

REVIEW ARTICLE**MOLECULAR BIOLOGY AND DRUG THERAPIES OF CHRONIC MYELOID
LEUKEMIA: A REVIEW OF RECENT LITERATURE**

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ABSTRACT

Background: Chronic myeloid leukaemia (CML) is a clonal myeloproliferative disorder of blood stem cells, which is typically characterized by the presence of a Philadelphia chromosome. Even though there have been several studies on the molecular genetics, pharmacogenomics, pharmacological treatments for CML, and its mechanism is still not fully understood. **Objectives:** This study is designed to provide new updates and better insights into CML molecular biology and drug therapy, along with their benefits and drawbacks. **Methodology:** For this review, the recent literature was searched from January 2019 to 2023 through various electronic databases. **Results:** Review findings further suggested that imatinib mesylate was the first tyrosine kinase inhibitor (TKI) licensed as first-line therapy for affected people with CML in the chronic, blast, and rapid phases. Dasatinib is another second-generation multi-target kinase inhibitor, for imatinib-resistant CML treatment in all stages, which is 325 times more effective than imatinib and 16-fold more effective than nilotinib. Nilotinib received approval from the Food and Drug Administration (FDA) for handling imatinib-resistant patients. Bosutinib and ponatinib are other renowned TKIs taken orally. European Medicine Agency (EMA) and FDA-approved asciminib in moderate to severe, rapid, and blast-phase CML patients intolerant to previous therapies. **Conclusion:** In conclusion, this study indicated the need to include advanced computational tools in addition to the large sample size of cohort studies, which may result in a better understanding of pathophysiology and better clinical outcomes.

Keywords: CML, Drug Therapies, TKIs, Molecular biology

INTRODUCTION

Chronic myeloid leukemia (CML) is a blood malignant disorder induced via *BCR::ABL1* in a cell having acquired or intrinsic biological capacity to develop leukemia (1, 2). It is an ongoing and at times mortal malignant neoplasm associated with erythroid, monocytic, myeloid, megakaryocytic-B, and sometimes T-lymphoid lineages (3). It is the first studied human malignancy with a consistent chromosomal abnormality (4) and the first human disease in which the pathogenetic events of leukemogenesis are associated with Philadelphia (Ph) chromosome (5) that is a particularly consistent chromosomal abnormality (6). The field of cancer biology was revolutionized after the Philadelphia chromosome's discovery in 1960 by the scientists David Hungerford and Peter Nowell. Owing to its particular disease biology, molecular genetics, and treatment, CML has been the most notable area of interest for hematologists (5). CML is genetically regarded as a homogeneous disease because of *BCR::ABL1* translocation (7). Recent studies have further described the molecular processes involved in initiation and progression of CML, and their association with disease progression, clinical manifestation, and therapeutic intervention. It was among the first neoplastic diseases in which leukemic clones were found to be suppressed by immunotherapies resulting in extended survival (8).

Overall, worldwide incidence of CML ranges from 1.0 – 2.0 cases per 100,000 adults annually, occurring 15% in adults (9). People having chronic myeloid leukemia (chronic phase) can be administered with tyrosine kinase inhibitors (TKIs), which impairs the biological action of *P210BCR::ABL1* (5), minimizing CML proliferation, blocking cell signaling and eliciting cell death of CML clones (10). Since the approval of TKIs to treat CML, the global survival rate increased to 70%. Chronic therapy causes the CML cancer stem cell to change, resulting in new resistance and the need for new TKI formulations (11). At present there are total six TKIs introduced i.e. imatinib, nilotinib, dasatinib, bosutinib, ponatinib (10) and asciminib (12). The very first TKI approved clinically was imatinib by the Food and Drug Administration (FDA) and European Medicines Agency (EMA), which is used in treating resistant/refractory CML patients.

Imatinib, dasatinib, nilotinib, and bosutinib drugs are considered to be the first-line treatments approved by the FDA and EMA for CML victims to be treated (12).

Despite several improvements and advancements in the treatment of CML, some patients show intrinsic or acquired resistance in the treatment course (13). A complex and intricate process called resistance to target therapy leads to the selection of cancer clones that may resist treatment (14). ABL kinase mutations, aberrant drug transporter activity, the activation of several signaling pathways, epigenetic dysfunction, the survival of leukemia stem cells, and immune system dysregulation are a few instances of resistance mechanisms (15). So, a prompt switch in therapy and the choice of the best therapies are made possible by the quantification of *BCR::ABL1* transcripts and the identification of *BCR::ABL1* kinase domain (KD) alterations. Although there are several targeted drug treatments for CML patients, it can be difficult to determine which targeted therapy is optimal for individual patients. To increase therapeutic efficacy, the application of intelligent approaches (such as artificial intelligence, mathematical modelling, and computer prediction methods) might foresee the underlying causes of drug resistance. This would make it easier to construct more efficient treatment plans (16).

Rationale

The prevalence of CML is rising in developed and developing countries, which is further associated with high mortality and morbidity rates. Moreover, therapeutic options are limited due to the adverse effect of genomic variants on disease outcomes, particularly in the late phase of CML. Thus, it is the need of the hour to analyze the recent literature available that can ultimately provide more insights into this fatal disease pathophysiology, including the most appropriate therapeutic options available depending on the molecular biology of the CML.

Objectives

The current study aims to examine the etiology and molecular biology of CML, as well as the advantages and disadvantages of current therapy options.

LITERATURE SEARCH

According to the standard approach literature selection was done through various electronic databases such as Google Scholar and PubMed.

Further, this study is restricted to the analyses of articles which were published from 2019 to 2023.

FINDINGS/ANALYSES OF LITERATURE REVIEW

The analysis of literature findings is divided into two sections, namely molecular biology and drug therapies perspective. The details for each section are given under the headings below.

A. Molecular biology

Chronic myeloid leukemia originates in bone marrow from myeloid CD34+/CD38-/CD90+ progenitors. In chronic-phase CML, proliferation is regulated, such that the leukemia cells mature normally and respond appropriately to normal regulators, such as granulocyte-colony-stimulating and macrophage-colony-stimulating factors (1). The incomplete differentiation of blood or hematopoietic stem cells into mature cells and aggregation of such immature hematopoietic stem cells into bone marrow and peripheral blood is the cause of CML.

At the cytogenetic level, CML disorder is attributed to a reciprocal translocation event occurring between chromosomes 9 and 22 generating a shortened “Philadelphia chromosome” (17). The 3’ segment of Abelson tyrosine-protein kinase 1 (ABL1) gene on chromosome 9q34 translocate to 5’ Breakpoint Cluster Region (BCR) on the chromosome 22q11 long arm [t(9;22)(q34;q11)], generating a Ph chromosome. This acquired mutation is a hallmark of leukemia and cancer and is identified in 95% of chronic myeloid leukemia patients (18).

At the molecular level, this translocation of gene marks the constitutive activation of the *BCR::ABL1* fusion oncogene that usually codes for 210 KD *BCR::ABL1* chimeric protein (P210*BCR::ABL1*) (1, 19). The resultant *BCR::ABL1* fusion oncoprotein has elevated TKI activity that further activates several other signaling pathways, resulting in leukemogenesis (19). This specific phenotype or leukemogenesis is indicated by abnormal proliferation, mobility, and decreased susceptibility to apoptotic signals (19) and produces a large progenitor population also referred to as leukemia or cancer stem cells (CSCs).

As a matter of fact, to trigger the growth of blood stem cell clones, the *BCR::ABL1* fusion oncogene production in particular multipotent hematopoietic stem cell population might be adequate, indicating

the first step for chronic myeloid leukemia development, accompanied by additional acquired genetic mutations apart from *BCR::ABL1* mutation (19). TKIs are anti-*BCR::ABL* medications that have helped more than 80% of CML patients achieve long-term remissions and even cured roughly one-third of patients. The illness progresses in roughly 30% of CML patients, resulting in morbidities and death, and many patients struggle with medication resistance (17). Because the mechanism of advancement is poorly understood, there are sadly no biomarkers for CML progression (17). However, the unregulated tyrosine kinase activity of *BCR::ABL1* is considered the most significant molecular marker for CML, providing a recognizable marker for therapeutic development (20).

B. Therapeutic strategies

Imatinib

Imatinib mesylate (Gleevec; Novartis Pharmaceuticals Corporation, East Hanover, NJ) stood primary TKI accepted by the FDA in 2001 for CML victims who got resistant or intolerant but later after 2 more years reported as the front-line therapy (21). Imatinib is used to treat those patients with newly diagnosed Ph-positive CML in the chronic phase, as well as individuals with Ph-positive CML in the blast phase, accelerated, or chronic having cytogenic irregularity (22). However, patients diagnosed at earlier stage show good response when given imatinib rather than those in advanced phases (21).

Because it obstructs the *BCR::ABL1* tyrosine kinase activity, this drug is classified as a tyrosine kinase inhibitor. Imatinib has also successfully substituted Interferon alpha as the front-line therapy and produced long-lasting effects. The International Randomized Study demonstrated that around 85% of patients who took imatinib mesylate survived. Imatinib mesylate (Gleevec), a phenylaminopyrimidine chemical, is considered to be a strong inhibitor of ABL tyrosine kinases and selective protein kinase inhibitor created for cancer treatment, and its improved clinical effectiveness was initially demonstrated in the treatment of CML. Imatinib works by blocking ATP by binding the ABL-catalytic protein's domain in an inactive state. As a result, it prevents phosphorylation and activation of substrates important in *BCR::ABL* downstream signal

transduction pathways (23). The pictorial depiction of this process is shown in Figure 1.

Imatinib is usually taken once a day at a 400 mg dosage. If 400 mg is not tolerated and gives optimal response in CP, then a lesser dosage of 300 mg might be administered. In AP, a dosage of 400 mg twice a day can be utilized, however, second-generation TKI is advised in patients who have progressed to more severe illness (24). Imatinib induced complete hematologic responses (CHR) in 98% of patients at doses of ≤ 300 mg per day, major cytogenetic responses (MCyR) in 60%, and complete cytogenetic responses (CCyR) in 41% of patients with a follow-up of 18 months (25). At 400mg dosage CCyR was observed in 66% and MMR in 28% of patients with a follow-up of 12 months (25). Overall, CCyR and MMR rates for CML patients receiving frontline imatinib at 10 years follow-up were observed 92% and 93% respectively (26). With a median follow-up of almost 10 years, it is found that only 20 percent of the patients progress to the advanced phase and the estimated overall survival rate on imatinib therapy was 83.3% (26).

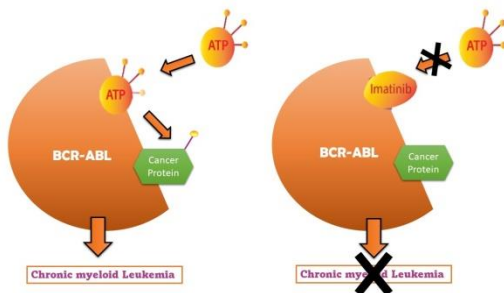


Figure 1. Imatinib, Mechanism of action (binds to the ATP-binding site of the *BCR-ABL* oncoprotein, avoiding ATP-binding and thus interrupting cancer signaling)

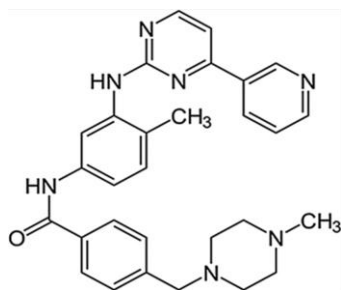


Figure 2. Molecular Formula of Imatinib (Gleevec or Glivec, Novartis) (27)

Dasatinib

Another powerful *BCR::ABL1* multitarget kinase inhibitor of the second generation is a drug called dasatinib (BMS-354825, Sprycel®; Bristol-Myers Squibb, New York, NY, USA). In vitro, this compound is 325 times more effective as compared to imatinib (28) and also 16-fold more powerful than nilotinib, another *BCR::ABL1* kinase inhibitor, against unmutated *BCR::ABL1* (28). Dasatinib, an oral second-generation TKI, was approved by the FDA in 2010 for the treatment of newly diagnosed CML patients who are in the chronic phase, as well as any stages of the disease that are resistant or intolerable to prior treatment (29). The *Src* family of kinases, which might be crucial in preventing key cell signaling pathways is also inhibited by dasatinib from being triggered. Dasatinib was first tested in the salvage scenario before being compared to imatinib and approved for frontline CML treatment (28). Dasatinib exhibited a significant cytogenetic response in 59 percent of patients following imatinib failure, 2 with 7-year and overall survival rates of 65 percent (30). Dasatinib 100 mg dose is taken orally once a day for CP patients however, a dosage of 70 mg two times daily for advanced CML patients. It is not advised to raise the dose. In CP, a dosage of 50 mg can also be given due to fewer side effects and equal response rates (28). At 100 mg dosage Dasatinib versus imatinib was observed to have higher rates of CCyR (77% against 66%, $p=0.007$) and major molecular response (MMR) (46% versus 28%, $p = 0.001$) in 12 months follow up. Dasatinib improved response rates more quickly than imatinib, and it slowed the development of patients into the accelerated or blast crisis phase (1.9% vs. 3.5%) (25). The CCyR was observed to be 86% in 2 years whereas the MMR was found to be 76% in 5 year follow-up study. The usage of dasatinib drug in 5 years led to an improvement in the overall survival rate to 91% (26).

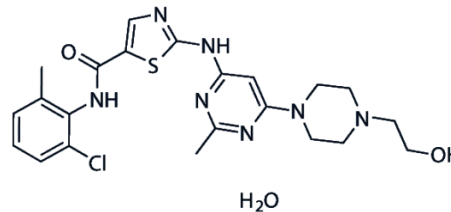


Figure 3. Molecular Formula of Dasatinib (Bristol-Myers Squibb) (31)

Nilotinib

Nilotinib was also compared to imatinib in a large, worldwide, randomized research, similar to dasatinib. In vitro, Nilotinib, being a better analog has 30 to 50 times greater effectiveness in comparison with imatinib at in vitro *BCR::ABL1* inhibition as compared to imatinib. Nilotinib, like dasatinib, showed early promise in inducing hematologic and cytogenetic responses in patients who had failed imatinib (24).

Nilotinib received approval from the FDA in 2007 for the conduct of imatinib-resistant and or intolerant (32) entities with Ph-positive CML in both acute as well as chronic phases (33) but it became authorized in 2010 by FDA as a front-line treatment of CML (32). The prescribed dosage of nilotinib is 300 mg orally 2 times a day for individuals with a recent diagnosis of chronic phase (33). Patients taking nilotinib with 300mg potency showed a response of MMR (43%) and CCyR (80%) in 12 months follow-up. The CCyR was observed to be 87% in 2 years whereas the MMR was found to be 78% in 5 year follow up study of nilotinib (26). Nilotinib therapy also slowed the development of AP or BP CML. Despite these advancements, there was no discernible difference between the groups in terms of overall survival. Long term medication of nilotinib increased the frequency of cardiovascular events (CVEs), including as ischemic heart disease, cerebral vascular events, and peripheral arterial disease (25).

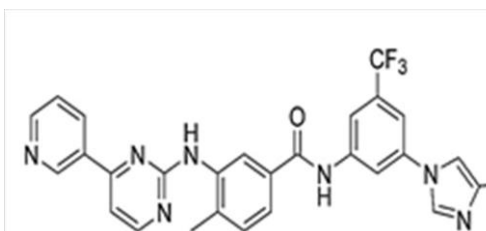


Figure 4. Molecular formula of Nilotinib (Novartis) (34)

Bosutinib

Bosutinib is a renowned *BCR::ABL1* tyrosine kinase inhibitor that is taken orally (TKI). According to the FDA, in 2012 it was endorsed for the first time in handling moderate to severe, rapid, and blast-phase CML patients who have

already received just one or few more TKIs and for them, other drugs either nilotinib, dasatinib or imatinib, are not regarded viable therapeutic alternatives, or in patients who have been intolerant or resistant to previous therapy (35). Whereas in 2013 it was authorized by EMA (36). The first-line dosage is 400 mg once a day, while the second-line dose is 500 mg once daily. It is not recommended that these dosages be increased. If the 500 mg or 400 mg doses are not tolerated and the reaction is still excellent, a lower dosage may be explored (24). The patients who are newly diagnosed with CML can be given as low as 200mg dosage of this drug, but the decision to use bosutinib as a first-line therapy or a second-line therapy depends on a variety of variables, including the patient's comorbidities, concurrent drugs, and risk factors (36). At a median of 24 months, 86% had attained a CHR, 53% had an MCyR, and 41% had a CCyR. 64% of those who received a CCyR also received an MMR (25). The CCyR was observed to be 83% in 2 years whereas the MMR was found to be 74% in 5 year follow-up study. The usage of the bosutinib drug in 5 years led to an improvement in the overall survival rate to 95% which was similar to that of imatinib 94% (26).

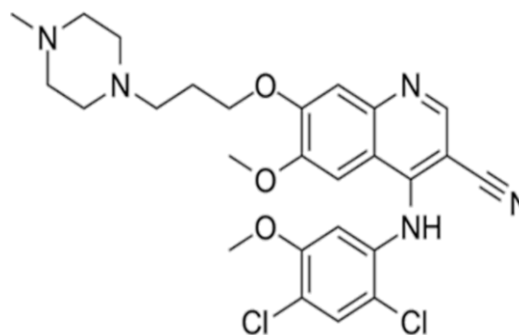


Figure 5. Molecular Formula of Bosutinib (Pfizer) (37)

Ponatinib

Ponatinib is a third-generation kinase inhibitor (38) that inhibits the gatekeeper kinase T315I mutant including ABL1 mutations (4). In multiple investigations, this medicine blocks the normal *BCR::ABL1* kinase also other various ABL1 mutations. As a consequence, ponatinib is now approved for the treatment of CML patients who

are resistant or intolerant to dasatinib or nilotinib and for whom imatinib is no longer a possibility, as well as those with the T315I mutation (39) but this drug has been found related to the significant risk of cardiovascular adverse effects which has limited its use.

The T315I mutation appears in up to 20% of CML patients who are resistant to all current TKIs. As a result, therapy options for individuals with CML who have the T315I mutation are strictly limited. Ponatinib is a third-generation TKI that extends from the purine scaffold and has a carbon-carbon triple bond due to which it is able to overcome T315I resistance due to its structure, which allows it to avoid the steric barrier induced by the amino-acidic substitution (40). Ponatinib inhibits *BCR::ABL1* 500 to 520 times more efficiently than imatinib (9, 40). The United States Food and Drug Administration authorized ponatinib for the treatment of extensively pretreated individuals with CML in 2012 whereas in 2013 EMA (40) had developed resistance or intolerance (US FDA) (40). The dose of ponatinib was 1 to 60 mg (41) specifically 45 mg once a day, and patients were divided into groups according to their illness stage and whether or not they had the T315I mutation (9). At a dose of 45 mg daily, the 12-month MCyR rate was 56%, the CCyR rate of 46%, the MMR rate of 34%, and 15% of patients achieved an MMR (25).

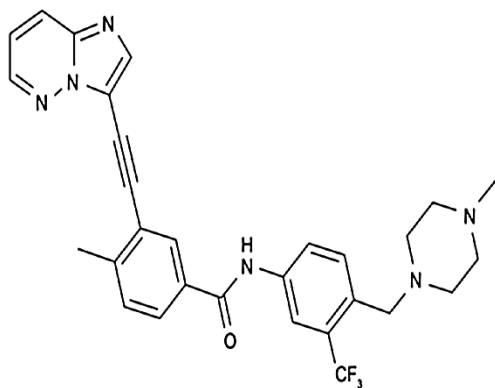


Figure 6. Molecular Formula of Ponatinib (41)
Asciminib

Subsequent development of *BCR::ABL1* tyrosine kinase inhibitors, the CML's prognosis has been upgraded tremendously, and the treatment choices for CML have evolved dramatically during the last two decades. Even though imatinib and second-

generation TKIs (nilotinib, dasatinib, and bosutinib) could be currently used in affected individuals of the CML chronic phase a significant proportion of patients must transition to alternate therapy due to resistance and/or intolerance (12). Asciminib (previously ABL001) would be the first orally accessible allosteric *BCR::ABL1* TKI that suppresses ABL1 kinase activity aiming at the ABL myristoyl pocket, being distinctive from the ATP binding pocket targeted by all other licensed TKIs. Thus, the only TKI that targets fusion protein multiple sites is asciminib, and this unique modelling makes it an appealing choice to be used by CML patients who didn't respond to other TKIs (12, 42). On February 9, 2021, the US FDA granted asciminib breakthrough treatment designation. The prescribed dose of asciminib is 40 mg orally twice a day for patients (43).

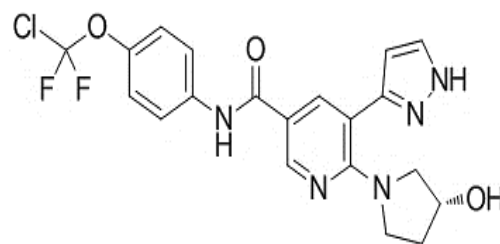


Figure 7. Molecular Formula of Asciminib (ABL001) (44)

Patients who have not reacted to more than two TKIs have been studied when using asciminib. Asciminib's effectiveness and safety suggest the prospect that it may be administered earlier, possibly even as first-line treatment, to improve the depth and speed of response. Additionally, the combination of an ATP-pocket targeting TKI with asciminib may be able to stop the emergence of resistance brought on by point mutations in one of the binding sites (45). Several studies are being carried out at present in order to get to know the response of patients. All the approved TKIs with their mode of action and their recurrently recorded adverse events have been shown in the table given below.

Table 1. TKIs, their mode of action and recurrently recorded adverse events

TKIs	Mode of action	Recurrently recorded adverse events
Imatinib (35)	suppresses <i>BCR::ABL1</i> , stem cell factor, PDGFR kinases, c-KIT	Incidence \geq 30%: fluid retention events, fatigue, vomiting, loss of muscle strength, cramps, looseness of the bowels, rash, lethargy, abdominal pain
Dasatinib (33)	<i>BCR::ABL1</i> , <i>Src</i> family, c-KIT, ephrin (EPH) receptor A2, and PDGFR kinases are all inhibited.	Incidence \geq 15%: myelosuppression, edema, looseness of the bowels, headache, allergy, hemorrhage, palpitation, lethargy, nausea, and loss of muscle strength
Nilotinib (35)	<i>BCR::ABL1</i> , platelet-derived growth factor receptor PDGFR, domain receptor-1 kinases, colony stimulating factor-1 receptor, c-KIT, discoidin are all suppressed	Incidence \geq 20% joint pain, nasopharyngitis, febrility, night sweats, queasiness, rash, headache, drowsiness, pruritus, vomiting, looseness of the bowels, cough, constipation, nasopharyngitis, pyrexia, thrombocytopenia, neutropenia, and anemia are the most prevalent hematologic disorders.
Bosutinib (35) (36)	<i>BCR::ABL1</i> and <i>Src</i> family Lyn and Hck, platelet-derived growth factor (PDGF) receptor and c-Kit are inhibited	Incidence \geq 20%, queasiness, thrombocytopenia, skin allergy, muscular spasm, anemia, febrility, liver test abnormalities, fatigue, looseness of the bowels, coughing, nuisance, and fluid retention events, vomiting
Ponatinib (40, 41)	inhibits <i>BCR::ABL1</i> , suppresses fibroblastic growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), the fms-like tyrosine kinase 3 (FLT3), the sarcoma kinase (SRC) and the stem growth factor receptor (KIT).	Incidence \geq 10%, abdominal pain, constipation, diarrhea, oral mucositis, headache, lethargy, weight loss, insomnia, fatigue, decreased appetite, cardiac failure (4%)
Asciminib (12)	<i>BCR::ABL1</i> is inhibited	Incidence \geq 20%, Fatigue, headache, increase in lipase, rash, arthralgia, nausea, thrombocytopenia and neutropenia.

CONCLUSIONS AND FUTURE RECOMMENDATIONS

Recapitulating, the development of TKIs has counteracted the *BCR::ABL1* function in CML treatment and is quickly becoming the industry norm. Imatinib, the very first renowned TKI licensed for frontline remedy of CML-affected individuals, has altered the disease's natural history. However, some individuals who get imatinib encounter resistance and intolerance, necessitating the development of alternate therapy. Individuals suffering from CML who have failed the frontline imatinib treatment should consider dasatinib or nilotinib as a second-line treatment. Long-standing output and sturdiness response of data has confirmed the effectiveness and tolerance of two other drug combinations as a second-line therapy namely nilotinib and dasatinib. The third-generation drug named ponatinib is also known for its efficiency but before taking this drug several baseline factors should be taken into account before initial dosage. Furthermore, depending on patient parameters like *BCR::ABL1* mutation status or the disease stage, these medicines have varied pharmacological properties and sensitivities. Despite the mind-blowing progress of the TKIs over the last two decades numerous patients still develop resistance against drugs. Following the positive findings of preclinical and clinical research, asciminib was recently authorized as a monotherapy for the treatment of CML. Longer-term effectiveness and safety outcomes of patients treated with asciminib are currently being awaited.

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DECLARATIONS

Authors' Contributions

SS and MFS contributed to study concept, study design and data collection. ZI and ZS contributed in data analysis and interpretation. SS, MAK and SA did the literature review, draft manuscript and critically reviewed the manuscript. All the authors read and approved the final manuscript.

Ethical Approval

Not applicable

Conflict of Interest

The authors declared no conflict of interest among them.

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