both T and B cells in the recipient, although one of them (grade III acute GvHD pt) had received anti-lymphocyte globulin for acute GvHD treatment. Our experience supports the results obtained with the same regime reported by the Nottingham team. The regime is well tolerated with sustained engraftment, acceptable toxicity, relapse risk and TRM.

77

FLUDARABIN AND BUSULFAN AS A CONDITIONING REGIMEN FOR ALLOGENEIC PERIPHERAL BLOOD STEM CELLS TRANSPLANTATION IN LEUKEMIC PATIENTS

Ghavamzadeh, A., Iravani, M., Evazi, M., Shamshiri, A., Mousavi, A., Bahar, B., Gholibeikian, S., Chardoli, B., Jahani, M. Hematology-Oncology & BMT Research Center, Tehran, Islamic Republic of Iran.

We evaluated Fludarabin (40 mg/m^2 on days -6 to -2) and Busulfan (4 mg/kg/day on days -5 to -2) as a new conditioning regimen for allogeneic peripheral blood stem cells transplantation in standard-risk leukemic patients. Enrolled were 29 reportable patients (9 ALL, 12 AML and 8 CML; F = 13 M = 16) from 52 transplanted patients with matched related donor. The median patient age was 29 (range, 15-42). Cyclosporine was used as a prophylactic agent for GVHD (3mg/kg IV till +4, 10 mg/kg oral from day +5). The median follow-up was 123 days (range, 77-217 days). About 89.3% and 27.6% of the patients developed mucositis (min + 3, max + 15) and hepatic toxicity (min + 7, max + 46) respectively which resolved with conservative therapy. There was no cardiac toxicity (except one patient with mild pericardial effusion). The median of highest serum creatinin level during hospitalization and synchronous cyclosporine level were 1.6 mg/dl (range, 1.1-3.6; 28.6% with Cr > 2) and 275 ng/ml (range, 9-814). One patient experienced hemorrhagic cystitis (infection was ruled out). 17.2% experienced moderate to severe headache. 34.5% and 10% of the patients showed grade 1, 2 and grade 3 Acute GVHD (there was no grade 4 Acute GVHD). Two ALL patients relapsed on days +95 and +100 and one died (unrelated to regimen). In day +38, 92.3% of the patients had more than 90% whole blood engraftment (with STR-PCR technique; median, 100%; range, 75-100).

It could be beneficial to use Fludarabin versus Cyclophosphamide in standard conditioning regimen for leukemic patients because of reduced toxicity, low incidence of acute GVHD and facilitated donor engraftment.

78

CORRELATION OF PRE-HEMATOPOIETIC CELL TRANSPLANT (HCT) PRO-INFLAMMATORY CYTOKINES IN BRONCHIOALVEOLAR LAVAGE (BAL) FLUID WITH PULMONARY COMPLICATIONS FOLLOWING HCT IN PATIENTS WITH INHERITED METABOLIC STORAGE DISORDERS (IMSDS)

Kharbanda, S., Peters, C., Blazar, B.R., Milla, C.E., Haddad, I.Y., Cornfield, D.N., Abel, S.L., Steiner, M., Grewal, S.S., Ramsay, N.K.C., Panoskaltsis-Mortari, A., Baker, S. University of Minnesota, Minneapolis, MN.

Introduction: HCT is recommended in selected patients with inherited lysosomal and peroxisomal storage disorders including the mucopolysaccharidoses (Hurler and Maroteaux-Lamy syndrome) and the leukodystrophies (adrenoleukodytsrophy [ALD], globoid cell leukodystrophy [GLD], metachromatic leukodystrophy [MLD]). However, patients with IMSDs undergoing HCT are at a higher risk of life threatening pulmonary complications such as diffuse alveolar hemorrhage (DAH) and idiopathic pneumonia syndrome (IPS). The etiology and risk factors for these complications are unknown. We obtained BAL fluid from IMSD patients prior to transplant and analyzed it for the levels of various pro-inflammatory cytokines in order to investigate their correlation with the development of subsequent pulmonary complications. **Methods:** Between August 1999 and March 2003, 60 BAL specimens were obtained from 48 IMSD patients pre-HCT (Hurler -21, ALD-16, MLD-6, Maroteaux-Lamy-2, GLD-1, Mucolipidosis II-1, and α-mannosidosis-1). BAL fluid was analyzed for various pro-inflammatory cytokines including IL-1β, TNF-α, IFN-γ, IL-2, IL-6, as well as chemokines including Migration Inhibitory Factor (MIP-1α) and Monocyte Chemotactic Protein (MCP). **Results:** In this series, the overall incidence of pulmonary complications was 54% (26/48), this included 25% (12/48) infectious complications and 29% (14/48) non-infectious complications (mainly DAH and IPS)). Evaluable pre-HCT BAL cytokine data was available on 35 patients. These included 5 patients in the infectious, 8 in the non-infectious and 22 in the no complications groups respectively. There were trends towards higher levels of pre-HCT IL-1β and IL-6 in patients who subsequently developed non-infectious complications(P = NS, however) **Conclusions:** Our study confirms a high incidence of pulmonary complications in the early post transplant period in patients with IMSDs. Patients with mucopolysacchridoses are at a higher risk of developing non-infectious complications like DAH as compared to patients with other IMSDs. In this study sample of 48 patients, the levels of pro-inflammatory cytokines were not found to be correlated with this increased risk; however, there were definite trends towards higher levels of IL-1β and IL-6 in the BAL fluids; this may be attributable to the small numbers of patients in the study. Further studies are needed to confirm the role of pro-inflammatory cytokines in the pathogenesis of pulmonary complications in patients with IMSDs.

79

GRAFT-VERSUS-LYMPHOMA EFFECT YIELDS HIGH PERCENTAGE OF DURABLE COMPLETE REMISSION IN HIGH-RISK PATIENTS FOLLOWING MINI-TRANSPLANTATION WITH MAP (MITOXANTRONE, ARA-C, AND PENTOSTATIN) REGIMEN

Liu, D., Seiter, K., Chiao, J.W., Qureshi, A., Ahmed, T. New York Medical College and Arlin Cancer Institute, Valhalla, NY.

We have developed a novel Non-myeloablative Stem Cell Transplantation (NST) conditioning regimen (MAP regimen) using Mitoxantrone (40mg/m2 day-6), AraC (2 gm/m2 on day -6, -5, and -4), and Pentostatin (5 mg/m2 on day -6 and -5, 3 mg/m2 on day -4) for patients with hematological malignancies. Equine ATG at 15 mg/kg/day x 4 (day -5 to -2) is added for unrelated and mismatched transplantation. 18 patients (15 related, 4 unrelated) with lymphoma are evaluable. Among them were 13 NHL, 5 HD. 14/18 patients had failed prior autologous stem cell transplantation (Auto-SCT). The rest were either in advanced relapse or had poor prognostic factors.

Median time to ANC > 500 was 12 days, and to Platelets > 20 was 11 days. Full donor Chimerism is achieved at 3 months. 10 pts received Donor Leukocyte Infusion of 1 to 7 doses. 4 of the 10 patients had remarkable disease response after DLI (2 converted to CR, 1 PR going into CR, 1 stable). 10/18 pts had acute GVHD (grade II-IV), 4 of them developed GVHD after DLI. Day 100 mortality is 5% (1/18). With a median follow-up of 28 months (1-38), the median duration of overall survival (OS) for these high-risk patients has not been reached. 1 year OS is 64%, 2 year OS is 52%. For the 14 pts who failed prior Auto-SCT, 1 year OS is 69%, 2 year OS is 52%. These data are highly suggestive of graft-vs-lymphoma effect. Therefore, mini-allogeneic transplantation after MAP is a favorable option for lymphoma patients, particularly for those who failed prior Auto-SCT.

80

TID COMPARED TO BID MYCOPHENOLATE MOFETIL (MMF) IMPROVES DONOR CHIMERISM AND ENGRAFTMENT RATES WITHOUT INCREASING POSTGRAFTING TOXICITIES AFTER UNRELATED PERIPHERAL BLOOD STEM CELL (PBSC) TRANSPLANTATION (HCT) WITH NONMYELOABLATIVE CONDITIONING

Maris, M.B.[1,2], Sandmaier, B.M.[1,2], Storer, B.[1,2], Stuart, M.[3], Agura, E.[4], Hegenbart, U.[5], Pulsipher, M.[6], Maziarz, R.T.[7], Bruno, B.[8], McSweeney, P.[9], Maloney, D.[1,2], Niederwieser, D.[5], Blume, K.[3], Storb, R.[1,2] 1. Fred Hutchinson Cancer Research Center; 2. University of Washington; 3. Stanford University; 4. Baylor University, Dallas; 5. University of Leipzig, Germany; 6. Oregon Health and Sciences University; 7. University of Turin, Italy; 8. University of Colorado.

The safety and efficacy of 10/10 HLA antigen matched PBSC HCT from unrelated donors (URD)s after nonmyeloablative conditioning with fludarabine (3 x 30 mg/m^2) and 2 Gy TBI (FLU/2 Gy TBI) followed by cyclosporine (CSP) and MMF (both given BID) for patients with hematologic malignancies ineligible for conventional HCT was previously demonstrated (Maris, Blood Vol 102, #6). Fifty-nine of the 71 pts who received PBSC grafts had sustained engraftment. In that study, the half-life of mycophenolate acid (active metabolite of MMF) was found to be 3 hours. This suggested that TID dosing of MMF could improve postgrafting immunosuppression and thereby increase engraftment rates. Subsequently, a trial of dose escalated MMF (15 mg/kg TID) while holding other HCT parameters constant was performed in 103 pts given PBSC grafts from URDs after FLU/2 Gy TBI, CSP and MMF, 15 mg/kg TID. The results in 69 patients with sufficient followup in this trial were compared to those in the previous 71 pts given MMF BID. Median (med) age of TID MMF pts was 58 (range 17-70) years and that of BID MMF pts was 54 (range 18-70) years. The med follow-up of pts given MMF TID and BID was 9 and 25 months. The med neutrophil nadir was 100/μl vs.740/μl (p = .01), but duration of absolute neutropenia was similar (8.5 vs 9 days, p = .43) for pts who received MMF TID and BID, respectively. There were trends toward less graft rejection at 1 year (7% vs.16%, p = .06) and higher peripheral blood donor CD3$^+$ chimerism at day 28 after HCT (90% vs 75%, p = .09) with TID versus BID MMF. Other outcomes were not statistically different between TID versus BID patient groups: The cumulative probabilities (CP) of acute grades, II, III and IV GVHD were 40%, 11%, and 1% versus 41%, 10% and 3%, respectively. The CP of chronic GVHD requiring therapy were 40% and 44%, respectively. The Kaplan-Meier estimates at 1 year were 60% and 58% for overall survival, and 44% and 44% for progression free survival, respectively. The CP of relapse was 34% and 41%, respectively. The CP of nonrelapse mortality (NRM) at day 100 and at 1 year were 9% vs.11% and 22% vs.16%, respectively. We tentatively conclude that MMF dosing for URD PBSC grafts after FLU/2 Gy TBI can be safely increased from BID to TID without increasing toxicities, NRM, or relapse rates. TID compared to BID dosing of MMF in this setting may result in higher donor day 28 CD3$^+$ chimerism values and sustained engraftment rates, while other outcomes were comparable.

Table. *Outcomes after Nonmyeloablative Conditioning Using URDs: TID vs BID MMF*

	TID MMF (n = 69)	BID MMF (n = 71)	P
1 year Graft Rejection	7%	16%	.06
Day 28 T-cell Chimerism	90%	75%	.09
100 day aGVHD Grades II, III, IV	40%, 11%, 1%	41%, 10%, 3%	.61
1-year CGVHD	40%	44%	.35
1-year NRM	22%	16%	.59
1-year Overall Survival	60%	58%	.88
1-year Progression Free Survival	44%	44%	.89

81

ONCE DAILY INTRAVENOUS BUSULFAN AS PART OF A BUSULFAN/CYCLOPHOSPHAMIDE CONDITIONING REGIMEN FOR ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Mates, M., Michalska, H., Hasegawa, W., Kiss, T., Daly, A., Loach, D., Messner, H., Lipton, J. Princess Margaret Hospital, Allogeneic Bone Marrow Transplant Program, University of Toronto, Toronto, ON, Canada.

Objective: Busulfan (Bu) is frequently used as part of myeloablative conditioning regimens prior to stem cell transplantation (SCT), especially to avoid total body irradiation. Hepatic venoocclusive disease (HVOD) is a well-recognized dose-limiting toxicity for oral Bu-preparative regimens. The purpose of this review was to evaluate the toxicity, efficacy, 100-day mortality, overall and disease free survival in patients treated with single daily dose intravenous (iv) Bu as part of a Bu/Cyclophosphamide (Cy) conditioning regimen for allogeneic SCT. **Patients and Methods:** 29 consecutive patients undergoing allogeneic SCT received iv Bu as part of their conditioning between March 2002 and August 2003. Conditioning consisted of iv Bu (3.2mg/kg once daily x 4 doses) followed by high dose Cy and allogeneic SCT. The donors were HLA-matched siblings (n = 23), 1 antigen mismatched related donors (n = 1) and matched unrelated donors (n = 5). All patients received graft versus host disease (GVHD) prophylaxis consisting of Cyclosporine A and Methotrexate. **Results:** 28 patients engrafted with a median time for neutrophil recovery of 21 days (12,29) and median time for platelets recovery of 18 days (10,49). 14 patients (48.3%) developed HVOD, 10 mild (34.5%), 2 moderate (6.9%) and 2 severe HVOD (6.9%). Acute GVHD grade II-IV occurred in 18 patients (64.3%). 3 patients (10.3%) died in the first 100 days after the transplant, with 1 death due to severe HVOD (3.4%), 1 due to graft failure (3.4%) and 1 to other transplant related toxicity (3.4%). After a median follow up of 8 months (1,16) chronic GVHD occurred in 12 out of 24 evaluable patients (50%), 2 patients relapsed (6.9%), 1 patient is still in a partial remission (3.4%) and a total of 7 patients died (24.1%). 22 patients (75.9%) were alive at their last follow up. Overall survival at 6 months was 84.5%, and at 1 year 69.4%. 6-month disease-free survival was 80.7% and at 1 year 67.3%. **Conclusions:** Conditioning regimens with single daily dose iv Bu allowed consistent engraftment from related and unrelated donors. Only one graft failure occurred in a patient undergoing a second allogeneic SCT from a second matched related donor. 14 patients met criteria for HVOD, but the majority of them were mild. Treatment related mortality was limited. Overall survival and disease-free survival rates are encouraging thus meriting further studies for defining the role of iv Bu as a preferred substitute for oral Bu.

82

NON-MYELOABLATIVE ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION WITH PRE-TRANSPLANT IMMUNE DEPLETION RESULTS IN RAPID FULL DONOR ENGRAFTMENT IN PEDIATRIC PATIENTS WITH MALIGNANCY

Fry, T.J.[1], Wayne, A.[1], Fowler, D.[2], Hakim, F.[2], Love, C.[1], Gress, R.[2], Bishop, M.[2], Mackall, C.L.[1] 1. Pediatric Oncology Branch, NCI, NIH, Bethesda, MD; 2. Experimental Transplantation and Immunology Branch, NCI, NIH, Behtesda, MD.

Background: There is limited experience with non-myeloablative (NM) allogeneic hematopoietic stem cell transplantation (alloSCT) in pediatric pts with cancer. In comparison to adults, children and adolescents have less immune depletion and improved reconstitution after chemotherapy, which might increase the risk of mixed donor hematopoietic chimerism after NM alloSCT. Prolonged periods of mixed chimerism may increase the risk of relapse in highly proliferative pediatric cancers. **Methods:** Twelve pediatric pts (age 7-20, median 14.5 years) with high-risk malignancies (Hodgkin's disease, ALL, AML, CML, rhabdomyosarcoma, Ewing's sarcoma) were treated with a novel immunoablative regimen. Fludarabine-based induction chemotherapy was administered for disease control and host immune depletion (1 to 3 cycles). This was followed by pre-transplant conditioning with cyclophosphamide (1,200 mg/m^2/day) and fludarabine (30 mg/m^2/day) x 4 days with or without melphalan (100 mg/m^2 x 1 dose). Unmodified, G-CSF mobilized peripheral blood stem cells collected from HLA-matched siblings were employed (CD34 doses of 6.9-19 x 10^6/kg). **Results:** The regimen was associated with sequential lymphocyte depletion, although to a lesser degree than in 18 adult pts (age 33-67, median 50 years) treated on a parallel trial (Table 1). IL7 levels were inversely correlated with CD4 counts (r^2 = 0.20, p = 0.0006). Hematopoietic recovery was rapid in all pts. Complete donor lymphoid chimerism (>97% by VNTR-PCR on CD3 sorted peripheral blood) was achieved in 9 of 11 pts by post-transplant day (D+) 14, while 2 had mixed chimerism that improved between D + 14 to D + 28 (70% → 85%, 85% → 95%