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Opinion Article

Precision Medicine in Leukemia: Realiing the Promise of Molecular Diagnostics

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DESCRIPTION

The molecular classification of leukemia has evolved rapidly over the past two decades. In Acute Myeloid Leukemia (AML), the 2016 revision of the World Health Organization classification incorporated specific genetic alterations as defining features of disease entities, acknowledging their fundamental importance in determining disease biology and clinical behavior. Similarly, the molecular landscape of Acute Lymphoblastic Leukemia (ALL) has been mapped in increasing detail, revealing distinct subtypes with characteristic genetic alterations and expression profiles. These molecular classifications have prognostic implications that guide treatment intensity decisions and have begun to inform specific therapeutic approaches.

The implementation of Next Generation Sequencing (NGS) in routine clinical practice has accelerated this transition to molecularly guided care. Comprehensive genomic profiling can now be performed with rapid turnaround times and decreasing costs, allowing for the detection of a broad spectrum of mutations, structural variants, and expression patterns. This technology has revealed the remarkable complexity of leukemia genetics, with most patients harboring multiple molecular alterations that interact in complex ways to drive disease phenotypes and therapeutic responses. The challenge now lies in distinguishing driver mutations with therapeutic relevance from passenger alterations that contribute little to disease biology.

The development of targeted therapies directed against specific molecular lesions represents a significant advance in leukemia treatment. The success of Tyrosine Kinase Inhibitors (TKIs) in Chronic Myeloid Leukemia (CML) established a paradigm for molecularly targeted therapy, transforming a once fatal disease into a chronic condition with life expectancy approaching that of the general population. This remarkable achievement has inspired similar approaches in other leukemia subtypes, with varying degrees of success. *FLT3* inhibitors in *FLT3*-mutated AML, IDH inhibitors in *IDH*-mutated disease, and *BCR-ABL1* *TKIs* in Philadelphia chromosome-positive ALL exemplify this trend toward genotype-directed therapy. However, the application of targeted agents in acute leukemias has revealed limitations that were not apparent in the CML experience. Unlike CML, which is driven by a single dominant oncogenic event (the *BCR-ABL1* fusion), acute leukemias typically harbor multiple genetic alterations that operate in complex networks. Targeting a single molecular lesion often yields only partial and transient responses as parallel pathways compensate for the inhibited target or resistant subclones emerge under selective pressure. This complexity necessitates combination approaches that address multiple vulnerabilities simultaneously or sequentially, an approach that introduces significant challenges in trial design and clinical implementation.

The integration of genomic information with functional assays represents a promising approach to address this complexity. *Ex vivo* drug sensitivity testing of patient-derived leukemic cells can identify unexpected vulnerabilities that may not be predicted by genomic profiling alone. These functional assays can capture the net effect of complex genetic interactions and epigenetic states that influence therapeutic response. Similarly, patient-derived xenograft models allow for the evaluation of therapeutic strategies in systems that preserve the clonal heterogeneity and microenvironmental interactions of the original disease. The combination of genomic and functional approaches may provide a more comprehensive assessment of leukemic vulnerabilities than either approach alone.

The concept of Minimal Residual Disease (MRD) assessment has further refined our approach to precision medicine in leukemia. The detection of residual disease at levels below the threshold of morphologic identification provides a powerful tool for risk stratification and treatment adaptation. MRD assessment by flow cytometry, polymerase chain reaction, or next-generation sequencing offers a dynamic measure of treatment response that complements the static information provided by diagnostic genetic profiling.

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