Abstract: P1033

Title: IMPACT OF TP53 MUTATION ALLELIC BURDEN ON OUTCOME OF PATIENTS WITH MYELOPROLIFERATIVE NEOPLASMS: A STUDY FROM COMMAND CONSORTIUM.

Abstract Type: Poster Presentation

Topic: Myeloproliferative neoplasms - Clinical

Background:

TP53 mutated (m) myeloproliferative neoplasms (MPN) can have rapid progression to MPN blast phase (BP) leading to dismal outcomes, however *TP53*m variant allele frequency (VAF) < 5% may remain indolent for years before progression (Kubesova et al. Leukemia 2018). We sought to explore the impact of *TP53*m allelic burden on clinical outcome of Philadelphia-chromosome negative (Ph-) MPNs, utilizing multi-institutional real-world data.

Aims:

We aim to understand the genomic landscape and clonal evolution patterns of *TP53*m MPN and the impact to *TP53*m allelic burden on time to progression (TTP) and clinical outcomes.

Methods:

We conducted a retrospective study through the COMMAND consortium and identified 102 adult (≥18 years) patient (pts) with *TP53*m MPN evaluated at participating institutions between 2012-2022; we evaluated TTP from chronic phase (CP) to accelerated (AP) or blast phase (BP), response to therapy at progression, and impact of *TP53*m* VAF on clinical outcome. Multi-hit (MH) *TP53* was defined as 2+ mutations, *TP53* variant allele frequency (VAF) ≥ 50% in a single mutation, *TP53*m with 17p deletion or with documented loss of heterozygosity.

Results:

Baseline characteristics and treatment outcomes summarized in **Table 1**. The median age was 64 years (yrs) (range [R], 24-85); 12%, 24.5%, 40%, 9%, and 15% had polycythemia vera (PV), essential thrombocytosis (ET), primary myelofibrosis (PMF), MPN-AP and MPN-BP, respectively at time of *TP53*m detection. MPN driver mutations were *JAK2* (77%), *CALR* (12%), and *MPL* (6%) (5% triple negative). Most common somatic co-mutations were *IDH1* (2%), *IDH2* (11%), *TET2* (22.5%), *DNMT3A* (19%), *ASXL1* (23%) and spliceosome mutations (22%); 32% of pts had MH-*TP53*m. The median TTP from MPN-CP to MPN-AP (12%) or MPN-BP (28%) was 95.7 months (mo) (R, 2-441). Twenty-nine percent of patients acquired complex cytogenetics at progression, one pt each acquired *ASXL1*, *IDH1* and *SRSF2*m at progression. Treatments given at progression are outlined in **Table 1**; 24% achieved complete remission and 9% received allogeneic stem cell transplantation. The median overall survival (OS) was 19.5, 11.17, 2.92, 1.53 and 0.63 yrs among pts with PV, ET, PMF, MPN-AP, and MPN-BP respectively (Figure A, p= 0.0002). Seventy-six (74.5%) had MPN-CP at *TP53*m detection; amongst these pts we looked at incidence of progression, TTP and OS based on VAF < 40% vs. ≥ 40%. There was no significant difference in incidence of progression to MPN-AP/BP (5 [45.5%] vs 14 [21%], p= 0.48) or TTP (123.1 vs 65.1 mo [p= >0.99]) with VAF ≥ 40% compared to < 40%, respectively. However, median OS was significantly shorter with VAF ≥ 40% (1.06 yrs) compared to VAF < 40% (8.19 yrs), p= 0.04 (Figure B). In another subset analysis for OS based on single-hit (SH) vs MH *TP53* among pts with MPN-AP or BP we found numerically higher median OS in MPN-AP (15.35 vs 1.77 mo, p= 0.10) but not in MPN-BP (5.35 vs 6.26 mo, p=0.53 [Figure C]) harboring SH vs MH *TP53*m, respectively.

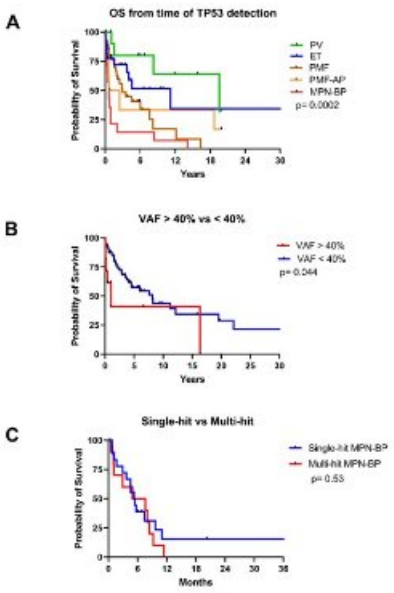
Summary/Conclusion:

In line with prior observations, we did not observe significant differences in progression among pts with *TP53*m

MPN-CP. Though, significantly inferior OS was observed among MPN-CP with TP53m VAF ≥ 40% compared to VAF < 40%. We did not observe significant OS difference between SH and MH *TP53* in MPN-BP although overall outcomes are poor much like what has observed in acute myeloid leukemia (Grob et al Blood 2022). Our findings suggest that MPN-CP with high *TP53*m VAF should be considered high-risk disease and for early intervention.

Table 1. Baseline characteristics of patients with TP53 mutated myeloproliferative neoplasm (N=102)

Variables	N (%)/Median [range]
Age, years	64 [24-85]
MPN diagnosis at TP53 detection	
Polycythemia Vera	12 (12)
Essential Thrombocytosis	25 (24.5)
Myelofibrosis	41 (40)
Myelofibrosis in accelerated phase	9 (9)
MPN in blast phase	15 (15)
MPN driver mutation	
JAK2	70 (77)
CALR	12 (12)
MPL	6 (6)
Triple negative	5 (5)
Additional CG abnormality at MPN diagnosis (evaluable N=67)	27 (40)
Most common somatic co-mutation at first detection	
IDH1	2 (2)
IDH2	11 (11)
TET2	23 (22.5)
DNMT3A	10 (10)
ASXL1	25 (25)
Spliceosome mutation (U2AF1, SF3B1, SRSF2)	23 (22)
Multi-hit TP53 mutation	33 (32)
Progression to AP/BP	12[12]/29 (28)
Time to progression (months)	95.7 [2-441]
Age at progression, years	68 [55-87]
Acquisition of complex cytogenetics at progression (N=41)	12 (29)
Treatment given at progression (N= 41)	
Intensive chemotherapy	8 (19.5)
Hypomethylating agent (HMA) plus venetoclax	18 (44)
HMA	8 (19.5)
IDH inhibitors	3 (7)
JAK inhibitors	2 (5)
Others	2 (5)
Complete remission	8 (24)
Allogeneic stem cell transplantation	9 (9)



Keywords: TP53, Myelofibrosis, Myeloid malignancies, Myeloproliferative disorder