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TP53 IN MYELOID NEOPLASMS

Maria Teresa Voso, Luca Guarnera

Department of Biomedicine and Prevention, University of Rome Tor Vergata, Italy

The *TP53* gene encodes the transcription factor p53, a central regulator of genomic integrity and stem-cell fitness. Loss of *TP53* function, through genetic mutations and/or deletion of chromosome 17, disrupts DNA damage checkpoints, promotes tolerance to genotoxic stress, and represents a key prognostic factor in myeloid neoplasms (MN). Across MN phenotypes, *TP53*-driven diseases (most commonly therapy-related neoplasms and myelodysplastic syndromes (MDS)) are characterized by an aggressive clinical course and high-risk chromosomal aberrations [1].

In acute myeloid leukemia (AML) and MDS, *TP53* mutations define one of the most adverse-risk biological subsets, associated with primary chemoresistance or only transient responses to hypomethylating agents and very poor overall survival [1-3]. Accordingly, contemporary classification systems recognize *TP53* alterations as a distinct disease entity or molecular category [4-5]. Despite these biological underpinnings, from a clinical perspective, *TP53*-mutated AML/MDS remain an urgent unmet medical need, as no current or investigational therapy consistently achieves durable disease control or long-term survival [1](Table 1). Mechanistic dissection of *TP53*-driven leukemogenesis has recently highlighted the critical role of allelic state. Experimental in vitro and in vivo models show that monoallelic *TP53* alterations confer selective clonal fitness under cytotoxic or radiation-induced stress with relatively limited genomic instability, whereas biallelic inactivation leads to defective p53 signaling, large-scale copy-number alterations, and acquisition of autonomous self-renewal culminating in leukemic transformation [6]. Despite these biological insights, the clinical implications of *TP53* biallelic status remain a matter of debate [7-9].

Consistent with these mechanisms, *TP53* mutations also confer adverse prognosis in myelodysplastic/myeloproliferative neoplasm (MDS/MPN) overlap syndromes. In chronic myelomonocytic leukemia (CMML), *TP53* alterations are among the strongest predictors of inferior survival and leukemic transformation [10], while in MDS/MPN not otherwise specified (NOS) they define a biologically distinct high-risk molecular subtype [11].

Beyond acute phenotypes, *TP53* mutations adversely affect outcomes in (MPN), including essential thrombocythemia and myelofibrosis [12-13]. Recent data suggest a context-dependent effect in MPN, where male sex, multi-hit status, absence of transplantation, and advanced versus chronic disease phase predict worse outcomes, findings further confirmed in the transplantation setting.

Collectively, *TP53* alterations represent a high-risk biological feature across myeloid neoplasm phenotypes. Further studies are required to clarify the leukemogenic processes driven by *TP53* dysfunction and to develop effective disease-modifying therapeutic strategies for this critical unmet clinical need.

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Table 1. Available and emerging treatment outcomes in *TP53*-mutated MDS and AML. Adapted from Naver et al. (1)

AML: acute myeloid leukemia; CR: complete remission; Cri: complete remission with incomplete complete blood count recovery; DOR: duration of response; HMA: hypomethylating agents; MDS: myelodysplastic syndromes; ND: newly diagnosed; NA: not available; NR: no response; ORR: overall response; OS: overall survival; pts: patients; R/R: relapsed/refractory.

Treatment	Type of study	Population	*TP53*-mutated pts	Response	CR rate	Median OS (months)
Azacitidine or decitabine	II; retrospective	ND AML	22	CR/CRi 22%-38%	13%-22%	2.1–7.3
Venetoclax + azacitidine or 5-day decitabine	Ib/II, III	ND AML	36, 54	CR/CRi 41%-47%	NR–20%	4.9–7.2
Venetoclax + 10-day decitabine	II; post hoc	ND AML	26	ORR 77%	48%	5.4
Magrolimab + azacitidine	Ib	ND AML	72	CR/CRi 49%	33%	10.8
Magrolimab + venetoclax + azacitidine	Ib/II	ND AML	14	ORR 86%	64%	NR
Eprenetapopt + azacitidine	Ib/II	ND AML	18	ORR 33%	17%	10.4
Sabatolimab + HMA	Ib	ND AML	5	CR/CRi 40%	20%	DOR 6.4
SGN-CD33A + HMA	I/II	ND AML	7	CR/CRi 86%	NR	NA
Nivolumab + intensive chemotherapy	Post hoc	ND AML	4	ORR 50%	NA	NA
Intensive chemotherapy	Retrospective	ND AML	various	ORR 47%-55%	45%-55%	6.8–8.8
Low-intensity chemotherapy	Retrospective	ND AML	various	ORR 14%-50%	36%	6.7–9.0
Flotetuzumab	I/II	R/R AML	15	ORR 60%	47%	4.0
Nivolumab + azacitidine	II	R/R AML	26	ORR 23%	NA	NA
Venetoclax + 10-day decitabine	II; post hoc	R/R AML	24	ORR 46%	19%	4.5
Azacitidine or decitabine	Post hoc	MDS	various	ORR 1%-100%	32%	9.4–12.4
Eprenetapopt + azacitidine	Ib/II	MDS	40	ORR 73%	50%	10.8
Sabatolimab + HMA	Ib	MDS	14	ORR 71%	29%	OS NR (DOR 21.5)
Magrolimab + azacitidine	IB	MDS	25	ORR 68%	40%	16.3