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Clinical Features of 62 Allogeneic Stem Cell Transplantations; the Evaluation of Prognostic Factor in a Single Institution

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A retrospective analysis of the clinical features of 62 patients with various hematological or other diseases who received allogeneic stem cell transplantation (SCT) between April 1990 and July 2002 in the Department of Pediatrics, Kobe University Hospital was conducted to investigate prognostic factors of allo-SCT. Among 62 allo-SCT, 51 (82%) were bone marrow transplantation (BMT), 5 (8%) were peripheral blood stem cell transplantation and 6 (10%) were cord blood transplantation. Disease-free survival rate (DFS) estimated according to the diagnosis group did not show any significant difference. For hematological malignant diseases, DFS estimated according to the disease stage was 66.7% for the patients in the standard stage and 30.0% for the patients in the advanced stage (p=0.0249). Of 47 evaluable patients receiving allo-BMT, DFS of patients receiving the last transfusion of platelets on or before day 21 was significantly higher than that of patients receiving the last transfusion after day 21 (66.7% vs 34.8%, p=0.0111).

These results demonstrate that more appropriate indications and points for SCT should be applied to patients in the advanced stage, and that whether the last transfusion of platelet is on or before or after day 21 is an important prognostic factor for allo-BMT because the necessity for platelet transfusion was vividly reflected in the status of the patients.

Despite improvements in the management of childhood hematopoietic malignant diseases, 20% to 40% patients are suffering from relapse or other complications[2,17,24]. Hematopoietic stem cell transplantation (SCT) improved their outcome and moreover the outcome of patients with such non-malignant diseases as severe aplastic anemia (SAA) or severe combined immunodeficiency (SCID) or others. After the progress made in the past two decades, we now have three available techniques for SCT, namely bone marrow transplantation (BMT), peripheral blood stem cell transplantation (PBSCT)[14] and cord blood transplantation (CBT)[10] and because of the improvements in supportive care, graft versus host disease (GVHD) prophylaxis and cytomegalovirus or other microorganism prophylaxis has now enabled many institutions to increase the number of cases receiving allogeneic stem cell transplantation (allo-SCT). We have performed 100 SCT between June 1989 and July 2002. Among these 100 SCT, 62 involved allo-SCT and 38 involved autologous SCT (auto-SCT). During the last two decades investigators have reported several prognostic factors for allo-SCT[3,4,12,13]. Our study reviewed the clinical course of 62 children receiving allo-SCT in our institution between April 1990 and July 2002 and analyzed the epidemiological and laboratory characteristics of allo-SCT. Furthermore, we tried to identify new prognostic factors based on these findings.

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MATERIALS AND METHODS

A total of 100 children underwent auto- or allo-SCT between June 1989 and July 2002 in the Department of Pediatrics, Kobe University Hospital. The study population comprised 62 patients, aged 6 months - 24 years, who were given allo-BMT or allo-PBSCT or allo-CBT. We recorded the clinical data of these patients on a standardized form, which included demographic and clinical data; age, gender, date of birth, diagnosis, disease stage, source of graft, cell counts of graft, disparity of human leukocyte antigen (HLA), ABO typing of red blood cells of both patients and donors, gender of donors, conditioning regimen, prophylaxis of GVHD, grade of acute and chronic GVHD, day of white blood cell (WBC) $\geq$ 1000/μl, absolute neutrophil count (ANC) $\geq$ 500/μl, platelet $\geq 5.0\times10^4$/μl, reticulocyte $\geq$ 10‰ and the last transfusion of platelet and red cells and outcome. We performed statistical analyses on these items.

The end point of follow-up was September 2002.

Statistical analysis

Data were analyzed as of September 30, 2002. Associations between pairs of covariates about the major clinical characteristics of patients were assessed by t-test. The Kaplan-Meier method was used to estimate disease-free survival rate (DFS) and the overall survival rate (OS) after transplantation and compared using the Mantel-Cox test and Breslow-Gehan-Wilcoxon test. A P-value of .05 or less was considered to represent significance.

RESULTS

Patient and donor characteristics

Patient and donor characteristics are shown in Table I. Among 62 patients who received allo-SCT, 51 patients (82%) received BMT, 5 patients (8%) received PBSCT and 6 patients (10%) received CBT. Thirty-six of 51 patients who received allo-BMT received grafts from related donors and the other 15 patients received grafts from unrelated donors facilitated by the Japan Marrow Donor Program (JMDP). All grafts of PBSCT were from related donors, whereas all grafts of CBT were from unrelated donors facilitated by the Japanese Cord Blood Bank Network. Thirty-seven patients were male and 25 were female. At the time of SCT, age of patients ranged from 6 months to 24 years, with a median of 7.0 years. Fifty-one patients had malignant diseases and 11 had non-malignant diseases. With regard to hematological malignant diseases, the standard stage included acute lymphoblastic leukemia (ALL) in the first or second complete remission (CR), acute myelogenous leukemia (AML) in the first CR, non-Hodgkin's lymphoma (NHL) in the first CR, chronic myelogenous leukemia (CML) in the first chronic phase (CP) and juvenile myelomonocytic leukemia (JMML) in the first CP whereas the advanced stage included every other status. Among patients who received related BMT, 17 patients were ALL, especially 6 were in the advanced stage, whereas only one patient was ALL in the first CR who received unrelated BMT. Disparity of HLA and ABO typing are shown in Table Ⅱ. High-resolution DNA typing was not done in every case depending on the sort of antigen or period when SCT was performed. Therefore statistic analyses were performed only by serologic typing. Because our institution obtained a license to perform one-locus-mismatched unrelated BMT from JMDP in 2002, only one patient has received one-locus-mismatched unrelated BMT to date.

Engraftment

Cell count of graft and hematological recovery are shown in Table Ⅲ. WBC and platelet engraftment were defined as WBC $\geq$ 1000/μl and unsupported platelet $\geq 5.0\times10^4$/μl on 3

consecutive laboratory analysis, respectively. All patients were given a minimum recommended threshold cell count which was reported previously for every source of graft. The day of transplantation was designed as day 0. The median day for WBC ≥ 1000/μl was 16 (range 9-32), 19 (range 14-40), 14 (range 8-15) and 20.5 (range 14-27) for patients receiving related BMT, unrelated BMT, PBSCT and CBT. There were no significant differences between the related BMT group and the unrelated BMT group. Comparing the CBT group and the other group, not only the median time for WBC ≥ 1000/μl, but also several other items concerning engraftment of the CBT group were significantly longer than those of any other group. In the same way, several items of the PBSCT group were significantly more rapid than those of any other group. These findings were consistent with several previous reports[7,20].

Table I. Patient and donor characteristics.

Gender					n (%)
male with male donor					22 (35.5)
male with female donor					15 (24.2)
female with male dono					10 (16.1)
female with female donor					15 (24.2)
Age (median, range)					7.0 y, 6m~24y
GVHD prophylaxis; CyA with or without MTX					48 (77.4)
FK506 with or without MTX					10 (16.1)
MTX alone					2 (3.2)
Non					2 (3.2)
Diagnosis and phase		related BMT	unrelated BMT	PBSCT	CBT	total
Malignant					2	51 (82.3)
	ALL in 1, 2 CR	11	1		1	14 (22.6)
	other (advanced)	6		3	1	10 (16.1)
	AML in 1 CR	2	5	1	1	9 (14.5)
	other (advanced)	6	1			8 (12.9)
	NHL in CR	2				2 (3.2)
	CML in CP	1	3			4 (6.5)
	C(J)MML	1	2			3 (4.8)
	Rhabdomyosarcoma			1		1 (1.6)
non-malignant						11 (17.7)
	SAA	5	3			8 (12.9)
	SCID	2			1	3 (4.8)
Source of graft (sibling/parent)		36 (29/7)	15	5(3/2)	6	62 (100)

ALL indicates acute lymphoblastic leukemia; AML, acute myelogenous leukemia; NHL, non-Hodgkin's lymphoma; CML, chronic myelogenous leukemia; C(J)MML, chronic (juvenile) myelomonocytic leukemia; SAA, severe aplastic anemia; SCID, severe combined immunodeficiency; CR, complete remission; CP, chronic phase; GVHD, graft versus host disease; CyA, cyclosporin; MTX, methotrexate; FK506, tacrolimus hydrate; BMT, bone marrow transplantation; PBSCT, peripheral blood stem cell transplantation; CBT, cord blood transplantation.

Acute and chronic GVHD

The methods used for prophylaxis for GVHD are shown in Table I and the numbers of patients with acute and chronic GVHD are shown in Table Ⅳ. Acute and chronic GVHD were classified according to previously published criteria[1,11,21]. Four patients were not evaluated for acute GVHD since they died of sepsis or interstitial pneumonia on day 10-32 after SCT, and 16 patients were not evaluated for chronic GVHD because 15 patients had

died or presented leukemia relapse before 100 days after SCT and the remaining one patient was gone within only about 50 days after allo-SCT. As described below, DFS was 59.5% and 43.8% for subjects without or with grade 1 acute GVHD and for those with grade 2 to 4 acute GVHD, respectively (p=NS). About chronic GVHD, all 9 patients with chronic GVHD of the limited type have survived without relapse, notwithstanding the lack of significant differences among patients with limited type, extensive type and absence of chronic GVHD, probably because of the disproportion between numbers of patients.

Table Ⅱ. Matching of HLA and red blood cell type.

	full match	1 locus mismatch	2 loci mismatch	3 loci mismatch
related BMT(sibling/parent)	22 (20/2)	10 (6/4)	3 (3/0)	1 (0/1)
mismatched by only DNA typing(sibling/parent)		4 (2/2)		
unrelated BMT	14	1		
mismatched by only DNA typing		1	1	
related PBSCT(sibling/parent)	2 (2/0)	1 (1/0)	2 (0/2)	
mismatched by only DNA typing(sibling/parent)				1 (0/1)
unrelated CBT	2	4		
mismatched by only DNA typing				

	patient	donor
A	34	30
B	11	12
O	9	16
AB	8	4
matched		24
minor mismatch		20
major mismatch		11
major and minor mismatch		7

See Table I for abbreviations.

Disease-free survival rate (DSF), subgroup analyses

DFS estimated according to the diagnosis group did not show any significant difference. For hematological malignant diseases, DFS estimated according to the disease stage was 66.7% for the standard group and 30.0% for the advanced group (p=0.0249, Figure 1-A and B). There was no significant difference between DFS in the group without or with grade 1 acute GVHD and that with grade 2 to 4 acute GVHD (Figure 2) as indicated above.

Among the items of engraftment, we noted the day of the last platelet transfusion after SCT, because platelet count is a routine examination in many institutions and we thought that the necessity for platelet transfusion is vividly reflected in the status of patients with hematological disease. So we compared DFS of patients, in the related and unrelated BMT groups, who received the last platelet transfusion on or before day 21 with that of patients receiving the last platelet transfusion after day 21. Of 47 evaluable patients, DFS of the group receiving an earlier last transfusion was significantly higher than that of the group receiving a later last transfusion (p=0.0111, Figure 3).

We also analyzed DFS estimated according to typing of ABO and HLA disparity. There was no significant difference in the relation to ABO typing and between HLA-mismatched sibling donor and parent donor (data not shown).

Table Ⅲ. Cell count of infusion.

BMT (ABO matched or minor mismatched)	PBSCT	CBT
n = 35 (NCC, $\times 10^8$/kg)	n = 5 (CD34+, $\times 10^6$/kg)	n = 6 (NCC, $\times 10^7$/kg)
4.26 ± 1.56	5.18 ± 2.71	6.27 ± 3.77

Hematological recovery

related BMT	unrelated BMT	PBSCT	CBT
n = 36	n = 15	n = 5	n = 6

day of	median (range, evaluable number)			
WBC≥1000/μl	16.0(9~32, 31)[#1]	19.0(14~40, 15)[#2]	14.0(8~15, 5)[#2, #3]	20.5(14~27, 6)[#1, #3]
ANC≥500/μl	15.0(9~39, 31)	20.0(14~37, 15)[#4]	14.5(7~16, 4)[#4, #5]	22.5(14~27, 4)[#5]
Plt≥5×10^4/μl	28.0(19~75, 23)[#6]	31.0(17~40, 12)[#7]	43.5(37~50, 2)	46.5(37~55, 6)[#6, #7]
Ret≥1%	21.0(8~49, 27)	22.5(16~41, 14)	21.0(14~32, 3)	35.0(17~47, 6)
last PC transfusion	18.5(10~60, 24)[#8]	21.0(13~31, 13)[#9]	35.5(34~37, 2)	37.0(28~39, 4)[#8, #9]
last CRC transfusion	17.0(6~53, 20)	18.5(9~26, 8)	32.5(29~36, 2)	26.0(20~49, 5)

#1 : p=0.0490 #2 : p=0.0303 #3 : p=0.0072 #4 : p=0.0385 #5 : p=0.0149
#6 : p=0.0445 #7 : p=0.0011 #8 : p=0.0126 #9 : p=0.0014

WBC indicates white blood cell; ANC, absolute neutrophil count; Plt, platelet; Ret, reticulocyte; PC, platelet concentrate; CRC, concentrated red cells. See Table I for abbreviations.

DISCUSSION

This study, despite the limits of a retrospective study, raises some interesting points.

In our study, there was no significant difference between DFS by diagnosis, but DFS of patients in the advanced stage was significantly lower than that of patients in the standard stage. More appropriate indications and points for SCT should be applied to patients in the advanced stage.

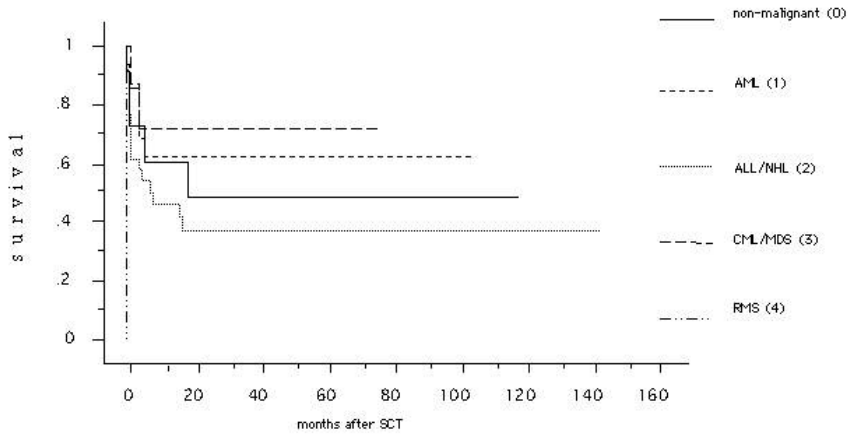
Table Ⅳ. DFS in acute and chronic GVHD.

acute GVHD	n (DFS)	chronic GVHD	n (DFS)
(−) ~ Grade I	42 (25)	(−)	31 (20)
Grade Ⅱ~Ⅳ	16 (7)	limited type	9 (9)
N.E.	4 (0)	Extensive type	6 (2)
		N.E.	16 (1)

DFS indicates disease-free survival rate; N.E., not evaluable. See Table 1 for abbreviations.

A very interesting finding was that DFS of the group receiving the last platelet transfusion on or before day 21 was significantly higher than that of the group receiving the last transfusion after day 21. Of course severe GVHD, severe infection, graft failure or other severe complications such as hepatic veno-occlusive disease (VOD) or thrombotic microangiopathy (TMA) influence the necessity for platelet transfusion. For example, the number of patients with grade 2 to 4 acute GVHD in the group receiving the last platelet transfusion after day 21 was significantly larger than that of patients with grade 2 to 4 GVHD in the group receiving the last transfusion on or before day 21 (p=0.05). The status of patients with these severe complications is usually very bad and the necessity for platelet transfusion increases. In addition to this, we did not perform multivariate analysis because only very few items showed a significantly difference in DFS. Nevertheless, we consider that the day of the last platelet transfusion very important, for this is a very simple and easy way

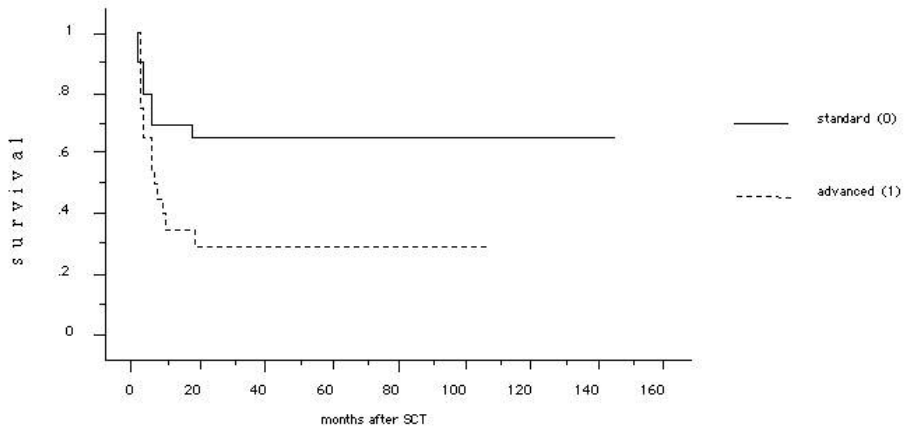
Figure 1 (A) Disease-free survival by diagnosis



Subjects	No. of cases	Survival rate	significance 0	1	2	3	4
0: non-malignant	11	0.545		N.S.	N.S.	N.S.	
1: AML	17	0.625	N.S.		N.S.	N.S.	
2: ALL/NHL	26	0.385	N.S.	N.S.		N.S.	
3: CML/MDS	7	0.750	N.S.	N.S.	N.S.		
4: RMS	1	0.000					

RMS indicates rhabdomyosarcoma.

(B) Disease-free survival by stage of hematological malignancy

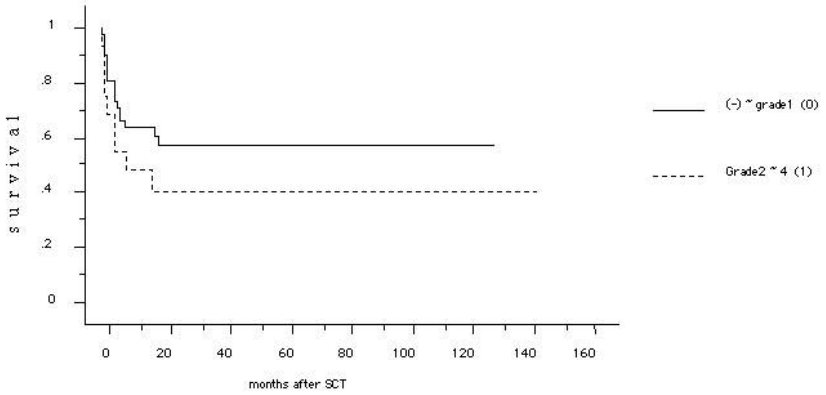


Subjects	No. of cases	Survival rate	significance 0	1
0: standard	30	0.667		0.0249
1: advanced	20	0.300	0.0249	

Figure 1. Disease-free survival. (A) The disease-free survival rate by diagnosis group. (B) In hematological malignant disease, the disease-free survival rate for the standard group and the advanced group.

to predict the outcome of a patient receiving allo-BMT because platelet count is a routine examination in many institutions and we thought that the necessity for platelet transfusion is vividly reflected in the status of patients receiving allo-BMT. Although the importance of platelet count or necessity for platelet transfusion after allo-SCT was already documented[8,18,23], no reports have concretely referred to the day of the last platelet transfusion after allo-SCT.

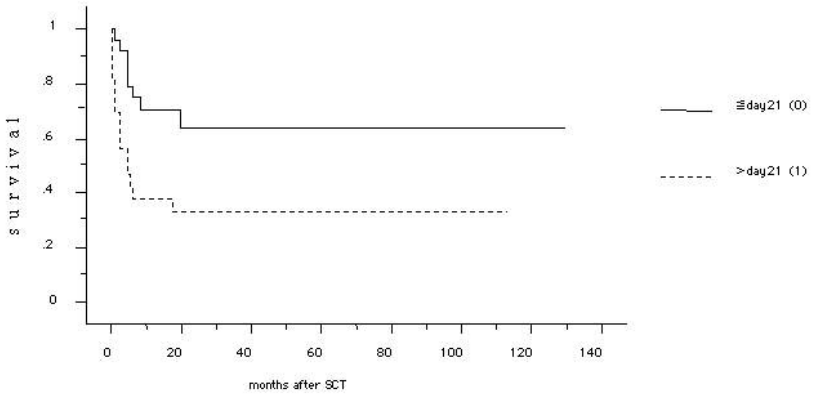
Figure 2 Disease-free survival by acute GVHD



Subjects	No. of cases	Survival rate	significance 0	1
0: (-)~grade1	42	0.595		N.S.
1: grade2~4	16	0.438	N.S.	

Figure 2. Disease-free survival. The disease-free survival rate for the group without or with grade 1 acute GVHD and with grade 2 to 4 acute GVHD.

Figure 3 Disease-free survival by the day of the last platelet transfusion



Subjects	No. of cases	Survival rate	significance 0	1
0: ≦day 21	24	0.667		0.0111
1: >day 21	23	0.348	0.0111	

Figure 3. Disease-free survival. (A) The disease-free survival rate by whether the day of the last platelet transfusion was on or before day 21 or after day 21.

The association of several minor antigens with outcomes of allo-SCT was demonstrated in previous reports. For example, a detrimental effect of donor-recipient ABO incompatibility on outcome has been suggested by some groups[5,22], but not others[6,9,15,16,19]. We could not find any significant difference in DFS due to incompatibility of ABO typing. We considered this result to be due to differences in samples or the number of patients because we analyzed only 62 patients with miscellaneous diseases.

In conclusion, our study suggests that more appropriate indications and points for SCT should be applied to patients in the advanced stage. And whether the last platelet transfusion is on or before or after day 21 is an important, simple and easy prognostic factor for allo-BMT.

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