Clinical correlates, prognostic impact and survival outcomes in chronic myelomonocytic leukemia patients with the *JAK2*V617F mutation

Mrinal M. Patnaik,[1] Prateek A. Pophali,[1] Terra L. Lasho,[1] Christy M. Finke,[1] Pedro Horna,[2] Rhett P. Ketterling,[3] Naseema Gangat,[1] Abhishek A. Mangaonkar,[1] Animesh Pardanani[1] and Ayalew Tefferi[1]

[1]Division of Hematology, Department of Medicine; [2]Division of Hematopathology, Department of Laboratory Medicine and Pathology and [3]Division of Cytogenetics, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

Correspondence: MRINAL M. PATNAIK.
patnaik.mrinal@mayo.edu
doi:10.3324/haematol.2018.208082

Supplementary table one: Clinical and laboratory characteristics of 92 patients with proliferative chronic myelomonocytic leukemia, stratified by, as to whether or not, they had the *JAK2*V617F mutation versus other cell signaling mutations (*CSF3R, CBL, KRAS, NRAS, PTPN11, FLT3, KIT)*

Variables	MP-CMML patients with *JAK2* mutation (*n*=23)	MP-CMML patients with other cell signaling mutations (*n*=69)	P value
Age in years; median (range)	72 (61-85)	69 (20-90)	0.14
Sex (Male); *n* (%)	16 (70)	42 (61)	0.44
Hemoglobin g/dL; median (range)	12.1 (7.2-16.9)	11.3 (6.4-15.4)	**0.04**
Hematocrit; median (range)	37 (23-55)	35.2 (20-47)	0.31
WBC x 10^9/L; median (range)	23.1 (11.9-131)	29.1 (13-185.7)	0.08
AMC x 10^9/L; median (range)	4.2 (1.2-36.4)	6 (1.3-37.8)	0.06
Platelets x 10^9/L; median (range)	201 (16-840)	107 (18-682)	**0.02**
Presence of immature myeloid cells; *n* (%)	14 (61)	57 (84)	**0.03**
Presence of leuko-erythroblastosis, Yes; *n* (%)	16/23 (70)	56/64 (87)	0.06
PB blasts %; median (range)	0 (0-10)	0 (0-19)	**0.01**
BM blasts %; median (range)	2 (0-15)	4 (0-18)	0.21
Lactate dehydrogenase; median (range)	364 (137-971)	250 (135-986)	**0.02**
2016 WHO CMML morphological subtypes; *n* (%) CMML-0 CMML-1 CMML-2	 14 (61) 7 (30) 2 (9)	 33 (48) 20 (29) 16 (23)	0.25
Myeloproliferative features: a. BM cellularity; median (range) b. Megakaryocytic atypia; *n* (%) c. Bone marrow fibrosis; *n* (%) i. Grade 1 ii. Grade 2 iii. Grade 3 iv. Grade 4 d. Palpable splenomegaly; *n* (%)	 90 (40-100) 16/23 (70) 9/13 (69) 8 (61) 0 (0) 0 (0) 1 (8) 11/23 (48)	 90 (40-100) 50/62 (81) 16/32 (50) 10 (31) 2 (6) 3 (9) 1 (3) 21/64 (33)	 0.11 0.28 0.23 0.09
Thrombotic events before diagnosis; *n* (%) a. Arterial thrombosis b. Venous thrombosis	7 (30) 6 (26) 1 (4)	10 (14) 9 (13) 1 (1)	0.10 0.15 0.44
Thrombotic events after diagnosis; *n* (%) a. Arterial thrombosis b. Venous thrombosis	2 (9) 2 (9) 0 (0)	5 (7) 4 (6) 1 (1)	0.82 0.64 0.44
Abnormal cytogenetics; *n* (%)	*n* = 21 1 (5)	*n* = 68 26 (38)	**0.001**
Mayo-French cytogenetic risk stratification; *n* (%) Low Intermediate High	*n* = 21 20 (95) 1 (5) 0 (0)	*n* = 68 45 (66) 16 (24) 7 (10)	**0.009**
Mayo prognostic model; *n* (%)	*n* = 23	*n* = 68	**0.008**

Low	6 (26)	4 (6)	
Intermediate	8 (35)	15 (22)	
High	9 (39)	49 (72)	
Next generation sequencing analysis; *n* (%)			
1. Epigenetic regulators			
TET2	16 (76)	31 (45)	**0.01**
DNMT3A	1 (5)	5 (7)	0.68
IDH1	0 (0)	0 (0)	.
IDH2	1 (5)	6 (9)	0.53
2. Chromatin regulators			
ASXL1	12 (55)	43 (62)	0.52
EZH2	3 (14)	3 (4)	0.13
3. Transcription factors			
RUNX1	4 (19)	5 (7)	0.14
BCOR	0 (0)	0 (0)	.
4. Spliceosome components			
SF3B1	1 (5)	0 (0)	0.08
SRSF2	10 (45)	32 (46)	0.93
U2AF1	1 (5)	6 (9)	0.53
ZRSR2	0 (0)	1 (1)	0.46
5. Cell signaling			
JAK2	23 (100)	0 (0)	**0.0001**
MPL	0 (0)	0 (0)	.
CALR	0 (0)	0 (0)	.
CBL	1 (5)	24 (35)	**0.002**
KRAS	1 (5)	6 (9)	0.53
NRAS	1 (5)	30 (43)	**0.0003**
PTPN11	1 (5)	5 (7)	0.68
CSF3R	0 (0)	3 (4)	0.19
C-KIT	0 (0)	5 (7)	0.09
FLT3TKD	1 (5)	5 (7)	0.67
NPM1	0 (0)	0 (0)	.
SH2B3	1 (5)	0 (0)	0.09
6. Tumor suppressor genes			
Tp53	1 (5)	1 (1)	0.40
7. Others			
SETBP1	2 (9)	15 (22)	0.18
Mayo Molecular Model; *n* (%)	*n* = 22	*n* =68	**0.01**
Low	3 (14)	1 (1)	
Intermediate-1	6 (27)	6 (9)	
Intermedaite-2	8 (36)	30 (44)	
High	5 (23)	31 (46)	
Deaths; *n* (%)	15 (65)	45 (65)	1.0
Overall survival in months; median (95% CI)	29 (18-42)	20 (13-33)	0.61
Leukemic transformation; n (%)	2 (9)	16 (23)	0.10
Follow- up in months; median (range)	54 (0-100)	54 (0-158)	0.94

The bold values represent p values that are statistically significant; $p < 0.05$.

Key: CMML: Chronic Myelomonocytic Leukemia, MP: Myeloproliferative, WBC: White Blood Cell count; AMC: Absolute Monocyte Count; PB: Peripheral Blood; BM: Bone Marrow; WHO: World Health Organization; CI: Confidence Interval

Supplementary table two: Clinical and laboratory characteristics of 30 patients with the *JAK2*V617F mutant chronic myelomonocytic leukemia (CMML), compared to 73 patients with primary myelofibrosis (PMF) with monocytosis

Variables	CMML patients with the *JAK2*V617F mutation (*n*=30)	PMF patients with monocytosis (*n*=73)	P value
Age in years; median (range)	72 (61-85)	69 (35-82)	**0.03**
Sex (Male); *n* (%)	21 (70)	47 (64)	0.58
Hemoglobin g/dL; median (range)	12.1 (7.2-16.9)	10.8 (7.7-16.3)	**0.03**
WBC x 10^9/L; median (range)	15.7 (4.1-131)	21.7 (6.8-236.1)	0.13
AMC x 10^9/L; median (range)	3.2 (1.2-36.4)	1.5 (1-13.5)	**0.03**
Platelets x 10^9/L; median (range)	162 (16-840)	196 (14-1354)	0.64
PB blasts %; median (range)	0 (0-10)	1 (0-16)	**0.0001**
Lactate dehydrogenase; median (range)	378 (137-971)	618 (195-2034)	**0.0043**
Bone marrow fibrosis; *n* (%) a. Grade 1 b. Grade ≥2	N=18 11 (61) 1 (6)	N=71 6 (8) 65 (92)	 **0.0001** **0.0001**
Palpable splenomegaly; *n* (%)	13/30 (43)	57/72 (79)	**0.0005**
Thrombotic events before diagnosis; *n* (%) c. Arterial thrombosis d. Venous thrombosis	8 (27) 6 (20) 2 (7)	13 (18) 8 (11) 5 (7)	0.31 0.23 0.97
Thrombotic events after diagnosis; *n* (%) c. Arterial thrombosis d. Venous thrombosis	2 (7) 2 (7) 0 (0)	10 (13) 6 (8) 4 (5)	0.21 0.78 0.09
Abnormal cytogenetics *n* (%)	*n* = 28 1 (4)	*n* = 72 26 (36)	 **0.0002**
Next generation sequencing analysis; *n* (%) **8. Epigenetic regulators** *TET2* *DNMT3A* *IDH1* *IDH2* **9. Chromatin regulators** *ASXL1* *EZH2* **10. Transcription factors** *RUNX1* *BCOR* **11. Spliceosome components** *SF3B1* *SRSF2* *U2AF1* *ZRSR2* **12. Cell signaling** *JAK2*V617F *Type 1 CALR* *Type 2 CALR*	 20 (67) 1 (4) 0 (0) 2 (7) 14 (48) 3 (10) 5 (18) 2 (7) 14 (48) 1 (4) 0 (0) 30 (100) 0 (0) 0 (0)	*N=21* 6 (29) 2 (10) 1 (5) 5 (22) 9 (43) 0 (0) 2 (10) 2 (10) 5 (24) 2 (10) 4 (19) 48/73 (66) 11/73 (15) 3/73 (4)	 **0.001** 0.39 0.19 0.12 0.70 0.06 0.40 0.76 0.07 0.39 **0.007** **0.0001** **0.004** 0.14

MPL	0 (0)	7/73 (10)	**0.03**
CBL	0 (0)	1 (4)	0.28
KRAS	1 (4)	11 (4)	0.93
NRAS	2 (7)	3 (14)	0.41
PTPN11	1 (4)	1 (5)	0.83
CSF3R	0 (0)	0 (0)	.
C-KIT	1 (4)	0 (0)	0.28
FLT3TKD	1 (4)	0 (0)	0.28
NPM1	0 (0)	1 (5)	0.18
13. Tumor suppressor genes			
Tp53	1 (4)	1 (5)	0.83
14. Others			
SETBP1	3 (11)	2 (10)	0.89
Risk stratification	**MMM**	**MIPPS**	0.87
Low	4 (14)	6 (8)	
Intermediate-1	9 (31)	25 (35)	
Intermediate-2	11 (38)	19 (40)	
High	5 (17)	12 (17)	
Deaths; *n* (%)	16 (53)	63 (86)	**0.0005**
Leukemic transformation; n (%)	3 (10)	11 (15)	0.48
Overall survival in months; median (95% CI)	31 (28-64)	27 (21-36)	0.39

The bold values represent p values that are statistically significant; $p < 0.05$.

Key: CMML: Chronic Myelomonocytic Leukemia; PMF: Primary Myelofibrosis; WBC: White Blood Cell count; AMC: Absolute Monocyte Count; PB: Peripheral Blood; WHO: World Health Organization; MMM: Mayo Molecular Model for CMML prognostication; MIPPS: Mutation enhanced International Prognostic Scoring for PMF; CI: Confidence Interval