WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL RESEARCH

Review Article

Coden USA: WJPPCL

2026
Volume: 03
Issue: 09
Page: 29-42

MECHANISM OF TYROSINE KINASE INHIBITOR RESISTANCE IN CHRONIC MYELOID LEUKAEMIA: SIGNALLING PATHWAY CROSSTALK AND THERAPEUTIC STRATEGIES

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Received: 02 July 2026 **Revised: 23 July 2026** **Accepted: 12 August 2026**

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DOI: http://doi.org/10.5281/zenodo.22261767,

ABSTRACT

Tyrosine kinase inhibitors (TKIs) have transformed chronic myeloid leukaemia (CML) from a fatal disease into a manageable chronic condition by targeting the BCR-ABL1 oncoprotein. However, primary and acquired resistance continue to compromise long-term outcomes. This review examines the molecular basis of TKI resistance, encompassing BCR-ABL1-dependent mechanisms such as kinase domain mutations and gene amplification, alongside BCR-ABL1-independent pathways including PI3K/AKT, RAS/MAPK, and JAK/STAT5 crosstalk, drug transporters, epigenetic changes, and leukemic stem cell persistence. Emerging therapeutic strategies—allosteric inhibitors, rational combinations, stem-cell-directed approaches, and novel degrader technologies—are discussed as promising avenues toward overcoming resistance and achieving durable, treatment-free remission.

KEYWORDS: Chronic Myeloid Leukemia; BCR-ABL1; Tyrosine Kinase Inhibitor Resistance; T315I Mutation; Signaling Pathway Crosstalk; Leukemic Stem Cells; Allosteric Inhibitors; Treatment-Free Remission.

INTRODUCTION

CML Pathophysiology & the Philadelphia Chromosome/BCR-ABL1 Fusion

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder originating from malignant transformation at the level of the pluripotent hematopoietic stem cell. The hallmark

of CML pathophysiology is the reciprocal chromosomal translocation t (9;22) (q34; q11.2), which generates the abnormal Philadelphia Ph chromosome.[2] This genetic rearrangement fuses the breakpoint cluster region BCR gene on chromosome 22 with the abelson murine leukemia viral oncogene homolog 1 ABL1gene on chromosome 9.

The resulting BCR-ABL1 fusion gene encodes a constitutively active chimeric tyrosine kinase protein (typically the p210 variant) that loses normal autoinhibitory regulation.[2] Unchecked downstream signaling through pathways such as Janus kinase/signal transducer and activator of transcription JAK-STAT, phosphatidylinositol 3-kinase/protein kinase B PI3K-AKT, and Ras/mitogen-activated protein kinase MAPK grants leukemic cells a powerful survival and proliferative advantage, ultimately driving uncontrolled myeloid expansion across the chronic, accelerated, and blast phases of the disease.[4]

Evolution of TKIs (1st–3rd Gen: Imatinib Nilotinib/Dasatinib Ponatinib/Asciminib)

The clinical management of CML was revolutionized by the advent of targeted therapy designed specifically to inhibit the BCR-ABL1 oncoprotein.[1,2] The therapeutic landscape has evolved through distinct generations:

- **First-Generation TKI:** Imatinib mesylate, introduced around 2000, established the paradigm of precision oncology by competitively binding to the ATP-binding pocket of the inactive ABL kinase domain, transforming CML from a fatal malignancy into a manageable chronic condition.[3]
- **Second-Generation TKIs:** Agents such as nilotinib and dasatinib were subsequently engineered to exhibit significantly higher potency (10- to 30-fold greater than imatinib) and overcome resistance driven by many common point mutations while managing broader kinase profiles.[1]
- **Third-Generation and Novel Inhibitors:** Ponatinib was developed to target refractory mutations, most notably the notorious gatekeeper mutation T315I, which confers resistance to earlier-generation agents. More recently, asciminib acts as an allosteric inhibitor (STAMP inhibitor) by binding to the myristoyl pocket of ABL1, offering exceptional specificity and minimizing off-target toxicities.[4]

Clinical Burden of Resistance & Rationale for Review

Despite the remarkable long-term survival rates achieved with modern TKIs, a subset of patients still encounters therapeutic failure due to primary (intrinsic) or secondary (acquired) resistance (4). Clinically, resistance manifests as treatment failure, disease progression to

advanced phases, or the persistence of measurable residual disease that hinders achieving treatment-free remission (TFR).[2,3]

While ABL1 kinase domain point mutations represent a classic mechanism of resistance, emerging evidence highlights complex compensatory survival networks—including signaling pathway crosstalk, epigenetic alterations, and bone marrow microenvironment protections.[4] This review aims to comprehensively evaluate the molecular mechanisms underpinning TKI resistance in CML, analyze intricate signaling pathway cross-talk, and appraise modern therapeutic strategies designed to bypass or overcome drug resistance in clinical practice.

Classification of TKI Resistance

Primary vs. Secondary (Acquired) Resistance

Therapeutic failure against tyrosine kinase inhibitors in chronic myeloid leukemia manifests in two clinically distinct patterns: primary and secondary resistance.[8] Primary (or intrinsic) resistance occurs when a patient fails to achieve established milestones of optimal response right from the start of therapy, showing an inadequate initial decrease in the BCR-ABL1 transcript levels despite adhering to the prescribed dosage.[5] This form of early failure often stems from pre-existing resistant leukemic clones, unfavorable baseline pharmacokinetics, or intrinsic cellular features that blunt drug efficacy from day one.

In contrast, secondary (or acquired) resistance develops after an initial optimal or good response has been successfully attained.[8] Patients experience a subsequent loss of hematologic, cytogenetic, or major molecular response, characterized by rising transcript levels or disease relapse.[5] Acquired resistance typically emerges due to the selective pressure of ongoing therapy, which drives the spontaneous outgrowth of secondary mutations or alternative survival adaptations within the leukemic stem cell pool.

BCR-ABL1–Dependent vs. BCR-ABL1–Independent Mechanisms

The underlying drivers of TKI resistance are broadly bifurcated into two categories based on their direct reliance on the target oncoprotein: BCR-ABL1-dependent and BCR-ABL1-independent mechanisms.[7]

- **BCR-ABL1-Dependent Mechanisms:** These involve modifications directly affecting the oncoprotein itself, preserving its kinase activity or preventing drug binding despite the presence of the inhibitor.[9] This category includes point mutations within the catalytic domain, gene amplification, and specific variant transcripts that directly interfere with

TKI binding efficacy. Because the target itself is altered or overproduced, cancer cells maintain oncogenic signaling that drives disease persistence.

- **BCR-ABL1-Independent Mechanisms:** These pathways allow leukemic cells to survive and proliferate even when BCR-ABL1 is successfully inhibited.[7] Driven by factors outside the direct target—such as aberrant activation of parallel survival pathways, epigenetic modifications, drug efflux transporter overexpression, and protective signals from the bone marrow microenvironment—these mechanisms bypass the drug's intended point of action entirely.[9]

BCR-ABL1–Dependent Resistance Mechanisms

Kinase Domain Point Mutations (T315I, Compound Mutations)

The single most frequent cause of acquired TKI resistance is the development of point mutations within the catalytic kinase domain of the ABL1 region.[9] More than 100 distinct single amino acid substitutions have been documented, each conferring varying degrees of cross-resistance to different inhibitors.[6] These mutations typically alter the spatial conformation of the ATP-binding pocket, steric bulk, or crucial hydrogen-bonding networks required for drug attachment, while still allowing ATP access or maintaining basal kinase activity.

Among these, the substitution of threonine with isoleucine at codon 315—known as the **T315I gatekeeper mutation**—is historically the most challenging clinical hurdle.[9] The bulky isoleucine side chain creates a steric clash that blocks the entry of imatinib, nilotinib, and dasatinib into the hydrophobic pocket. Furthermore, prolonged exposure to sequential therapies can lead to **compound mutations**, where two or more distinct point mutations occur sequentially within the same BCR-ABL1 allele.[6] Compound mutations severely narrow treatment options by blocking almost all second- and third-generation inhibitors, necessitating alternative strategies like ponatinib or allosteric inhibition.

BCR-ABL1 Gene Amplification/Overexpression

Beyond structural alterations in the kinase domain, quantitative overexpression of the BCR-ABL1 transcript serves as another direct mechanism of resistance.[7] Amplification of the fusion gene or increased transcription rates can lead to an overabundance of the target protein. When intracellular oncoprotein levels exceed the stoichiometric binding capacity of a standard therapeutic dose of a TKI, sufficient active kinase molecules remain uninhibited to

sustain downstream proliferative signaling.[9] This dosage-dependent evasion highlights why monitoring transcript copy numbers is critical in clinical management.

Splice Variants

Alternative mRNA splicing adds another layer of complexity to BCR-ABL1-dependent resistance. Variations in how the fusion transcript is processed can produce structurally altered isoforms—such as distinct insertions or variations in the ATP-binding region—that impact drug susceptibility.[6] These variant transcripts alter protein conformation or expression stability, allowing the leukemic clone to diminish drug binding affinity while preserving the essential downstream signals needed for cellular survival and disease progression.

BCR-ABL1–Independent Mechanisms & Signalling Crosstalk

PI3K/AKT/mTOR Pathway Activation

Even when tyrosine kinase inhibitors successfully block the BCR-ABL1 oncoprotein, leukemic cells can evade apoptosis by upregulating parallel survival networks, most notably the phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin PI3K/AKT/mTOR axis.[12] This pathway acts as a major cellular hub governing protein synthesis, cell growth, and survival.

In drug-resistant chronic myeloid leukemia (CML) cells, autocrine growth factor loops or alternative receptor tyrosine kinases maintain AKT phosphorylation independently of BCR-ABL1. Once activated, AKT inhibits pro-apoptotic proteins like Bad and Bax while stimulating mTOR, ensuring that leukemic cells continue to proliferate despite drug-induced target suppression.[10]

RAS/MAPK Pathway

The Ras/mitogen-activated protein kinase RAS/MAPK cascade represents another vital survival route utilized by resistant clones.[12] Normally, BCR-ABL1 heavily signals through this pathway to drive cell division. However, secondary genetic alterations, such as downstream activating mutations in NRAS or KRAS, or enhanced signaling from alternative cytokine receptors (e.g., interleukins), can reactivate the Raf-MEK-ERK module. This bypasses the blocked BCR-ABLkinase domain entirely, continuously transcribing proliferation-associated genes and preventing cell cycle arrest.

JAK/STAT5 Signalling

The Janus kinase/signal transducer and activator of transcription JAK/STAT pathway—specifically STAT5—is constitutively hyperactivated in CML and plays a central role in leukemic stem cell (LSC) maintenance.[11] During TKI treatment, alternative hematopoietic cytokines present within the bone marrow microenvironment can stimulate JAK family members to phosphorylate STAT5 directly. Activated STAT5 translocates to the nucleus to transcribe anti-apoptotic genes like BCL-XL, effectively neutralizing the apoptotic signals triggered by TKI therapy and protecting the malignant clone from drug-induced cell death.

SRC-Family Kinases (LYN, HCK)

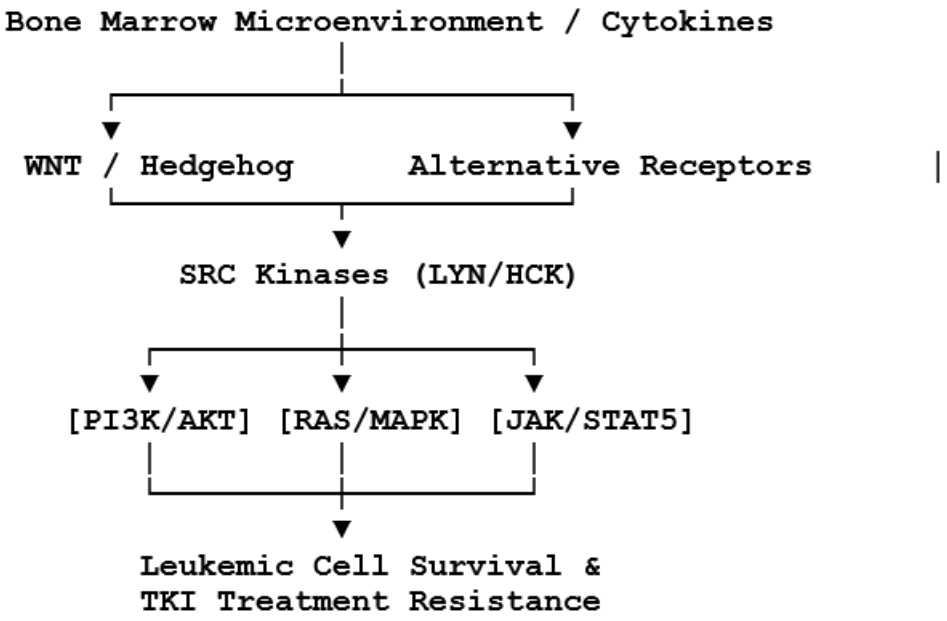
Overexpression and hyperactivation of SRC-family kinases, particularly LYN and HCK, are classic hallmarks of BCR-ABL1-independent resistance.[10] LYN forms a complex with BCR-ABL1 and remains active even in the presence of imatinib. By taking over downstream phosphorylation duties, LYN compensates for inhibited ABL1, maintaining active PI3K/AKT and MAPKsignaling networks and driving survival in primitive leukemic stem cells.

WNT/β-Catenin and Hedgehog Pathways

Primitive CML stem cells capable of surviving prolonged TKI exposure frequently rely on embryonic developmental pathways, including WNT/β -catenin and Hedgehog signaling.[10] These pathways are largely independent of BCR-ABL1 enzymatic activity. Instead, they are regulated by niche interactions within the bone marrow microenvironment. Their activation promotes self-renewal, stemness preservation, and dormancy, shielding a reservoir of quiescent leukemic cells from standard antiproliferative therapies and seeding eventual relapse.

Integrated Crosstalk Model

To conceptualize how these survival routes interconnect, the network can be visualized as a multi-layered web surrounding the blocked target:



As illustrated in this crosstalk model, when a TKI shuts down BCR-ABL1, compensatory inputs from the microenvironment activate SRC kinases and parallel pathways PI3K, MAPK, JAK/STAT. This interconnected signaling architecture explains why single-agent targeted inhibition often fails to eradicate primitive leukemic stem cells, providing a strong rationale for combination treatment strategies.[10,11]

Non-Signalling Resistance Contributors

Drug Transporters (OCT1 Influx, ABCB1/ABCG2 Efflux)

Intracellular drug bioavailability is a primary determinant of therapeutic efficacy in chronic myeloid leukemia (CML). Resistance frequently arises not from target mutation, but from altered transmembrane transport that limits intracellular drug accumulation.[38] Organic Cation Transporter 1 (OCT1), expressed on the basolateral membrane of hepatocytes and leukemic cells, is principally responsible for the cellular influx of imatinib.[18] Reduced OCT1 expression or impaired transport activity significantly decreases intracellular drug concentrations, blunting target inhibition.

Conversely, active efflux pumps belonging to the ATP-binding cassette (ABC) superfamily—namely ABCB1 (P-glycoprotein) and ABCG2 (BCRP)—are frequently upregulated in drug-resistant leukemic clones.[19] These membrane proteins actively pump tyrosine kinase inhibitors (TKIs) out of the intracellular compartment against a concentration gradient, preventing the drug from reaching its threshold inhibitory concentration at the BCR-ABL1 catalytic domain.

Epigenetic Dysregulation (DNA Methylation, miRNAs)

Beyond genetic mutations and transporter anomalies, epigenetic modifications drive stable, heritable changes in gene expression that facilitate TKI evasion without altering the underlying DNA sequence.[23] Aberrant DNA hypermethylation of tumor suppressor gene promoters silences pro-apoptotic pathways, while global hypomethylation can destabilize genomic integrity.

Furthermore, non-coding RNAs, particularly microRNAs miRNAs, play pivotal regulatory roles in CML progression and drug resistance.[31] Downregulation of tumor-suppressive miRNAs miR-217 or miR-451 and overexpression of oncogenic miRNAs such as miR-21 directly modulate apoptotic machinery, promote cell cycle progression, and upregulate survival networks independently of BCR-ABL1 activity.

Leukemic Stem Cell (LSC) Persistence & Bone Marrow Niche

A major obstacle in curing CML is the persistence of quiescent, self-renewing leukemic stem cells LSCs residing within specialized microenvironmental niches in the bone marrow.[15] Unlike proliferating progenitor cells, primitive LSCs are largely independent of BCR-ABL1 kinase activity for survival, rendering standard {TKIs} ineffective against them.[25]

The bone marrow niche—comprising mesenchymal stem cells, osteoblasts, endothelial cells, and extracellular matrix components—provides biochemical and physical protection through adhesion molecules VLA-4, CXCR4-CXCL12 and hypoxia responses.[21] This microenvironment shields LSCs from drug-induced cytotoxicity, establishing a dormant cellular reservoir capable of triggering clinical relapse upon drug withdrawal.

Immune Evasion

Leukemic cells actively subvert host anti-tumor immune surveillance to evade elimination by the immune system.[32] Resistant CML clones frequently up regulate immune checkpoint ligands, such as Programmed Death-Ligand 1 PD-L1, which bind to corresponding inhibitory receptors PD-1 on cytotoxic T-cells and natural killer NK cells, inducing exhaustion and functional anergy.[26] Additionally, the secretion of immunosuppressive cytokines e.g. TGF-beta, IL-10 within the leukemic microenvironment suppresses effector lymphocyte proliferation, creating an immune-privileged niche that facilitates disease persistence.

Therapeutic Strategies to Overcome Resistance

Next-Gen/Allosteric TKIs (Ponatinib, Asciminib/STAMP Inhibitors, Olverembatinib)

To combat resistance driven by kinase domain mutations, particularly the notorious T315I gatekeeper mutation, a new generation of targeted inhibitors has been engineered.[16] Ponatinib, a third-generation pan-BCR-ABL1 inhibitor, utilizes a carbon-carbon triple bond in its structure to fit snugly into the hydrophobic pocket despite steric hindrance, effectively neutralizing almost all single and compound mutations.[16]

Representing a paradigm shift, asciminib acts as an allosteric inhibitor (specifically targeting the Myristoyl Pocket STAMP by binding to the myristoyl-binding site rather than the ATP-binding pocket.[20] This mechanism mimics natural autoinhibition, providing exceptional specificity and avoiding off-target toxicities while overcoming ATP-competitive resistance. Concurrently, novel third-generation agents like olverembatinib (HQP1351) have shown promising clinical activity against refractory CML populations in Asian cohorts.[27]

Rational Combination Therapies (TKI + IFN, TKI + Asciminib)

Combining therapeutics with distinct mechanisms of action represents a robust approach to deepening molecular responses and targeting drug-resistant clones.[34] The combination of a standard TKI with pegylated interferon-alpha IFN-alpha leverages immune-mediated clearance and anti-proliferative effects to target residual cycling leukemic cells, improving rates of treatment-free remission.[30]

Similarly, combining an ATP-competitive TKI with the allosteric inhibitor asciminib provides dual-targeting of the BCR-ABL1 onco protein.[33] This dual-site inhibition prevents the emergence of secondary mutations, as a single mutant clone would need to acquire simultaneous resistance alterations at two structurally distinct protein domains, a statistically improbable event.

LSC-Directed Approaches (Autophagy Inhibitors, Metabolic Targeting)

Because quiescent leukemic stem cells survive standard TKIs, specialized metabolic and survival dependencies are increasingly being exploited.[35] Autophagy acts as a survival mechanism that allows LSCs to withstand cellular stress induced by drug treatment. Consequently, combining TKIs with autophagy inhibitors (such as hydroxychloroquine) blocks this recycling pathway, sensitizing dormant LSCs to apoptotic cell death.[13]

Furthermore, targeting altered cellular metabolism—such as inhibiting oxidative phosphorylation via mitochondrial complex inhibitors or suppressing fatty acid oxidation—depletes the energy reserves required by quiescent LSCs, selectively eradicating the resistant reservoir.[28]

Emerging Modalities: PROTACs/Degraders, CAR-T/Immunotherapy, Epigenetic Agents (HDAC + Proteasome Inhibition)

Cutting-edge pharmacological modalities are transforming the future management of refractory CML:

- **PROTACs (Proteolysis Targeting Chimeras):** These bifunctional molecules bind simultaneously to BCR-ABL1 and an E3 ubiquitin ligase, tagging the oncoprotein for targeted destruction via the ubiquitin-proteasome system rather than merely inhibiting its enzymatic function.[14]
- **CAR-T Cell Therapy and Immunotherapy:** Chimeric antigen receptor CAR T-cells and bispecific T-cell engagers BiTEs directed against surface antigens on leukemic cells are being explored to harness patient immunity for clearing resistant clones.[37]
- **Epigenetic Combinations:** The addition of histone deacetylase HDAC inhibitors (e.g., vorinostat) or DNA methyltransferase inhibitors alongside proteasome inhibitors reactivates silenced tumor suppressor genes and induces terminal differentiation in resistant blasts.[22]

Conclusion & Future Perspectives

Treatment-Free Remission Outlook, Unmet Needs

The management of chronic myeloid leukemia has evolved from palliative care into one of the greatest success stories of precision oncology. With the availability of diverse generations of tyrosine kinase inhibitors, allosteric agents, and multi-targeted therapeutic strategies, long-term survival rates for CML patients now approach those of the general age-matched population.[26] A major modern therapeutic objective is achieving treatment-free remission TFR, allowing successfully managed patients to safely discontinue therapy without experiencing molecular recurrence.[29]

Despite these monumental clinical strides, significant unmet needs persist. The emergence of compound mutations, the resilience of dormant leukemic stem cells residing within the protective bone marrow microenvironment, and long-term drug-related toxicities remain formidable barriers to a universal cure.[36] Future clinical research must focus on optimizing

combination regimens, translating novel single-cell omics discoveries into practice, and deploying targeted degraders and immunotherapies. Addressing these intricate challenges will pave the way toward eradicating drug resistance entirely and achieving sustained, treatment-free functional cures for all patients with CML.

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