The Prognostic Impact of the Mutational Profile in Patients With Myelofibrosis in the Era of the JAK1/JAK2-Inhibitor Ruxolitinib

Abstract 1860

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Introduction & Objectives

- In retrospective studies, CALR mutation is found to be a favorable prognostic variable in myelofibrosis (MF) compared with JAK2 or MPL mutations
- With the availability of the JAK1/JAK2 inhibitor ruxolitinib (RUX) for treatment of MF, it is not yet known whether response varies across mutational subgroups and whether the prognostic implication of the driver mutations in terms of survival (OS) changes under RUX
- We studied the prevalence and prognostic weight of clinical parameters in the IPSS and DIPSS plus and the impact of RUX on OS in the context of mutation status

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Patients & Methods

- Restrospective analysis of 127 patients (pts) with MF seen at the University Hospital Leipzig from Sept 2009 to May 2014
- Screening for the JAC2V617F, CALR, and MPL mutations was performed as previously published
- JAK2 mut+ (group A; 60.6%) constituted the largest group, followed by CALR mut+ (group B; 19.7%), and “triple-negative” (group C; 19.7%)
- Median follow-up was 31 (range 1-204) months

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Clinical Parameters According to Molecular Subgroups

Variable	Group A JAK2 mut +	Group B CALR mut +	Group C Triple Negative	*P* Value
N (%)	77 (60.6)	25 (19.7)	25 (19.7)	
Median age (years)	59	51	61	.02
Constitutional symptoms	69	52	46	.08
Median palpable spleen, cm	10	4	3	.001
Int-2 & high-risk IPSS, %	79	52	96	.01
WBC>25x10^9/L, %	21	11.5	44	.008
Median peripheral blasts, %	1	0.5	2	ns
Median Hb g/L	106	99	86	.008
Hb<100g/L, %	42	54	80	.03
Transfusion dependency, %	33	32	67	.009
Platelets <100x10^9/L	30	8	52	.04
Unfavorable cytogenetics, %	31	14	48	.06
Leukemic transformation, n (%)	12 (15.6)	1 (3.8)	9 (36)	.004

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Patient Characteristics

Characteristics	
Sex, F:M	55:72
Years of age, median (range)	58 (23-85)
Type of MF	
PMF	n = 93
Post-PV	n = 17
Post-ET	n = 17
IPSS Risk Groups (n = 125)	
Low + Int-1, n (%)	29 (23.2)
Int-2 + High, n (%)	96 (76.8)

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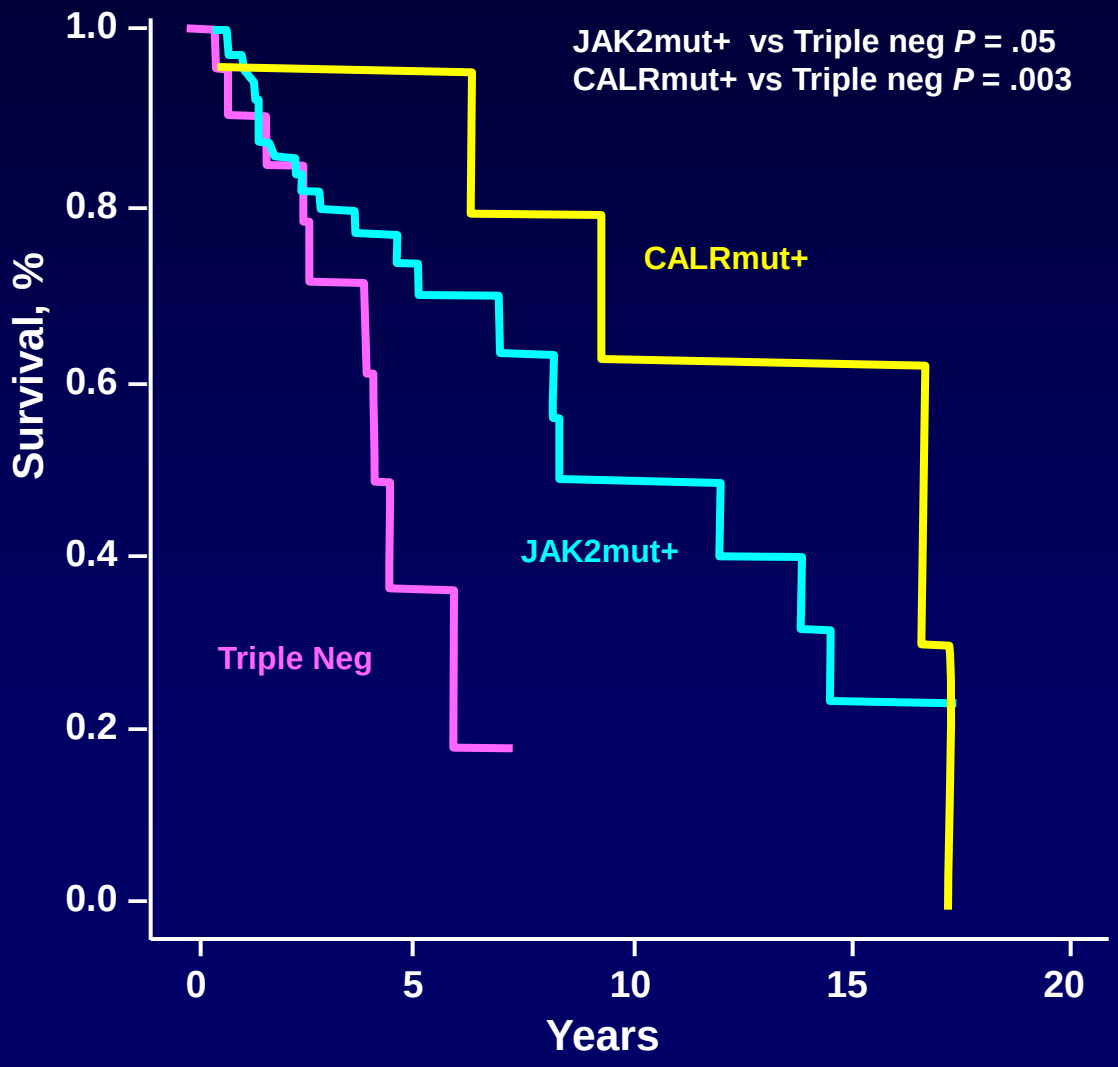
Survival at 3 Years



OS at 3 years

- Entire cohort: 82%
- JAK2mut+: 80%
- CALRmut+: 96%
- Triple-neg: 72%

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The Impact of Mutation Status With Treatment With Ruxolitinib on Survival in Patients With Int-2/High-Risk IPSS

	P value
JAK 2 mut+ vs CALR mut+ vs triple negative	.07
JAK 2 mut+ treated with RUX vs CALR mut+ (irrespective of RUX)	.4
JAK 2 mut+ treated with RUX vs CALR mut+ treated with RUX	.4

Interestingly, in pts with int-2/high risk IPSS, OS in group A pts treated with RUX (n = 41) was similar to the OS of pts in group B irrespective of whether these pts were treated with ruxolitinib or not (*P* = .4)

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Conclusions (1)

- **The mutation status in MF bestows distinct clinical phenotypes and has crucial prognostic and therapeutic implications. Patients with nonmutated MF had the worst prognosis, unfavorable cytogenetics, and the highest rate of leukemic transformation**
- **Although the IPSS retains its value, the prognostic power of certain factors such as anemia and constitutional symptoms in *CALR*-mutated pts needs to be re-evaluated**

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Conclusions (2)

- **Response to ruxolitinib seems to be independent of the mutation status**
- **More importantly, a JAK1/JAK2 inhibition with ruxolitinib appears to be capable of attenuating the prognostic implication of the different mutation profiles by improving the less-favorable survival associated with non-*CALR*-mutated MF through a disease-modifying effect**
- **The full potential of a sustained JAK1/JAK2 inhibition in modifying survival in the context of the various mutational profiles needs to be further studied in a larger cohort of patients.**

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