First Successful Cord Blood Transplantation from the National Marrow Donor Program for Acute Myeloid Leukemia in Japan

Naomi Kawashima, Yusuke Kagaya, Sonoko Kamoshita, Kyoko Watakabe, Emi Yokohata, Shingo Kurahashi, Yukiyasu Ozawa, Koichi Miyamura

Department of Hematology, Japanese Red Cross Nagoya First Hospital, Nagoya, Japan

Cord blood is an alternative graft source for patients lacking sibling or unrelated marrow donors, however since there has been no affiliation with cord blood banks overseas, foreign cord blood unit (CBU) is not available in Japan. Here we report the first successful case of cord blood transplantation coordinated through the National Marrow Donor Program (NMDP) for a 34-year-old Filipina of mixed race, weighing 78.5 kg. She underwent a conventional preparative regimen and was infused with a 4/6 serologically HLA-matched Asian female CBU with sufficient total nucleated cells and CD34+ cell count. Neutrophil recovery was delayed as late as on 42 days post transplantation. This was caused by a low viability of only 31.5% measured in our facility before infusion, whereas the viability before cryopreservation at the cord blood bank was reportedly 91.0%. The patient developed no fatal complications including graft-versus-host disease. The duration of the coordination process is expected to become shorter with the full collaboration between the cord blood banks in Japan and NMDP. Relatively high nucleated cell number of CBU in NMDP also serves to overcome the difficult task of finding a donor for patients with heavy weight. The great cost is also a major problem. (Journal of Hematopoietic Cell Transplantation 5(1): 18-21, 2016.)

Introduction

It is especially difficult for patients of mixed race or ethnic minorities to find a Human Leukocyte Antigen (HLA) identical unrelated donor. Cord blood is an alternative graft source for patients lacking an HLA identical sibling or unrelated marrow donor. In the United States registry, the 8/8 match rate for white patients is estimated to be 72%, 44% for Hispanics, 46% for Asian/Pacific islanders and 30% for African-Americans. In Japan, we often have had this problem in patients with mixed races. In terms of marrow donors, for those who have no candidate in the Japanese Marrow Donor Program (JMDP) because of their rare HLA type, today we can coordinate with donors in foreign marrow donor programs through JMDP, including the National Marrow Donor Program (NMDP), Buddhist Tzu Chi Stem Cells Center (BTC-SCC), Korea Marrow Donor Program (KMDP) and China Marrow Donor Program (CMDP), since the cooperation between the JMDP and the NMDP began in April 1997.

Although cord blood has advantages including acceptable 2 locus HLA mismatches, low cell dose can restrict their chance to be a donor source. To overcome this obstacle, double-unit cord blood transplantation is widely used in Europe and the United States. However, in Japan, it is not accepted since a nationwide prospective multicenter phase II study showed unsatisfactory event-free survival in 2013.

However, unfortunately, there has been no affiliation to date with cord blood banks overseas, so foreign cord blood is not available. Here we report the first successful case of cord blood transplantation from NMDP for a female patient of mixed race with AML in Japan.

Submitted May 4, 2015; Accepted August 29, 2015

Key words: allogeneic transplantation, cord blood, viability, engraftment, AML

Correspondence: Naomi Kawashima, Department of Hematology, Japanese Red Cross Nagoya First Hospital, 3-35 Michishita-cho, Naka-mura-ku, Nagoya 453-8511, Japan. E-mail: nkubota24@gmail.com

dx.doi.org/10.7889/hct.5.18 © The Japan Society for Hematopoietic Cell Transplantation
A 34-year-old Filipina was diagnosed with AML (FAB: M1) with normal karyotype in January 2012. She achieved complete remission (CR) after the first induction chemotherapy and completed four courses of consolidation therapy in June 2012. However, she relapsed a year later and was assigned to receive hematopoietic stem cell transplantation. After re-induction therapy, she achieved her second CR and consolidation therapy was continued while searching for a suitable donor. She had no HLA-matched or haploidentical siblings available. As her racial background was mixed (Philippines, Iranians and Spanish), there were no appropriate candidates for unrelated marrow donors in JMDP, NMDP, BTCSCC, KMDP or CMDP. Moreover, there was no cord blood unit (CBU) with enough total cell counts in the Japanese cord blood bank network (JCBBN) because of her heavy body weight of 78.5 kg. Upon the receipt of donor candidates’ inventory during the donor coordination process with NMDP, we finally found an appropriate CBU in it. First we contacted a coordinator in NMDP and sent the required documents, which were “Non-network search form” including the basic information of our transplantation center such as the number of cases, staffs or HLA match criteria, “24-months History Form” which is a list of transplant cases undergone within 2 years in our institution and curriculum vitae of all the physicians of our transplantation team.

This registration of our transplantation center in the NMDP network at last enabled us to request a CBU search. We asked for a list of CBU with a minimal total nuclear cell dose of $2 \times 10^7$ and more than 4 of 6 HLA antigens matched. Four CBUs from NMDP and 3 from other foreign registry were available by the search result. The CBU information report included HLA antigens, blood type, volume, total nucleated cell count, CD34+ cell count, colony forming unit, viability, the result of infection test, maternal risk information and family medical history. We picked up one of the four CBUs with sufficient total nucleated cell count and CD34+ cell count to ask an HLA typing test including all HLA-A, B, C and DR loci with a high resolution assay. Receiving its report in 9 days, we finally made a shipping request. Three days later, CBU was carried to our institution in a dry shipper by World Courier and was preserved in a freezer by the conventional method in our institution. No problems were observed in terms of its dry shipper or cartridge at the time of arrival. Temperature was monitored by attached thermometer but we were unable to view the record. As liquid nitrogen was left properly in the cartridge, the temperature was considered to be managed. The total cost of these processes amounted to 43,970 US dollars, all of which was covered by voluntary contributions at the time of the shipping request (Figure 1).

At the time of cord blood transplantation (CBT), the patient’s bone marrow had relapsed with 8% of leukemia blasts after receiving 3 courses of consolidation therapy. The woman received cytarabin (8 g/m²), cyclophosphamide (120 mg/kg) and 12 Gy of fractionated TBI combined with G-CSF as conditioning. Tacrolimus and short-term methotrexate were administered for prophylaxis against graft-versus-host disease (GVHD). Serial samples of peripheral-blood mononuclear cells were analyzed for chimerism using a PCR of informative microsatellite regions after transplantation, as described previously.6

The patient was infused with 4/6 serologically HLA-matched Asian female CBU with a total nucleated cell count of $2.75 \times 10^7$ and CD34+ cell count of $2.05 \times 10^7$ after the thawing process. Its viability was only 31.5% measured in
Table 1. Cell count and viability of CBU

|                      | Total Cell Count (×10^7/kg) | CD34+ Cell Count (×10^5/kg) | Viability (%) |
|----------------------|-----------------------------|-----------------------------|---------------|
| Pre-Cryopreservation | 2.75                        | 2.05                        | 91.0          |
| Post-Thawing         | 2.21                        | 1.24                        | 31.5          |

Discussion

The number of foreign residents in Japan has increased from 1.35 million to 2.12 million over the past 20 years according to a report from the Ministry of Justice (not published). Therefore the probability of taking care of mixed-race or foreign patients requiring stem cell transplantation, namely the patients lacking appropriate donors in Japanese conventional registry, will increase in the future.

CBU from NMDP was successfully transplanted for the first time in Japan, which can be an alternative graft source for Japanese patients lacking HLA-matched siblings, JMDP, NMDP, BTCSCC, KMDP or CNDP marrow donors or JCBBN donors. As an HLA mismatch is better tolerated in CBT than other sources, it has been particularly beneficial for racial and ethnic minority patients who have had more difficulty finding a suitably matched marrow or PBSC donor from volunteer donor registries. In addition, because of the patient’s heavy weight we could not find an appropriate CBU in JCBBN with sufficient cell number, however, several candidates of CBU were found in NMDP inventory due to the relatively high number of cell counts.

This patient achieved engraftment and did not develop acute GVHD by our institutional conventional method performed for CBU from JCBBN. However neutrophil engraftment was delayed as late as day +42 post transplantation, compared to the previous reports describing around 20–29 days post CBT.1,2,7 Except for the delayed engraftment, there were no remarkable difference in her clinical course until day +180 between transplantation of CBU from JCBBN and that from NMDP. The causes of delayed engraftment in this case are thought to be the low viability of infused CD34+ cells and HHV-6 reactivation before engraftment.

Primary graft failure and engraft delays are major obstacles to the overall success of CBT. The total nucleated cell dose, CD34+ cell dose and total colony-forming units are reportedly critical determinants of engraftment and survival after CBT.8-11 CBU with low viability of CD34+ cells postthaw has also been described to have a low probability of engraftment.12

In our case, there was a difference in viability between the report from the CB bank which was measured post processing before cryopreservation and the result acquired in our facility after thawing at bedside and before infusion. Processing, freezing, storage, transport or thawing of a CBU can damage CB cells at any point. The shipped CBU was preserved in our facility before infusion, which was reported to be 91.0% before cryopreservation at a cord blood bank (Table 1). Cytomegalovirus serology was both positive in CBU and the recipient. Blood type was major-minor mismatched. The patient carried no HLA antibody before transplantation. CBU was infused immediately after thawing without washing process. No bacterial contamination was proven by CB bag culture.

G-CSF was administered from day +7, however hematological recovery was not observed even on day +28 post CBT. Though the sign of engraftment was not observed in the bone marrow specimen of day +28, the chimerism of nucleated cells in her peripheral blood had already reached 98.5% of donor-type on day +14 and 100% on day +28. In case of rejection, we reserved the second CBU for salvage transplantation on day +35, which was ready to be shipped after our final request. However neutrophil engraftment was finally achieved on day +42. On day +52, the chimerism of granulocytes, CD3-positive T cells and CD56-positive NK cells were all 100% donor-type. Platelet engraftment was achieved on day +91. Her bone marrow maintained CR from day +0 until day +180, which was examined very week until neutrophil engraftment and followed by day +54 and 100.

The patient had skin rash on day +26 and skin biopsy revealed no evidence of engraftment syndrome but viral infection was suspected. At the same time, human herpes virus 6 (HHV-6) DNA PCR was detected in her peripheral blood with 2.0 × 10^4 copies/mL on day +12 and increased to 1.6 × 10^6 copies/mL on day +20. However it naturally decreased to 3.2 × 10^4 copies/mL on day +26 and 1.7 × 10^3 copies/mL on day +33, turning negative on day +40. Febrile neutropenia was observed before engraftment which was well controlled with antibiotics. She developed no fatal infection. Acute and chronic GVHD were not observed until day +180.
freezer with the conventional method. The condition of the dry shipper was inspected carefully, and no major problem was observed including the liquid nitrogen properly left in the shipper. There was no problem in the cartilage and no damage or breakage found in the CBU bag. It is unknown whether long-distance shipping may have impaired the cord blood. However, it is expected to establish a stable procedure for shipping, preserving or thawing cord blood throughout the long process beginning overseas.

Secondly, HHV-6 reactivation occurs more frequently after CBT and showed a higher viral load than other graft sources. Previous reports revealed that HHV-6 reactivation before neutrophil and platelet recovery was associated with significant delays in both engraftment. In this case, HHV-6 DNA PCR became positive on day +12, and skin eruption and the increase of viral load were observed subsequently. Though both disappeared by day +40 without anti-viral treatment, the delayed engraftment of both neutrophil and platelet could be prevented with the preemptive treatment of HHV-6.

It took 27 days in total from registration to the receipt of CBU in this case. This duration no doubt will become shorter with the full collaboration of the coordinating system between JMDP or cord blood banks in Japan and NMDP. A high cost will be a difficult problem to overcome patients in Japan, given the demanding quality control of cord blood. The health insurance system also differs from country to country.

Acknowledgement

The authors are very grateful to the staff members of NMDP for their generous coordination. We also thank Ms. Ikeguchi for a manipulating cord blood cells.

Conflict of interest

There are no relevant conflicts of interest to declare.

References

1. Rocha V, Labopin M, Sanz G, et al. Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. N Engl J Med. 2004; 351: 2276–2285.
2. Laughlin MJ, Eapen M, Rubinstein P, et al. Outcomes after transplantation of cord blood or bone marrow from unrelated donors in adults with leukemia. N Engl J Med. 2004; 351: 2265–2275.
3. Dehn J, Buck K, Maiers M, et al. 8/8 and 10/10 high-resolution match rate for the be the match unrelated donor registry. Biol Blood Marrow Transplant. 2015; 21: 137–141.
4. Murata M, Kanie T, Hamaguchi M, et al. Unrelated bone marrow transplantation from the National Marrow Donor Program. Int J Hematol. 1997; 66: 239–243.
5. Kai S, Wake A, Okada M, et al. Double-unit cord blood transplantation after myeloablative conditioning for patients with hematologic malignancies: a multicenter phase II study in Japan. Biol Blood Marrow Transplant. 2013; 19: 812–819.
6. Ohashi H, Kato C, Fukami S, Saito H, Hamaguchi M. Leukemic relapse in the central nervous system after allogeneic stem cell transplantation with complete remission in the bone marrow and donor-type chimerism: report of two cases. Am J Hematol. 2005; 79: 142–146.
7. Matsuno N, Wake A, Uchida N, et al. Impact of HLA disparity in the graft-versus-host direction on engraftment in adult patients receiving reduced-intensity cord blood transplantation. Blood. 2009; 114: 1689–1695.
8. Page KM, Zhang L, Mendizabal A, et al. Total colony-forming units are a strong, independent predictor of neutrophil and platelet engraftment after unrelated umbilical cord blood transplantation: a single-center analysis of 435 cord blood transplants. Biol Blood Marrow Transplant. 2011; 17: 1362–1374.
9. Terakura S, Azuma E, Murata M, et al. Hematopoietic engraftment in recipients of unrelated donor umbilical cord blood is affected by the CD34+ and CD8+ cell doses. Biol Blood Marrow Transplant. 2007; 13: 822–830.
10. Gluckman E, Rocha V, Boyer-Chammard A, et al. Outcome of cord-blood transplantation from related and unrelated donors. Eurocord Transplant Group and the European Blood and Marrow Transplantation Group. N Engl J Med. 1997; 337: 373–381.
11. Wagner JE, Barker JN, DeFor TE, et al. Transplantation of unrelated donor umbilical cord blood in 102 patients with malignant and nonmalignant diseases: influence of CD34 cell dose and HLA disparity on treatment-related mortality and survival. Blood. 2002; 100: 1611–1618.
12. Scaradavou A, Smith KM, Hawke R, et al. Cord blood units with low CD34+ cell viability have a low probability of engraftment after double unit transplantation. Biol Blood Marrow Transplant. 2010; 16: 500–508.
13. Tomonari A, Takahashi S, Ooi J, et al. Human herpesvirus 6 variant B infection in adult patients after unrelated cord blood transplantation. Int J Hematol. 2005; 81: 352–355.
14. Chevallier P, Hebia-Fellah I, Planche L, et al. Human herpesvirus 6 infection is a hallmark of cord blood transplantation in adults and may participate to delayed engraftment: a comparison with matched unrelated donors as stem cell source. Bone Marrow Transplant. 2010; 45: 1204–1211.
15. Duley R, Salleron J, Dewilde A, et al. Early human herpesvirus type 6 reactivation after allogeneic stem cell transplantation: a large-scale clinical study. Biol Blood Marrow Transplant. 2012; 18: 1080–1089.