syndrome (HPS) early after cord blood transplantation (CBT). Although both can be serious and potentially fatal, not much data have been available regarding their mechanisms underlying them. Recently, we observed a group of patients who presented relative lymphocytosis (LC) early after CBT before engraftment. We decided to conduct a retrospective analysis of those who presented LC early after transplant to characterize clinical features and to evaluate possible relevance to above mentioned immune-mediated complications.

Patients and Definition: Patients who underwent RI-CBT at our institute from Jan.2005 to July 2007 were retrospectively reviewed. LC was defined by early lymphocyte-dominant (≥80%) increase of WBC for at least 3 consecutive days. Lymphocyte count must be over 200/ul at least once. **Result:** We observed 11 cases who presented LC. Eight out of 11 were of donor-type and 3 of recipient-type chimerism. Median onset of LC of donor cells was 8.5 (8–10) days, and the maximum number of lymphocyte was 519 (242–2828)/ul, primarily CD3-positive T cells with CD4–8+ dominancy (60.6(13–68.1)%). Fever and diarrhea were observed in all patients, liver damage in 7, skin eruption in 4, and HPS in 6. Six out of 8 experienced graft failure, whereas the remaining 2 experienced severe acute GVHD, resulted in 6 early death up to 50 days post-transplant. LC of recipient cells developed on median 13 (12–16) days post-transplant, and the maximum number of lymphocyte was 550 (280–880)/ul, in which CD4–8+ cells dominated (93.1(83.1–96.6)%). All 3 experienced graft rejection and 2 of them were rescued by second RI-CBT, while 1 died of infection. **Conclusion:** LC of either donor- or recipient-derived was suggestive of high incidence of graft failure. Further analyses are currently going on to investigate possible relevance of LC to PIR or HPS.

139

HOW REALISTIC IS IT TO EXPECT A FULLY ALLELE LEVEL MATCHED DONOR FROM A SEARCH THROUGH THE NMDP? A 10 YEAR, SINGLE INSTITUTION EXPERIENCE

Askar, M.[1], Sobecks, R.[2], Kalaycio, M.[2], Dean, R.[2], Copelan, E.[2], Rybicki, L.[3], Pohlman, B.[2], Bolwell, B.[2] [1]Transplant Center; [2]Taussig Cancer Center; [3]Cleveland Clinic.

The National Marrow Donor Program (NMDP) continues to expand its donor pool. Transplant outcome correlates with the degree of HLA matching. Ideally, NMDP searches result in fully matched donors at the allele level. The odds of finding such a donor, however, has not been widely discussed.

We performed a retrospective analysis of 517 searches to the NMDP from November, 1996 through November, 2006. Of these, 213 resulted in a transplant. This analysis is limited to the patients that actually proceeded to transplant because of multiple potential reasons beyond HLA matching that may have prevented patients from receiving a transplant. Only 36 (17%) of 213 transplanted patients had donors that were fully matched at the allele level. Ninety-four (44%) patients were mismatched at only DP. Sixty-seven (31%) patients had a class 1, or DRB1 mismatch. The median duration from the initiation from NMDP search to transplant was 5.2 months. We conclude that finding fully matched donors is still a challenge, and highlights the need for continued recruitment for volunteers to the NMDP registry. Indeed, a result of 17% is likely an overestimate of the number of fully matched searches, because this analysis only included the patients who proceeded to transplant. Additionally, 8/8 matched donors with DP mismatches are common.

140

BORTEZOMIB PLUS TACROLIMUS/METHOTREXATE FOR PROPHYLAXIS OF ACUTE GVHD AFTER HLA MISMATCHED ALLOGENEIC NON-MYELOABLATIVE TRANSPLANTATION: RESULTS OF A DOSE FINDING PHASE I STUDY

Koreth, J.[1], Kim, H.T.[2], Ho, V.T.[1], Cutler, C.S.[1], Soiffer, R.J.[1], Antin, J.H.[1], Alyea, E.P.[1] [1]Dana Farber Cancer Institute, Boston, MA; [2]Dana Farber Cancer Institute, Boston, MA.

There is a need for better control of graft versus host disease (GVHD) after HLA mismatched peripheral blood stem cell (PBSC) allogeneic transplantation. Bortezomib is a small molecule proteasome inhibitor approved for treatment of multiple myeloma. It has immunomodulatory properties, and preclinical data indicate utility in GVHD control after allogeneic transplantation. Here we report the dose finding portion of a Phase I/II trial of bortezomib (dose levels A, B, C: 1, 1.3, 1.5 mg/m^2) plus tacrolimus and mini-methotrexate for GVHD prophylaxis after HLA mismatched non myeloablative allogeneic stem cell transplantation (NST) for patients with hematologic malignancies. Dose limiting toxicity (DLT) by day 45 post PBSC infusion is the primary endpoint, both acute bortezomib toxicity (e.g. neuropathy) and negative impact on stem cell function (e.g. delayed neutrophil recovery or poor donor engraftment) in the absence of disease progression. Secondary endpoints include incidence of acute and chronic GVHD.

Patients with 1–2 locus antigen/allele mismatch (HLA-A, -B, -C, -DRB1) were eligible. Pretransplant conditioning was busulfex (0.8 mg/kg/d) and fludarabine (30 mg/m^2/d) each for 4 days. GVHD prophylaxis was bortezomib per dose level (day +1, +4, +7) plus tacrolimus (day –3 to +180) and mini-methotrexate (5 mg/m^2 on day +1, +3, +6, +11).

13 patients were enrolled. No neurotoxicity was noted. At dose level A, 1 of 5 patients had a possible DLT, with poor engraftment likely related to progression of underlying MDS/AML. At dose level B, 0 of 3 patients had a DLT. At dose level C, 2 of 5 patients had a DLT. One patient, with minimally treated myeloproliferative disease failed to engraft; another patient, with CLL, experienced an immunologic graft rejection.

Grade 2–4 aGVHD occurred in 2 of 13 patients (1 each at dose level A and C). Chronic GVHD occurred in 3 patients, all at dose level A, albeit with limited follow up. Disease relapse has occurred in 5 patients (2 of whom died), one at dose level B, and 2 each at dose levels A and C. In summary, GVHD prophylaxis with bortezomib 1.3 mg/m^2 plus tacrolimus/mini-methotrexate is convenient and well tolerated after busulfex/fludarabine conditioning in HLA mismatched NST. It may have efficacy in GVHD control, and phase II accrual is proceeding.

LATE EFFECTS/QUALITY OF LIFE

141

SIMILAR RISKS FOR HYPOTHYROIDISM IN MYELOABLATIVE AND REDUCED-INTENSITY ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT SURVIVORS

Al-Hazzouri, A., Cao, Q., Burns, L.J., Weisdorf, D.J., Majhail, N.S. University of Minnesota, Minneapolis, MN.

Upto 15% of adult myeloablative (MA) allogeneic hematopoietic cell transplant (HCT) survivors can develop hypothyroidism. HCT using reduced-intensity conditioning (RIC) is associated with lower morbidity and mortality, but the risk of hypothyroidism after RIC HCT is not known. We conducted a retrospective cohort study to compare the incidence of hypothyroidism after MA and RIC HCT. Adult allogeneic HCT recipients were eligible if (1) they had received an allogeneic HCT using a total body irradiation (TBI) based MA or RIC regimen between 2000 and 2005, (2) survived for ≥1 year post-HCT, and (3) had no history of hypothyroidism pre-HCT. TBI dose in MA and RIC regimens was 1320 cGy (165 cGy twice daily × 4 days) and 200 cGy (single fraction), respectively. Hypothyroidism was classified as subclinical (elevated thyroid stimulating hormone [TSH] and normal free thyroxine [FT4]) or overt (elevated TSH and low FT4). All patients had thyroid studies performed at least annually after HCT; if clinically indicated, more frequent assessments were conducted at the discretion of the treating physician. Study eligibility criteria were met by 181 patients (MA = 84, RIC = 97); median follow-up was 28 (range, 12–75) months for MA and 25 (range, 12–67) months for RIC group. MA recipients were younger (median age 37 vs. 54 years, $P < 0.01$), the two groups were otherwise comparable with respect to gender, race, HCT co-morbidity index scores, disease status, donor source and incidences of acute and chronic GVHD. Eleven patients developed hypothyroidism (subclinical - 9, overt - 2). The 3-year cumulative incidence of hypothyroidism was 8% (95% confidence intervals [CI], 1–14%) in MA and 5% (95% CI, 0–11%) in RIC groups ($p = 0.41$). In multivariate analyses that included age, gender, race, conditioning regimen intensity,

HCT co-morbidity index scores, disease status, donor source, and acute and chronic GVHD, similar risks for developing hypothyroidism were observed between the two types of conditioning regimens (relative risk for MA 1.6 [95% CI, 0.4–5.8] vs. RIC). Female gender was the only factor predictive for hypothyroidism (relative risk 4.5 [95% CI, 1.1–18.0] vs. males). In conclusion, hypothyroidism is relatively infrequent in adult allogeneic HCT survivors. At least in the first few years post-HCT, RIC is associated with similar risks for hypothyroidism as MA conditioning.

142

HIGH PREVALENCE OF IRON OVERLOAD IN ADULT SURVIVORS OF ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

Majhail, N.S.[1], DeFor, T.E.[1], Kang, B.[2], Paley, C.[2], Lazarus, H.[3], Burns, L.J.[1] [1] University of Minnesota, Minneapolis, MN; [2] Novartis Pharmaceuticals, East Hanover, NJ; [3] Case Western Reserve University, Cleveland, OH.

Iron overload is a well recognized complication of transfusion dependent anemias. A large number of allogeneic hematopoietic cell transplant (HCT) recipients receive red blood cell (RBC) transfusions and pre-HCT serum ferritin has been reported to be an independent predictor for early transplant related mortality. However, the prevalence of iron overload in long-term allogeneic transplant survivors is not known. We report a cross-sectional study of iron overload in this population. Adult allogeneic HCT recipients were eligible if they: (1) had survived for ≥12 months from their transplant, (2) had no active infections, (3) had no active flare of chronic graft-versus-host disease, and (4) had no contraindication for magnetic resonance imaging (MRI) scan. Patients who consented for participation were screened with serum ferritin (normal range 10–300 ng/mL), and those with serum ferritin >1000 ng/mL underwent R2 MRI of the liver to measure liver iron concentration (LIC, normal range 0.17–1.8 mg/g dry tissue) using the FerriScan™ technology, a highly sensitive and specific technique for measuring hepatic iron content (St Pierre et al, Blood 2005, 105: 855). Iron overload was defined as LIC above the normal range (>1.8 mg/g). Forty eight patients were enrolled and were a median of 27 (range, 12–151) months from HCT. All were RBC transfusion independent at the time of study enrollment. Median age was 49 (range, 24–69) years and 54% were males. The most common indications for HCT were acute leukemia (44%) and non-Hodgkin's lymphoma (31%). Eighteen patients had serum ferritin >1000 ng/mL (median 1516 [range, 1003–7311]); of these 17 had iron overload on MRI (median LIC 7.5 (range, 2.8–28.3) mg/g), with an overall prevalence rate of 35% (95% confidence intervals [CI], 22–51%). Clinically significant iron overload (LIC >5 mg/g) was present in 11 patients (23% [95% CI, 12–37%]). LIC level on MRI was only moderately correlated with serum ferritin level (r = 0.49 [95% CI, 0.10–0.88]) and transferrin saturation level (r = 0.55 [95% CI, 0.13–0.97]). In conclusion, iron overload is a frequent late complication of allogeneic HCT. Serum ferritin is a good initial screening test but it may not predict the level of hepatic iron content and may not be useful by itself for identifying clinically significant iron overload. More studies are needed to determine the natural history and treatment of iron overload in allogeneic HCT survivors.

Total patients (N = 48)	Myeloablative/ Non-myeloablative	Related/ Unrelated	Median RBC units transfused	Median ferritin	Median LIC
Ferritin ≤1000 (N = 30)	18/12	20/10	8	364 ng/mL	Not done per protocol
Ferritin >1000 (N = 18)	13/5	12/6	24	1516 ng/mL	7.5 mg/g*

*17/18 patients had iron overload (liver iron concentration >1.8 mg/g on liver R2 MRI).

143

PRE-TRANSPLANT PULMONARY FUNCTION AND DAY 100 NON-RELAPSE MORTALITY AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

Basu, S.K.[1], Liesveld, J.L.[1], Trawick, D.R.[2], Fernandez, D.[3], Nichols, D.[1], Fisher, S.G.[3] [1] University of Rochester, Rochester, NY; [2] University of Rochester, Rochester, NY; [3] University of Rochester, Rochester, NY.

This study's purpose was to evaluate the association between pulmonary function, as measured by the diffusion capacity of the lung for carbon monoxide (DLCO), before hematopoietic stem cell transplantation (HSCT) and non-relapse mortality (NRM) at 100 days post-transplant. The rationale was that DLCO, as an early indicator of lung disease or as a measure of pre-existing systemic endothelial damage, might be a predictor of NRM.

Methods: This was a retrospective cohort study of all patients undergoing their first HSCT at the University of Rochester between 1995 and 2004. NRM at 100 days (Day100NRM) was the primary outcome. DLCO, as percent predicted, corrected for hemoglobin, was the main independent variable. The chi-square test, Mantel-Haenszel test of trend, and analysis of variance were used for categorical, ordinal, and continuous variables respectively in bivariate analyses. Logistic regression was used for multivariate analysis. **Results:** Data regarding DLCO, mortality, and patient characteristics were available from 677 (95%) patients. By 100 days, 59 subjects died without having a relapse. Day100NRM was 8.5% (95% confidence interval: 6.4, 10.8%). Pulmonary complications (27%), graft-versus-host disease (15%), and multi-organ failure (14%) were the most frequent causes of Day100NRM. On crude analysis, using DLCO in quartiles, there was a statistically significant association (chi-square p = 0.0179) and dose response relationship (trend test p = 0.0023) between DLCO and Day100NRM. Of multiple variables analyzed, only race, smoking status, diagnosis, body mass index, forced expiratory volume at one second, forced vital capacity, serum alkaline phosphatase, and serum albumin, had a statistically significant association with DLCO and were included in multivariate testing. In the final multivariate model, low DLCO, low serum albumin, and type of cancer diagnosis remained significantly associated with Day100NRM. The odds ratio for DLCO was 1.442 (95% confidence interval: 1.103, 1.885), using DLCO in quartiles as an ordinal variable. Patients in the lowest quartile of DLCO were almost three-times (odds ratio = 2.99) as likely as patients in the highest quartile of DLCO to experience Day100NRM. **Conclusions:** There was a statistically significant association and a dose-response relationship between pre-transplant DLCO and Day100NRM. These results suggest that the DLCO may be helpful at the time of the pre-transplant evaluation in predicting risk of Day100NRM.

144

FREQUENCY OF ABNORMAL FINDINGS DETECTED BY COMPREHENSIVE EVALUATION AT ONE YEAR AFTER HEMATOPOIETIC CELL TRANSPLANTATION

Lee, S.J.[1], Seaborn, T.[2], Massey, S.[2], Mao, F.J.[2], Luu, N.[2], Moravec, C.[1], Carpenter, P.A.[1], Martin, P.J.[1], Flowers, M.E.D.[1] [1] Fred Hutchinson Cancer Research Center, Seattle, WA; [2] University of Washington, Seattle, WA.

Medical records of 118 adults (88% of eligible patients alive without relapse) who returned for evaluation at one year after allogeneic hematopoietic cell transplantation (HCT) in 2005 were reviewed in order to document the frequency of abnormal findings and to assess the value of routine long-term follow-up (LTFU) assessments after HCT. Most (n = 102, 86%) spent 2–3 days in Seattle for testing and consultation, while 16 (14%) brought results of diagnostic testing performed elsewhere. The cohort included 69 (58%) men and 49 women (42%), 47 (40%) who received reduced intensity conditioning, 62 (53%) with unrelated donors, 105 (89%) who received growth-factor mobilized blood cells, and 18 (15%) who had second transplants. Sixteen additional patients were alive at 1 year without known recurrent malignancy who did not return for evaluation. There were no statistically significant differences in the age, gender,