Journal of Leukemia
ISSN: 2329-6917
OPEN ACCESS Freely available online
Short Communication

Therapeutic Resistance in Leukemia: Mechanisms and Strategies to Overcome

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DESCRIPTION

Therapeutic resistance remains the most formidable obstacle to improving outcomes in leukemia, representing the primary cause of treatment failure and disease relapse. Despite remarkable advances in understanding leukemia biology and the development of novel targeted therapies, the emergence of resistance continues to limit the durability of responses and the achievement of long-term remissions or cures. The mechanisms underlying therapeutic resistance in leukemia are multifaceted, involving genetic, epigenetic, microenvironmental, and pharmacological factors that operate through diverse pathways. Unraveling these mechanisms and developing strategies to overcome them represents one of the most pressing challenges in leukemia research and clinical practice [1-4].

Genetic mechanisms of resistance have been extensively characterized across leukemia subtypes. In Chronic Myeloid Leukemia (CML), point mutations in the *BCR-ABL1* kinase domain that impair drug binding represent a well-established mechanism of resistance to Tyrosine Kinase Inhibitors (TKIs). The spectrum of these mutations varies with different TKIs, reflecting their distinct binding modes and inhibitory profiles. The *T315I* "gatekeeper" mutation exemplifies this phenomenon, conferring resistance to first- and second-generation TKIs but retaining sensitivity to ponatinib. Similarly, in *FLT3*-mutated Acute Myeloid Leukemia (AML), secondary point mutations in the *FLT3* kinase domain or activation loop can emerge during treatment with *FLT3* inhibitors, reducing drug binding affinity and efficacy. The anticipation of these resistance mechanisms has informed the rational design of next-generation inhibitors with activity against common resistance mutations, exemplifying how understanding resistance can drive therapeutic innovation [5-8].

Clonal evolution represents another genetic mechanism of resistance that operates across leukemia subtypes. The selective pressure exerted by therapy may eliminate sensitive clones while allowing the expansion of pre-existing resistant subclones that harbor alternative driver mutations or activate compensatory pathways. This evolutionary process can result in disease recurrence with a genetic profile distinct from that observed at diagnosis, necessitating a different therapeutic approach. The recognition of this phenomenon has highlighted the importance of comprehensive genetic profiling at relapse to identify actionable alterations that may not have been present or detectable at diagnosis. It has also inspired therapeutic strategies aimed at addressing clonal heterogeneity through combination approaches that target multiple vulnerabilities simultaneously.

Epigenetic mechanisms contribute significantly to therapeutic resistance in leukemia, operating through alterations in DNA methylation, histone modifications, and chromatin structure that influence gene expression without changing the underlying DNA sequence. These epigenetic changes can modulate the expression of drug targets, activate alternative signaling pathways, or induce cellular states that confer resistance to specific therapeutic agents. For instance, alterations in DNA methylation patterns have been implicated in resistance to cytarabine in AML, while histone deacetylase activity has been associated with resistance to various agents across leukemia subtypes. The reversible nature of epigenetic modifications offers an opportunity for therapeutic intervention, with epigenetic modifiers such as hypomethylating agents and histone deacetylase inhibitors showing promise in overcoming certain resistance mechanisms.

The bone marrow microenvironment plays a crucial role in mediating therapeutic resistance through multiple mechanisms. Direct interactions between leukemic cells and stromal components through adhesion molecules activate pro-survival signaling pathways and confer protection against various therapeutic agents, a phenomenon known as Cell Adhesion-Mediated Drug Resistance (CAM-DR). Soluble factors secreted by stromal cells, including cytokines, chemokines, and growth factors, can similarly promote leukemic cell survival and proliferation while attenuating therapeutic sensitivity. The hypoxic nature of the bone marrow niche further contributes to resistance by altering cellular metabolism, promoting quiescence, and activating hypoxia-inducible factors that regulate numerous resistance-associated genes. Strategies to disrupt these protective microenvironmental interactions, such as *CXCR4* antagonists that mobilize leukemic cells from their protective niches, represent promising approaches to overcome this dimension of resistance [9,10].

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Received: 03-Mar-2025, Manuscript No. JLU-25-38105; **Editor assigned:** 05-Mar-2025, PreQC No. JLU-25-38105 (PQ); **Reviewed:** 18-Mar-2025, QC No. JLU-25-38105; **Revised:** 25-Mar-2025, Manuscript No. JLU-25-38105 (R); **Published:** 01-Apr-2025, DOI: 10.35248/2329-6917-25.13.434

Citation: Richter D (2025). Therapeutic Resistance in Leukemia: Mechanisms and Strategies to Overcome. J Leuk. 13:434.

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