Methods: 20 pts with hematological malignancies were given MSC (1–2 × 10E6 cells/kg) from third party donors a few hours before PBSC from HLA-mismatched unrelated donors, after conditioning with 2 Gy TBI and fludarabine 90 mg/m^2. Postgrafting immunosuppression included tacrolimus (day -3 to +180; tapered by day +365) and mycophenolate mofetil (tid days 0 to +42). HLA-compatibility was assessed at the HLA-A, -B, -C, -DRBI and DQBI loci. 12 pairs were mismatched for at least one HLA class I antigen (including 4 pairs who were also mismatched for 1 HLA-class II antigens (n = 3) or 1 HLA-class I allele (n = 1)), 1 pair was mismatched for 2 HLA class II alleles, and 7 pairs were mismatched for a single HLA class I (n = 4) or HLA class II (n = 3) alleles.

Results: Median follow-up for surviving pts was 219 (range, 13–519) days, and 17 pts are already evaluable for day 100 nonrelapse mortality (primary endpoint). Thus far, 1 patient with secondary AML had primary graft rejection, while the remaining pts had sustained engraftment. Median donor T-cell chimerism levels on days 28, 100, 180 and 365 after HCT were 91%, 97%, 96%, and 98%, respectively. Grade II, III and IV acute GVHD were seen in 4, 2 and 0 pts, respectively. Two pts died of non-relapse causes on days 74 and 114 after HCT, while 3 pts died of disease progression. Projected 1-yr overall and progression-free survivals were 74% and 62%, respectively.

Conclusions: HLA-mismatched nonmyeloablative HCT with MSC co-infusion appeared to be safe. These encouraging results, suggesting improved outcomes compared to similar pts not co-infused with MSC, should be confirmed in a larger multicenter study.

334

ANTITHYMOCYTE GLOBULINS (ATG) AS PART OF THE MYELOABLATIVE CONDITIONING (MAC) REGIMEN CAN REDUCE THE RISK OF SEVERE GRAFT-VS.-HOST DISEASE (GVHD) AFTER ALLOGENEIC STEM CELL TRANSPLANTATION (ALLO-SCT) FROM MATCHED-UNRELATED DONORS (MUD) [A SFGM-TC STUDY]

Mohty, M.[1], Balere, M.L.[2], Socie, G.[3], Milpied, N.[4], Ifrah, N.[5], Kuentz, M.[6], Harousseau, J.L.[1], Vernant, J.P.[7], Michallet, M.[8], Buzyn, A.[9], Cahn, J.Y.[10], Bourhis, J.H.[11], Blaise, D.[12], Raffoux, C.[2], Esperou, H.[2], Yakoub-Agha, I.[13] [1] CHU de Nantes, Nantes, France; [2] Agence de Biomedecine, Paris, France; [3] Hopital Saint-Louis, Paris, France; [4] CHU de Bordeaux, Bordeaux, France; [5] CHU d'Angers, Angers, France; [6] Hopital Henri Mondor, Creteil, France; [7] Hopital La Pitie, Paris, France; [8] CHU de Lyon, Lyon, France; [9] Hopital Necker, Paris, France; [10] CHU de Grenoble, Grenoble, France; [11] Institut Gustave Roussy, Paris, France; [12] Institut Paoli-Calmettes, Marseille, France; [13] CHU de Lille, Lille, France

Here, we report the results of a multicenter retrospective study analyzing the effect of ATG, incorporated within the MAC regimen for MUD-transplants in leukemic patients. The purpose of the study was to compare the incidence and severity of acute and chronic GVHD as well as overall outcome. 171 adult patients with acute leukemia and MDS, for whom detailed allelic HLA typing (4 digits) was available, were included. 81% of patients were transplanted from 10/10 allelic MUD, and 19% from a MUD with at least one allelic difference. 120 patients (70%) did not receive ATG ("no-ATG" group), while 51 patients received ATG ("ATG" group; Thymoglobuline*, Genzyme in all cases) as part of the MAC regimen. Except for a significantly higher number of allelic differences between recipient and donor (33% vs. 13%; P = 0.002), the "no-ATG" and "ATG" groups were strictly comparable. With a median follow-up of 30.3 (range, 2.6–68.1) months, grade 0–1 and 2–4 acute GVHD occurred in 74 (46%) and 88 patients (54%) respectively, with grade 3–4 acute GVHD being significantly lower in the "ATG" group (18% vs. 32%; P = 0.04). Limited and extensive chronic GVHD were observed in 22 and 25% of assessable patients respectively, with extensive chronic GVHD being significantly lower in the "ATG" group (5% vs. 33%; P = 0.001). Interestingly, patients from the "ATG" group had a higher incidence of limited chronic GVHD (33% vs. 18%; P = 0.06). Moreover, infection-related mortality was comparable between both groups (23% vs. 27%, P = NS). Also, NRM was comparable between both groups (30% vs. 29%; P = NS). In multivariate analysis, an HLA allelic mismatch and the non-use of ATG were associated with an increased risk of grade 3–4 acute GVHD (RR = 2.80, 95%CI, 1.5–5.3, P = 0.001; and RR = 2.4, 95%CI, 1.1–5.0, P = 0.02 respectively). Similarly, multivariate analysis showed that the absence of use of ATG was the unique parameter associated with an increased risk of extensive chronic GVHD (RR = 6.9; 95%CI, 1.7–29.0, P = 0.008). Finally, LFS and OS at 2 years were not significantly different between the "no-ATG" and "ATG" group (48.8% vs. 41.3%, P = NS; and 53.6% vs. 54.3%, P = NS; respectively). These results suggest a global long-term beneficial effect of ATG when used as part of the MAC regimen prior to allo-SCT from MUD (especially in the HLA mismatch setting). Such protective effect of ATG against severe GVHD can be likely achieved without an increased risk of infections or leukemia recurrence.

335

HUMAN MEMORY T CELL S ELICIT DECREASED CYTOTOXICITY AGAINST ALLOGENEIC TARGETS

Zheng, Q., Deoliveira, D., Chao, N.J., Chen, B.J. Duke University Medical Center, Durham, NC

Several groups have independently demonstrated that memory T cells do not induce graft-versus-host disease in several different animal models. To test whether the same concept applies to humans, we compared the ability of memory T cells to respond to alloantigens with that of naive T cells. Purified T cells were first obtained from peripheral blood from healthy donors and then separated into memory and naive T cell subsets based on the expression of CD45RA (memory: CD45RA-, naive: CD45RA+). Memory T cells were then tested for their ability to respond to alloantigens by using several standard in vitro assays. In contrast to the mouse data, memory T cells proliferated equally well as naive T cells did in mixed lymphocyte culture. Despite the similar proliferative responses against alloantigens as those mediated by naive T cells, these same memory T cells failed to kill the allogeneic targets. Limiting dilution assay demonstrated that the frequency of allospecific cytotoxicity T cells was 6–68.5 fold less in memory T cells than that in naive T cells. Interleukin 2 was unable to restore the cytotoxicity against alloantigens. The results from skin explant assay further suggested that, in contrast to naive T cells, memory T cells might not be able to induce graft-versus-host disease. These data suggest that human memory T cells contain less alloantigen-specific cytotoxicity T cells and may not cause graft-versus-host disease upon in vivo transfer. Since clinical grade antibody is now available, this approach will soon be tested in humans for the prevention of graft-versus-host disease.

336

PROGNOSTIC FACTORS AND OUTCOMES OF SEVERE GASTROINTESTINAL GRAFT-VS-HOST DISEASE (GI GVHD) AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

Castilla-LLorente, C.[1,2], Nash, R.A.[1], McDonald, G.B.[1], Storer, B.E.[1], Martin, P.J.[1] [1] Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA; [2] Hospital Morales Meseguer, Murcia, Spain

Treatment of severe GI GVHD poses a challenge, as little progress has been made in developing better treatments, survival remains poor and it is difficult to know the ultimate severity of GVHD and the outcome at the onset of symptoms. We reviewed the records of 117 consecutive patients transplanted between 2000–2005 who developed stages 3–4 GI GVHD. Data were collected for more than 20 parameters including stool volume, abdominal pain, melena, upper GI symptoms, serum albumin, number of treatments, visual findings at endoscopy and histopathologic grade of GI biopsies. Clinical parameters were measured as the peak value during each 14 day period starting from 2 weeks before the diagnosis of GI GVHD to the resolution of symptoms, loss of follow-up or patient death. Median onset of symptoms was day 29 (range 4 – 135); 11 (9.6%) patients presented after day 80. Mean daily stool volume at diagnosis was 1831.12 ±1438.16mL/day. At onset of GI symptoms, 56% of patients had ≥ stage 1 skin GVHD and 62% had ≥ stage 1 liver GVHD. At onset, 78% had upper GI symptoms and 55% of patients presented with severe abdominal pain. Within the first 2 weeks after the diagnosis of GI GVHD, 62 (53%), 37 (31.6%), 4 (3.4%), 13 (11.2%) and 1 (0.8%) patients had a peak GI stage of 4, 3, 2, 1 and 0 respectively. All patients received high dose prednisone/prednisolone as initial treatment; 67 received 2nd line therapy; and 32 received three or more lines of treatment. Non-relapse mortality was 71% and 41% at 1 year after transplant in patients with steroid-refractory and steroid-responsive GVHD, respectively. Overall survival was