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Mismatch of minor histocompatibility antigen contributes to graft-versus-leukemia effect rather than to acute GVHD resulting in long-term survival after HLA-identical stem cell transplantation in Japan

Running title: Minor histocompatibility contributes GVL effect

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Summary

We determined the alleles of 5 polymorphic molecules including HA-1 and four adhesion molecules for 106 patients transplanted HLA-identical stem cell grafts and investigated the association of mismatches as rates of relapse and GVHD. All 106 recipients underwent stem cell transplantation after myeloablative conditioning between 1985 and 2002. Risk status of the disease at SCT was standard (n=63) and high (n=42). After SCT, 36, 49 and 33 developed acute GVHD, chronic GVHD and relapsed, respectively. Our patients relapsed at rates of 16.7% and 38.6% with one or more and without incompatibilities (P=0.013). The relapse rates of patients with CD62L, CD31 codon 563, CD31 codon 125, HA-1 and CD49b incompatibilities were 5.9%, 11.8%, 15.4%, 16.0% and 33.3% respectively. The frequency of acute GVHD did not differ regardless of incompatibilities.

In standard risk group, the accumulated relapse rates of 19 and 44 patients with and without mHag incompatibility were 22% and unexpected 66%, respectively (P=0.02). The probability of 12-year survival rates was 88% in the former and 66% in the latter patients (P=0.03). Our data suggests that incompatibility of CD62L, CD31 codon 563 and CD31 codon 125 contribute to GVL effect rather than to GVHD, resulting in prolonged survival after HLA-identical SCT.

Key words

Minor histocompatibility antigen

Graft-versus-host disease

Graft-versus-leukemia effect

HLA identical pairs

Introduction

Donor-derived T lymphocytes that cause graft-versus-host disease (GVHD) might also induce graft-versus-leukemia (GVL) reactivity in an HLA identical combination. Minor histocompatibility antigens that induce GVHD are potential candidates for a GVL effect after allogeneic stem cell transplantation (SCT).¹⁻⁵⁾

HA-1 is an established minor histocompatibility antigen (mHag) that was discovered by Goulmy et al.^{1,2)} and polymorphic adhesion molecules including CD31, CD49b and CD62L are immunodominant mHags that contribute to acute GVHD in Japanese⁶⁾ and in Caucasian⁷⁻⁹⁾ populations.

Since the GVL effects are similar in both populations whereas the incidence and severity of acute GVHD is low among Japanese after allogeneic SCT and DLI^{10, 11)}, the roles of mHags in Japanese patients might differ from that of Western SCT patients. We therefore investigated the association of mHag mismatches with, acute GVHD, as well as relapse and survival rates.

Materials and Methods

Patients

During May 1998, 2002 and 2004, we collected various samples from donors and recipients before myeloablative stem cell transplantation to analyze HA-1 and four polymorphic adhesion molecules. The patients underwent the procedure at Kanazawa University Hospital, Niigata University Medical and Dental Hospital and the University Hospital of Occupation and Environment Health. Patients transplanted before May 1998 were also enrolled in this study. The peripheral blood cells from patients after SCT were of donor origin and nail or buccal membrane samples were collected as host cells. Primary physicians were asked to report three times regarding the outcomes of stem cell transplantation. All of the patients were followed up for at least 2 years after SCT.

Data included patient age, sex, diagnosis, stage of disease at transplantation, donor sex, date of transplant, conditioning regimen, GVHD prophylaxis, severity of acute and chronic GVHD, other major complications after transplantation, time of relapse, HLA serological identified antigens and allele type in 35 out of the patients. For patients with CML, the type of relapse (molecular, cytogenetic or hematological) during stable, accelerated or blast phases was included. Treatment-related information included donor

leukocyte infusion (DLI), chemotherapy and α -interferon therapy. The outcome of the treatment was assessed according to the severity of GVHD and the response of leukemia to DLI. Survival, morbidity and recurrence of leukemia also were evaluated. Table 1 shows the characteristics of 65 male and 41 female patients who were transplanted with stem cells from 60 HLA-A, -B, -DR matched related donors and from 46 HLA-A, -B, -DR matched unrelated donors where 5 of the 60 and 30 of the 46 were allele type compatible donors.

Conditioning regimens consisted of 12 Gy fractionated TBI as 3 Gy x4 or 2Gy x6 in 99 of 106 patients and 7 of the 106 patients received a non-TBI regimen. Stem cell sources were BM (88), PBSC (15) and both (3). Post transplant immunosuppression consisted of short-term MTX+CyA (98), short-term MTX+FK (5) and only CyA (3). None of the patients received T cell depleted marrow.

Table 1 describes the diagnoses of the patients. Patients at standard risk were defined as those transplanted at the 1st complete remission of acute leukemia, in the chronic phase of chronic myeloid leukemia and refractory anemia of myelodysplastic syndrome¹⁷. High-risk patients consisted of those who were not assessed as being of standard risk. Patients with complications included 36 who developed acute GVHD (≥ 2), 53 who developed chronic GVHD and 33 who relapsed after allogeneic stem cell transplantation.

Methods

Samples

The Institutional Review Board of Kanazawa University Hospital has approved the use of DNA analysis for mHag typing. We obtained the written, informed consent of patients and donors to obtain DNA from their peripheral blood samples before transplantation. Peripheral blood and nail or buccal membranes were obtained from post-transplant patients. The former was used as donor cells and nail or buccal membrane, as host cells.

Allele typing of HA-1 and four polymorphic adhesion molecules

Alleles of HA-1 and four polymorphic molecules were typed as described by Maruya et al.⁶ Briefly, purified genomic DNA for HA-1 and the polymorphic adhesion molecules were amplified by PCR using sequence-specific primers (Table 2). Amplification proceeded in 50 μ l of PCR buffer (Applied Biosystems, Foster City, CA USA), containing 10 mmol/L Tris-HCL (pH 8.3), 50 mmol/L KCL, 1.5mmol/L MgCl₂, 0.2

mmol/L each of the 4 deoxyribonucleotides (Applied Biosystems), 20 pmol of each primer, and 1.25 units of Taq polymerase (AmpliTaq Gold; Applied Biosystems). Four micro liters of DNA (80 ng) was denatured at 98°C for 5 minutes, and then 35 cycles of denaturation (96°C, 1 minute), annealing (58°C, 1 minute) and extension at 72°C for 5 minutes were applied using an automated PCR thermal cycler (PERKIN ELMER CETUS).

The PCR products (10 μ l) were digested with 5 U of Mva I for CD31 codon 125, Bfa I for CD31 codon 563, Mnl I for CD49b, Hph I for CD62L at 37°C for 4 h and with Tsp45 I for HA-1 overnight. The fragments were resolved by electrophoresis on 10% polyacrylamide gels for 1 h at 150V. The RFLP profiles in the gel were visualized by silver staining.

Diagnosis of incompatibility of each polymorphic molecule

The combination of HA-1 positive recipients (HA-1^{H/R} or HA-1^{H/H}) and an HA-1 negative donor (HA-1^{R/R}) was defined as incompatible. HA-1 was restricted to HLA-A2, but patients with the other class I superfamilies were also evaluated. The incompatibility of the other four polymorphic adhesion molecules was defined as a combination of HLA-restricted patients transplanted with material from CD31, CD49b, CD62L incompatible donors as defined by Maruya⁶⁾. The CD31 molecules are restricted to the HLA-B44-like superfamily (B37, B41, B44, B45, B47, B49, B50, B60 and B61), CD49b molecules to the HLA-A3-like superfamily (A3, A11, A31, A33 and A*6861) and CD62L molecules to the HLA-A3-like or B44-like superfamilies or both.¹²⁾

Statistical analysis

Acute GVHD was classified according to the described criteria¹³⁾. Relapse was diagnosed as emerging original leukemic cells after allogeneic stem cell transplantation. Relapse rate between incompatible and compatible patients was compared by a chi-square test. Multivariate analysis performed with logistic regression analysis. Variables include mHag, standard risk at SCT, TBI regimen over 10 Gy, stem cell source (PBSC), UR-BMT, sex incompatibility, acute GVHD and chronic GVHD. Survival rates and curves were estimated using the Kaplan-Meier method and the logrank statistical test analyzed differences.

Results

Characteristics of mHag incompatible and compatible patients

Table 1 shows comparison between the two groups. 36 of 106 patients were incompatible with at least one of these molecules and the other 70 patients were compatible with the donor. The comparison revealed that the relapse rate was lower in the incompatible (n=36) than in the compatible (n=70) patients ($P < 0.013$), although the other characteristics were compatible. The distribution of HA-1 allele type compatibility was identical with published data in Japan.¹⁴⁾

Multivariate analysis

Table 3 shows multivariate analysis. Incompatibility of at least one mHag was most powerful and significant factor to induce GVL effect among evaluated factors with logistic regression analysis.

Difference of GVL effect among each mHag

Table 4 shows different intensity of GVL effect among each mHag. Compared with compatible patients, the relapse rate was significantly low only those with CD62L incompatibilities. The relapse rate tended to be low in those with CD31 and HA-1 incompatibility but not statistically significant. The relapse rate of HA-1 incompatible patients with HLA-A2 and with other HLA class 1 super families tended to be low (16.6% and 13.3%) but the value was not statistically significant due to the small numbers. Interestingly, the incidence of acute GVHD (\geq II) between compatible and incompatible patients did not differ. The incidence of a-GVHD of patients with CD62L, CD31 codon 563, CD31 codon 125, HA-1 and CD49b incompatibilities were 35.3%, 35.3%, 30.8%, 32% and 33.3% respectively which were comparable to those of compatibilities. Table 5 showed different effect on GVL and a-GVHD among each mHags. Mismatches of CD62L, CD31 codon 563 and CD31 codon 125 induce GVL effect rather than a-GVHD.

Long-term effect

Figure 1 shows accumulated relapse rate and survival rate in standard risk group. The estimated 12-year accumulated relapse rates of incompatible and compatible patients were 22% and 68%, respectively ($P = 0.02$). After treatment, the 15-year probability of survival among patients in the standard risk group who were incompatible and compatible was improved to 88% and that of compatible patients was 66% ($P = 0.03$). In the high-risk group, there was no significant difference between compatible and incompatible group in the relapse rate.

Discussion

We demonstrated here that mHag incompatibility in HLA-identical stem cell recipients could induce GVL effect rather than acute GVHD after myeloablative stem cell transplantation. Since neither an increase of acute GVHD nor fatal complications developed during long-term follow up in the standard risk group, these mHags except CD49b may be ideal targets for donor derived T cells after SCT. Difference of CD49b is not any influence on GVL.

In the standard risk group, the relapse rate in patients with mHag incompatibility was lower than that of compatible patients (14% vs. 44%, $P=0.02$). In the latter group, 18 out of 41 patients relapsed after allogeneic SCT. Nine of the relapsed patients were CML. 4 were cytogenetic and 3 were hematological relapse at 2, 14, 21, 39, 16, 68 and 132 months after SCT. The remaining two were blastic and extramedullary relapse at 22 and 36 months after SCT. Six of the 7 CML in chronic phase relapse were treated with DLI and the other one patient discontinued CyA to enhance the GVL effect. All of the 7 CML patients achieved CR 2 to 6 months after DLI. The other nine of the 18 patients with relapse died due to relapse-related complications at 8, 32, 34, 43, 44, 48, 55, 59 and 122 months after SCT. Interestingly none of the 7 CML patients with mHag incompatibilities in the standard risk group has relapsed. These suggest that mHag incompatibility induce prolonged anti-leukemia effect and induce long-term survivors after SCT.

In contrast to the study by Goulmy et al., our data did not show any increase in acute GVHD. These findings are compatible with those of Murata et al.¹⁴⁾, which shows that HA-1 mismatch is not significantly associated with acute GVHD in Japanese patients⁶⁾. The difference is probably due to intensified immunosuppressants for GVHD prophylaxis and smaller number of mHag contributing to GVHD in Japan than in Western countries. Goulmy et al. reported that recipient incompatibility with HA-1 is associated with the acute GVHD development since acute GVHD (≥ 2) developed in all HA-1- positive adult patients ($n=10$) who received marrow from a HA-1-negative donor. However, they received either MTX or CyA as GVHD prophylaxis. Among our patients, 103 of 106 received short-term MTX+CyA (98) or short-term MTX+FK 506 (5) as prophylaxis for acute GVHD. Since the combination of MTX+CyA significantly decreases the incidence of acute GVHD compared with either MTX or CyA alone, the

strength of the association might be lower in patients who received either MTX+CyA or FK506 than in those who received either MTX or CyA.

Recently, a large-scale study has performed to know the association of ethnicity and the incidence of GVHD and revealed that lower risk of acute GVHD and early post-transplantation toxicity in Japanese and Scandinavian populations¹⁵⁾ which suggest to a less diverse genetic background among HLA-identical pairs in Japan. A large-scale survey of Japanese patients transplanted from HLA-identical sibling¹⁶⁾ and HLA identical unrelated donors¹⁷⁾ have a similar GVL effect with lower incidence of a-GVHD than that of Western countries. Furthermore, the results of donor leukocytes infusion for relapsed patients showed similar GVL effect with relatively low incidence of acute GVHD in Japan compared to Western country.¹⁰⁾ These results together with our data suggested the number of mismatched mHag is even small, these molecules have enough power to induce GVL effect rather than a-GVHD in Japanese patients transplanted from HLA identical pairs.

Among the four polymorphic adhesion molecules, relapse rate were significantly low in patients with CD62L-incompatibility. Mismatches of CD31 codon 563 and CD31 codon 125 also induce GVL effect rather than acute GVHD. The anti-leukemia effect by CD62L was associated only with the HLA-A3-like and/or B44-like super families, which are grouped as HLA class I alleles based on the similarity of their peptide binding motifs¹²⁾. Since these phenomenon has been described with respect to CTL lines that are specific for melanoma-associated antigens within the A2-like superfamily¹⁸⁾ and to HIV-specific peptides within the A3-like superfamily¹⁹⁾, molecules from incompatible CD62L and CD31 combination could be an immunodominant mHag in HLA identical stem cell recipients.

From these data we suggested that polymorphic adhesion molecule such as CD62L, CD31 codon 563 and codon 125 could function as immunodominant mHag to induce GVL effect rather than a-GVHD in the Japanese patients transplanted from HLA-identical stem cell grafts and contribute to long-term survival. To confirm this hypothesis, prospective randomized study is needed. Detection of the mHag specific cytotoxic T cells in a patient transplanted from the mHag negative graft is now under investigation.

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Titles and legends

Figure1; Probability of survival and accumulated rate of relapse among mHag incompatible and compatible patients in standard risk group.

Legend; Total 63 cases were studied where 88% of 10 year survival and 22% of accumulated rate of relapse in mHag incompatible patients comparing to 64% of 10 year survival ($P < 0,03$) and 66% of accumulated of relapse ($P < 0,02$) in mHag compatible patients after HLA identical SCT.

Table1 Characteristics of mHag incompatible and compatible patients.¹⁾

	All patients	106	mHag compatibility	
			IC	C
			36	70
Sex, n (%)				
Male		65	21(58.3)	44(62.9)
Female		41	15(40.5)	26(37.1)
Diagnosis, n (%)				
ALL		27	7(19.4)	20(28.6)
AML		29	11(29.7)	18(25.7)
CML		34	9(24.3)	25(35.7)
HD		1	0(0)	1(1.42)
NHL		5	2(5.40)	3(4.29)
MDS		10	7(18.9)	3(4.29)
Source of BMT, n (%)				
Sibling		60	22(61.1)	38(54.2)
Unrelated donor		46	14(37.8)	32(45.7)
Source of stem cell, n (%)				
BM		88	29(80.5)	59(84.3)
PBSC		15	4(10.8)	11(15.7)
BM+PBSC		3	3(8.10)	0(0)
Risk at transplantation, n (%)				
Standard		63	19(51.4)	44(62.9)
High		42	17(47.2)	25(35.7)
Not evaluated		1	0(0)	1(1.42)
Complications, n (%)				
Relapse		33	6(16.7) ²⁾	27(38.6)
Acute GVHD(≥ 2)		35	12(33.3)	23(32.9)
Chronic GVHD		52	17(47.2)	35(50.0)
Direction of transplantation, n (%)				
Female to male		25	9(25.0)	16(22.9)
Other		81	27(73.0)	54(77.1)
Time of transplantation, n (%)				
1985—1997		35	13(36.1)	32(45.7)
1998—2002		61	23(62.2)	38(54.3)
Immunosuppressant, n (%)				
Short term MTX+CyA		98	33(89.2)	65(92.8)
Short term MTX+FK		5	3(8.10)	2(2.86)
Other ²⁾		3	0(0)	3(4.29)
Irradiation, n (%)				
TBI		97	34(94.4)	63(90.0)
Non-TBI		9	2(5.40)	7(10.0)

1) ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CML,

chronic myelogenous leukemia; HD, Hodgkin's disease; NHL, non-Hodgkin's lymphoma; MDS, myelodysplastic syndrome and MDS including 4 refractory anemia, 4 refractory anemia with excessive blasts, 1 refractory anemia with excessive blasts in transformation and 2 overt leukemia; IC, incompatible; C, compatible; TBI, total body irradiation. MTX, Methotrexate; CyA, Cyclosporine, FK, Tacrolimus hydrate; PSL, prednisolone

- 2) Short term MTX+PSL, CyA, MTX
- 3) Relapse rate of incompatible group was significantly lower than that of compatible group.

Fig. 1 Probability of survival and accumulated rate of relapse

