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# Imatinib Resistance in Chronic Myeloid Leukemia: A Comprehensive Review

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**ABSTRACT**

Chronic myeloid leukemia (CML) is a hematological malignancy driven by the BCR::ABL1 fusion gene, which encodes a constitutively active tyrosine kinase. Imatinib mesylate, the first-generation tyrosine kinase inhibitor (TKI), significantly improved survival and disease management in CML patients. However, resistance to imatinib remains a major clinical challenge. Resistance mechanisms include BCR::ABL1 kinase domain mutations, gene amplification, activation of alternative signaling pathways, and drug efflux. This review summarizes the molecular mechanisms underlying imatinib resistance, diagnostic methods, and current therapeutic strategies to overcome resistance.

**Keywords:** Imatinib Resistance, Chronic Myeloid Leukemia, tyrosine kinase inhibitor.

**Introduction**

Chronic myeloid leukemia (CML) is a malignant myeloproliferative disorder characterized by a clonal hematopoietic stem cell proliferation. CML was the first malignant disease related to a cytogenetic abnormality(1)and its pathogenesis has been extensively studied. The advances in this field allowed the development of targeted therapies with tyrosine kinase inhibitors (TKIs) with high rates of therapeutic success, increasing substantially patient survival and disease prevalence(2). As for its incidence, CML affects about 0.7-1.0/100000 individuals per year and this rate has been stable over the last few years. With regard to the sociodemographic profile of CML patients, there is a slightly higher predominance among men, and the diagnosis usually occurs around the sixth or seventh decade of life(3).

CML is characterized by the presence of the Philadelphia chromosome, which is the result of a balanced reciprocal translocation between the long arms of 9 and 22 chromosomes [t (9; 22) (q34; q11)]. The fusion of the *Abelson murine leukemia* (*ABL*) gene on chromosome 9 with the *breakpoint cluster region (BCR)* gene on chromosome 22 results in the *BCR-ABL1* fusion gene, which encodes the BCR-ABL oncoprotein(4). This protein is a persistently active tyrosine kinase that promotes unrestricted replication, inadequate differentiation, and resistance to apoptosis(5). The continuous proliferation of these stem cells with a high capacity for differentiation favors the appearance of additional mutations that can provide resistance to standard treatment representing a negative impact on prognosis(6).

Despite the high success rate in treatments with TKIs, the emergence of resistance to TKIs has led to the development of new drugs and immunotherapy has been considered as an alternative to these patients, aiming to reduce disease recurrence and chronic use of medication(7).

. While most patients experience sustained responses, approximately 20–30% develop resistance, resulting in treatment failure. Understanding the mechanisms of imatinib resistance is critical to improving patient outcomes.

**1. Mechanisms of Imatinib Resistance**

**1.1. BCR::ABL1 Kinase Domain Mutations**

Mutations within the kinase domain of BCR::ABL1 are the most common cause of resistance. These mutations disrupt imatinib binding and maintain kinase activity. Examples include:

- **T315I mutation**: A gatekeeper mutation that confers resistance to imatinib and most second-generation TKIs.
- **P-loop mutations (e.g., Y253H, E255K)**: Reduce imatinib binding affinity and are associated with poor prognosis.

**1.2. BCR::ABL1 Gene Amplification**

Amplification of the BCR::ABL1 gene leads to overproduction of the protein, overwhelming the inhibitory capacity of imatinib.

**1.3. Drug Efflux and Influx**

- Overexpression of efflux transporters like P-glycoprotein (P-gp) reduces intracellular drug concentration.
- Downregulation of influx transporters such as OCT1 (organic cation transporter 1) further diminishes imatinib uptake.

**1.4. Clonal Evolution**

The emergence of additional cytogenetic abnormalities or mutations (e.g., in TP53 or RAS) during disease progression leads to reduced TKI sensitivity.

### 1.5. Activation of Alternative Pathways

Leukemic cells may activate signaling pathways like PI3K/AKT, JAK/STAT, or MAPK to bypass BCR::ABL1 dependence.

### 1.6. Pharmacokinetic Variability

Variations in drug absorption, metabolism, and adherence can contribute to subtherapeutic drug levels, resulting in resistance.

## 2. Clinical Implications

Imatinib resistance is classified into:

- **Primary resistance**: Failure to achieve therapeutic milestones (e.g., complete cytogenetic response) within expected timeframes.
- **Secondary resistance**: Loss of response after an initial period of effective therapy, often due to acquired mutations.

Imatinib resistance increases the risk of disease progression to accelerated phase (AP) or blast crisis (BC), necessitating alternative therapeutic strategies.

## 3. Diagnostic Approaches

### 3.1 Molecular Testing

- **BCR::ABL1 Mutation Analysis**: Detects kinase domain mutations via Sanger sequencing or next-generation sequencing (NGS).
- **Quantitative PCR**: Monitors BCR::ABL1 transcript levels to assess treatment response.

### 3.2. Cytogenetic Testing

Identifies clonal evolution and additional chromosomal abnormalities using karyotyping or fluorescence in situ hybridization (FISH).

### 3.3. Drug Transporter Assays

Evaluates expression and activity of OCT1 and P-gp to determine pharmacokinetic resistance.

## 4. Management of Imatinib Resistance

### 4.1. Switching to Second-Generation TKIs

- **Dasatinib**, **nilotinib**, and **bosutinib** are effective against most BCR::ABL1 mutations except T315I(8).
- Selection depends on the patient's mutation profile and comorbidities.

### 4.2. Third-Generation TKIs

**Ponatinib**: Effective against the T315I mutation but associated with vascular toxicity, reserved for resistant cases.

### 4.3. Combination Therapies

Combining TKIs with other agents (e.g., interferon-alpha or novel inhibitors) is under investigation to prevent resistance(9).

### 4.4. Allogeneic Stem Cell Transplantation (SCT)

SCT is a curative option for patients with advanced disease or failure of multiple TKIs.

### 4.5. Investigational Therapies

- **Asciminib**: A STAMP (Specifically Targeting the ABL Myristoyl Pocket) inhibitor with a unique mechanism of action.
- Novel agents targeting alternative pathways or epigenetic modifications are in clinical trials(10).

### 4.6. Future Directions

- **Personalized Medicine**: Development of predictive biomarkers for individualized TKI therapy.
- **Prevention of Resistance**: Exploring upfront combination therapies to delay or prevent resistance.
- **Novel TKIs**: Designing inhibitors that target resistance mutations like T315I with reduced toxicity.

## Conclusion

Imatinib resistance poses a significant challenge in CML management. While second- and third-generation TKIs have improved outcomes, patients with certain mutations, such as T315I, require advanced strategies like ponatinib or SCT. Continuous research into the molecular mechanisms of resistance and the development of novel therapeutic agents is essential to optimize CML care.

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