induction regimens [35]. However, second malignancy should not be an issue with allo-SCT, and no patients in the present study developed second malignancy during a median follow-up period of 35.1 months. Therefore, this conditioning regimen for ALL would be an ideal venue to reintroduce this drug.

Although our analysis has limitations because of its retrospective fashion and small sample size, a medium-dose VP/CY/TBI regimen seems to be a promising treatment for adult patients with ALL, and a prospective study on this regimen for adult ALL is warranted. Although age was not a risk factor for survival in our analysis limited to ALL, age ≥40 years and non-CR at transplantation have been reported as risk factors for TRM, and we confirmed that patients with these risk factors were also at high risk for TRM after medium-dose VP/CY/TBI for hematologic malignancies (not limited to ALL). Therefore, we think that suitable patients for a prospective study are those aged <40 years and those in CR at transplantation.

In summary, the use of medium-dose VP/CY/TBI as a conditioning regimen for adult patients with ALL and related disorders enabled very good disease control without increase in TRM, resulting in better survival of patients.

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ORIGINAL ARTICLE

Heart rate variability during and after peripheral blood stem cell leukapheresis in autologous transplant patients and allogeneic transplant donors

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Abstract Side effects of varying severity are frequent in peripheral blood stem cell harvest (PBSCH). Life-threatening complications associated with PBSCH have also been reported. Heart rate variability (HRV), which reflects sympathovagal balance and autonomic cardiovascular control, has been a subject of intense interest in various diseases precipitating sudden death. Here, we prospectively assessed the impact of leukapheresis on HRV among autologous hematopoietic cell transplant patients and healthy donors. We found that HRV indicators, the standard deviation of normal-to-normal intervals (SDNN) value, the square root of the mean of the sum of squared differences between the adjacent normal-to-normal interval (r-MSSD) value, total frequency (TF), high frequency (HF) and low frequency (LF) powers decreased significantly to morbid levels during leukapheresis (all $P < 0.01$). Morbid changes in SDNN value, TF and LF powers were significantly sustained for 6–9 h after leukapheresis (all $P < 0.05$). Furthermore, TF and LF powers prior to leukapheresis were significantly lower in subjects with symptomatic hypotension than in the other subjects [3282 (3121–4427) vs. 6018 (4983–9816) ms^2, $P = 0.03$; 93 (42–144) vs. 237 (142–360) ms^2, $P = 0.03$, respectively]. Our results suggest that HRV analysis might be of use in evaluating and predicting the adverse effects of cardiovascular complications in PBSCH.

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1 Introduction

Peripheral blood stem cell harvesting (PBSCH) has been widely used for rescue following high-dose chemotherapy, or as an alternative to bone marrow as a stem cell source for allogeneic hematopoietic cell transplantation. The most common side effects are associated with recombinant human granulocyte colony-stimulating factor (rhG-CSF) administration, securing peripheral venous access, or anticoagulation with acid-citrate-dextrose (ACD) solution. These adverse effects are usually transient, not severe and easily controlled with adequate treatment. Severe adverse events in PBSC donors, the majority of which are acute and transient, occur at an incidence of 0.6% [1]. However, although extremely rare, life-threatening complications relating to PBSC donation, including sudden death or transient cardiac arrest, have been reported [2–5]. In several sudden death cases following PBSCH, the underlying mechanisms that led to the occurrence of sudden death have not been clearly described or clarified.

In normal sinus rhythm, the heart rate varies from beat to beat. The impulse generated by the sinus node is affected by the automatic nervous system and various humoral factors. The cardiovascular signal variability of the R–R period (heart rate variability, HRV) is an established tool that can be used to assess autonomic control. HRV assessment enables the evaluation of dynamic changes in the automatic nervous system and humoral factors without an invasive procedure. Recent evidence shows that a decrease in HRV is strongly associated with sudden death

and/or a cardiac event after a myocardial infarction. The usefulness of HRV as a clinical tool has been explored in numerous conditions, such as ischemic sudden death, sustained ventricular tachycardia, myocardial infarction, congestive heart failure, vasovagal syncope, hypertrophic cardiomyopathy, obstructive sleep apnea, diabetic neuropathy and various neurological alterations [6–14]. Two types of analysis, time domain and frequency domain, are included in HRV analysis. In time domain analysis, acknowledged simple markers are the standard deviation of normal-to-normal intervals (SDNN) and the square root of the mean of the sum of squared differences between adjacent normal-to-normal intervals (r-MSSD). In frequency domain analysis, markers include TF, total frequency (0.0001–0.5 Hz); LF, low-frequency power (0.04–0.15 Hz); HF, high-frequency power (0.15–0.4 Hz); and LF/HF ratio. These HRV power spectrum analyses are used to investigate sympathovagal balance, autonomic cardiovascular control and/or target function impairment. The LF component, which is called perfusion rhythmicity, reflects the rennin–angiotensin system or angiokinetic activity. The HF component, called respiratory rhythmicity, reflects breathing variability. Thus, the LF/HF ratio and HF have been used as markers of sympathetic and parasympathetic activity, respectively [15]. The aim of this study was to assess HRV during or after leukapheresis in autologous transplant patients and healthy PBSC donors.

2 Subjects and methods

2.1 Baseline characteristics

In this study, we enrolled 29 subjects (22 allogeneic transplant donors and 7 autologous transplant patients; 10 males, 19 females; median age: 38 years; interquartile range (IQR): 27–53). Median age of the autologous transplant patients and healthy allogeneic donors was 56 (IQR: 33–62) and 35 (IQR: 27–50) years, respectively. Diagnoses of the 7 autologous transplant patients were non-Hodgkin's lymphoma (6 patients) and plasmacytoma (1 patient). All the autologous transplant patients had a history of previous chemotherapy including anthracycline. The median cumulative dose of anthracycline in the 7 autologous transplant patients was 245 mg/m^2 (IQR: 160–297).

The study was conducted in accordance with a protocol approved by the IRB at our institution. Written informed consent was obtained from each patient or healthy donor.

2.2 Peripheral blood collection procedure

Autologous PBSCH was performed during the recovery phase after chemotherapy and was supported by subcutaneous administration of 10 μg/kg/day of rhG-CSF. In allogeneic PBSCH from healthy donors, on the other hand, leukapheresis was initiated following the administration of 10 μg/kg/day of rhG-CSF for 4 days. Of the 29 leukapheresis, 18 were performed using a CS3000 Plus (Baxter, Tokyo, Japan), 4 using an Amicus^{TM} Separator (Baxter, Tokyo, Japan) and 7 using a COBE Spectra (BCT Japan, Tokyo, Japan). In all 7 autologous harvest patients and 7 allogeneic harvest donors, central venous access via the subclavian, internal jugular or femoral vein was secured.

2.3 HRV analysis

In all patients and donors, ambulatory ECG recording was performed for 24 h during the first leukapheresis day but also for 24 h prior to leukapheresis to obtain control data. As control data, we employed the values of HRV indicators obtained during the same time period as leukapheresis on another day before leukapheresis. The data obtained from the 24-h ambulatory ECG recording were stored in a computer. Beat-by-beat cardiac cycle data were obtained by off-line computer analysis methods. The maximum entropy spectral analysis method was used to calculate HRV (MemCalc/CHIRAM version 1, Suwatrust, Tokyo, Japan). This program can perform time domain and frequency domain analyses simultaneously, and is superior to the fast Fourier transform and autoregressive methods in terms of the reproducibility of the original time series. The analysis was automatically performed in short segments and then averaged. In the program, all extrasystolic beats and artifacts were eliminated. We used markers, including heart rate (HR), normal-to-normal intervals (NN), SDNN and r-MSSD in time domain analysis, and TF, LF, HF and LF/HF ratio in frequency domain analysis. The program represents the average values of all markers every 5 min. In the program, TF was defined as the frequency range from 0.0001 to 0.5 Hz and included HF, LF, very low frequency and ultra low frequency. Therefore, at least 3 h of data are needed for TF power measurement; however, since leukapheresis took less than 3 h in 3 of the 29 subjects, TF power during leukapheresis was used in only 26 subjects. We applied the average values of all markers during the leukapheresis periods to assess HRV during leukapheresis, and applied the average values of all markers every 3 h following leukapheresis to assess HRV after leukapheresis.

We compared HRV control data measured for 24 h before leukapheresis between autologous transplant patients and allogeneic transplant donors in all 29 subjects. Control data were available in 26 of the patients, obtained on the day before leukapheresis during the same time period as leukapheresis. We therefore compared HRV data obtained during leukapheresis with control data acquired

during the same time period prior to leukapheresis in 26 evaluable subjects. Furthermore, to evaluate HRV changes after leukapheresis, we compared HRV data obtained during the nine-hour period after leukapheresis with control data obtained during the same time period prior to leukapheresis. This last comparison was possible in 24 subjects.

2.4 Statistical analysis

To evaluate the association between Hb levels just before leukapheresis and HRV indicators, we used Pearson's correlation coefficient. The Mann–Whitney U test was employed to analyze differences in HRV value between autologous transplant patients and healthy donors. The Wilcoxon's rank test was used to compare differences between HRV values during leukapheresis, or transitional changes in HRV values following leukapheresis, with control data measured during the same time period as the measurements taken during or following leukapheresis. Repeated measurements of analysis of variance were used to evaluate the effect of factors [age (>60 or ≤60), sex, weight (>50 or ≤50 kg) and autologous transplant patients] on rate of change in HR and HRV values from before to during leukapheresis. All P values less than 0.05 were considered significant.

3 Results

At HRV measurement, the median processed whole blood volume was 173 ml/kg (IQR: 140–196 ml/kg), the median leukapheresis time was 215 min (IQR: 188–248 min) and the median leukapheresis rate was 43 ml/min (IQR: 37–52 ml/min).

In all subjects, the r-MSSD value, TF, LF and HF powers at baseline showed a significant correlation with Hb levels before leukapheresis [Correlation coefficients: 0.61, 0.45, 0.58 and 0.45 (all $P < 0.05$), respectively]. In the autologous transplant patients, Hb levels before leukapheresis were significantly lower than in the healthy donors [(Median (IQR): 10.2 (9.4–11.5) vs. 13.5 (12.2–14.1) g/dl, respectively, $P = 0.0007$]. The NN and r-MSSD values and LF power were significantly lower in the autologous transplant patients than in the healthy donors in the data for the 24 h prior to leukapheresis [Median (IQR); 755 (709–788) vs. 833 (787–890) ms, $P = 0.03$, 21.8 (15.3–28.0) vs. 30.3 (26.1–39.4) ms, $P = 0.01$, 393 (205–416) vs. 603 (436–761) ms^2, $P = 0.03$, respectively] (Fig. 1).

In all the 26 evaluable subjects, SDNN, r-MSSD, TF, LF and HF values significantly and markedly decreased to morbid levels during leukapheresis (all $P < 0.001$) (Fig. 2). The HR and NN values and LF/HF ratio during leukapheresis did not change significantly compared with the control data. Similarly, among the allogeneic transplant donors, SDNN, r-MSSD, TF, LF and HF values decreased significantly (all $P < 0.05$) and the HR and NN values and LF/HF ratio did not change significantly during leukapheresis. When limited to the autologous transplant patients, HR became significantly elevated during leukapheresis [Median (IQR): 84.3 (77.4–88.4) vs. 93.4 (82.6–97.6) beats/min, respectively, $P = 0.03$]. NN, SDNN, r-MSSD, LF and HF values decreased significantly (all $P < 0.05$) and TF tended to decrease ($P = 0.07$) during leukapheresis. The LF/HF ratio did not change significantly during leukapheresis.

Advanced age (>60) significantly affected HR elevation during leukapheresis in comparison to baseline (Mean ± SD: 76.4 ± 12.9 and 87.7 ± 9.4 beats/min, $P = 0.02$). However, the factors including age (>60 or ≤60), sex, weight (>50 or ≤50 kg) and autologous transplant did not significantly affect the degree of decrease in HRV values during leukapheresis from the baseline.

Furthermore, r-MSSD power improved almost to control levels 6–9 h following leukapheresis (Table 1). On the other hand, SDNN, TF and LF values did not normalize to control levels even 6–9 h following leukapheresis (all $P < 0.05$). Furthermore, HF also did not completely normalize to control levels even 6–9 h following leukapheresis; however, this was not statistically significant ($P = 0.22$).

Of the 29 harvest cases, symptomatic hypotension occurred during leukapheresis in 2 subjects and about 3 h after leukapheresis in 1 subject. All 3 subjects were female, their systolic blood pressure decreasing significantly from 108, 96 and 114 mmHg to 82, 72 and 76 mmHg, respectively. In a 47-year-old female, anginal chest pain and dyspnea occurred; in a 52-year-old female, nausea, blurry vision and chest oppression were evident; and another 52-year-old female experienced nausea and dizziness with hypotension. However, symptomatic hypotension immediately improved with saline infusion, tilting the patient head-down, or discontinuance of leukapheresis. Notably among the HRV indicators, in the three subjects with symptomatic hypotension, TF and LF powers were significantly lower prior to leukapheresis than those in the other subjects [3282 (3121–4427) vs. 6018 (4983–9816) ms^2, $P = 0.03$; 93 (42–144) vs. 237 (142–360) ms^2, $P = 0.03$, respectively].

4 Discussion

In the present study we detected that the time domain indicators including SDNN and r-MSSD, and the frequency domain indicators including TF, HF and LF markedly decreased during leukapheresis and that this decrease was sustained over several hours after leukapheresis.

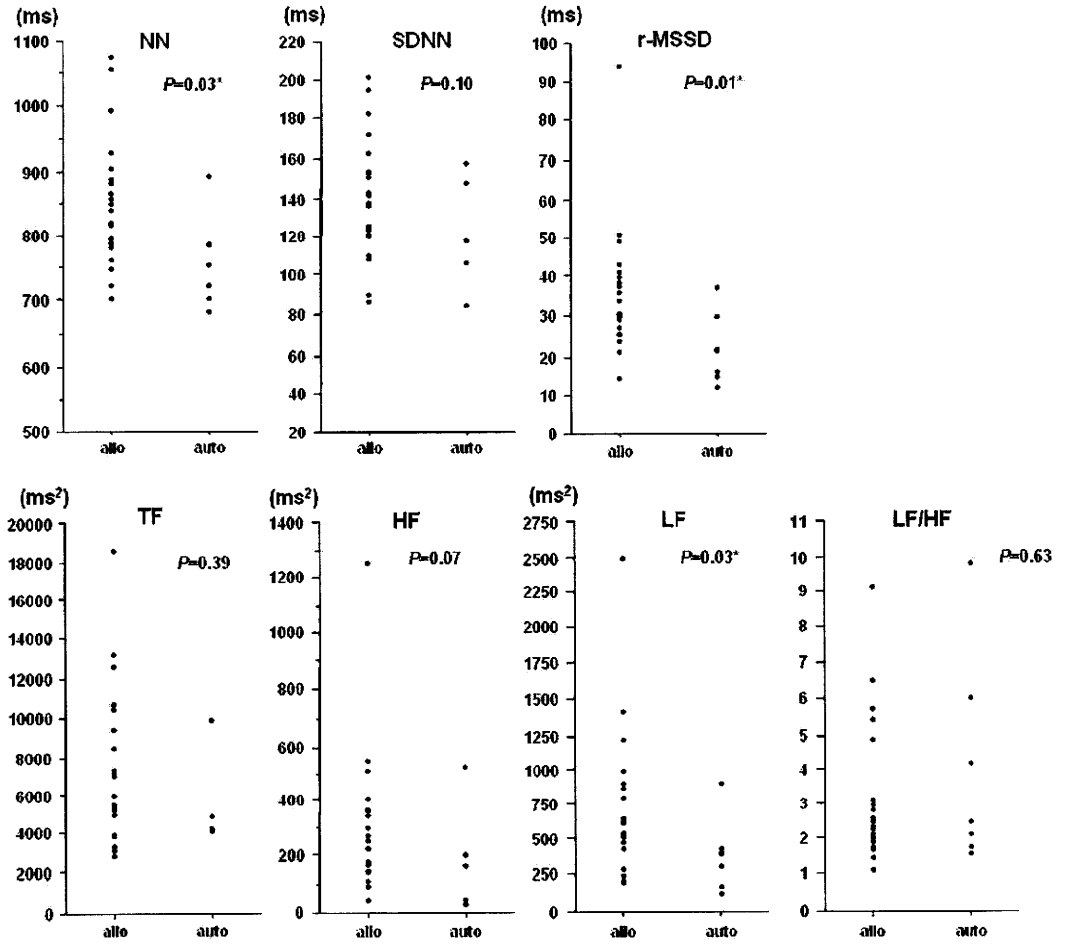

Fig. 1 Comparison of heart rate variability (HRV) indicator values between autologous transplant patients and healthy donors. NN, r-MSSD and LF were significantly lower in the autologous hematopoietic cell transplant patients than in the healthy donors. *auto* autologous hematopoietic cell transplant patients, *allo* allogeneic hematopoietic cell transplant healthy donors, *NN* normal-to-normal intervals, *SDNN* standard deviation of normal-to-normal intervals, *r-MSSD* square root of mean of sum of squared differences between adjacent normal-to-normal intervals, *TF* total frequency, *HF* high frequency, *LF* low frequency

Interestingly, in subjects who had symptomatic hypotension, TF and LF powers at baseline were significantly lower than for subjects without adverse cardiovascular effects.

It is reported that in patients with chronic heart failure, those with an SDNN value of less than 44 ms are at risk of cardiac events and all-cause mortality [16]. Surprisingly, in the 6 (86%) out of the 7 autologous transplant patients and in 7 (32%) out of the 22 allogeneic transplant donors, the SDNN value decreased to less than 44 ms during leukapheresis. Additionally, in 2 out of the 3 subjects with symptomatic hypotension, SDNN values decreased to less than 44 ms during leukapheresis.

Although we cannot clearly explain the underlying mechanism of HRV alteration during leukapheresis, we speculate that such a major change in HRV indicators was induced by heightened sympathetic activity and parasympathetic withdrawal, mediated by a hemodynamical or neural effect of the leukapheresis procedure and/or other pathogenesis, including altered concentrations of electrolytes in serum and metabolic alkalosis [17]. Both r-MSSD and HF are known to reflect parasympathetic activity; thus the significant reduction in the r-MSSD value and HF power suggested parasympathetic activity was reduced during leukapheresis. It has been reported that

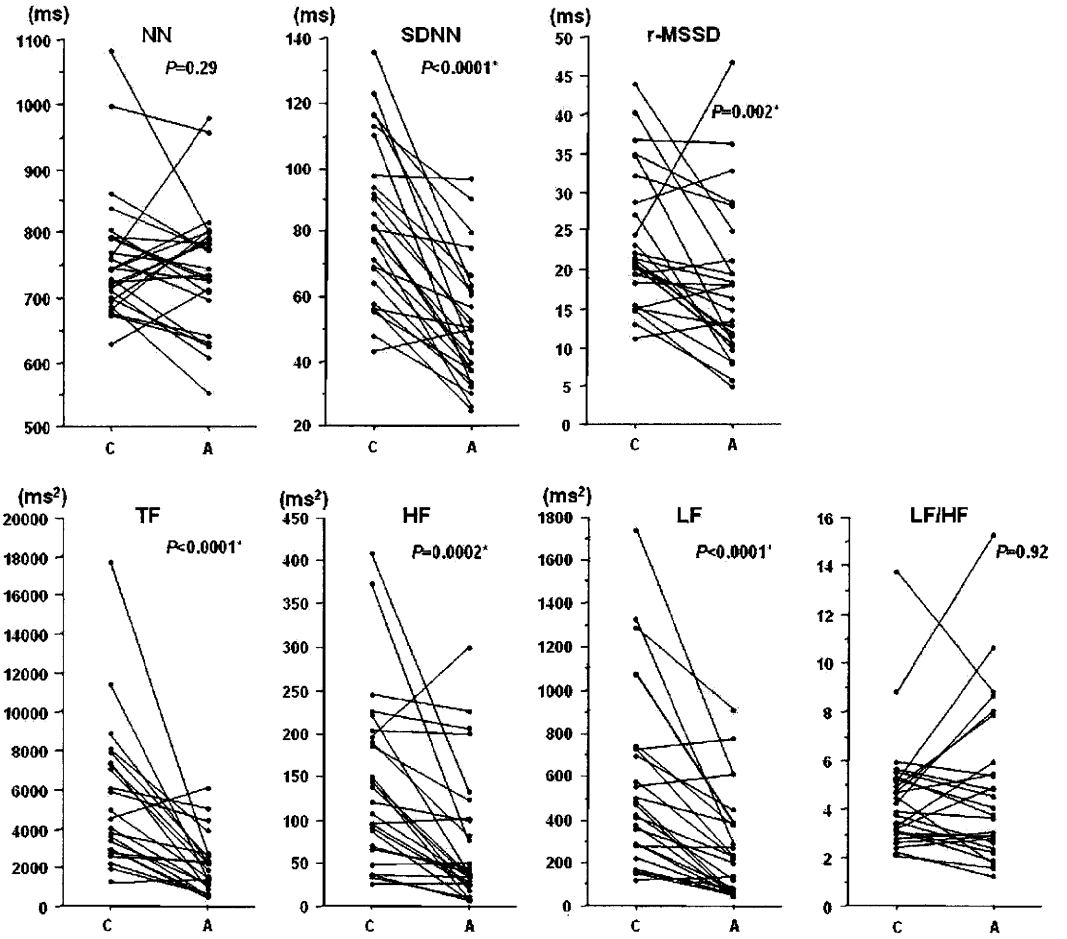

Fig. 2 Comparison of control data and heart rate variability (HRV) indicator values during leukapheresis. Many HRV indicators decreased significantly during leukapheresis. *C* control HRV values, *A* HRV values during leukapheresis, *NN* normal-to-normal intervals, *SDNN* standard deviation of normal-to-normal intervals, *r-MSSD* square root of mean of sum of squared differences between adjacent normal-to-normal intervals, *TF* total frequency, *HF* high frequency, *LF* low frequency

parasympathetic withdrawal is seen in patients with congestive heart failure and parasympathetic withdrawal causes a decrease in HRV [18]. Therefore, we speculated that the suppression of parasympathetic activity might be causally related to critical cardiovascular complications in PBSCH.

In this study, LF power also significantly decreased during leukapheresis. In recent reports, reduced LF spectral power was also identified as a risk of all-cause mortality [19] and sudden cardiac death [20] in chronic heart failure. LF power is more complicated because it is jointly mediated by the sympathetic and parasympathetic nervous systems [21]. Reduced R–R interval variability and parasympathetic activity withdrawal might also be associated with reduced LF power.

In addition, citrate-based anticoagulants, such as the ACD solution used for leukapheresis, decrease the concentration of electrolytes in serum by chelation and cause hypocalcemia, hypomagnesemia [22] and intermittent hypotension [23] in leukapheresis. A previous report showed that electrolyte abnormalities mediated by citrate, such as hypocalcemia, may change HRV [24].

Life-threatening complications associated with PBSC donation reportedly occur after, rather than during, leukapheresis [2, 3]. Notably, our data showed that abnormal HRV indicators persisted 6–9 h after leukapheresis

Table 1 Changes in HRV indicators following leukapheresis

	0–3 h [Median (IQR)]			3–6 h [Median (IQR)]			6–9 h [Median (IQR)]		
	Control	Post-leukapheresis	*P*	Control	Post-leukapheresis	*P*	Control	Post-leukapheresis	*P*
SDNN (ms)	92 (74–110)	75 (65–82)	0.002*	96 (82–110)	69 (60–86)	0.002*	86 (74–103)	75 (60–91)	0.01*
r-MSSD (ms)	26 (15–37)	23 (13–31)	0.002*	30 (24–37)	19 (12–34)	0.001*	33 (22–42)	28 (15–42)	0.34
TF (ms^2)	5996 (3861–10229)	4291 (2925–5188)	0.02*	5723 (3408–8008)	3772 (2760–6092)	0.04*	4909 (3647–7392)	3097 (2556–5145)	0.01*
HF (ms^2)	157 (44–266)	107 (27–196)	0.02*	215 (83–300)	74 (28–235)	0.002*	277 (120–430)	180 (46–417)	0.22
LF (ms^2)	489 (382–751)	471 (136–685)	0.04*	523 (340–846)	287 (160–605)	0.0008*	688 (387–879)	337 (190–579)	0.0004*
LF/HF	3.6 (2.9–5.1)	4.0 (3.3–5.8)	0.27	2.9 (2.3–4.5)	3.1 (2.1–7.3)	0.10	2.6 (1.5–5.5)	2.3 (1.1–3.6)	0.15

IQR interquartile range, *SDNN* standard deviation of normal-to-normal intervals, *r-MSSD* square root of mean of sum of squared differences between adjacent normal-to-normal intervals, *TF* total frequency, *HF* high frequency, *LF* low frequency

* $P < 0.05$

(Table 1). The altered concentration of electrolytes in serum, mediated by ACD solution or hypovolemia, which remained long after leukapheresis, might cause symptomatic hypotension and reduce HRV. Such pathologic conditions might, in extremely rare instances, lead to severe cardiovascular complications in a patient with latent cardiovascular diseases.

In the 3 subjects with symptomatic hypotension, tachycardia was not observed at the onset of hypotension (Subject 1: 82/46 mmHg, 72 beats/min; Subject 2: 72/42 mmHg, 66 beats/min; Subject 3: 76/48 mmHg, 60 beats/min). Vasovagal hypotension, which occasionally occurs during leukapheresis, is a neurally mediated reaction due to blood pressure decreases without compensatory tachycardia. In patients with vasovagal hypotension, bradycardia is therefore often observed. We therefore speculate that vasovagal reflex played a critical role in the development of symptomatic hypotension in these subjects.

Finally, some HRV indicators in the autologous transplant patients were significantly lower than those in healthy donors. In the present study, ages were higher and Hb levels before leukapheresis were lower in autologous transplant patients than in the healthy donors. Furthermore, all patients scheduled to receive an autologous transplant had a history of chemotherapy. Chemotherapy including anthracycline has been reported to reduce the values of HRV indicators [25]. Therefore, decreased values of some HRV indicators might have been caused by advanced age, anemia and/or the cumulative toxicity of chemotherapy, especially that caused by anthracycline drugs.

The major obstacle which precludes translating HRV analysis into clinical practice is that we can analyze HRV during leukapheresis only retrospectively. However, our data suggest that HRV prior to leukapheresis might have potential as a useful non-invasive tool for predicting autonomic or cardiovascular complications. Therefore, in the future, we need to examine the prognostic value of HRV for autonomic or cardiovascular complications in more detail by using a larger cohort.

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Conflict of interest statement All the authors declare no conflict of interest.

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Transplantation of allogeneic hematopoietic stem cells for adult T-cell leukemia: a nationwide retrospective study

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Allogeneic hematopoietic stem cell transplantation (HSCT) is increasingly used as a curative option for adult T-cell leukemia (ATL), an intractable mature T-cell neoplasm causally linked with human T-cell leukemia virus type I (HTLV-I). We compared outcomes of 386 patients with ATL who underwent allogeneic HSCT using different graft sources: 154 received human leukocyte antigen (HLA)–matched related marrow or peripheral blood; 43 received HLA-mismatched related marrow or peripheral blood; 99 received unrelated marrow; 90 received single unit unrelated cord blood. After a median follow-up of 41 months (range, 1.5-102), 3-year overall survival for entire cohort was 33% (95% confidence interval, 28%-38%). Multivariable analysis revealed 4 recipient factors significantly associated with lower survival rates: older age (> 50 years), male sex, status other than complete remission, and use of unrelated cord blood compared with use of HLA-matched related grafts. Treatment-related mortality rate was higher among patients given cord blood transplants; disease-associated mortality was higher among male recipients or those given transplants not in remission. Among patients who received related transplants, donor HTLV-I seropositivity adversely affected disease-associated mortality. In conclusion, allogeneic HSCT using currently available graft source is an effective treatment in selected patients with ATL, although greater effort is warranted to reduce treatment-related mortality. (*Blood*. 2010;116(8):1369-1376)

Introduction

Adult T-cell leukemia (ATL) is a mature T-cell neoplasm developing in a minority of persons infected with human T-cell leukemia virus type I (HTLV-I), the first retrovirus isolated from a human malignant disease.[1-4] HTLV-I is estimated to infect 10 to 20 million people worldwide and is endemic in some areas of Japan, sub-Saharan Africa, the Caribbean Basin, and South America.[5,6] The area with the highest HTLV-I prevalence is the Kyushu district in southwestern Japan, where more than 10% of the general population is infected and the cumulative incidence of developing ATL among adult virus carriers is estimated at approximately 6.6% for males and 2.1% for females.[7] The onset of ATL after HTLV-I infection appears to require a long latency period because the median age at diagnosis ranges from 40 to 60 years in most endemic regions where mother-to-child viral transmission had been previously common.[4-6]

Clinical manifestation of ATL is heterogeneous and characterized by various degrees of lymphadenopathy, abnormal lymphocytosis, hepatosplenomegaly, skin lesions, and hypercalcemia, dividing the disease into 4 subtypes: acute, lymphomatous, chronic, and smoldering.[8] Patients with acute or lymphomatous type had extremely poor prognosis, mainly because of resistance to a variety of cytotoxic agents and susceptibility to opportunistic infections. Chronic and smoldering forms have relatively indolent clinical courses but can transform into more aggressive subtypes. During the past 3 decades since the clinical discovery of ATL,[1] the results of conventional cytotoxic chemotherapy remain dismal because of low response rates and lack of long-term efficacy. The

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median survival time that followed the best clinical results to date is approximately 13 months[9,10]; complete response can only be achieved in 25%-40% of treated cases and most of them eventually relapsed with the median progression-free survival time of 5 to 7 months, whereas available treatment options are extremely limited in those who failed initial chemotherapy.[11-14]

Although the early experience of ablative chemoradiotherapy with autologous hematopoietic stem cell rescue for ATL resulted in a high incidence of relapse and fatal toxicities,[15] allogeneic hematopoietic stem cell transplantation (HSCT) has been explored as a promising alternative that can provide long-term remission in a proportion of patients with ATL.[16-19] Although the mechanisms by which allografting can eradicate HTLV-I–infected neoplastic T cells are not fully elucidated, several reports have suggested the role of graft-versus-HTLV-I or graft-versus-ATL effects.[20-23] Over the past decade, improved access to alternative stem cell sources and the development of less toxic conditioning regimens have led to a rapid increase in the number of cases of ATL treated with allogeneic HSCT, albeit without consistent efficacy.[24-30] Therefore, we conducted a nationwide retrospective cohort study to identify pretransplantation factors that affect survival after allografting for ATL, with special emphasis on the effect of graft source: we compared the outcomes of human leukocyte antigen (HLA)–mismatched related bone marrow or peripheral blood transplantation, unrelated bone marrow transplantation, and unrelated cord blood transplantation with those of HLA-matched related bone marrow or peripheral blood transplantation as treatment for ATL. We also evaluated the effect of donor HTLV-I serostatus on outcomes among patients who received transplants from related donors.

Methods

Collection of data

Data on 417 patients with acute or lymphomatous type ATL who had received T-cell–replete allogeneic bone marrow, peripheral blood, or cord blood transplantation between January 1, 1996, and December 31, 2005, were collected through the 3 largest hematopoietic cell transplant registries in our country: the Japan Society for Hematopoietic Cell Transplantation (JSHCT), the Japan Marrow Donor Program (JMDP), and the Japan Cord Blood Bank Network (JCBBN). The patients were included from 102 transplant centers; the data were updated as of December 2008. To evaluate the effect of HTLV-I infection in donors on transplantation outcomes, additional questionnaires were sent to 77 centers in January 2010 to retrieve data on donor HTLV-I serostatus in 217 related transplants registered with the JSHCT. Our analysis included patients for whom there was data on age at transplantation, sex, donor type, stem cell source, and agents used in the conditioning regimen and graft-versus-host disease (GVHD) prophylaxis. Twenty-two patients who missed any of these data, and 8 patients who had a history of prior autologous or allogeneic stem cell transplantation were excluded from the analysis. One patient who had received an ex vivo T-cell–depleted graft was also excluded. Two independent physicians reviewed the quality of collected data, and a total of 386 patients (209 males and 177 females), with a median age of 51 years (range, 18-79 years), were found to fulfill the inclusion criteria: 197 patients from JSHCT, 99 from JMDP, and 90 from JCBBN. No overlapping cases were identified. Data on engraftment or graft failure were missing in 23 patients. Data on acute GVHD were not available in 53 patients because of early death or missing data.

The JSHCT registry currently includes more than 390 transplant centers variously located in Japan and collects data on transplantation by use of autologous or related stem cell grafts. The JMDP includes more than 190 centers and collects data on unrelated bone marrow transplantation. The JCBBN, a national network of 11 cord blood banks, collects data on unrelated cord blood transplantations reported individually from more than 220 transplant centers to each bank. Participating centers to these registries are requested to report each type of transplantation consecutively and longitudinally. Until 2005, the 3 registries were operated separately from one another; however, a project attempting to unify them has been launched via development of the Transplant Registry Unified Management Program, which enables participating centers to use a shared format for data submission to each registry.[31] All unrelated donor transplants in Japan were facilitated through the JMDP and JCBBN, although peripheral blood donation from unrelated volunteers has not yet been instituted as of March 2010. The study was approved by the data management committees of the JSHCT, JMDP, and JCBBN, as well as by the institutional review boards of Kyoto University, Graduate School of Medicine, where this study was organized.

End points

The primary end point of the study was overall survival, defined as the time from the date of transplantation until date of death from any cause. Patients who remained alive at the time of last follow-up were censored. Reported causes of death were reviewed and categorized into disease-associated or treatment-associated deaths. Disease-associated deaths were defined as deaths from relapse or progression of ATL among patients who survived for at least 30 days after transplantation. Treatment-related deaths were defined as any death other than disease-associated deaths. Neutrophil recovery was considered to have occurred when an absolute neutrophil count exceeded 0.5×10^9/L for 3 consecutive days after transplantation. Primary graft failure was evaluated in patients who survived at least 30 days and was defined as no evidence of neutrophil recovery after transplantation. Acute and chronic GVHD were diagnosed and graded using traditional criteria by the physicians who performed transplantations at each center.[32,33] The incidence of acute GVHD was evaluated in patients who survived for at least 7 days, and that of chronic GVHD was evaluated in patients who survived for at least 100 days.

Statistical analysis

Descriptive statistics were used for summarizing variables related to patient demographics and transplant characteristics. Comparisons among the groups were performed by use of the χ^2 statistic or extended Fisher exact test as appropriate for categorical variables, and the Kruskal-Wallis test for continuous variables. The probability of overall survival was estimated according to the Kaplan-Meier method, and univariable comparisons among the groups were made using the log-rank test. Probabilities of acute and chronic GVHD, treatment-related mortality, and disease-associated mortality were estimated with the use of cumulative incidence curves to accommodate the following competing events[34]: death without GVHD for acute and chronic GVHD, disease-associated death for treatment-related mortality, and treatment-related death for disease-associated mortality. Data on patients who were alive at the time of last follow-up were censored. Cox proportional-hazards regression was used to evaluate variables potentially affecting overall survival, whereas Fine and Gray proportional-hazard model was used to evaluate variables affecting other outcomes.[35] The variables considered were recipient age group ($\leq$ 50 years or $>$ 50 years at transplantation), recipient sex; disease status before transplantation; type of conditioning regimen; type of GVHD prophylaxis; type of graft source; time from diagnosis to transplantation (within 6 months or longer than 6 months); and year of transplantation. Only factors differing in distribution among the graft source groups and factors associated with outcomes by univariable comparison were included in the final models. The effect of donor HTLV-I seropositivity on outcomes after related donor transplantation was also evaluated by univariable and multivariable analysis with the use of data on 156 patients given transplants from siblings or other related family members for whom data on the HTLV-I serostatus were available. Results were expressed as hazard ratios and their 95% confidence interval (CI). All tests were 2-sided, and a P value of less than .05 was considered to indicate statistical significance. All statistical analyses were performed with STATA software (Version 11; Stata Corporation).

Results

Patients

Table 1 shows characteristics of the patients and transplantation procedures. Compared with HLA-matched related bone marrow or

Table 1. Characteristics of allografted patients with ATL

Patient variables	No. of recipients by graft source type (%)				
	HLA-matched related bone marrow or peripheral blood (N = 154)	HLA-mismatched related bone marrow or peripheral blood (N = 43)	Unrelated bone marrow (N = 99)	Unrelated cord blood (N = 90)	*P*
Age range at transplantation, y					.001
30 or younger	4 (3)	1 (2)	2 (2)	1 (1)	
30-40	21 (14)	4 (9)	8 (8)	3 (3)	
40-50	56 (36)	12 (28)	44 (44)	21 (23)	
50-60	57 (37)	22 (51)	43 (43)	47 (52)	
Older than 60	16 (10)	4 (9)	2 (2)	18 (20)	
Sex					.257
Male	76 (49)	21 (49)	60 (61)	52 (58)	
Female	78 (51)	22 (51)	39 (39)	38 (42)	
Disease status					.001
Complete remission	50 (32)	7 (16)	35 (35)	26 (29)	
Not in complete remission	102 (66)	35 (81)	52 (53)	57 (63)	
Unknown	2 (1)	1 (2)	12 (12)	7 (8)	
Conditioning regimen					< .001
CY-TBI or BU-CY	51 (33)	6 (14)	43 (43)	14 (16)	
Purine analog–containing	72 (47)	23 (53)	37 (37)	64 (71)	
Others	31 (20)	14 (33)	19 (19)	12 (13)	
GVHD prophylaxis					< .001
Cyclosporine-based	146 (95)	11 (26)	29 (29)	60 (67)	
Tacrolimus-based	6 (4)	31 (72)	68 (69)	25 (28)	
Others	2 (1)	1 (2)	2 (2)	5 (6)	
Source of stem cells					< .001
Bone marrow	46 (30)	12 (28)	99 (100)	-	
Peripheral blood	106 (69)	31 (72)	-	-	
Bone marrow + peripheral blood	2 (1)	0 (0)	-	-	
Cord blood	-	-	-	90 (100)	
HLA compatibility*					
Matched	154 (100)	-	83 (84)	3 (3)	< .001
One-antigen mismatch		19 (44)	12 (12)	29 (32)	
Two-antigen mismatch		13 (30)	0 (0)	57 (63)	
Three-antigen mismatch		7 (16)	0 (0)	1 (1)	
Uncertain/missing		4 (9)	4 (4)	0 (0)	
Time from diagnosis to transplantation					< .001
6 months or less	92 (60)	26 (60)	22 (22)	49 (54)	
More than 6 months	52 (34)	16 (37)	75 (76)	41 (46)	
Uncertain/missing	10 (6)	1 (2)	2 (2)	0 (0)	
Year of transplantation					< .001
1995-1999	18 (12)	1 (2)	5 (5)	0 (0)	
2000-2002	66 (43)	15 (35)	26 (26)	12 (13)	
2003-2005	70 (45)	27 (63)	68 (69)	78 (87)	
Follow-up of survivors†					
Median mo (range)	40.5 (1.5-102.3)	36.7 (8.8-85.1)	40.2 (16.0-81.2)	48.9 (1.6-73.5)	.847

ATL indicates adult T-cell leukemia; HLA, human leukocyte antigen; GVHD, graft-versus-host disease; CY-TBI, cyclophosphamide with total-body irradiation; BU-CY, busulfan and cyclophosphamide; purine analog–containing, conditioning regimens containing fludarabine, cladribine, or pentostatin; cyclosporine-based, cyclosporine with or without other agents; and tacrolimus-based, tacrolimus with or without other agents.

*HLA compatibility was defined according to the results of serologic or low-resolution molecular typing for HLA-A, HLA-B, and HLA-DR antigens.

†Data are time interval in months.

peripheral blood recipients, HLA-mismatched bone marrow or peripheral blood recipients were more likely to receive tacrolimus for GVHD prophylaxis; unrelated bone marrow recipients took a longer time from diagnosis to transplantation, were more likely to have attained complete remission at transplantation, and were more likely to receive tacrolimus for GVHD prophylaxis; unrelated cord blood recipients were older, underwent transplantation more recently, and were more likely to receive purine analog–containing conditioning regimens. All unrelated cord blood recipients received a single cord blood unit that was not manipulated ex vivo. The median weight of unrelated cord blood recipients was 52.0 kg (range, 31.0-90.2 kg); the median dose of nucleated cells and $CD34^+$ progenitor cells in the grafts, measured before freezing, was 2.55×10^7 (range, $1.39\text{-}5.34 \times 10^7$) and 0.79×10^5 (range, $0.07\text{-}3.15 \times 10^5$) per kg of recipient body weight, respectively.

Engraftment and GVHD

Of 310 patients who survived 30 days after transplantation and were evaluable for engraftment, primary graft failure was reported in 2 (6%) of 35 recipients of HLA-mismatched related grafts and in 12 (17%) of 70 recipients of unrelated cord blood, whereas the remaining 296 patients had evidence of initial engraftment. Acute GVHD of grades II, III, or IV occurred in 158 (47%) of 333

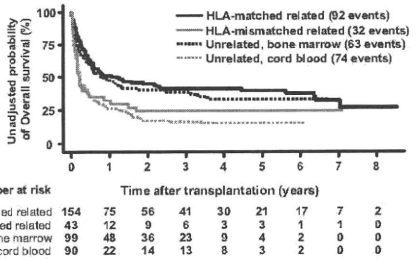

Figure 1. Unadjusted probability of overall survival according to type of graft source. The unadjusted Kaplan-Meier estimates of overall survival stratified according to type of graft source are shown.

evaluable patients; 69 (49%) of 140 HLA-matched related bone marrow or peripheral blood recipients, 20 (56%) of 36 HLA-mismatched related bone marrow or peripheral blood recipients, 40 (44%) of 91 unrelated bone marrow recipients, and 29 (44%) of 66 unrelated cord blood recipients. In a multivariable analysis, rates of grades II to IV acute GVHD did not significantly differ among the 4 groups (supplemental Table 1; available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article). Chronic GVHD occurred in 94 (48%) of 195 evaluable patients at a significantly lower rate among the unrelated cord blood recipients than among HLA-matched graft recipients (hazard ratio, 0.25; 95% CI, 0.10-0.61, $P = .002$).

Relapse and disease progression

Of 333 patients who survived 30 days after transplantation, 136 patients experienced relapse or progression of ATL at a median of 76 days (range, 1-1964 days) after transplantation. ATL recurred or progressed in 52 (37%) of 141 recipients of HLA-matched related grafts, in 19 (51%) of 37 recipients of HLA-mismatched related grafts, in 27 (32%) of 85 recipients of unrelated bone marrow, and 38 (54%) of 70 recipients of unrelated cord blood. Of 113 patients who were evaluable for the date of relapse or disease progression, the median time from transplantation to relapse or progression of ATL was 65.5 days (range, 1-1964 days) for HLA-matched related bone marrow or peripheral blood recipients, 63 days (range, 22-269 days) for HLA-mismatched related bone marrow or peripheral blood recipients, 152 days (range, 42-819 days) for unrelated bone marrow recipients, and 83 days (range, 7-596 days) for unrelated cord blood recipients.

Overall survival

Of 386 patients included in the study, a total of 125 patients were alive and 101 patients were alive in continuous complete remission after a median follow-up of 41 months (range, 1.5-102 months). The unadjusted 3-year probability of overall survival was 33% (95% CI, 28%-38%) for the whole cohort; 41% (95% CI, 33%-49%) in HLA-matched related graft recipients; 24% (95% CI, 12%-38%) in HLA-mismatched related graft recipients; 39% (95% CI, 29%-49%) in unrelated bone marrow recipients; and 17% (95% CI, 9%-25%) in unrelated cord blood recipients (Figure 1). The median overall survival time after transplantation was 9.8 months for HLA-matched related bone marrow or peripheral blood recipients, 2.5 months for HLA-mismatched related bone marrow or peripheral blood recipients, 9.6 months for unrelated bone marrow recipients, and 2.6 months for unrelated cord blood recipients. Patients who received transplants in complete remission had a higher probability of survival than those who received transplants not in complete remission (51% [95% CI, 41%-60%] vs 26% [95% CI, 20%-31%], $P < .001$). Multivariable analyses revealed 4 factors that adversely affected overall survival: older recipient age (> 50 years; hazard ratio, 1.56; 95% CI, 1.14-2.12, $P = .005$), male recipient (hazard ratio, 1.37; 95% CI, 1.07-1.77, $P = .014$), lack of complete remission at transplantation (hazard ratio, 2.01; 95% CI, 1.50-2.71, $P < .001$), and transplantation of unrelated cord blood. Hazard ratios for death among recipients of HLA-mismatched related transplants, unrelated bone marrow transplants, and unrelated cord blood transplants, compared with that among recipients of HLA-matched related transplants, were 1.55 (95% CI, 0.98-2.45, $P = .063$), 1.24 (95% CI, 0.82-1.88, $P = .312$), and 2.08 (95% CI, 1.43-3.02, $P < .001$), respectively (Table 2).

Treatment-related mortality and disease-associated mortality

Overall, 161 (43%) of 376 evaluable patients succumbed to treatment-related complications. Cumulative incidence of treatment-related mortality at 3 years after transplantation was 37% (95% CI, 29%-45%) in HLA-matched related bone marrow or peripheral blood recipients, 43% (95% CI, 28%-57%) in HLA-mismatched related bone marrow or peripheral blood recipients, 42% (95% CI, 32%-51%) in unrelated bone marrow recipients, and 52% (95% CI, 41%-62%) in unrelated cord blood recipients (Figure 2A). When adjusted by multivariable analysis, patients given unrelated cord blood (hazard ratio, 1.77; 95% CI, 1.10-2.86, $P = .019$) had higher treatment-related mortality rates (Table 2).

Deaths from progression of ATL occurred in 90 (24%) patients. Cumulative incidence of disease-associated mortality at 3 years after transplantation was 21% (95% CI, 14%-28%) in HLA-matched related bone marrow or peripheral blood recipients, 32% (95% CI, 19%-47%) in HLA-mismatched related bone marrow or peripheral blood recipients, 19% (95% CI, 12%-28%) in unrelated bone marrow recipients, and 30% (95% CI, 21%-40%) in unrelated cord blood recipients (Figure 2B). In multivariable analysis, patients given transplants not in remission (hazard ratio, 2.55; 95% CI 1.50-4.33, $P = .001$) or male recipients (hazard ratio, 1.86; 95% CI, 1.17-2.95, $P = .008$) had higher rates of disease-associated mortality (Table 2).

Causes of death after transplantation are summarized in Table 3. Of the 161 patients who died of treatment-related complications, 51 (32%) succumbed to infection and 53 (33%) to organ failure. Treatment-related events were principal causes of early death, whereas death from relapse or progression of ATL was more common later than 100 days after transplantation, irrespective of types of graft source.

Effect of donor HTLV-I serostatus on outcomes

Data on donor HTLV-I serostatus were available for analysis in 156 of 197 patients given related transplants; 68 received transplants from an HTLV-I–seropositive donor and 88 from an HTLV-I–seronegative donor. Patients who received transplants from HTLV-I–seropositive donors and those from HTLV-I–seronegative donors had similar background characteristics (supplemental Table 2). Among 113 patients who had data on donor HTLV-I serostatus and maintained or attained complete remission after transplantation, relapse of ATL was observed in 18 (38%) of 48 patients who received transplants from an HTLV-I–seropositive donor, and 16 (25%) of 65 patients who received transplants from an HTLV-I–seronegative donor with a median follow-up time for survivors of 40 months (range, 7.3-102 months). In univariable and

Table 2. Multivariable analysis of transplantation outcomes

Variables	Overall survival			Treatment-related mortality			Disease-associated mortality		
	Number*	Hazard ratio (95% CI)	P	Number*	Hazard ratio (95% CI)	P	Number*	Hazard ratio (95% CI)	P
Age group, y									
50 or younger	109/177	1.00	Reference	70/173	1.00	Reference	35/173	1.00	Reference
Older than 50	152/209	1.56 (1.14-2.12)	.005	91/203	1.40 (0.96-2.05)	.084	55/203	1.22 (0.71-2.10)	.465
Sex of recipient†									
Female	105/177	1.00	Reference	68/171	-	-	31/171	1.00	Reference
Male	156/209	1.37 (1.07-1.77)	.014	93/205	-	-	59/205	1.86 (1.17-2.95)	.008
Disease status									
Complete remission	60/118	1.00	Reference	43/117	1.00	Reference	16/117	1.00	Reference
Not in complete remission	184/246	2.01 (1.50-2.71)	< .001	106/238	1.30 (0.92-1.84)	.137	70/238	2.55 (1.50-4.33)	.001
Unknown	17/22	2.01 (1.15-3.50)	.014	12/21	1.74 (0.89-3.40)	.105	4/21	1.42 (0.45-4.52)	.554
Conditioning regimen									
CY-TBI or BU-CY	68/114	1.00	Reference	45/112	1.00	Reference	21/112	1.00	Reference
Purine analog–containing	136/196	1.05 (0.75-1.48)	.777	79/191	0.86 (0.56-1.32)	.487	52/191	1.34 (0.72-2.48)	.360
Others	57/76	1.26 (0.86-1.84)	.240	37/73	1.23 (0.78-1.95)	.377	17/73	1.10 (0.56-2.13)	.784
GVHD prophylaxis‡									
Cyclosporine-based	160/246	1.00	Reference	99/241	1.00	Reference	56/241	1.00	Reference
Tacrolimus-based	91/130	1.09 (0.78-1.51)	.614	55/127	1.13 (0.72-1.75)	.599	33/127	1.05 (0.57-1.93)	.887
Others	10/10	1.74 (0.89-3.42)	.105	7/8	2.29 (1.14-4.62)	.020	1/8	0.32 (0.04-2.42)	.268
Type of graft source									
Matched related bone marrow or peripheral blood	92/154	1.00	Reference	57/149	1.00	Reference	30/149	1.00	Reference
Mismatched related bone marrow or peripheral blood	32/43	1.55 (0.98-2.45)	.063	18/42	1.12 (0.59-2.12)	.722	13/42	1.50 (0.67-3.37)	.329
Unrelated bone marrow	63/99	1.24 (0.82-1.88)	.312	41/99	1.19 (0.71-1.98)	.512	22/99	1.06 (0.46-2.48)	.888
Unrelated cord blood	74/90	2.08 (1.43-3.02)	< .001	45/86	1.77 (1.10-2.86)	.019	25/86	1.49 (0.80-2.80)	.211
Time from diagnosis to transplantation									
6 months or less	128/189	1.00	Reference	81/183	1.00	Reference	41/183	1.00	Reference
More than 6 months	125/184	1.03 (0.78-1.35)	.834	76/180	0.86 (0.61-1.22)	.395	45/180	1.32 (0.82-2.12)	.258
Uncertain/missing	8/13	1.01 (0.49-2.09)	.971	4/13	0.64 (0.25-1.60)	.340	4/13	1.93 (0.77-4.87)	.163
Year of transplantation									
1995-1999	18/24	1.00	Reference	11/24	1.00	Reference	7/24	1.00	Reference
2000-2002	85/119	1.01 (0.58-1.74)	.979	56/113	1.13 (0.59-2.13)	.716	23/113	0.61 (0.26-1.46)	.269
2003-2005	158/243	0.73 (0.41-1.32)	.296	94/239	0.75 (0.37-1.51)	.416	60/239	0.70 (0.29-1.73)	.442

CI indicates confidence interval; GVHD, graft-versus-host disease; CY-TBI, cyclophosphamide with total-body irradiation; BU-CY, busulfan and cyclophosphamide; purine analog–containing, regimens containing fludarabine, cladribine or pentostatin; cyclosporine-based, cyclosporine with or without other agents; tacrolimus-based, tacrolimus with or without other agents; and Reference, reference category in regression models.

*Number of events/number of evaluable patients.

†Sex of recipient was not included as a confounder in the multivariable final model for treatment-related mortality because it was not found to be a significant factor in univariable comparison.

‡GVHD prophylaxis other than cyclosporine- or tacrolimus-based regimen was not considered as a significant variable associated with treatment-related mortality because of the small number of patients in this group.

multivariable analysis, patients who received transplants from an HTLV-I–seropositive donor had a higher risk of disease-associated mortality compared with those who received transplants from an HTLV-I–seronegative donor, whereas they had similar overall survival and treatment-related mortality rates (Table 4).

Discussion

The aim of this nationwide registry-based study was to compare overall survival after allogeneic HSCT with the use of various graft sources as treatment for ATL, and to identify factors that may influence transplantation outcomes. Despite the retrospective nature of the study, the validity of our analysis is strengthened by the fact that our cohort included most of the related transplants and nearly all unrelated transplants for ATL performed over a decade in our country.

We found that a substantial proportion of patients with ATL, including those who did not achieve complete remission, could enjoy long-term survival after allogeneic HSCT, validating the results of earlier observations.[18,19] However, our analysis in this cohort also revealed a high rate of treatment-related mortality. In particular, frequent incidence of fatal infectious complications may reflect preexisting profound immunodeficiency observed in patients with ATL.[4,5] Improved supportive care for opportunistic infection might be especially important for reducing treatment-related mortality in allografting for ATL.

Multivariable analysis revealed 4 factors that affected survival: recipient age, recipient sex, disease status before transplantation, and type of graft source. Although higher age of the recipient was associated with lower posttransplantation survival, most of the patients with ATL were older than age 50 years and were less likely to be candidates for fully ablative conditioning. Recently, 2 small prospective trials have demonstrated the feasibility and efficacy of allogeneic stem cell transplantations using reduced-intensity conditioning.[26,29] Although we observed no significant differences in overall survival between patients who received conventional conditioning regimens and those who received purine analog–

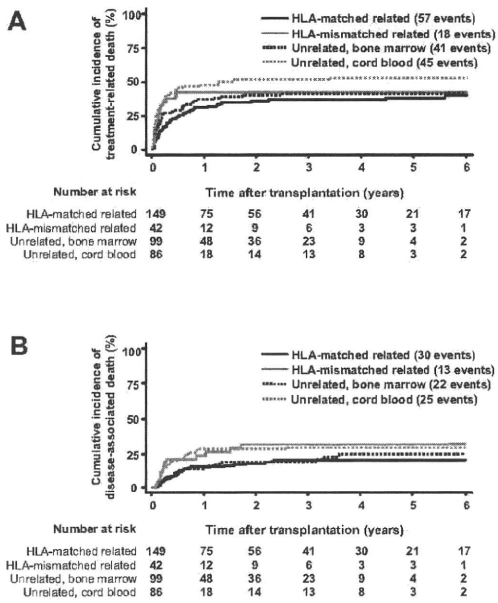

Figure 2. Cumulative incidence of treatment-related mortality and disease-associated mortality according to type of graft source. The unadjusted cumulative incidence curves for treatment-related mortality (A) and disease-associated mortality (B) stratified according to type of graft source are shown after allogeneic hematopoietic stem cell transplantation in patients with adult T-cell leukemia.

based regimens in the present study, it was difficult to evaluate the effect of conditioning dose intensity because data on doses of agents or total-body irradiation used in these regimens were not fully available in our cohort. Further studies are warranted to identify unfit or elderly ATL patients who can benefit from allogeneic stem cell transplantation with the use of less toxic conditioning.

A further novel finding in this study was that female patients with ATL had a more favorable outcome after allogeneic stem cell transplantation compared with male patients. Incidence of ATL in Japan is generally higher in male than in female populations, which was partly explained by the difference in routes of HTLV-I transmission between males and females. Sexual transmission of the virus can also occur, predominantly from males to females in adult life, thereby lowering the apparent incidence of ATL among female HTLV-I carriers.[7] However, the estimated ATL mortality among a prospective cohort of perinatally infected HTLV-I carriers was still higher for male patients,[36] suggesting that female sex itself might have a protective role against ATL development. Although much of the underlying mechanism for male predominance in ATL remains to be elucidated,[37] unidentified biologic or immunologic aspects of sex difference may contribute not only to development of ATL in HTLV-I carriers, but also to outcomes in allografted patients with ATL.

Despite the high risk for relapse after transplantation, survival rates observed in patients who received transplants not in complete remission were encouraging. Intriguingly, withdrawal of immunosuppressive agents or donor lymphocyte infusion can induce remission in relapse of ATL after allogeneic HSCT, implying the presence of a graft-versus-ATL effect.[19-23] Because several antigens have recently been identified as putative targets for cytotoxic T-cell responses against ATL,[38,39] future development of cellular immunotherapy targeting these molecules would reduce the incidence of relapse and improve survival in patients with residual ATL after allogeneic transplantation. Further investigations are warranted to elucidate the association between the occurrence of GVHD and disease response among allografted patients with ATL because our preliminary analysis using a similar cohort[40] suggested that patients who developed mild acute GVHD had a better posttransplantation survival compared with those who did not develop acute GVHD (J.K., M. Hishizawa, A.U., S.T., T.E., Y. Moriuchi, R.T., F.K., Y. Miyazaki, M.M., K.N., M. Hara, M.T., S. Kai, Y.A., R.S., T.K., K.M., T.N.-I., S. Kato, H.S., Y. Morishima, J.O., T.I., and T.U., manuscript in preparation).

Finally, the use of unrelated cord blood was associated with lower survival, most likely a result of higher treatment-related mortality. Two major causes of early treatment-related death were infection and organ failure. Because the development of ATL usually worsens preceding immunodeficiency associated with HTLV-I infection, it is imperative to establish effective measures to manage posttransplantation infections in allografted patients with ATL. In addition, the use of more intense conditioning for refractory disease in relatively elderly recipients may increase the risk of regimen-related toxicities especially in the setting of unrelated donor transplantation. However, direct comparison of

Table 3. Cause of death according to type of graft source

	Deaths within 100 days per graft source (%)				Deaths later than 100 days per graft source (%)			
Cause of death	HLA-matched related bone marrow or peripheral blood	HLA-mismatched related bone marrow or peripheral blood	Unrelated bone marrow	Unrelated cord blood	HLA-matched related bone marrow or peripheral blood	HLA-mismatched related bone marrow or peripheral blood	Unrelated bone marrow	Unrelated cord blood
Primary disease	11 (28)	9 (35)	6 (18)	15 (30)	19 (37)	4	16 (53)	10 (42)
Treatment-related								
GVHD	3 (8)	1 (4)	2 (6)	2 (4)	4 (8)	1	2 (7)	1 (4)
Infection	7 (18)	5 (19)	9 (27)	12 (24)	9 (17)	0	4 (13)	5 (21)
Organ failure	12 (30)	3 (12)	13 (39)	11 (22)	9 (17)	1	4 (13)	0 (0)
Others	6 (15)	7 (27)	3 (9)	10 (20)	7 (13)	0	4 (13)	4 (17)
Undetermined	1 (3)	1 (4)	0 (0)	0 (0)	4 (8)	0	0 (0)	4 (17)
Total no. of deaths	40 (100)	26 (100)	33 (100)	50 (100)	52 (100)	6	30 (100)	24 (100)
Patients at risk	154	43	99	90	113	17	66	39

HLA indicates human leukocyte antigen; GVHD, graft-versus-host disease.

Data are number of deaths to total deaths (%) after transplantation in the group according to type of graft source. Percentages are not provided for groups having fewer than 10 patients in total.

Table 4. Effect of donor HTLV-I serostatus on transplantation outcomes

		Univariable analysis		Multivariable analysis	
Outcome	Number*	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Overall survival†					
Donor HTLV-I antibody positive	43/68	1.00	Reference	1.00	Reference
Donor HTLV-I antibody negative	52/88	0.90 (0.60-1.35)	.603	0.83 (0.54-1.28)	.395
Treatment-related mortality‡					
Donor HTLV-I antibody positive	20/64	1.00	Reference		
Donor HTLV-I antibody negative	37/86	1.51 (0.88-2.58)	.133		
Disease-associated mortality§					
Donor HTLV-I antibody positive	19/64	1.00	Reference	1.00	Reference
Donor HTLV-I antibody negative	13/86	0.44 (0.22-0.89)	.022	0.43 (0.21-0.90)	.026

CI indicates confidence interval; and HTLV, human T-cell leukemia virus.

*Number of events/number of evaluable patients.

†Other variables considered in the multivariable analysis were disease status before transplantation, type of GVHD prophylaxis, and type of graft source. Variables significantly associated with overall survival were disease status before transplantation and type of GVHD prophylaxis: not in complete remission versus complete remission (hazard ratio, 1.95; 95% CI, 1.17-3.24, $P = .010$); tacrolimus- versus cyclosporine-based (hazard ratio, 4.22; 95% CI, 1.58-11.26, $P = .004$).

‡Multivariable analysis was not performed because no variable was significantly associated with treatment-related mortality by univariable analysis.

§Other variables considered in the multivariable analysis were disease status before transplantation, type of GVHD prophylaxis, and type of graft source. The only variable significantly associated with disease-associated mortality was disease status before transplantation: not in complete remission versus complete remission (hazard ratio, 2.88; 95% CI, 1.01-8.24, $P = .049$).

transplantation outcomes by graft source was not feasible because the selection of graft source is an individual process strongly influenced by donor availability and disease status of patients. It should also be noted that the study period encompassed the developmental phase of cord blood transplantation in adults. Because rates of disease-associated death were similar irrespective of type of graft source, new strategies to reduce early treatment-related mortality would improve the results of alternative donor transplantations for ATL.

Another concern related to selection of graft source involves the use of HTLV-I-seropositive-related donors. Sibling donors for patients with ATL are frequently infected with HTLV-I, because mother-to-child transmission by breastfeeding is a major route of HTLV-I acquisition.[5,6] The use of HTLV-I–seropositive donors raises the risk of ATL development in donor-derived HTLV-I–infected cells under immunosuppressive conditions after transplantation,[41] whereas it may enhance the therapeutic effect by the adoptive transfer of viral-specific immunocompetent cells.[21] However, the latter possibility seems less likely because transplantation from HTLV-I–seropositive donors was associated with higher risk for disease-associated mortality in our study cohort. Given that donor-derived HTLV-I–specific cytotoxic T-cell response can be observed in transplantation from an HTLV-I–seronegative donor,[21] it is important to note that the magnitude of specific T-cell responsiveness to HTLV-I might widely differ among healthy HTLV-I carriers. The impairment of HTLV-1–specific T-cell responses was observed not only in patients with advanced ATL but also in a subpopulation of asymptomatic carriers, which was associated with insufficient control of HTLV-I.[42] Although whether donor anti–HTLV-I immunity can harness graft-versus-ATL responses is still elusive, further investigations are clearly needed to resolve this issue.

This study had inherent limitations that are common among observational studies: eligibility for transplantation, as well as choice of transplantation protocol, including the selection of graft source, was determined by the treating physicians of each institution; the confounding effect of some variables, such as disease subtype, could not be fully evaluated because of missing data, although adjustment for other key risk factors enabled as controlled a comparison as possible.

In conclusion, allogeneic HSCT is an effective treatment that confers long-term survival in selected patients with ATL, but at the cost of substantial risk of treatment-related mortality. Posttransplantation outcomes are influenced by recipient age, recipient sex, and disease status at transplantation, as well as by type of graft source. More definitive conclusions on the role of allografting in the therapeutic algorithm for ATL will be drawn from future prospective studies that aim to compare the survival outcomes after transplantation with those after conventional chemotherapy.

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Authorship

Contribution: M. Hishizawa, J.K., T.I., and T.U. reviewed and analyzed data and wrote the paper; J.K., K.M., and T.I. performed statistical analysis; A.U., S.T., T.E., Y. Moriuchi, R.T., F.K., Y. Miyazaki, M.M., K.N., M. Hara, M.T., S. Kai, and J.O. interpreted data and reviewed and approved the final manuscript; Y.A., R.S., and H.S. collected data from the JSHCT; T.K. and Y. Morishima collected data from the JMDP; T.N.-I. and S. Kato collected data from the JCBBN; and T.I. and T.U. designed the research and organized the project.

T.U., the senior author, died after acceptance of the final manuscript.

In addition to authors, other members who contributed data on allogeneic hematopoietic stem cell transplantation for adult T-cell

leukemia to the JSHCT, JMDP, and JCBBN are listed in the supplemental Appendix.

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Disease-specific analyses of unrelated cord blood transplantation compared with unrelated bone marrow transplantation in adult patients with acute leukemia

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We made a disease-specific comparison of unrelated cord blood (CB) recipients and human leukocyte antigen allele–matched unrelated bone marrow (BM) recipients among 484 patients with acute myeloid leukemia (AML; 173 CB and 311 BM) and 336 patients with acute lymphoblastic leukemia (ALL; 114 CB and 222 BM) who received myeloablative transplantations. In multivariate analyses, among AML cases, lower overall survival (hazard ratio [HR] = 1.5; 95% confidence interval [CI], 1.0-2.0, $P = .028$) and leukemia-free survival (HR = 1.5; 95% CI, 1.1-2.0, $P = .012$) were observed in CB recipients. The relapse rate did not differ between the 2 groups of AML (HR = 1.2; 95% CI, 0.8-1.9, $P = .38$); however, the treatment-related mortality rate showed higher trend in CB recipients (HR = 1.5; 95% CI, 1.0-2.3, $P = .085$). In ALL, there was no significant difference between the groups for relapse (HR = 1.4, 95% CI, 0.8-2.4, $P = .19$) and treatment-related mortality (HR = 1.0; 95% CI, 0.6-1.7, $P = .98$), which contributed to similar overall survival (HR = 1.1; 95% CI, 0.7-1.6, $P = .78$) and leukemia-free survival (HR = 1.2; 95% CI, 0.9-1.8, $P = .28$). Matched or mismatched single-unit CB is a favorable alternative stem cell source for patients without a human leukocyte antigen–matched related or unrelated donor. For patients with AML, decreasing mortality, especially in the early phase of transplantation, is required to improve the outcome for CB recipients. (Blood. 2009;113:1631-1638)

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) with bone marrow (BM) or peripheral blood, the curative treatment of choice for acute leukemia, is limited by the inadequate supply of human leukocyte antigen (HLA)–identical related donors. Bone marrow from HLA-matched unrelated donors has been a major alternative graft source.[1-3] Umbilical cord blood (CB), an alternative stem cell source to BM or peripheral blood stem cells, has been used primarily in children,[4-10] but its use in adults is increasing.[11,12]

Clinical comparison studies of cord blood transplantation (CBT) and bone marrow transplantation (BMT) for leukemia from unrelated donors in adult recipients showed comparable outcomes.[11-13] Recipients of CBT showed delayed neutrophil recovery and lower incidence of acute graft-versus-host disease (GVHD).[11-13] Overall treatment-related mortality (TRM) was reported to be similar[12] or higher[11] compared with HLA-matched BM. Acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) are different disease entities that require different chemotherapy regimens for treatment. However, previous comparison studies have included both diseases because of limitation in the number of CBTs given to adults.

In addition, the study periods of previous studies encompass the pioneering period of CBT, when the general practice was to use these grafts in patients in whom there were no other curative options and when the relevance of cell dose and HLA matching had not yet been recognized.[6,7,14]

Accumulation of a larger number of CBT results enabled us to make a controlled comparison with unrelated BMTs. To avoid the inclusion of the pioneering period of CBT, the subjects were limited to those who received transplantations in and after 2000.

Methods

Collection of data and data source

The recipients' clinical data were provided by the Japan Cord Blood Bank Network (JCBBN) and the Japan Marrow Donor Program (JMDP).[15]

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Peripheral blood stem cell donation from unrelated donors is not permitted in Japan. All 11 CB banks in Japan are affiliated to JCBBN. Both JCBBN and JMDP collect recipients' clinical information at 100 days after transplantation. Patients' information on survival, disease status, and long-term complications, including chronic GVHD and second malignancies, are renewed annually by follow-up forms. This study was approved by the data management committees of JMDP and JCBBN.

Patients

Between January 2000 and December 2005, a total of 1690 adult patients at least 16 years of age with acute leukemia (999 AML, 261 CB and 738 BM; and 691 ALL, 178 CB and 513 BM) received first HSCT with myeloablative conditioning either CB or BM from unrelated donors. Of these, patients who received a single CB unit with 0 to 2 HLA mismatches, or HLA-A, -B, -C, and DRB1 allele-matched BM from unrelated donors were analyzed. HLA matching of CB was performed using low-resolution molecular typing methods for HLA-A and -B, and high-resolution molecular typing for HLA-DRB1. Of 1023 BM recipients with complete HLA high-resolution data, the following recipients with HLA HLA-A, -B, -C, and DRB1 allele mismatches were excluded: 306 recipients with 1 of 8 mismatches (39 for HLA-A, 6 for HLA-B, 137 for HLA-C, and 124 for HLA-DRB1), 150 recipients with 2 of 8 mismatches (36 for 2 class I antigens, and 114 for class I and class II antigens), 33 recipients with 3 of 8 mismatches, and 1 recipient with 4 of 8 mismatches. Of 390 recipients of CB with complete HLA data, 95 recipients with 3 mismatches and 8 patients with 4 mismatches were excluded. A total of 484 patients with AML (173 CBTs and 311 BMTs) and 336 patients with ALL (114 CBTs and 222 BMTs) were the subjects for the analyses. Eighty-five centers performed 287 CBTs analyzed in this study, and 114 centers performed 533 BMTs.

Definitions

Neutrophil recovery was defined by an absolute neutrophil count of at least 500 cells/mm^3 for 3 consecutive points; platelet recovery was defined by a count of at least 50 000 platelets/mm^3 without transfusion support. Diagnosis and clinical grading of acute GVHD were performed according to the established criteria.[16] Relapse was defined as a recurrence of underlying hematologic malignant diseases. Treatment-related death was defined as death during a continuous remission. Leukemia-free survival (LFS) was defined as survival in a state of continuous remission.

Statistical analysis

Separate analyses were performed for AML and ALL. Descriptive statistical analysis was performed to assess patient baseline characteristics, diagnosis, disease classification, disease status at conditioning, donor-patient ABO mismatches, preparative regimen, and GVHD prophylaxis. The 2-sided χ^2 test was used for categorical variables, and the 2-sided Wilcoxon rank sum test was used for continuous variables. Cumulative incidence curves were used in a competing-risks setting to calculate the probability of neutrophil and platelet recovery, acute and chronic GVHD, relapse, and TRM.[17] For neutrophil and platelet recovery, death before neutrophil or platelet recovery was the competing event; for GVHD, death without GVHD and relapse were the competing events; for relapse, death without relapse was the competing event; and, for TRM, relapse was the competing event. Gray test was used for group comparison of cumulative incidence.[18] Overall survival (OS) and LFS were calculated using the Kaplan-Meier method. The log-rank test was used for group comparisons. Adjusted comparison of the stem cell source on OS and LFS was performed with the use of the Cox proportional-hazards regression model. For other outcomes, the Fine and Gray proportional-hazards model for subdistribution of a competing risk was used.[19] Adjusted probabilities of OS and DFS were estimated using the Cox proportional-hazards regression model, with consideration of other significant clinical variables in the final multivariate models. The variables considered were the patient's age at transplantation, patient's sex, donor-patient sex mismatch, donor-patient ABO mismatch, disease status at conditioning, and t(9;22) chromosome abnormality or others for ALL, cytogenetic information and French-American-British (FAB) classification of M5/M6/M7 or others for AML, the conditioning regimen, and the type of prophylaxis against GVHD. Factors differing in distribution between CB and BM recipients ($P < .10$) and factors known to influence outcomes (such as patient age at transplantation and chromosome abnormalities and FAB classification of leukemia) were included in the final models. Variables with more than 2 categories were dichotomized for the final multivariate model. The cutoff points of the variables were chosen to make optimal use of the information, with the proviso that smaller groups contain at least 20% of the patients. Variables were dichotomized as follows: patient age greater or younger than 45 years at transplantation, female donor to male recipient donor-recipient sex mismatch versus others for donor-recipient sex matching, donor-recipient ABO major mismatch versus others for ABO matching, M5/M6/M7 FAB classification versus others for classification of AML, chromosome abnormality other than favorable abnormalities for cytogenetics of AML, cyclophosphamide and total body irradiation (TBI) or busulfan and cyclophosphamide or others for conditioning regimen of AML, cyclophospohamide and TBI, or others for conditioning regimen of ALL, and cyclosporine-based versus tacrolimus-based prophylaxis against GVHD. Disease status at transplantation was categorized as first complete remission (1CR), second or later complete remission (2CR), or more advanced disease; which was included in the final model using dichotomized dummy variables. All P values were 2-sided.

The statistical power to detect hazard ratios (HRs) of 2.0 and 1.5 (a regression coefficient equal to 0.6931 and 0.4055, respectively) on Cox regression of the log hazard ratio at a .05 significance level adjusted for event rate were 99% and 78%, respectively, for 484 patients with AML and 97% and 60%, respectively, for 336 patients with ALL. The levels of statistical power for subgroup analyses were as follows: 54% and 22% for 1CR, 51% and 21% for 2CR, 96% and 58% for more advanced in AML patients, 62% and 26% for 1CR, 47% and 20% for 2CR, and 67% and 29% for more advanced in ALL patients.[20]

Results

Patient characteristics

The characteristics of the patients are shown in Table 1. There was no significant difference in recipients' age at transplantation in AML (median age, CB vs BM = 38 vs 38 years, $P = .61$) and in ALL (median age, CB vs BM = 34 vs 32 years, $P = .29$). The female/male ratio was higher (CB vs BM = 54% vs 38% in AML patients, and CB vs BM = 54% vs 38% in ALL patients, $P < .001$ and $P = .005$, respectively) in CB recipients, resulting in the lower donor-patient sex match rate (CB vs BM = 48% vs 69% in AML patients, and CB vs BM = 46% vs 65% in ALL patients, $P < .001$ and $P = .002$, respectively) in CB recipients. The proportion of ALL patients with Philadelphia chromosome abnormality was higher (CB vs BM = 38% vs 23%) in CB recipients. CB recipients were likely to have more advanced disease status at transplantation (relapse or induction failure, CB vs BM = 47% vs 31% in AML patients, and CB vs BM = 26% vs 19% in ALL patients), and the difference was significant in AML ($P = .003$). HLA-A, -B (low-resolution typing), and -DRB1 (high-resolution typing) was mismatched in 93% of both AML and ALL among CB recipients, whereas HLA -A, -B, -C, and -DRB1 were all genotypically matched for BM recipients. The ABO-matched donor-patient pair proportion was consistently lower for CB (CB vs BM = 34% vs 59% in AML patients and CB vs BM = 32% vs 58% in ALL patients).

A preparative regimen with TBI and cyclophosphamide was used in almost all patients, and cytosine arabinoside was supplemented for CB recipients with AML (36%) in addition to TBI and cyclophosphamide. For GVHD prophylaxis, tacrolimus (CB vs BM = 29% vs 56% in AML patients, and CB vs BM = 37% vs 53% in ALL patients) and