Brief report

Chronic graft-versus-host disease following umbilical cord blood transplantation: retrospective survey involving 1072 patients in Japan

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We have little information on chronic graft-versus-host disease (GVHD) after cord blood transplantation (CBT). We investigated its clinical features in 1072 Japanese patients with hematologic malignancies who received a transplant through the Japan Cord Blood Bank Network. The primary end point was to investigate the incidence of any chronic GVHD. Median age of the patients was 33 years (range, 0-79 years). The cumulative incidence of chronic GVHD 2 years after transplantation was 28%. Chronic GVHD was fatal in 29 patients. Multivariate analysis demonstrated that development of chronic GVHD was favorably associated with both overall survival and event-free survival. Multivariate analysis identified risk factors of chronic GVHD: higher patient body weight, higher number of mismatched antigens for GVHD direction, myeloablative preparative regimen, use of mycophenolate mofetil in GVHD prophylaxis, and development of grades II to IV acute GVHD. Although chronic GVHD is a significant problem after CBT, it is associated with improved survival, perhaps due to graft-versus-malignancy effects. (Blood. 2008;112:2579-2582)

Introduction

Chronic graft-versus-host disease (GVHD) is a significant concern in allogeneic hematopoietic stem cell transplantation (HSCT). Many studies have been published on clinical features of chronic GVHD following bone marrow transplantation (BMT) and peripheral blood stem cell transplantation (PBSCT). In contrast, we have limited information on chronic GVHD following cord blood transplantation (CBT).

Methods

Informed consent was obtained in accordance with the Declaration of Helsinki. According to local policy, the study was approved by Japan Cord Blood Bank Network. We had no direct contact with human subjects during our study; data on patients who underwent CBT were obtained from the Japan Cord Blood Bank Network. The primary end point of this study was to investigate the incidence of any chronic GVHD after CBT. Cord blood units are provided with written informed consent. Between June 1997 and August 2006, 2713 cord blood transplant recipients were registered with the Japan Cord Blood Bank Network. All recipients received a single cord blood unit. We included those with hematologic malignancies who underwent CBT without T-cell depletion. We excluded patients with a history of any type of allogeneic HSCT prior to CBT. A total of 2015 patients met the criteria. Of those, we excluded 943 with disease progression, death without progression, and graft failure within 100 days after transplantation. In this study, we retrospectively investigated clinical features of chronic GVHD in the remaining 1072 patients. Cytomegalovirus-seropositive cord blood unit was not provided to transplantation centers. Acute and chronic GVHD were diagnosed and graded according to standard criteria.[1,2] GVHD that developed after day 100 was defined as chronic GVHD. If the mode of presentation for chronic GVHD was progressive, the date of onset was defined as day 100. SAS version 9.1.3 (SAS Institute, Cary, NC) was used for all statistical analyses.

Results and discussion

The median age of the 1072 patients was 33 years (range, 0-79 years) and the median patient body weight was 50.0 kg (range, 4.0-96.1 kg). The median follow up of the surviving patients was 18.1 months (range, 3.3-110.1 months). Of the 1072 patients, 492 (46%) developed grades II to IV acute GVHD within 100 days of transplantation. Chronic GVHD was diagnosed in 312, and the cumulative incidence of chronic GVHD 2 years after transplantation was 28% (95% confidence interval [CI], 25%-31%; Figure 1).

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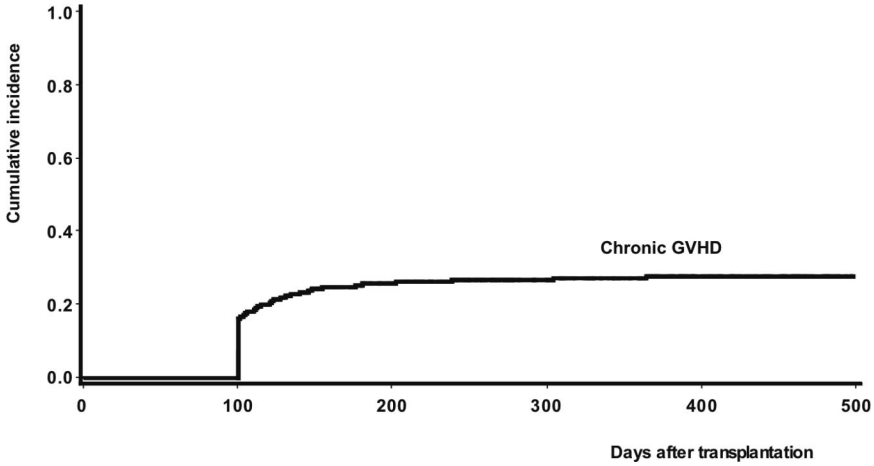

Figure 1. Cumulative incidence of chronic GVHD. The cumulative incidence of chronic GVHD 2 years after transplantation was 28% (95% confidence interval [CI], 25%-31%). Cumulative incidence curves were used to calculate the probability of chronic GVHD to take account of competing risks: disease progression, death without disease progression, and onset of graft failure.

Of the 299 patients in whom the information on types of chronic GVHD was available, 184 and 115 patients developed limited and extensive diseases, respectively.

The onset of chronic GVHD was quiescent (n = 225), de novo (n = 48), progressive (n = 18), and unknown (n = 8). Information on involved organs of chronic GVHD was available in 145 patients. Their involved organs were skin (n = 94), oral cavity (n = 35), liver (n = 32), lung (n = 24), gastrointestinal tract (n = 20), and eye (n = 16). Of 224 patients from whom information on both the treatment of chronic GVHD and its response was available, 93 patients (42%) received systemic immunosuppressive agents including corticosteroids (n = 63), calcineurin inhibitors (n = 15), both (n = 13), and others (n = 2). Of those 93 patients, 64 patients (68%) responded to the treatment. Chronic GVHD was refractory in the remaining 29, and fatal in 5.

Multivariate analysis identified prognostic factors of chronic GVHD: higher patient body weight (hazard ratio [HR], 1.01; 95% CI, 1.01-1.02; $P = .001$), higher number of mismatched antigens for graft-versus-host direction (HR, 1.31; 95% CI, 1.07-1.60; $P = .01$), reduced-intensity preparative regimen (HR, 0.69; 95% CI, 1.11-3.28, $P = .02$), use of mycophenolate mofetil in GVHD prophylaxis (HR, 1.91; 95% CI, 1.11-3.28, $P = .02$), and development of grades II to IV acute GVHD (HR, 1.51; 95% CI, 1.18-1.93; $P = .001$; Table S1, available on the *Blood* website; see the Supplemental Materials link at the top of the online article).

Of the 1072 patients, 307 died during follow up due to disease progression (n = 189), chronic GVHD (n = 29), infection (n = 23), and others (n = 66). Prognostic factors of transplantation outcomes are shown in Table 1. Overall survival (OS) and event-free survival (EFS) at 3 years after CBT were 63% (95% CI, 36%-90%) and 54% (95% CI, 27%-80%), respectively.

The present study is the first larger report addressing features of chronic GVHD in CBT. The incidence of chronic GVHD after CBT was 28% in our study, which was comparable with the previous smaller reports on CBT conducted in Western countries[3-6] and was lower than that after BMT from unrelated donors (UR-BMT) in Japanese patients.[7,8] Since the genetic backgrounds of the Japanese people are relatively homogeneous compared with those of the Western people, the incidences of chronic GVHD following UR-BMT are reportedly low in Japanese patients; our results in CBT contrast with such previous investigations.[7,8] The present study suggests that the mechanism of GVHD development is possibly affected by factors other than the genetic backgrounds of the patients' ethnicities. There are few previous studies on treatment responses of chronic GVHD after CBT. The present study suggests a higher response rate and lower mortality in chronic GVHD patients after CBT than that after UR-BMT and PBSCT.[9-16] The low overall incidence despite HLA mismatches, relatively low need for systemic immunosuppression, and positive survival impact indicate milder nature of chronic GVHD after CBT. This may be related to the immature lymphocytes in cord blood that are immunologically tolerant,[17,18] although the basic mechanism is unknown and awaits further investigations.

The present study demonstrated that chronic GVHD after CBT improved EFS and reduced the risk of disease progression. Although graft-versus-malignancy (GVM) effects of chronic GVHD after CBT have not been reported, our results were comparable with previous studies in BMT and PBSCT.[2,19,20] Chronic GVHD following CBT probably has clinically significant GVM effects. Interestingly, chronic GVHD after CBT improved OS as well. These findings contrasted with the unclear effects of chronic GVHD on OS improvement in conventional allogeneic HSCT.[2,19,20] The observations are probably associated with the possible favorable impact of chronic GVHD after CBT on nonrelapse mortality.

The present study provided useful information on chronic GVHD after CBT, although some issues remain to be discussed. First, since our study was retrospective, unrecognized bias may have affected the results. Second, we used the classical diagnostic criteria of chronic GVHD[2] and did not distinguish the late onset acute GVHD that occurs after day 100 from the classic chronic GVHD as the National Institutes of Health consensus project proposed.[21] Third, suggestions by our study on future strategies for cord unit selection and GVHD prophylaxis would be informative. Our multivariate analysis suggested an association of mycophenolate mofetil with development of chronic GVHD, whereas methotrexate was associated with better nonrelapse mortality. Although the mechanism is uncertain, clinicians may prefer to use methotrexate as GVHD prophylaxis. Since GVM effects of chronic GVHD were suggested, risk stratification may be possible in cord blood selection. Using cord blood with higher HLA mismatches for patients with high-risk primary diseases might be permissible. Finally, the applicability of our results to patients with higher body weight with heterogeneous genetic backgrounds in Western countries remains to be discussed. All of our patients received single cord blood units, whereas the majority of cord blood transplants are double cord blood units in Western countries. However, the incidence of chronic GVHD is lower and response to immunosuppressants is

Table 1. Risk factors of overall survival and event-free survival in multivariate analysis

	Overall survival			Event-free survival†			Disease progression			Nonrelapse mortality‡		
Multivariate factors*	**HR 95%**	**CI**	***P***	**HR 95%**	**CI**	***P***	**HR 95%**	**CI**	***P***	**HR 95%**	**CI**	***P***
Patient age, 40 y or older vs younger than 40 y	1.80	1.32-2.44	.0002	1.72	1.36-2.17	<.001	‡‡			2.76	1.86-4.10	<.001
Primary diseases§												
Acute myeloid leukemia	1.00			1.00			1.00			‡‡		
Acute lymphoblastic leukemia	1.42	1.03-1.97	.03	1.30	0.99-1.70	.06	1.14	0.84-1.54	.40	‡‡		
Adult T-cell leukemia/lymphoma	1.38	0.72-2.64	.33	1.54	0.87-2.72	.14	1.83	0.91-3.67	.09	‡‡		
Myelodysplastic syndrome	0.76	0.52-1.11	.16	0.65	0.46-0.91	.01	0.58	0.39-0.86	.01	‡‡		
Chronic myelogenous leukemia	0.50	0.24-1.04	.07	0.64	0.38-1.11	.11	0.61	0.32-1.14	.12	‡‡		
Non-Hodgkin lymphoma	0.82	0.53-1.26	.36	0.86	0.61-1.23	.42	0.84	0.55-1.29	.42	‡‡		
Hodgkin lymphoma	2.44	0.73-8.16	.15	3.41	1.35-8.58	.01	3.58	1.11-11.51	.03	‡‡		
Multiple myeloma	0.59	0.28-1.25	.17	0.79	0.42-1.49	.46	0.77	0.34-1.78	.54	‡‡		
Disease status at transplantation‖												
Early¶	1.00			1.00			1.00			‡‡		
Intermediate#	1.15	0.78-1.71	.49	1.09	0.79-1.52	.60	1.11	0.76-1.62	.60	‡‡		
Advanced**	2.44	1.78-3.35	<.001	2.32	1.78-3.02	<.001	2.65	1.94-3.62	<.001	‡‡		
ABO mismatch												
Match	1.00						‡‡			‡‡		
Major mismatch	0.69	0.50-0.94	.02	‡‡			‡‡			‡‡		
Minor mismatch	0.88	0.63-1.22	.44	‡‡			‡‡			‡‡		
Major/minor mismatch	1.10	0.79-1.54	.56	‡‡			‡‡			‡‡		
Higher no. of serologic HLA disparity for host-versus-graft direction, linear by 1 antigen increase	‡‡			0.80	0.69-0.92	.002	0.79	0.67-0.92	.004	‡‡		
Sex of the donor, female vs male	‡‡			‡‡			1.35	1.06-1.72	.02	‡‡		
Preparative regimen, reduced-intensity vs myeloablative regimen	1.25	0.92-1.70	.15	‡‡			‡‡			‡‡		
Methotrexate use in GVHD prophylaxis	‡‡			‡‡			‡‡			0.58	0.39-0.86	.01
Acute GVHD††												
Grades 0-I	1.00			1.00			‡‡			1.00		
Grade II	0.95	0.72-1.26	.73	0.85	0.67-1.08	.18	‡‡			1.26	0.79-2.02	.33
Grades III-IV	1.77	1.29-2.43	.001	1.37	1.03-1.81	.03	‡‡			3.66	2.31-5.81	<.001
Chronic GVHD	0.71	0.54-0.94	.02	0.64	0.50-0.82	.001	0.65	0.48-0.87	.003	0.66	0.42-1.03	.07

Associations between potential prognostic factors and outcomes were evaluated using Cox proportional hazard regression models. Occurrence of chronic GVHD was included into models as a time-dependent covariate. We used a stepwise procedure at a significance level of 5% to construct prognostic models. The proportional hazards assumption of Cox model was assessed mainly by a graphic approach.

HR indicates hazard ratio; 95% CI, 95% confidence interval; and GVHD, graft-versus-host disease.

*The following variables were considered in univariate analysis: recipient age at transplantation; recipient body weight; HLA mismatch; blood type mismatch; sex mismatch; infused nuclear cell dose and $CD34^+$ cell dose; primary diseases; stage of primary diseases at transplantation; previous history of hematopoietic transplantation; preparative regimen and GVHD prophylaxis; and previous acute GVHD.

†EFS was defined as the time from transplantation to the following events: first progression of the primary diseases, death without progression, and graft failure. Progressions of leukemia and myelodysplastic syndrome were defined as relapse of primary diseases on the basis of morphologic evaluation in the bone marrow or other sites. Progression of malignant lymphoma was defined as involvement of new sites, recurrence in originally involved sites, or increase of more than 25% in original tumor masses. Progression of multiple myeloma was defined as an increase in serum or urine M-component, development of new soft tissue plasmacytomas, and/or increase in the size of soft tissue plasmacytomas.

‡ Nonrelapse mortality was defined as death without progression of the primary diseases.

§Those included acute lymphoblastic leukemia (n=347), acute myeloid leukemia (n=323), adult T-cell leukemia (n=28), myelodysplastic syndrome (n=171), chronic myelogenous leukemia (n=50), non-Hodgkin lymphoma (n=117), Hodgkin lymphoma (n=7), and multiple myeloma (n=29).

‖Disease status at CBT was classified into 3 groups according to the standardized report forms of the International Bone Marrow Transplant Registry (IBMTR).

¶The early group including first complete remission of acute leukemia and lymphoma, first chronic phase of chronic myeloid leukemia, first complete or partial remission of multiple myeloma, and myelodysplastic syndrome refractory anemia.

#The intermediate group including second or subsequent complete remission of acute leukemia and lymphoma, accelerated phase of chronic myeloid leukemia, and second or subsequent complete or partial remission of multiple myeloma.

**The advanced group including refractory disease, relapse or partial response of acute leukemia and lymphoma, blastic crisis of chronic myeloid leukemia, and other malignancies.

††Those included grade 0 (n=252), grade I (n=297), grade II (n=328), grade III (n=148), and grade IV (n=16).

‡‡Those factors were not included in the multivariate prognostic models because those *P* values did not exceed .05 in univariate analysis.

better in CBT than in UR-BMT in Western countries[22]; hence, the milder nature with lower incidence in chronic GVHD following CBT is probably common among Japanese and Westerns patients. The features of chronic GVHD following CBT in Western adult patients require further investigations.

In conclusion, the present study demonstrated that the incidence of chronic GVHD after CBT is probably lower than BMT or PBSCT, and is associated with improved survival. More intensive studies on the biology of chronic GVHD in CBT are warranted for our understanding and better management of chronic GVHD.

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Authorship

Contribution: H.N., S.M., and M.K. designed the research and wrote the paper; T.Y. analyzed data; T.M., K.Y., N.M., E.K., Y. Kodama, T.K., H.S., Y. Kouzai, M.O., Y.O., R.K., M.I., and S. Takahashi performed research; S. Kai, K.K., T.I.-N., and S. Taniguchi managed the data; and S. Kato took leadership of the authors.

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