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Brief report

# Unrelated cord blood transplantation for adult patients with de novo acute myeloid leukemia

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**We report the results of unrelated cord blood transplantation (CBT) for 18 adult patients with de novo acute myeloid leukemia (AML). The median age was 43 years, the median weight was 55.2 kg, and the median number of cryopreserved nucleated cells was 2.51 × $10^7$/kg. Seventeen patients had myeloid reconstitution and the median time to more than 0.5 × $10^9$/L absolute neutrophil count was 23 days. A self-sustained platelet count more than 50 × $10^9$/L was achieved in 16 patients at a median time of 49 days. Acute graft-versus-host disease (GVHD) above grade II occurred in 11 of 17 evaluable patients and chronic GVHD occurred in 14 of 17 evaluable patients. Fourteen patients are alive and free of disease at between 185 and 1332 days after transplantation. The probability of disease-free survival at 2 years was 76.6%. These results suggest that adult AML patients without suitable related or unrelated bone marrow donors should be considered as candidates for CBT. (Blood. 2004;103: 489-491)**



## Introduction

Although allogeneic stem cell transplantation from a human leukocyte antigen (HLA)–identical related donor offers a potential cure for patients with acute myeloid leukemia (AML), a suitably matched related donor is unavailable for approximately two thirds of patients. Recently, umbilical cord blood from unrelated donors has been used as an alternative stem cell source for adult patients with hematologic disorder.[1-5] Also, we have previously reported the results of a group of 13 adult patients with advanced myelodysplastic syndrome (MDS), including 11 MDS-related secondary AML patients who received unrelated cord blood transplants (CBT).[6] However, there have been no reports detailing the results of adult de novo AML patients treated with CBT. Therefore the role of unrelated CBT is not well defined in adult patients with de novo AML. Here, we report our clinical results for a group of 18 adult patients with de novo AML treated with unrelated CBT.

## Study design

Between January 1999 and November 2002, 18 adult patients with de novo AML were treated with unrelated CBT at The Institute of Medical Science, University of Tokyo. The diagnosis of AML was made for all patients according to the French-American-British (FAB) Cooperative Group criteria.[7,8] Analyses of data were performed on June 1, 2003. All but one patient received 4 fractionated 12 Gy total body irradiation (TBI) on days −9 and −8 or on days −8 and −7. Cytosine arabinoside (Ara-C) was administered intravenously over 2 hours at a dose of 3 g/$m^2$ every 12 hours on days −6 and −5 or days −5 and −4 (total dose 12 g/$m^2$). Recombinant human granulocyte colony-stimulating factor (G-CSF) was administered by continuous infusion at a dose of 5 μg/kg/day. Infusion of G-CSF was started 12 hours before the first dose of Ara-C and stopped at the completion of the last dose. Cyclophosphamide (CY) was administered intravenously over 2 hours at a dose of 60 mg/kg once daily on days −4 and −3 or days −3 and −2 (total dose 120 mg/kg). One patient (case 15), who had cardiac damage as a result of extensive prior therapies, received 4 fractionated 12 Gy TBI on days −9 and −8, G-CSF combined Ara-C 3 g/$m^2$ every 12 hours on days −6 to −3 (total dose 24 g/$m^2$), and fludarabine 50 mg/body once daily on days −6 to −4. Two days or 3 days after the completion of conditioning, patients received a cord blood transplant. Sixteen patients received standard cyclosporine A (CyA) and methotrexate (MTX), and 2 patients (cases 1 and 2) received CyA only as a graft-versus-host disease (GVHD) prophylaxis. CyA was given every day starting on day −1 at a dose of 3 mg/kg/day. MTX (15 mg/$m^2$ intravenously) was given on day 1 and 10 mg/$m^2$ on days 3 and 6. Both acute and chronic GVHD were graded according to the previously published criteria.[9-11] All patients received G-CSF by intravenous infusion starting on day 1 until durable granulocyte recovery was achieved. Cord blood unit was selected according to the number of nucleated cells per recipient's weight and HLA compatibility (HLA-A and -B by serology and HLA-DRB1 high-resolution DNA typing). The chimerism status after CBT was determined either by fluorescence in situ hybridization with a Y chromosome probe for sex-mismatched CBT or by polymerase chain reaction DNA typing of HLA antigen for HLA-mismatched CBT. Five patients with AML in complete remission (CR) included in our previous study were also included (cases 3, 4, 7, 8, and 10).[4] No patients had a related or unrelated bone marrow donor available at the time of transplantation. Written informed consent for treatment was obtained from all patients. The probability of disease-free survival (DFS) was estimated by the Kaplan-Meier method.

## Results and discussion

The characteristics of the 18 patients and cord blood units are shown in Tables 1 and 2. Among the patients the median age was 43 years (range, 21-52 years), the median weight was 55.2 kg (range,

From the Department of Hematology and Oncology, Institute of Medical Science, University of Tokyo, Tokyo, Japan.

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**Reprints:** Jun Ooi, Department of Hematology and Oncology, Institute of Medical Science, University of Tokyo, 4-6-1, Shirokanedai, Minato-ku, Tokyo 108-8639, Japan; e-mail: jun-ooi@ims.u-tokyo.ac.jp.

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**Table 1. Characteristics of patients**

| Case | FAB | Age, y/sex | Body weight, kg | Recipient CMV status | Mo from diagnosis to transplantation | Disease status at transplantation | Cytogenetics at diagnosis |
|---|---|---|---|---|---|---|---|
| 1 | M1 | 45/F | 54.9 | Positive | 18 | Relapse | Normal |
| 2 | M5 | 26/M | 56.4 | Positive | 17 | Relapse | 11q23 |
| 3 | M0 | 41/M | 55.4 | Negative | 10 | CR1 | Normal |
| 4 | M2 | 45/F | 46.2 | Positive | 38 | CR2 | Normal |
| 5 | M2 | 51/F | 45.8 | Positive | 22 | Relapse | Normal |
| 6 | M5 | 33/F | 36.2 | Positive | 7 | PIF | 11q23 |
| 7 | M0 | 21/F | 56.0 | Positive | 29 | CR2 | Normal |
| 8 | M2 | 51/M | 65.4 | Positive | 11 | CR1 | Normal |
| 9 | M2 | 46/M | 55.4 | Positive | 87 | Relapse | t(8;21) |
| 10 | M1 | 40/M | 72.8 | Positive | 32 | CR2 | Normal |
| 11 | M1 | 24/M | 51.2 | Negative | 20 | Relapse | Normal |
| 12 | M2 | 48/M | 54.8 | Negative | 85 | CR4 | Normal |
| 13 | M5 | 48/M | 62.2 | Positive | 20 | CR1 | Normal |
| 14 | M0 | 27/F | 46.8 | Positive | 8 | CR1 | Normal |
| 15 | M2 | 46/M | 76.2 | Positive | 51 | Relapse | Normal |
| 16 | M4 | 24/M | 56.4 | Positive | 31 | CR2 | inv(16) |
| 17 | M3 | 52/F | 43.6 | Positive | 27 | CR2 | t(15;17) |
| 18 | M0 | 22/F | 37.6 | Positive | 9 | PIF | 8 |

FAB indicates French-American-British; CMV, cytomegalovirus; CR1, first complete remission; and PIF, primary induction failure.

36.2-76.2 kg), and the median number of cryopreserved nucleated cells was $2.51 \times 10^7$/kg (range, 1.16-5.29 $\times$ $10^7$/kg). Among the 18 patients 14 were beyond first remission at transplantation. All but 1 patient had myeloid reconstitution and median time to more than $0.5 \times 10^9$/L absolute neutrophil count was 23 days (range, 16-41 days). A self-sustained hemoglobin level of more than 85.0 g/L (8.5 g/dL) was achieved in 16 patients at a median time of 65 days (range, 16-308 days). A self-sustained platelet count more than $50 \times 10^9$/L was achieved in 16 patients at a median time of 49 days (range, 31-263 days). All patients with myeloid reconstitution showed full donor chimerism at the time of first bone marrow examination after CBT. Acute GVHD occurred in 16 of 17 evaluable patients. The grading of acute GVHD was grade I in 5 patients, grade II in 10 patients, and grade III in 1 patient. Chronic GVHD occurred in 14 of 17 evaluable patients. Among 14 chronic GVHD patients, 3 patients were extensive type. One patient died of multiple organ failure on day 27. Three patients died of relapse on days 260, 648, and 202. Fourteen patients are alive and free of disease at between 185 and 1332 days after transplantation (Table 2). The probability of disease-free survival at 2 years was 76.6%.

Several studies have suggested the promising results of unrelated CBT for adult patients.[1-6] In the report of Laughlin et al,[1] 68 adult patients received CBT. Among the 68 patients, 19 had AML. In the report of the Eurocord group,[2] 108 adult patients received CBT. Among the 108 patients, 23 had AML. However, these 2 reports did not detail the preparative regimens and prophylaxis against GVHD and the results of transplantation for AML patients. Sanz et al[3] reported the results of 22 adult patients who received

**Table 2. Characteristics of cord blood units and transplantation outcomes**

| Case | Cord blood cell dose $\times 10^7$/kg, cryopreserved | No. of HLA-A, -B, -DRB1 mismatches | Neutrophil count more than $0.5 \times 10^9$/L, d | Reticulocyte count more than 1%, d | Hemoglobin level more than 8.5 g/dL, d | Platelet count more than $50 \times 10^9$/L, d | Acute GVHD grade (organ involvement and stage) | Chronic GVHD | Survival, d* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1.63 | 1 (DRB1) | NE | NE | NE | NE | NE | NE | 27 |
| 2 | 1.16 | 2 (A, B) | 41 | 67 | NE | NE | II (skin 3, liver 1, gut 0) | Extensive | 260 |
| 3 | 2.04 | 3 (A, DRB1, DRB1) | 25 | 33 | 38 | 56 | II (skin 3, liver 0, gut 1) | Limited | 1332+ |
| 4 | 2.25 | 2 (B, DRB1) | 20 | 24 | 59 | 31 | II (skin 1, liver 0, gut 1) | Limited | 1318+ |
| 5 | 3.3 | 2 (DRB1, DRB1) | 21 | 28 | 33 | 52 | I (skin 2, liver 0, gut 0) | Limited | 1130+ |
| 6 | 5.29 | 1 (DRB1) | 28 | 33 | 67 | 53 | II (skin 3, liver 0, gut 1) | None | 648 |
| 7 | 3 | 2 (B, DRB1) | 24 | 34 | 97 | 46 | I (skin 1, liver 0, gut 0) | Limited | 926+ |
| 8 | 2.57 | 3 (B, B, DRB1) | 20 | 34 | 22 | 39 | II (skin 3, liver 0, gut 0) | Extensive | 919+ |
| 9 | 3.71 | 1 (DRB1) | 26 | 46 | 63 | 81 | II (skin 3, liver 0, gut 0) | None | 202 |
| 10 | 2.21 | 2 (B, DRB1) | 23 | 32 | 76 | 44 | I (skin 1, liver 0, gut 0) | None | 815+ |
| 11 | 3.31 | 2 (B, DRB1) | 20 | 26 | 16 | 36 | II (skin 3, liver 0, gut 1) | Limited | 640+ |
| 12 | 2.44 | 2 (A, DRB1) | 21 | 32 | 308 | 130 | I (skin 2, liver 0, gut 0) | Limited | 542+ |
| 13 | 2.34 | 2 (B, DRB1) | 26 | 43 | 270 | 263 | II (skin 3, liver 0, gut 1) | Extensive | 535+ |
| 14 | 2.6 | 3 (B, B, DRB1) | 34 | 96 | 111 | 109 | II (skin 2, liver 0, gut 1) | Limited | 493+ |
| 15 | 2.23 | 4 (A, B, DRB1, DRB1) | 22 | 28 | 22 | 35 | I (skin 2, liver 0, gut 0) | Limited | 436+ |
| 16 | 3.93 | 2 (B, DRB1) | 16 | 21 | 24 | 37 | II (skin 1, liver 0, gut 1) | Limited | 430+ |
| 17 | 2.23 | 1 (DRB1) | 24 | 35 | 76 | 46 | 0 | Limited | 381+ |
| 18 | 3.33 | 3 (B, DRB1, DRB1) | 23 | 41 | 69 | 116 | III (skin 3, liver 0, gut 3) | Limited | 185+ |

Cases 2, 6, and 9 relapsed on day 249, day 406, and day 175. GVHD indicates graft-versus-host disease; and NE, not evaluable.
*Fourteen patients are alive in complete remission at the time of writing.

CBT following a standardized preparative and GVHD regimen. Among the 22 patients, however, only 3 had AML. Recently, Barker et al[5] reported the results of 43 adult patients who received CBT after reduced-intensity preparative regimens. Although among the 43 patients 18 had AML, all patients were not eligible for conventional conditioning regimens and some patients received 2 units of cord blood and the follow-up duration after CBT was short. Although 3 recent reports showed comparative data of unrelated CBT and unrelated bone marrow transplantation (BMT) in children[12,13] and adults,[4] there have been no larger comparative studies of unrelated CBT and unrelated BMT in adult AML patients. At present, therefore, the role of unrelated cord blood as an alternative stem cell source is not well defined in adult AML patients eligible for conventional conditioning regimens.

As well as our previous report,[6] which included 11 patients with MDS-related secondary AML (sAML), the DFS rate of our 18 patients in this study was high (76.6% at 2 years). In addition, 29 total adult patients with AML (11 with sAML,[6] 18 with de novo AML in this study) received unrelated CBT in our hospital. Among the 29 patients, 22 are alive and free of disease at the time of writing. As previously described,[6] relatively higher incidence of chronic GVHD and the use of G-CSF–combined preparative regimen, which was capable of reducing the posttransplantation relapse rate in refractory myeloid malignancies,[14] may be associated with a high DFS rate in this study. Also, all patients who are alive and free of disease in our study received more than $2 \times 10^7$ nucleated cells per weight, perhaps due to the smaller size of our patients. This may be one of the possible reasons for our favorable result.

These results suggest that adult AML patients without suitable related or unrelated bone marrow donors should be considered as candidates for CBT and provide the rationale for a larger clinical study of CBT.

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