation. The main outcome measures were survival and the incidence of graft-versus-host disease (GVHD). The presence of serologic HLA-mismatch, higher age, and high-risk disease were identified as independent risk factors for both shorter survival and the development of grade III to IV acute GVHD. The impact of HLA-mismatch on survival was more relevant in standard-risk patients. These findings persisted when we used genotypic HLA matching. Survival after one-locus–mismatched HSCT was equivalent to that after HLA-matched unrelated HSCT. We concluded that when a one-locus–mismatched family donor is available for high-risk patients, immediate HSCT using this donor is warranted. In standard-risk patients, however, survival after one-locus–mismatched HSCT is significantly shorter than that after HLA-matched HSCT, and the indications for HSCT should be considered carefully. (Blood. 2003;102:1541-1547)

Introduction

Hematopoietic stem cell transplantation (HSCT) from HLA-identical siblings is an established treatment for hematologic malignancies. However, in most developed countries such donors are available for only approximately 30% of patients.[1,2] Therefore, hematopoietic stem cell transplants from family members other than HLA-matched siblings or unrelated volunteers has been investigated. The advantages of family members over unrelated donors are immediate availability and the ability to collect additional donor cells for immunotherapy.

A mismatch in HLA antigens between the donor and recipient increases the risk of both graft rejection and graft-versus-host disease (GVHD) after HSCT. There have been several reports regarding the outcome of HSCT from family members other than HLA-matched siblings.[3-10] Reports from Seattle showed that the probability of survival for patients who underwent one-locus–mismatched HSCT from family members was similar to that of patients who received grafts from HLA-identical siblings, because the increased risk of GVHD was counterbalanced by an increase in the graft-versus-leukemia effect.[3,6] In contrast, in a large study from the International Bone Marrow Transplant Registry (IBMTR), leukemia-free survival for patients who received grafts from one-locus–mismatched family donors was significantly shorter than that for patients who received grafts from HLA-identical siblings.[10] This discrepancy could be explained by the difference in the method for HLA typing. In the IBMTR report, matching at the HLA-DR locus was based exclusively on serologic data, whereas the Seattle group assigned HLA-D antigens by testing the donors, recipients, and available family members with homozygous typing cells.[3,10] Therefore, some donor-recipient pairs that were considered to be mismatched for only one HLA locus in the IBMTR report might actually be more genetically disparate than those in the Seattle report.[1]

Recently, molecular techniques have made it possible to identify HLA alleles that cannot be identified serologically (genomic typing).[11,12] Several groups have reported that a genotypic mismatch at DRB1 allele increased the risk of acute GVHD in HSCT from serologically HLA-matched unrelated donors.[13,14] On the other hand, a Japanese study showed that genotypic incompatibility for class I HLA was more important than class II mismatch as a predictor of severe acute GVHD.[15] These findings suggest the

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Table 1. Patient characteristics

	Match	1-locus mismatch		2-or 3-loci mismatch
		Class I	Class II	
n	2805	70	42	30
Donor, n (%)				
Sibling	2736 (98)	39 (56)	28 (67)	9 (30)
Others	69 (2)	31 (44)	14 (33)	21 (70)
Sex, n (%)				
Male	1711 (61)	42 (60)	21 (50)	17 (57)
Female	1094 (39)	28 (40)	21 (50)	13 (43)
Age, n (%)				
Younger than 40 y	1742 (62)	45 (64)	22 (52)	14 (47)
40 y and older	1063 (38)	25 (36)	20 (48)	16 (53)
Diagnosis, n (%)				
AML	962 (34)	21 (30)	15 (36)	10 (33)
ALL	672 (24)	15 (21)	13 (31)	7 (23)
CML	804 (29)	22 (31)	11 (26)	12 (40)
MDS	367 (13)	12 (17)	3 (7)	1 (3)
Disease risk, n (%)				
Standard	2093 (75)	41 (59)	26 (62)	7 (23)
High	712 (25)	29 (41)	16 (38)	23 (77)
Conditioning regimen, n (%)				
Non-TBI	1126 (40)	19 (27)	15 (36)	9 (30)
TBI	1679 (60)	51 (73)	27 (64)	21 (70)
Use of PBSCs, n (%)				
No	2465 (88)	54 (77)	35 (83)	14 (47)
Yes	340 (12)	16 (23)	7 (17)	16 (53)
Experienced engraftment failure, n (%)	67 (2.4)	6 (9)	0 (0)	3 (10)
Number of genotype mismatches				
0	2771	0	0	0
1	3	22	20	0
2	0	3	0	18
3	0	0	0	8
ND	31	45	22	4

ND indicates not done (ambiguous loci).

importance of genomic typing and the possibility that HLA mismatch may have different effects on the outcome of HSCT among ethnic groups. However, no previous studies have examined the outcome of HSCT using HLA-mismatched family donors considering genotypic HLA mismatches. Furthermore, studies based on registry data have included the outcome of HSCT from various countries as well as HSCT using ex vivo graft manipulation, including T-cell depletion or $CD34^+$ cell selection, which can strongly affect the incidence of acute GVHD.

The object of this study was to evaluate the true impact of HLA mismatch by using recent data from a homogenous population, excluding HSCT procedures that used graft manipulations, and by considering data on genotypic HLA mismatch. We also aimed to clarify the impact of class I versus class II mismatch on the outcome of HSCT from HLA-partially mismatched family donors.

Patients and methods

Study population

A total of 3356 patients who underwent allogeneic HSCT from a family donor for the first time between 1991 and 2000 for chronic myelocytic leukemia (CML), acute myeloblastic leukemia (AML), acute lymphoblastic leukemia (ALL), or myelodysplastic syndrome (MDS) were reported to the Japan Society for Hematopoietic Cell Transplantation (JSHCT).[16] Those younger than 16 year of age, those who received a graft from a syngeneic donor, those who received a manipulated graft, and those who received cord blood were excluded from the study. Finally, full serologic HLA datasets for HLA-A, -B, and -DR loci were available in 2947 patients.

After the completion of the following analyses regarding HSCT from a family donor, data of 1002 patients, who underwent HSCT from a

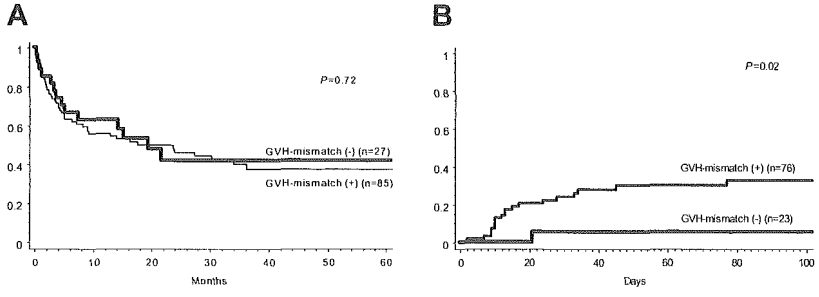

Figure 1. Impact of HLA mismatch in the GVH vector. Comparison of overall survival (A) and the incidence of grade III to IV acute GVHD (B) after serologically one-locus–mismatched HSCT between patient-donor pairs with or without an HLA mismatch in the GVH vector.

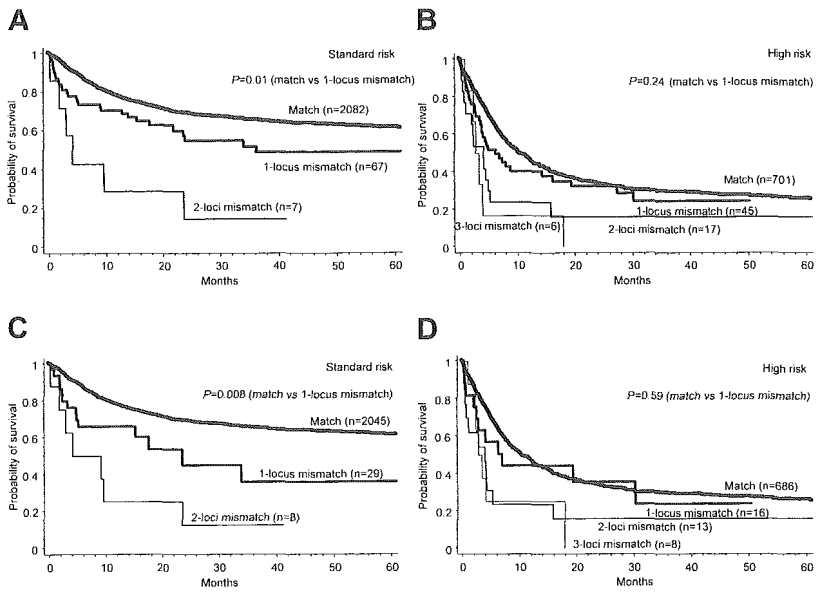

Figure 2. Overall survival based on mismatched loci. Overall survival after transplantation grouped according to the number of mismatched loci at the serologic level (A-B) and DNA level (C-D), and according to the disease status (A,C: standard-risk disease; B,D: high-risk disease). *P* values for the HLA-matched versus one-locus–mismatched group are shown.

serologically HLA-matched unrelated donor and fulfilled the conditions cited, were additionally extracted from the database of JSHCT. Unrelated HSCT exclusively used a bone marrow graft.

Transplantation procedure

The conditioning regimen before HSCT was mainly either a cyclophosphamide/total body irradiation (TBI)–based regimen (49%) or a busulfan/cyclophosphamide-based regimen (43%). Prophylaxis for GVHD mainly consisted of a combination of cyclosporine A and methotrexate (87%). Other prophylactic regimens were cyclosporine A with prednisolone (4%), tacrolimus with methotrexate (4%), and so on.

Histocompatibility

Data on serologic typing for HLA-A, -B, and -DR loci were obtained from reports from the institutions performing the transplantations. Genomic typing was performed at the discretion of the attending physicians at each institute. In pairs without data for genomic typing, we estimated genotype donor-recipient matching as follows.

Serologically HLA-matched sibling pairs were considered to be genotypically HLA-identical. In fact, 65 serologically HLA-matched sibling pairs underwent genomic typing of HLA-A, -B, and -DRB1 alleles, and all were completely matched. Another 302 serologically HLA-matched sibling pairs were tested only for DRB1 alleles and a mismatch was found in only one donor-recipient pair (1501 of 1501 versus 1501 of 1502).

In pairs other than serologically HLA-identical sibling pairs, loci that were serologically matched and were known to be associated with less than a 5% risk of genotype mismatch in the Japanese population were considered to be genotypically matched loci.[17] On the other hand, loci that were serologically matched but were known to be associated with a 5% or greater risk of genotype mismatch (A2, A26, B13, B39, B61, B62, DR4, DR8, DR12, DR13, DR14, and DR15) were treated as ambiguous loci.[17]

HLA-mismatch in the graft-versus-host (GVH) vector was defined as when the recipient's antigens or alleles were not shared by the donor, whereas mismatch in the host-versus-graft (HVG) vector was defined as when the donor's antigens or alleles were not shared by the recipient.

Statistical considerations

The primary end point was survival after transplantation. Data for August 2001 were available in all 2947 patients. The incidence of grade III to IV acute GVHD, which was graded according to published criteria,[18] was a secondary end point, and was analyzed in 2811 patients who achieved donor cell engraftment. The incidence of chronic GVHD was evaluated in 2150 patients who survived without relapse more than 100 days after HSCT. Engraftment failure was also analyzed with engraftment defined as a neutrophil count more than 500/mm^3 for 3 consecutive days. Engraftment failure was diagnosed as when engraftment was not achieved at any time after transplantation.

The probability of survival and the cumulative incidence of acute GVHD were calculated using the Kaplan-Meier method. The cumulative incidence of relapse was calculated by the Gray method considering death without relapse as a competing risk.[19] Univariate comparisons for dichotomous and time-to-event variables between groups were performed with the Fisher exact test and the log-rank test, respectively, and multivariate analyses were performed using logistic regression analysis and proportional hazards modeling, respectively. Potential confounding factors considered in the analysis were recipient age, sex, donor-recipient relationship (mother-child or not), disease status, stem cell source, and serologic/genotypic HLA mismatch. Acute leukemia in first or second remission, CML in first or second chronic phase, and MDS without leukemic transformation were considered standard-risk diseases, whereas others were considered high-risk diseases. Patients who received both bone marrow (BM) and peripheral

Table 2. Results of proportional hazards modeling for overall survival

	Relative risk (95% CI)	*P*
Serologic matching		
Age		
Younger than 40 y	1.00	< .0001
40 y and older	1.26 (1.13-1.41)	
HLA		
Match	1.00	.014
Mismatch	1.38 (1.07-1.78)	
Disease		
Standard risk	1.00	< .0001
High risk	2.82 (2.52-3.16)	
Genotypic matching		
Age		
Younger than 40 y	1.00	< .0001
40 y and older	1.27 (1.14-1.43)	
HLA		
Match	1.00	.036
Mismatch	1.53 (1.03-2.27)	
Disease		
Standard risk	1.00	< .0001
High risk	2.83 (2.52-3.18)	

Two- or 3-loci–mismatched transplants were excluded.