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EVALUATION OF HLA MATCHING REQUIREMENTS IN UNRELATED HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR NONMALIGNANT DISORDERS

Woolfrey, A.[1], Horan, J.[2], Wang, T.[3], Haagenson, M.[4], Ayas, M.[5], Baxter-Lowe, L.A.[6], Bielorai, B.[5], Davies, S.[7], Dehn, J.[8], Frangoul, H.[9], Gajewski, J.[10], Gupta, V.[11], Hale, G.A.[12], Hurley, C.K.[13], Marino, S.[14], McCarthy, P.[15], Orchard, P.[16], Oudshoorn, M.[17], Pollack, M.S.[18], Reddy, V.[19], Shaw, P.J.[20], Spellman, S.R.[4], Lee, S.J.[1] [1] Fred Hutchinson Cancer Research Center; [2] Children's Healthcare of Atlanta at Egleston; [3] Medical College of Wisconsin; [4] CIBMTR, Minneapolis; [5] King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia; [6] University of San Francisco Medical Center; [7] Cincinnati Children's Hospital Medical Center; [8] National Marrow Donor Program; [9] Vanderbilt University Medical Center; [10] Oregon Health & Science University; [11] Princess Margaret Hospital; [12] All Children's Hospital, St. Petersburg, FL; [13] Georgetown University Medical Center; [14] University of Chicago Medical Center; [15] Roswell Park Cancer Institute; [16] University of Minnesota Amplatz Children's Hospital; [17] Leiden University Medical Centre; [18] UTHSC Veterans Health Care System; [19] Florida Hospital Cancer Institute Florida Center for Cellular Therapy; [20] Children's Hospital at Westmead, Sydney, Australia

Previous studies of HLA matching in unrelated donor (URD) transplantation have focused largely on patients with leukemia. The effect of donor-recipient mismatching in patients with nonmalignant disorders (NMD) may differ and remains poorly defined.

We analyzed data from the CIBMTR database on 667 URD transplants performed for a NMD between 1995 and 2007. The initial analysis was restricted to donor-recipient pairs that were allele matched at the A, B, C and DRB1 loci (375), matched at 7/8 alleles (191) or matched at 6/8 alleles (101). The median patient age was 9 years and did not differ between the three groups. The distribution of the types of NMD was similar in the three groups.

Across all groups, the most common were severe aplastic anemia (54%), immunodeficiencies (18%), inborn errors of metabolism (14%) and histiocytic disorders (10%). Transplants involving 8/8 matched pairs were more likely to have been performed after 2001 (72% vs. 60% vs. 36%, $p < 0.0001$), to involve a Caucasian recipient (78% vs. 68% vs. 62%, $p = 0.009$) and to involve donor and recipients who were both CMV seronegative (39% vs. 24% vs. 27%, $P = 0.004$), respectively. The unadjusted overall survival at five years was 65%, 57% and 47% after transplants involving 8/8, 7/8 and 6/8 matches ($p = 0.004$). The cumulative incidence of grade 2-4 acute GVHD was 43, 40 and 44% ($p = 0.76$) at 100 days and of chronic GVHD was 32, 29, and 30% ($p = 0.82$) at 2 years. The multivariate analyses demonstrated an association between degree of mismatch and mortality. The hazard ratio for 7/8 matched transplants was 1.31 (95% CI, 0.98-1.75, $p = 0.066$) and for 6/8 matched transplants was 1.75 (1.25-2.45, $p = 0.0012$) compared to 8/8 matched pairs. No association between degree of mismatching and acute GVHD II-IV, acute GVHD III-IV or chronic GVHD was noted.

Our results underscore the importance of HLA matching in transplants for NMD. They also suggest that the effects of mismatching are mediated by a complication other than GVHD. Graft failure may be an important cause of treatment failure; we are currently collecting the chimerism data necessary to analyze this outcome.

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THE RISK FACTORS FOR SURVIVAL IN HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION: A SINGLE-CENTER STUDY OF 440 CASES

Wu, T., Zhao, Y.-L., Wang, J.-B., Cao, X.-Y., Yin, Y.-M., Sun, Y., Lu, Y., Zhou, J.-R., Gao, Y.-Q., Da, W.-M., Ji, S.-Q., Zhang, Y.-C., Lu, D.-P. Beijing Daopei Hospital, Beijing, China

To determine the risk factors for survival in haploidentical hematopoietic stem cell transplantation (haplo-HSCT), the clinical outcomes of a large series of haplo-HSCT in our hospital are analyzed. From April 2002 to April 2010, consecutive 440 patients with hematological malignancies who underwent haplo-HSCT were included. The median age was 23 (3-59) years old. The diagnosis included AML (39.8%), ALL (35.9%), MDS (3.6%), CML (16.1%), and others (4.6%). Transplants at CR1 or CML-CP1, ≥ CR2 or CML-CP2/AP, and advanced disease (refractory/relapsed acute leukemia or CML-BC) were 33.4%, 40.9% and 25.7%. HLA mismatched at 1, 2, 3 loci was 13.2 %, 27.5%, 59.3%, respectively. All patients received unmanipulated combined marrow and peripheral blood for transplant after BUCy2/CyTBI plus ATG conditioning. Prophylaxis and treatment of GVHD were reported previously (Dao-Pei Lu et al., Blood 2006; 107:3065). Steady hematopoietic reconstitution was seen in 98.6% of recipients. The cumulative incidences of grade II to IV acute GVHD and chronic GVHD were 32.6%, 61.3%. With the median follow-up of 32 (3-99) months, 2-year overall survival (OS) rates were 76.1%, 59.8% and 31.1% in CR1 or CML-CP1, ≥ CR2 or CML-CP2/AP and advanced disease, respectively. Univariate analysis showed that lower $CD34^+$ cell infused ($< 2.85 \times 10^6$/kg) has much poor OS compared with higher $CD34^+$ cell transplanted ($> 2.85 \times 10^6$/kg) ($p = 0.006$); Transplants in sex-mismatched donor-recipient pair has remarkable worse 2-year OS (37.6% in male donor to female recipient, 55.3% in female donor to male recipient) compared with sex-matched transplants (65.6%) ($p = 0.000$). Multivariate analysis showed that disease status before transplant, $CD34^+$ cell infused and sex-matched or not between donor and recipient were pivotal impact factors on survival. In conclusion, our clinical results from a large series of haplo-HSCT demonstrate that advanced disease, low $CD34^+$ cell infused, and sex-mismatched between donor and recipient are the risk factors for OS.

IMMUNE RECONSTITUTION

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DIFFERENTIAL PROTEOMIC SIGNATURES AND PATHWAYS IN CORD BLOOD (CB) VS PERIPHERAL BLOOD (PB) $CD56^{+dim}$ NK CELLS: OVER EXPRESSION OF CELSR1, BLM AND BDNF EARLY DEVELOPMENTAL STAGE PROTEINS IN CB VS PB $CD56^{+dim}$ NK CELLS

Day, N.S.[1], Shereck, E.[1], Ayello, J.[1], McGuinn, C.[1], Satwani, P.[1], Atallah, J.[1], van de Ven, C.[1], Wapner, R.[2], Lim, M.[3], Cairo, M.S.[1,4,5] [1] Columbia University, New York, NY; [2] Columbia University, New York, NY; [3] University of Michigan, Ann Arbor, MI; [4] Columbia University, New York, NY; [5] Columbia University, New York, NY

Background: Umbilical cord blood (UCB) transplantation is associated with delayed hematopoietic and immune reconstitution (Szabolcs/Cairo et al Seminars in Hematology 2010). NK cells play important roles in both innate and adaptive immunity and are characterized as a $CD56^+$ cell population (Shereck/Cairo et al PBC 2007). We demonstrated the ability to ex-vivo expand CB MNC into various phenotypes of $CD56^{+dim}$ and $CD56^{+bright}$ NK (totally 60%) and NKT cells (40%) with profound *in vitro* and *in vivo* cytotoxicity against hematological malignancies (Ayello/Cairo BBMT 2006 & Exp. Hematology 2009). Our genomic studies showed highly expressed CD34 and other genes in CB vs PB $CD56^{+dim}$ NK cells (Day/Cairo et al ASH 2010).

Objective: We sought to determine proteomic signatures in CB vs PB $CD56^{+dim}$ NK cells.

Methods: CB NK $CD56^+16^{+dim}$ cells (94% enrichment) isolated using a standard kit (Miltenyi Biotec). Proteomic studies were performed by LC MS/MS with iTRAQ™ labeling and analyzed with SEQUEST, ProteinProphet, and INTERACT. Proteomic pathways were analyzed using Ingenuity pathway analysis (IPA). CY5 and CY3 two-color ECL Plex fluorescence Western blotting (WB) images were scanned with TYPHOON and analyzed using ImageQuant to validate the proteomic data.

Results: CB vs PB $CD56^{+dim}$ cells significantly over expressed 35 proteins, including CELSR1 (25.0F), BLM (25.0F), BDNF (20.0F), PKD1 (16.7F), NOTCH2 (16.7F), BIRC2 (12.5F), AIFM1 (12.5F), EP400 (5.3F), PBX1 (3.9F), SIRT2 (2.9F), LETM1 (2.9F), and ESR2 (2.4F). WB results validated the proteomic results. IPA results indicate that top molecular functions of these proteins include gene expression ($p < 0.03$), apoptosis ($p < 0.03$), cellular development ($p < 0.03$). CELSR1, BDNF, ESR2, TAGLN, SIRT2, PBX1, and AIFM1 together with HOX variants, FOXA1, FOS, and SP1 facilitate a cell developmental network. NOTCH2, BDNF, PKD1, LETM1, AIFM1, SIRT2, ESR2, and EP400 together with cMYC, NFkB, TP53 build a network toward apoptosis.

Conclusion: Considering that CB is of fetal origin, it is not surprising that CB $CD56^{+dim}$ populations may be earlier in development (pro-NK) with over expression of CD34 gene and CELSR1, BLM and BDNF early developmental stage proteins. Decrease in CB vs PB NK cytotoxicity maybe in part secondary to increase programmed cell death (apoptosis). Our CB proteomic signatures suggest a possible explanation for immaturity of CB innate and adaptive immunity. (The first two authors contribute equally).