SOMATO PUBLICATIONS ISSN: 2688-9587

Annals of Leukemia Research

Review Article

Prognostic Significance of TP53 Alterations in Patients with Therapy-Related Myeloid Neoplasms

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Received: 21 March 2024; **Accepted:** 06 July 2024; **Published:** 17 November 2024

Citation of this article: Vasileiou, E., Juric, M., Pawlak, J. (2024) Prognostic Significance of TP53 Alterations in Patients with Therapy-Related Myeloid Neoplasms. Ann Leuk Res, 5(1): 04-06. doi: 10.5281/zenodo.22227599

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Summary

Therapy-related myeloid neoplasms are enriched for TP53 mutations three to four times over de novo disease, which for years was taken to mean that chemotherapy causes them. Sequencing showed otherwise: the mutant clone is usually present years before treatment, and cytotoxic therapy selects it rather than creating it.

Objectives: To review the published evidence on TP53 alterations in therapy-related myeloid neoplasms: how often they occur, where they come from, what they predict for survival, whether variant allele frequency and allelic state carry the same meaning as in de novo disease, and what follows for classification.

Material and Methods: Narrative review of sequencing studies, cohort analyses, classification documents and mechanistic work indexed in PubMed and the major haematology and genetics journals. Studies were eligible if they reported TP53 alteration frequency, clonal origin or outcome in a defined therapy-related or de novo myeloid neoplasm population. No new patient data were generated and no patients were recruited; every estimate quoted is one published by the original investigators.

Results: TP53 mutations occur in 21 to 38 per cent of therapy-related myeloid neoplasms against 5 to 10 per cent of de novo disease, rising to 70 to 80 per cent where the karyotype is complex or chromosome 17p, 5q or 7q is lost. Median overall survival was 6.1 months with mutation against 14.1 months without ($p < 0.0001$ univariate, $p = 0.0020$ multivariate). Whole-genome sequencing of therapy-related disease found the mutational burden and the proportion of chemotherapy-related transversions no higher than in de novo disease, and in four patients the exact mutation was detectable at 0.003 to 0.7 per cent in blood collected three to six years before the neoplasm appeared. In 488 patients, a variant allele frequency of 10 per cent or above, or loss of the TP53 locus, defined the poor-prognosis group, and single-hit and multi-hit disease carried equally poor outcome, unlike de novo disease.

Conclusion: The allelic state distinction that governs classification of de novo TP53-mutated disease does not transfer to the therapy-related setting, where outcome is uniformly poor once the clone exceeds a modest variant allele frequency. Detecting these clones before cytotoxic treatment is the more consequential opportunity.

Abbreviations: t-MN – Therapy-Related Myeloid Neoplasm, t-AML – Therapy-Related Acute Myeloid Leukaemia, t-MDS – Therapy-Related Myelodysplastic Syndrome, VAF – Variant Allele Frequency, CH – Clonal Haematopoiesis, CHIP – Clonal Haematopoiesis of Indeterminate Potential, LOH – Loss of Heterozygosity, cnLOH – Copy-Neutral Loss of Heterozygosity, ICC – International Consensus Classification, WHO – World Health Organization, ELN – European LeukemiaNet, HSPC – Haematopoietic Stem and Progenitor Cell.

Keywords: *Therapy-Related Myeloid Neoplasm; TP53; Clonal Haematopoiesis; Variant Allele Frequency; Prognosis*

Introduction

Therapy-related myeloid neoplasms arise after cytotoxic chemotherapy or radiotherapy given for an unrelated malignancy, and they differ from de novo disease in ways that have been recognised for decades: a higher incidence of TP53 mutation, abnormalities of chromosomes 5 or 7, complex cytogenetics and reduced response to chemotherapy [1,2].

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The obvious interpretation was that the treatment caused the mutations. Cytotoxic agents damage DNA, TP53 is the canonical guardian of genomic integrity, and a mutation appearing after exposure looks like a consequence of it [3,4]. That reading shaped how the disease was discussed for years and it turns out to be wrong.

TP53-altered myeloid disease carries the worst outcome of any molecular subgroup, with response rates to induction chemotherapy, hypomethylating agents and venetoclax-based regimens all lower than in unmutated disease and median survival of five to ten months [5,6]. Recent classifications have recognised it as a distinct entity rather than a risk modifier [7,8,9].

This review sets out how often TP53 alterations occur in the therapy-related setting, where the mutant clone actually comes from, what it predicts, and why the allelic-state rules developed for de novo disease do not appear to apply here.

Material and Methods

Search strategy: PubMed and the archives of the major haematology and genetics journals were searched for studies of TP53 in therapy-related myeloid disease. Search terms combined therapy-related myeloid neoplasm, secondary acute myeloid leukaemia and therapy-related myelodysplastic syndrome with TP53, variant allele frequency, allelic state, multi-hit, clonal haematopoiesis and complex karyotype. Reference lists of retrieved sequencing studies and classification documents were screened by hand.

Eligibility: Studies were included if they reported TP53 alteration frequency, clonal origin, variant allele frequency distribution or outcome in a defined myeloid neoplasm population. Studies of de novo disease are cited where they provide the comparator or established the allelic-state framework, and are identified as such throughout.

Data extraction and handling: Design, cohort size, sequencing platform, variant allele frequency threshold and reported survival estimates were extracted as published. The threshold and the method of assessing allelic state are stated alongside every figure, because detection of loss of heterozygosity depends on whether copy-number and single-nucleotide polymorphism array data were available. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 4 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

How much commoner the mutation is: TP53 mutations are found in 5 to 10 per cent of de novo myelodysplastic syndrome and acute myeloid leukaemia, where they associate with complex karyotype and shortened survival [10,11,12]. In therapy-related disease the figure is 21 to 38 per cent [1,2]. Where the karyotype is complex, or chromosome 17 or 17p, 5 or 5q, or 7 or 7q is lost, the frequency of TP53 abnormality rises to 70 to 80 per cent (Figure 1) [5,13].

The mutations themselves are unremarkable. In therapy-related disease they cluster in the DNA-binding domains at a median allelic frequency of 37.0 per cent (range 7.1 to 98.8), most are single nucleotide changes with transitions outnumbering transversions at 65.9 against 34.1 per cent, and missense mutations predominate over frameshift and nonsense [2]. That pattern is strikingly similar to what is seen in de novo disease, which is the first clue that something other than direct mutagenesis is at work [2].

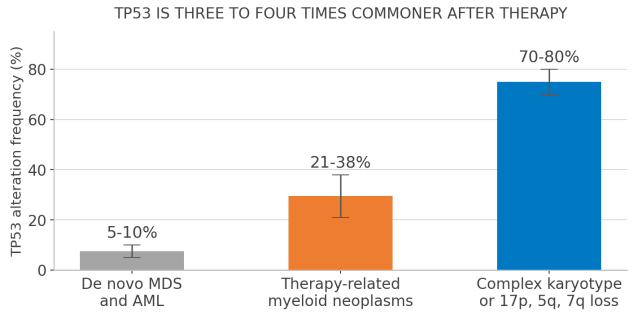

Figure 1: Frequency of TP53 alteration by disease context [1,2,5,13]

The clone predates the treatment: Whole-genome sequencing of 22 patients with therapy-related acute myeloid leukaemia settled the question of causation. The total number of somatic single-nucleotide variants and the proportion of chemotherapy-related transversions were similar to de novo disease, indicating that cytotoxic therapy neither produces genome-wide DNA damage of the expected kind nor directly induces the TP53 mutation [3].

The decisive observation followed. In four patients whose leukaemia carried a TP53 mutation, that exact mutation was detectable at frequencies of 0.003 to 0.7 per cent in mobilised blood leucocytes or marrow collected three to six years before the neoplasm appeared [3]. The clone was present before the chemotherapy that supposedly caused it.

The mechanism is selection rather than mutagenesis. Haematopoietic stem cells carrying a TP53 mutation have a relative fitness advantage under cytotoxic stress, so treatment does not create the clone but clears the competition around it [3,14]. Cellular stressors more generally expand haematopoietic clones of varying leukaemic potential [15], and cancer therapy has been shown to shape the fitness landscape of clonal haematopoiesis, with TP53, CHEK2 and PPM1D clones associated with chemotherapy exposure while DNMT3A and TET2 clones are not [16].

Clinical data support the same picture. Among patients with tubo-ovarian cancer treated with a PARP inhibitor, pre-existing TP53-mutant clonal haematopoiesis at a variant allele frequency of 1 per cent or above was present in 45.0 per cent of those who went on

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to develop a therapy-related neoplasm against 13.6 per cent of those who did not (p = 0.009) (Figure 3), with clones detectable up to six years before diagnosis [17].

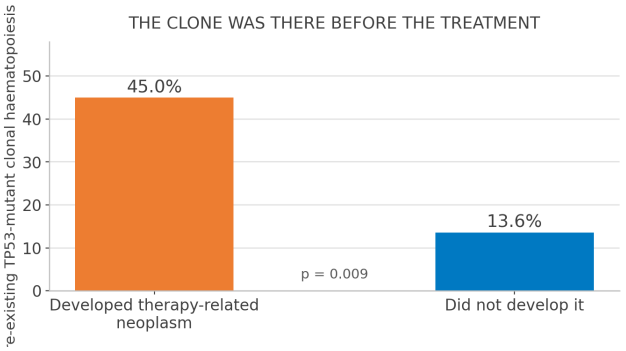

Figure 3: Pre-existing TP53-mutant clonal haematopoiesis before treatment, by subsequent outcome [17]

Study	n	Focus	Principal reported finding
Bowen et al. 2009 [11]	—	Complex karyotype	TP53 frequent and associated with very poor outcome
Rücker et al. 2012 [13]	—	Complex karyotype	Correlates with copy number change and dismal outcome
Wong et al. 2015 [3]	22	Origin	Mutation present 3-6 years before the neoplasm
Papaemmanuil 2016 [12]	—	Classification	Genomic classification of acute myeloid leukaemia
Bolton et al. 2020 [16]	—	Clonal fitness	Therapy shapes the clonal haematopoiesis landscape
Shah et al. 2023 [18]	488	Prognosis	VAF 10% threshold; single and multi-hit equally poor

Table 1: Principal studies reviewed, with focus and the finding as reported by the original investigators

What the mutation predicts: In therapy-related disease, TP53 mutation was associated with complex karyotype ($p < 0.0001$), a higher number of chromosomal abnormalities ($p < 0.0001$) and inferior overall survival, at a median of 6.1 against 14.1 months, significant on both univariate ($p < 0.0001$) and multivariate analysis ($p = 0.0020$) (Figure 2) [2]. Those figures sit within the five to ten month median reported for TP53-mutated myeloid disease generally [5].

The poor outcome is not confined to one treatment modality. Response rates are lower with induction chemotherapy, with hypomethylating agents and with venetoclax-based regimens alike [5,6], which is what distinguishes this from a resistance phenotype specific to a class of drug. In transplantation, TP53 mutation is among the strongest predictors of poor outcome after stem-cell transplant for myelodysplastic syndrome [19].

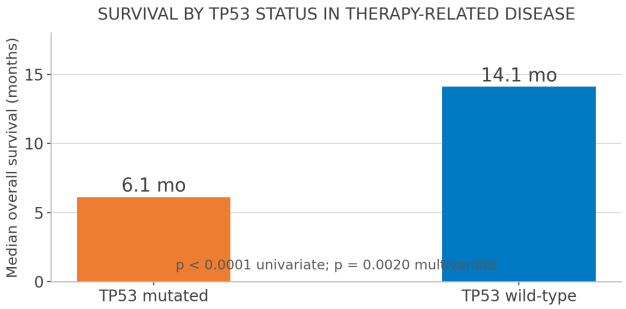

Figure 2: Median overall survival by TP53 status in therapy-related myeloid neoplasms [2]

Where the therapy-related setting diverges: Classification of de novo TP53-mutated disease turns on allelic state. A single mutation with the second allele intact behaves differently from biallelic or multi-hit disease, and current criteria from both the International Consensus Classification and the World Health Organization incorporate that distinction [7,8,9]. Mechanistic work supports it: stem cells with monoallelic mutation gain clonal fitness while retaining genomic integrity, whereas biallelic loss produces the genomic instability required for transformation [20].

Analysis of 488 therapy-related patients tested whether the same rules apply and found that they largely do not. Survival was equally poor in single-hit and multi-hit disease, which is the opposite of the de novo pattern (Figure 4) [18]. What did separate outcome was variant allele frequency: mutation at 10 per cent or above, or loss of the TP53 locus, identified the poor-prognosis group, while mutation below 10 per cent behaved more like wild-type disease [18].

An explanation is available within the same data. Among patients with a single mutation at variant allele frequency between 10 and 50 per cent, loss-of-heterozygosity information was available in only a subset, and 80 per cent of those without such information had a complex karyotype and would be considered equivalent to multi-hit under the consensus criteria [18]. Much apparent single-hit disease in this setting may therefore be biallelic disease that the available assays did not resolve.

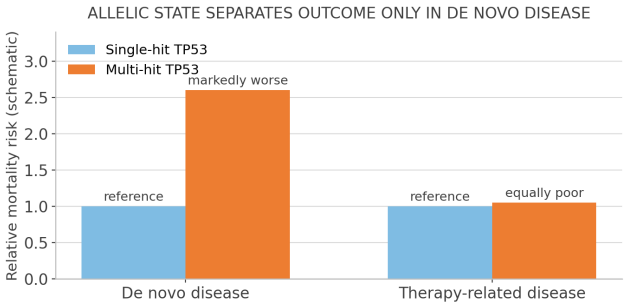

Figure 4: How allelic state relates to outcome in de novo against therapy-related disease [18,20]

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Feature	De novo disease	Therapy-related disease
TP53 mutation frequency	5-10%	21-38% [1,2]
Mutation spectrum	DNA-binding domain, missense	Indistinguishable [2]
Allelic state separates outcome	Yes	No; equally poor [18,20]
Variant allele frequency threshold	Debated	10% discriminates [18]
Median overall survival	5-10 months	6.1 months if mutated [2,5]

Table 2: How TP53-altered disease differs between the de novo and therapy-related settings

A practical question follows from the threshold finding. Variant allele frequency is not a fixed property of the leukaemia: it scales with blast percentage and with the purity of the sample sequenced, so the same clone measured in a hypocellular marrow and in a blast-rich one will return different values [18]. A 10 per cent cutoff is therefore a threshold on a quantity that is partly an artefact of sampling, which is the same difficulty that undermined the FLT3-ITD allelic ratio.

Residual disease in a disease defined by a resistant clone: Measurable residual disease has become central to risk-adapted management of acute myeloid leukaemia generally [22,23], and its behaviour in TP53-altered disease is instructive. Because the mutant clone often predates the leukaemia and persists in non-leukaemic haematopoiesis, a sequencing assay tracking TP53 may remain positive in a patient who has cleared their leukaemia, detecting clonal haematopoiesis rather than residual disease [16,24].

This is the same interpretive problem that arises with DNMT3A and TET2 mutations, which persist in remission without indicating impending relapse [25]. It argues for pairing molecular measurement with an immunophenotypic or morphological assessment in this subgroup rather than relying on the mutation alone, and it is one reason current recommendations treat certain mutations as unsuitable residual disease markers [22,23].

The revised genetic risk classifications place TP53-altered disease in the adverse category on the strength of outcome data of the kind reviewed here, and validation across independent cohorts supports that placement [7,24]. What classification cannot do is change the outcome, and for this subgroup it remains the worst in the disease.

Question	What the evidence shows	Source
Does chemotherapy cause the mutation?	No; mutational spectrum matches de novo disease	Genome sequencing of 22 cases [3]
When does the clone appear?	Detectable 3-6 years before the neoplasm	Banked pre-treatment samples [3]
Can it be found before treatment?	Yes; 45% against 13.6% in those who later develop disease	Prospective PARP inhibitor cohort [17]
Does allelic state matter here?	No; single and multi-hit equally poor	488 therapy-related patients [18]
What threshold separates outcome?	Variant allele frequency of 10% or locus loss	Same cohort [18]

Table 3: The principal questions about TP53 in therapy-related disease and what the published evidence answers

Discussion

The causal story here was revised by sequencing and the revision matters clinically. If chemotherapy created these mutations, the response would be to give less of it. Because chemotherapy selects clones that already exist, the response is to find them beforehand, and that is a screening question rather than a dosing one [3,16,17].

The evidence for pre-existence is unusually direct. Detecting the identical mutation at 0.003 per cent in a sample banked six years earlier is not an inference from mutational signatures; it is the clone itself, observed before the exposure [3]. The prospective data in PARP inhibitor-treated patients extend it: pre-treatment TP53 clonal haematopoiesis was more than three times commoner in those who later developed a neoplasm [17].

Why the allelic-state rules do not transfer

Classification of de novo TP53-mutated disease depends on distinguishing monoallelic from biallelic involvement, and that distinction is well founded biologically [20]. In the therapy-related setting the distinction loses its discriminating power [18], and there are two candidate explanations that the data do not fully separate.

The first is technical. Establishing biallelic status requires loss-of-heterozygosity and copy-number data that were incomplete in a substantial proportion of cases, and most of those lacking it had complex karyotypes suggesting hidden biallelic loss [18]. On that reading, single-hit therapy-related disease is largely a measurement artefact.

The second is biological. Therapy-related disease arises in a marrow that has already been through selection, so even a monoallelic clone reaching clinical disease has demonstrated fitness that a comparable de novo clone has not. On that reading the

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equivalence is real. Distinguishing the two would require systematic copy-number analysis in a therapy-related cohort, which has not been reported [18].

Study limitations

The limitations belong to the underlying literature. The sequencing study establishing pre-existence examined 22 patients and demonstrated the mutation in banked samples from four of them, so the proportion of therapy-related disease arising this way is not established [3]. Loss-of-heterozygosity data were incomplete in the largest prognostic cohort, which directly affects the single-hit versus multi-hit comparison [18]. Therapy-related neoplasms are heterogeneous in the primary malignancy treated, the agents used and the interval to presentation, and cohorts differ in their composition [1,21]. Variant allele frequency depends on blast percentage and sample purity, so the 10 per cent threshold is not a fixed biological quantity [18]. And classification criteria changed during the period covered, so the entity being described is not constant across studies [7,8,9].

Two gaps deserve naming. No study has tested whether screening for TP53-mutant clonal haematopoiesis before cytotoxic therapy, and modifying treatment accordingly, reduces the incidence of therapy-related neoplasms [16,17]. And no trial has evaluated whether the poor outcome in therapy-related TP53-mutated disease responds differently to any available regimen than the equivalent de novo disease does [5,6].

Conclusion

TP53 mutations occur in 21 to 38 per cent of therapy-related myeloid neoplasms against 5 to 10 per cent of de novo disease, and reach 70 to 80 per cent where the karyotype is complex. They are not caused by the treatment: mutational spectra are indistinguishable from de novo disease, the burden of chemotherapy-related transversions is no higher, and the identical mutation has been detected at fractions of a per cent in blood banked three to six years before the neoplasm appeared. Cytotoxic therapy selects a pre-existing clone rather than creating it. Once present, the mutation halves survival from 14.1 to 6.1 months, and the allelic-state distinction that governs classification of de novo disease does not separate outcome here, where a variant allele frequency above 10 per cent identifies the poor-prognosis group irrespective of hit number. The actionable implication is upstream of the diagnosis rather than after it.

Two lines of work follow from that. The first is whether pre-treatment screening for TP53-mutant clonal haematopoiesis can identify patients in whom an alternative regimen would avoid the second malignancy, which is testable and has not been tested [16,17]. The second is whether the apparent equivalence of single-hit and multi-hit disease survives systematic copy-number analysis, or whether it dissolves once biallelic loss is properly ascertained [18,20].

Neither question requires a new drug. Both require applying existing assays before the point at which this disease currently comes to attention, which is after it has already formed and when almost nothing works.

Acknowledgements

The authors thank the sequencing consortia and clinical cohorts whose published analyses form the substance of this article.

Funding

No dedicated funding from public, commercial or charitable sources supported this review.

Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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