Stem Cell Transplantation

Graft-versus-leukemia effect of allogeneic stem cell transplantation; a Japanese single center study

To clarify graft-versus-leukaemia effect of graft-versus-host disease, we studied 166 patients treated with allogeneic stem cell transplantation for haematologic malignancies. The cumulative incidence of relapse in patients with acute GVHD was significantly lower than that in patients without acute GVHD, but there was no similar GVL effect for chronic GVHD.

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The therapeutic effect of allogeneic haematopoietic stem cell transplantation (SCT) was previously assumed to be produced by high-dose chemoradiotherapy. Weiden *et al.* first demonstrated the favorable effect of graft-versus-host disease (GVHD) on leukemic relapse, and subsequent reports have confirmed such a graft-versus-leukemia (GVL) effect.[1-5] Although several reports documented a GVL effect associated with chronic GVHD (cGVHD), some patients relapse with leukemia despite developing extensive cGVHD. To clarify these issues, we studied 209 patients who underwent allogeneic SCT at our hospital for treatment of haematologic malignancies.

Table 1A summarizes patient characteristics. Of 166 patients surviving more than 30 days after SCT, 71 patients (43%) developed acute GVHD (aGVHD) on day 9~67 (median; 25). Ninety-five percent of aGVHD occurred within 40 days after SCT. The number of aGVHD+ patients was 39 for grade I, 17 for grade II, 11 for grade III and 4 for grade IV. The incidence of aGVHD+ patients from HLA-matched sibling donors (38%) was comparable to those from HLA-matched unrelated donors (59%) and HLA-mismatched sibling donors (44%). cGVHD appeared in 87 of 158 (55%) patients. The onset type of cGVHD was progressive in 9, quiescent in 16 and *de novo* in 62 patients. Relapse occurred in 47 of 166 (28%) patients, 3~102 months after SCT. Cox regression multivariate analysis showed that none of the factors affected the relapse rate in standard-risk patients while aGVHD significantly lowered the relapse rate in high-risk patients (Table 1B). Table 1C shows the relationship between aGVHD and relapse. The relapse rate was significantly lower in aGVHD ≥ grade II patients (6%), but not in cGVHD$^+$ patients analyzed by the Fisher's exact probability test (p<0.001). *De novo* onset cGVHD did not reduce the rate of relapse either; 19 of 62 (31%) patients with *de novo* cGVHD relapsed and 23 of 68 (34%) without *de novo* cGVHD did. The cumulative incidence of relapse that was evaluated in patients who survived more than 100 days after SCT was significantly lower in aGVHD ≥ grade II patients than the other (Figure 1A, p<0.05). Estimated 5-year survival was comparable between aGVHD ≥ grade II (69%) and aGVHD-patients (75%) as well as between in cGVHD+ patients (64.0%), and in cGVHD-patients (63.9%). Figure 1b shows the overall survival in high-risk patients according to different grades of aGVHD; the 5-year probability of survival was 71% in aGVHD ≥ grade II patients, while it was 52% in the other (p=0.17). The probability of survival of patients who developed aGVHD ≥ grade I (66%) was significantly higher than patients without aGVHD, p<0.05).

This study revealed the low relapse rates amongst

Table 1A. Patients' characteristics.

No. of patients	*166*
Gender (male/female)	102/64
Median age (range)	24 (1-59)
Donor	
Sibling, HLA-matched	123
Sibling, HLA-mismatched	9 (1 locus 8, 2 loci 1)
Unrelated, matched	34
Diagnosis	
AML	57
ALL	42
CML	41
NHL	17
MDS	9
Disease status at transplantation	
CR	117 (incl. CML-CP 33)
non-CR	49 (incl. CML-AP 5, BC 3)
Source of graft	
Bone marrow	140
PBSC	25
Cord blood	1
Conditioning regimen	
Chemotherapy + TBI	115
BU + CY (+ Ara-C)	49
Flu + CY	2
GVHD prophylaxis	
None	20
Short MTX + CyA	127
MTX	9
CyA	3
FK506	7

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia, NHL, Non-Hodgkin's lymphoma; MDS, myelodysplastic syndrome; CR, complete remission; CP, chronic phase; AP, accelerated phase; BC, blastic crisis; PBSC, peripheral blood stem cell; TBI, total body irradiation; BU, busulfan; CY, cyclophosphamide; Ara-C, cytarabine; Flu, fludarabine; MTX, methotrexate; CyA, cyclosporine A; FK506, tacrolimus.

Table 1B. Multivariate analysis on factors affecting relapse after transplantation.

Characteristics	*Relative risk of relapse*	*95% CI*	*P value*
Standard-risk (n=79)			
Sex, female	1,27	0.95-1.70	0.4-0.3
Conditioning, including TBI	1,19	0.71-2.01	0.4-0.3
aGVHD, I-IV	1,43	0.81-2.54	0.2-0.1
cGVHD	1,32	0.73-2.39	0.4-0.3
PBSCT	1,20	0.54-2.65	0.4-0.3
High-risk (n=79)			
Sex, female	1,25	0.87-1.79	0.2-0.1
Conditioning, including TBI	1,15	0.76-1.76	0.4-0.3
aGVHD, I-IV	0,57	0.38-0.85	<0.005
cGVHD	0,90	0.57-1.40	0.4-0.3
PBSCT	0,79	0.44-1.42	0.3-0.2

TBI: total body irradiation.

Table 1C. Effect of GVHD on the rate of relapse after SCT.

		Acute GVHD aGVHD			
Status at SCT	Yes		No		
Standard-risk	0%	(0/13)	28%	(19/69)	p<0.03
High-risk	11%	(2/19)	40%	(26/65)	p<0.02
		Chronic GVHD cGVHD			
Status at SCT	Yes		No		
Standard-risk	19%	(8/42)	30%	(11/37)	n.s.
High-risk	29%	(13/45)	35%	(12/34)	n.s.

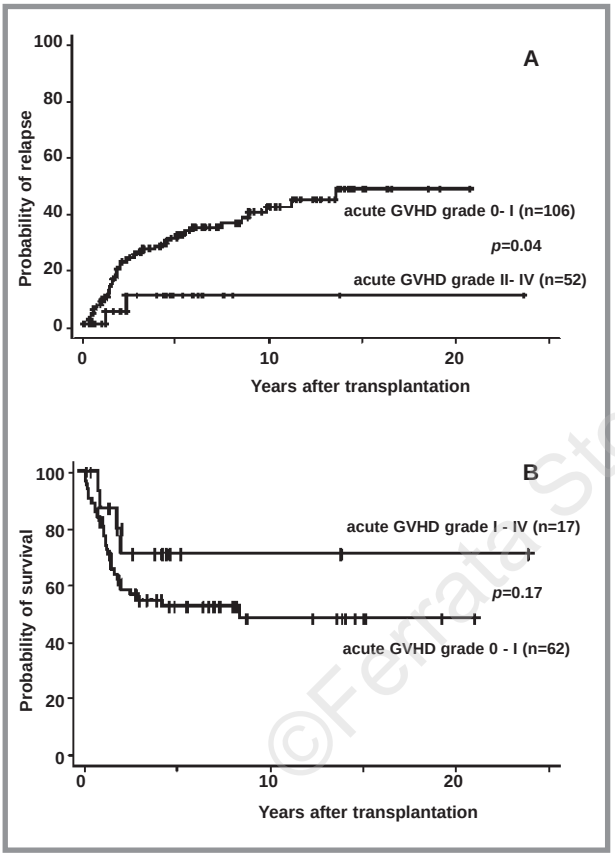

Figure 1 A.Probability of relapse in 158 patients receiving allogeneic SCT patients grouped by the existence of acute GVHD, using Kaplan-Meier method and Wilcoxon test. B. Probability of overall survival in 79 high-risk patients grouped by the existence of acute GVHD, using Kaplan-Meier method.

Japanese patients developing aGVHD ≥ grade II regardless of risk at SCT, supporting previous findings.[6] Development of aGVHD also contributed to improving survival in high-risk patients; when grade I aGVHD patients were included in GVHD$^+$ patients, the difference in survival rates between GVHD$^+$ and GVHD$^-$ patients became significant (p<0.05). To our knowledge, this is the first report documenting the significant beneficial effect of aGVHD on survival of high-risk patients after SCT. Thus, aGVHD appears to be associated with potent GVL effect. In contrast, the development of cGVHD was not associated with a decrease in the relapse rate. Weiden *et al.* reported an improvement of overall survival and a decrease of relapse rate in GVHD$^+$ patients compared with GVHD$^-$ patients.[1]

This effect was especially evident in cGVHD$^+$, and several studies supported these results.[2-5] However, cGVHD in most patients is preceded by aGVHD in Caucasians; the proportion of *de novo* cGVHD among all cGVHD patients is only 12~36%.[7,8] Thus, low relapse rates in cGVHD$^+$ patients may be affected by preceding aGVHD. Remberger M *et al.* reported that grade II aGVHD possessed GVL effect in unrelated SCT.[9]

However, aGVHD ≥ grade II did not improve the survival compared to grade I. In this study, aGVHD ≥_grade I significantly lowered relapse rate and improved the survival of high-risk patients. Thus, it may be reasonable to prevent aGVHD in standard-risk patients as much as possible and give weak immunosuppression to high-risk patients to induce grade I aGVHD. It is believed that cGVHD is useful in preventing relapses of leukemia. Since there is no other means to prevent relapses, physicians tend to intentionally induce cGVHD for aGVHD-patients with a high-risk of relapse. Such patients may be untreated even if they have developed extensive cGVHD. Our results suggest that this approach may be incorrect. cGVHD can be a fatal complication by itself and many patients succumb to infection associated with cGVHD. The best strategy to prevent relapses in high-risk patients may be to induce aGVHD ≥ grade I and treating it intensively to prevent subsequent cGVHD.

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Transfusion Medicine

Infectious disease markers in autologous blood donors and first-time volunteer blood donors: 14 years' experience in a blood center

The proportion of blood donors with positive infectious disease markers was statistically higher in our population of 3,614 autologous donors than in our population of 276,106 first-time volunteer donors ($p<0.005$). Our data suggest that our autologous donor population is not as safe as our first-time volunteer donor population.

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In Spain, it is a current legal requirement[1] that both autologous and homologous blood donors pass the same ordinary predonation blood donor interview. Moreover, all samples from both autologous and homologous donors are tested for the presence of antibodies to HCV (anti-HCV) and HIV viruses (anti-HIV), HBsAg and RPR. If one of these tests is positive, then the donor is deferred. Moreover, it has also been suggested that the infectious markers frequency in autologous and volunteer donors may vary geographically and should be determined locally.[2]

With these controversies in mind, we decided to collect data to calculate the frequency of positive infectious disease markers in our population of autologous and first-time volunteer donors.

We evaluated the presence of the infectious disease markers from January 1989 to December 2002 both in 3,614 autologous and in 276,106 first-time volunteer blood donors who were eligible for blood donation. Both groups of donors followed the same medical history screening procedure. Minimal hemoglobin level, however, was 105 g/L for autologous donors, 125 g/L for first-time female and 135 g/L for first-time male volunteer donors.

Screening (ELISA kit) and confirmatory (RIBA kit) tests to analyze for the presence of anti-HIV 1/2 and anti-HCV were implemented in 1986 and 1989, respectively. Screening (enzyme immunoassay kit) and confirmatory (neutralization kit) tests to analyze for the presence of HBsAg were implemented in 1971. RPR was performed with RPR-Carbon (BioSystems, Barcelona, Spain) and was

Table 1. Infectious markers in autologous and first-time volunteer blood donors per year.

		Autologous donors											
		Positive HBsAg[1]		*Positive HIV*[2]		*Positive HCV*[2]		*Ind HCV*[3]		*Positive RPR*[1]		*ALT>88 IU/L*	
Year	N	n	%	n	%	n	%	n	%	n	%	n	%
1989	10	0	0	0	0	0	0	0	0	0	0	0	0
1990	10	0	0	0	0	0	0	0	0	0	0	0	0
1991	24	1	4.17	0	0	0	0	0	0	0	0	0	0
1992	82	0	0	0	0	2	2.44	2	2.44	0	0	1	1.22
1993	104	0	0	0	0	0	0	0	0	0	0	0	0
1994	276	2	0.72	0	0	17	6.16	4	1.45	0	0	1	0.36
1995	305	3	0.98	1	0.33	13	4.26	1	0.33	1	0.33	1	0.33
1996	248	0	0	0	0	7	2.82	3	1.21	1	0.4	0	0
1997	402	1	0.25	0	0	7	1.74	2	0.5	1	0.25	0	0
1998	232	1	0.43	1	0.43	6	2.59	2	0.86	0	0	1	0.43
1999	350	1	0.29	0	0	5	1.43	4	1.14	1	0.29	1	0.29
2000	461	2	0.43	0	0	10	2.17	0	0	1	0.22	0	0
2001	566	2	0.35	0	0	8	1.41	3	0.53	0	0	0	0
2002	544	5	0.92	0	0	8	1.47	2	0.37	1	0.18	0	0
All	3,614	18	0.5	2	0.06	83	2.3	23	0.64	6	0.17	5	0.14