planted in the last 3 years of the study following protocol modifications is encouraging.

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Does Having CLL Confer a Greater Risk of Graft Versus Host Disease in Patients Who Have Undergone Allogeneic Hematopoietic Stem Cell Transplantation?

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Background: Despite the potential benefit of allogeneic hematopoietic stem cell transplant (HSCT) in improving progression-free survival in patients with high-risk chronic lymphocytic leukemia (CLL), there remains concern that this therapy leads to more significant complications post-HSCT, potentially due to immune dysregulation observed with this disease. We sought to determine the incidence of graft-versus-host disease (GVHD) following HSCT in patients with CLL compared to patients with other hematologic malignancies.
Methods: Using The Ottawa Hospital Blood and Marrow Transplant Database and medical chart review, patients undergoing HSCT for CLL (n = 47) from 1998 to 2015 were compared to a cohort of patients undergoing HSCT for AML, ALL or MDS (n = 121). The primary outcome was incidence of overall GVHD, defined as acute or chronic GVHD requiring systemic immunosuppressive therapy.
Results: There were no significant differences in age, gender, graft source, CMV status of recipient/donor, conditioning intensity, HLA match, or median CD34+ cell dose infused between the CLL and non-CLL cohorts ($P > .05$). The median time to neutrophil engraftment in the CLL and non-CLL cohorts was 17 days ($P = .27$) and the median time to platelet engraftment was 18 and 19 days respectively ($P = .21$). The cumulative incidence of overall GVHD was higher at 5 years in the CLL compared to the non-CLL cohort (90.1% vs. 69.1% respectively, $P = .0003$, see Figure 1). GVHD-free-relapse-free survival was significantly worse in the CLL cohort at 5 years post-HSCT (0 vs. 17.8%, $P = .0003$). There was no difference in 5 year relapse-free survival (69.1% vs. 68.1%, $P = .11$) or 5 year overall survival (46.0% vs. 60.2%, $P = .20$) between the CLL and non-CLL cohorts respectively. In multivariate analysis, diagnosis of CLL was not significantly associated with
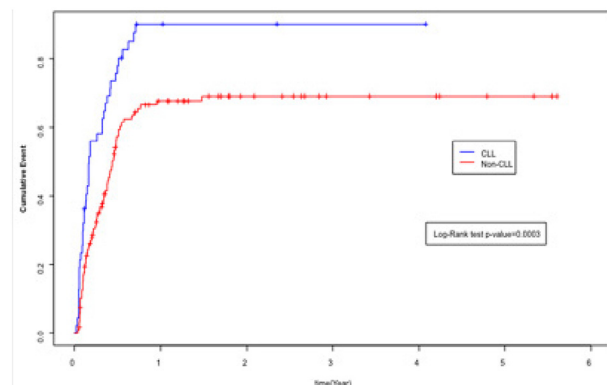
overall GVHD (HR = .82, 95% CI .40-1.7), but ATG use and non-myeloablative conditioning were associated with a trend towards reduction in risk of GVHD (HR = .69, 95% CI .46-1.04, $P = .07$ and HR = .65, 95% CI .41-1.02, $P = .06$, respectively).
Conclusions: Patients undergoing HSCT for CLL have a very high incidence of GVHD, leading to poor GVHD-free-relapse-free survival compared to those with other hematologic malignancies. Further clinical and biologic investigation into the immune dysregulation observed in CLL is warranted to determine the role this disease itself may play in HSCT outcomes.

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An Early Biomarker Algorithm Predicts Lethal Graft-Vs-Host Disease and Survival after Allogeneic Hematopoietic Cell Transplantation

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The graft-versus-host reaction is underway by day +7 after HCT even though graft-versus-host disease (GVHD) symptoms are not yet present. We sought to identify a blood biomarker signature that could predict lethal GVHD and sixmonth NRM at this early time point when pre-emptive treatment might be effective. Patient samples on day +7 after HCT were obtained from 1,287 patients (pts) from 11 centers in the Mount Sinai Acute GVHD International Consortium

Figure 1. Cumulative Incidence of GVHD in CLL and non-CLL cohorts.

(MAGIC). Samples from two large centers (n = 929) were combined and randomly assigned to a training set (n = 620) and test set (n = 309). 358 pts from nine other centers constituted an independent validation set. The overall cumulative incidences of 6month NRM were 11%, 12%, and 13% for the training, test, and validation sets respectively. The incidence of lethal GVHD, defined as death without relapse while receiving steroids for acute GVHD, were 8%, 8%, and 9% in the same groups, respectively. The median day of GVHD onset was 28 days in the training set and 29 days in both the test and validation sets. We tested algorithms of all 13 possible combinations of four GVHD related biomarkers [ST2, REG3α, TNFR1, and IL2Rα], using samples from the training set alone to develop competing risk regression models that predicted 6month NRM. The best algorithm included ST2 and REG3α and no combination of 1, 3, or 4 biomarkers was superior to this combination. The algorithm identified high risk (HR) and low risk (LR) groups with 6month NRM of 28% and 7%, respectively (*P* < .001) (Figure 1A). Relapse rates did not differ between risk groups and overall survival (OS) was 60% for HR and 84% for LR (*P* < .001) (Figure 1B). When we applied the algorithm to both the test set (Figure 1C/D) and to the vali-
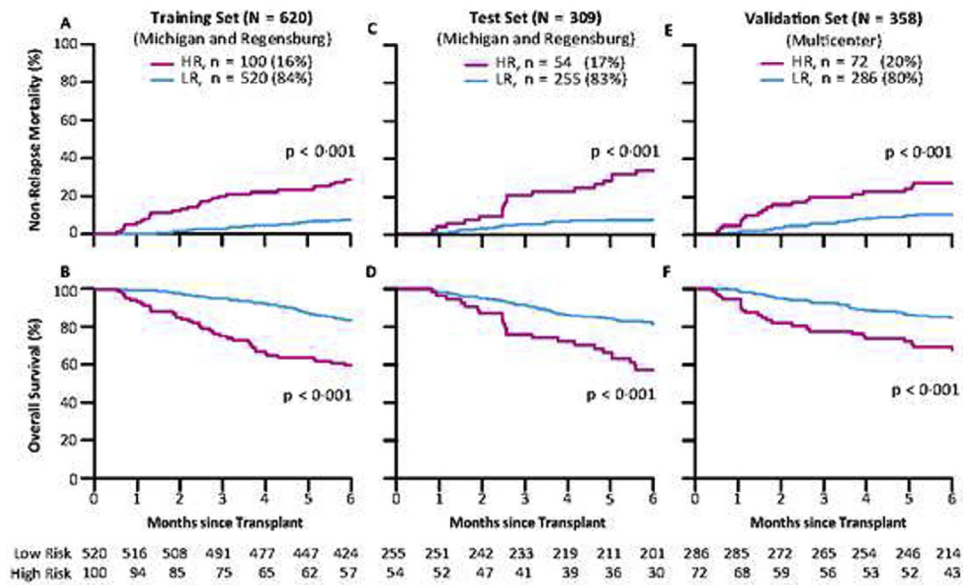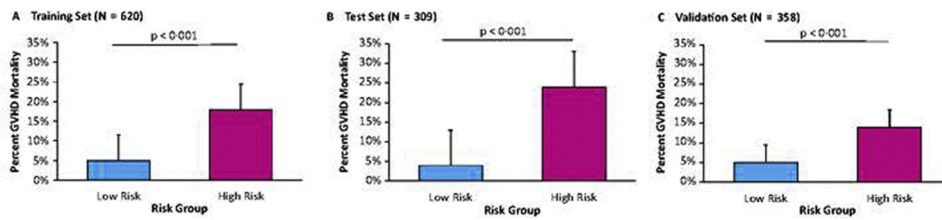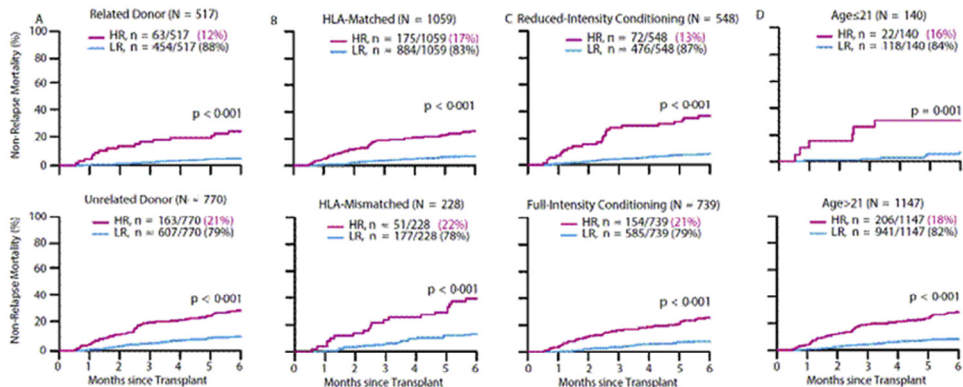

Figure 1.

Figure 2.

Figure 3.

dation set (Figure 1E/F), we observed similar proportions of pts identified as HR with equally high rates of NRM and low OS. HR pts were 3 times more likely to die from GVHD than LR pts in each cohort (P < .001) (Figure 2). The GI tract, the GVHD target organ most resistant to treatment, represents a major cause of NRM; we observed twice as much severe GI GVHD (stage 3 or 4) in HR pts as in LR pts (P < .001, data not shown). We evaluated whether preclinical transplant characteristics would influence algorithm performance and observed that the algorithm successfully separated HR and LR strata in several groups with differing risks for GVHD and NRM, including donor type, degree of HLAmatch, age group, and conditioning regimen intensity (Figure 3). When an unfavorable pre-transplant risk factor increased overall NRM, the algorithm identified more pts as high risk (e.g. 21% of unrelated donors v 12% of related donors). In conclusion, we have developed and validated a blood biomarker algorithm that predicts the development of lethal GVHD at 7 days after HCT and identifies risk strata in several patient groups which should prove useful for BMT clinical research.

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The Impact of Febrile Neutropenia after Allogeneic Hematopoietic Cell Transplantation on Graft-Versus-Host Disease and Relapse in Patients with Acute Myeloid Leukemia

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Background: Febrile Neutropenia (FN) occurs in ~ 50% of allogeneic hematopoietic cell transplant (HCT) recipients during the pre-engraftment period (Hefazi et al, 2016). An infectious etiology is identified in ~ 20-30% of patients and it is postulated that non-infectious causes are secondary to a pro-inflammatory cytokine response (Pagano et al, 2011). As graft-versus leukemia (GVL) and graft-versus-host disease (GVHD) are mediated by a complex array of cytokines and inflammatory events, we hypothesized that culture negative FN during the pre-engraftment period could influence the risk of GVHD and relapse after HCT.

Methods: After due IRB approval, consecutive patients with AML who underwent HLA-matched peripheral blood allogenic HCT at our institution between 2004 and 2014 were retrospectively reviewed. Culture-negative early FN (CN-

Table 1
Baseline characteristics in patients *with* or *without* culture negative febrile neutropenia (CN-FN).

Total patients N = 203	With CN-FN n = 74 (%)	Without CN-FN n = 129 (%)	P. Value
Age in years, median (range)	53 (20-69)	55 (18-72)	0.08
Male	44 (60)	66 (51)	0.30
HCI-CI comorbidity index, median	1	2	0.11
Karnofsky Performance Score			0.23
90-100	46 (62)	68 (53)	
≤ 80	28 (38)	61 (47)	
Donor Relationship			0.65
Related	45 (61)	74 (57)	
Unrelated	29 (39)	55 (43)	
Cytogenetic Risk			
Favorable	2 (3)	7 (5)	0.26
Intermediate	56 (76)	84 (65)	
Unfavorable	16 (21)	38 (30)	
Disease status at HCT			0.92
CR1	49 (66)	83 (64)	
CR2	15 (20)	26 (20)	
Other	10 (14)	20 (16)	
Conditioning Regimen			0.003
Myeloablative	49 (66)	57 (44)	
Reduced Intensity	25 (34)	72 (56)	
ABO Compatibility			0.25
Compatible	42 (58)	87 (67)	
Major/Bidirectional Mismatch	16 (21)	24 (19)	
Minor Mismatch	16 (21)	18 (14)	
CMV Status			1.0
D+/R+, D+/R-, D-/R+	62 (84)	108 (84)	
D-/R-	12 (16)	21 (16)	
Immunosuppression			0.65
Cyclosporine ± Methotrexate	40 (54)	75 (58)	
Tacrolimus ± Methotrexate	34 (46)	54 (42)	

FN) was defined as temperature of > 38ºC for an hour or > 38.3 occurring between day 3-15 post HCT in patients with absolute neutrophil count (ANC) of < 500 and no identifiable source of infection. Acute and chronic GVHD (aGVHD, cGVHD) were diagnosed and graded according to previously published criteria (Glucksberg et al, 1974; Madan et al, 2014.The cumulative incidence of aGVHD grade III-IV, moderate-severe cGVHD, and relapse were estimated using competing risk models. Two-sided P values of < .05 were considered statistically significant.

Results: Of 203 patients (median age 54 yrs., 54% male) who were transplanted during the study period, 74 (36%) developed CN-FN. Except for the higher proportion of myeloablative conditioning in patients with CN-FN (66% vs. 44%, P = .003), baseline characteristics were similar in patients with and without CN-FN (Table 1). Patients who developed CN-FN had a significantly higher cumulative incidence of aGVHD grade III-IV (24% vs. 7% at 100 days, P = .02) and a trend towards higher incidence of moderate-severe cGVHD (42% vs. 30% at 2 years, P = .06) in comparison to patients who did not develop
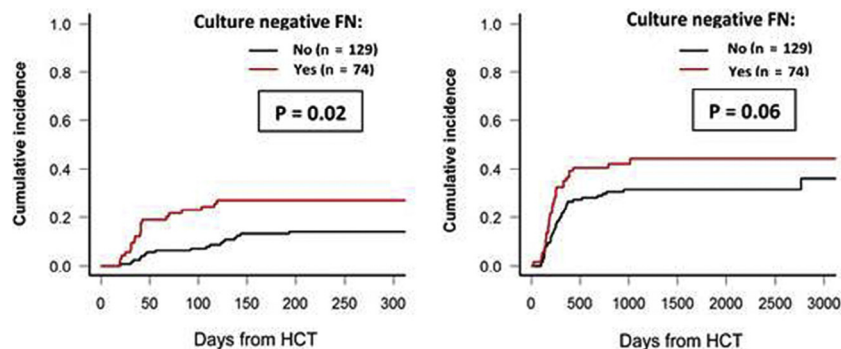

Figure 1. (A) Cumulative incidence of aGVHD grade III-IV in patients *with* or *without* culture negative FN early after HCT. (B) Cumulative incidence of moderate to severe cGVHD in patients *with* or *without* culture negative FN after HCT.