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# Mechanisms of *BCR-ABL* in the pathogenesis of Chronic Myeloid Leukemia (CML): A Review

*Review Article*

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## Abstract

The most frequent myeloproliferative condition among chronic neoplasms is chronic myeloid leukemia (CML). CML was the first blood malignancy to be linked to a recurrent chromosomal change, a reciprocal translocation between chromosome 9's long arms and the Philadelphia chromosome 22. Ph not only compromises genomic stability but also damages physiological signaling pathways in leukemia. The breakpoint cluster region-proto-oncogene tyrosine-protein kinase (BCR-ABL) oncogenic protein with continuously increased tyrosine kinase activity is encoded by this abnormal fusion gene. The kinase activity is responsible for cell proliferation, differentiation inhibition, and cell death resistance, and we present an overview of tyrosine kinase activity and inhibitors in relation to leukemogenesis here. The focus of this review will be on BCR-ABL-independent processes, with a particular focus on those with therapeutic implications in the treatment of CML patients.

**Keywords:** CML (Chronic myeloid leukemia), AML (Acute myeloid leukemia), ALL (Acute lymphoid leukemia), CLL (Chronic lymphoid leukemia)

## Introduction

Leukemia is a heterogeneous group of hematopoietic disorders which includes several diverse and biologically distinct subgroups [1]. It usually starts with the bone marrow which results in the development of alterations in white blood cells. These white blood cells are not fully developed and are called blasts cells [2]. This uncontrolled proliferation of white blood cells (leukocytes) in the bone marrow and lymphatic system leads to progression towards a leukemic state [3] as shown in (Figure 1).

Differentiation of leukemia is based on the developmental phases of the disease (acute or chronic), the cells involved (lymphoid or myeloid), and the type of blood cells affected, depending on the stages of disease progression [5]. Acute lymphoid leukemia (ALL), acute myeloid leukemia (AML), chronic lymphoid leukemia (CLL), and chronic myeloid leukemia (CML) are the four primary subtypes of leukemia. ALL and AML progress quickly, necessitating more severe treatment to extend the patient's life expectancy, but CLL and CML progress more slowly and may lie untreated for year [6]. .CML is a form of CML that has a higher survival rate than the other subtypes and is triggered by chromosomal translocation.

### Incidence

The American Cancer Society (ACS) estimated that 8990 new cases of CML were diagnosed in 2019, out of which 5250 were males and 3740 females [7]. CML the commonest adult leukemia and the annual incidence ranges from 0.8-2.2/100,000 population in males and 0.6-1.6/100,000 population in females in India [8].

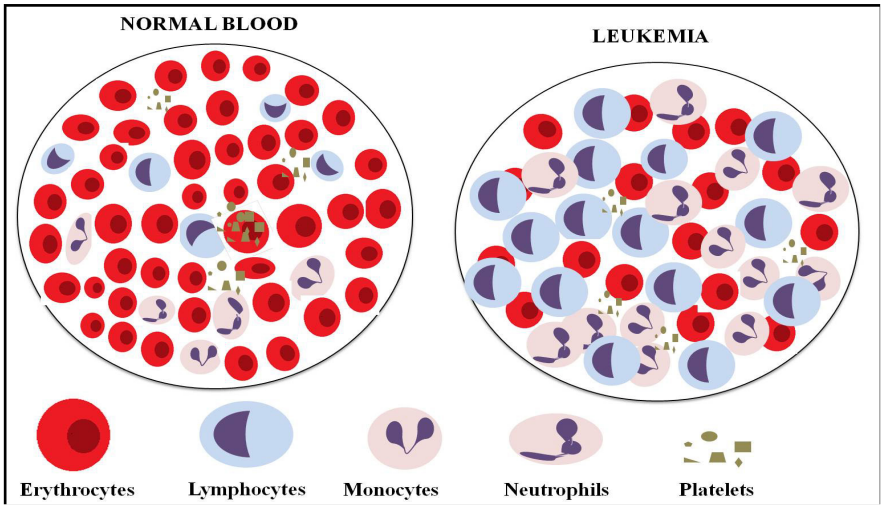


**Figure 1:** Showing the difference between normal cells and leukemia cell [4].

### Chronic Myeloid Leukemia

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder characterized by the Philadelphia (Ph) chromosome, which results from t(9;22) (q34;q11) balanced reciprocal translocation [9]. The molecular consequence of the Philadelphia chromosome is the generation of the *BCR*- ABL oncogene that encodes for the chimeric *BCR*-ABL oncoprotein, with constitutive kinase activity that promotes the growth advantage of leukemia cells as shown in (Figure 2).

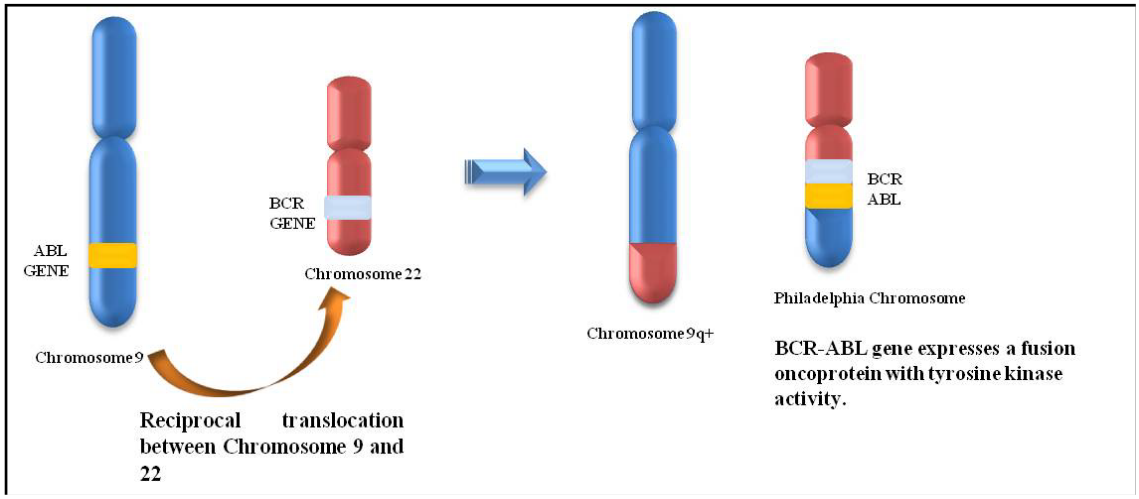


**Figure 2:** A reciprocal translocation t (9:22) produces the Philadelphia chromosome leading to Chronic Myeloid Leukemia (CML).

## Mechanism of Chronic Myeloid Leukemia (CML)

The t (9;22) Philadelphia chromosome (Ph) produces the BCR/ABL fusion oncogene in 3 main types (P190, P210, and P230). Different markers in the BCR gene on chromosome 22 produce these proteins [10]. These oncogenes produce three separate fusion proteins with molecular masses of 190, 210, and 230 kD, respectively, that contain the similar portion of the c-ABL tyrosine kinase in the COOH terminus but varied in the amount of BCR sequence at the NH2 terminus. Consistent genomic recombination between two genes BCR on the long arm of chromosome 22 and ABL on the long arm of chromosome 9 results in their juxtaposition, resulting in the BCR-ABL fusion gene [11].

The genomic breakpoints for BCR and ABL are highly variable although recombination frequently occurs when intron 1, intron 13/14, or exon 19 of BCR are fused with a 140-kb stretch of ABL between exons 1b and 2 [12]. The fusion of BCR exon 13 and ABL exon 2 (e13a2) or e14a2 (p210 BCR- ABL1) forms the main BCR- ABL1 transcript (M- BCR, formerly known as b2a2 and b3a2) [13] lly found in CML, however it can also be found in ALL or AML The minor BCR-ABL1 transcript (m-BCR) encodes a hybrid 190-kDa protein that is encoded by p190 BCR-ABL (e1a2) as shown in (Figure 3).

Figure 3: Showing *BCR*- ABL translocation with three breakpoint regions. Exon e1 of *BCR* and a2 of ABL fuse they form e1a2 (p190) minor *BCR*- ABL breakpoint. When exon b2 of *BCR* and exon a2 of ABL fuse they form major b2a2 or b3a2 (p210) BCR- ABL breakpoint and last breakpoint is when e19 of *BCR* and exon a2 of ABL fuse they form p230 *BCR*-ABL.

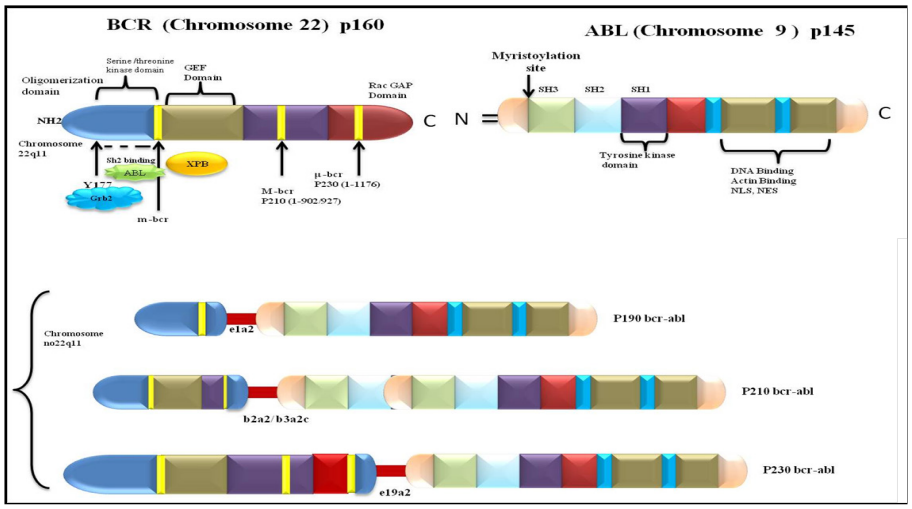


**Figure 3:** Showing BCR- ABL translocation with three breakpoint regions.

## Importance of BCR-ABL in Subtypes of Leukemia

### Acute Lymphoblastic Leukemia

*BCR*-ABL1 is not only limited to CML. It is also present in 11%-29% of ALL patients [14]. but is relatively rare in childhood ALL (1%-3%) [15]. The $p210^{BCR-ABL}$ transcript is detected in 30% of adults and 20% of childhood patients with Ph-positive ALL [16]. The *BCR*-ABL variant e3a2 (exon 3 of *BCR* and exon 2 of ABL) is also detected in some cases of Ph-positive ALL, which is similar to ALL with p190 BCR-ABL transcript [17].

### Acute Myeloid Leukemia

*BCR*-ABL transcripts are hardly found in AML [18]. Ph-positive AML is cytogenetically indistinguishable from Ph-positive CML, but molecular studies show that, in 50% of cases, the breakpoint on chromosome 22 in Ph-positive AML is different from those very consistently found in CML [19]. Some studies have confirmed that *BCR*-ABL -positive AML is unique acute leukemia with some features distinct from myeloid CML-BC [20]. as shown in (Table 1).

**Table 1:** Showing some cytogenetic Abnormalities Leading to Positive and Negative CML Progression.

| Cytogenetics Abnormalities Leading to the expression of Deregulated Tyrosine Kinase in Chronic Myeloid Leukemia | | | |
|---|---|---|---|
| Cytogenetic Abnormality | Tyrosine Kinase Fusion Protein | Disorder | Reference |
| t(9;22) (q34;q11) | BCR- ABL | Chronic Myeloid Leukemia | [21-23] |
| | | Acute Myeloid Leukemia | [24] |
| | | Acute Lymphoblastic Leukemia | [25] |
| t(8;22) (p11;q11) | BCR-FGFR1 | BCR- ABL-negative CML | [26,27] |
| t(8;22) (p11;q11) | BCR-PDGFRA | A typical CML | [28,29] |
| t(9;12) (q34;p13) | TEL- ABL | Atypical CML or BCR- ABL negative CML | [30-32] |
| t (9;22) (p24; q11) | BCR-JAK2 | Atypical CML or BCR- ABL negative CML | [33-35] |

## Downstream Signaling Pathway of BCR-ABL Kinase

The ABL protein shuttles between the cytoplasm and the nucleus; when fused to *BCR*, the oncoprotein loses this property and is mainly retained within the cytoplasm, where it interacts with the majority of proteins involved in the oncogenic pathway [36]. ABL tyrosine kinase activity is constitutively activated by the juxtaposition of *BCR*, thus favoring dimerization or tetramerization and subsequent autophosphorylation [37]. This increases the number of the phosphor tyrosine residues on BCR-ABL and, as a consequence, the binding sites for the SH2 domains of other protein (38). Ras mitogen-activated protein kinase (MAPK) leading to increased proliferation, the Janus-activated kinase (JAK)–STAT pathway leading to impaired transcriptional activity, and the phosphoinositide 3-kinase (PI3K)/ AKT pathway resulting in increased apoptosis [39].

### Ras and the Mitogen-Activated Protein kinase Pathways

*BCR*- ABL binds directly to proteins that activate Ras [40]. Autophosphorylation of tyrosine 177 generates a binding site for the adapter molecule Grb-2 [41]. Grb2 associates with the Sos protein, which stimulates the conversion of the inactive GDP-bound form of Ras to the active GTP-bound state [42]. Ras also may be activated by two other adapter molecules, Shc and CrkL (CRK like protein), which are substrates of BCR- ABL [43]. Activated Ras binds to the serine-threonine kinase Raf-1, recruiting it to the plasma membrane where it is activated by tyrosine phosphorylation and initiates a signaling cascade by way of the mitogen-activated protein kinase (MAPK) pathway (44).

### Janus kinase– signal transducer and activator of transcription pathway

Phosphorylation of members of the signal transducer and activator of transcription (STAT) family of transcription factors has been reported in BCR ABL–positive cells. STATs are phosphorylated by Janus kinases (JAK) that are downstream of growth factor receptors [45]. In contrast, phosphorylation of STAT5 in BCR- ABL - expressing myeloid cells appears to be mediated by the Src family kinase, Hck, which binds the SH2 and SH3 domains of BCR- ABL [46]. JAK2 pathway targets BMI1 (oncogene) member of PRC1 and PRC2 complex. BMI1 and PRC complex help in chromatin remodeling and mutation in BMI1 can disrupt the P14ARF and P16Ink4A [47]. which leads to leukemogenesis.

## Phosphatidylinositol 3 Kinase Pathway

The proliferation of the BCR- ABL signaling pathway mostly is dependent on PI-3 kinase [48]. BCR- ABL apparently activates this pathway by forming a multimeric complex with PI-3 kinase and the adaptor molecules CBL and Crk. In BCR- ABL–expressing cells, activated PI-3 kinase stimulates the serine-threonine kinase Akt [49]. Besides, activated Akt may function in an antiapoptotic capacity [50]. Bad promotes cell death by binding to and thereby inactivating the antiapoptotic Bcl-2 and Bcl-Xl [51]. Thus, phosphorylation of Bad by Akt may prevent it from binding to these proteins, resulting in reduced apoptosis. Indeed, increased Bad phosphorylation was seen in BCR-ABL positive with Bad completely dephosphorylated, a fraction of cells survived, indicating the existence of Bad-independent survival pathways [52].

### TP53 Pathway

The TP53 mutation rate is known to increase with CML disease progression, a 30% reported rate of BC CML cell mutations [53]. PI3K activates MDM2 which is regulated by Bcr-Abl and may play an essential role in the progression of CML. the activation of p53 via MDM2 inhibition induces cell death and enhances the efficacy of chemotherapeutic agents in hematological malignancies [54]. Over expression of MDM2 has been reported to correlate with nutlin3a sensitivity in both AML and ALL [55].as shown in (Figure 4).

Figure 4: Cytoplasmic BCR- ABL1 signaling pathways activated in chronic myeloid leukemia (CML) cells.

Imatinib mesylate binds to the ATP-binding site in the kinase domain of the BCR/ ABL tyrosine kinase, thus preventing ATP binding and activation of the kinase [56]. Several highly potent next-generation BCR- ABL inhibitors have been developed to overcome imatinib resistance and improve the prognosis of patients with CML. These include novel and more potent multi-TKIs such as dasatinib, an orally bioavailable dual BCR- ABL and Src inhibitor, and potent selective BCR- ABL inhibitors such as nilotinib [57]. Dasatinib blocks BCR- ABL at low concentrations but is less selective than imatinib [58]. Similarly, to imatinib, it inhibits BCR- ABL, Kit, and platelet-derived growth factor receptor (PDGFR) and blocks Src, Tec, and Eph kinases. Nilotinib blocks BCR- ABL at lower concentrations but, like imatinib, it appears to be more selective than dasatinib in targeting tyrosine kinases [36]. Imatinib thus induced the complete hematologic responses in more than 95 percent of patients with CML [59].as shown in (Figure 5).

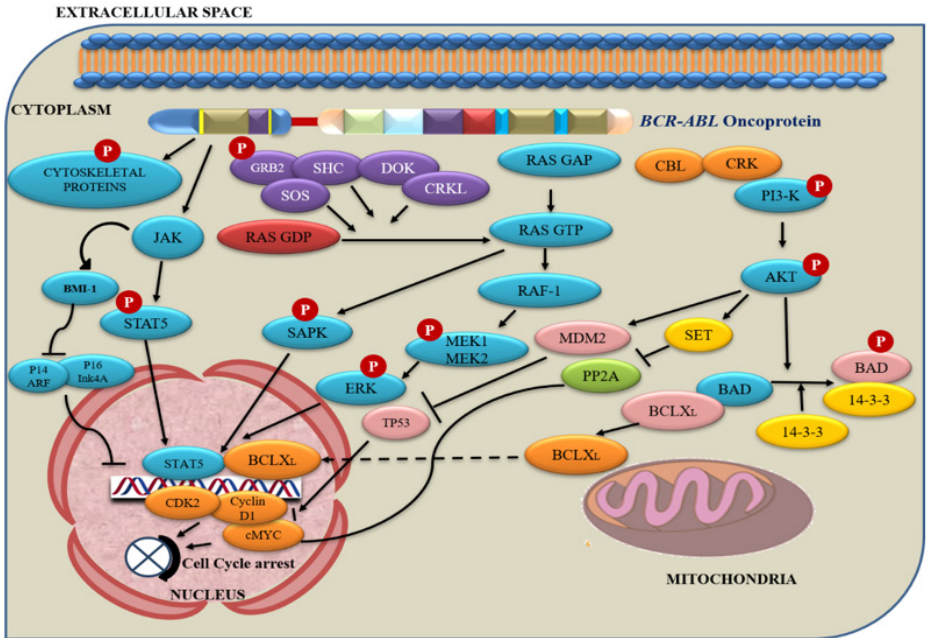


**Figure 4**: Cytoplasmic *BCR*- ABL1 signaling pathways activated in chronic myeloid leukemia (CML) cells.

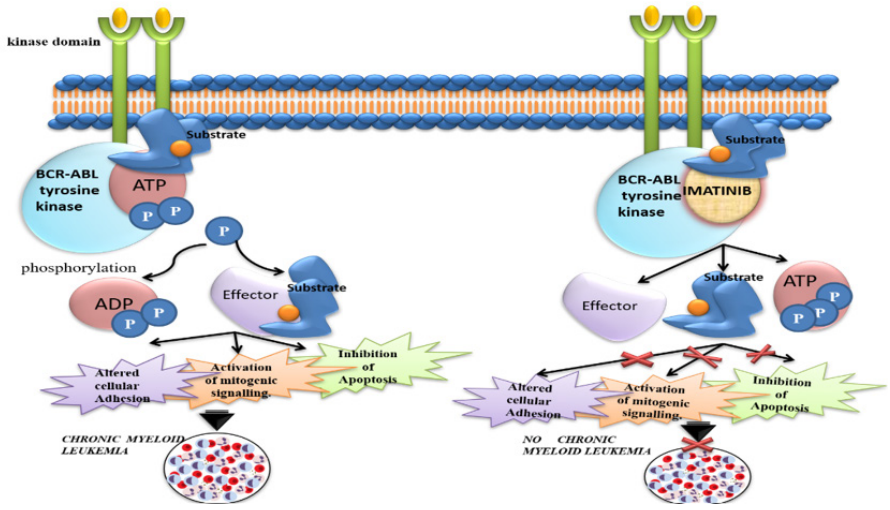


**Figure 5:** Mechanism of action with imatinib (A) The constitutively active BCR- ABL tyrosine kinase functions by transferring phosphate from ATP to tyrosine residues on various substrates to cause excess proliferation of myeloid cells leading to the formation of leukemia. (B) Imatinib blocks the binding of ATP to the BCR- ABL tyrosine kinase, thus inhibiting kinase activity.

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Imatinib directly inhibits the constitutive tyrosine kinase activity, which results in the modification of the function of various genes involved in the control of the cell cycle, cell adhesion, cytoskeleton organization, and finally in the apoptotic death of leukemic cells [60]. As a result, the transmission of proliferative signals to the nucleus is blocked and leukemic cell apoptosis is induced [61]. Therapy with imatinib mesylate results in a durable and complete cytogenetic response in the early stages of CML.

These findings can act as a predictive or prognostic biomarker for the earlier diagnosis of leukemia. The findings of the study will pave a way for designing therapeutic interventions.

## Conclusion

The BCR-ABL chimeric protein plays central role in the pathogenesis of chronic myeloid leukemia and Acute myeloid leukemia. The translocation leads to persistent TK activation and genomic instability during leukemogenesis. Disorders in multiple signaling pathways and genetic abnormalities combined with the Ph are essential for the evolution of different types of leukemia. A greater understanding of leukemogenesis and the effect of treatment on clonal evolution will provide novel insights into the design of future therapeutic strategies for Ph-positive leukemia.

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## Contribution of Author

A.B wrote the review. R.S, GRB and M critically edits the manuscript. RK finalized the review article.

## Conflict of interest/Competing Interests

There is no conflict of interest.

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