on outcomes. A lower risk of late relapse was seen with several cGVHD specific variables (P<0.0001), i.e., mild, moderate or severe cGVHD; de novo or progressive cGVHD; or involvement of any organ with cGVHD. These results demonstrate a protective effect of cGVHD on late relapse only in CML. In addition, presence of cGVHD by 1 year after HCT was associated with a higher risk of TRM and inferior OS in all patients (CML, AML, ALL, MDS). Since the protective effect of cGVHD on late relapse was seen only in CML patients, more aggressive measures to control cGVHD may be beneficial especially in AML, ALL and MDS patients after high intensity conditioning regimen.

20

PRIMING OF HEMATOPOIETIC PROGENITOR CELLS (HPC) WITH COMPLEMENT FRAGMENT 3A (C3A) TO PROMOTE HOMING OF UMBILICAL CORD BLOOD (UCB): SAFETY PROFILE

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Pre-clinical data showed that C3a priming of CD34+ HPC leads to activation of CXCR4, improved migration towards an SDF1 gradient, and faster hematopoietic recovery and better human engraftment in mice. On the basis of these data, we hypothesized that preincubation with C3a would be safe and enhance engraftment. To test this hypothesis, we incubated the smaller of the two UCB units with C3a 1 mcg/mL (Calbiochem, Gibbstown, NJ) for 30 minutes, and infused without washing. Ten patients, median age 62 (r: 30-68), 8 males, with AML (n = 6), MDS (n = 3) and Hodgkin's (n = 1) were enrolled. Units were selected using the University of Minnesota published criteria and all met lot release (endotoxin <5 EU/kg, negative gram stain, viability >45%). Conditioning consisted of cyclophosphamide 50 mg/kg/x1day, fludarabine 40 mg/m^2/x5d, total body irradiation 200cGy/x1d with antithymocyte globulin added in three since they had not had recent chemotherapy. Immunoprophylaxis consisted of cyclosporine A/mycophenolate mofetil (MMF). The unmanipulated unit was infused first with the C3a primed unit infused 30 min later. Patients were monitored for 24 h for evidence of infusional toxicities and activation of pathways downstream of C3a by assessment of coagulation factors, IL-6, TNF-alpha, histamine, tryptase and C-reactive protein before and 15, 30 and 60 min post-infusion. Grade 3 hypertension was the only notable infusional toxicity in 5; no patient had demonstrable activation of the complement pathway. Nine patients had neutrophil recovery at a median of 9 days (range 6-26). On day 21, hematopoiesis was primarily derived from the C3a primed unit in 6 of 9 (67%) evaluable patients and present but non-predominating in another. While not expected to enhance the speed of neutrophil recovery after a non myeloablative therapy where initial host recovery in expected, these data suggest a potential repopulating advantage especially since the C3a primed unit is smaller and infused last. Based on the safety profile and potential impact on engraftment, a randomized phase II clinical trial in the myeloablative setting where neutrophil recovery rates are suboptimal (median 23 days) is being developed.

21

IMPACT OF HEMOCHROMATOSIS GENE (HFE) POLYMORPHISMS AND IRON OVERLOAD ON OUTCOME OF ALLOGENEIC STEM CELL TRANSPLANTATION FOR CHRONIC MYELOID LEUKEMIA

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Iron overload is a common complication following hematopoietic stem cell transplantation (HSCT), and recent evidence suggests that it has an important influence on both morbidity and mortality. The C282Y and H63D polymorphisms of the hemochromatosis gene (HFE) are associated with increased iron absorption. We evaluated 119 patients with CML in chronic phase (CML-CP) undergoing myeloablative HSCT for the presence of HFE polymorphisms. The frequency of polymorphisms was consistent with that of the normal population. The presence of the HFE polymorphisms was not associated with ferritin levels pre or post-transplant and there was no impact on OS, TRM, or relapse rate. Serum samples were available for 84 patients at regular intervals post-transplant. We evaluated serum markers of iron overload and regulation including ferritin, iron, transferrin saturation (%TSAT), Hepcidin-25, and growth differentiation factor-15 (GDF-15) as well as markers of inflammation such as CRP and interleukin-6 (IL-6).

We found significant associations between Hepcidin-25 levels (< or > median of 119ng/ml) measured within 3 months of HSCT (median 50.5 days) and 1-year OS (92.9% vs 69 %, p = 0.002) and 1-year TRM (7.6% vs. 29.2% P = 0.04). The cause of death in all patients was secondary to infection. There was no impact of Hepcidin-25 on the occurrence/severity of GVHD (p = 0.64) or the incidence of relapse (p = 0.13). Hepcidin-25 plays a pivotal role in iron metabolism and its expression can be upregulated by iron overload as well as by inflammatory stimuli such as IL-6. In keeping with these findings, increased levels of GDF-15, a member of the TGF-β family and regulator of Hepcidin-25, were also associated with increased TRM and inferior 1-year OS (p = 0.07 and p = 0.021, respectively). In multivariate analysis, Gratwohl score (RR = 13.8, p = 0.001) and Hepcidin-25 (RR = 4.2 and p = 0.027) were the only independent predictors for 1-year OS. Our results suggest that post-transplant Hepcidin-25 and GDF-15 levels may be useful biomarkers for predicting 1-year TRM and OS after HSCT. Larger prospective studies are warranted to confirm our findings.

22

EXPRESSION OF CD30 IS INCREASED ON CD8+ T-CELLS IN PATIENTS WITH ACUTE GRAFT-VS-HOST DISEASE

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Background: Acute graft-vs.-host disease (GVHD) remains a major source of morbidity and mortality after allogeneic hematopoietic cell transplantation (HCT). CD30 is a cell surface membrane protein of the tumor necrosis factor receptor family and is expressed on activated T-cells. We hypothesized that CD30 could be used as a biomarker of acute GVHD after allogeneic HCT.
Methods: Peripheral blood mononuclear cells were collected from 12 patients at the time of presentation of symptoms of acute GVHD, but prior to the initiation of systemic corticosteroids. 15 patients without GVHD were used as controls (CONTROL). In the GVHD group, sample collection ranged from day +23 to day +165 after HCT and was based on symptoms or signs suggestive of acute GVHD. One patient developed GVHD following donor leukocyte infusion (DLI). In the control group, sample collection ranged from day +58 to +98 after HCT.
Results: There were no significant differences in baseline characteristics between the two groups. Analysis by flow cytometry showed that patients with acute GVHD had a higher percentage of CD30 expressing CD8+ T-cells: median 2.7% (range 0.5%-10.2%) in GVHD vs. 0.4% (0.2%-3.2%) in CONTROL, (p < 0.001). Further immunophenotypical analysis showed that the difference was quite pronounced in the effector memory subset (defined by CD8+,CD45RO+,CD62L-): 3.4% (0.7%, 10.8%) GVHD vs 0.8% (0.4%, 2.9%) CONTROL, (p = 0.003) and the central memory subset (defined by CD8+,CD45RO+,CD62L+): median 15.6% (2.8%, 25.0%) GVHD vs. 2.3% (1.3%, 10.4%) CONTROL, (p < 0.001). There was no significant difference in CD30 expression in naïve cells (CD8+,CD45RO-,CD62L+), CD4+ T-cell subsets, or regulatory (CD127-,CD25+) T-cells. Time after HCT had no effect on expression of CD30.
Conclusions: These results suggest that CD30 expression on CD8+ T-cells after allogeneic HCT may be a potential biomarker for acute GVHD. More importantly, this study suggests that CD30 may represent a novel target for the therapy of acute GVHD after HCT. Analysis with a larger number of samples is ongoing to confirm these results.