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POSTER ABSTRACTS

722.ALLOGENEIC TRANSPLANTATION: ACUTE AND CHRONIC GVHD, IMMUNE RECONSTITUTION

A Pilot Study of Reduced Intensity HLA-Haploidentical Hematopoietic Cell Transplantation (HaploHCT) with Post-Transplant Cyclophosphamide in Patients with Advanced Myelofibrosis

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Allogeneic hematopoietic cell transplantation (HCT) is the only curative option for patients with myelofibrosis (MF); however, a significant obstacle to proceed to HCT is availability a matched donor, especially since MF is most often diagnosed in older adults. The effective development of haploidentical transplant (haploHCT), with post-transplant cyclophosphamide (PTCy) as graft-versus-host disease (GVHD) prophylaxis, has been a major therapeutic advance for patients without an available matched donor. Based on the excellent survival rates seen in older patients with myeloid malignancies using fludarabine/Melphalan-based (Flu/Mel) regimen with PTCy GVHD prophylaxis, we designed a pilot trial (NCT03118492) to evaluate safety and tolerability of reduced intensity condition (RIC) regimen of Flu/Mel and TBI (2Gy) for peripheral blood stem cells (PBSC) HaploHCT with PTCy in patients with advanced MF (Figure 1a).

At the time of this report, we have enrolled 17 patients (out of 22) in two cohorts. After treating the first 4 patients in cohort 1 (CH-1), eligibility was updated to exclude accelerated disease, severe pulmonary hypertension, with stricter fluid management for a stricter monitoring and eligibility criteria (cohort 2; CH-2). Our primary objective was to determine safety of this regimen in patients with MF. Key secondary endpoints were grade 2-4 acute GVHD, chronic GVHD, engraftment, overall survival (OS), progression-free survival (PFS), non-relapse mortality (NRM), and relapse.

Detailed patient/HCT characteristics are listed in Table 1. Briefly, median age at the time of HCT was 59 years (range: 48-70), and 53% of patients were male. MF diagnosis was primary MF in 53% of patients, and 71% had intermediate-2 risk level. Karnofsky performance status was 80-100 in 94.1% of patients and HCT comorbidity index was 0-2 in 82.4%. Median time from MF diagnosis to HCT was 935 days (range: 27-7651).

In CH-1, unacceptable toxicity (UT) was defined as any of the following considered at least possibility related to PTCy: any death; grade 3-4 adverse events (AEs) that does not improve to grade $\leq$2 within 4 weeks except for hematologic toxicities. For hematologic toxicities, UTs were primary graft failure. Two out of the 4 patients in CH-1 experienced UTs. [UPN1: grade 3 anorexia that did not improve to grade $\leq$2 within 4 weeks; UPN4: grade 3 kidney injury (per Bearman Scale), and grade 4 neutropenia lasting more than 42 days]. Since >1/6 patients had UTs, per protocol monitoring rules and after a full IRB review, the definition of UT was updated to the following in CH-2: any regimen-related grade 3-4 toxicity per Bearman scale, or for hematologic toxicities, per NCI CTCAE v4.03 toxicity scale, any grade 4 neutropenia associated with fever or infection and lasting for more than 21 days, or grade 4 neutropenia lasting for more than 42 days, or death. In CH-2, one out of 16 patients experienced a UT of acute kidney injury. UPN17 has not reached the 100-day UT period, at the time of this report.

One-year OS, PFS and NRM for all patients were 80% (95%CI: 39-95), 68% (95%CI: 30-89) and 21% (95%CI: 3-50), respectively. All patients engrafted (n=12), with the median time to neutrophils engraftment of 19 days (range: 13-23) for CH-1 and 16 days (range: 12-22) for the CH-2. One-year OS for CH-2 was 91% compared to 50% in CH1 and was reduced to 78% and 50% at 2 years, respectively. RFS in CH-2 was 91% at 1 year, and 62% at 2 years compared to 50% in CH-1 at both time points. Relapse was not seen at 1 and 2 years in CH-1, whereas in CH-2 there were no relapses at 1-year but 15% of patients relapsed by the end of year 2. NRM at 100-days was 25% in CH1 vs non in CH-2 and at 2 years-NRM were 50% and 22% in CH-1 and CH-2,

respectively. Grade 3-4 GVHD was not seen in either cohort. Similarly moderate and severe chronic GVHD was not seen in either cohort at 1 or 2 years. One and 2 years GRFS was 81 and 61% respectively.
In conclusion, early results of this pilot study indicate that HaploHCT in MF patients undergoing HCT is safe and feasible, with low NRM and higher grade acute and chronic GVHD. We are currently accruing in CH2. If successful, this approach can be tested in a multi-center setting as a phase II trial, and likely extend this potentially curative procedure to most patients of minority populations in the United States and to a significant proportion of the Caucasian population without an HLA matched.

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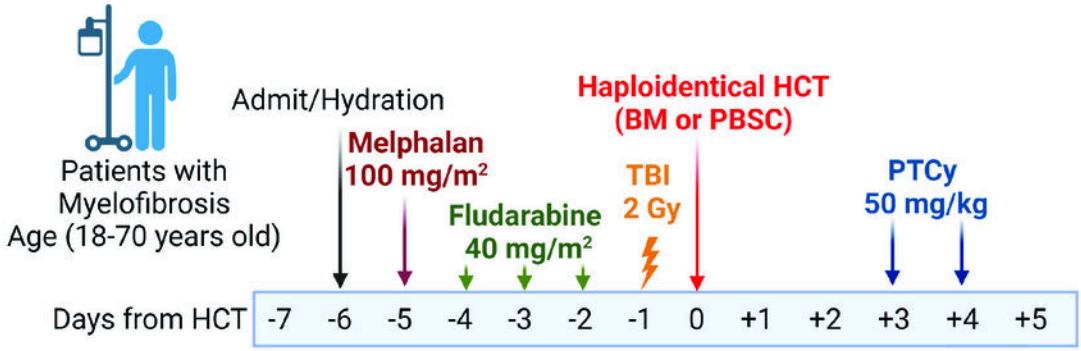

Table 1. Patient and Transplant Characteristics

	Cohort 1 (N=4)	Cohort 2 (N=13)	Total (N=17)
Age on study, years			
Median (Range)	60 (48-68)	59 (50-70)	59 (48-70)
Sex			
Male	2 (50%)	7 (53.8%)	9 (52.9%)
Female	2 (50%)	6 (46.2%)	8 (47.1%)
Race/ethnicity			
Non-Hispanic White	2 (50%)	2 (15.4%)	4 (23.5%)
African American	0 (0%)	4 (30.8%)	4 (23.5%)
Asian	1 (25%)	2 (15.4%)	3 (17.6%)
Hispanic	1 (25%)	5 (38.5%)	6 (35.3%)
HCTCI			
0	1 (25%)	7 (53.8%)	8 (47.1%)
1-2	2 (50%)	4 (30.8%)	6 (35.3%)
≥3	1 (25%)	2 (15.4%)	2 (11.8%)
Karnofsky Score			
70	1 (25%)	0 (0%)	1 (5.9%)
80	2 (50%)	3 (23.1%)	5 (29.4%)
90	1 (25%)	7 (53.8%)	8 (47.1%)
100	0 (0%)	3 (23.1%)	3 (17.6%)
Days from MF diagnosis to alloHCT			
N	4	11	15
Median (Range)	1067 (449-2500)	427 (27-7651)	935 (27-7651)
MF Type			
Primary	1 (25%)	8 (61.5%)	9 (52.9%)
Secondary	3 (75%)	5 (38.5%)	8 (47.1%)
MF Risk (DIPSS)			
High	2 (50%)	3 (23.1%)	5 (29.4%)
Intermediate II	2 (50%)	10 (76.9%)	12 (70.6%)
Extra Medullary Exam			
No	4 (100%)	12 (92.3%)	16 (94.1%)
Yes	0 (0%)	1 (7.7%)	1 (5.9%)

Figure 1

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