Timing of TP53 Mutation Acquisition as a Determinant of Outcomes in Patients with Myeloproliferative Neoplasms and Myeloproliferative Neoplasms/Myelodysplastic Syndromes.

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BACKGROUND

While TP53 mutations have been studied in MDS and AML, their clinical significance in MPN and MDS/MPN remains incompletely understood.

Emerging evidence suggests that TP53 mutations are often not present at diagnosis, acquired over the disease course, and enriched in older patients.

The primary objective of this study was to evaluate whether the interval between diagnosis and the detection of TP53 mutation impacts OS and/or PFSs.

METHODS

All patients with a TP53 mutation were identified via our in-house NGS panel between 2018–2024 were included (n=497).

Spearman correlation, Kruskal–Wallis, and chi-square tests were used to evaluate associations between age, VAF, and the presence of co-mutations with the interval from diagnosis to TP53 detection.

The Kaplan–Meier method and Cox proportional hazards models were used to analyze OS and PFS.

PATIENT CHARACTERISTICS

54 patients [ET-27, MF-9, CMML-9, PV-7] with median age at diagnosis 65.1 years were included of which 56% were male, 81% were Caucasian. 22% [n=12] were diagnosed with MPN or MDS/MPN at the time of tp53 identification.

52% pts were treated with hydroxyurea prior to TP53 identification. At the time of TP53 detection, 13 pts had progressed to AML and 11 pts to MF. The most common co-mutations were JAK2[19], CALR[11], TET2[10] and ASXL1[9]

Time to TP53 Acquisition

Q) In patients diagnosed with MPN & MDS/MPN, at what point in their disease do they develope a TP53 mutation?

Pts were divided into 4 quartiles depending on timing of TP53 acquisition-

- <6 months [13]
- 6months -7 years [15]
- 7.1-14 years [13]
- >14 years [13].

Median Time from Initial Dx to TP53 Detection [years]

Early TP53 Aquisition (<6 months)

Q) After onset of disease, is the early aquisition of TP53 random or are there patient groups where it occurs more often?

Feature	< 6 Months	≥ 6 Months	p-value
Median age at TP53 detection	74.9 years	64.0 years	0.005
High clone size (VAF > 41%)	69.20%	43.90%	NS
≥ 3 co-mutations at diagnosis	53.80%	26.80%	NS

Older patients had shorter interval between Dx & TP53 Detection

Early TP53 patients were older, with increased VAF and co-mutaions. Age was the only statistically significant risk factor in our study.

TP53 & Survival

Q) Does Age at TP53 Detection impact Survival?

Group	Overall Survival	Progression-Free Survival	p-value
Older patients	3.6 months	3.6 months	OS: p=0.002 PFS: p<0.001
Younger patients	27.2 months	17.5 months	—

Older age at TP53 detection = significantly worse survival

Q) After adjusting for age, does interval between Dx & TP53 detection impact survival?

Quartile (vs. 1st)	Timing	OS Hazard Ratio	PFS Hazard Ratio
1st (reference)	< 6 months	1.0 (ref)	1.0 (ref)
2nd quartile	6 mo – 7 yr	1.2× worse	1.2× worse
3rd quartile	7.1 – 14 yr	2.5× worse	2.9× worse
4th quartile	> 14 yr	4.3× worse	4.5× worse
p for trend		0.002	0.001

Longer disease history before TP53 = progressively worse survival (age-adjusted)

CONCLUSIONS

This study demonstrates that after adjusting for age, a longer interval between MPN or MDS/MPN diagnosis and TP53 detection is associated with worse OS and PFS.

Older age has previously been identified as an adverse prognostic factor. Our findings suggest that timing of TP53 acquisition may also be an important predictor of clinical outcomes in pts with MPNs and MDS/MPNs.

DISCLOSURES

No Financial Disclosures.