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Perspective

Emerging Strategies for Individualized Therapy in Chronic Myeloid Leukemia

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DESCRIPTION

Chronic Myeloid Leukemia (CML) is a clonal myeloproliferative disorder of the hematopoietic stem cells characterized by the presence of the philadelphia chromosome, resulting from the reciprocal translocation between chromosomes 9 and 22, t(9;22) (q34;q11). This translocation generates the *BCR-ABL1* fusion gene, which encodes a constitutively active tyrosine kinase responsible for uncontrolled proliferation and reduced apoptosis of myeloid cells. CML typically progresses through three phases: the chronic phase the accelerated phase, and the blast crisis, with the chronic phase being the most manageable stage for therapy.

Clinical trials comparing these agents to imatinib demonstrated faster and deeper molecular responses, with a higher proportion of patients achieving complete cytogenetic and major molecular responses. These deeper responses correlate with improved long-term outcomes, including progression free survival and overall survival. Dasatinib additionally inhibits other kinases such as SRC family kinases, which may contribute to its efficacy in resistant cases. Nilotinib, on the other hand is structurally related to imatinib but with modifications enhancing affinity for *BCR-ABL1,* allowing it to overcome many imatinib-resistant mutations. These advances provide clinicians with multiple therapeutic options to tailor treatment based on patient-specific factors, disease phase, comorbidities, and mutation profiles.

Third-generation TKIs, exemplified by ponatinib, were specifically designed to overcome the *T315I* mutation, which is highly resistant to both first and second generation TKIs. The availability of multiple TKIs with differing efficacy, safety and pharmacologic profiles underscores the importance of individualized therapy and ongoing monitoring of disease response using Quantitative Polymerase Chain Reaction (qPCR) to assess BCR-ABL1 transcript levels.

The introduction of TKIs has not only improved survival outcomes but also shifted the paradigm of CML management from a potentially fatal disease to a chronic, manageable condition. Many patients achieve deep molecular responses that allow for consideration of Treatment-Free Remission (TFR), an emerging concept in CML therapy. TFR refers to sustained remission after discontinuation of TKI therapy, with careful monitoring for molecular relapse. Clinical studies have shown that a substantial proportion of patients who achieve sustained deep molecular response may maintain remission off therapy, providing a potential cure-like state and minimizing long-term drug toxicity. The ability to achieve TFR further emphasizes the precision of targeted therapy in eradicating the disease at a molecular level rather than merely controlling hematologic parameters.

Monitoring treatment response is a critical component of targeted therapy in CML. The use of hematologic, cytogenetic, and molecular assessments provides a structured framework to guide therapy adjustments. Hematologic response, measured by normalization of blood counts, is an early indicator of therapeutic efficacy. Cytogenetic response, determined by the proportion of Philadelphia chromosome-positive metaphases in bone marrow, provides intermediate prognostic information. Molecular response, quantified by reduction in *BCR-ABL1* transcripts *via* qPCR, offers the most sensitive measure of disease burden and is pivotal in decisions regarding therapy discontinuation or switching. Current guidelines recommend regular monitoring at defined intervals to ensure timely identification of suboptimal responses, emerging resistance, or molecular relapse.

Adverse effects associated with TKIs, although generally manageable are an important consideration in long-term therapy. Common side effects include cytopenias, fluid retention, gastrointestinal disturbances, hepatic enzyme elevation, and musculoskeletal pain. Second and third generation TKIs may carry additional risks, such as pleural effusions with dasatinib, vascular events with ponatinib, and metabolic complications with nilotinib. These adverse effects necessitate careful patient selection, dose adjustments and supportive care strategies to maintain adherence and optimize outcomes.

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