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POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Impact of Pre-Transplant Molecular and Cytogenetic Remission on Outcomes of Allogeneic Stem Cell Transplant in Patients with Myelodysplastic Syndrome

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Background: Allogeneic stem cell transplant (allo-SCT) carries a high relapse rate (~35% within 2 years) in patients (pts) with myelodysplastic syndrome (MDS). Pre-transplant measurable residual disease (MRD) increases the risk of relapse and death in acute myeloid leukemia (Thol et al, *Blood* 2018). However, the impact of pre-transplant MRD on post-transplant outcomes is less clear in MDS. Prior studies have compared outcomes between myeloablative (MAC) and reduced intensity conditioning (RIC) in pts with pre-transplant MRD persistence based on either cytogenetic remission alone or ultra-deep genomic sequencing with a limited 10-gene panel, suggesting reduced risk of relapse in pts receiving MAC (Festuccia et al, *Biol Blood Marrow Transplant* 2016; Dillon et al, *JCO PO* 2021). However, pre-transplant MRD assessment using a commercial next-generation sequencing (NGS) panel in addition to cytogenetic testing to assess post-transplant outcomes has not been evaluated in MDS.

Methods: We conducted a multicenter retrospective review of MDS pts who underwent allo-SCT from 2015-2022. Pts with FISH/cytogenetic (FC) and/or molecular abnormalities at diagnosis and MRD assessment by commercial myeloid-panel NGS (with a variant-allele frequency detection limit up to 5%) and FC performed on peripheral blood (PB) or bone marrow (BM) aspirate within 3 months prior to transplant were included for analysis. The Kaplan-Meier method and log-rank tests were used to estimate overall survival (OS). Gray's test/cumulative incidence functions were used to estimate relapse-free survival (RFS) with non-relapse mortality (NRM) as competing risk.

Results: Table 1 includes baseline pt characteristics. Of 81 pts, 69 pts (85.2%) had residual FC and/or molecular abnormalities (MRD+) at pre-transplant PB/BM assessment. Twelve (14.8%) pts were in both FC and molecular remission (MRD-) prior to transplant. With a median follow-up of 13.9 months [IQR 6.8 - 38.9], 43 (53%) died and 24 (30%) pts experienced a relapse. Twenty-three of 69 (33%) MRD+ pts had relapsed disease with a 38% cumulative incidence of relapse (CIR) at 2 years. In contrast, only 1/12 (8.3%) MRD- pts experienced a relapse after 7 years, with chromosomal loss of *TP53* not present at initial diagnosis. CIR at 2 years was 33% and 41% (p=0.207) for MRD+ pts who received MAC vs RIC, respectively with NRM of 34.5% associated with MAC vs 28.2% for RIC (p=0.61).

TP53 mutations were most frequently associated with relapse in 8/24 (33%) pts with a median OS of 9.8 months [8.2 - NR]. Besides the previously defined 10-gene panel (Dillon et al, *JCO PO* 2021), relapses were also driven by *SRSF2, U2AF1, KRAS, SETBP1* and *NF1* mutations present in the original clone. Six pts had *DNMT3A, TET2* and/or *ASXL1* (DTA) mutations only on pre-transplant NGS, with 2/6 pts relapsing without the re-emergence of DTA mutations.

Median OS was not reached for MRD- pts and was 14.1 months [11.35-NR] for MRD+ pts, p = 0.061 [Fig.1]. OS probability at 2 years was 35% for MRD+ pts vs 75% for MRD- pts. Type of conditioning regimen, RIC vs MAC, did not impact OS (p= 0.6). An equal number of deaths, 35% each, were attributable to GvHD and relapse, respectively. Thirteen (30%) pts died from other causes, primarily infections and bleeding complications. NRM was 25% and 36% for MRD- and MRD+ cohorts, respectively.

Pts received a median of 6 cycles [range, 2-36] of hypomethylating agent (HMA) +/- venetoclax prior to transplant with no association between the number of cycles and MRD status (p=0.80). The incidence of grade 3-4 acute GvHD and chronic GvHD requiring systemic therapy did not significantly differ, at 25% and 18.8% (p= 0.696) and 33.3% and 31.8% (p= 1.00) in MRD+ and MRD- pts, respectively.

Conclusions: MRD assessment using commercially available NGS panels and cytogenetic testing that are routinely performed in MDS pts in real-world practice can predict risk of relapse. Pre-transplant MRD is associated with worse OS irrespective of the intensity of conditioning regimen. Although limited in statistical power due to a small sample size of MRD- pts in our cohort, further studies with a larger cohort are underway to better clarify the role of MRD on transplant outcomes in MDS. Our data also highlights that only a small minority of MDS pts (<15%) achieve complete molecular and cytogenetic remission at the time of transplant; strategies to eliminate the pre-transplant MDS clone are urgently needed.

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Table 1: Baseline patient and transplant characteristics

	N=81
Age at diagnosis (median [IQR] in years)	59 [52, 65]
Sex (%)	
Male	48 (59.3)
Female	33 (40.7)
IPSS-R at diagnosis (%)	
Very low	4 (4.9)
Low	17 (21.0)
Intermediate	18 (22.2)
High	18 (22.2)
Very high	24 (29.6)
TP53 mutations at diagnosis (%)	16 (19.7)
Complex Karyotype at diagnosis (%)	16 (19.7)
HCT Comorbidity Index (%)	
0	13 (16)
1-2	24 (29.6)
3+	42 (51.8)
NA	2 (2.6)
Age at transplant (median [IQR] in years)	60 [54, 66]
Time from diagnosis to transplant (median [IQR] in months)	10.33 [6.81, 17.87]
Pre-transplant treatment (%)	
HMA only	52 (64.2)
HMA + Venetoclax	14 (17.2)
Cytotoxic chemotherapy	2 (2.5)
Investigational agents	12 (14.8)
None	1 (1.2)
Product type (%)	
Peripheral blood stem cell (PBSC)	70 (86.4)
Bone marrow	9 (11.1)
Umbilical cord blood	2 (2.5)
Donor type (%)	
Matched related	19 (23.5)
Matched unrelated	42 (51.9)
Haploidentical	6 (7.4)
Umbilical cord blood	2 (2.5)
Mismatched related/unrelated	12 (14.8)
Conditioning regimen (%)	
MAC	37 (45.7)
RIC	44 (54.3)

Figure 1. Overall survival by pre-transplant MRD status

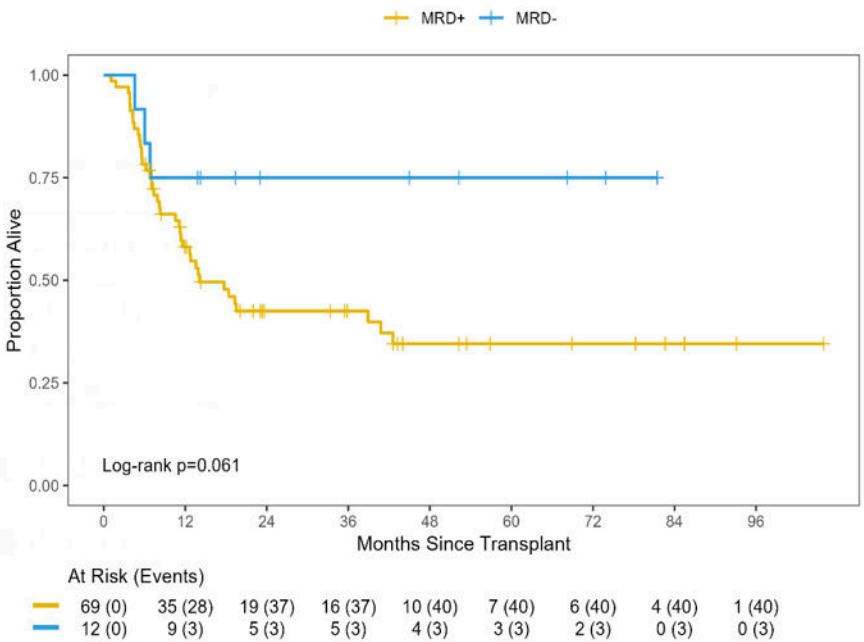

Fig.1: MDS patients with pre-transplant MRD had an overall survival probability of only 35% at 48 months as compared to 75% for MRD- patients

Figure 1