Background: Various doses of ATG have been utilized in RIC allogeneic transplantation targeting T cell depletion, with the goal of decreasing the incidence and severity of both acute and chronic GVHD. This is an update to the previously published data where we showed that lower ATG dose resulted in improved non-relapse mortality and infection rate without compromising control of GVHD.
Methods: We retrospectively analyzed 136 consecutive patients who received RIC HSCT between 2006 and 2010. Following October 2007, ATG dosing was lowered from 7.5 mg/kg (R-ATG) to 6 mg/kg (r-ATG). Progression-free (PFS) and overall survival (OS) were analyzed using the log-rank test. Cumulative incidences of GVHD were analyzed using Gray's test, accounting for competing risks.
Results: Thirty-nine patients received R-ATG and 97 received r-ATG. There were no significant differences in age, gender, KPS, degree of HLA match, prior autografts, donor/recipient CMV status, and CD34 cell dose between the two groups ($P >$ .15). More patients were transplanted with r-ATG than R-ATG for CLL and fewer with AML/MDS/NHL/HD/other histologies ($P = .02$). Time to platelet engraftment as well as donor-cell chimerism at days +30, +90, +180 were not significantly different between the groups, but time to neutrophil engraftment was shorter with R-ATG ($P = .001$). Proportions of aGVHD II-IV were 52% and 41% ($P = .34$) in r-ATG and R-ATG respectively and proportions of cGVHD were 40% and 53% ($P = .23$). Further, no significant differences in the cumulative incidence of GVHD were observed (Figure 1). The R-ATG group experienced more episodes of bacterial infections than the r-ATG cohort (54% vs. 8%; $P < .0001$). No differences in PFS ($P = .69$) or OS ($P = .95$) were observed between the cohorts.
Conclusion: r-ATG did not result in an increase incidence of acute or chronic GVHD. No PFS or OS differences were observed between the cohorts; however, R-ATG resulted in a higher proportion of bacterial infections.

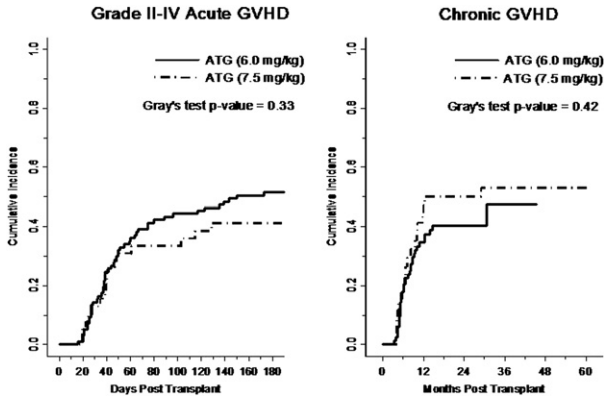

Figure 1. Acute and chronic GVHD

392

Soluble Aminopeptidase N (CD13) Is a Diagnostic Biomarker of Late-Onset Chronic Graft Vs. Host Disease in Adults

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Background: Chronic graft vs. host disease (cGVHD) is a major cause of morbidity and mortality after allogeneic HSCT. As an insidious onset and heterogeneous presentation renders this disease difficult to diagnose, there is a need for validated diagnostic biomarkers. Previously, soluble aminopeptidase N (CD13) was identified in a pediatric study as a biomarker for early onset cGVHD (diagnosed 3-9 months post transplant). Aminopeptidase N is a protease involved in immunoregulation on several levels; functions include attraction of T cells, antigen presentation, facilitation of adhesion and phagocytosis. Although it is integrated in the membrane of several cell types it can also be cleaved into soluble aminopeptidase N. In this study, we tested the potential plasma biomarker soluble aminopeptidase N in an adult population of late onset cGVHD patients using both a targeted method (enzymatic assay) as well as a non-targeted approach (proteomics).
Methods: Samples used in this study were frozen, EDTA-treated plasma samples derived from a single institution participating in the Chronic GVHD Consortium and consisted of 17 cases and 21 time-matched controls, all from adult patients. Cases were within 1 month of diagnosis of late-onset cGVHD (onset >9 months post transplant). Time posttransplant for cases vs. controls was 12 (9.2-26.8) vs. 11.9 (5.3-13.5) months, respectively. Other potential clinical variables included age at sample collection, gender, graft source, donor type, conditioning intensity, prior acute grade II-IV GVHD, and months from sample collection. Aminopeptidase N activity was determined by cleavage of L-leucine-p-nitroaniline; quantitative proteomic analyses were done with iTRAQ.
Results and Conclusions: Plasma from cGVHD patients had significantly higher mean levels of aminopeptidase N enzyme activity than did plasma from control patients (0.30 vs. 0.18 mU/ml, respectively $P = .0008$). Proteomic analyses using the same samples revealed that this difference was not restricted to activity; aminopeptidase N showed the most significant difference in protein levels corresponding to presence or absence of cGVHD of all the proteins identified. Relative amounts of soluble aminopeptidase N were 1.44 vs. 0.9, in cases and controls, respectively ($P = .0042$). This study supports soluble aminopeptidase N as a potential diagnostic biomarker in adult GVHD. These results will be validated in a larger population which also includes early onset cGVHD.

393

Long-Term Survival After Allogeneic Haematopoietic Cell Transplantation for Acute Myeloid Leukemia. Comparable Results From Myeloablative and Non-Myeloablative Conditioning in Young and Elderly Patients

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Nonmyeloablative (NM) conditioning in allogeneic transplantation is increasingly used in patients aged over 50 years with acute myeloid leukemia (AML). In this single-center retrospective study, we report the results of NM and myeloablative (MA) conditioning in 207 consecutive AML

patients. NM conditioning consisted of fludarabine 90 mg/m^2 plus 2 Gy TBI, while MA conditioning was cyclophosphamide 120 mg/m2 in combination with 12 Gy TBI or 12.8 mg/kg busilvex. MA conditioning was given to 122 patients and NM to 85 patients. Median age at transplant was 39 (range 15-56) in MA patients and 59 (range 27-73) in NM patients. Donor source, cytogenetic risk, CMV antigen status recipient/donor, sex match, Karnofsky score, and body mass index were not different among MA and NM patients. Disease stages CR1, CR2, and >CR2/Primary Induction Failure (PIF) were analyzed separately. Survival of patients with advanced stage (>CR2/PIF) was short in both groups; 6.1 and 5.2 months in MA and NM, respectively. Patients in CR1 and CR2 were analyzed in details. Patient numbers in MA and NM transplants were 60 vs. 62 in CR1 and 50 vs. 17 in CR2. In CR1 and CR2 MA patients 68% and 48% received bone marrow, whereas all of the NM patients received peripheral stem cells, $P < .001$. Day 100 TRM in MA vs. NM transplants was 8.3% vs. 1.6% in CR1patients and 14% vs. 5.9% in CR2 patients, which was not significantly different. Relapse incidence was comparable among the MA and NM transplants, both in CR1 and CR2 patients. The cumulative incidence of relapse at 1 year was 18.4% (CI: 5.0-28.2) versus 20.9% (CI: 5.2-31.1) in MA and NM patients transplanted in CR1, and 14.5% (CI: 5.1-24.5) versus 11.8% (CI: 0- 27.1) in CR2 patients (n.s.). The 5 year overall survival (OS) probability in the CR1 patients with MA conditioning vs NM conditioning was 63.9% (CI:51.4-76.4) vs 64.0% (CI:51.4-76.6), and among CR2 patients 51.2% (CI:36.0-66.4) vs 64.7 (CI:41.9-87.4), (n.s.). The median survival follow-up time was 55 months (range: 9-137) among CR 1 patients, and 54 months (range: 7-133) among CR2 patients. The 3-year cumulative incidence of chronic GVHD in CR1 patients was 52.8% (CI:39.9-65.8) and 41.9% (CI:29.3-54.7) in MA and NM patients, respectively. In CR2 patients, the incidences were 32.7% (CI:19.0-46.3) and 41.2% (CI:17.8-64.6). In conclusion, OS, TRM and relapse in NM transplants were comparable to MA transplants despite a truly NM regimen and a substantial age difference between groups.

394

Outcomes of Children with Hematologic Malignancies Who Relapse After Allogeneic Hematopoietic Cell Transplantation (AlloHCT)

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Background: Relapse is the primary cause of treatment failure after alloHCT for hematologic malignancies. We describe the presentation, management, and outcomes of children with post-HCT relapse, specifically focusing on post-HCT minimal residual disease (MRD), to improve monitoring and intervention strategies.

Design: This was a single institution, retrospective cohort study of children with relapse or progression of acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), mixed phenotypic acute leukemia (MPAL) or myelodysplastic syndrome (MDS) post-alloHCT between January 1, 2003 and December 31, 2010. MRD was defined as disease detectable by immunophenotypic, cytogenetic or molecular methods that did not meet classic morphologic criteria for relapse (defined as $\geq$ 5% disease). Relapse was defined as any evidence for disease detected after previously negative results, including MRD. Progressive disease was defined as an increase in any measure from baseline results.

Results: 40 of 93 (43%) patients who underwent a first alloHCT experienced relapse, including patients with AML (n=18), ALL (n=16), MPAL (n=4) and MDS (n=2). The median time from alloHCT to relapse was 144 days (range 1 month-58 months). Nine patients with post-HCT MRD as the first evidence for relapse, presented at a median time of 35 days post-HCT (range 28-182 days), with the majority having rapid progression of disease. Median survival after relapse was 123 days (range 4 days-5 years). Estimated 6-month and 1-year post-relapse survival was 30% and 17.5%, respectively. Five of 40 (12.5%) patients are currently alive with a median follow-up of 39 months, including 1 patient with active disease. 1 survivor had MDS and presented with MRD alone. The remaining 4 (with leukemia) presented with overt disease between 146 and 411 days post-HCT. 3 of 5 survivors underwent a second HCT. 11 patients who were able to undergo a second transplant, experienced a 3-year 27% OS starting after relapse. (Figure 1). No patients with AML survived after relapse.

Conclusion: Although pre-emptive treatment of relapse in the setting of MRD is felt to be ideal, it may not be feasible. In our study, patients with MRD presented very early post-HCT at a time when complications can be high and therapeutic options are limited. Once MRD was detected, disease progression was rapid limiting the chance to respond to frontline immunotherapeutic options. Accordingly, there was no survival advantage for pediatric patients with leukemia whose relapse was detected as MRD compared to overt disease. Given the poor outcomes of post-HCT relapse and limited ability to treat relapse at the stage of MRD, efforts should focus on developing effective therapies for relapse prevention by identifying those at highest risk of relapse as candidates for novel methods to enhance efficacy of alloHCT.

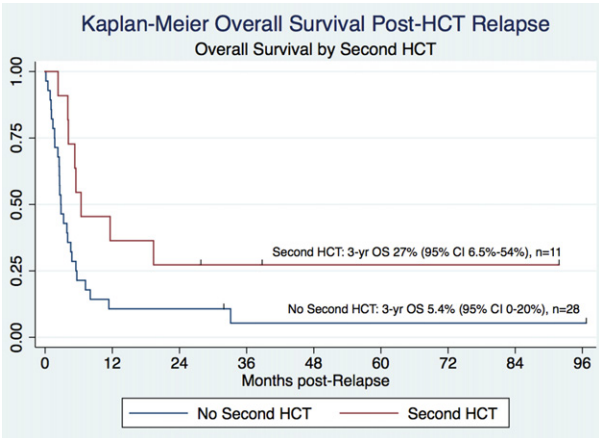

Figure 1. OS by Second HCT for Patients with Post-HCT Relapse

395

Primary Hemophagocytic Lymphohistiocytosis and Hematopoeitic Stem Cell Transplantation in Iran

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