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Perspective

The Evolving Role of FLT3 Inhibitors in Acute Myeloid Leukemia: From Salvage Therapy to Frontline Standard of Care

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DESCRIPTION

Mutations in the FMS-like tyrosine kinase 3 (FLT3) gene represent the most common genetic alteration in Acute Myeloid Leukemia (AML), occurring in approximately 30% of newly diagnosed patients. These mutations, predominantly internal tandem duplications (FLT3-ITD) or point mutations in the tyrosine kinase domain (FLT3-TKD), confer constitutive activation of proliferative and anti-apoptotic signaling pathways, contributing to leukemogenesis and treatment resistance. The recognition of FLT3 mutations as a critical driver of leukemic pathophysiology stimulated intensive efforts to develop targeted inhibitors, culminating in a transformative shift in the therapeutic landscape for this historically challenging subtype of AML.

The first-generation FLT3 inhibitors, including sorafenib, lestaurtinib, and midostaurin, demonstrated broad-spectrum kinase inhibitory activity with moderate selectivity for FLT3. Despite promising preclinical activity, early clinical trials with these agents as monotherapy yielded disappointing results characterized by transient reductions in peripheral blast counts without durable responses. The limited efficacy of single-agent approaches led to exploration of combination strategies with conventional chemotherapy. The pivotal RATIFY trial demonstrated that addition of midostaurin to standard induction and consolidation chemotherapy significantly improved overall survival in patients with newly diagnosed FLT3-mutated AML, leading to FDA approval in 2017. This landmark study established the principle that FLT3 inhibition could enhance outcomes when integrated with intensive chemotherapy, though the modest magnitude of benefit suggested room for improvement with more potent and selective agents.

Second-generation FLT3 inhibitors, including quizartinib, gilteritinib, and crenolanib, were developed with enhanced potency and selectivity for FLT3. These agents demonstrated more impressive single-agent activity in relapsed/refractory AML with response rates of 40-50% in FLT3-mutated disease. The ADMIRAL trial evaluating gilteritinib monotherapy *versus* salvage chemotherapy in relapsed/refractory FLT3-mutated AML showed significantly improved overall survival, leading to FDA approval in 2018. Similarly, quizartinib demonstrated survival benefit in the QUANTUM-R trial. These studies established FLT3 inhibitors as the standard of care in the relapsed/refractory setting, representing a significant advance from the dismal outcomes previously observed with conventional approaches.

The remarkable efficacy of second-generation FLT3 inhibitors in advanced disease naturally prompted investigation in the frontline setting. The addition of midostaurin to induction chemotherapy has become standard practice based on the RATIFY trial, but emerging data suggest greater benefit with more potent agents. The QUANTUM-First study evaluating quizartinib with standard chemotherapy demonstrated improved event-free survival (HR 0.76, p=0.0023) and overall survival (HR 0.76, p=0.005) compared to chemotherapy alone. Similar trials with gilteritinib (HOVON 156) and crenolanib are ongoing, with preliminary results suggesting improved measurable residual disease clearance rates compared to historical controls.

Beyond combination with intensive chemotherapy, FLT3 inhibitors have shown particular promise in conjunction with venetoclax-based regimens for older or unfit patients. The combination of gilteritinib with venetoclax and azacitidine demonstrated an impressive composite complete remission rate of 92% in a phase 1b study of newly diagnosed FLT3-mutated AML patients ineligible for intensive chemotherapy. This "triplet" approach is being compared to azacitidine plus venetoclax in the ongoing VENGATE trial, with preliminary data suggesting superior MRD clearance rates with the triplet.

The remarkable progress in targeting FLT3 mutations has transformed the treatment paradigm for a significant subset of AML patients. From early skepticism regarding the feasibility of kinase inhibition in this complex disease, we have witnessed evolution to evidence-based integration of FLT3 inhibitors across treatment settings. Future directions include combination with other targeted agents based on co-occurring mutations,

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development of more potent and selective inhibitors, integration with immunotherapeutic approaches, and exploration in related disorders including myelodysplastic syndromes with FLT3 mutations. As we refine our approach to FLT3-mutated AML, this historically challenging subtype has become a model for successful precision medicine in myeloid malignancies.