Drug Combination to Overcome Resistance in CML

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Therapeutic management of chronic myeloid leukemia (CML) relies on the use of BCR::ABL1 tyrosine kinase inhibitors (TKIs) as monotherapy. However, a variety of combination strategies are being investigated in preclinical models and clinical trials, whether for newly diagnosed high-risk patients, to facilitate treatment-free remission, or in resistant and advanced-phase disease. In the latter two settings, research directions focus on reinforcing BCR::ABL1 blockade, as well as on targeting complementary mechanisms critical to leukemic cell survival.

Dual TKI combinations—particularly ATP-competitive inhibitors with allosteric inhibitors—are promising strategies to enhance BCR::ABL1 kinase inhibition. Such dual therapy may help prevent the emergence of *BCR::ABL1* mutations or restore the sensitivity of leukemic cells to kinase inhibition, especially in the presence of compound *ABL1* mutations. Early-phase studies indicate that combining asciminib with imatinib, nilotinib, or dasatinib is feasible in patients with CP-CML. However, clinical efficacy and safety data remain limited. Patient populations most likely to benefit from such combinations are undefined, and this strategy has not yet become part of standard clinical practice. In preclinical models ponatinib and asciminib have been shown to be able to provide synergistic inhibition of BCR-ABL1, suppressing the emergence of resistant clones and restoring efficacy against compound mutants that are refractory to either agent alone. Clinical evidence for the efficacy combination is currently limited to individual case reports and validation in clinical trials is required.

The rationale for combining TKI to other targeted agents is mainly to address BCR::ABL1-dependent or -independent resistance mechanisms, improve outcomes in advanced or refractory CML or eradicate leukemic stem cells. The use of epigenetic modifiers such as histone deacetylase inhibitors or DNA methyltransferase inhibitors is supported by preclinical and early clinical data showing that epigenetic dysregulation contributes to CML pathogenesis and resistance to TKIs. Anti-apoptotic agents such as venetoclax have shown synergistic pro-apoptotic effects when combined with TKIs in cell lines and primary resistant cells. Early-phase clinical trials are investigating these combinations, particularly in advanced-phase CML and TKI-resistant cases. Other therapeutic combinations may also be of interest, particularly those aimed at modulating the leukemic microenvironment or enhancing immune-mediated elimination of leukemic cells.

In conclusion, combination therapies designed to overcome resistant CML represent promising strategies; however, their use should be carefully evaluated within the context of well-designed clinical trials and tailored to address the molecular heterogeneity of the disease.