adjusted as needed. Here, we evaluate the pharmacokinetic effects of concomitant voriconazole administration on blood TAC levels in 27 consecutive allogeneic HSCT recipients (28–64 y; median 55) in whom pre-emptive dose-modification was used during the first 2 weeks. A total of 170 levels (3–12 per patient; median 5) were checked between day +1 and day +16. None of the levels was subtherapeutic (<5 ng/mL), and 34 (20%) were >15 ng/mL. 24 of 27 patients required dose-reduction from day 0 to day +1 based on levels. Each patient required dose-reduction at least twice. An increase in the dose was needed in only 2 patients after initial dose-reduction. TAC doses (median, range) on days 0, 7 and 14 were 1.6 (1–2), 0.6 (0.13–1.4), and 0.4 (0.13–1.1) respectively indicating that the median absolute TAC dose, the median TAC mg/kg dose, and the median per cent TAC dose (100% being the baseline) declined substantially. However, the median TAC level over the first 2 weeks remained between 10 and 14.5. It is clear that lack of pre-emptive dose-reduction would have resulted in TAC levels climbing steadily. Based on this, we recommend starting TAC at 0.02–0.022 mg/kg rather than at 0.03 mg/kg if patients are on concomitant voriconazole, checking levels regularly, and reducing the dose by 30–40% if the 48-h level is 7–10 and by 40–50% if it is 10–15.

314

LOW RELAPSE RATE AFTER ALLOGENEIC-SCT FOLLOWING A MYELOABLATIVE PREPARATIVE REGIMEN WITH FLAMSA CHEMOTHERAPY AND TOXICITY-REDUCED CONDITIONING IN PATIENTS WITH HIGH RISK MYELOID MALIGNANCIES AGED 60 YEARS OR OLDER

Schleuning, M.[1], Judith, D.[1], Heshmat, M.[1], Burlakova, I.[1], Taube, R.[1], Jedlickova, Z.[1], Baurmann, H.[1], Kolb, H.-J.[2], Schwerdtfeger, R.[1]. [1] German Diagnostic Clinic Foundation, Wiesbaden, Germany; [2] University of Munich and GSF Research Center for Environment and Health, Munich, Germany.

With the introduction of toxicity-reduced conditioning (TRC) allogeneic stem cell transplantation (allo-SCT) may be considered also for elderly patients (pts). However, non-myeloablative regimens are associated with a high relapse risk. Our strategy combined intensive chemotherapy to induce a status of minimal residual disease, TRC, GVHD prophylaxis with in vivo T-cell depletion and adjuvant donor lymphocyte transfusions (aDLT). This report summarizes our cumulative experience in a cohort of 45 consecutive elderly pts (60–70 y, median 63 y) with myeloid malignancies (18 with high risk cytogenetics) treated with the FLAMSA-RIC protocol, consisting of a 4-day course of chemotherapy (AraC 2 g/m^2, Fludarabine 30 mg/m^2 and Amsacrine 100 mg/2) followed by 3 days rest and TRC with 4Gy TBI, cyclophosphamide and antithymocyte globuline prior to allo-SCT. The underlying diseases were AML (de novo n = 20; sAML n = 16) or progressive MDS (n = 8) with only 5 pts being in CR at the time of transplant. One pt suffered from CML in refractory myeloid blast crisis. To further reduce toxicity TBI was replaced by intravenous Busulfan (8 × 3.2 mg/kg) in the last 16 pts. All but one pt received mobilized peripheral blood stem cells as graft and 9 pts had a sibling and 36 an unrelated donor. GVHD prophylaxis consisted of Cyclosporine A and MMF. The procedure as a whole was clearly myeloablative as evidenced by full donor chimerism at d + 30 in all pts. Engraftment occurred after 10–48 d (median 18 d). Of 25 eligible pts (being alive and free of leukaemia at d + 120) 8 pts actually received aDLT and none of these relapsed. Despite the high relapse risk we observed only 6 deaths because of recurrent leukaemia. Severe acute GVHD occurred in 20% and the non relapse mortality was 31% with 3 pts dying from GVHD, 10 from infection and one from cardiac failure. With a median follow-up of 10 months for surviving pts the Kaplan-Meyer procedure estimates a 43% probability of survival at 2 y after transplantation. Although, the follow-up of pts having received i.v. Busulfan is rather short there seems to be a strong tendency of further reduced toxicity without increased relapse incidence in this cohort. Our data support the notion that toxicity-reduced but still myeloablative conditioning followed by allo-SCT from related or unrelated donors can safely be applied in elderly pts with high risk myeloid malignancies and provides an excellent platform for adoptive immunotherapy after induction of tolerance.

315

SIMILAR SURVIVAL AFTER SIBLING VS UNRELATED DONOR ALLOGENEIC STEM CELL TRANSPLANTATION WITH REDUCED INTENSITY CONDITIONING

Stein, S., Goldstein, S.C., Smith, J., Luger, S., Loren, A., Stadtmauer, E., Schuster, S., Nasta, S., Tsai, D., Perl, A., Andreadis, B., Frey, N., Kasner, M., Cole, S., Hinkle, J., Porter, D.L. Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA.

Although recent studies have shown comparable survival outcomes between unrelated donor (URD) and sibling donor stem cell transplantation in the myeloablative transplant setting, little comparative data based on donor source is available in the setting of non-myeloablative/reduced intensity conditioning (RIC), where it is presumed that GvL effects must play a key role in long term survival. In this retrospective analysis, we compare the outcome of 111 patients receiving RIC followed by either matched sibling (n = 65) or unrelated donor (n = 46) peripheral blood stem cell (PBSC) transplantation for hematologic malignancies. All patients were deemed ineligible for myeloablative conditioning based on institutional standards for age, comorbid disease, and/or prior therapy. All sibling and 38 of 46 unrelated recipients received A, B, DR matched grafts. The median recipient age in both cohorts was identical; sibling 52 y (range 12–75 y) and unrelated 52 y (range 29–69 y). Conditioning regimens were primarily fludarabine/cytoxan-based in both cohorts, with URD recipients skewed toward the addition of Alemtuzumab pre-transplant (69% URD vs 25% sib), and the use of TBI 200 for 21/23 myeloma pts. The distribution of diagnoses was similar between both cohorts in patients with lymphoid malignancies (NHL, HD, CLL n = 66) 34 sib vs 32 URD, and leukemia/MDS (n = 22), 10 sib vs 12 URD; the diagnosis of myeloma (n = 23) was skewed toward sibling donors (21 vs 2 URD). Kaplan-Meier estimate of overall survival (OS) for all patients at 2 years was 31%. At a median f/u of 43 weeks in both cohorts, overall survival was nearly identical (57% sibs; 55% URD). Of note, there was no statistically significant difference in 2 year OS between sibling and URD recipients (p = 0.25), nor was there a difference in K-M estimates of OS between sibling and URD recipients when patients with lymphoid and myeloid disease were analyzed separately. Among expired patients, there was no difference in the incidence of disease-related (26/42 sibs vs 18/32 URD) or treatment-related [organ failure, infection and GvHD] (16/42 sibs vs 14/32 URD) causes of death. Furthermore, a statistically significant higher proportion of GvHD-related death among URD patients was not seen. These data support the pursuit of unrelated donors for RIC transplantation as an alternative to sibling donors without compromising overall survival.

316

DEVELOPMENT AND ANTI-BALB.B REACTIVITY OF T CELLS EMERGING FROM BONE MARROW CELLS TRANSDUCED WITH A CLONAL TCRVβ14-Jβ2.4 SEQUENCE

Appel, M.Y.[1], Friedman, T.M.[2], Korngold, R.[2]. [1] Thomas Jefferson University, Philadelphia, PA; [2] Hackensack University Medical Center, Hackensack, NJ.

In previous experiments utilizing spectratype-sequencing, we reported a dominant T cell receptor (TCR) Vβ14-Jβ2.4 sequence prevalent in the thoracic duct lymphocyte (TDL) population of irradiated BALB. B mice transplanted with C57BL/6 (B6) mouse bone marrow and CD8$^+$ T cells. CD4-dependent CD8$^+$ Vβ14$^+$ T cells mediate lethal graft versus host disease (GVHD) in a B6→BALB. B transplantation model. Therefore, we wanted to investigate the alloreactive potential of T cells expressing the particular isolated TCRβ sequence. We harvested bone marrow from 5-fluorouracil (5-FU) treated TCRβ$^{-/-}$ mice. The bone marrow cells were retrovirally transduced with a construct containing the cDNAs for Green Fluorescent Protein (GFP) and the specific Vβ14-Jβ2.4 TCR sequence. The marrow was then used to reconstitute irradiated B6 mice. 20–40% of the peripheral blood mononuclear cells (PBMC) in these mice were GFP$^+$Vβ14$^+$, of which greater than 95% were CD4$^+$ and 1–4% were CD8$^+$. When the marrow was used to reconstitute MHC II$^{-/-}$ mice, bred to a B6 background,