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POSTER ABSTRACTS

732.ALLOGENEIC TRANSPLANTATION: DISEASE RESPONSE AND COMPARATIVE TREATMENT STUDIES

Impact of Clinical and Genetic Factors on Myelofibrosis Outcomes after Allogeneic Transplantation

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Introduction:
The reported impact of gene mutations, including JAK2-V617F, other MPN phenotypic drivers and additional cooccurring mutations on outcomes after allogeneic transplantation (HCT) in myelofibrosis (MF) has been inconsistent. While the MTSS score incorporated ASXL1 and JAK2 (non MPL/CALR mutations) as unfavorable predictors after HCT, other studies reported JAK2 mutations to be favorable (Blood 2010). Further, in some studies, mutations known to affect disease progression in MF pre-HCT (high-molecular risk or HMR mutations) have not been predictors of post-HCT outcomes. Here we present outcomes in all MF patients undergoing HCT at Dana-Farber Cancer Institute (DFCI) from 2000-2020 and examine clinical and genetic predictors of outcomes, stratified by year of HCT (<2011 or pre-2011 and >2011 or post-2011). Of note, ruxolitinib was available for use post-2011 only, following its FDA approval that year.

Methods:
Patients with MF who underwent HCT from 2000-2020 at DFCI (n=166) were included in this retrospective cohort analysis. Outcomes were analyzed for the whole cohort as well as sub-group analyses in the pre-2011 (n=39) and post-2011 era (n=127). Mutational analysis was performed by targeted next-generation sequencing of available pre-HCT samples in 115/127 patients in the post-2011 era.

Results:
Median age was 61 years and follow up 56.2 months. 25% had massive splenomegaly. DIPSS-plus scores were high in 45.2% and 45.1% received rux. HCT and patient characteristics (including KPS and median time from diagnosis to HCT) were similar pre and post 2011, with differences in conditioning regimens. Majority (77.1%) had HLA-matched donors, underwent reduced intensity (69.3%) HCT with peripheral blood stem-cells (92.2%) and received tacrolimus/methotrexate based GVHD prophylaxis (90.1%). FluMel100/140 (n=65), FluBu4 (n=34) and FluBu2 (n=11) were commonly used in the post-2011 era, while Flu/Bu1 (n= 34), ablative Bu/Cy (n=5) and Cy/TBI (n=12) were predominant pre-2011. Few patients underwent pre-HCT splenectomy (10.2%) or splenic irradiation (9%). Median D100 donor chimerism was 68% for Flu/Bu1, 86% for Flu/Bu2, 98% for Flu/Bu4, and 100% for Flu/Mel100-140.

At 4 years, overall survival (OS) for the whole cohort was 58% (50,66), progression-free survival (PFS) 55% (47,63), non-relapse mortality (NRM) 23% (17,30) and relapse rate 21%. 4 year OS was significantly better in the post-2011 era compared to pre-2011 (69% vs 26%, p<0.0001), as was PFS, driven by lower relapse rates in the post-2011 era (15% vs 41%, p<0.0001). 4-yr NRM was also marginally better (20% vs 33%, p= 0.17).

In the post-2011 era, 115/127 patients had NGS panel-based genetic analysis prior to HCT (Fig 1), demonstrating 91.3% of patients had at least one driver mutation (JAK2 62.6%, CAL-R 13.9%, MPL 14.8%) while 8.7% patients were triple negative. The most frequent cooccurring mutations were *ASXL1* (40%), *TET2* (28.7%) and *U2AF1* (17.4%).In univariable analysis (UVA), the presence of *JAK2* mutations (JAK2+) was associated with superior PFS (HR 0.5, 95% CI 0.27,0.94, p= 0.03) while *CALR* (HR 1.86, p=0.12) and *MPL* (HR:1.21, p=0.65) mutations were not significant for PFS. Triple negative patients showed a trend towards poorer PFS (HR 2.27, p=0.05). OS results mirrored those of PFS. No cooccurring myeloid gene mutations were associated

with PFS or OS. Superior 4-year OS for JAK2+ versus JAK2- recipients (80% versus 58%, p=0.01) is shown in Figure 2. *TP53* (p=0.03), *TET2* (p=0.015) and *EZH2* (p=0.002) mutations were associated with higher relapse rates in UVA. Patients with JAK2+ and cooccurring ASXL1 mutations had poorer OS compared to those with JAK2+/no cooccurring ASXL1 mutations (HR=2.69, p=0.031).

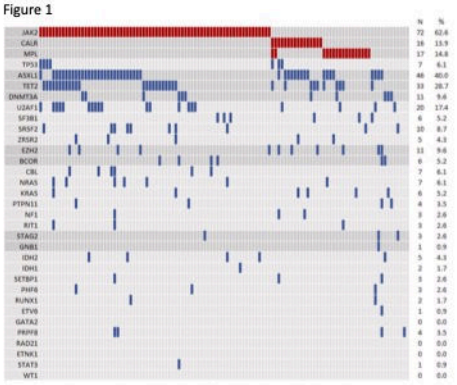
Combining clinical and molecular features in the post-2011 era, in MVA, only DIPSS high (HR=4.76, p=0.03) and KPS < 90% (HR=2.66, p=0.024) were significantly associated with poorer OS/PFS while JAK2+ (HR=0.32, 95% CI 0.14,0.75,p=0.009) was significantly associated with better OS/PFS; *JAK inhibitor use* spleen size/management, conditioning regimen or other mutations including HMR mutations and *TP53* were not significantly associated with OS/PFS.

Conclusions:

In this single-institution retrospective analysis, the presence of a JAK2-V617F mutation was associated with better OS and PFS following HCT in MF in the post-2011 era. Survival outcomes are significantly better in the post-2011 era compared to pre-2011, in our cohort.

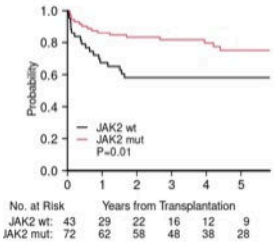
Disclosures Mullally: *Aclaris, Cellarity, Morphic, Biomarin:* Consultancy; *Constellation, Protagonist:* Other: Advisory Board ; *AOP Health:* Speakers Bureau; *Relay, Morphic:* Research Funding; *PharmaEssentia, Incyte:* Other: Steering Committee . **Cutler:** *Sanofi:* Consultancy; *Allovir:* Other: Data Safety Monitoring Board (DSMB); *Pluristem Therapeutics:* Other: DSMB; *Ruth L. Kirschstein Postdoctoral Individual National Research Service Award:* Research Funding; *InhibRx:* Consultancy; *Astellas:* Consultancy; *Rigel:* Consultancy; *Oxford Immune Algorithmics:* Membership on an entity's Board of Directors or advisory committees; *Cimeio:* Membership on an entity's Board of Directors or advisory committees. **Kelkar:** *CareDx:* Research Funding. **Koreth:** *Mallinckrodt:* Membership on an entity's Board of Directors or advisory committees; *Equillium:* Consultancy; *Gentibio:* Consultancy; *Cue Biopharma:* Consultancy; *Biolojic Design:* Consultancy; *Tr1x:* Consultancy; *Amgen:* Research Funding; *Clinigen Labs:* Consultancy, Research Funding; *BMS:* Research Funding; *Miltenyi Biotec:* Research Funding; *Regeneron:* Research Funding; *Equillium:* Research Funding; *Cugene:* Membership on an entity's Board of Directors or advisory committees. **Soiffer:** *Neovii:* Consultancy; *Bluesphere Bio:* Consultancy; *NMPD - Be the Match, USA:* Membership on an entity's Board of Directors or advisory committees; *Jasper:* Consultancy; *Juno Therapeutics/ BMS/Celgene USA:* Other: Data Safety Monitoring Board; *Smart Immune:* Consultancy; *Vor Bipharma:* Consultancy; *Astellas:* Consultancy. **DeAngelo:** *Servier:* Honoraria; *Amgen:* Honoraria; *Autolus:* Honoraria; *Takeda:* Honoraria; *Gilead:* Honoraria; *Novartis:* Research Funding; *Blueprint:* Research Funding; *AbbVie:* Research Funding; *GlycoMimetics:* Research Funding; *Pfizer:* Honoraria; *Novartis:* Honoraria; *Kite:* Honoraria; *Incyte:* Honoraria; *Blueprint:* Honoraria; *Jazz:* Honoraria. **Garcia:** *Bristol Myers Squibb:* Consultancy; *Astellas:* Consultancy; *Gilead:* Consultancy; *Genentech:* Consultancy, Research Funding; *New Wave:* Research Funding; *AstraZeneca:* Research Funding; *Pfizer:* Research Funding; *Prelude:* Research Funding; *AbbVie:* Consultancy, Research Funding; *Servier:* Consultancy. **Luskin:** *Novartis:* Honoraria; *Novartis:* Research Funding; *Pfizer:* Honoraria; *Jazz:* Honoraria; *AbbVie:* Research Funding. **Stone:** *Rigel:* Consultancy; *Ligand Pharma:* Consultancy; *AvenCell:* Consultancy; *Takeda:* Other: DSMB; *Amgen:* Consultancy; *Syntrix:* Other: DSMB; *Kura One:* Consultancy; *Cellularity:* Consultancy; *BerGenBio:* Consultancy; *Jazz:* Consultancy; *Lava Therapeutics:* Consultancy; *Hermavant:* Consultancy; *GSK:* Consultancy; *Epizyme:* Other: DSMB; *Aptevo:* Other: DSMB; *CTI Biopharma:* Consultancy; *Abbvie:* Consultancy. **Winer:** *Curis Inc:* Consultancy; *Abbvie:* Consultancy. **Lindsley:** *Vertex Pharmaceuticals:* Consultancy; *Verve Therapuetics:* Consultancy; *Jazz Pharmaceuticals:* Consultancy; *Bluebird bio:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Qiagen:* Consultancy; *Sarepta Therapuetics:* Consultancy; *Takeda Pharmaceuticals:* Consultancy. **Ho:** *Orca Bio:* Consultancy; *Omeros:* Consultancy; *Allovir:* Consultancy; *Alexion, AstraZeneca Rare Disease:* Consultancy; *CareDx:* Research Funding; *Jazz Pharmaceuticals:* Research Funding; *Omeros:* Research Funding; *Alexion, AstraZeneca Rare Disease:* Speakers Bureau.

Figure 1



Pre-HCT NGS panel based mutational analysis in 115/127 patients in the post-rux/2011 era showing driver (red) and cooccurring (blue) mutations

Figure 2



Significantly improved overall survival in JAK2 mutated (JAK2+) versus JAK2negative (JAK2-) myelofibrosis patients in the post-rux/2011 era

Figure 1

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