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Clinical and Gene Expression Patterns Associated With Disease Progression in Patients With Low-Risk Myelofibrosis Enrolled in the Myelofibrosis and Essential Thrombocythemia Observational Study (MOST)

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Introduction

- Patients with myelofibrosis (MF) can be risk stratified using prognostic scoring systems such as the Dynamic International Prognostic Scoring System (DIPSS)[1]
- Low-risk MF is associated with relatively good prognoses vs intermediate-2 risk or high-risk MF (median survival, ~11 years vs ~2-4 years)[2]
- Few data exist to identify patients with low-risk MF who are likely to experience progression to intermediate- or high-risk disease
- The Myelofibrosis and Essential Thrombocythemia Observational Study (MOST; NCT02953704) is a prospective observational study that enrolled patients with low-risk MF defined by DIPSS criteria

Objective

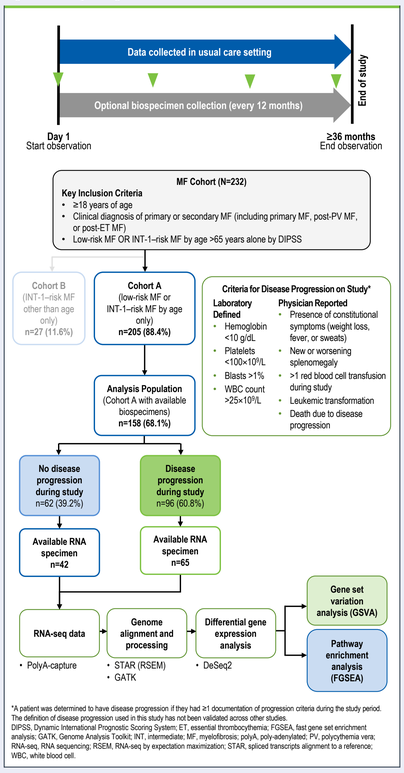
- To identify clinical and molecular characteristics of patients enrolled in MOST who progressed from low-risk to intermediate- or high-risk MF

Methods

Study Design

- MOST enrolled patients with MF at clinical practices across the United States **(Figure 1)**
- Physician-reported data were collected during usual-care visits as previously described[3]
  - The study included an optional peripheral blood collection (RNA) every 12 months
- Disease progression on study was defined as meeting ≥1 of the progression criteria outlined in **Figure 1**
- Due to the observational nature of the study, this analysis is limited by the lack of randomization and control over external variables, as well as missing data

Figure 1. Study Design



*A patient was determined to have disease progression if they had ≥1 documentation of progression criteria during the study period. The definition of disease progression used in this study has not been validated across other studies.
DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; FGSEA, fast gene set enrichment analysis; GATK, Genome Analysis Toolkit; INT, intermediate; MF, myelofibrosis; polyA, poly-adenylated; PV, polycythemia vera; RNA-seq, RNA sequencing; RSEM, RNA-seq by expectation maximization; STAR, spliced transcripts alignment to a reference; WBC, white blood cell.

RNA Sequencing

- RNA sequencing (RNA-seq) was performed on samples from 107 patients with available RNA specimens (65 patients with and 42 without MF progression) using Illumina NovaSeq™ X Plus (100 paired-end [PE] base reads with >50 M PE reads per sample)
- RNA-seq data were analyzed as outlined in **Figure 1**
  - Driver mutation genotyping was performed on DNA if RNA was unavailable

Results

Patient Disposition, Demographics, and Clinical Characteristics

- Of 232 patients enrolled with MF, 158 were low risk at enrollment, had available biospecimens, and were included in this analysis
  - 96 patients (61%) met ≥1 progression criterion
    - The most commonly met criteria were hemoglobin <10 g/dL (49%), presence of constitutional symptoms, and platelet count <100×10⁹/L (30% each)
- Baseline demographics for patients with vs without MF progression are outlined in **Table 1**

Table 1. Baseline Demographics and Clinical Characteristics in Patients With and Without Progression

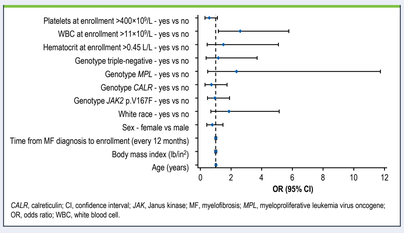
Variable	No MF Progression (n=62)	MF Progression (n=96)	Total (N=158)
Age at diagnosis, median (range), years	63.9 (35, 86)	66.7 (21, 84)	64.8 (21, 86)
Male, n (%)	31 (50.0)	42 (43.8)	73 (46.2)
White race, n (%)	53 (85.5)	88 (91.7)	141 (89.2)
Time from MF diagnosis to enrollment, median (range), years	1.5 (0, 24)	1.4 (0, 38)	1.5 (0, 38)
DIPSS risk status,* n (%)			
Low risk	27 (43.5)	33 (34.4)	60 (38.0)
INT-1 risk by age alone	34 (54.8)	62 (64.6)	96 (60.8)
Driver mutation testing,† n (%)			
JAK2 p.V617F	44 (71.0)	67 (69.8)	111 (70.3)
CALR	11 (17.7)	13 (13.5)	24 (15.2)
MPL	2 (3.2)	7 (7.3)	9 (5.7)
Triple-negative	5 (8.1)	9 (9.4)	14 (8.9)

*Risk status missing for 1 patient each in the progression and no progression groups. †Each patient only had 1 *JAK2* p.V617F, *CALR*, or *MPL* mutation, or were triple-negative.
CALR, calreticulin; DIPSS, Dynamic International Prognostic Scoring System; INT, intermediate; *JAK*, Janus kinase; MF, myelofibrosis; *MPL*, myeloproliferative leukemia virus oncogene.

Associations Between Patient Characteristics and Disease Progression

- Univariate analysis of baseline covariates identified white blood cell (WBC) count >11×10⁹/L at enrollment as the only covariate significantly associated with increased progression risk (odds ratio [OR] [95% confidence interval (CI)], 2.60 [1.17, 5.78], *P*=0.019; **Figure 2**)
  - WBC >11×10⁹/L was retained as a significant covariate in multivariate analyses (OR [95% CI], 2.51 [1.03, 6.11]; *P*=0.043)

Figure 2. Univariate Logistic Regression on Disease Progression

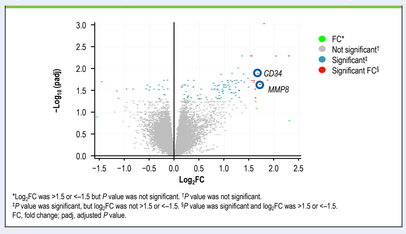


CALR, calreticulin; CI, confidence interval; *JAK*, Janus kinase; MF, myelofibrosis; *MPL*, myeloproliferative leukemia virus oncogene; OR, odds ratio; WBC, white blood cell.

Differences in Gene Expression Between Patients With and Without MF Progression

- In total,104 upregulated and 20 downregulated genes were identified in patients with MF progression **(Figure 3)**
- Notably, *CD34* and *MMP8* were among the upregulated genes identified in patients with MF progression
  - CD34 is a marker of myeloid stem/progenitor cells with a function in stem cell activity
  - MMP8, a collagenase largely secreted by neutrophils and monocytes, is considered an important mediator of microenvironment remodeling

Figure 3. Differential Expression of Genes in Patients With MF Progression

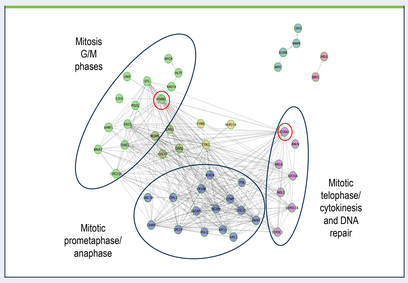


*Log_2FC was >1.5 or <–1.5 but *P* value was not significant. †*P* value was not significant.
‡*P* value was significant, but log_2FC was not >1.5 or <–1.5. §*P* value was significant and log_2FC was >1.5 or <–1.5.
FC, fold change; padj, adjusted *P* value.

Pathway Enrichment Analysis

- Fast gene set enrichment analysis identified significantly upregulated pathways, including G2M checkpoint and MYC
- Pathway enrichment analysis of significantly differentially expressed genes via reactome also indicated that cell cycle processes in patients with MF progression were upregulated **(Figure 4)**
- *FOXM1* and *CCNA2* had a high number of connections across pathways, further supporting the multifunctional role of these genes in MF progression

Figure 4. Reactome Analysis



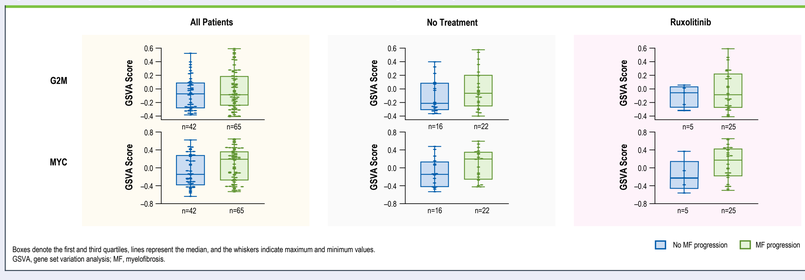
Patient Expression of Gene Pathways

- Signatures were calculated per patient utilizing hallmark gene lists (gene set variation analysis [GSVA])
- Treatment effects were observed for G2M but not for MYC gene signatures
- In patients with no treatment at enrollment, G2M GSVA score was higher in patients with vs without MF progression. Among patients who received ruxolitinib at enrollment, no significant differences were observed between patients with vs without MF progression **(Figure 5)**
- MYC GSVA score was higher in patients with vs without MF progression, independent of treatment status

JAK/STAT Signaling

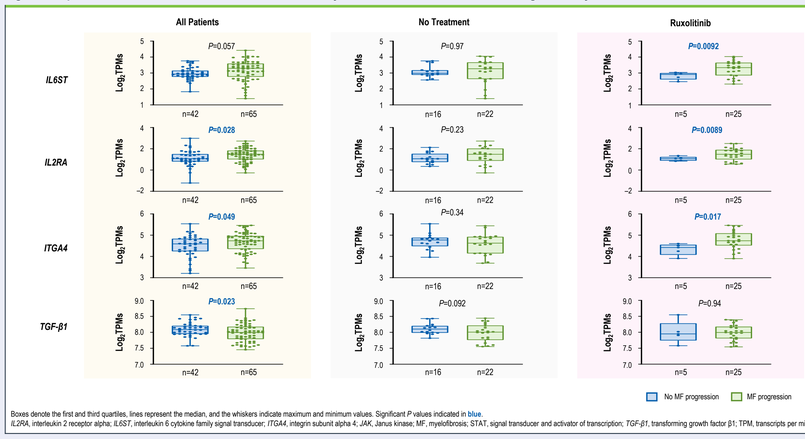
- *IL6ST* and *IL2RA* were upregulated in all patients with MF progression **(Figure 6)**
- *TGF-β1* and *ITGA4* were downregulated in patients with MF progression with no treatment at enrollment, but upregulated in patients with MF progression who received ruxolitinib at enrollment
  - These data support that downregulation of *ITGA4* may correlate with disease progression, and ruxolitinib treatment may upregulate expression levels

Figure 5. G2M and MYC Signatures in Patients With and Without MF Progression by Treatment Status at Enrollment



Boxes denote the first and third quartiles, lines represent the median, and the whiskers indicate maximum and minimum values.
GSVA, gene set variation analysis; MF, myelofibrosis.

Figure 6. Expression of Genes Related to the JAK/STAT Pathway in Patients With and Without MF Progression by Treatment Status at Enrollment



Boxes denote the first and third quartiles, lines represent the median, and the whiskers indicate maximum and minimum values. Significant *P* values indicated in blue.
IL2RA, interleukin 2 receptor alpha; *IL6ST*, interleukin 6 cytokine family signal transducer; *ITGA4*, integrin subunit alpha 4; *JAK*, Janus kinase; MF, myelofibrosis; STAT, signal transducer and activator of transcription; *TGF-β1*, transforming growth factor β1; TPM, transcripts per million.

Conclusions

- **This analysis of prospective data from MOST found the majority of patients with low-risk MF experienced disease progression over a median ~54 months of follow-up**
- **Multivariate regression analysis identified WBC >11×10⁹/L at enrollment as a significant risk factor for progression**
- **RNA-seq analysis demonstrated differences in gene expression patterns in relevant cell types in patients with vs without MF progression**
  - **Differential gene expression of *MMP8* and *ITGA4* were detectable via whole blood expression profiling and suggest a role for microenvironment remodeling in MF progression**
  - **Cell cycle genes and pathways were upregulated in the progressive MF cohort in a treatment-dependent manner. The transcription factor *FOXM1* was found to impact multiple genes in this pathway and further supports a role for cell cycle regulation in MF progression**
  - **MYC pathway genes were upregulated in the progressive MF cohort independent of treatment status, suggesting limited impact of ruxolitinib on MYC function in these patients**

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Disclosures

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