Myelofibrosis with Monocytosis is Clinically and Prognostically Similar to CMML

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INTRODUCTION

Chronic myelomonocytic leukemia (CMML) is a myelodysplastic / myeloproliferative neoplasm characterized by peripheral monocytosis and risk of acute leukemic transformation.

Myelofibrosis (MF), a myeloproliferative neoplasm (MPN), may exhibit monocytosis (MF-M), associated with increased progression risk.

Considerable diagnostic overlap exists between these two entities, but direct comparisons between their characteristics and outcomes is lacking.

AIM

To compare disease characteristics and outcomes between MF, MF-M, and CMML.

METHODS

This single-center study included patients meeting 2022 WHO monocytosis criteria: absolute monocyte count ≥0.5 x10^9/L, ≥10% of white blood cells (WBC), persistent >3 months.

Baseline characteristics and outcomes were compared using Wilcoxon rank sum, Pearson's Chi-Squared, and Fisher's exact test. Overall survival (OS) was estimated by Kaplan-Meier analysis.

REFERENCES

1. Boiocchi L, Espinal-Witter R, Geyer JT, Steinhilber J, Bonzheim I, Knowles DM, Fend F, Orazi A. Development of monocytosis in patients with primary myelofibrosis indicates an accelerated phase of the disease. Mod Pathol. 2013 Feb;26(2):204-12
2. Tefferi A, Shah S, Mudireddy M, Lasho TL, Barraco D, Hanson CA, Ketterling RP, Elliott MA, Patnaik MS, Pardanani A, Gangat N. Monocytosis is a powerful and independent predictor of inferior survival in primary myelofibrosis. Br J Haematol. 2018 Dec;183(5):835-838
3. Morsia E, Gangat N. Myeloproliferative Neoplasms with Monocytosis. Curr Hematol Malig Rep. 2022 Feb;17(1):46-5
4. Petrova-Drus K, Chiu A, Margolskee E, Barouk-Fox S, Geyer J, Dogan A, Orazi A. Bone marrow fibrosis in chronic myelomonocytic leukemia is associated with increased megakaryopoiesis, splenomegaly and with a shorter median time to disease progression. Oncotarget. 2017 Oct 17;8(61):103274-103282
5. Chapman J, Geyer JT, Khanlari M, Moul A, Casas C, Connor ST, Fan YS, Watts JM, Swords RT, 6. Vega F, Orazi A. Myeloid neoplasms with features intermediate between primary myelofibrosis and chronic myelomonocytic leukemia. Mod Pathol. 2018 Mar;31(3):429-441

RESULTS

Baseline Characteristics

MF vs MF-M

Variable	MF (N = 193)	MF Monocytosis (N = 53)	p-value
WBC at diagnosis (×10^9/L)	8.8 (5.9, 15.7)	11.6 (6.6, 24.5)	**0.039**
Hemoglobin at diagnosis (g/dL)	10.5 (9.2, 12.3)	10.7 (9.3, 11.7)	0.691
Platelets at diagnosis (×10^9/L)	344.0 (171.0, 506.0)	338.0 (172.0, 475.0)	0.879
Peripheral blood blasts (%)	0.0 (0.0, 1.0)	0.4 (0.0, 2.0)	**0.005**
Bone marrow blasts (%)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.377
Marrow fibrosis grade			**0.372**
MF-0	4 (2.1%)	0 (0.0%)	
MF-1	27 (14.1%)	7 (13.2%)	
MF-2	100 (52.1%)	26 (49.1%)	
MF-3	61 (31.8%)	20 (37.7%)	
Unknown	1	0	
Abnormal cytogenetics	95 (49.2%)	19 (35.8%)	0.116
Transfusion dependence	20 (10.4%)	6 (11.3%)	>0.999
Splenomegaly	118 (61.1%)	29 (54.7%)	0.492
Risk score			**0.504**
Low	20 (10.4%)	5 (9.4%)	
Intermediate-1	71 (36.8%)	24 (45.3%)	
Intermediate-2	84 (43.5%)	19 (35.8%)	
High	18 (9.3%)	5 (9.4%)	

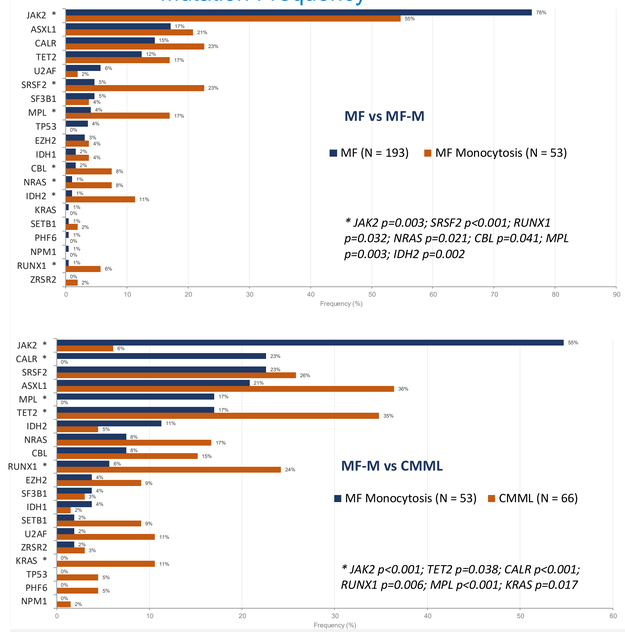
Table 1. Baseline Characteristics: MF vs MF Monocytosis
Median (Q1, Q3) for continuous variables, n (%) for categorical variables
Wilcoxon rank sum test (continuous) or Pearson's chi-squared test (categorical)

MF-M vs CMML

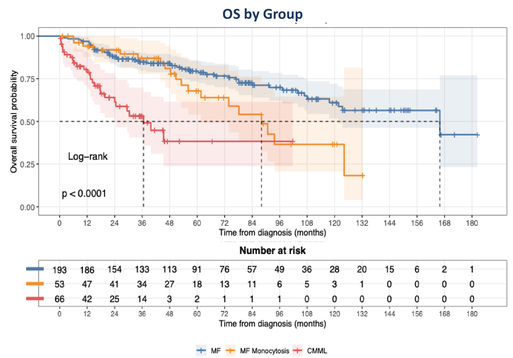
Variable	MF Monocytosis (N = 53)	CMML (N = 66)	p-value
WBC at diagnosis (×10^9/L)	11.6 (6.6, 24.5)	16.5 (9.2, 34.8)	0.056
Hemoglobin at diagnosis (g/dL)	10.7 (9.3, 11.7)	9.7 (8.3, 11.4)	0.079
Platelets at diagnosis (×10^9/L)	338.0 (172.0, 475.0)	102.0 (63.0, 147.0)	**<0.001**
Peripheral blood blasts (%)	0.4 (0.0, 2.0)	0.4 (0.0, 3.0)	0.431
Bone marrow blasts (%)	0.0 (0.0, 1.0)	2.0 (1.0, 8.0)	**<0.001**
Marrow fibrosis grade			**<0.001**
MF-0	0 (0.0%)	20 (40.0%)	
MF-1	7 (13.2%)	22 (44.0%)	
MF-2	26 (49.1%)	7 (14.0%)	
MF-3	20 (37.7%)	1 (2.0%)	
Unknown	0	16	
Abnormal cytogenetics	19 (35.8%)	32 (48.5%)	0.231
Transfusion dependence	6 (11.3%)	12 (18.2%)	0.435
Splenomegaly	29 (54.7%)	26 (39.4%)	0.139
Risk score			**0.684**
Low	5 (9.4%)	18 (27.3%)	
Intermediate-1	24 (45.3%)	15 (22.7%)	
Intermediate-2	19 (35.8%)	12 (18.2%)	
High	5 (9.4%)	21 (31.8%)	

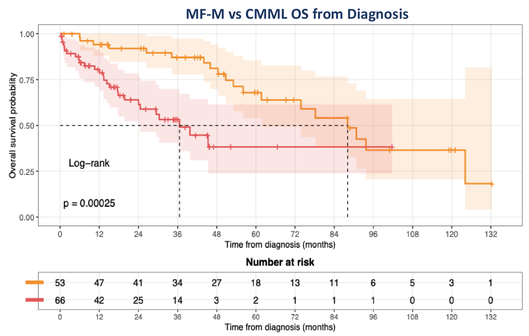
Table 2. Baseline Characteristics: MF Monocytosis vs CMML
Median (Q1, Q3) for continuous variables, n (%) for categorical variables
Wilcoxon rank sum test (continuous) or Pearson's chi-squared test (categorical)

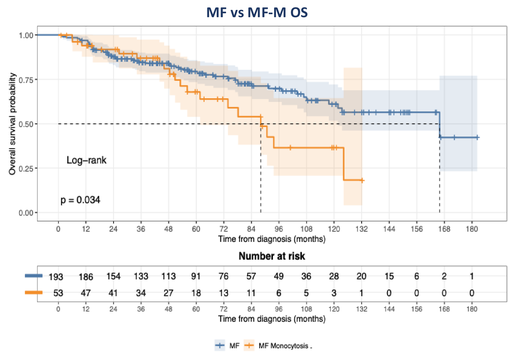
Mutation Frequency

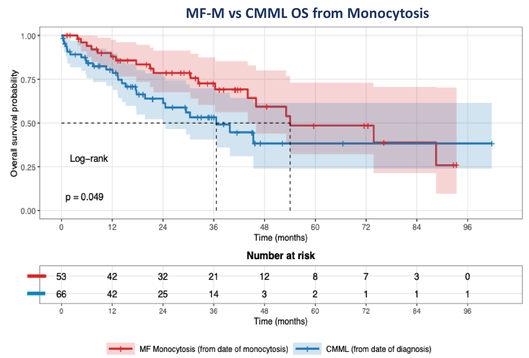


Overall Survival









Multivariable Cox PH — OS from Diagnosis

Variable	HR (95% CI)	p-value
Group (ref: MF Monocytosis)		
MF Monocytosis	—	
CMML	2.81 (1.31, 6.01)	**0.008**
Age at diagnosis (years)	1.02 (0.99, 1.05)	0.211
Bone marrow blasts (%)	1.02 (0.95, 1.10)	0.553
Adverse risk cytogenetics		
No	—	
Yes	1.80 (0.86, 3.75)	0.117

Multivariable Cox PH — OS from Monocytosis

Variable	HR (95% CI)	p-value
Group (ref: MF Monocytosis)		
MF Monocytosis	—	
CMML	1.55 (0.79, 3.07)	0.204
Age at diagnosis (years)	1.02 (0.99, 1.04)	0.252
Bone marrow blasts (%)	1.03 (0.96, 1.10)	0.435
Adverse risk cytogenetics		
No	—	
Yes	1.58 (0.76, 3.26)	0.219

CONCLUSIONS

- Median baseline WBC was greater in MF-M compared to MF but did not differ significantly from CMML. Median peripheral blast percentage was higher in MF-M than MF, but equivalent to CMML.
- Marrow fibrosis grade was similar between MF-M and MF, though higher in MF-M than CMML.
- MF-M had more frequent CMML-associated mutations than MF: *SRSF2*, *RUNX1*, *NRAS*. *JAK2* mutations were less frequent in MF-M than MF.
- Transfusion dependence and splenomegaly did not differ between groups.
- From diagnosis, median OS was shorter in CMML than MF-M. From monocytosis onset, this difference was less pronounced. Adjusting for age, BM blasts, and adverse cytogenetics, CMML demonstrated worse OS than MF-M from diagnosis, but not monocytosis onset.
- MF-M exists on a clinical and prognostic spectrum between MF and CMML.
- Despite possessing MF features (high-grade fibrosis and MPN-specific mutations), MF-M displays a higher burden of CMML-associated mutations with survival approaching CMML, suggesting CMML-directed therapies may be reasonably extended to this population.