ALLOGENEIC TRANSPLANTS

7

PRESERVATION OF PULMONARY DIFFUSING CAPACITY WITH ORAL BECLOMETHASONE DIPROPIONATE: RESULTS FROM TWO RANDOMIZED, PLACEBO-CONTROLLED TRIALS IN ALLOGENEIC GRAFT RECIPIENTS

Chien, J.W., Gooley, T., Sakai, M., Schoh, H.G., McDonald, G.B.; Fred Hutchinson Cancer Research Center, Seattle, WA.

Randomized trials show that oral BDP allows rapid tapering of prednisone while controlling gastrointestinal GVHD following allogeneic hematopoietic cell transplant and results in better outcomes (Blood 2007;109:4557–63). In reviewing adverse event data, we noted fewer pulmonary infiltrates in the BDP arm, perhaps because oral BDP is metabolized in the gut to the potent immunosuppressive metabolite 17-beclomethasone monopropionate (17-BMP), some of which is transported via the portal circulation and pulmonary artery directly to the lung. To test the hypothesis that 17-BMP preserved lung function after HCT, we reviewed prospective pulmonary function tests in 120 randomized patients who had been randomized at FHCRC.

Methods: Two studies had randomized patients with GI GVHD to a 10-day induction course of prednisone 1 mg/kg/day for 10 days plus either oral BDP 8 mg/day or placebo. Patients whose symptoms were under control at study day 10 had prednisone tapered rapidly but study drug was continued for 30–50 days. GVHD treatment failures were treated with prednisone 1–2 mg/kg/day. Change in lung function was assessed by comparing pulmonary function tests (PFTs: FEV1, FVC, TLC, DLCO) performed prior to start of con-

Results:

Baseline to HCT day 80 (% decreased/total #)

<table>
<thead>
<tr>
<th>PFT</th>
<th>Placebo</th>
<th>BDP</th>
<th>P</th>
<th>Placebo</th>
<th>BDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLCO 32/44 (79%)</td>
<td>27/49 (50%)</td>
<td>.02</td>
<td>.79 (.40, .23)</td>
<td>.57 (.74, +1.15)</td>
<td></td>
</tr>
<tr>
<td>FVC 24/44 (55%)</td>
<td>35/50 (50%)</td>
<td>.66</td>
<td>.85 (.20, .16)</td>
<td>.34 (.30, +3)</td>
<td></td>
</tr>
<tr>
<td>TLC 25/42 (60%)</td>
<td>20/50 (58%)</td>
<td>.88</td>
<td>.67 (.25, .16)</td>
<td>1.61 (.27, +3)</td>
<td></td>
</tr>
<tr>
<td>FEV1 21/44 (48%)</td>
<td>25/50 (50%)</td>
<td>.83</td>
<td>.55 (.25, +1.09)</td>
<td>1.61 (.27, +3)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: These data suggest that oral BDP may have a protective effect on early decline in pulmonary diffusing capacity, which commonly occurs by day 80 after transplant because of interstitial lung injury. We hypothesize that preservation of diffusing capacity was due to delivery of the potent immunosuppressive metabolite 17-BMP to the lungs via GI mucosa, portal vein, and pulmonary artery.

8

FACTORS AFFECTING 100-DAY AND 1-YEAR MORTALITY FOLLOWING MYELOABLATIVE SINGLE-UNIT CORD BLOOD TRANSPLANTATION IN ADULTS AND ADOLESCENTS: A COMPREHENSIVE META-ANALYSIS OF CIBMTR, NCBP AND EUROCORD

Cohen, Y.C., Saradavou, A.; Stevens, C.E.; Rubinstein, P.; Gluckman, E.; Pascale, D.; Eapen, M.; Horowitz, M.M.

A retrospective meta-analysis was conducted to examine factors affecting mortality following myeloablative, single-unit cord blood transplantation (CBT) for hematological malignancies in adolescents and adults. Data was collected from three cord-blood transplant registries, Center for International Blood and Marrow Transplant Research (CIBMTR), National Cord Blood Program (NCBP) and Eurocord, and included all records of single, unmanipulated, first myeloablative allogeneic CBT conducted in North America or Europe from 1995 to 2005, with HLA match #4/6 in patients with acute leukemia, chronic myeloid leukemia, myelodysplastic syndrome or lymphoma aged 12 to 55, for which 100-day survival data was available. Data was pooled after screening for specified eligibility criteria, creation of common classifications, checking for integrity and consistency, and removal of duplicates. Analysis involved comparison of survival outcomes according to known and exploratory prognostic factors. These covariates were used to build logistic regression models for 100-day and 1-year mortality. Five hundred and fourteen of 742 potential records were found to meet eligibility criteria and were included in the meta-analysis. Overall 100-, 180-day and 1-year mortalities (Kaplan-Meier) were 44%, 55% and 58%, respectively with no significant heterogeneity across registries. Some heterogeneity was observed in the prognostic factors. Multivariable analysis showed cell dose < 2.3 x 10^7/Kg (Odd's Ratio 2.74, p < 0.0001), disease stage (p = 0.04), positive CMV sero-status (OR 1.46 p = 0.056), age (p = 0.002), female gender (OR 1.45, p = 0.059) and transplant center with less CBT experience (contribution of <10 registry records, OR 2.02, p = 0.0007) to be associated with higher 100-day mortality; A multivariate model predictive of 1-year mortality included similar covariates: cell dose (OR 1.66, p = 0.011), disease stage (p = 0.03), CMV (OR 2.25 p < 0.0001), age (p = 0.02) and center experience (OR 2.45, p = 0.0002). Transplant year was not independently predictive of mortality in either of these models. This is the first meta-analysis to pool records from three major CBT registries in the US and Europe. Despite differences in practice patterns, survival data showed remarkable homogeneity. The resulting models will be used in the analysis of the Pivotal Study of StemEx®; transplantation of cord blood expanded ex vivo with a copper chelator along with the non-manipulated fraction of the same cord blood unit.

9

RISK FACTORS ASSOCIATED WITH GRAFT FAILURE AFTER UMBILICAL CORD BLOOD TRANSPLANTATION (UCBT): A SINGLE CENTER ANALYSIS IN 539 PATIENTS

Doshi, K., Brunstein, C.G., Cao, Q., Wagner, J.E.; University of Minnesota, Minneapolis, MN.

UCBT has proved to be a viable alternative for pediatric and adult patients who do not have an HLA matched related or unrelated donor. However, the incidence of graft failure (GF), an often fatal complication, has been reported to be as high as 30% in some series. Therefore, we attempted to identify potential risk factors associated with GF in 539 patients (adult, n = 297; pediatric, n = 242) transplanted with UCB at University of Minnesota between 1994–2006. Patients received one (n = 231) or two (n = 208) UCB units after a myeloablative (MA, n = 338) or reduced intensity (RIC, n = 201) conditioning regimen for malignant (n = 418) or non-malignant (n = 121) disease. GF was defined as evidence of <5%
chimerism or failure to achieve neutrophil recovery by day 42. Median patient age and weight was 22 years (r: 0.6–9.9) and 61 kg (r: 4.1–149 kg), respectively, with 66 having had a prior autologous transplant. Time from diagnosis to transplant was 13.3 months (r: 1.26–250 months), 57 patients were CMV+, 186 received a sex-matched graft, 132 ABO-matched, 168 minor ABO-MM, and 229 major ABO-MM. Median graft cell doses were 3.8 × 10^7 nucleated cells (NC)/kg (r: 0.7–48.9) and 4.6 × 10^7 CD34/kg (r: 0.4–275.3). Fifty-seven received 6/6 HLA-matched units, 196 received at least one 5/6 matched unit and 286 reached at least one 4/6 matched unit. GF was observed in 43/338 (12.7%) after MA and 36/201 (17.9%) after RI UCBT. Risk factors associated with GF in logistic regression were transplantation of HLA mismatched units (5/6 match, OR 9.13, 95%CI: 1.19–70.38; 4/6 match, OR 11.66, 95%CI: 1.53–89.00; p < .01), treatment of non-malignant disease (OR 2.35, 95%CI: 1.35–4.81; p < .01), low CD34 cell dose (top quartile OR 2.33, 95%CI: 1.07–5.05; bottom quartile, OR 3.11, 95%CI: 1.44–6.70; p < .01), and use of a RIC (OR 2.40, 95%CI: 1.35–4.26; p < .01). Patients who received a prior autologous transplant had lower odds of GF (OR 0.12, 95%CI: 0.03–0.52, p < .01). Factors not impacting risk of GF were recipient age, sex-match, ABO-match, CMV serostatus, performance status, diagnosis, disease risk, interval from diagnosis to transplant, NC dose, and CD34 cell dose. In addition to CD34 cell dose and HLA match, patients with non-malignant disease and recipients of a RIC are at higher risk of GF. These results support the need for greater investment in banking UCB with larger cell doses and HLA diversity and development of improved strategies for overcoming GF in high risk patient populations.

**COSTIMULATORY BLOCKADE (CSB) DURING MIXED LYMPHOCYTE RESPONSE (MLR) PREVENTS IL27 UPREGULATION AND SIGNALLING**

Gorgun, G.1, Philpot, P.A.1, Naxerova, K.1, Kabani, J.S.2, Nadler, L.M.1, Guinan, E.C.1,2. 1 Dana-Farber Cancer Institute; 2 Children’s Hospital, Boston, MA.

Numerous methods for selectively depleting or manipulating allogeneic (alloAg) specific CD4 T cells (CD4 T) are being studied for their potential in improving transplant outcomes by limiting GVHD or graft rejection. However, their effects on off-target CD4 T cellular pathways and functions and on other PBMC are not well described. We used global gene expression profiling (GEP) to elucidate the molecular impacts on bystander PBMC after inducing alloAg specific CD4 T anergy by CD28:B7 costimulatory signal blockade (CSB) via humanized anti B7:1/B7:2 MoAbs. Mimicking our ex vivo clinical anergization protocol, PBMC were isolated from fully–HLA mismatched healthy donors (n = 12) to perform ex vivo primary MLR+/–anti B7:1/B7:2 MoAbs. CSB inhibited mean proliferation by 73% after 72 h of MLR. GEP was performed using Affymetrix hu133 plus2 chips on monocytes (Mo), CD4 and CD8 T, B and NK cells purified from these MLR. Despite low published frequencies (1–10%) of alloAg specific CD4 T, we detected global gene expression variance (p < 0.05) between CD4 T isolated from MLR+/–CSB suggesting effects on non-alloAg specific CD4 T. Analysing these differentially expressed genes by cellular pathway highlighted those active in cell proliferation and differentiation. Particularly, differences in IL27 signaling molecules in Mo and CD4 T were prominent. IL27, a heterodimer of p28 and EBI3 gene and protein expression levels decreased in Mo from MLR+. After CSB, CD4 T showed decreased IL27R and STAT3 expression and inactivation of pSTAT1 and NFκB. Intracellular cytokine (ICC) analysis showed decreased IL2 and IFNγ expression in CD4 T, decreased IL15 and increased IL10 in Mo from MLR+ CSB supporting the negative effect of IL27 on Th1 differentiation. These data suggest that CD28:B7 signaling during MLR is required for Mo production of IL27. Decreased expression of IL27R, pSTAT1 and NFκB after CSB may contribute to CD4 T alloAg anergy induction by suppressing effector cytokines and Th1 differentiation. CD28:B7 modulation of IL27 and IL27R emphasizes that targeted therapies used in the complex environment of human PBMC may have effects unpredicted by in vitro clonal systems, which may be important in the functional outcome of the intervention.

**RISK FACTOR ANALYSIS FOR THE DEVELOPMENT OF RESTRICTIVE AND OBSTRUCTIVE PULMONARY FUNCTION CHANGES AFTER ALLOGENEIC STEM CELL TRANSPLANTATION**

Rabanas, R., Habn, J., Andreesen, R., Holler, E., Hildebrandt, G.C. University of Regensburg Medical Center, Regensburg, Germany.

Pulmonary complications after allogeneic stem cell transplantation (allo-SCT) significantly contribute to morbidity and mortality. We analyzed 207 patients receiving allo-SCT at our institution between 1998 and 2005 for the development of restrictive (PRC) and obstructive (POC) pulmonary function changes. Pulmonary function tests (PFT) were performed before and routinely every 3 to 6 months after allo-SCT. After follow-up > 2 years, PFTs were obtained yearly. 142 patients were included according to the availability of PFTs; 65 patients were excluded due to early mortality and/or the lack of PFT data. PRC were defined as a forced expiratory volume (FVC) at least once ≤ 90% of pre-transplant values, POC as a forced expiratory volume (FEV1) at least once ≤ 80% of baseline. Median time of follow-up was 1071 days (107–2924). For PRC, median time of first onset was at 180 days (30–1482) and for POC at 270 days (60–1800) after allo-SCT. The cumulative incidence for PRC was 70.7% and for POC 34.2%. Risk factor analysis included patient/donor age and gender, type of transplant, stem cell source, conditioning regimen intensity, TBI, T cell depletion, pretransplant CMV serology of donor and recipient, acute (gVHD) and chronic GVHD (cGVD) and previous thoracic irradiation.

In univariate analysis, positive patient CMV serology was associated with the development of both PRC (p = 0.05) and POC (p = 0.005), whereas CMV immunity of the donor affected only the risk of POC (p = 0.002). In addition, the cumulative incidence of POC rose to 57.3% when both donor and recipient had positive pretransplant anti-CMV immunity (p = 0.0005) and to 51.4% in patients with proven CMV reactivation (p = 0.01). cGVD increased the risk of POC (p = 0.0045) but not of POC (p = 0.127). Risk factors for PRC but not POC were bone marrow derived stem cells (p = 0.045) and female patient gender (p = 0.057). In multivariate analysis, cGVD (p = 0.037; HR 2.3 [1.1 – 5.0]), anti-CMV IgG positivity of the donor (p = 0.02); HR 2.3 [1.1 – 5.0] and of both donor and recipient combined (p = 0.004); HR 3.7 [1.5 – 9.3] in dependent risk factors for POC, the latter also being the only independent risk factor identified for PRC. Therefore, our data confirm the previously described association between cGVD and the development of pulmonary obstructive changes. In addition, this analysis strengthens the concept, that anti-CMV immunity and CMV reactivation contribute to pulmonary function impairment after allo-SCT.

**UNRELATED CORD BLOOD TRANSPLANTATION (UCBT) FOR TRANSFUSION-DEPENDENT THALASSEMAIA — A CBMTR AUDITED RETROSPECTIVE ANALYSIS OF 51 CONSECUTIVE PATIENTS**

Jiang, T.-H.1, Tan, P.2, Roentbelt, J.3, Chan, L.L.1,4, Lin, H.-P.5, Tan, P.-L.6, Nadeemauer, A.1, Karanaz, C.1, Gjerton, D.1, Wang, B.1, Petz, L.1, Chov, R.1, 1 Chang Gung Children’s Hospital & University, Linko, Taiwan; 2 Mount Elizabeth Hospital, Singapore; 3 City of Hope National Medical Center, Duarte, CA; 4 University of Mahajara Medical Center, Khuda Lumbur, Malaysia; 5 Subang Jaya Medical Center, Malaysia; 6 National University Hospital, Singapore; 7 UCLA School of Public Health, Los Angeles, CA; 8 StemCyte International Cord Blood Center, Arcadia, CA.

UCBT offers a cure for thalassemia and has advantages as a stem cell source for minorities where thalassemia is prevalent, but cell