Clonal Emergence of Multi-Hit TP53 Mutations Predicts Progression and Therapeutic Failure in High-Risk Myelodysplastic Syndromes

Bishal Tiwari MBBS , Nassau University Medical Center, NY, USA



Introduction

•TP53-mutant MDS is associated with poor survival, rapid progression, and therapy resistance.
•Multi-hit TP53 mutations represent an ultra-high-risk disease phenotype.
•Clonal expansion of TP53 mutations under treatment predicts leukemic transformation.
•Variant allele frequency (VAF) of TP53 mutations is a critical prognostic biomarker.
•Hypomethylating agents (HMAs) and lenalidomide show limited efficacy in TP53-mutant cases.
•Understanding the dynamics of TP53 mutations can inform therapeutic strategies.

Objectives

•Evaluate TP53 mutation burden and dynamics in high-risk MDS patients.
•Correlate TP53 VAF with overall survival (OS), AML transformation, and treatment failure.
•Assess differences between mono-hit and multi-hit TP53 cases.
•Determine response to HMAs and lenalidomide in TP53-mutant versus wildtype MDS.
•Explore the impact of emerging TP53 clones during therapy.
•Advocate for serial sequencing as a monitoring strategy.

Methods

•Retrospective analysis of longitudinal sequencing data (2010–2024).
•Multi-center registries and trials involving ~800 higher-risk MDS patients.
•Focus on patients receiving HMAs or lenalidomide with serial NGS.
•TP53 mutation types, VAF, and hit status evaluated.
•OS, AML transformation, and therapy response assessed in relation to mutation profile.
•Multi-hit defined by biallelic TP53 mutations or loss of heterozygosity (LOH).

Figure 1: Survival by TP53 Mutation Status in High-Risk MDS

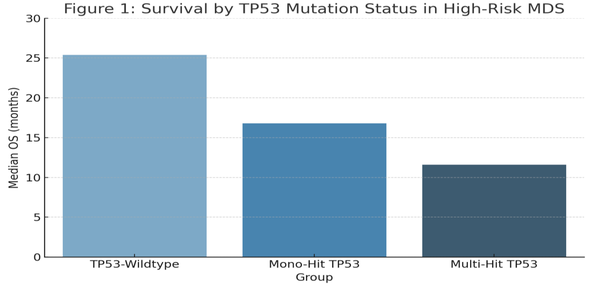


Figure 2: Impact of TP53 VAF ≥10% on Survival

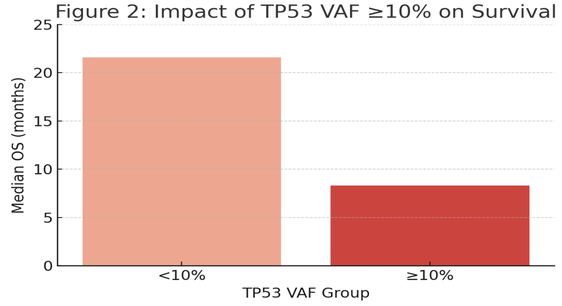
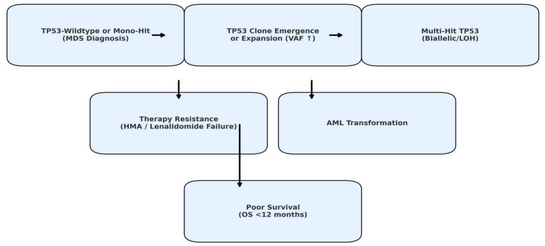


Figure 3: TP53 Clonal Dynamics Driving Progression and Therapy Resistance in High-Risk MDS



Results

•TP53 mutations present in 20–30% of high-risk MDS; multi-hit associated with OS ~11.6 months.
•TP53 VAF ≥10% predicts inferior survival (OS ~8.3 vs 21.6 months).
•Clonal TP53 expansion during treatment is linked to AML transformation and relapse.
•In del(5q) MDS, lenalidomide selects for TP53-mutant subclones, hastening progression.
•Persistent TP53 post-HMA correlates with relapse; clearance improves survival.
•TP53-mutant clone clearance post-therapy predicts longer OS (HR ~0.28, P<0.001).

Conclusion

TP53 clonal evolution under therapy drives poor outcomes in high-risk MDS.
VAF ≥10% is a high-risk marker requiring intensified monitoring and early intervention.
Multi-hit TP53 cases benefit minimally from conventional therapy.
Serial NGS should be routine in high-risk MDS for risk stratification.
TP53 clearance post-therapy is a strong predictor of favorable prognosis.
TP53-targeted therapies are urgently needed for this MDS subset.

References

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