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Umbilical Cord Blood for Unrelated Bone Marrow Replacement; Asia Bank and Japan Cord Blood Bank Network Update

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Abstract

Cord blood offers many advantages including a high concentration of hematopoietic stem cells, a large number of potential donors, and ease of harvest. Furthermore, since there is no risk for either the mother or baby, few people refuse to donate. There is thought to be a low risk for virus contamination and also probably a low incidence and severity of GVHD. Cord blood can be obtained quickly without the assistance of a coordinator and one or 2 locus-mismatched HLA is usually acceptable. In Japan, there are 10 cord blood banks supported by the government. Between 1996 and June 2002, 9,500 units were registered with the Japan cord blood bank network (JCBBN). 630 units were delivered and most of these were transplanted. The status of registered cord blood units worldwide is shown. 59,081 units have been registered by NETCORD. The Japan cord blood bank network accounts for 13% of these units. I will discuss the Tokyo cord blood tank (TCBB). The bank at Tokyo, to which we belong, is one of the largest banks in Japan. We helped to establish Asia CORD in 2000 and have held annual conferences and meetings in Tokyo to exchange information. So far, China, Korea, Taiwan, Thailand, Viet Nam and Japan have participated. We accepted three trainees from the Ho Chi Minh City Blood Transfusion and Hematology Center for training in cord blood transplantation in May 2001. In January 2002, a patient with ALL received cord blood and was successfully engrafted at Ho Chi Minh City Blood Transfusion and Hematology Center. We present here the clinical outcome of these patients through Tokyo cord blood bank and Japan cord blood bank network. First, the number of CB units stored and registered at JCBBN and TCBB has increased rapidly over the past two years. Second, the survival rate of acute leukemia patients in release was significantly lower than that in patients in CR. Third, the engraftment rate in patients with metabolic disease (50%) was lower than that in patients with leukemia. Fourth, there was no significant difference in the incidence of acute GVHD greater than grade II between patients with a 1-locus and 2-locus mismatch. Finally, the incidence of acute GVHD was relatively low, and there were no deaths related to acute GVHD.

I will talk about the status of unrelated cord blood transplantation in Japan and divide my talk into two parts.

Part 1 addresses the history of cord blood transplantation and banking in Japan and Part 2 presents the clinical outcome of cord blood transplantation in Japan. Cord blood offers many advantages including a high concentration of hematopoietic stem cells, a large number of potential donors, and ease of harvest. Furthermore, since there is no risk for either the mother or baby, few people refuse to donate. There is thought to be a low risk for virus contamination and also probably a low incidence and severity of GVHD. Cord blood can be obtained quickly without the assistance of a coordinator and one or 2 locus-mismatched HLA is usually acceptable.

In Japan, there are 10 cord blood banks supported by the government.

The first cord blood transplantation in Japan was performed from an HLA-matched sibling donor in June 1995, and the first local bank in Japan was established the next month.

In 1997, guidelines for cord blood transplantation were established by a committee supported by the government. (Ministry of Health, Labor and Welfare) and the Tokyo Cord Blood Bank was established.

In 1998, the technical guidelines for cord blood processing and transplant were established by committee members and the Japan cord blood bank network was established with 9 member banks.

It became possible for anyone to access the Japan cord blood bank network to find HLA typing in September 2000. Another local bank was allowed to join the Japan cord blood bank network, which now has 10 member banks in December 2001. This network is partially supported by the Ministry of Health, Labor and Welfare and consists of 10 local banks connected by computer. The general administration office is in the Japanese Red Cross Society. Each bank sends cord blood information, including HLA typing, cell count, and so on, to the office every month.

The annual increase in the number of cord blood transplants from each local bank in Japan is shown.

The number of cord blood transplants has dramatically Increased every year since 1996 and about 200 transplants were performed in 2001.

Between 1996 and September 2001, 8386 units were registered with the Japan cord blood bank network. 576 units were delivered and most of these were transplanted. The status of registered cord blood units worldwide is shown. 59,081 units have been registered by NETCORD. The Japan cord blood bank network accounts for 13% of these units.

I will discuss the Tokyo cord blood bank. The bank at Tokyo, to which we belong, is one of the largest banks in Japan.

The division of cell processing at the Institute of Medical Science University of Tokyo was established in 1995. Tokyo Cord Blood Bank was established and we helped to establish NETCORD in 1997. We shipped the first cord blood unit next year. In 1999, we introduced the Bio Archive system at the Institute of Medical Science University of Tokyo and at Nihon University School of Medicine. We helped to establish AsiaCORD in 2000 and have held annual conferences and meetings in Tokyo to exchange information.

So far, China, Korea, Taiwan, Thailand, Viet Nam and Japan have participated. We accepted three trainees from the HoChiMinh City Blood Transfusion and Hematology Center for training in cord blood transplantation in May 2001. In January 2002, a patient with ALL received cord blood and was successfully engrafted at Ho Chi Minh City Blood Transfusion and Hematology Center.

The organization of the Tokyo Cord Blood Bank consists of the management committee, clinical judgment committee, selection committee of the hospital for harvesting cord blood, and the ethical committee.

The Foundation for donated blood distribution is responsible for transport and shipping. There are two processing and storage centers: one at theNihon University School of Medicine (NUSM) and the other at the Institute of Medical Science University of Tokyo (IMSUT).

Cord blood is harvested at 9 hospitals.

The mean volume of cord blood at Tokyo Cord Blood Bank has been 71.8 ml and more than 1,000 units have been collected in each of these 3 groups: 60 ml to 70 ml, 70 to 80 ml, and 80 to 90 ml. The methods used to count cord blood cells are; CBC and nucleated red blood cells were measured by Sysmex XE, colony assay was performed using MethoCult, and CD34-positive cells were counted using Pro Count Kit.

As of March 2002, we have collected 3768 units. The mean values of volume, nucleated cells, nucleated cell recovery, CD34-positive cells, CD34-positive cells recovery, CFU, and CFU recovery are 71.8±21.9 ml, $6.34\pm3.3\times10^{8}$, 82.1±7.0%, $14.1\pm9.6\times10^{5}$, 90.0±21.9%, $10.5\pm8.3\times10^{5}$, 96.1±28.9% respectively.

I will discuss the clinical outcome of cord blood transplantation.

I will first address the data from the Tokyo Cord Blood Bank and then those from the Japan Cord Blood Bank Network overall.

The patient characteristics are summarized. Ninety two patients received cord blood between 1997 and March 2002.

Fifty four were children, aged less than 15 years, and thirty eight were adults. The mean age among the children was 4.7 years, ranging from 0 to 14 years, while the adults averaged 33 years, ranging from 15 to 58 years.

Most of the patients among both the children and adult had acute leukemia.

The mean nucleated cell dose per kg in the children and adults was 6.1×10^{7} and 2.4×10^{7} respectively.

With regard to HLA disparity, 29 children showed a one-locus mismatch (5/6) and 21 showed a two locus mismatch (4/6) while 12 adults showed a one-locus mismatch (5/6)and 21 showed a two-locus mismatch.

With regard to engraftment after transplantation,while the engraftment rate for children between 2 and 5 years of age, is very low, the overall engraftment rates in children and adults have been about 69% and 63% respectively. With regard to the nucleated cell dose ,the engraftment rates in both children and adults with a nucleated cell dose of less than 2.5×10^{7} per kg are lower than those with a dose of more than 2.5×10^{7} per kg.

The engraftment rates in children and adults with acute leukemia ranging from 54% to 100%. However, these differences are not significant.

With regard to HLA disparity the engraftment rate in the one-locus mismatch (5/6) group is not significantly different from that in the two-locus mismatch (4/6) group for both children and adults. The engraftment rate ranges from 62% to 74%. For most of the patients among both

children and adults, this was their first cord blood transplant and among these patients the engraftment rate ranges from 67% to 73%.

With regard to the incidence and severity of acute GVHD, among the engrafted patients, GVHD greater than grade III developed in 4 of 37, or 11%, in children, and in 1of 24, or 4% in adults.

The clinical outcome is shown.

The overall survival rates in children and adults are 52% and 57% respectively. Death has mostly been transplant-related, which mainly involves infection and relapse or progression of the disease.

I will discuss the clinical outcome of cord blood transplantation for the Japan Cord Blood Bank Network overall.

The patient characteristics are summarized. 477 patients received cord blood transplantation between 1997 and September 2001. 331 were children, and 146 were adults.

The mean age among children was 4.9 years, ranging from 0 to 14 years, while adults averaged 32.8 years, ranging from 15 to 64 years.

The mean nucleated cell dose per kg in children and adults was 5.55×10^7 and 2.83×10^7 respectively.

The body weight in children and adults was18.5kg and 52.1 kg respectively.

Seventy-six percent of the patients had hematological malignancy, including ALL, AML, CML, MDS and other types of leukemia.

About 10% had a non-hematological malignancy including metabolic disease, immunodeficiency, and aplastic anemia.

With regard to the relationship between HLA disparity and engraftment, there were no significant differences in engraftment between a full match (6/6) one locus mismatch (5/6) and two locus mismatch (4/6).

The incidence and severity of acute GVHD in 346 engrafted patients are shown. Twenty-three percent of the patients did not develop any GVHD while only 21% showed GVHD greater than grade III.

The relationship between HLA disparity and the incidence and severity of acute GVHD is shown.

The incidence of GVHD greater than grade II in the one locus mismatch (5/6) group two locus mismatch (4/6) group was 41% and 52% respectively. This difference was not statistically significant.

The relationship between transplanted nucleated cell dose and disease free survival is shown.

Patients who received nucleated cell dose of more than 4×10^7 per kg have had a better disease free survival rate than those who received less than 4×10^7 per kg. This difference was significant. Overall survival in patients with ALL by disease status at transplant is shown.

The survival probability of patients who received a transplant in their 1^{st} or 2^{nd} CR was 54.8%. On the other hand, that in advanced CR or relapse was only 9.9%. This difference was significant.

In children, event free survival in patients with ALL by disease status at transplant is shown. This difference was also significant.

Overall survival in patients with AML by disease status at transplant is shown. The survival probability of patients who received a transplant in their 1^{st} and 2^{nd} CR or more advanced was 63.7% and 58.6% respectively.

In contrast, that in relapse was 14.3%. Again, there was a significant difference between these groups.

In children, event free survival in patients with AML by disease status at transplant is shown. This difference was also significant.

The survival rates among patients with metabolic disease, including Hunter syndrome, Hurler syndrome and adrenoleukodystrophy were about 50%.

With regard to acute GVHD, two of eight engrafted patients developed grade II GVHD, which is only 25%, but again only half of the patients were engrafted.

In summary First, the number of CB units stored and registered at JCBBN and TCBB has increased rapidly over the past two years.

Second, the survival rate of acute leukemia patients in relapse was significantly lower than that in patients in CR.

Third, the engraftment rate in patients with metabolic disease (50%) was lower than that in patients with leukemia.

Fourth, there was no significant difference in the incidence of acute GVHD greater than grade II between patients with a 1-locus and 2-locus mismatch.

Finally, the incidence of acute GVHD was relatively low, and there were no deaths related to acute GVHD.