Authorship

Contribution: S. Takagi performed transplantation, analyzed extracted data, and contributed to writing the paper; Y.O. analyzed histologic sections; N.U., K.T., K.I., M.T., H.Y., Y.A.-M., K.M., A.W., and S.M. performed transplantation and contributed to writing the paper; N.M. performed transplantation and supported statistical analysis; K.O. reviewed histologic sections and contributed to writing the paper; and S. Taniguchi reviewed the study method and organized this study.

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Title: Successful sustained engraftment after reduced-intensity umbilical cord blood transplantation for adult patients with severe aplastic anemia

Running title: RI-UCBT for adults with SAA

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Abstract

We retrospectively analyzed 12 consecutive adult severe aplastic anemia (SAA) patients who received unrelated umbilical cord blood transplantation after a reduced-intensity conditioning regimen (RI-UCBT). The conditioning regimen consisted of fludarabine 125 mg/m^2, melphalan 80 mg/m^2, and 4 Gy of total body irradiation. The median infused total nucleated cell number and CD34$^+$ cell number were 2.50 x 10^7/kg and 0.76 x 10^5/kg, respectively. Eleven of the twelve patients achieved primary neutrophil and platelet engraftment. All patients who achieved engraftment had complete hematological recovery with complete donor chimerism, except for one patient who developed late graft failure 3 years after RI-UCBT. Two of the twelve patients died from idiopathic pneumonia syndrome, and the remaining 10 patients are alive, having survived for a median of 36 months. Our encouraging results indicate that RI-UCBT may become a viable therapeutic option for adult SAA patients who lack suitable HLA-matched donors and fail immunosuppressive therapy.

Key words:

severe aplastic anemia; adult patients; umbilical cord blood transplantation; reduced intensity conditioning regimen;

Introduction

Bone marrow transplantation from an HLA-matched sibling is recommended as first-line therapy for younger patients with severe aplastic anemia (SAA) [1,2]. However, many patients lack HLA-matched sibling donors. Bone marrow transplantation from an HLA-matched unrelated donor has been an alternative therapeutic option for patients who fail one or more courses of immunosuppressive therapy (IST), but high rates of graft failure (GF), graft-versus–host disease (GVHD), and infection still remains to be solved [3]. The number of unrelated umbilical cord blood transplantation (UCBT) has been increasing [4]. However, little information has been available on whether UCBT is feasible for SAA patients. We reported successful urgent UCBT using reduced-intensity (RI) conditioning for a 70-year-old SAA patient in 2003 [5]. Here we present successful sustained engraftment of 11 consecutive patients with SAA who received RI-UCBT with the same RI conditioning regimen following the first report.

Methods

This study included 12 consecutive adult patients with acquired SAA who underwent RI-UCBT at our institute from September 2002 through January 2009. The patients' characteristics and umbilical cord blood (UCB) units are summarized in Table 1A. Their median age was 49 (range, 20-70) years. Four cases of severe, 6 of very severe, and 2 of fulminant type were included according to criteria as previously reported [2 6]. Fulminant type was defined as no neutrophils in the peripheral blood at diagnosis despite administration of granulocyte-colony stimulating factor. Ten patients, except for the two patients with fulminant type, had failed at least one course of IST. All patients gave their written informed consent in accordance with the Declaration of Helsinki, and the study was approved by the Toramon Hospital institutional review board. UCB units were obtained from the Japanese Cord Blood Bank Network, and single UCB unit was infused in all the studied patients. All UCB units were serologically typed for HLA-A, -B, and –DR antigen before selection, and were tested by high-resolution DNA typing before transplant. The degree of mismatch is expressed by using antigen level at HLA-A and -B, and allele level at DRB1. ABO incompatibility was not incorporated as one of the factors used in CB unit selection. The median total nucleated cell (TNC) number and $CD34^+$ cell number at

cryopreservation were 2.50 (range, 1.83-4.39) x 10^7/kg and 0.76 (range, 0.27-1.52) x 10^5/kg, respectively. Anti-HLA antibodies were screened before transplant in 6 patients using a FlowPRA method (One Lambda), and LAB Screen PRA or Single Antigen (One Lambda) was used to identify HLA antibody specificities [7,8]. All patients were conditioned with fludarabine 25 mg/m^2 daily for 5 days, melphalan 40 mg/m^2 daily for 2 days, and 4 Gy of TBI in 2 fractions in 1 day. GVHD prophylaxis consisted of cyclosporine in 2, tacrolimus in 2, and tacrolimus plus mycophenolate mofetil in 8. Assessment of engraftment, GF, chimerism, GVHD and supportive care during transplantation were performed as previously reported [9] [10]. Karnofsky performance status score was assessed as surrogate for Quality of life of the survivors. Overall survival (OS) was estimated using the Kaplan-Meier method.

Results and discussion

Patients' outcomes are summarized in Table 1B. Eleven of the twelve patients achieved primary neutrophil and platelet engraftment. The median times to achieve neutrophil engraftment and platelet count >20 $\times 10^9$/L were 18 (range, 12-28) and 42 (range, 26-64) days, respectively. All patients who achieved engraftment had complete hematological recovery and were free from transfusion, and they showed complete donor chimerism at the time of the first chimerism analysis (median, 14 days; range,

11-73 days). One patient developed primary GF and was later found to have antibody against mismatched HLA on donor cells. Another patient developed secondary GF 3 years after UCBT. Both patients underwent a second RI-UCBT, and obtained rapid donor engraftment. The negative impact of multiple transfusions before transplant was not detected (Table 1A and 1B). Among 11 evaluable patients, 2 developed grade I and 5 developed grade II acute GVHD. Of the 9 patients who survived longer than 100 days post-transplant, 3 developed limited type of chronic GVHD. No patients developed grade III-IV acute GVHD and extensive type of chronic GVHD. Two of the twelve patients died from idiopathic pneumonia syndrome, and the remaining 10 patients are alive, having survived for a median of 36 months (range, 14-91 months). The probability of OS at 3 years was 83.3% (Figure 1). The surviving patients had high KPS score with the median of 90% (range; 60-100%).

The present study demonstrated that our RIC regimen allows a sufficient sustained engraftment of UCB in adult SAA patients. The RIC regimen was originally developed in our institute for UCBT for various hematological malignancies [9]. Eleven of the twelve patients achieved primary engraftment, which compares favorably with previously reported engraftment rates of UCBT for SAA [11-14 15 16]. Our RIC regimen would be more potent than the others to overcome immunological barriers for

engraftment. Cell dose has been known to significantly influence the rate of engraftment after UCBT [14]. In the present study, although the cell dose was not very large, sufficient engraftment was seen. Any significant relationship between cell dose (TNC; ≥ 2.5 vs $<2.5\times10^7$/ kg, $CD34^+$; ≥ 0.8 vs $<0.8\times10^5$/ kg) and engraftment kinetics were observed (data not shown). Thus, not just cell dose but other factors, such as the intensity of the conditioning regimen and post-transplant immunosuppression, may be important to achieve better engraftment after UCBT for SAA patients. Interestingly, all 6 patients who were screened for HLA antibodies before transplant had HLA antibodies, and the one case, who had positive HLA antibodies against an HLA on a transplanted UCB unit, was the only one who failed primary engraftment. Recently, Takanashi et al. reported that, in large number of UCBT for various hematological malignancies, the patients with anti-HLA antibodies, when the specificity corresponding to mismatched antigen in UCB graft, showed significantly lower neutrophil or platelet recovery than those with antibodies-negative or –positive but not corresponding to UCB graft [17]. Although the observations may differ from that of diverse populations and warrants further investigation, if possible, the use of a UCB unit with corresponding HLA antibodies in the recipient should be avoided.

Three-year survival in the studied patients was 83.3%. In addition to high rate of

engraftment, the low risk of severe GVHD might contribute to high survival rate with good QOL, and which seems to be one of the important advantages of using a UCB unit for SAA patients. The other advantage of the use of UCB units is rapid availability. In the present study, 2 patients with fulminant type could be rescued by urgent hematopoietic stem cell transplantation using UCB units. More than 90% of recipients can find a suitable UCB unit in Japan, and thus, UCB expands the chance to receive transplantation for those who need it urgently.

In conclusion, this retrospective study strongly suggests the feasibility and effectiveness of RI-UCBT for adult SAA patients. RI-UCBT may become a viable therapeutic option for those who lack suitable HLA-matched donors and who fail or relapse after IST. Although our results should be interpreted with caution because of the small number of patients and still short follow-up duration, we believe that RI-UCBT with the conditioning regimen presented here deserves further evaluation in a prospective trial, hopefully in a multi-center setting.

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Authors' contribution

H.Y. and D.K. performed transplantation and analyzed extracted data and contributed to writing the paper; A.Y. reviewed histopathological section; H.Y. and N.M. performed statistical analysis; N.U. K.Izutsu. and S. Taniguchi reviewed study design and methods; K.Ishiwata., H.A., S. Takagi, M.T., N.N., Y.A-M., K.M., A.W., S.M performed transplantation and contributed to writing the paper.

Conflict-of-interest disclosure

The authors declare no competing financial interests.

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Table 1A. Characteristics of Patient, Grafts, and GVHD prophylaxis

Case	Age (years)	Previous treatment	Interval Dx to UCBT (months)	Previous transfusion (RBC / platelet) (times)	Disease status at UCBT	HLA match	HLA Ab (reactive to CB)	ABO group (R/D)	TNC ($\times 10^7$/kg)	$CD34^+$ ($\times 10^5$/kg)	GVHD prophylaxis
1	70	CSA	3	11 / 14	SAA	4 / 6	N.T	A/A	4.00	1.23	CSA
2	20	ATG+CSA	78	>20 / >20	VSAA	4 / 6	N.T	B/O	2.65	1.07	CSA
3	22	ATG+CSA, PSL	157	>20 / >20	SAA	4 / 6	N.T	A/O	2.26	0.27	Tac
4	26	ATG+CSA	3	>20 / >20	VSAA	5 / 6	N.T	A/A	2.65	0.70	Tac
5	59	ATG+CSA	8	>20 / >20	SAA	5 / 6	Positive (no)	O/O	2.15	1.52	Tac+MMF
6	49	ATG+CSA, PSL	12	>20 / >20	VSAA	3 / 6	N.T	A/A	2.04	0.62	Tac+MMF
7	70	None	1	5 / 8	Fulminant	4 / 6	Positive (yes)	A/O	4.39	1.29	Tac+MMF
8	52	None	1	4 / 6	Fulminant	4 / 6	N.T	AB/A	3.20	0.49	Tac+MMF
9	46	ATG+CSA	45	>20 / >20	VSAA	4 / 6	Positive (no)	AB/O	1.83	0.42	Tac+MMF
10	49	ATG+CSA, PSL	327	>20 / >20	VSAA	6 / 6	Positive (no)	B/O	2.34	0.82	Tac+MMF
11	65	CSA	6	16 / >20	VSAA	6 / 6	Positive (no)	A/A	3.31	0.56	Tac+MMF
12	31	ATG+CSA, PSL	215	>20 / >20	SAA	4 /6	Positive (no)	B/O	2.09	1.26	Tac+MMF

Dx, diagnosis; UCBT, unrelated cord blood transplantation; RBC, red blood cell; HLA, human leucocyte antigen; CB, cord blood; R, recipient; D, donor; TNC, total nucleated cells; GVHD, graft-versus-host disease; CSA, ciclosporin-A; ATG, antithymocyte globulin; PSL, prednisone; SAA, severe aplastic anemia; VSAA, very severe aplastic anemia; N.T, not tested; M, male; F, female; Tac, tacrolimus; MMF, mycophenolate mofetil

Table 1B. Outcomes of 12 patients after reduced-intensity unrelated cord blood transplantation

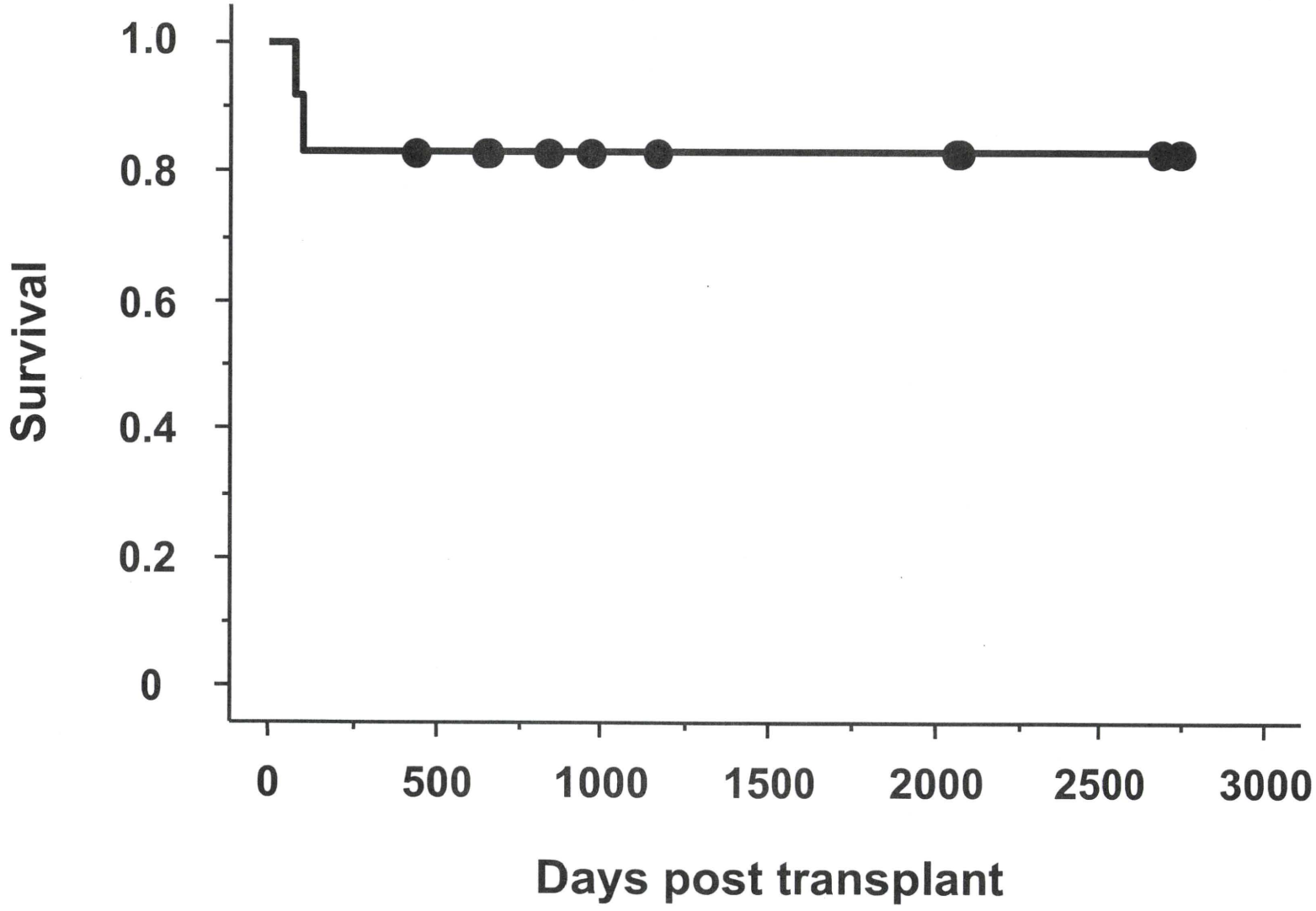
Case	Days to ANC $>0.5\times10^9$/l	Days to PC $>20\times10^9$/l	% Donor chimerism (Days tested, Methods)	aGVHD	cGVHD	Discontinuation of IS (months)	Complication	Survival (months)
1	12	52	100 (14, FISH)	gradeII(skin)	No	Yes (3)	Possible IPA	Alive (91)
2	20	64	90< (49, PCR-STR)	gradeII(skin)	limited	Yes (2)	No	Alive (90)
3	26	42	100 (26, FISH)	No	No	Yes (26)	Yes	Alive (69)
4	18	53	100 (18, FISH)	No	No	Yes (5)	Pneumocystis jirovecii, Late GF, rescued by 2nd UCBT	Alive (69)
5	16	26	96.6 (14, FISH)	gradeI(skin)	limited	Yes (14)	Norwalk virus colitis, EBV-PTLD	Alive (39)
6	28	64	99.6 (11, FISH)	No	N.E	No	IPS	Dead; IPS (3)
7	No	No	48.8 (10, FISH), 4.3 (15, FISH)	N.E	N.E	N.E	Primary GF, rescued by 2nd UCBT	Alive (32)
8	18	28	99.2 (13, FISH)	gradeII(skin, gut)	No	Yes (7)	CMV colitis, EBV-PTLD	Alive (28)
9	28	43	90< (14, PCR-STR)	gradeI(skin)	N.E	No	HSV pneumonia, IPS	Dead; IPS (3)
10	15	27	99 (73, FISH)	No	limited	No	No	Alive (22)
11	15	27	100 (20, FISH)	gradeII(skin, gut)	No	No	No	Alive (22)
12	13	28	100 (14, FISH)	gradeII(gut)	No	No	No	Alive (14)

ANC, absolute neutrophil count; PC, Platelet count; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; IS, immunosuppressant; FISH, fluorescent in situ hybridization; PCR-STR, PCR of short tandem repeat; N.E, not evaluable; IPA, invasive plumonary aspergillosis; GF, graft failure; EBV-PTLD, EBV associated posttransplantation lymphoproliferative disorders; IPS, idiopathic pneumonia syndrome

Figure legend

Figure 1. Survival of 12 patients with SAA undergoing unrelated cord blood transplantation.

Figure 1


1.0
0.8
0.6
0.4
0.2
0
Survival
0
500
1000
1500
2000
2500
3000
Days post transplant

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LETTER TO THE EDITOR

T-cell post-transplant lymphoproliferative disorder in a patient with chronic idiopathic myelofibrosis following allogeneic PBSC transplantation

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Post-transplant lymphoproliferative disorder (PTLD) is a well-recognized complication after solid organ and hematopoietic SCTs (HSCTs). The majority are of B-cell origin and EBV related.[1] Most of the T-cell PTLD cases have been described as occurring after solid organ transplantations;[2] T-cell PTLD cases following HSCT are exceedingly rare. There are only three reported cases of T-cell PTLD following allogeneic HSCT[3] and four cases following autologous HSCT.[4–7] Here we report a case of T-cell PTLD after allogeneic-PBSC transplantation (allo-PBSCT) in a patient with chronic idiopathic myelofibrosis (CIMF).

A 44-year-old Japanese woman with anemia and fever was diagnosed with CIMF in November 2006. At the time of her diagnosis, her WBC count was 900/μl, Hb 6.9 g/dl, plt count 39 000/μl with no morphologically abnormal cells in her peripheral blood, and an abdominal CT scan showed mild splenomegaly without hepatomegaly, lymphadenopathy or liver tumor. A specimen of her biopsied BM showed diffuse fibrosis and a decreased number of hematopoietic cells. No abnormal cell proliferation was observed. In December 2006, she underwent allo-PBSCT from an HLA-identical brother. Neutrophil engraftment was achieved on day 17 after transplant, and BM analysis showed full hematological recovery with 100% donor-type chimerism assessed by Y chromosome-based FISH analysis. As grade II acute GVHD involving the skin and subsequently an extensive type of chronic GVHD (cGVHD) developed; continued immunosuppressive therapy with cyclosporine and prednisolone was required for several months after the transplant. At 5 months after transplant, a liver tumor, 2 cm in diameter, was detected by an abdominal CT scan. Although PTLD was raised as a differential diagnosis, biopsied liver tissue was inadequate for pathological examination. Immunosuppressive therapy was reduced, resulting in a decrease in liver tumor size to 1.6 cm in 2 months. However, a subsequent flare-up of cGVHD required more intensive immunosuppressive therapy, and the liver tumor's diameter increased twice in size. A liver tumor biopsy performed at this time showed a diffuse proliferation of atypical lymphoid cells (Figure 1a). Immunohistochemically, these tumor cells were positive for LCA, CD3, CD7 and CD8, and negative for CD4, CD5, CD34, CD79a, MPO, CD30, CD56 and TdT (Figure 1b). These pathological findings are compatible with peripheral T-cell lymphoma-unspecified (Figure 1c). EBV infection was not detected by *in situ* hybridization. Y chromosome-based FISH analysis revealed the tumor cells were of recipient origin. She suffered from fever, pancytopenia and decreased liver function, and was hospitalized for further therapy in November 2007. BM examination showed infiltration of 4% abnormal lymphoid cells and the proliferation of macrophage with hemophagocytosis, with no sign of CIMF recurrence. Chromosome analysis of the BM cells showed 44, X, der(X)t(X;7)(q13;q11.2), add(2)(q21), add(4)(p11), add(4)(p16), der(9;17)(q10;q10), −10, −13, add(15)(p11), +mar [2/20]. An abdominal CT scan showed that the liver tumor grew rapidly to a size of $12 \times 6\,cm^2$ (Figure 1d). Serological tests for HIV, HBV, HCV and HTLV-1 were negative, and the EBV VCA IgG was positive but negative for IgM. Analyses by real-time PCR were negative for human herpesvirus-6, VZV, CMV and EBV in her peripheral blood. She was diagnosed with T-cell PTLD with lymphoma-associated hemophagocytic syndrome. CHOP therapy was started, but the disease progressed within 2 weeks after this. She underwent urgent unrelated cord blood transplantation (UCBT) from an HLA two antigen-mismatched donor. Her post-transplant course was complicated by sepsis, renal failure and respiratory failure. She died on day 6 after UCBT. An autopsy was not performed.

To our knowledge, there have been only four cases of T-cell PTLD following allo-SCT, including our case (Table 1). Time to T-cell PTLD diagnosis ranges from 2 to 43 months after a transplant. Although the type of PTLD was not consistent, ranging from precursor to peripheral T-cell neoplasms, none of them were associated with EBV infection. Our case was negative for EBV, and the type was peripheral T-cell lymphoma-unspecified.

There have been a few reports describing myelofibrosis in association with T-cell lymphoma.[8] In these cases, PDGF and tumor growth factor β, which may have been secreted by neoplastic T lymphocytes, had an important role in the development of myelofibrosis. In our case, there was no clinical evidence of T-cell lymphoma at the time of CIMF diagnosis, and no sign of myelofibrosis recurrence at the onset of T-cell lymphoma. Thus, the development of T-cell lymphoma in this case was considered to be independent of the CIMF.

All three patients reported as having T-cell PTLD following allo-SCT had severe GVHD and received a heavy dose of immunosuppressive agents, suggesting some viral agents in an immunosuppressed state may have an important role in the development of T-cell PTLD. However, we were unable to find any evidence of viral

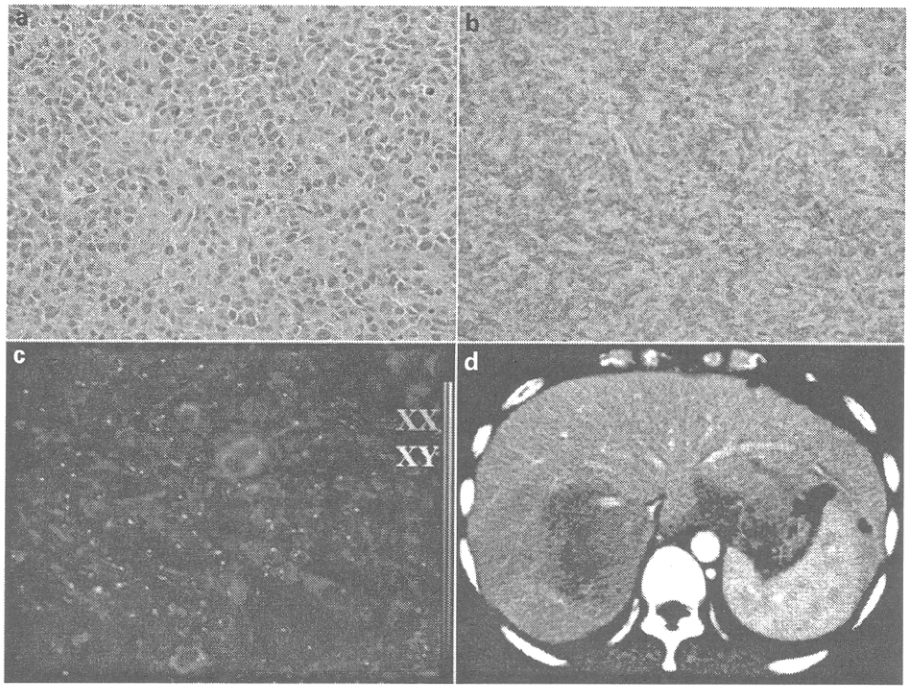

Figure 1 (**a**) Liver tumor biopsy shows monotonous infiltration of atypical lymphoid cells (H&E stain ×400). (**b**) Immunostaining for CD3 shows a large number of positive cells within the tumor. (**c**) Y chromosome-based FISH reveals the tumor cells are of recipient origin (XX signal). (**d**) Abdominal CT scan shows a low-density area with 12 cm diameter on the right side of the liver.

Table 1 T-cell post-transplant lymphoproliferative disorder after allogeneic stem cell transplantation

Authors	*Age/sex*	*Initial Dx*	*HSCT*	*Type of PTLD Dx (months after HSCT)*	*Origin*	*EBV*	*GVHD*	*Outcome (months after Dx)*
Zutter *et al.*[3]	14/M	AML	HLA-identical BM graft	T-lymphoblastic lymphoma (43)	Recipient	Neg	Mild aGVHD(S,L,Gut) Severe cGVHD(S,L,Gut)	Death (28)
	9/M	ALL	HLA-identical BM graft	T-lymphoblastic lymphoma (21)	Donor	Neg	Mild aGVHD(S) Severe cGVHD(S,L)	Death (6)
	2/F	ALL	HLA-2 mismatched BM graft	Polymorphic T-cell lymphoma (2)	Donor?	Neg	Severe aGVHD(S,L)	Death (0)
Present case	44/F	CIMF	HLA-identical allogeneic PBSC	PTCL-u (5)	Recipient	Neg	aGVHDII(S3,L0,Gut0) Extensive cGVHD(S,L)	Death (2)

Abbreviations: aGVHD = acute GVHD; cGVHD = chronic GVHD; CIMF = chronic idiopathic myelofibrosis; Dx = diagnosis; F = female; Gut = gastrointestinal tract; HSCT = hematopoietic stem cell transplantation; L = liver; M = male; neg = negative; PTCL-u = peripheral T-cell lymphoma-unspecified; PTLD = post-transplant lymphoproliferative disorder; S = skin.

infection and reactivation in our case and previously reported cases. It has been reported that only 15 of 76 cases of T-cell PTLD after solid organ transplantation were EBV positive,[9] and any other viral involvement has not been clearly demonstrated. These findings suggest that not only viral infection but also other factors, such as chronic antigenic stimulation, impaired immunoregulation and genetic factors, may be associated with the development of T-cell PTLD.[10]

The outcomes of reported T-cell PTLD so far are poor. All patients died because of the progression of the disease. In our patient, a transient response was observed by reducing immunosuppression, suggesting a graft-versus-lymphoma effect, which was necessitated to increase the immunosuppression. Standard cytotoxic chemotherapy led to a poor response in our patient, similar to the other cases previously described. More intensive chemotherapy, donor lymphocyte infusion or second HSCT should be considered at an early stage of the disease.

In conclusion, T-cell PTLD rarely occurs after allo-HSCT. Further research, however, is needed to fully characterize the clinicopathological features of this condition and to investigate the optimal therapy.

Conflict of interest

The authors declare no conflict of interest.

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LETTER TO THE EDITOR

What is the upper age limit for performing allo-SCT? Cord blood transplantation for an 82-year-old patient with AML

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Since morbidity and mortality associated with hematologic malignant diseases in elderly patients is higher than that in younger patients,[1] elderly patients are less likely to be candidates for allo-SCT, due to the facts that they are more likely to have comorbid organ conditions, either clinically or subclinically, which results in a higher rate of procedure-related mortality,[2] and that they are less likely to have HLA-matched related donors available, as siblings also tend to be elderly.

The development of reduced-intensity (RI) conditioning for transplants, which results in less toxicity and depends largely on GVL effects rather than high-dose therapy to eliminate leukemic cells, has been shown to allow elderly patients to undergo allo-SCT.[3–5] The use of umbilical cord blood transplantation (UCBT) for adults has been increasing due to the potential advantage of rapid availability and the lower risk of GVHD, thus permitting less stringent HLA matching.[4,5] RI-UCBT for adults, mostly elderly patients, has been increasingly reported and shown to be applicable.[6,7] However, there has been no clear description on the upper age limit of receiving allo-SCT, and it varies among institutes at this moment. We report here an 82-year-old man with refractory AML who had successfully treated with RI-UCBT.

The patient was diagnosed as AML (M5b) with adverse risk karyotype (46, XY, −7, +8) and complicated with disseminated intravascular coagulation (DIC). Although DIC was resolved soon after remission induction therapy consisted of idarubicin and cytarabine, and the patient achieved hematological remission, the disease subsequently progressed with lung infiltration and systemic skin tumor formation (Figure 1a). Immunohistochemical analysis of skin tumor showed positive for CD45, myeloperoxidase, and CD68 consistent with leukemic cell infiltration. Skin and lung infiltration was refractory to following high-dose Ara-C-containing chemotherapy. At 4 months after diagnosis of AML, following careful discussion and consent among the patient, his family and transplant staff, he received an RI-UCBT using two antigen- and three allele-mismatched CB in August 2007. His Eastern Cooperative Oncology Group (ECOG) performance status was 2, and HCT-CI score was 1. The preparative regimen consisted of i.v. fludarabine 25 mg/m^2 daily for 5 days (total dose 125 mg/m^2), i.v. melphalan 40 mg/m^2 daily for 2 days (total dose 80 mg/m^2) and 4 Gy of TBI fractionated by 2. GVHD prophylaxis consisted of tacrolimus by continuous infusion and 15 mg/kg twice daily of oral mycophenolate mofetil from day −1. CB unit contained 2.5×10^7 per kg of total nucleated cells and 0.98×10^5 per kg of CD34+ cells before cryopreservation. G-CSF 300 μg/m^2 was administered from day 1 until neutrophil engraftment. On day 14, the patient developed erythema, fever (39 °C) and diarrhea, and was diagnosed as having preengraftment immune reactions (PIR).[8] The symptoms disappeared immediately after initiation of methylprednisolone 0.5 mg/kg for 3 days. There was no episode of bacterial infection during neutropenia. ANC recovered to 0.5×10^9 per liter on day 25, and platelet count reached 2.0×10^9 per liter on day 64. Complete donor-cell chimerism was confirmed on day 27 by BM analysis using short tandem repeat-PCR method. Human herpesvirus-6 limbic encephalitis developed on day 17, which was successfully managed with foscarnet. The regimen-related toxicities observed were mucositis (grade 2), nausea (grade 2), renal dysfunction (grade 2) and diarrhea (grade 1), according to the National Cancer Institute Common Toxicity Criteria version 3.0. Acute GVHD of grade III (gut: stage 2) on day 46 was observed, but successfully managed with oral beclomethasone dipropionate. He finally achieved CR in BM, and his lung lesion and skin tumors also disappeared (Figure 1b). He was discharged from hospital on day 123 after RI-UCBT. To our surprise, his level of performance status got improved thereafter, almost as score 1 measured by ECOG PS scoring system, and returned to his work in 1 month after discharge. In the meantime, chronic GVHD of limited type developed, which was managed without treatment. One year after RI-UCBT, unfortunately, his disease relapsed and he died from disease progression 1 month later.

This remarkable case told us two important issues. First, some, may be not all, patients older than 80 years still can tolerate RI-UCBT. TRM has been shown to be correlated with several factors including age, or more comprehensively, the number of coexisting comorbidities.[9] According to our previous report, those older than 54 years showed cumulative incidence of TRM reaching to approximately 50%, and most of TRM occurred early period post-UCBT.[10] This patient had also faced life-threatening events, such as PIR or viral encephalitis, and was successfully managed by corticosteroid and foscarnet. In allo-SCT settings, there are always several factors that cannot be modulated intentionally, and there may have been good coincidences for him to reach this successful outcome. Nevertheless, this case strongly claims higher age should not be the single determinant of not performing allo-SCT. Second, the most powerful antileukemic activity was observed with RI-UCBT. Although, the patient had finally disease relapse, it was obvious that only RI-UCBT sufficiently suppressed leukemic cells and gave him a