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Review Article

Chemotherapy Resistance in Hematological Cancers: A Scoping Review of Molecular Pathways and Therapeutic Innovations

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Abstract

Chemotherapy continues to serve as a cornerstone of treatment for hematological malignancies. However, the emergence of resistance to chemotherapy significantly undermines its effectiveness and can adversely impact long-term patient survival. A comprehensive understanding of the multifactorial mechanisms driving resistance is imperative for enhancing outcomes. This scoping review synthesizes current evidence on the molecular pathways underpinning chemotherapy resistance in hematological cancers and highlights emerging therapeutic innovations aimed at overcoming these challenges. A systematic review of the extant literature was conducted, with a focus on the genetic, epigenetic, cellular, and microenvironmental mechanisms of resistance in leukemia, lymphoma, and multiple myeloma. The examination also encompassed recent advancements in targeted therapies, immunotherapies, epigenetic modulators, novel drug delivery systems, and personalized medicine. The phenomenon of resistance can be attributed to a multifaceted interplay of dynamic genetic mutations (e.g., TP53, FLT3-ITD), epigenetic dysregulation (e.g., DNA methylation, microRNA alterations), drug efflux mechanisms, cancer stem cell quiescence and metabolic reprogramming, enhanced DNA repair capacity, and tumor microenvironment-mediated protection. A range of novel therapeutic strategies have emerged, including FLT3, IDH, and BCL-2 inhibitors; CAR T-cell therapies; bispecific antibodies; and functional precision medicine approaches. These strategies hold great promise for addressing the challenges posed by drug resistance. However, they also face their own unique challenges related to resistance. Overcoming chemotherapy resistance in hematological malignancies necessitates a comprehensive, mechanism-driven approach that addresses the complex interplay of genetic, epigenetic, cellular, and microenvironmental factors. Future strategies should integrate multi-omics profiling, rationally designed combination therapies, targeted disruption of the tumor microenvironment, and adaptive precision medicine to achieve sustained remissions and improved long-term outcomes.

Keywords: *Chemotherapy Resistance, Hematological Malignancies, Cancer Stem Cells, Targeted Therapy, Tumor Microenvironment.*

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Introduction

Overview of Hematological Cancers (Leukemia, Lymphoma, Multiple Myeloma)

Hematological malignancies are a diverse group of cancers originating from hematopoietic or lymphoid tissues, impacting the blood, bone marrow, and lymphatic system. These include acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL); lymphomas such as diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and mantle cell lymphoma (MCL); and plasma cell disorders like multiple myeloma (MM), each with distinct clinical and molecular features (Bogdanovic et al., 2025). Each of these malignancies exhibits distinct genetic, molecular, and clinical characteristics, necessitating precise diagnostic and therapeutic strategies.1 The World Health Organization (WHO) classification system, particularly its 5th edition (2022), integrates comprehensive cytogenetic and molecular genetic information to provide a precise categorization for these diseases (HemOnc.Org - A Hematology Oncology Wiki, n.d.).

Role of Chemotherapy in Treatment

Conventional chemotherapy continues to serve as a fundamental component in the management of numerous hematological malignancies. It is frequently employed in conjunction with other modalities, including radiation therapy, hematopoietic stem cell transplantation, and, more recently, targeted therapies (Bogdanovic et al., 2025). The treatment approach generally consists of two primary phases: an induction phase aimed at achieving remission, followed by a post-remission consolidation or intensification phase designed to reduce the risk of relapse (PDQ Pediatric Treatment Editorial Board, 2002). For instance, the standard first-line treatment for AML has historically relied on regimens combining daunorubicin or idarubicin with cytosine arabinoside (Gourzones et al., 2019).

Significance and Impact of Chemotherapy Resistance

Despite the initial effectiveness and foundational role of chemotherapy, the emergence of chemotherapy resistance poses a formidable challenge in the management of hematological cancers. This resistance is a primary driver of high relapse rates and significantly limits the long-term efficacy of treatment, ultimately impacting patient survival (Gourzones et al., 2019). For instance, approximately two-thirds of AML patients who achieve complete remission after initial chemotherapy experience a relapse within 18 months, largely due to drug resistance (Pinto et al., 2020). This phenomenon can manifest in two distinct ways: intrinsic resistance, wherein cancer cells are inherently insensitive to drugs before exposure, or acquired resistance, which develops after an initial response to therapy (PDQ Pediatric Treatment Editorial Board, 2002). The multifaceted nature of drug resistance is a significant factor in cancer-related mortality, accounting for up to 90% of deaths in certain cancer types (PDQ Adult Treatment Editorial Board, 2002).

While several reviews have examined chemotherapy resistance in hematological malignancies, this scoping review uniquely integrates molecular, cellular, and microenvironmental mechanisms with a detailed analysis of emerging therapeutic innovations, including targeted agents, immunotherapies, and novel delivery systems. The objective of this study is to provide a mechanism-to-therapy framework that can guide both research prioritization and clinical decision-making by synthesizing recent advances across these domains.

Methods

A comprehensive literature search was conducted in PubMed, Scopus, and Web of Science for studies published between January 2013 and May 2025. The search was conducted using predefined search strings that combined terms related to "chemotherapy resistance," "hematological malignancies," and specific cancer types (e.g., AML, lymphoma, MM). The inclusion criteria for the present study encompassed peer-reviewed original research and reviews that reported on the molecular, cellular, or therapeutic aspects of chemotherapy resistance. The exclusion criteria encompassed non-English articles, conference abstracts, and studies with a exclusive focus on solid tumors. Two reviewers independently evaluated titles and abstracts, documented the data in a standardized extraction form, and resolved discrepancies through consensus.

Molecular Pathways of Chemotherapy Resistance

Genetic and Epigenetic Alterations

Gene Mutations and Clonal Heterogeneity

The phenomenon of chemotherapeutic resistance in cancerous cells is significantly influenced by the dynamic clonal evolution of these cells. In this process, early mutations are present across most cancer cells (clonal), while later mutations are confined to subpopulations (subclonal). As Ngu et al. (2022) have demonstrated, relapses frequently occur when chemotherapy fails to eliminate dominant or rare pre-existing resistant subclones. Chemotherapy itself has been shown to act as a selective pressure, driving the expansion of these resistant clones (Ngu et al., 2022).

In the context of Acute Myeloid Leukemia (AML), specific gene mutations have been demonstrated to be significantly associated with resistance. TP53 mutations, for instance, are recognized as poor prognostic markers. These alterations disrupt the DNA damage repair and apoptosis pathways, thereby accelerating the generation and expansion of resistant clones through enhanced genomic instability (Cao et al., 2025). Furthermore, the presence of RAS mutations has been observed to be selected by chemotherapy, particularly in elderly AML patients, contributing to unfavorable outcomes (J. Zhang et al., 2019). FLT3-ITD (FMS-like tyrosine kinase 3-internal tandem duplication) mutations have been identified as critical drivers of disease progression and resistance, often persisting at relapse with an increased allele burden (J. Zhang et al., 2019). Other significant contributors to chemotherapy resistance include KMT2A rearrangements, IDH1/2 mutations (which lead to epigenetic dysregulation), DNMT3A mutations (causing aberrant methylation patterns and transformation into chemotherapy-resistant leukemia stem cells), and ASXL1 mutations (disrupting epigenetic regulation and sustaining undifferentiated leukemia stem cells) (J. Zhang et al., 2019).

In Lymphoma, ongoing somatic hypermutation processes facilitate the acquisition of additional genetic lesions, thereby promoting resistance (Cao et al., 2025). The presence of mutated oncogenes, such as EZH2, CREBBP, MYD88, CD79B, NOTCH1, BCL6, PIM1, and BCL2, in conjunction with chromosomal translocations, including t(14;18) (which juxtaposes BCL2 to the immunoglobulin heavy chain locus, IGHV), has been identified as a contributing factor to the development of aggressive phenotypes and drug resistance (Klener & Klanova, 2020). Furthermore, the inactivation of tumor suppressor genes, including TP53, ATM, CDKN2A, and KMT2D, has been demonstrated to lead to genomic instability, which in turn drives lymphoma evolution and resistance (Klener & Klanova, 2020).

Multiple Myeloma (MM) cells are distinguished by significant genomic abnormalities, including chromosomal instability, various mutations, and microsatellite instability, as well as IgH translocations. These abnormalities accumulate throughout the course of the disease and are central to the development of drug resistance (Gourzones et al., 2019). The activation of oncogenes such as cyclins, FGFR3, and MYC also plays a significant role in MM resistance (Pinto et al., 2020).

MicroRNA (miRNA) Dysregulation

MicroRNAs (miRNAs) are a class of small non-coding RNAs that play a crucial role in regulating gene expression. These molecules influence a variety of processes, including cell division, self-renewal, invasion, and DNA damage response (J. Zhang et al., 2019). Alterations in the expression of microRNAs (miRNAs) have been demonstrated to exert a substantial influence on the upregulation of drug resistance, a process that is facilitated by the impact on DNA damage repair mechanisms. For instance, the over-expression of microRNA-181a in AML cells has been demonstrated to downregulate Ataxia Telangiectasia Mutated (ATM), a DNA damage response protein, resulting in unrepaired DNA damage and drug resistance. In a similar manner, the expression of microRNA-182 has been observed to result in a decrease in Rad51 protein levels, thereby increasing residual DNA damage and reducing cell survival following exposure to DNA-damaging agents (J. Zhang et al., 2019). Furthermore, the function of microRNAs in causing cell cycle arrest has been demonstrated, as evidenced by the study of microRNA-638, which has been shown to inhibit cyclin-dependent kinases (CDK), and their role in the suppression of apoptosis, as illustrated by the observation that low levels of microRNA-181a have been found to downregulate Bcl-2 (J. Zhang et al., 2019). In the context of MM, aberrant expression patterns of miRNAs have been observed during the progression of the disease, with these patterns contributing to resistance (Pinto et al., 2020).

Epigenetic Modifications (DNA Methylation, Histone Modifications)

Aberrant epigenetic changes, which refer to heritable modifications to gene function without altering the DNA sequence itself, have been identified as critical contributors to cancer progression and drug resistance. These include DNA methylation, characterized by both hypermethylation of tumor suppressor gene promoters and global hypomethylation, and histone modifications, particularly an imbalance in acetylation and deacetylation (Eslami et al., 2024). Non-coding RNAs (ncRNAs), including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), have also been identified as pivotal epigenetic regulators, impacting chromatin structure and gene expression (Eslami et al., 2024).

In Multiple Myeloma (MM), hypomethylation of DNA and hypermethylation of tumor suppressor genes result in aberrant gene expression, including the upregulation of ABCG2, which enhances drug efflux (Pinto et al., 2020). Abnormal microRNA expression, such as the upregulation of miR-21 or the downregulation of miR-15a and miR-16, has been shown to further disrupt pathways involved in the pathogenesis and drug resistance of multiple myeloma (Pinto et al., 2020). In lymphomas, epigenetic modifications have been shown to cause alterations in chromatin and DNA methylation, thereby promoting

oncogenesis, metastasis, angiogenesis, and drug resistance (Klener & Klanova, 2020).

The intricate relationship between genetic mutations and epigenetic modifications creates a robust resistance phenotype. Genetic mutations, including TP53 deletion, have been demonstrated to exert a direct influence on epigenetic regulators. This influence can be illustrated by the stabilization of BCL2 through the modulation of microRNAs, as reported by Klener and Klanova (2020). In contrast, epigenetic changes, including DNA methylation, have been shown to modify gene expression, resulting in the increased expression of drug efflux pumps (Pinto et al., 2020). This finding suggests the presence of a complex, bidirectional regulatory network in which genetic and epigenetic alterations are not isolated events but rather mutually reinforcing, contributing to a more entrenched resistance. Given the mutual reinforcement between these factors, it is imperative to implement effective strategies that target both genetic mutations and their epigenetic consequences concurrently. This approach is crucial to preemptively halting compensatory resistance pathways.

Altered Drug Transport and Metabolism

Drug Efflux Pumps (ABC Transporters: P-glycoprotein, MRP1, BCRP)

The active extrusion of anticancer drugs by members of the ATP-binding cassette (ABC) transporter family is one of the most widely recognized mechanisms contributing to multidrug resistance (MDR) (Pinto et al., 2020). These transporters, including P-glycoprotein (P-gp, also known as MDR1 or ABCB1), Multidrug Resistance-associated Protein 1 (MRP1 or ABCC1), and Breast Cancer Resistance Protein (BCRP or ABCG2), actively pump a wide range of chemotherapeutic agents out of cancer cells. This action has been demonstrated to reduce intracellular drug concentrations, thereby limiting therapeutic efficacy (Pinto et al., 2020).

The presence of P-gp overexpressions has been demonstrated to be significantly associated with adverse outcomes in patients diagnosed with AML, including elevated white blood cell counts, the presence of chromosomal abnormalities, and a reduced overall survival rate (J. Zhang et al., 2019). Its expression is frequently linked to the activation of critical signaling pathways, such as NF-κB and PI3K/AKT/mTOR (J. Zhang et al., 2019). Furthermore, Lung Resistance Protein (LRP) has been shown to contribute to drug resistance by either blocking nuclear pores or facilitating the transport of drugs via exocytosis (J. Zhang et al., 2019). In multiple myeloma (MM), P-gp overexpression has been observed in resistant cells and is increased after treatment with drugs like vincristine and doxorubicin, predicting MDR and relapse (Pinto et al., 2020).

Drug Inactivation and Detoxification

Enzymes such as Glutathione S-transferases (GSTs), particularly GSTπ, are highly expressed in AML cells and contribute to drug resistance. These enzymes facilitate the detoxification of reactive electrophiles and cytotoxic therapeutic agents by binding them to glutathione, thereby reducing their cytotoxic effects (J. Zhang et al., 2019). In AML, increased expression of UDP-glucuronosyltransferase 1 A (UGT1A) and GLI1 has been observed to induce glucuronidation, a process that results in the inactivation and subsequent elimination of drugs from the body (Talib et al., 2021). Conversely, a reduction in the levels of equilibrative nucleoside transporter 1 (ENT1), which facilitates drug entry into cells, can also lead to resistance (Talib et al., 2021).

The data suggest that cancer cells utilize not only a single, discrete strategy, but rather multiple interconnected mechanisms to restrict intracellular drug concentrations. This includes active efflux via ABC transporters that pump drugs out (J. Zhang et al., 2019), mechanisms that prevent drug entry, such as reduced ENT1 levels (Emran et al., 2022), and enzymatic inactivation processes mediated by enzymes like GSTs and UGT1A (Niu et al., 2022). This multi-layered approach suggests a redundant and highly adaptive system for drug evasion, where if one mechanism is inhibited, others may compensate. Consequently, the successful overcoming of this resistance necessitates a multifaceted approach, which must address diverse aspects of drug transport and metabolism. The efficacy of a single efflux pump inhibitor may be limited if other mechanisms can compensate. Future therapeutic interventions may necessitate the combination of efflux pump inhibitors with strategies designed to enhance drug uptake or inhibit detoxification enzymes to achieve more comprehensive and durable responses.

Leukemia/Cancer Stem Cells (LSCs/CSCs)

Leukemia Stem Cells (LSCs) and cancer stem cells (CSCs) represent a small, distinct population within the tumor that possesses unique properties, including self-renewal capabilities, quiescent cell cycle characteristics, and intrinsic drug resistance. These characteristics render them a significant contributor to the occurrence of relapse and treatment failure in hematological malignancies (Pinto et al., 2020). These cells have demonstrated a high degree of resilience, capable of surviving conventional chemotherapy regimens that effectively eliminate the majority of tumor cells. However, subsequent repopulation of the malignancy by these cells often results in disease recurrence (Cao et al., 2025).

Quiescence and Self-Renewal Properties

LSCs and CSCs frequently exist in a quiescent or non-proliferative (G0) state. This dormancy confers a substantial protective benefit against cell cycle-specific chemotherapeutic agents, which predominantly target rapidly dividing cells (Pinto et al., 2020).

Drug Efflux Capacity in LSCs/CSCs

A critical mechanism of resistance in LSCs and CSCs is their augmented capacity for drug efflux. It has been observed that these cells frequently overexpress various ABC transporters, including ABCB1, ABCA3, and ABCG2. This enables them to rapidly expel chemotherapeutic agents from within the cell. This active expulsion mechanism has been demonstrated to contribute significantly to their intrinsic drug resistance (Pinto et al., 2020).

Metabolic Reprogramming in LSCs/CSCs

LSCs and CSCs manifest disparate metabolic profiles that contribute to their drug resistance. In contrast to mature, glycolysis-dependent AML blasts, quiescent LSCs frequently depend on mitochondrial oxidative phosphorylation (OXPHOS) and maintain low levels of reactive oxygen species (ROS), which enhance their resistance to chemotherapy (Cao et al., 2025). At the time of relapse, LSCs may undergo further metabolic shifts, such as transitioning to fatty acid metabolism to compensate for OXPHOS and meet their energy demands (Cao et al., 2025). In multiple myeloma (MM), cancer stem cells (CSCs) exhibit elevated activity in oxidative phosphorylation (OXPHOS), the serine synthesis pathway (SSP), and the tricarboxylic acid (TCA) cycle (Pathak et al., 2023). In a similar manner, lymphoma cells are distinguished by their elevated glucose uptake, deregulated glycolysis, and increased glutamine and fatty acid synthesis. These characteristics contribute to their survival and resistance (Pathak et al., 2023).

The consistent identification of LSCs and CSCs as primary drivers of relapse highlights their critical role in chemotherapy resistance. Their inherent resistance mechanisms, such as quiescence and drug efflux, coupled with their ability to repopulate the tumor, highlight their critical contribution to treatment failure (Cao et al., 2025). The concept of "primary" and "secondary" resistance mechanisms in acute myeloid leukemia (AML), wherein LSCs can intrinsically resist or reacquire stemness under therapeutic pressure (Niu et al., 2022), further illustrates their dynamic and adaptive nature. Their metabolic adaptability — shifting from glycolysis to OXPHOS or fatty acid metabolism (Cao et al., 2025) indicates that their resistance phenotype is not static. Thus, achieving effective long-term remission requires eliminating not just the bulk tumor but also specifically targeting and eradicating these LSCs and CSCs. Targeting LSCs/CSCs requires therapies that disrupt dormancy and exploit metabolic vulnerabilities because these cells evade conventional cytotoxic regimens. Metabolic dependencies, such as OXPHOS reliance, have been identified in resistant stem cell populations; however, the strength of clinical evidence remains limited, as most studies are small-scale or exploratory. Future studies should prioritize longitudinal metabolic profiling in patient cohorts to validate these targets and determine their therapeutic exploitability.

Evasion of Apoptosis and Cell Death

Intrinsic or acquired resistance to apoptosis (programmed cell death) is a hallmark of human cancers and a major cause of treatment resistance (Pinto et al., 2020). This is significant because most current anticancer therapies function by activating cell death pathways, including apoptosis, in cancer cells (Castro-Muñoz et al., 2023).

Dysregulation of Apoptotic Pathways (Bcl-2 Family, NF-κB)

The Bcl-2 family of proteins includes both pro-apoptotic members, such as BAX and BAK, and anti-apoptotic members, including Bcl-2, Bcl-xL, and Mcl-1. These proteins are key regulators of the intrinsic apoptotic pathway. Overexpression of anti-apoptotic Bcl-2 proteins is often seen in hematologic malignancies and contributes directly to both chemotherapy and radioresistance (Pinto et al., 2020).

The nuclear factor kappa B (NF-κB) pathway also plays a crucial role by mediating the expression of multiple genes involved in cell proliferation and anti-apoptosis. Constitutive activation of NF-κB is common in multiple myeloma (MM), and drug-sensitive MM cells typically exhibit lower NF-κB activity than their resistant counterparts (Pinto et al., 2020). Additionally, the PI3K/AKT signaling pathway is a critical pro-survival pathway that promotes cell growth, proliferation, and invasion while inhibiting apoptosis. This makes it a significant target for antitumor drugs (Pinto et al., 2020).

Autophagy Activation

Autophagy is a cellular process involving self-phagocytosis and the recycling of cellular components that can be induced by chemotherapeutic drugs. It is a significant factor in tumor cells developing drug resistance (Pinto et al., 2020). Autophagy can contribute directly to drug resistance by reducing intracellular drug concentrations and preventing apoptosis via a protective mechanism (J. Zhang et al., 2019). For instance, hypoxia-induced autophagy has been demonstrated to decrease chemosensitivity in T-cell lymphomas (Klener & Klanova, 2020).

Evasion of apoptosis is achieved through a complex interplay of dysregulated pro-survival pathways and adaptive cellular processes, not a single mechanism. Simultaneous activation of multiple anti-apoptotic pathways—such as overexpression of Bcl-2 family proteins, constitutive activation of NF-κB, and PI3K/AKT signaling dysregulation—combined with protective autophagy activation suggests cancer cells have multiple "escape routes" from drug-induced death. This indicates that therapies targeting apoptosis must consider this redundancy and the potential for compensatory mechanisms. Consequently, single-agent pro-apoptotic drugs might be insufficient if multiple anti-apoptotic pathways are active or if autophagy provides a survival advantage. Combination therapies that simultaneously inhibit multiple pro-survival pathways or block protective autophagy are likely to be more effective in overcoming this fundamental hallmark of drug resistance.

Enhanced DNA Damage Response and Repair

Chemotherapeutic drugs often induce DNA damage, particularly double-strand breaks (DSBs), to trigger cell death (Denizot et al., 2022). Resistance to these agents can occur through mechanisms that suppress the accumulation of DSBs or enhance their repair (Talib et al., 2021). Cancer cells often have alterations in their DNA repair pathways, which contribute to their genomic instability and subsequent resistance (Fletcher et al., 2016).

DNA Repair Pathways (HR, NHEJ, NER, BER, MMR)

The two main pathways for repairing DNA double-strand breaks (DSBs) are homologous recombination (HR) and nonhomologous end joining (NHEJ) (Fletcher et al., 2016). Defects in HR, such as BRCA1/2 mutations, initially sensitize cancers to DNA-damaging agents. However, the reactivation of HR repair is a major mechanism of acquired resistance (Álvarez-Carrasco et al., 2025). Elevated NHEJ activity and the overexpression of its components also contribute to chemoresistance. Nucleotide excision repair (NER) is crucial for resolving cisplatin-induced intrastrand DNA crosslinks, and NER inactivation can increase drug sensitivity (Niu et al., 2022). Base excision repair (BER) and mismatch repair (MMR) also play roles in the DNA damage response. Loss of MMR can sometimes drive resistance (Mazewski & Platanias, 2023).

Replication Stress Tolerance Mechanisms

Many chemotherapeutic agents interfere with DNA replication. To counteract this, cancer cells activate various replication stress response mechanisms, such as translesion synthesis (TLS), template switching (TS), fork reversal, and repriming. These mechanisms enable cells to repair DNA lesions and prevent the formation of lethal double-strand breaks (DSBs), thereby contributing to drug resistance (Choi et al., 2024).

Specific to Hematological Cancers

In Chronic Lymphocytic Leukemia (CLL), the ability of CLL cells to efficiently repair alkylator-induced DNA damage explains their poor response to certain chemotherapies (Phi et al., 2018). Mutations in genes such as TP53, ATM, CHEK1/2, POT1, BRCA1, and CHD2 have been identified. The ATM-Chk2-p53 signaling axis plays a critical role in the apoptotic response to DNA damage (Jung & McCarty, 2010). ATM mutant cells, in particular, exhibit impaired DSB repair (Roszkowska, 2024).

In Lymphoma, Hodgkin and Reed-Sternberg (HRS) cells in classical Hodgkin lymphoma (cHL) exhibit genetic instability and an abnormal DNA damage response and repair process (Solimando et al., 2022). Studies have shown that inhibiting DNA repair mechanisms using small molecules (e.g., ATR, CHK1, and Wee1 inhibitors) can induce apoptosis and inhibit proliferation in cHL cell lines (X. Chen et al., 2020). In non-Hodgkin lymphoma (NHL), an increase in DNA repair machinery can decrease drug efficacy. Aberrations in TP53, ATM, and CDKN2A are linked to resistance (Matamala Montoya et al., 2023).

Despite their slow proliferation rate, Multiple Myeloma (MM) cells exhibit extensive genomic rearrangements and intense genomic instability. They depend on robust DNA repair mechanisms to survive damage induced by chemotherapy (Matamala Montoya et al., 2023). Although mutations in DNA damage response (DDR) genes, such as ATM and ATR, are uncommon in MM, oncogenes like MYC and RAS can induce intense replicative stress, underscoring the significance of DNA damage in MM pathogenesis (Matamala Montoya et al., 2023).

The data reveal a paradox: cancer cells exhibit genomic instability yet rely on robust DNA repair mechanisms to survive damage caused by chemotherapy (Yu et al., 2022). This indicates that DNA repair is essential for cancer cell survival and represents a vulnerability that can be exploited therapeutically. This concept is known as "synthetic lethality," which occurs when inhibiting a specific repair pathway in cells already deficient in another pathway leads to selective cell death (J. Li et al., 2025). Thus, targeting DNA repair pathways is a promising therapeutic strategy. By inhibiting specific repair mechanisms, especially those that compensate for existing defects or are upregulated in resistant cells, clinicians can push cancer cells beyond their "tolerance limit" for DNA damage. This makes them more susceptible to conventional chemotherapy or induces

cell death directly. This also underscores the importance of identifying specific DNA repair deficiencies in individual tumors to guide personalized treatment strategies. These molecular alterations often act in concert with extrinsic factors, such as the tumor microenvironment. For instance, TP53 or ATM mutations can disrupt DNA repair and modulate stromal signaling, thereby reinforcing resistance phenotypes.

Tumor Microenvironment (TME) and Stromal Support

The tumor microenvironment (TME) is a complex, dynamic ecosystem consisting of cancer cells and various stromal cells, such as fibroblasts, mesenchymal stem cells, endothelial cells, and immune cells. It also includes the extracellular matrix (ECM) and soluble factors, including cytokines and growth factors (Hsiao et al., 2025). The TME is not a passive bystander; it actively promotes tumor growth, survival, and drug resistance. It provides a "safe haven" for cancer cells, especially leukemia/cancer stem cells (LSCs/CSCs) (Cao et al., 2025). Much of the evidence on stromal-mediated resistance in hematological malignancies comes from preclinical or in vitro co-culture models, which may not fully replicate the complexity of patient tumors. Translating these findings into clinical practice will require well-designed trials that quantify the extent to which TME-targeting strategies improve patient outcomes.

Cell Adhesion-Mediated Drug Resistance (CAM-DR)

Direct interactions between tumor cells and stromal cells or the extracellular matrix (ECM) significantly contribute to drug resistance (Pang et al., 2023). In multiple myeloma (MM), MM cells adhere to the ECM and bone marrow stromal cells (BMSCs) via adhesion molecules, including VLA-4, LFA-1, ICAM1, and VCAM1. This adhesion can induce MM cells to produce cell cycle inhibitors, anti-apoptotic proteins (including members of the Bcl-2 family), and ABC drug transporters, thereby promoting drug resistance (Pinto et al., 2020). In acute lymphoblastic leukemia (ALL), culturing ALL cells with mesenchymal stem cells (MSCs) induces hERG1 channel expression on lymphoblast plasma membranes. This activates prosurvival signaling pathways, leading to drug resistance (Yu et al., 2022). Similarly, mantle cell lymphoma-initiating cells (MCL-ICs) exhibit resistance largely due to their quiescent properties and enriched ABC drug transporters (Jung & McCarty, 2010).

Soluble Factor-Mediated Drug Resistance (SFM-DR)

Cytokines and growth factors, such as interleukin-6 (IL-6), insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), tumor necrosis factor-alpha (TNF-α), stromal cell-derived factor-1 alpha (SDF-1α), and hepatocyte growth factor (HGF), are secreted within the tumor microenvironment (TME). These factors provide crucial survival and proliferative signals to tumor cells (Pinto et al., 2020). For instance, IL-6 is known to activate the JAK/STAT3 and PI3K/AKT pathways, which are central to cell survival. AML cells can actively reprogram mesenchymal stromal cells (MSCs) within their niche to increase the expression of IL-6, CCL2, and VCAM-1, further promoting AML cell survival and chemoresistance (Cao et al., 2025). In lymphoma, IL-6 has been associated with acquired resistance to PI3K inhibitors (Klener & Klanova, 2020).

Role of Specific Stromal Cells (MSCs, Osteoclasts, Fibroblasts)

Mesenchymal stem cells (MSCs) play a critical role in protecting leukemia cells from drug-induced apoptosis and supporting leukemia stem cell (LSC) survival. This is partly achieved by increasing oxidative phosphorylation (OXPHOS) and the tricarboxylic acid (TCA) cycle in these cells (Cao et al., 2025). Myeloma-specific inflammatory MSCs create an environment that fosters tumor cell proliferation and recruits and modulates immune cells (Solimando et al., 2022).

In multiple myeloma (MM), osteoclasts and osteoblasts are key components of the bone marrow microenvironment. MM induces bone lysis; in turn, osteoclasts secrete factors that support MM cell survival and progression (Pinto et al., 2020). Concurrently, MM cells inhibit osteoblasts, further contributing to bone disease and creating a vicious cycle that enhances resistance (Solimando et al., 2022).

Cancer-associated fibroblasts (CAFs) secrete pro-tumorigenic factors, contribute to fibrosis within the tumor microenvironment (TME) (which can impede drug penetration), and can transfer exosomes containing microRNAs (miRNAs) that promote chemoresistance and metastasis (Fulda, 2010).

Various immune cells within the TME, such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), contribute to an immunosuppressive environment. This suppresses anti-tumor immune responses and actively promotes drug resistance (Klener & Klanova, 2020).

Hypoxia and its Influence on Resistance

Hypoxia, or insufficient oxygen supply, is a common feature of rapidly growing tumors. This low-oxygen environment promotes a more aggressive phenotype and enhances chemoresistance (Klener & Klanova, 2020). Hypoxia-inducible factor 1 alpha (HIF-1α) is a crucial mediator of tumor cell response to therapy under hypoxic conditions. HIF-1α can upregulate ABC transporters, increasing drug efflux; reduce DNA damage in cancer cells; accommodate

cancer stem cells; and promote immunosuppression (Emran et al., 2022). HIF-1α also maintains quiescence in LSCs (Choi et al., 2024) and leads to acidosis within the TME. This acidosis inhibits host immune functions and reduces the activity of several chemotherapeutic agents (Klener & Klanova, 2020). Furthermore, hypoxia can induce autophagy, contributing to multidrug resistance.

Exosomes

Exosomes are small vesicles secreted by cells that facilitate intercellular communication within the tumor microenvironment (TME). They transport molecules such as growth factors, cytokines, and microRNAs (miRNAs), which promote tumorigenesis and contribute to drug resistance (Emran et al., 2022).

The TME is an active, dynamic entity that profoundly influences drug resistance through a complex interplay of physical barriers, chemical signals, and cellular interactions (Wei & Konopleva, 2023). The dense extracellular matrix and chaotic vasculature can create physical impediments to drug penetration (Emran et al., 2022). Soluble factors and direct cell-to-cell contact provide pro-survival signals that counteract drug efficacy. TME can also induce metabolic changes in cancer cells that favor resistance and protect LSCs/CSCs from therapeutic agents (Solimando et al., 2022; Cao et al., 2025). This complex microenvironment fosters survival and resistance, indicating that disrupting stromal support and immune suppression is essential for durable responses.

Table 1. Key Molecular Pathways Contributing to Chemotherapy Resistance in Hematological Cancers

Mechanism Category	Specific Pathway/Factor	Key Effect on Resistance	Relevant Cancer Types (Examples)
Genetic Alterations	TP53 mutations	Disrupts DNA damage repair and apoptosis; accelerates resistant clone generation	AML, Lymphoma, MM
Genetic Alterations	FLT3-ITD mutations	Drives progression and resistance; persists at relapse	AML
Genetic Alterations	BCL2 overexpression	Prevents programmed cell death (apoptosis)	Lymphoma, MM
Epigenetic Alterations	DNA Methylation (e.g., promoter hypermethylation)	Silences tumor suppressor genes; alters gene expression leading to drug efflux	AML, Lymphoma, MM
Epigenetic Alterations	miRNA dysregulation	Affects DNA repair, cell cycle, and apoptosis	AML, MM
Altered Drug Transport	P-glycoprotein (P-gp) overexpression	Actively expels drugs from cell; reduces intracellular drug concentration	AML, ALL, Lymphoma, MM
Altered Drug Transport	Glutathione S-transferases (GSTs)	Detoxifies/inactivates chemotherapeutic agents	AML
Cancer Stem Cells	LSC/CSC Quiescence	Evades cell cycle-specific chemotherapeutic agents	AML, ALL, Lymphoma, MM
Cancer Stem Cells	LSC/CSC Drug Efflux (ABC transporters)	Rapidly expels chemotherapeutic agents from cell	AML, ALL, Lymphoma, MM
Cancer Stem Cells	LSC/CSC Metabolic Reprogramming (e.g., OXPHOS reliance)	Provides energy and survival advantage; alters drug sensitivity	AML, Lymphoma, MM
Evasion of Apoptosis	Bcl-2 Family Overexpression (e.g., Bcl-2, Bcl-xL, Mcl-1)	Prevents programmed cell death; promotes cell survival	ALL, Lymphoma, MM
Evasion of Apoptosis	NF-κB pathway activation	Mediates cell proliferation and anti-apoptosis	AML, MM
Evasion of Apoptosis	Autophagy activation	Reduces drug concentration; prevents apoptosis (protective autophagy)	AML, Lymphoma, MM
Enhanced DNA Damage Response	Homologous Recombination (HR) Repair	Efficiently repairs double-strand DNA breaks (DSBs)	MM, Lymphoma
Enhanced DNA Damage Response	Nonhomologous End Joining (NHEJ)	Efficiently ligates broken DNA ends; contributes to chemoresistance	MM, Lymphoma
Enhanced DNA Damage Response	Replication Stress Tolerance (e.g., TLS)	Resolves DNA lesions; avoids DSB generation	General Cancer, Lymphoma
Tumor Microenvironment	Cell Adhesion-Mediated Drug Resistance (CAM-DR)	Induces pro-survival signals and drug efflux pumps via cell-cell/ECM contact	ALL, Lymphoma, MM
Tumor Microenvironment	Soluble Factor-Mediated Drug Resistance (SFM-DR)	Provides survival/proliferative signals (e.g., IL-6, IGF-1)	AML, Lymphoma, MM
Tumor Microenvironment	Hypoxia (HIF-1α upregulation)	Upregulates ABC transporters; promotes immunosuppression; induces autophagy	General Cancer, AML, MM, Lymphoma
Tumor Microenvironment	Immunosuppressive Cells (e.g., MDSCs, Tregs)	Suppresses anti-tumor immune responses; protects cancer cells	MM, Lymphoma

Therapeutic Innovations to Overcome Resistance

Targeted Therapies

Targeted therapies are a significant advancement in cancer treatment. They aim to selectively inhibit the oncogenic drivers and survival pathways that are critical to hematological malignancies, while minimizing toxicity to normal cells (Qian et al., 2022).

FLT3 Inhibitors

FLT3 mutations, including internal tandem duplications (ITDs) and tyrosine kinase domain (TK) mutations, are prevalent in about 30% of acute myeloid leukemia (AML) patients and are important therapeutic targets (Fowler-Shorten et al., 2024).

Midostaurin, a first-generation FLT3 inhibitor, is approved for treating newly diagnosed FLT3-mutated (FLT3m) AML in combination with standard chemotherapy. The pivotal RATIFY trial demonstrated a significant improvement in overall survival (OS): the median OS was 74.7 months in the midostaurin group and 25.6 months in the placebo group (Pillozzi et al., 2011).

Gilteritinib, a second-generation FLT3 inhibitor, is approved for treating relapsed or refractory FLT3-mutated acute myeloid leukemia (AML). The ADMIRAL trial demonstrated its superiority, showing a median overall survival (OS) of 9.3 months compared to 5.6 months with salvage chemotherapy (Mandal, n.d.). Second-generation FLT3 inhibitors generally demonstrate significant improvement in overall survival (OS), with a hazard ratio of 0.717 compared to control groups (Nesic et al., 2025).

Quizartinib, another second-generation FLT3 inhibitor, is approved for R/R FLT3-ITD AML and improves OS to 6.2 months versus 4.7 months in the QuANTUM-R trial (Mandal, n.d.). Quizartinib is also approved for treating newly diagnosed FLT3-ITD AML when used with chemotherapy. In the QuANTUM-First trial, median OS was 31.9 months with quizartinib versus 15.1 months with chemotherapy alone (Fojo, 2001).

Crenolanib, an investigational FLT3 inhibitor, has received FDA fast track designation for R/R FLT3m AML. A phase II trial combining crenolanib with intensive chemotherapy in patients with newly diagnosed AML demonstrated high overall response rates (86%) and complete remission rates (77%) (Devin et al., 2020).

Despite these successes, challenges persist. Resistance to FLT3 inhibitors can develop through mechanisms such as point mutations in FLT3-ITD (J. Zhang et al., 2019). Second-generation inhibitors are associated with safety concerns, including QTc prolongation (a frequent adverse event with an odds ratio of 6.311), anemia, and potential myelosuppression (Kiss et al., 2021).

IDH Inhibitors

Isocitrate dehydrogenase (IDH) inhibitors target mutant IDH1/2 in acute myeloid leukemia (AML) (Cao et al., 2025). Ivosidenib and enasidenib, which target mutant IDH1 and IDH2, respectively, are FDA-approved for treating relapsed/refractory (R/R) AML (L. Li et al., 2021). These inhibitors show promise for treating R/R AML, with reported complete remission and overall response rates of 21% and 40%, respectively (L. Li et al., 2021). However, they may not be optimal for newly diagnosed AML patients due to lower complete remission rates (47%) (X. Chen et al., 2023).

A significant challenge is the emergence of drug resistance, which leads to low response rates and relapse after short-term remission (Lee et al., 2022). Secondary resistance mechanisms include clonal evolution and selection, isoform switching (where the tumor restores 2-HG production by switching IDH isoforms), enhanced mitochondrial metabolism, activation of RTK pathway mutations (NRAS, PTPN11, SRSF2, and ASXL1), and development of secondary IDH mutations (J. Chen et al., 2024).

BCL-2 Inhibitors

BCL-2 inhibitors target anti-apoptotic Bcl-2 family proteins, which are often overexpressed in hematological malignancies and contribute to their survival and resistance (Choi et al., 2024). Venetoclax is a notable breakthrough that has been successfully used to treat drug-resistant chronic lymphocytic leukemia (CLL) by inducing the intrinsic apoptotic cascade independently of TP53 expression (Fowler-Shorten et al., 2024). Venetoclax has also demonstrated efficacy in acute myeloid leukemia (AML) and small lymphocytic lymphoma and activity in multiple myeloma (MM), particularly in cases with the t(11;14) translocation (Solimando et al., 2022). However, challenges with Bcl-2 inhibitors include the development of drug resistance, disease relapse, the risk of tumor lysis syndrome, and cytopenias (Fowler-Shorten et al., 2024). The efficacy of BCL-2 inhibitors as single agents in treating solid tumors has been limited (Ma et al., 2025).

Proteasome Inhibitors

Proteasome inhibitors (PIs) target the ubiquitin-proteasome pathway, which plays an essential role in degrading regulatory proteins involved in cell-cycle progression, apoptosis, and DNA repair. Disrupting this pathway results in growth arrest and apoptosis in cancer cells (Pinto et al., 2020).

Bortezomib, the first PI to be developed, has significantly improved survival rates for patients with multiple myeloma (MM) and is now predominantly used in combination regimens and as maintenance therapy (Pinto et al., 2020). Second-generation PIs, such as carfilzomib and ixazomib, were developed to overcome bortezomib resistance. These PIs demonstrate potent inhibition and activity, even in bortezomib-resistant MM cell lines (Pinto et al., 2020). However, resistance to PIs can arise from proteasome alterations, upregulation of heat shock proteins, genetic changes, and activation of autophagy (Matamala Montoya et al., 2023).

BTK Inhibitors

Bruton's tyrosine kinase (BTK) inhibitors have become the standard of care for several B-cell malignancies, including chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), Waldenstrom macroglobulinemia, and marginal zone lymphoma (Piggott, n.d.). Ibrutinib, a first-generation BTK inhibitor, has been shown to be more effective than standard chemoimmunotherapy regimens for CLL. It significantly improves progression-free survival (PFS) and overall survival (OS), even in high-risk patients with TP53 aberrations (Sampath & Plunkett, 2007). However, these inhibitors are associated with resistant mutations outside the C481 hotspot, which can lead to cross-resistance among different inhibitors. Safety concerns include cardiovascular side effects, such as atrial fibrillation and hypertension, as well as bleeding. These side effects are attributed to off-target effects on related kinases. BTK inhibitors are also being explored for repurposing in the treatment of chemotherapy-resistant solid tumors (Müller et al., 1998).

The development of targeted therapies, including FLT3, IDH, BCL-2, proteasome, and BTK inhibitors, is a significant advancement over conventional chemotherapy. These therapies offer improved efficacy and reduced off-target effects (Bogdanovic et al., 2025). However, it has been consistently observed that even these highly specific agents eventually encounter acquired resistance. This often occurs through new mutations in the target gene, such as point mutations in FLT3-ITD (J. Zhang et al., 2019), or through activation of compensatory pathways. One example is RTK pathway mutations in IDH-mutated AML (Shatnyeva et al., 2015). This dynamic illustrates a continuous evolutionary arms race between therapeutic interventions and cancer adaptation. Therefore, monotherapy with targeted agents, while initially effective, is unlikely to achieve long-lasting cures. Future strategies must anticipate and counteract emerging resistance mechanisms by employing combination therapies that target multiple pathways simultaneously or developing sequential therapies guided by real-time monitoring of resistance-driving mutations. These strategies underscore the ongoing need for research into novel targets and next-generation inhibitors that can overcome evolving resistance mechanisms.

Immunotherapies

Immunotherapy uses a patient's immune system to recognize and destroy cancer cells. This treatment offers significant clinical benefits and long-lasting results (Knittel et al., 2015).

CAR T-Cell Therapy

Chimeric antigen receptor T (CAR T)-cell therapy has transformed the treatment of hematological malignancies, including acute lymphoblastic leukemia (ALL), B-cell lymphoma (e.g., diffuse large B-cell lymphoma [DLBCL] and mantle cell lymphoma [MCL]), and multiple myeloma (MM). This therapy has demonstrated remarkable effectiveness, significantly improving patient outcomes and prognosis (Ngu et al., 2022). The FDA has approved CD19-targeted CAR T-cells for ALL and DLBCL and BCMA-targeted CAR T-cells for MM (Mahadevan & Fisher, 2011).

However, despite high initial response rates, most patients eventually relapse (Saitoh & Oda, 2021). Resistance mechanisms stem from several factors:

- Tumor cell-related factors: These include downregulation or complete loss of target antigen expression (e.g., CD19 or BCMA) due to genetic mutations or trogocytosis (the active transfer of antigens from tumor cells to T cells). Mutations in death receptor pathways also contribute to resistance (Tonon, 2024).

- T cell-related defects: These include intrinsic defects in the patient's own T cells, from which CAR T cells are manufactured, as well as CAR T cell exhaustion. CAR T cell exhaustion is a state of dysfunction resulting from persistent antigen exposure or the influence of cytokines, such as IL-4.

- Tumor Microenvironment (TME) immunosuppression: The TME is rich in immunosuppressive cells, such as cancer-associated fibroblasts (CAFs), myeloid-derived suppressor cells, and regulatory T cells, as well as inhibitory factors, such as TGF-β. These components contribute to suboptimal CAR T-cell activity and persistence by creating a protective barrier and dampening immune responses. Circulating extracellular vesicles (EVs) can also induce CAR T-cell dysfunction (Dzobo et al., 2023).

Challenges associated with CAR T-cell therapy include safety concerns, such as cytokine release syndrome (CRS) and immune-effector cell-associated neurotoxicity syndrome (ICANS); potential off-target toxicities; prolonged cytopenias; high manufacturing costs; and the time required for cell preparation (Li & Dalton, 2006).

Bispecific Antibodies (bsAbs)

Bispecific antibodies (bsAbs) are engineered molecules that target two different epitopes or antigens simultaneously. This dual-targeting strategy enhances the therapeutic efficacy of traditional monoclonal antibodies and helps prevent resistance (Liu et al., 2024). BsAbs can function by linking immune cells with tumor cells, a process known as T-cell engagement (TCEs), or by blocking dual signaling pathways.

Several bsAbs have received approval for hematological malignancies.

- Blinatumomab (CD3xCD19): This first-in-class TCE was approved for relapsed/refractory (R/R) B-cell precursor acute lymphoblastic leukemia (ALL), demonstrating significant improvement in overall survival compared to standard chemotherapy (Tredan et al., 2007).

- Mosunetuzumab, epcoritamab, and glofitamab (CD3xCD20): These are approved for R/R NHL, including follicular NHL and DLBCL.

- Teclistamab, elranatamab (CD3xBCMA), and talquetamab (CD3xGPRC5D) are approved for R/R MM. These are approved for R/R MM and show high overall response rates.

- Innate-cell engagers (ICEs), such as acimtamig (CD30xCD16A), are also emerging as promising agents for Hodgkin lymphoma (HL) and T-cell lymphoma.

Challenges associated with bispecific antibodies (bsAbs) include their short half-life, which often necessitates continuous administration (e.g., blinatumomab); the risk of on-target/off-tumor toxicities, particularly cytokine release syndrome (CRS) and neurotoxicity with T-cell engagers (TCEs); and the inherent issue of tumor heterogeneity (Y. Zhang et al., 2024).

Immune Checkpoint Inhibitors (ICIs)

Immune checkpoint inhibitors (ICIs), which target proteins such as PD-1, PD-L1, and CTLA-4, boost the immune system's capacity to identify and eliminate tumor cells by obstructing pathways that typically suppress immune responses (Garcia et al., 2024).

These drugs have revolutionized cancer treatment, demonstrating significant efficacy in Hodgkin lymphoma (HL) and showing promise in other hematological malignancies, particularly in relapsed or refractory cases (Aoki et al., 2025). However, patients can exhibit primary or acquired resistance to ICIs (Casagrande et al., 2022). Resistance mechanisms include T-cell exhaustion (e.g., in acute lymphoblastic leukemia [ALL]), hyper-progression in some T-cell lymphomas, and specific polymorphisms within PD-1/CTLA-4 genes.

Challenges associated with ICIs in hematological malignancies include variable efficacy in non-Hodgkin lymphomas (NHLs), hyper-progression in T-cell lymphomas, limited benefit and severe adverse events in multiple myeloma (MM) (which have led to premature trial halts), mixed responses in myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), and an increased risk and severity of graft-versus-host disease (GVHD) following allogeneic stem cell transplantation (alloHCT) (Khurana & Ansell, 2020). Future research directions include exploring combination therapies with chemotherapy, radiotherapy, targeted agents, and CAR T-cells; investigating novel checkpoint molecules, such as LAG-3, TIM-3, TIGIT, and CD47; and developing more personalized approaches (Khurana & Ansell, 2020).

Synergistic Approaches with Chemotherapy, Targeted Agents, and Immunotherapies

- Antibody-drug conjugates (ADCs) + chemotherapy: Combining ADCs (e.g., sacituzumab govitecan) with traditional chemotherapy (e.g., cisplatin) takes advantage of synergistic effects to overcome resistance, enhance efficacy, and induce DNA damage and cell death (W.-C. Yang & Lin, 2015).

- ADCs + immune checkpoint inhibitors (ICIs): Combining ADCs with ICIs (e.g., PD-1/PD-L1 inhibitors) harnesses the immune system to enhance T-cell activation and immune responses (Shah et al., 2020).

- ADCs + Targeted Therapies: Combining ADCs with tyrosine kinase inhibitors (TKIs) or anti-angiogenic agents blocks specific molecular pathways and improves ADC penetration into tumors (Pashkina et al., 2025).

- DNA Damage Response (DDR) Inhibitors + Chemotherapy/Radiotherapy: DDR inhibitors can amplify the effectiveness of established treatments by increasing tumor susceptibility to DNA damage (Rahul Gangurde et al., 2025).

- Metabolic inhibitors + targeted drugs/immunotherapy: Combining metabolic inhibitors (e.g., GPX4 and ACOX1 inhibitors) with FLT3 inhibitors or immunotherapies (e.g., CAR T-cells and ICIs) can disrupt metabolic vulnerabilities and enhance immune recognition of drug-tolerant persister (DTP) cells (Mandal, n.d.).

- Epigenetic drugs + chemotherapy/immunotherapy/targeted therapy: Epigenetic agents can prevent chemoresistance, enhance antigen presentation, and reverse resistance mechanisms against targeted therapies (Lin et al., 2024).

Developing combination therapies presents several challenges, including a poor understanding of underlying mechanisms, eventual development of acquired resistance, tumor heterogeneity, overlapping toxicities, and activation of compensatory pathways (Chen et al., 2023).

The data strongly support combination therapies as the most promising approach. However, the literature also highlights the pitfalls of empirical combinations. These include a poor understanding of underlying mechanisms, potential overlapping toxicities, and activation of compensatory pathways that can undermine efficacy. These findings suggest that a rational, mechanism-driven approach is critical, as simply combining drugs is insufficient. Future research must therefore focus on deciphering complex signaling networks and resistance mechanisms in order to design truly synergistic combinations. This involves identifying optimal drug pairings that target distinct, non-overlapping vulnerabilities, minimize toxicity, and anticipate compensatory pathways. Functional precision medicine approaches can play a crucial role in identifying patient-specific vulnerabilities and enabling the development of tailored combination regimens (Yao et al., 2022).

Epigenetic Modulators

Epigenetic modifications are reversible changes in gene expression that do not involve alterations to the underlying DNA sequence. This makes them attractive targets for cancer therapy (Pathak et al., 2023). Epigenetic drugs (epidrugs) aim to reverse these changes, reactivate silenced tumor suppressor genes, and restore normal cell function.

DNA methyltransferase inhibitors (DNMTi), such as azacitidine and decitabine, are approved for acute myeloid leukemia (AML), chronic myelomonocytic leukemia (CMML), and myelodysplastic syndrome (MDS) (Pathak et al., 2023). These agents induce demethylation and reactivate epigenetically silenced genes (Castro-Muñoz et al., 2023).

Histone deacetylase inhibitors (HDACi), including vorinostat (approved for peripheral T-cell lymphomas) and panobinostat (approved for multiple myeloma [MM] in combination with other agents), inhibit HDACs. This action promotes chromatin decompaction and gene transcription, thereby influencing gene expression (Pathak et al., 2023).

Challenges associated with epigenetic modulators include the reversibility of methylation patterns, which can lead to the re-silencing of genes; the toxicity and instability of some epigenetic drugs; a lack of specificity, which can lead to the activation of normally silenced genes; and limited efficacy as monotherapies in solid tumors. Selecting patients based on specific epigenetic signatures also remains a significant challenge (Pathak et al., 2023).

The reversibility of epigenetic modifications allows for the "reprogramming" of cancer cells to become less malignant or more sensitive to drugs. However, this same reversibility means that resistance can reemerge through remethylation or other epigenetic adaptations (Pathak et al., 2023). Therefore, epigenetic therapies may be most effective when combined with agents that prevent the re-establishment of resistant epigenetic states, or when applied in a maintenance setting to sustain therapeutic effects. Continuous monitoring of epigenetic markers may be necessary to adapt treatment strategies dynamically and prevent disease relapse.

Novel Drug Delivery Systems

Novel drug delivery systems are being developed to improve therapeutic precision, reduce systemic toxicity, and enhance drug stability and bioavailability at the tumor site (Pashkina et al., 2025).

One such system is nanoparticle-based delivery, which utilizes nanotechnology to enable selective targeting of tumor cells while sparing normal tissues. This approach addresses issues such as drug efflux and aims to increase drug concentration at the tumor site specifically (Emran et al., 2022).

Hyaluronic acid (HA)-based systems leverage the overexpression of HA receptors, such as CD44, in subpopulations of cancer cells, including those in hematological malignancies. These systems can be designed to target these receptors for selective drug delivery, enhancing treatment specificity (Pashkina et al., 2025).

However, challenges in this area include poor drug accumulation in solid tumors due to superficial penetration, low cellular uptake, and non-specific drug release. The widespread presence of HA receptors on healthy tissues can lead to nonspecific binding, and the dense intercellular matrix in tumor tissue can impede drug delivery deep into the tumor (Pashkina et al., 2025). Additionally, high expression of CD44 on blood cells can hinder transport of the drug delivery system in the bloodstream. Therefore, more advanced, multi-component delivery systems are needed to achieve greater efficacy and selectivity with less toxicity.

Physical and biological barriers within tumors, such as dense extracellular matrices, leaky vasculatures, and active efflux pumps, significantly limit drug penetration and efficacy (Emran et al., 2022). Novel drug delivery systems address these challenges directly by improving targeted delivery and reducing systemic toxicity. This suggests that highly potent drugs may be ineffective if they cannot reach target cells within the complex tumor microenvironment. Therefore, investing

in advanced drug delivery systems is crucial to maximizing the therapeutic index of existing and new agents, especially in the challenging microenvironments characteristic of hematological malignancies.

Personalized Medicine Approaches

The goal of personalized medicine is to tailor treatment strategies based on the unique molecular and biological characteristics of a patient's tumor. This allows for more effective prediction of response and monitoring of resistance (Bogdanovic et al., 2025).

Biomarker-Guided Treatment Selection

Genomic profiling identifies specific mutations (e.g., FLT3, JAK2, and TP53) and allows for the selection of tailored therapies (Rahul Gangurde et al., 2025). Minimal residual disease (MRD) monitoring utilizes advanced techniques, such as next-generation sequencing (NGS) and flow cytometry, to enable the early detection of relapse and guide treatment adjustments (Rahul Gangurde et al., 2025). Predictive biomarkers, such as PD-L1 expression, tumor mutational burden (TMB), and microsatellite instability (MSI), are increasingly used to predict the efficacy of immune checkpoint inhibitors (ICIs) (Ploumaki et al., 2023).

Functional Precision Medicine (FPM)

Functional Precision Medicine (FPM) is a complementary approach that predicts drug responsiveness ex vivo through functional assays such as image-based, single-cell FPM. This approach can directly inform treatment decisions for aggressive hematologic cancers (Moreau et al., 2012).

Challenges to implementing personalized medicine include logistical complexities such as procuring viable cells for ex vivo testing and managing heterogeneous patient populations. Many patients are heavily pretreated, which can limit their response to guided therapies. Other challenges include the limitations of non-randomized trial designs and the ongoing need for faster diagnostic result turnaround times (Ruschak et al., 2011).

Historical reliance on broad chemotherapy regimens is gradually shifting towards highly individualized approaches (Bogdanovic et al., 2025). This shift is driven by the growing awareness of tumor heterogeneity and the urgent need to align specific tumor vulnerabilities with targeted therapies. FPM, in particular, offers a direct means to assess drug sensitivity, moving beyond purely genomic predictions. This signifies a paradigm shift in oncology, transitioning from a "one-size-fits-all" approach to a more dynamic, patient-centric model. Overcoming resistance in the future will require integrating comprehensive molecular profiling with functional assays to adapt treatment strategies dynamically as the disease evolves, ensuring the right drug is delivered to the right patient at the right time.

Table 2: Overview of Novel Therapeutic Innovations and Their Clinical Status in Hematological Cancers

Therapy Class	Specific Agents/Approaches	Mechanism of Action	Clinical Status/Key Outcomes (Examples)	Challenges/Resistance Mechanisms
Targeted Therapies	FLT3 Inhibitors (Midostaurin, Gilteritinib, Quizartinib, Crenolanib)	Inhibit mutated FLT3 kinase, crucial for AML cell proliferation/survival	Approved for ND & R/R AML; improved OS (e.g., Gilteritinib mOS 9.3 vs 5.6 mo in ADMIRAL) (Mandal, n.d.)	Targeted Therapies
	IDH Inhibitors (Ivosidenib, Enasidenib)	Target mutant IDH1/2, reducing oncometabolite 2-HG	Approved for R/R AML; CR 21%, ORR 40% in R/R AML (Chen et al., 2023)	Low response rates, relapse after short-term remission; clonal evolution, isoform switching, RTK pathway mutations (Yao et al., 2022)
	BCL-2 Inhibitors (Venetoclax)	Inhibit anti-apoptotic BCL-2 family proteins, inducing apoptosis	Approved for CLL, AML, SLL; active in t(11;14) MM (Solimando et al., 2022)	Drug resistance, disease relapse, tumor lysis syndrome, cytopenias (Fowler-Shorten et al., 2024)
	Proteasome Inhibitors (Bortezomib, Carfilzomib, Ixazomib)	Inhibit ubiquitin-proteasome pathway, leading to protein accumulation and apoptosis	Approved for MM; improved OS, used in combinations (Bortezomib) (Pinto et al., 2020)	Proteasome alterations, HSP upregulation, autophagy activation (Matamala Montoya et al., 2023)
	BTK Inhibitors (Ibrutinib, Acalabrutinib, Zanubrutinib)	Inhibit Bruton's tyrosine kinase, crucial for B-cell signaling	Standard of care in CLL, MCL, WM; improved PFS/OS in CLL (Tam & Thompson, 2024)	Resistant mutations (non-C481), cross-resistance; cardiovascular side effects (Uckun & Venkatachalam, 2021)
Immunotherapies	CAR T-cell Therapy (e.g., CD19-targeted, BCMA-targeted)	Genetically engineered T-cells target specific tumor antigens for lysis	Approved for ALL, B-cell lymphoma, MM; high initial response rates (Multiple	Antigen loss/downregulation, T-cell exhaustion, TME immunosuppression, CRS,

			Myeloma - Cancer Research Institute, n.d.)	ICANS, cost (Sakemura et al., 2021)
	Bispecific Antibodies (e.g., Blinatumomab, Teclistamab)	Dual-targeting to link immune cells to tumor cells or block dual pathways	Approved for ALL, NHL, MM; improved OS/ORR (Wu et al., 2025)	Short half-life, on-target/off-tumor toxicities (CRS, neurotoxicity), tumor heterogeneity (Wu et al., 2025)
	Immune Checkpoint Inhibitors (e.g., anti-PD-1/PD-L1, anti-CTLA-4)	Block inhibitory pathways to enhance anti-tumor immunity	Significant efficacy in HL; emerging utility in R/R hematologic malignancies (Yang et al., 2024)	Primary/acquired resistance, T-cell exhaustion, hyper-progression, GVHD risk (Yang et al., 2024)
Combination Strategies	ADCs + Chemotherapy/ICIs/Targeted Therapies	Synergistic effects by attacking multiple mechanisms	Improved ORR, PFS, OS in various cancers(Fujiwara et al., 2020)	Poor understanding of mechanisms, overlapping toxicities, compensatory pathways (Fujiwara et al., 2020)
	DDR Inhibitors + Chemotherapy/Radiotherapy	Heighten tumor susceptibility to DNA damage	Amplifies effectiveness of established treatments (Piggott, n.d.)	Complex interactions, need for precise patient selection (Ma et al., 2025)
	Metabolic Inhibitors + Targeted Drugs/Immunotherapy	Disrupt metabolic vulnerabilities, enhance immune recognition	Potential to eliminate DTP cells, enhance sensitivity (Tsumura et al., 2023)	Preclinical stage, need for clinical translation (Tsumura et al., 2023)
	Epigenetic Drugs + Chemotherapy/Immunotherapy/Targeted Therapy	Reverse aberrant epigenetic changes, restore gene function, prevent resistance	Prevent chemoresistance, enhance antigen presentation (Pathak et al., 2023)	Reversibility of methylation, toxicity, lack of specificity (Pathak et al., 2023)
Novel Drug Delivery Systems	Nanoparticle-Based Delivery, HA-Based Systems	Improve therapeutic precision, reduce toxicity, enhance drug stability/targeting	Selective drug targeting, improved drug concentration (Pashkina et al., 2025)	Poor accumulation/penetration, non-specific release, binding to healthy tissues (Pashkina et al., 2025)
Personalized Medicine	Biomarker-Guided Treatment, Functional Precision Medicine	Tailor treatment based on patient/tumor characteristics, predict response	Improved patient outcomes, early relapse detection (Rahul Gangurde et al., 2025)	Logistical challenges for cell procurement, heterogeneity, turnaround time

Challenges and Future Directions

The landscape of chemotherapy resistance in hematological malignancies is characterized by persistent and evolving challenges that necessitate continuous innovation. The multifactorial and dynamic nature of resistance mechanisms, driven by clonal evolution and cellular plasticity, poses a significant hurdle (Gourzones et al., 2019). Tumor heterogeneity, in which different cell populations coexist within a single tumor, enables resistant subclones to persist and cause relapse, complicating the development of a universal treatment (Gourzones et al., 2019).

Despite significant advancements, current therapeutic approaches still face limitations, including inherent toxicity, off-target side effects, and limited efficacy in specific patient subsets or advanced disease stages (Bogdanovic et al., 2025). The manufacturing complexities and high costs associated with cellular therapies, such as CAR T-cell therapies, also limit their accessibility (Shah et al., 2020). Additionally, the gap between laboratory discoveries and clinical implementation remains significant, as many promising preclinical findings do not successfully translate into effective human therapies (Eslami et al., 2024).

The future of overcoming chemotherapy resistance in hematological malignancies relies on a multi-pronged approach.

- Integrated Multi-Omics and Functional Approaches: Integrating advanced multi-omics technologies (e.g., genomics and proteomics) with single-cell resolution and sophisticated disease models, combined with advanced biocomputational approaches and artificial intelligence (AI), will provide a more comprehensive understanding of resistance mechanisms (Eslami et al., 2024). This will allow for the identification of novel therapeutic targets and the development of more precise diagnostic and prognostic biomarkers. For example, integrated multi-omics approaches could identify co-occurring FLT3 mutations and BCL-2 overexpression. This would enable the design of dual-inhibitor regimens to prevent resistance.

- Novel Therapeutic Targets and Drug Development: Researchers are actively pursuing next-generation inhibitors that can overcome current resistance mechanisms. These include more potent and selective FLT3, IDH, BCL-2, and proteasome inhibitors (Mazewski & Platanias, 2023). Exploring natural products and strategies that target abnormal alternative

splicing events also shows promise for developing new drugs (Mathias et al., 2025).

- Rational Combination and Adaptive Therapies: Moving beyond empirical combinations, future strategies will focus on rationally designed combination therapies that target multiple nonoverlapping resistance mechanisms simultaneously (Pathak et al., 2023). These strategies include combining chemotherapy with targeted agents, immunotherapies, and epigenetic modulators. Adaptive dosing strategies and sequential treatments guided by real-time monitoring of disease evolution are also being explored to prevent resistance (Shi et al., 2025). These strategies could be particularly effective against resistance driven by metabolic plasticity, such as the shift from glycolysis to OXPHOS observed in quiescent leukemia stem cells.

- Enhanced Drug Delivery Systems: Innovations in drug delivery, such as nanoparticle-based systems and targeted drug delivery vehicles, are essential for improving drug concentration at the tumor site, overcoming physical barriers, and reducing systemic toxicity (Emran et al., 2022).

- Targeting the Tumor Microenvironment (TME) and Cancer Stem Cells (CSCs): Due to the active role of the TME in fostering resistance, future therapies will increasingly target specific stromal cells, soluble factors, and immune components within the microenvironment to disrupt the protective niche (Pinto et al., 2020). Strategies that specifically eradicate quiescent and metabolically adaptable LSCs/CSCs are also paramount to preventing relapse (Delou et al., 2019).

- Personalized and Biomarker-Driven Approaches: The shift toward precision oncology will intensify by utilizing comprehensive genomic profiling, liquid biopsies, and functional biomarkers to personalize treatment, predict responses, and monitor resistance (Bogdanovic et al., 2025). This includes identifying specific DNA repair deficiencies and epigenetic signatures to guide personalized treatment regimens.

Conclusion

Chemotherapy resistance in hematological cancers is a multifactorial and evolving challenge. It is driven by genetic and epigenetic alterations, adaptive stem cell behaviors, enhanced DNA repair mechanisms, and the protective tumor microenvironment. These mechanisms interact dynamically and often compensate for one another, rendering monotherapies insufficient. Although emerging therapies, such as targeted agents, immunotherapies, and epigenetic drugs, have significantly advanced treatment outcomes, they too face acquired resistance. Future success hinges on rational combination therapies, innovative drug delivery systems, and personalized medicine informed by multi-omics and real-time functional profiling. A paradigm shift is needed—from treating the tumor bulk alone to dismantling the adaptive ecosystem that sustains resistance and relapse. Based on the synthesized evidence, priority areas for translation include: (1) developing multi-targeted combinations that disrupt parallel resistance pathways, (2) integrating real-time molecular monitoring into treatment workflows, and (3) rigorously evaluating TME- and metabolism-targeting agents in combination with existing regimens.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Material

No new data was generated or analyzed in this study.

Conflicts of Interest / Competing Interests

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Author Contributions

S.H.A: Conceptualization, Methodology, Writing of the original draft.

A.F.A: Conceptualization, Methodology, Writing of the original draft.

N.A.S.A: Conceptualization, Methodology, Writing of the original draft.

A.M.K: Investigation, Resources.

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