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Ten-year journey with myelofibrosis: real-world data and clinical outcomes from a tertiary care center

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ABSTRACT

Aims: The aim of this study was to document the last decade of experience with primary myelofibrosis (PMF) and provide mature risk-stratified survival data and disease complication estimates.

Methods: This retrospective study included all patients diagnosed with PMF according to World Health Organization criteria between 2009 and 2019 at İstanbul Medipol University. The follow-up period extended until March 2019.

Results: A total of 74 patients (median age 60.5 years, range 30-85) were included, with 35 males (47.3%) and 39 females (52.7%). During the study period, 34 deaths (45.9%), 3 leukemic transformations (4%), and 3 thrombotic events (4.2%) were recorded, including bilateral pulmonary artery thrombosis, cephalic vein thrombosis, and left lower extremity deep vein thrombosis. The median overall survival was 6 years. There was no statistically significant difference in life expectancy between patients treated with ruxolitinib and those receiving other medications (erythropoiesis-stimulating agents, androgens, immunomodulatory agents, cytoreductive drugs such as hydroxyurea, and splenectomy) (Chi-square statistic: 3.5149, p=0.0608). One of the 11 patients treated with ruxolitinib died (9%), while the remaining 10 patients survived (91%).

Conclusion: PMF remains a serious disease with high mortality and morbidity, requiring effective treatment interventions. Despite recent advances, treatment remains unsatisfactory for most patients. Although ruxolitinib, a JAK2 inhibitor, shows promise in managing symptoms, its impact on life expectancy remains unclear, highlighting the need for novel therapeutic strategies and well-designed clinical trials.

Keywords: Myelofibrosis, ruxolitinib, thrombosis, leukemic transformation, JAK2 inhibitor

INTRODUCTION

Primary myelofibrosis (PMF) is a BCR-ABL1–negative myeloproliferative neoplasm of the bone marrow (BM), which is characterized by three situations: clonal myeloproliferation, dysregulated kinase signaling, and the release of abnormal cytokines. MF is a clonal proliferation originating from a pluripotent hematopoietic stem cell.[1] Cytokines and growth factors that are released from the BM trigger fibrosis of the marrow, changes in the stroma and colonization in the extramedullary organs such as the spleen and liver.[2]

Mutations in *Janus kinaz* 2 (JAK2), calreticulin (CALR), MPL and ASXL1, EZH2, IDH1/2, and SFSF2 can be used for molecular prognostication of primary MF (PMF).[3] The discovery of the JAK2 mutation triggered development of molecular targeted therapies for MF. The first oral agent approved for JAK1/2 inhibitor is "ruxolitinib", currently treatment of MF.[4]

Recent studies have highlighted that overall survival in patients with PMF is significantly influenced by risk stratification models such as DIPSS, mutational profiles, transfusion dependency, and the presence of constitutional symptoms. In particular, high-risk patients, as defined by DIPSS or DIPSS-Plus, demonstrate markedly reduced median survival compared to those in lower risk categories. Furthermore, molecular mutations such as JAK2, CALR, and MPL also have prognostic implications. These findings underscore the importance of integrating prognostic scoring and clinical variables in survival analysis of PMF.[15,16]

In this study, it was aimed to present the treatment results of MF patients, to compare the effect of ruxolitinib to the other treatment preferences such as erythropoiesis stimulating agents, androgens, immunomodulatory agents for anemia, cytoreductive drugs or splenectomy in terms of the life expectancy.

METHODS

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the İstanbul Medipol University Non-interventional Clinical Researches Ethics Committee (Date: 27.08.2021, Decision No: E-10840098-772.02-4093).

The study included patients diagnosed with MF according to the World Health Organization Criteria between 2009-2019.[5] Clinical and laboratory data of patients, presence of transfusion dependence, driver mutation status, cytogenetic results, presence of constitutional symptoms and palpable splenomegaly, arterial or venous thrombosis before, during, and/or after the definitive diagnosis, presence of fibrotic progression or leukemic transformation, and presence of allogenic stem cell transplantion were recorded and analysed retrospectively. Dynamic international prognostic scoring system (DIPSS) was utilised as risk-stratification method by including age (>65 years), hemoglobin value (<10 g/dl), leukocyte count (>25×10^9/L), circulating blasts (≥1%), and presence of constitutional symptoms in order to classify patients into four risk groups: low, intermediate-1, intermediate-2, and high risk.[6]

Statistical Analysis

While making the statistics of the continuous structure, the mean and standard deviations, minimum and maximum values of the features; While defining categorical variables, n (%) values and 95% Confidence interval values were given. Total survival curves were estimated by the Kaplan-Meier method. Differences according to risk factors were determined by the Log-Rank test (Chi-square statistic) and the Hazard ratio was given at a 95% confidence interval. Time to the event (death) or follow-up time including time (months) were used as variables. The statistical significance level of the data was taken as $p<0.05$. In the evaluation of the data, www.e-picos.com New York software and MedCalc statistical package program were used.

RESULTS

The clinical and laboratory features at the time of diagnosis and follow-up clinical data were shown in Table 1. The median age of 74 patients included in our study was 60.5 (range: 30-85), a total of 35 patients were male (47.3%). The most common underlying disease was PMF with 57 patients (77%), followed by myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN) (8 patients, 10.8%). During the follow-up period, a total of 34 patients died (34%). The most common complication during follow-up was thrombotic event and hemorrhage (3 patients for both, 4.2%). The number of patients with a driver mutation was 45 (40.8%), the number of JAK2 positive patients was 9 (26.5%), and the number of triple negative patients was 4 (11.8%). Overall survival was resulted as a mean of 72 months (42-109) (Figure 1).

Table 1. Descriptive statistics

Variable	All patients (n=74)
Age (y), median (range)	60.5 (30-85)
Male sex (number, [%])	35 (47.3)
Underlying diseases (no. [%])	
Polycythemia vera	3 (4.1)
Essential thrombocythemia	5 (6.8)
Chronic myeloid leukemia	1 (1.4)
Myelodysplastic syndrome	8 (10.8)
Primary myelofibrosis	57 (77)
Mortality (no. [%])	34 (45.9)
Thrombotic events (no. [%])	3 (4.2)
Transfusion events (no. [%])	20 (27)
Abnormal karyotype (no. [%])	3 (4.2)
Constitutional symptoms (no.[%])	17 (23)
Hemorrhage (no. [%])	3 (4.2)
Hematoma in spleen (no. [%])	1 (1.3)
Epistaxis (no. [%])	2 (2.7)
Allogeneic hematopoietic stem cell transplantation (no. [%])	2 (2.7)
Driver mutational (no. [%])	45 (60.8)
JAK-2 positive (no. [%])	9 (26.5)
CALR (no .[%])	1 (2.9)
JAK-2 negative (no. [%])	20 (58.8)
Triple negative (no. [%])	4 (11.8)
Overall survival (months), median (range)	72 (42-109)
Hemoglobin (g/dl), median (range)	9.75 (3.8-20)
Platelet (10^3/μL), median (range)	510.11 (4000-222.800)
Leukocyte (10^3/μL), median (range)	9.14 (1420-290000)
Spleen size (mm), median (range)	185 (84-280)
Peripheral blood blast percentage median (range)	2 (0-17)
Echocardiography control (no. [%])	21 (0.28)
Pulmonary hypertension (no. [%])	12 (0.57)

JAk-2: Janus kinaz 2, CALR: Calreticulin

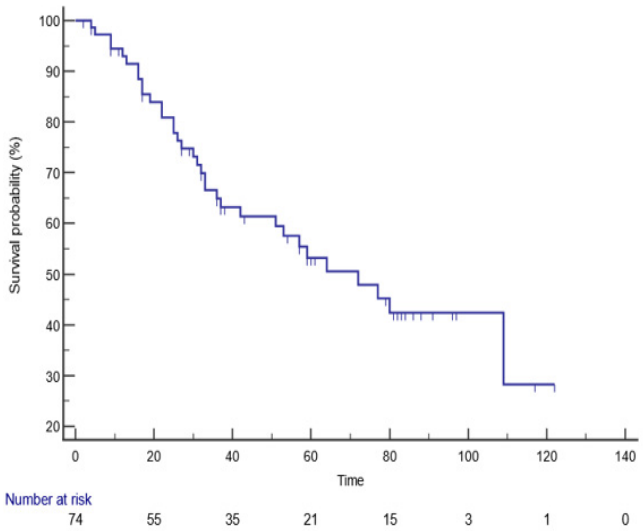

Figure 1. Overall survival of the cohort

Echocardiography control was performed in 21 patients to reveal pulmonary hypertension (PHT). It was normal in 9 patients, 12 patients had PHT (0.57%). The range of resting pulmonary artery systolic pressure was 25 to 70 mmHg above the mean right atrium by echocardiography (**Table 1**).

The DIPSS scores of the patients at the time of diagnosis were shown in **Table 2**. The most common risk score was resulted as "intermediate-2" (30 patients, 44%). The number of patients with a high risk resulted as 5 (8%).

Table 2. DIPSS scores of the cohort

DIPSS score	n	%	95% confidence interval
High	5	8	0.01-0.14
Intermediate-1	24	35	0.24-0.47
Intermediate-2	30	44	0.32-0.56
Low	9	13	0.05-0.21
Total	68	100.0	

DIPSS scores n (%) and 95% CI values in patients, DIPSS: Dynamic international prognostic scoring system, CI: Confidence interval

In the statistical analysis performed considering the overall survival of patients, there was no significant difference between the PMF and other patients (p=0.24). There was no significant difference between patients with a DIPPS score of intermediate-2/high DIPPS and low/intermediate-1 (p=0.38). Considering the treatment subtypes, there was no significant difference between the patients receiving ruxolitinib and others, but the p value was near the statistical significance limit (p=0.06) (**Table 3, Figure 2**).

DISCUSSION

The present study provides experience about PMF, mature risk-stratified survival data and associated complications. We observed several confirmatory as well as novel findings. First, PMF was validated as a disease that is more common in middle or advanced age adults, the median age of diagnosis previously reported slightly higher (67 year old), but we found it to be 60.5 year old.[7] This may reflect increased awareness of the disease and contemporary accessibility to molecular diagnostics, resulting in early diagnosis. Preponderance of PMF in females was confirmed. The driver mutational status was not available in all patients with PMF.

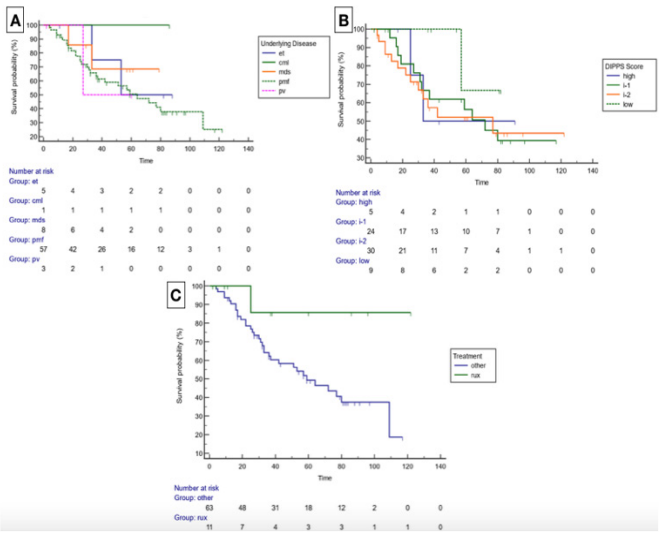

Figure 2. Overall survival curves between subgroups: A. Underlying diseases, B. Initial DIPSS scores, C. Treatment preferences (ruxolitinib and others)
DIPSS: Dynamic international prognostic scoring system

The life curves didn't differ significantly and the underlying disease type such as post chronic myeloid leukemia MF, post-essential thrombocythemia (post-ET MF) and post-polycythemia vera (post-PV MF) had no significant effect on the survival period. In the literature, survival was significantly different among the four risk categories (p<0.001).[6] Median survival was 14.6 years in low-risk, 7.4 years in intermediate-1, 4 years in intermediate-2, and 2.3 years in high risk patients. In our study, DIPSS had no effect on survival; median survival was not reached in low risk, 72 months in intermediate-1, 77 months in intermediate-2, and 33 months in high risk categories. This could be due our limited patients or availability of novel drugs.

Based on the COMFORT-1 and COMFORT-2 clinical trials, treatment discontinuation rate for ruxolitinib (JAK1 and JAK2 inhibitor) was 50% at 3 years and 75% patients did so by 5 years. Resistance and intolerance to ruxolitinib eventually develops and patients relapses. Increased splenomegaly, cytopenias, increased blood transfusion dependence and limiting thrombocytopenia are clinical feature of failure to ruxolitinib therapy.[8] It was not observed any intolerance or failure in our cohort. Neither COMFORT-1 nor COMFORT-2 trials showed benefit on survival. In COMFORT-1 trial, after median follow-up of 149 weeks, survived patients were 42 (27%) versus 54 (35%) (Hazard ratio=0.69, 95% CI=0.46–

Table 3. Comparison of survival curves (Log-rank test) and Hazard ratios with 95% confidence interval

	Non-survivors n (%)	Survivors n (%)	Mean survival (95% CI)	Hazard ratio (95% CI)	Log-rank p value
Underlying disease					
Other	5 (29.41)	12 (70.59)	67.3 (52.4-82.1)	1.63 (0.73-3.64)	0.24
PMF	29 (50.88)	28 (49.12)	67.6 (54.9-80.4)		
DIPSS score					
Low|intermediate-1	13 (39.39)	20 (60.61)	78.3 (62.8-93.8)	1.39 (0.66-2.95)	0.38
Intermediate-2 |high	15 (42.86)	20 (57.14)	71.2 (52.9-89.5)		
Treatment					
Ruxolitinib	1 (9.1)	10 (90.9)	108.1 (82.9-133.3)	2.55 (0.96-6.77)	0.06
Other	33 (52.4)	30 (47.6)	65.6 (54.3-76.8)		

CI: Confidence interval, PMF: Primary myelofibrosis, DIPSS: Dynamic international prognostic scoring system

1.03).[9] In COMFORT-2 trial, after a median follow-up of 151 weeks however, a survival advantage for ruxolitinib versus best available treatment was reported as 29 (20%) versus 22 (30%) (Hazard ratio=0.48, 95% CI=0.28–0.85).[10] Comparison of ruxolitinib to other treatment preferences (erythropoiesis-stimulating agents, androgens, or immunomodulatory agents for anemia, cytoreductive drugs such as hydroxyurea and splenectomy) has no prominent difference on life expectancy; this can be due to low number of cases in the study. From 34 patients with a mortal course, only 1 patient was treated with ruxolitinib and the other 10 patients treated with ruxolitinib were survived (90%). Therefore, further efforts like longer follow-ups or more cases are necessary to improve the results for ruxolitinib.

In the literature, JAK2 mutation was found to be negative as 60-65%, CALR mutation as 20-25%, MPL mutation as 5%, JAK2, CALR or MPL mutation ("triple negative") as 8-10%.[11,12] We were able to analysis 3 patients with abnormal karyotypes, 45 of 74 evaluated patients had a driver mutational status. Nine patients were JAK2 positive (20%), one patient was CALR positive (2%), twenty patients were JAK2 negative (44%) and four patients were triple negative (8%). Mutation rates were similar in our study compared to the literature data.

PHT is a well described complication of myeloproliferative disorders.[13] Lopez-Mattei et al.[14] reported 20 (14%) patients with echocardiographic findings consistent with PHT in a total of 143 patients diagnosed with MF. Older age, male gender, hypertension, hyperlipidemia, coronary artery disease, dyspnea, high hematocrit, high brain natriuretic peptide (BNP) and N-terminal-pro hormone BNP were found to be clinical predictors for PHT. Female gender was protective from PHT (OR=0.21, 95% CI: 0.049–0.90, p=0.035).[14] We found PHT in 12 patients in our cohort. Due to the small number of patients, it was not able to compare these parameters between the subgroups.

Limitations

The major limitations of the study were its retrospective nature and limited patients' data. It was not able to compare parameters statistically between subgroups. Ruxolitinib is a relatively new drug, there is not enough follow-up period to reveal a data.

Our study reinforces the known epidemiologic and clinical characteristics of PMF and highlights several important observations that may inform clinical practice. Notably, our cohort's median age was slightly lower than those reported in broader registries, suggesting earlier diagnosis potentially due to improved molecular diagnostics. While DIPSS risk scores are known to predict prognosis, our data did not show a statistically significant survival difference between risk groups, which may be attributable to the limited sample size or heterogeneity in treatment exposure.

Importantly, our real-world analysis found no significant difference in survival between ruxolitinib and conventional therapies, although the p-value approached significance (p=0.06). This may reflect insufficient statistical power due to the small number of ruxolitinib-treated patients. Interestingly, the absence of ruxolitinib intolerance or discontinuation in our cohort diverges from previous clinical trials, where long-term treatment discontinuation rates were substantial. This discrepancy underscores the necessity for longer follow-up and larger studies to fully assess treatment durability and tolerability.

Additionally, the observed prevalence of PHT was consistent with previous studies. However, due to limited echocardiographic screening and lack of multivariate analysis, its clinical relevance within our cohort remains uncertain.

CONCLUSION

As a result, PMF is a heterogeneous disease with significant morbidity and mortality. Our findings emphasize the need for personalized risk stratification and continued efforts to improve therapeutic outcomes. While ruxolitinib remains a valuable option for symptom management, its effect on survival remains inconclusive in our limited cohort. Prospective, multicenter studies with larger sample sizes and standardized endpoints are essential to determine optimal treatment strategies and long-term outcomes for patients with PMF.

ETHICAL DECLARATIONS

Ethics Committee Approval

Approved by the İstanbul Medipol University Non-interventional Clinical Researches Ethics Committee (Date: 27.08.2021, Decision No: E-10840098-772.02-4093).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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