British Journal of Haematology, 2001, **114**, 834–836

SHORT REPORT

Unrelated cord blood transplantation for adult patients with myelodysplastic syndrome-related secondary acute myeloid leukaemia

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Received 10 April 2001; accepted for publication 31 May 2001

Summary. Seven adult patients with myelodysplastic syndrome (MDS)-related secondary acute myeloid leukaemia (AML) were treated with total body irradiation (TBI), cytosine arabinoside (Ara-C) and cyclophosphamide (CY), followed by unrelated human leucocyte antigen (HLA)-mismatched cord blood transplantation (CBT). Granulocyte colony-stimulating factor (G-CSF) was infused continuously from 12 h before until the end of Ara-C therapy to enhance the antileukaemia effect of Ara-C. Five patients are alive and free of disease at 7–31 months after transplantation. These preliminary results suggest that adult MDS-related secondary AML patients without suitable related or unrelated bone marrow donors should be considered as candidates for CBT.

Keywords: myelodysplastic syndrome, secondary leukaemia, adult, cord blood transplantation, G-CSF.

The prognosis of myelodysplastic syndrome (MDS)-related secondary acute myeloid leukaemia (AML) is poor. Although some patients with MDS-related secondary AML achieve remission with standard remission induction chemotherapy, the duration is usually short (de Witte *et al*, 1995). Therefore, allogeneic stem cell transplantation is considered to be the only curative treatment choice for MDS-related secondary AML patients (Anderson *et al*, 1996, 1997; Runde *et al*, 1998; Okamoto *et al*, 1999; de Witte *et al*, 2000). Recently, alternative donor sources other than human leucocyte antigen (HLA)-identical siblings have been used as allogeneic stem cell sources (Anderson *et al*, 1996, 1997; de Witte *et al*, 2000). Here, we report our clinical experience with adult patients with MDS-related secondary AML treated with unrelated cord blood transplantation (CBT).

PATIENTS AND METHODS

Patients. Between August 1998 and August 2000, seven adult patients with MDS-related secondary AML were treated with unrelated CBT at The Research Hospital, The Institute of Medical Science, University of Tokyo. MDS-related secondary AML was defined as AML which developed during the follow-up period of MDS, morphologically diagnosed according to the French–American–British (FAB) Cooperative Group criteria. Among the seven patients, four did not receive any induction therapy before transplantation. The other three patients received induction therapy and could not achieve complete remission. Therefore, all patients received CBT as an up-front treatment not a post-remission consolidation. Among the patients the median age was 38 years (range, 20–50 years), the median weight was 51 kg (range, 43–63 kg) and the median number of infused nucleated cells was $2{\cdot}18 \times 10^7$/kg (range, $2{\cdot}09$–$4{\cdot}06 \times 10^7$/kg). Although it is difficult to obtain a large number of cord blood nucleated cells for adult patients, it was shown that the number of infused cells was associated with the probability of engraftment after CBT (Gluckman *et al*, 1997; Rubinstein *et al*, 1998; Gluckman, 2000). In addition, a relationship between the time to neutrophil and platelet recovery and HLA compatibility has been documented (Gluckman *et al*, 1997; Rubinstein *et al*, 1998; Gluckman, 2000). Therefore, cord blood units were selected according to the number of nucleated cells per recipient's weight and HLA compatibility (HLA-A and B by serology and HLA-DRB1 DNA typing). The characteristics of the seven patients and cord blood units are shown in Table I. Two patients included in our previous studies were

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Table I. Characteristics of patients and cord blood units.

UPN	Age (years) /Sex	Body weight (kg)	Number of HLA-A, B, DRB1 mismatches	Cord blood cell infused; dose $\times 10^7$/kg
305	27/Female	43	2 (B, DRB1)	4·06
314	37/Female	51	2 (DRB1,DRB1)	2·30
324	49/Female	53	1 (A)	2·13
349	47/Female	44	1 (B)	2·09
356	50/Male	63	1 (A)	2·50
361	38/Female	45	1 (DRB1)	2·09
372	20/Male	57	2 (B, DRB1)	2·18

UPN, unique patient number.

also included (UPN305, UPN314) (Nagayama *et al*, 1999; Machida *et al* 2000). No patients had a related or unrelated bone marrow donor available at the time of transplantation. Informed consent for treatment was obtained from all patients.

Transplant procedure. All patients received three to four fractionated 12 Gy total body irradiation (TBI) on d −9, −8 and −7 or d −9 and −8. Cytosine arabinoside (Ara-C) was administered intravenously (i.v.) over 2 h at a dose of 3 g/m^2 every 12 h on d −6 and −5 or d −5 and −4 (total dose 12 g/m^2). Recombinant human granulocyte colony-stimulating factor (G-CSF) (Lenograstim) was administered by continuous infusion at a dose of 5 μg/kg/d. Infusion of G-CSF was started 12 h before the first dose of Ara-C and stopped at the completion of the last dose. Cyclophosphamide (CY) was administered i.v. over 2 h at a dose of 60 mg/kg/d on d −4 and −3 or d −3 and −2 (total dose 120 mg/kg). Two days or 3 d after the completion of conditioning, patients received a cord blood transplantation. All patients received standard cyclosporine (CyA) and methotrexate (MTX) as a graft-versus-host disease (GVHD) prophylaxis. CyA was given every day by 10 h infusion starting on d −1 at a dose of 3 mg/kg/d. MTX (15 mg/m^2 i.v.) was given on d 1, with 10 mg/m^2 MTX on d 3 and 6. Both acute and chronic GVHD were graded according to the previously published criteria. All patients received G-CSF (5 μg/kg/d) by i.v. infusion starting on d 1 until durable granulocyte recovery was achieved. Two patients (UPN324, UPN361) received recombinant human erythropoietin (EPO) by i.v. infusion at a dose of 6000 U, starting on d 1 and then every other day because they were participating in a randomized, prospective study.

RESULTS AND DISCUSSION

All patients had myeloid reconstitution and the median time to $>0{\cdot}5 \times 10^9$/l absolute neutrophil count was 24 d (range, 19–35 d). A self-sustained platelet count greater than 50×10^9/l was achieved in six patients at a median time of 49 d (range, 35–164 d). Acute GVHD occurred in five out of seven patients and chronic GVHD in four out of six evaluable patients. Two patients died of relapse on d 107 and 307, and five patients are alive and free of disease between 7 and 31 months after transplantation (Table II). Among the five patients who are alive and free of disease, four had not received any induction therapy before transplantation.

Although allogeneic stem cell transplantation from an HLA-identical related donor offers a potential cure for MDS-related secondary AML patients, a suitably matched related donor is unavailable for approximately two-thirds of patients. Recently, results of transplantation from unrelated

Table II. Outcome.

UPN	Neutrophil $> 0{\cdot}5 \times 10^9$/l (d)	Reticulocyte $> 1\%$ (d)	Platelet $> 50 \times 10^9$/l (d)	Acute GVHD	Chronic GVHD	Survival (months)*	Cause of death
305	19	25	50	II	Limited	31+	
314	35	50	164	III	Limited	10	Relapse
324	26	35	49	0	None	23+	
349	24	NE	NE	0	NE	3	Relapse
356	25	33	88	I	Extensive	12+	
361	19	28	35	I	None	10+	
372	22	32	40	I	Limited	7+	

*Five patients are alive in complete remission at the time of writing.

UPN, unique patient number; NE, not evaluable; GVHD, graft-versus-host disease. Patients UPN 314 and UPN329 relapsed on d 266 and d 33 respectively.

bone marrow donors have been reported (Anderson *et al*, 1996). As non-relapse mortality was higher in patients who received transplants from HLA-identical unrelated bone marrow donors than from HLA-identical related donors, Anderson *et al* (1997) suggested that the outcome after transplantation for MDS-related secondary AML may be improved by transplanting as soon as possible after the diagnosis of AML in an attempt to reduce toxicity. Although the patients required early transplantation, none of our patients had any related or unrelated bone marrow donors and unrelated cord blood was used as an alternative stem cell source. The long-term disease-free survival (DFS) rate for MDS-related secondary AML patients receiving allogeneic stem cell transplantation is approximately 30% (Anderson *et al*, 1997; Runde *et al*, 1998; de Witte *et al*, 2000) and high relapse rates may result in a poor rate of DFS. Our previous experience suggested that a G-CSF-combined preparative regimen was capable of reducing the post-transplant relapse rate in refractory myeloid malignancies (Takahashi *et al*, 1994; Okamoto *et al*, 1999); thus, G-CSF and Ara-C were combined with a standard TBI and CY regimen to reduce the incidence of relapse. Although the relatively small number of patients studied do not permit firm conclusions concerning the relative effectiveness of the preparative regimens and the usefulness of unrelated cord blood as an alternative stem cell source, our preliminary results suggest that adult MDS-related secondary AML patients without suitable related or unrelated bone marrow donors should be considered as candidates for CBT.

ACKNOWLEDGMENTS

The authors would like to thank the physicians and nurses who cared for patients in this study.

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