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We investigated the potential correlation between the characteristics prior transplantation and the subsequent clinical outcomes in 175 consecutive patients who received HSC transplantation from HLA-mismatched/haploidentical donors. Patients eligible for study were those with a diagnosis of leukemia, all lacking an HLA matched sibling or unrelated donor. Patients ranged in age from 6 to 53 years (median 25 years) and donors from 13 to 66 years (median 40 years). Compatibility testing of family members included serology and intermediate resolution DNA typing for HLA-A, -B, and -C antigens, plus high resolution DNA typing for HLA-DRB1, -DQB1, and -DPB1. Donors included 72 mothers (41%), 29 fathers (16.6%), 54 siblings (31%), 16 children (9%), 4 cousins (2.3%), with various grades of HLA disparity: 28 (16%) with 1; 79 (45%) with 2; 68 (39%) with 3 antigen mismatch. Grafts (BM+PB) was harvested from donor BM collected after four days of G-CSF, and PB collected after 5 days of G-CSF. The graft was analyzed for content of $CD34^+$ cells and subsets of lymphoid cell populations, $CD3^+$, $CD4^+$, $CD8^+$, and $CD14^+$, using standardized Multi-set kits (Becton-Dickinson, San Jose, CA, USA). All patients enrolled in this study were treated with a uniform conditioning regimen (BuCy2+ATG), given GVHD prophylaxis (CsA+ short term MTX), and followed from 36 to 1191days after transplantation (median 401 days). Univariate analysis for survival indicated that disease status prior transplantation and donor $CD3^+$ cell dose were the only predictors of the 2-year probability of survival: early disease (77.8%), intermediate disease (38%), and those with advanced disease (52%), [P=0.018]; survival in those given a $CD3^+$ cell dose $<150 \times 10^6$/kg was 52% and $CD3^+$ cell dose $\geq 150 \times 10^6$/kg was 74%, respectively [P=0.0215]. This was confirmed by multivariate analysis: patients transplanted with intermediate/advanced stage disease [RR=1.568 (95% CI, 1.128-2.17); P=0.007] had a worse overall survival; Infusion of a high dose of $CD3^+$ cells ($\geq 150 \times 10^6$/kg) had improved survival [0.530 (0.300-0.95); P=0.03] without increase the incidence of developing Grade 3-4 aGVHD [1.27 (0.58-2.76); P=0.56]. Our data have indicated that with the current protocol, patients given a relatively high dose of $CD3^+$ cells ($\geq 150 \times 10^6$/kg) have a significantly better overall survival after transplantation than those given lower doses of $CD3^+$ cells ($<150 \times 10^6$/kg).

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HLA-DRB1 ALLELE AND DRB1-DQB1 HAPLOTYPE FREQUENCY AS PREDICTION CRITERION FOR THE DURATION OF AN UNRELATED BLOOD STEM CELL DONOR SEARCH

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Identification of at least one fully compatible unrelated blood stem cell donor requires confirmatory typing (CT) of 2-5 potentially matched donors. We developed an algorithm, based on the frequency of the HLA-DRB1 alleles and the estimated DRB1-DQB1 haplotypes of the patient, which defined the number of potentially matched donors requested for CT. This strategy aimed to result to a shorter UDS duration as well as to cost-effectiveness in the process of a Unrelated donor search (UDS).

HLA-DRB1 allele frequencies were calculated based on the National Marrow Donor Program dataset of 65752 individuals. HLA-DRB1-DQB1 haplotype data were obtained from the German National Donor Registry (ZKRD). HLA-DRB1 allele frequencies within a given broad allele family (e.g. HLA-DRB1*11) were the main point of consideration, since for most donors only a low resolution typing was available. HLA-DRB1 alleles with a frequency of 80-100% within their broad allele family were considered as very frequent. Alleles with a frequency of 30-79% within their broad allele family as average, and a frequency of 0-29% as rare. In addition, if the association of a particular HLA-DRB1 allele with the corresponding HLA- DQB1 allele was more frequent than 80%, this DRB1-DQB1 haplotype was considered as very common. A haplotype corresponding to 20% to 79% of a given DRB1 allele was classified as average, whereas a haplotype frequency of lower than 20% of a particular DRB1 allele was considered as rare. Based on this algorithm, the probability to find a fully compatible donor for a patient was considered high, medium or low. For the patients with high, medium or low probability, three, 4 or 5 potentially matched unrelated donors were requested for CT at the beginning of a UDS, respectively.

In a group of 794 patients, the average duration of UDS and the average number of identified donors has been calculated. Eighty percent of the searches showed a high, 7% a medium and 13% a low probability to find a fully compatible donor. The average UDS duration was 55, 105, and 135 days in the three groups, respectively. An average of 2.0, 1.6, and 1.0 donors were found in the groups with high, medium, and low probability, respectively.

The algorithm used in our search unit, allows a prediction of UDS duration and the estimation of the UDS success rate. A variable number of potentially matched donors should be requested for CT, which allows economising the UDS process without prolongation of the UDS duration.

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UNRELATED CORD BLOOD TRANSPLANTATION AFTER MYELOABLATIVE CONDITIONING IN ADULT PATIENTS WITH ACUTE MYELOID LEUKEMIA NOT IN REMISSION

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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) not in remission, a suitably matched related donor is unavailable for approximately two-thirds of patients. Recently, umbilical cord blood from unrelated donors have been used as an alternative stem cell source for adult patients with AML. Here, we report our clinical results of unrelated cord blood transplantation (CBT) after myeloablative conditioning for 30 adult patients with AML not in remission. Between August 1998 and November 2005, 30 adult patients with AML not in remission were treated with unrelated CBT at The Institute of Medical Science, University of Tokyo. Diagnoses at transplantation included de novo AML (n=14) and MDS-related secondary AML (n=16). All patients received four fractionated 12 Gy total body irradiation and chemotherapy as myeloablative conditioning. 27 patients received standard cyclosporine (CyA) and methotrexate, and 3 patients received CyA only as a graft-versus-host disease (GVHD) prophylaxis. Among the patients the median age was 45.5 years (range, 19-55 years), the median weight was 55 kg (range, 36-76 kg) and the median number of cryopreserved nucleated cells was 2.43×10^7/kg (range, 1.16-5.29×10^7/kg). 28 patients had myeloid reconstitution and the median time to more than 0.5×10^9/L absolute neutrophil count was 21.5 days. A self-sustained platelet count more than 50×10^9/L was achieved in 23 patients at a median time of 42 days. Acute GVHD above grade II occurred in 15 of 28 evaluable patients and chronic GVHD occurred in 17 of 23 evaluable patients. Among 17 chronic GVHD patients, 7 patients were extensive type. 16 patients are alive and free of disease at between 280 and 2937 days after transplantation. With a median follow-up of 2013 days, the probability of disease-free survival at 5 years was 51.8%. These results suggest that adult patients with AML not in remission should be considered as candidates for CBT.

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REDUCED-INTENSITY ALLOGENEIC UMBILICAL CORD BLOOD TRANSPLANTATION (RI-UCBT) IN PEDIATRIC RECIPIENTS WITH MALIGNANT AND NON-MALIGNANT DISEASES

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There is a significant amount of morbidity and mortality following myeloablative UCBT, in part secondary to a log less TNC/CD34+ cells/kg infused compared to matched BM or PBSC (Cairo et al, Blood, 1997). RI conditioning followed by BM or matched PBSC may potentially reduce the incidence of TRM and the late effects associated with myeloablative regimens without increasing the risk of graft failure or relapse (Satwani/Cairo, BBMT, 2005). Since UCB has a log less cells, it remains to be determined whether RI conditioning will be as successful when combined with UCBT. We currently report the results of RI-UCBT in 21 pediatric pts, median age 7.5 years (0.33-20 yrs). HLA match: 4/6 -13, 5/6-5, 6/6-3. Malignant diseases n=14, Hodgkin's disease n=5 (CR2-2, SD -1 and PD-2), NHL n=2 (ALCL-PR1 and DLBCL-SD), CML (CP-1), AML n=3 (CR1-2and CR2-1), MDS n=3 and non-malignant diseases n=7, HLH-2, WAS-1, B-Thal-1, SAA -1, SCID's-2. RI conditioning consisted of fludarabine (150-180mg/m^2)with either busulfan (8mg/kg)+ATG (n=16) or cyclophosphamide+ATG±etoposide (n=5). GHVD prophylaxis consisted of FK-506 and MMF (Osunkwo/Cairo, BBMT, 2004). The median TNC/ kg was 3.58×10^7(0.92-22.61) and the median CD34$^+$ cell dose/kg was 2.54×10^5(0.34- 9.57). The median time for neutrophil and platelet engraftment was 17.5 days (1-47) and 52 days (6-170), respectively. There were 6 primary graft failures (1 CML, 1 b-Thal, 2 HLH, 1 MDS, and 1 AML), 4/6 who were regrafted with myeloablative conditioning followed by a UCBT achieved100% engraftment. In the remainder 14 evaluable patients the donor chimerism at 30 and 180 days was 74± 20% and 90± 10%, respectively. The probability of developing grade II-IV aGVHD and cGVHD was 28.6% and 16.7%, respectively. Incidence of TRM was 14%. The 2yr OS in all patients was 59.8% (CL_{95}: 37.9-81.6). The 2yr OS for patients with average risk malignancy was 77.8% (CL_{95}: 50.6-100) and poor risk malignancy was 20.2% (CL_{95}: 0-55.1). These preliminary results indicate that despite a log less TNC/CD34+ cells/kg infused compared to matched BM or PBSC, RI-UCBT may result in rapid hematopoietic reconstitution while decreasing TRM compared to myeloablative UCBT and be associated with high donor chimerism. Patients with some diseases such as CML, b-Thal, and HLH may require increased intensity of conditioning. Further follow-up is required to evaluate long-term effects in pediatric patients following RI-UCBT.

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GVHD PROPHYLAXIS WITH TACROLIMUS OFFERS LOW EARLY MORTALITY AND BETTER SURVIVAL AFTER REDUCED-INTENSITY CORD BLOOD TRANSPLANTATION IN ELDERLY PATIENTS (≥55 YEARS)

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We have reported the feasibility of reduced-intensity cord blood transplantation (RICBT) for elderly patients with hematological malignancies at the last Tandem meeting (Abstract#18). Despite of its efficacy, treatment-related mortality (TRM) at day 100 post-transplant was considerably high (50%). Our preliminary data suggested that tacrolimus (TAC) as GVHD prophylaxis reduced TRM. Therefore, we conducted a retrospective analysis of 35 consecutive patients ≥55 years who underwent RICBT with single CB unit at our institute using TAC as GVHD prophylaxis from Jan. 2004 to Apr. 2006. Diagnoses were AML/MDS (21), CML (4), ALL (6), and ML (4), 11 of them were categorized as standard risk (those who were in CR, CP, and untreated MDS) and 24 of them were as high risk diseases (other than standard). Median total nucleated cell and CD34$^+$ cell numbers were 2.25 ×10E7 /kg (range, 1.82-3.6) and 0.78 ×10E7 /kg (range, 0.11-1.9), respectively. Thirty-two patients (91%) were conditioned with 125 mg/sqm of fludarabine, 80 mg/sqm of melphalan, and 4 Gy of TBI, and the other 3 were with slight modification. TAC was started at day -1 of transplant at 0.03 mg/kg for 24 hr. Thirty-three of them were treated with TAC alone, and 2 were with TAC and mycophenolate mofetile. Eight patients died before day 28. Among the remaining 27 patients, 24 (88.9%) of them achieved neutrophil engraftment at a median 19 days (range, 12-33). Fifteen out of 25 (60%) and 9 out of 17 (53%) evaluable patients experienced acute GVHD (grade II-IV: 12, III-IV: 8) and chronic GVHD (limited: 5, extensive: 4), respectively. Twelve patients (37%) died before day 100 post-transplant. At the median 420 days post-transplant (range, 54-773), 18 survived, with 16 being disease-free. Overall (OS) and progression-free survival at 1 year post-transplant were 54.6% and 41.3%, respectively. Remarkably, OS at 1 year post-transplant for those with standard risk diseases was 91%, whereas it was 38% for those with high risk. Among 17 deaths observed, 6 were from disease progression and the other 11 were from non-relapse causes. Multivariate analyses revealed that age older than 60, poor ECOG performance status (≥2) before transplant, higher disease risk were associated with an increased risk for mortality. To conclude, RICBT with TAC is a feasible approach for elderly patient, especially for those with standard risk diseases. Longer follow-up is necessary to further evaluate the curability of this approach.

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OUTCOMES OF UNRELATED DONOR HEMATOPOIETIC STEM CELL TRANSPLANTATIONS FOR PEDIATRIC PATIENTS IN THAILAND

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Clinical trials using unrelated donors are accepted choices worldwide for patients in need of transplant but lacking HLA-matched related donors. To study the outcome we reviewed our experience with 28 Thai pediatric patients (22 male; 6 female) given hematopoietic stem cell transplantations from unrelated donors (UD-HSCT) selected using DNA high-resolution typing of both HLA class I and II loci, from May 2001 to September 2006. Median age and weight were 7 years 7 months (1 y 3 m-16 y 9 m), and 24.5 kg (7.8-68.8), respectively. Twenty patient/donor pairs (71.43%) were fully matched; eight (28.57%) were 5/6 matched. Patients had either non-malignant (n=23) or malignant (n=5) diseases. Among non-malignant group there were beta-thalassemia major (n=16), adrenoleukodystrophy (n=3), severe aplastic anemia (n=2), Wiskott-Aldrich syndrome (n=1), and Griscelli syndrome (n=1); while there were acute lymphoblastic leukemia (n=2), chronic myeloid leukemia (n=1), juvenile chronic myelomonocytic leukemia (n=1), and relapsed Hodgkin disease (n=1) in malignant group. Besides umbilical cord blood transplant (CBT) recipients (n=3) for whom graft-versus-host disease (GvHD) prophylaxis with mainstay cyclosporine was used, GvHD prophylaxis for bone marrow (BMT) and peripheral blood stem cell transplant (PBSCT) composed of cyclosporine plus short-term methotrexate in first 12 recipients; tacrolimus plus short-term methotrexate in last 13. Median numbers of infused CD34+ cells were 5.15×10^6/kg (1.24-33.6) in BMT (n=17), 6.8×10^6/kg (3.91-17.17) in PBSCT (n=8), and 3×10^5/kg (2.26-25) in CBT (n=3). The probability of hematopoietic recovery at day 30 was 85.71%. Of the engrafted patients (n=25) the cumulative probability of acute and chronic GvHD were 32 and 16%, respectively. Ten patients died of transplant-related complications. The probability of transplant-related mortality (TRM) at 30 days, 100 days, 1 year, and 2 years were 10.71, 28.57, 28.57, and 35.71%, respectively. Median follow-up time for surviving patients was 1 year 6 months (2 m-5 y 4 m). Overall (OS) and disease-free survival (DFS) rates were 64.29 and 57.14%, respectively. Of the beta-thalassemia patients group (n=16) the OS and DFS rates were superior; 81.25 and 75%, respectively. UD-HSCT with donor selection based on high-resolution HLA typing is associated with low incidence of graft failure and GvHD. This observed outcome is favorable and comparable to that of children transplanted from HLA-identical siblings.