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Commentary

Venetoclax in Acute Myeloid Leukemia: A Transformative Therapeutic Approach Beyond Cytotoxic Chemotherapy

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DESCRIPTION

The therapeutic landscape for Acute Myeloid Leukemia (AML) has been fundamentally transformed by the introduction of venetoclax, a selective BCL-2 inhibitor that exploits the intrinsic apoptotic dependencies of myeloid malignancies. After decades of stagnation with intensive cytotoxic chemotherapy regimens remaining standard of care despite modest improvements in outcomes, venetoclax-based combinations have ushered in a new era of targeted therapy with remarkable efficacy and more favorable toxicity profiles than conventional approaches. The evolution of venetoclax from a promising preclinical compound to a cornerstone therapy across multiple AML treatment scenarios represents one of the most significant therapeutic advances in myeloid malignancies in recent decades.

The development of venetoclax emerged from fundamental research elucidating the role of BCL-2 family proteins in regulating the intrinsic apoptotic pathway. AML cells, particularly leukemic stem cells, demonstrate upregulation of anti-apoptotic proteins including BCL-2 as a survival mechanism and mediator of treatment resistance. The selective inhibition of BCL-2 by venetoclax liberates pro-apoptotic proteins sequestered by BCL-2, triggering mitochondrial outer membrane permeabilization and initiating apoptosis. This mechanism is particularly effective when combined with agents that induce cellular stress, providing a strong rationale for combining venetoclax with Hypomethylating Agents (HMAs) or Low-Dose Cytarabine (LDAC).

The landmark phase 1b and phase 3 VIALE-A trials evaluating venetoclax combined with azacitidine in older or unfit patients with newly diagnosed AML demonstrated impressive efficacy, with composite complete remission rates of 66-74% and median overall survival of 14.7 months compared to 9.6 months with azacitidine alone. Remarkably, responses were observed across cytogenetic and molecular risk groups, including traditionally adverse subsets such as TP53-mutated AML. The combination of venetoclax with LDAC similarly demonstrated superior outcomes compared to LDAC alone in the VIALE-C trial, though with more modest benefit. These results led to FDA approval of venetoclax combinations for previously untreated AML in patients ineligible for intensive chemotherapy, establishing a new standard of care for this patient population.

Beyond the frontline treatment of older/unfit patients, venetoclax has demonstrated promising activity in multiple other AML scenarios. In relapsed/refractory disease, venetoclax combinations with HMAs or LDAC achieve response rates of 30-40%, though durability remains limited. Emerging data suggest particular efficacy when venetoclax is combined with targeted agents addressing specific genetic alterations, such as IDH inhibitors in IDH-mutated AML or FLT3 inhibitors in FLT3-mutated disease. The role of venetoclax in post-remission therapy, including maintenance after intensive chemotherapy or allogeneic stem cell transplantation, is under active investigation with promising early results suggesting reduced relapse rates.

Perhaps most intriguingly, venetoclax is being evaluated in combination with intensive chemotherapy for fit patients with newly diagnosed AML. The CAVEAT trial demonstrated that addition of venetoclax to standard 7+3 induction was feasible with appropriate dose modifications and produced promising efficacy signals including 89% complete remission and 71% measurable residual disease negativity. Multiple ongoing randomized trials (VIALE-A, VIALE-M) are further exploring this approach, with potential to significantly improve outcomes in younger patients with AML. The anticipated results from these studies may further expand the role of venetoclax across the full spectrum of AML treatment.

The remarkable clinical efficacy of venetoclax has stimulated intensive research into resistance mechanisms and biomarkers of response. Several patterns have emerged from clinical experience and correlative studies. First, specific genetic subgroups demonstrate differential sensitivity to venetoclax combinations. NPM1-mutated AML appears particularly responsive, with complete remission rates exceeding 90% and substantial long-term survival. Conversely, adverse cytogenetics, TP53 mutations, and RAS/MAPK pathway alterations confer relative resistance. Second, mitochondrial metabolism appears central to venetoclax

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sensitivity, with metabolic adaptations involving amino acid metabolism and fatty acid oxidation mediating resistance. Third, leukemia stem cells may evade venetoclax through altered BCL-2 family protein dependencies, including upregulation of MCL-1 or BCL-XL. These insights have informed rational combination strategies and biomarker development to optimize patient selection.

The evolution of venetoclax dosing represents another important aspect of its clinical implementation. Initial studies utilized continuous dosing, but subsequent experience demonstrated that time-limited therapy with treatment-free intervals may enhance durability while reducing toxicity, particularly myelosuppression.