TP53 IN LYMPHOPROLIFERATIVE NEOPLASTIC DISORDERS

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TP53 disruption represents a central event driving clonal evolution, therapeutic resistance, and adverse outcome in several B-cell neoplasms, including chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), and diffuse large B-cell lymphoma (DLBCL). These diseases represent paradigmatic models to show how TP53-mutant subclones emerge, expand under treatment pressure, and differentially respond to novel therapeutic strategies.

In normal cells, TP53 regulates DNA damage responses, cell-cycle arrest, and apoptosis, acting as tumor suppressor gene. In CLL, MCL, and DLBCL, TP53 disruption may occur through point mutations, deletions of chromosome 17p, or loss of heterozygosity, often resulting in dominant-negative or gain-of-function effects. Importantly, TP53 alterations are frequently subclonal at diagnosis but confer a strong selective advantage during therapy, leading to clonal expansion and disease progression.

In CLL, TP53 abnormalities are detected in approximately 5–10% of patients at diagnosis and increase to over 30% at relapse. TP53 disruption is the strongest prognostic and predictive biomarker, anticipating failure of chemo-immunotherapy and guiding the upfront use of targeted agents. BTK inhibitors and the BCL2 inhibitor venetoclax partially overcome TP53-mediated resistance by inducing p53-independent cell death, resulting in effective clonal containment rather than eradication.

In MCL, TP53 alterations are present in 20–30% of cases and are enriched in blastoid and pleomorphic variants. TP53-mutated MCL is characterized by primary chemoresistance and adverse outcome, even with intensive regimens. BTK inhibitor–based approaches and venetoclax combinations achieve partial suppression of TP53-mutant clones but rarely induce durable disease control, supporting early consideration of cellular therapies.

In DLBCL, TP53 disruption occurs in 15–25% of cases and is strongly associated with genomic complexity, MYC cooperation, and primary refractoriness to conventional treatments. In this context, TP53 serves as a marker of chemoresistant biology and identifies patients who may benefit from early intensification strategies, including T-cell directed therapies.

Overall, TP53 alterations define an evolutionary high-risk state across B-cell neoplasms. Understanding how novel therapies differentially modulate TP53-mutant clonal dynamics is essential for biology-driven risk stratification and for the development of new therapeutic strategies.

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