Results: 18 patients with HLA-Ab against UCB unit 1 (9), UCB unit 2 (2) or both UCB units (7) were identified. No differences in cell doses, viability or baseline characteristics were noted between patients with/without HLA-Ab. The presence of HLA-Ab was associated with an increased risk of graft failure (HLA-Ab against either UCB unit: OR 8.67, 95%CI 1.89–39.68, p = 0.0055; HLA-Ab against both UCB units: OR 16.27, 2.82–93.87, p = 0.0034). Neutrophil engraftment was delayed in the presence of HLA-Ab (median 21 vs. 29 days, p = 0.04) and fewer patients engrafted platelets in the presence of HLA-Ab (76.4% vs. 50%, p = 0.03). HLA-Ab against UCB unit 1 was associated with UCB unit 2 dominance (OR 9.43, 95%CI 1.16–76.47, p = 0.015), while HLA-Ab against UCB unit 2 was associated with a non-significant trend toward UCB unit 1 dominance (OR 2.70, 95%CI 0.63–12.5, p = 0.28). Overall survival was inferior in the presence of HLA-Ab against UCB unit 2 (p = 0.044) or both UCB units (p = 0.027), but not with HLA-Ab against UCB unit 1 only.

Conclusions: In DUBCT, the presence of HLA-Ab increases the risk of graft rejection, prolongs time to engraftment, predicts UCB dominance and is associated with inferior outcome. HLA-Ab screening should be incorporated into UCB unit selection strategies in DUCBT.

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EX VIVO TREATMENT OF HEMATOPOIETIC STEM CELLS WITH 16,16-DIMETHYL PROSTAGLANDIN E2 (FT1050) IMPROVES ENGRAFTMENT AND HEMATOPOIETIC RECONSTITUTION

Cutler, C.S.[1], Desponts, C.[3], Robbins, D.[3], North, T.E.[4], Goessling, W.[5], Kao, G.[6], Ritz, J.[6], Ballen, K.K.[2], Antin, J.H.[1], Spitzer, T.R.[2], Soiffer-ChenY.-B.A., R.J.[1,2], Ho, V.T.[1], Armand, P.[1], Koreth, J.[1], Alyea, E.[1], McAfee, S.[2], Dey, B.R.[2], Shoemaker, D.[3], Multani, P.S.[3] [1] Dana-Farber Cancer Institute, Boston, MA; [2] Massachusetts General Hospital, Boston, MA; [3] Fate Therapeutics, San Diego, CA; [4] Beth Israel Deaconess Medical Center, Boston, MA; [5] Brigham and Women's Hospital, Boston, MA; [6] Dana-Farber Cancer Institute, Boston, MA

Through an in vivo zebrafish screen for modulators of hematopoietic stem cell (HSC) development, a small molecule, 16,16-dimethyl prostaglandin E2 (FT1050) was identified (North, 2007). FT1050 was shown to enhance the engraftment potential of HSCs from murine bone marrow (mBM) or human umbilical cord blood (hCB) in murine engraftment models through an increase in proliferation, survival, migration and homing after a brief (1 to 2 hr) ex vivo treatment (North, 2007; North, 2009; Hoggatt, 2009; North, Goessling, Zon, unpublished data). We further optimized the ex vivo hCB incubation protocol using whole genome expression arrays and determined that HSC-containing cell products should be incubated with 10μM FT1050 for 2 hrs at 37°C to obtain the optimal response. In addition, we observed that FT1050 induces similar gene expression changes in hBM- and mobilized peripheral blood-derived CD34+ cells. Subsequent functional studies demonstrated that in keeping with increases of up to 18-fold in CXCR4 gene expression, cell surface CXCR4 protein expression was also significantly increased. One hour after treatment with10μM FT1050 for 2 hrs at 37°C, 48±1.9% of CB CD34+ cells expressed CXCR4 compared to 3.5±0.01% in DMSO control ($p < 0.05$). In vivo CFU-S12 analysis showed that treatment of mBM cells with 10μM FT1050 for 2 hrs at 37°C resulted in greater proliferation with a statistically significant increase in colony formation, 11.5±1.4, compared to 4±0.8 colonies with DMSO control ($p < 0.001$). This short-term ex vivo incubation protocol, 10μM FT1050 for 2 hrs at 37°C, has been introduced into an ongoing Phase Ib clinical trial in adults with hematologic malignancies receiving a nonmyeloablative conditioning (melphalan, fludarabine and ATG) followed by double hCB transplantation, in which one of the two hCBs is incubated with FT1050 prior to infusion. The primary objective of the study is to determine the safety of FT1050 treatment of hCB. Preliminary data demonstrate that this ex vivo incubation can be reliably performed at the clinical site on the day of infusion with good cell recovery and viability. 11 subjects with a median age of 44 years have been accrued to date, of which two have been treated using the optimized ex vivo incubation protocol. 10 of 11 patients have achieved an ANC > 500 before Day 42. Transplant related mortality has been low with one death at Day 53 from respiratory failure. 9 patients are alive, of which 7 are disease-free. Accrual is ongoing.

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ALLOGENEIC TRANSPLANTATION USING HAPLOIDENTICAL DONOR VERSUS UNRELATED CORD BLOOD DONOR: A SINGLE CENTER RETROSPECTIVE STUDY

Gonzalez-Vicent, M., Molina, B., Andion, M., Sevilla, J., Ramirez, M., Perez, A., Lassaletta, A., Diaz, M.A. Niño Jesus Childreńs Hospital, Madrid, Spain

We have performed a retrospective comparison of pediatric patients with leukemia receiving a haplo transplant (n = 29) or UCBT (n = 38) in Niño Jesus Children's Hospital since 1996 to 2010. There were not significant differences in immunophenotype, disease status and antecedent of prior autograft. However, haplo recipients tended to be older and of male gender.

Engraftment failure was significantly higher following UCBT 9±5% compared to 7±5% in haplo transplants (p = 0.001). Median neutrophil engraftment were at 13 days for haplo and 20 days for UCBT (p = 0.01) and platelet engraftment at 11 days for haplo and 56 days for UCBT (p = 0.0001). Supportive care (transfusions, antibiotics, parenteral nutrition and hospitalization days) were significantly higher for cord blood transplants.

TRM and acute GVHD (more than grade II) incidence was higher in UCBT compared to haplo transplants. There were not significant differences in chronic GVHD and relapse probability between the two groups. Results are summarized in table 1.

Disease-free survival (DFS) with a median follow-up of 16 months (range: 1-42) and 57 months (range: 1-150) were of 44±10% and 32±7% (p = 0.03) for haplo transplants and UCBT respectively. When we analyzed AML, there were not differences in DFS with both type of donor (p = 0.6). However, DFS for ALL was better with haplo (41±13%) against cord blood (26± 9%) (p = 0.03). According to phase of disease, DFS was similar in early phase (p = 0.7), but in advanced phase outcome was better with haplo (37±14%) versus cord blood (21±8%) (p = 0.05).

Multivariate analysis of DFS showed that the main prognostic factors were disease status at transplant (HR 2.49, p = 0.02), chronic GVHD (HR 0.21, p = 0.0001) and source of stem cells (HR 5.75, p = 0.001).

In conclusion, our data suggest that haploidentical donor is a good alternative for patients lacking an HLA identical donor.

Table 1. Results.

	aGVHD >II	TRM	Relapse	DFS
Haplo (n=29)	19±7%	25±9%	48±12%	44±10%
UCB (n=38)	44±10%	57±9%	25±9%	32±7%
P	0.03	0.05	0.7	0.03

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CD34+ STEM CELL SELECTION AND CD3+ ADDBACK FOR PEDIATRIC RECIPIENTS OF MATCHED UNRELATED ADULT DONOR (MUD) PERIPHERAL BLOOD STEM CELL TRANSPLANTATION (PBSCT) PRELIMINARY RESULTS OF DAY 100 TRM, IMMUNE RECONSTITUTION (IR), PTLD, SYSTEMIC VIRAL INFECTIONS (SVI), AND INVASIVE FUNGAL INFECTIONS (IFI)

Ricci, A.M.[1], Geyer, M.B.[1], Jacobson, J.S.[2], Majzner, R.[1], Satwani, P.[1], Bhatia, M.[1], George, D.[1], Bradley, M.B.[1], Garvin, J.H.[1], Harrison, L.A.[1], Morris, E.[1], Duffy, D.[1], Semidei-Pomales, M.[3], Baxter-Lowe, L.A.[3], Daniel-Johnson, J.A.[3], Schwartz, J.[3], Baxter-Lowe, L.A.[4], Cairo, M.S.[1,3,5] [1] Columbia University, New York, NY; [2] Columbia University, New York, NY; [3] Columbia University, New York, NY; [4] University of California San Francisco, San Francisco, CA; [5] Columbia University, New York, NY

Background: CD34+ stem cell selection depletes T cells responsible for severe aGVHD (Lang et al., Blood, 2003). CD34+ selected grafts have been associated with delayed IR (Ball et al, BMT, 2005, Eyrich et al, BJH, 2001). Delayed IR is a significant risk factor for

severe opportunistic infections, a major cause of transplant related mortality (Lang/ Handgretinger, BMT, 2008). We sought to determine engraftment, survival, IR, infection risk and frequency of PTLD and GVHD in pediatrics recipients following CD34-selected MUD PBSCT.

Methods: Pts ≤ 30 yrs requiring a MUD transplant for selective malignant and nonmalignant disease who were eligible. HLA matching included 8/10, 9/10 and 10/10 at intermediate resolution HLA A and B and high resolution HLA C, DRB1 and D2. Isolex 300i (Nexell, Irvine, CA) immunomagnetic cell selection system was used for CD34 selection with a goal of achieving ≥ 5 x106 CD34/kg PBSC. T cells were added back to reach a total CD3 dose of 1.0-2.6x105/kg. GVHD prophylaxis consisted only of tacrolimus (Bhatia/Cairo et al, BBMT, 2010). Supportive care was as we have previously described (Bradley/Cairo, BMT, 2007).

Results: 19 pts, median f/u: 534d, median age: 15.3 yrs (10-23); 12:7 M:F, HLA match 26% 10/10, 31% 9/10, 42% 8/10; 68% malignant. Infused grafts contained a median of 1.6x105 CD3+/kg (0.1-4.8) and 5.1x106 CD34+/kg (2.0-13.3). Probabilities of neutrophil and platelet engraftment, grade II-IV aGVHD, cGVHD and day 100 TRM were 100%, 82.3%, 15.8%, 24.2% and 0%, respectively. CD3, CD4, CD8, CD19 and CD56 counts at day +180/365 reached normal in 11/30, 0/15, 22/46, 56/76 and 94/100% of patients, respectively. IgG, IgM, and IgA reached normal in 47/50, 59/50, and 59/33% of patients, respectively. One pt (5.2%) developed PTLD. 11 donor/pts were CMV positive, and 2 pts experienced CMV SVI. The 1-yr probability of developing SVI and IFI was 42.3% and 28.0%, respectively. Despite the high incidence of SVI and IFI, the 1-yr probability of mortality due to SVI and IFI was 5.3% (CI95: 0-65%) and of OS was 84.2% (CI95: 59-95).

Conclusions: Rapid neutrophil engraftment, low rate of PTLD, aGVHD/ cGVHD, and low day 100 TRM were observed. Although immune reconstitution was not mature at 1 yr post transplant, the overall probability of infection related mortality was relatively low. These results support continued investigation of CD34-selected MUD PBSCT in selective pediatric AlloSCT recipients.

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HAPLOIDENTICAL STEM CELL TRANSPLANTATION FOR MINORITIES

Ciurea, S.O., Saliba, R.M., Rondon, G., Sharma, M., Montes, N., Bosque, D., McMannis, J., Fernandez-Vina, M., Xie, S., Konopleva, M., Parmar, S., Nieto, Y., Kebriaei, P., Quazilbash, M., Alousi, A., Popat, U., Hosing, C.M., Shpall, E.J., Khouri, I.F., de Lima, M., Champlin, R.E. The University of Texas MD Anderson Cancer Center, Houston, TX

Hematopoietic stem cell transplants have been performed mostly from matched related or unrelated donors (MUD). Given the racial composition of the unrelated donor registries, it has been difficult to identify a MUD for non-Caucasian patients (pts). A review of all the MUD pts transplanted at MD Anderson (MDACC) past 25 years revealed that of 2117 pts, 1677 (79.2%) were whites (W), 271 pts (12.8%) Hispanics (H), 109 (5%) Afican-Americans (AA) and 33 (1.5%) were Asians (A). Similar racial distribution was noted with pts receiving a 9/10 MUD during the same period of time. We hypothesized that haploidentical stem cell transplantation (HaploSCT) would be an alternative for the minorities without a matched donor and treated 24 consecutive pts with a conditioning regimen consisting of fludarabine (40mg/m2/day × 4), melphalan (140mg/m2) and thiotepa (10mg/kg). 4 pts > 55 years/comorbidities received a RIC with fludarabine and lower doses of melphalan (100mg/m2) and thiotepa (5mg/kg). GVHD prophylaxis consisted of post transplant cyclophosphamide (50mg/kg/day × 2), tacrolimus and mycophenolate.

Results: Racial distribution in this group was 8/24 (33.3%) W, 6/24 (25%) H, 5/24 (21%) AA, 4/24 (16.6%) A, 1/24 (4%) other, for a total of 66.6% minority population. Median age was 47 years (24-65). All pts but one received bone marrow stem cells. 4 pts had prior allogeneic transplants. 13 pts had AML/MDS (8 poor-risk cytogenetics), 6 pts had CML/MPD (5/5 blast phase CML), 5 pts had lymphoma/CLL. Donor-recipient HLA matching was: 5/10 in 12 pts (50%), 6/10 in 3/25 pts (12%), 7/10 in 5/25 pts (20%) and 8/10 in 4/25 (16%). 10 pts (42%) were in remission at the time of transplant. All 23 evaluable pts (one had early death) engrafted with 100% donor chimerism (100% engraftment) after a median of 19 days (5-40). Cumulative incidence of day-100 treatment-related mortality (TRM) was 14%. No patients less than 50 years died of TRM. Grade II-IV aGVHD occurred in 4 patients and cGVHD in 1 patient. 7/18 (39%) pts relapsed while only 1 for the pts in remission at the time of transplant. After a median follow-up of 6 months (range 3-18) for survivors of > 100 days (N = 14), OS for the whole group was 80%, while PFS for pts in remission at the time of transplant was 89% (N = 10, CI 43-98%). No differences in OS/PFS were noted between the Caucasian and non-Caucasian population.

Conclusion: HaploSCT is a feasible and safe transplant alternative for minority pts who lack a matched donor.

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HLA-HAPLOIDENTICAL ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION USING DEPLETION OF CD3±CD19 IN CHILDREN AND ADOLESCENTS: EXPERIENCE AT A SINGLE INSTITUTION

Im, H.J., Park, M., Koh, K.N., Kim, B.E., Choi, E.S., Seo, J.J. Asan Medical Center Children's Hospital, Seoul, Republic of Korea

Objective: To evaluate the safety and efficacy of haploidentical HCT (h-HCT) with T-cell depleted graft in children and adolescents

Patients and methods: Between July 2008 and April 2010, 11 patients received allogeneic PBSCT from mismatched family donors. Of 11 patients, 6 had SAA (5 acquired, 1 Fanconi anemia), and 5 had hematologic malignancy (HM), of which 3 were AML (1 CR2, 1 refractory, 1 graft failure after CBT), 1 was ALL in CR3, and 1 was MDS-RA. A total of 13 h-HSCTs were performed in 11 patients. All 13 cases were conditioned with non-myeloablative regimen containing fludarabine, and busulfan at a dose of 8mg/kg was added for hematologic malignancies. ATG was also included except for cases of graft failure and none of enrolled patients received any kind of irradiation. The mobilized and collected product was processed for CD3 alone or CD3/CD19 depletion using CliniMACS®.

Results: Of 11 patients, 9 achieved neutrophil engraftment at a median of 11 days of whom 2 experienced late graft failure (GF) on day +25 and +200, respectively. Four patients developed acute GVHD of grade II and none had > II aGVHD. Of 4 patients who experienced GF (2 primary and 2 late), 2 received the 2nd h-HCT from different donors and all 2 are alive with complete donor chimerism. At a median follow-up of 12.2 (5.9∼27.7) months, all 11 patients are alive. Of 6 patients with SAA, 4 are well and alive in a complete donor chimerism without transfusion (TF) need, 1 remains on infrequent need of TF with 95% donor chimerism at day +221, and 1 received a 2nd h-HCT for primary GF, after which the patient remains on infrequent need of TF with full donor chimerism at day +145. Of 5 patients with HM, 3 patients with AML are alive in CR at days +178, +412, and +812, respectively, although 1 of those experienced late graft failure. The remaining 2 patients are alive with disease at days +334 and +377, respectively, of whom 1 with MDS experienced 1° GF and the other with ALL relapsed at day +269. Although no infection-related death occurred, most of the patients had a viral reactivation or disease, including PTLD and CMV retinitis.

Conclusions: The HCT using haploidentical family donors is a feasible option for children with diseases curable with HCT, but lack a suitable related or unrelated donor. However, graft failure and infection are still obstacles to overcome to improve the outcome of hHCT in children and adolescents.

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TREOSULFAN-BASED CONDITIONING IS SUFFICIENT TO PROMOTE ENGRAFTMENT IN CORD BLOOD TRANSPLANTATION

Newell, L.F.[1,2], Milano, F.[1], Gutman, J.A.[3], Riffkin, I.[1], Lopez, M.[1], Ziegler, D.[1], Nemecek, E.R.[4], Delaney, C.[1,5] [1] Fred Hutchinson Cancer Research Center, Seattle, WA; [2] University of Washington School of Medicine, Seattle, WA; [3] University of Colorado, Denver, CO; [4] Oregon Health & Science University, Portland, OR; [5] University of Washington School of Medicine, Seattle, WA