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POSTER ABSTRACTS

723.ALLOGENEIC TRANSPLANTATION: LONG-TERM FOLLOW-UP AND DISEASE RECURRENCE

Favorable Survival Outcomes in AML Patients Undergoing Allogeneic Hematopoietic Cell Transplant with Fludarabine/Melphalan-Conditioning with Tacrolimus/Sirolimus-Based Gvhd Prophylaxis

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Introduction: Fludarabine/melphalan (F/M) conditioning is associated with superior disease-free survival (DFS) compared to busulfan-based reduced-intensity conditioning (RIC) regimens in patients with AML/MDS undergoing allogeneic hematopoietic cell transplantation (alloHCT). A recent CIBMTR analysis in AML patients reported 5-year OS, cumulative incidence of Relapse (CIR) and NRM of 29%, 36% and 36% respectively after F/M conditioning when Tac/MTX was used for graft-vs-host disease (GVHD) prophylaxis (Blood Adv 2020). At City of Hope (COH), tacrolimus and sirolimus (T/S)-based GVHD prophylaxis has been used in patients undergoing HLA-matched sibling and unrelated donor alloHCT, based on the results of a phase 2 study by Rodriguez et al (Blood 2010). Here, we retrospectively reviewed clinical outcomes of 409 consecutive AML patients who underwent RIC alloHCT at COH from 2008-2019 with F/M conditioning and T/S-based GVHD prophylaxis. The primary objective was to assess long term survival outcomes and associated risk factors adjusted for secular trends in patient demographics undergoing alloHCT over time.

Methods: Descriptive statistics were used to summarize patient demographics, and disease characteristics. Kaplan-Meier curves and log-rank test were used to evaluate OS and LFS. Cumulative incidence curves and Gray test were used to examine differences in relapse and NRM. The assumptions of proportionality for Cox regression and Fine-Gray models were checked by corresponding tests and plots of the scaled Schoenfeld residuals. To study changes in patient demographics, we divided patients into early era of 2008-2012 (n=140; 34%) and late era of 2013-2019 (n=269; 66%).

Results: Patient and HCT characteristics are shown in **Table 1**. Briefly, the median age was 63 years (range: 19-78) and 70% of patients underwent alloHCT in CR-1. Cytogenetics (ELN 2017) were classified as adverse risk in 25% (n=104) and intermediate risk in 65% (n=265) patients. By disease risk index (DRI), patients were categorized as low (32%; n=131), intermediate (47%; n=193), or high/very high risk (20%; n=84). KPS of 80-100 was recorded in 93% of patients and HCT comorbidity index score of ≥3 was seen in 41%. AML-from prior hematologic disorder (secondary AML) or therapy related was documented in 32% (n=133) and data on somatic mutations and measurable residual disease (MRD) were available only in the recent era. Compared to the early era, HCT recipients of the recent era were significantly older(64 vs 60 years; p=0.0001), had higher HCT-CI (median score of 3 vs 1; p<0.0001), and more patients with KPS < 80 (9% vs 2 %; p=0.0024).

With the median follow-up duration of 4 years (range: 0.3-12.5) for the whole cohort, the 5-year OS and DFS were 53% (95% CI: 0.48-0.58) and 51% (95% CI: 0.46-0.56), respectively. The cumulative incidence of relapse (CIR) at 5 years was 23% (95% CI: 0.19-0.28). The non-relapse mortality (NRM) at day+100 and 5 years were 5% (95% CI: 0.03-0.08) and 25% (95% CI:0.20-0.29), respectively. Day +100 grade 2-4 acute GVHD was 37% (95% CI: 0.32-0.42) and 2-year chronic GVHD was 70% (95%

CI: 0.65-0.74). Overall survival (OS) and disease-free survival (DFS) were not significantly different in the two eras (Figure 1). Despite high incidence of cGVHD, only 21% (n=86) required prednisone at one year with median dose of 10 mg/day (range: 2-60mg/day). In key subgroups of interest, the 5-year OS were: 70% for FLT3-ITD mutation (n=50), 70% for NPM1 mutation (n=47), 83% for IDH 1/2 mutation (n=30), 65% for patients older than ≥70 (n=55), and 55% (95%CI :43-63) for secondary AML (n=102). MRD by multi-color flow cytometry was available in 58 patients in CR of whom 18 were MRD-positive; this was associated with worse 5-year OS (26%: 95% CI: 5.5-53%). Multivariate analyses (MVA) identified DRI high/very high-risk as the only independent variable associated with worse OS (HR=1.62, [95%CI: 1.16-2.27]) and DFS (HR=1.76, [95%CI: 1.28-2.41]), primarily due to increased NRM (HR 1.86, 95%CI [1.21-2.87]), while its impact on relapse was insignificant.
Conclusion: Fludarabine-melphalan with T/S associated with favorable long-term OS with good disease control without excessive NRM, even in high-risk patient subgroups and changing demographics of older adults with higher comorbidity. However, cGVHD rates remain high and novel strategies are being explored to realize the OS benefits of the FM backbone while attenuating chronic GVHD and NRM.

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Table 1. Patient and HCT Characteristics

	2008-2012 (N=140)	2013-2019 (N=269)	Total (N=409)
Age at HCT, years			
Median (Range)	60 (19-72)	64(20-78)	63(19-78)
Disease Status			
CR1	86 (61.4%)	198 (73.6%)	284 (69.4%)
CR2+	23 (16.4%)	35 (13.0%)	58 (14.2%)
Active Disease	31 (22.1%)	36 (13.4%)	67 (16.4%)
Disease Risk Index score			
Low/Intermediate	107 (76.4%)	217 (80.7%)	324 (79.2%)
High/Very High	32 (22.9%)	52 (19.3%)	84 (20.6%)
AML type			
Missing	26 (18.6%)	0 (.%)	26 (6.4%)
De Novo	79 (56.4%)	171 (63.6%)	250 (61.1%)
Secondary	24 (17.1%)	78 (29%)	102 (24.9%)
Transformed	11 (7.9%)	20 (7.4%)	31 (7.6%)
Karnofsky performance status %			
80-100	138 (98.6%)	244 (90.7%)	382 (93.4%)
<80	2 (1.4%)	25 (9.3%)	27 (6.6%)
HCT comorbidity index			
0	69 (49.3%)	54 (20.1%)	123 (30.1%)
1-2	37 (26.4%)	80 (29.7%)	117 (28.6%)
≥3	34 (24.3%)	135 (50.2%)	169 (41.3%)
Donor Type			
Match Related	44 (31.4%)	103 (38.3%)	147 (35.9%)
Match Unrelated	75 (53.6%)	140 (52%)	215 (52.6%)
Mismatch Unrelated	21 (15%)	26 (9.7%)	47 (11.5%)

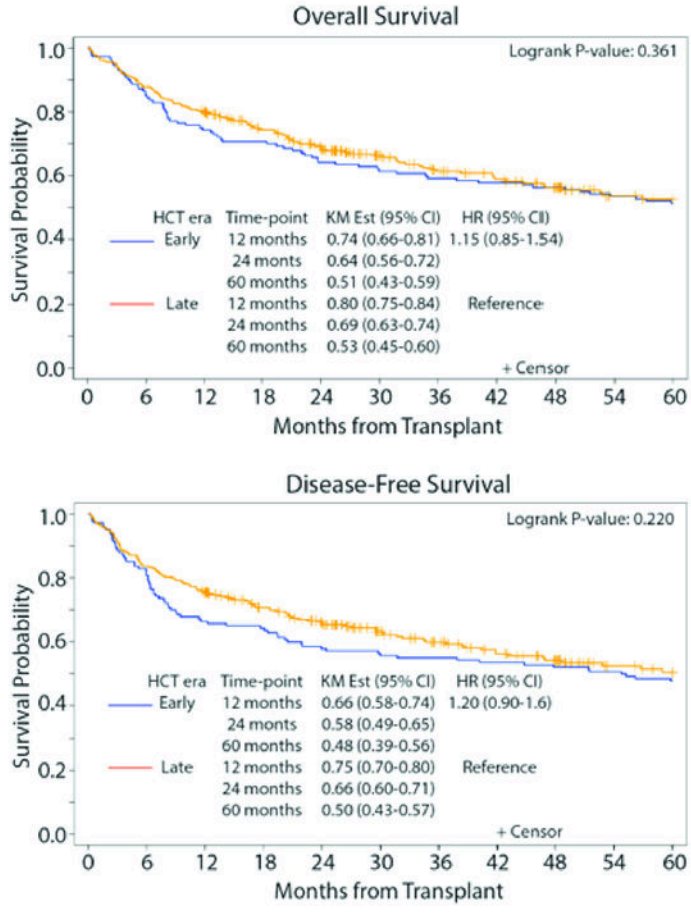

Figure 1

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