Journal of Leukemia
ISSN: 2329-6917
OPEN ACCESS Freely available online
Opinion Article

Adaptive Resistance in Leukemia and Role of Rational Combination Therapies

Julia Weber*

Department of Cancer Biology, Karolinska Institutet, Stockholm, Sweden

DESCRIPTION

Novel combination therapies for leukemia represent one of the most transformative and promising directions in modern hematologic oncology, reflecting a shift away from traditional, monolithic treatment strategies toward a more integrated, mechanism driven and patient centered approach. Leukemia, in its various forms, continues to challenge clinicians with its biological complexity, its ability to evolve resistance, and the diversity of patient responses even within the same diagnostic category. Standard treatments chemotherapy, radiation, hematopoietic stem cell transplantation, and more recently, targeted therapies have undoubtedly contributed to improved survival rates over the past several decades. Yet, for a considerable portion of patients, particularly those with relapsed or refractory disease, outcomes remain unsatisfactory. This reality has intensified interest in combining existing and emerging therapies in ways that exploit complementary mechanisms, synergize therapeutic effects, and minimize the likelihood of resistance.

The rationale for combination therapies lies partly in the genetic and molecular heterogeneity of leukemia cells. Even within a single clone, leukemia often contains diverse subpopulations with distinct vulnerabilities. Monotherapies, no matter how advanced, often target only a subset of these vulnerabilities, enabling resistant subclones to expand and eventually dominate. Combination treatments address this issue by simultaneously attacking multiple pathways essential for leukemic cell survival, proliferation, or immune evasion. For instance, pairing tyrosine kinase inhibitors with BCL-2 inhibitors has already demonstrated success in certain subsets of Acute Myeloid Leukemia (AML) and Chronic Lymphocytic Leukemia (CLL), offering a blueprint for future strategies. The concept is not simply to add more drugs but to intelligently pair agents whose mechanisms intersect meaningfully to produce deeper, more durable remissions.

One of the most compelling trends is the combination of targeted therapies that individually show modest effects but, when paired, create a more robust biological response. In AML, combinations of *FLT3* inhibitors with hypomethylating agents have gained traction. The *FLT3* mutation, long associated with poor prognosis, has historically been difficult to manage, with monotherapy *FLT3* inhibitors offering short-lived remissions due to the rapid emergence of resistance mutations or compensatory signaling. However, when combined with agents like azacitidine or decitabine, which alter the epigenetic landscape and sensitize leukemia cells to apoptotic signaling, the therapeutic effect becomes significantly stronger.

CLL has arguably seen some of the most dramatic advancements in combinational therapy, especially through the integration of BCL-2 inhibitors like venetoclax with anti-CD20 monoclonal antibodies or Bruton Tyrosine Kinase (BTK) inhibitors. These regimens have redefined expectations for remission depth and duration, enabling time-limited treatment courses that would have been unthinkable a decade ago. The synergy between venetoclax and BTK inhibitors results from venetoclax priming leukemia cells for apoptosis, while BTK inhibition disrupts survival signals from the microenvironment. This combination has shown the ability to clear measurable residual disease to unprecedented levels, providing patients with both prolonged survival and improved quality of life.

Beyond targeted agents, immunotherapy continues to reshape leukemia treatment paradigms. Novel combinations involving immune checkpoint inhibitors, bispecific T-cell engagers, and CAR-T cell therapy are rapidly gaining attention. While immune checkpoint inhibitors have limited stand-alone efficacy in most leukemias, their ability to enhance T-cell activation makes them appealing partners for therapies that bring T cells into close proximity with leukemia cells. Bispecific antibodies, which simultaneously bind leukemic cells and T cells, already show encouraging activity in Acute Lymphoblastic Leukemia (ALL). When combined with checkpoint inhibitors, the hope is that the immune system's cytotoxic response can be sustained and amplified, overcoming T-cell exhaustion a major barrier to durable responses.

Correspondence to: Julia Weber, Department of Cancer Biology, Karolinska Institutet, Stockholm, Sweden, E-mail: weberj@gmail.com

Received: 04-Sep-2025, Manuscript No. JLU-25-39352; **Editor assigned:** 08-Sep-2025, PreQC No. JLU-25-39352 (PQ); **Reviewed:** 22-Sep-2025, QC No. JLU-25-39352; **Revised:** 29-Sep-2025, Manuscript No. JLU-25-39352 (R); **Published:** 06-Oct-2025, DOI: 10.35248/2329-6917-25.13.463

Citation: Weber J (2025). Adaptive Resistance in Leukemia and Role of Rational Combination Therapies. J Leuk. 13:463.