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Management of chronic myeloid leukaemia: current treatment options, challenges, and future strategies

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ABSTRACT
Small molecule therapy is a critical component of targeted anticancer treatment, with tyrosine kinase inhibitors (TKIs) being the first compounds to treat the clonal Chronic Myelogenous Leukaemia (CML) translocation t (9;22) (q34; q11) effectively since 2001. TKIs, such as imatinib, have improved the 10-year survival rate of CML patients to 80%. They bind the *BCR::ABL1* kinase and inhibit downstream signaling pathways. However, therapy failure may be seen in 20-25% of CML patients due to intolerance or inadequacy related to *BCR::ABL1* dependent or independent mechanisms. This review aimed to summarize current treatment options involving TKIs, resistance mechanisms and the prospective approaches to overcome TKI resistance. We highlight *BCR::ABL1*-dependent mechanisms of TKI resistance by reviewing clinically-documented *BCR::ABL1* mutations and their consequences for TKI binding. In addition, we summarize *BCR::ABL1* independent pathways, including the relevance of drug efflux, dysregulation of microRNA, and the involvement of alternative signaling pathways. We also discuss future approaches, such as gene-editing techniques in the context of CML, as potential therapeutic strategies.

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Tyrosine kinase inhibitors (TKIs); *BCR::ABL1*;; Chronic Myeloid Leukaemia (CML); resistance; therapeutic targets; cancer; personalized medicine; precision medicine

1. Introduction

Chronic myelogenous leukaemia (CML) is associated with the presence of the Philadelphia (Ph) chromosome, resulting from a reciprocal chromosomal translocation between chromosome 22 and chromosome 9. In this translocation, regions from the first exon of *ABL1* (*c-Abl*) are translocated into the *BCR* gene, generating a fusion oncogene referred to as *BCR::ABL1* [1]. This fusion gene encodes for a hybrid truncated protein with uncontrollable tyrosine kinase activity. It accounts for approximately 95% of all CML cases [2].

For many years, CML was considered a fatal disease that could solely be cured through hematopoietic stem cell transplantation [3]. However the discovery of Imatinib which targets *BCR::ABL1* kinase activity, the CML 10-year survival rates was found to be improved to 83.3% [4] and tyrosine kinases became feasible targets for anti-cancer therapy. A timeline that highlights some of the important breakthroughs that led to the development of *BCR::ABL1* TKIs is depicted in Figure 1.

As homologs of adenosine triphosphate (ATP), tyrosine kinase inhibitors (TKIs) occupy the ATPs-binding site of protein tyrosine kinases (PTKs) competitively and block PTK-mediated signaling pathways, reducing the growth and proliferation of cancer cells. TKIs have substantial advantages over conventional chemotherapeutic drugs, including high efficacy, low toxicity, and good specificity. However, therapeutic resistance may occur [5]. In fact, TKI resistance is the major cause of recurrence, progression, therapy failure, low compliance, and death. Resistance mechanisms to TKIs are complicated. Previous research has confirmed the association between TKI resistance and mutations in the target gene. Growing research shows that other variables, such as epigenetic

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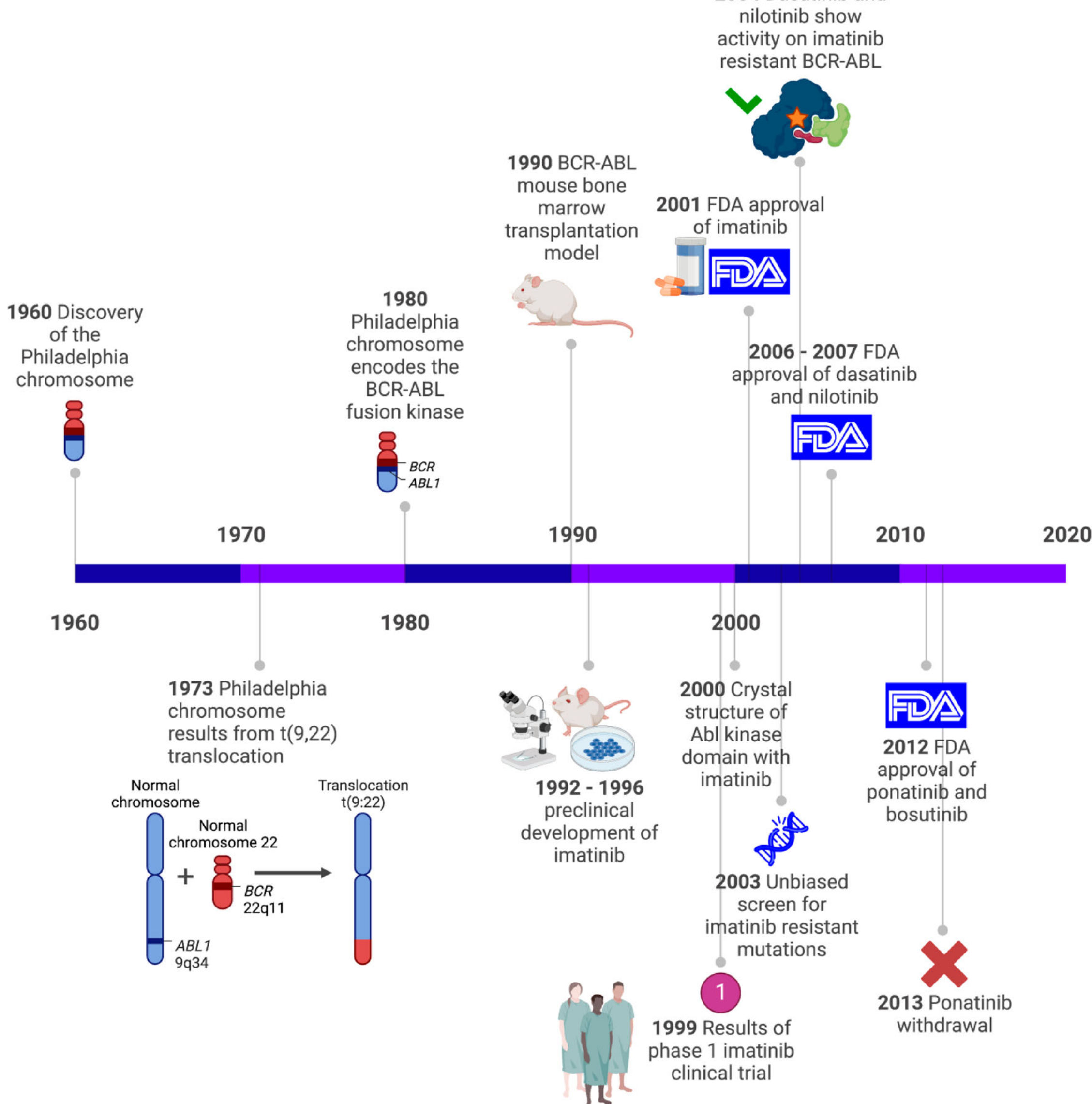

Figure 1. Key events in the development of *BCR::ABL1* TKIs. A timeline highlighting significant research breakthroughs that led to the development of TKIs for CML treatment.

alterations and activation of alternative survival pathways, also contribute to TKI resistance [6].

Despite the extraordinary success of TKIs in targeted therapy, TKI resistance is on the rise. Here, we summarize the underlying mechanisms of TKI resistance and discuss potential approaches to overcome TKI resistance, and future treatment options aiming to establish a theoretical foundation for CML management.

2. Current treatment strategies: TKIs in CML

2.1. Overview of TKIs in CML

Ph^+ cells have a constitutively active *BCR::ABL1* gene, which causes malignant CML formation. Due to the structural similarity between TKIs and ATPs, TKIs can bind the tyrosine kinase domain of *BCR::ABL1* and prevent ATP from binding to the ATP binding domain, thus blocking downstream target protein phosphorylation and signaling pathway activation, inhibiting tumor growth (Figure 2). Through this mechanism, imatinib, among other TKIs, targets CML and other cancers [7]. A detailed list of currently available TKIs for the treatment of CML is presented in Table S1.

Besides *BCR::ABL1*, imatinib interacts with several other proteins, including ABL1 and ABL2. Suppressing both ABL paralogs has been reported to contribute to imatinib adverse effects. Side effects, such as nausea, vomiting, eczema, leukopenia (in severe cases), heart failure, and liver disease, are among the most frequent side effects of TKI treatment [8]. Compared to conventional chemotherapeutic drugs, these side effects are less severe, and no definitive contraindications or life-threatening issues have been observed. Nevertheless, some patients may experience specific side effects that result in therapy interruption or termination. In fact, research has shown that up to 10% of patients may discontinue

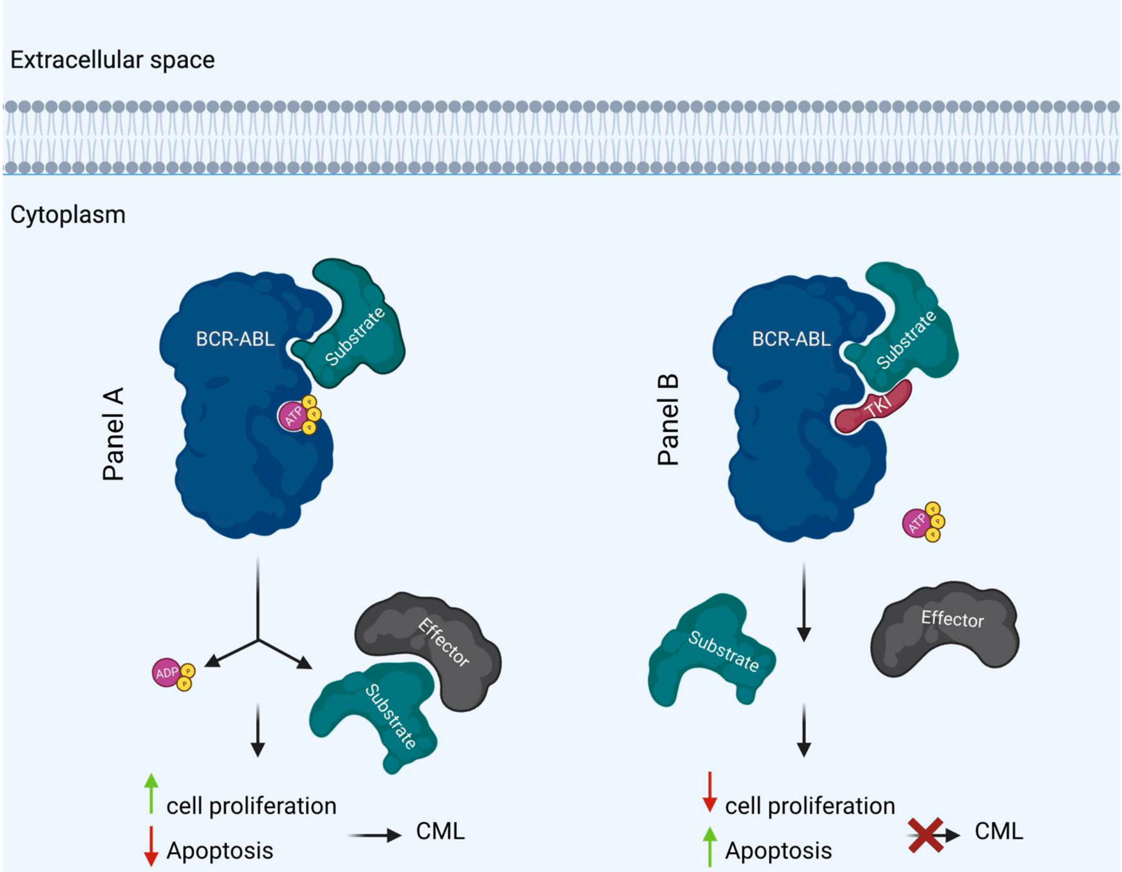

Figure 2. Mechanism of action of *BCR::ABL1* tyrosine kinase and TKI in CML. *BCR::ABL1* tyrosine kinase in CML (left). TKI in treatment of CML (right). P indicates phosphate. Figure was created with BioRender.com.

TKI treatment due to side effects. In addition, as a manifestation of TKIs resistance, some patients may exhibit weak response to TKIs, and nearly a quarter of CML would gradually lose their cytogenetic or substantial molecular response after five years of treatment [9–11]. TKIs resistance results in recurrence or rapid tumor progression, which has a detrimental effect on patient survival. Therefore, finding TKI-resistance solutions is an urgent priority.

Second and third-generation TKIs were designed to address this challenge. To date, the second-generation TKIs (dasatinib, nilotinib, and bosutinib), and the third-generation ponatinib have been developed for CML treatment with different side effects, targets, potencies, and effectiveness against different mutations in *BCR::ABL1* (Table S1). Nilotinib, for example, is 20 times more potent than imatinib and poses a lower risk of arterial occlusive events (AOEs) in dyslipidemic CML patients via lowering both LDL and cholesterol plasma levels but may cause cardio-vascular events (CVEs) in 20% of patients via binding the Mitogen Activated Protein (MAP)-kinases in comparison to the (5%) incidence of CVEs seen with imatinib.

On the other hand, the second-generation TKI, dasatinib, is likely to induce pleural effusion toxicity in ~30% of patients [12]. Moreover, bosutinib (SRC/ABL inhibitor) was designed to inhibit SRC in SRC-overexpressing tumors and was found to have high activity against ABL and *BCR::ABL1* [13] It binds the inactive state of *BCR::ABL1*, namely the DFG-out motif independent of its conformation. It may lead to increased transaminase levels, and is associated with transient diarrhea in ~30% of patients [14]. Ponatinib, the only approved third-generation TKI, is utilized for first and second-generation resistant diseases due to the T315I mutation [15]. Its most adverse events occur during therapy, with cardiovascular damage and cardiovascular risk factors accounting for 30% of contraindications [16].

2.2. TKI resistance

Within this complex interplay between different cells; CML, LSCs, drugs; TKIs, and homeostatic microenvironment, resistance to therapy develops. Drug resistance mechanisms have been thoroughly explored and are either *BCR::ABL1* dependent or independent. A fundamental understanding of the tyrosine kinase domain of *BCR::ABL1* and mechanisms of resistance are summarized in Figure 3.

2.2.1. BCR::ABL1-dependent TKI resistance mechanisms

2.2.1.1. Point mutations in BCR::ABL1. According to the types of mutations that confer resistance to a

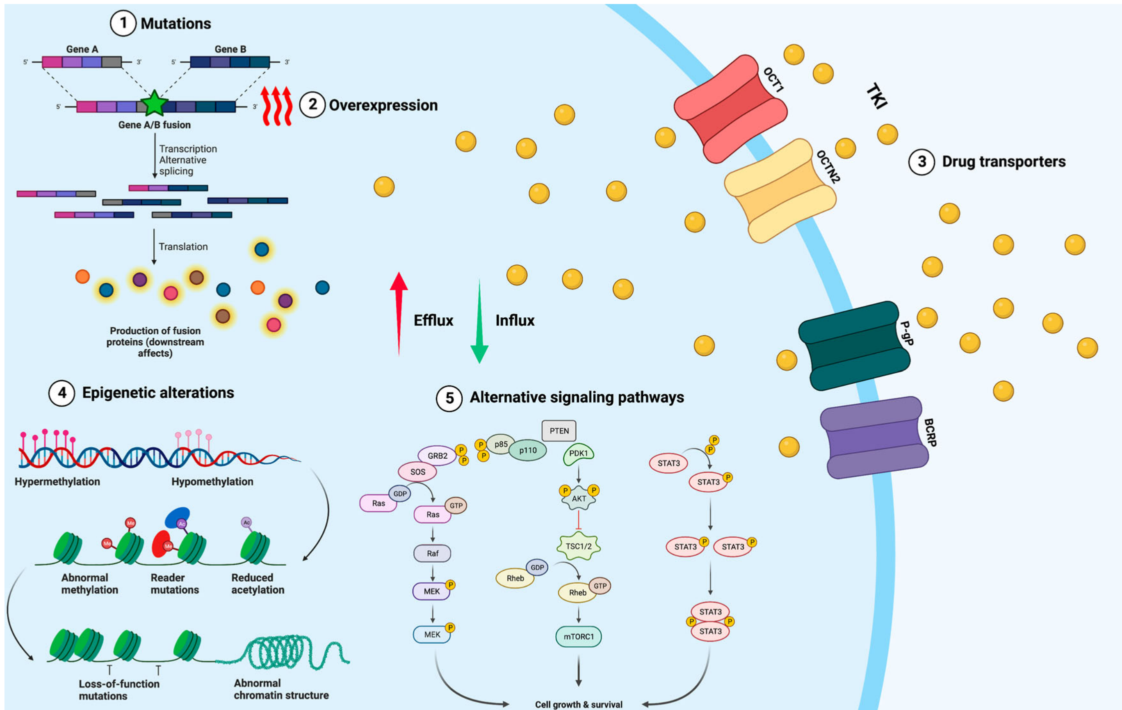

Figure 3. Mechanisms of TKI resistance in CML. *BCR::ABL1* dependent mechanisms include (1) mutations that affect TKI binding. (2) overexpression or amplification of *BCR::ABL1* leading to elevated kinase activity. *BCR::ABL1* independent mechanisms include (3) increased expression of drug efflux pumps, including P-glycoprotein (Pgp), and reduced expression of drug influx pumps, including the organic cation transporter hOCT1. Other mechanisms that play a role *BCR::ABL1* independent TKI resistance include (4) epigenetic alterations and (5) activation of alternative signaling pathways downstream of *BCR::ABL1*. Figure was created with BioRender.com.

particular TKI medication, TKIs are classified into two primary groups, both of which overlap with the ATP-binding site. Type 1 inhibitors target the active conformation, which is catalytically competent, whereas type 2 inhibitors target the inactive conformation. Dasatinib is a type I inhibitor, whereas Imatinib, nilotinib, ponatinib, and ponatinib are type II inhibitors. Bosutinib has traits of both kinds of TKIs [17]. Type II inhibitors have better selectivity but are subjected to larger mutational vulnerabilities due to their strict binding requirements [18], whereas type I inhibitors are often less prone to mutational escape and more promiscuous. Despite being less prone to mutational escape, type I inhibitors are more promiscuous than type II inhibitors.

Imatinib has to engage with the activation domain and P-loop conformation switch and make six hydrogen bonds with it to prevent the transition from the inactive to active conformation of the ATP binding pocket of *BCR::ABL1*. The effectiveness and safety of the drug may thus be significantly impacted by mutations that change the required amino acids. It is known that approximately 50% of patients who relapse on imatinib have mutations within the ABL kinase domain, affecting imatinib binding within the kinase pocket [19].

When imatinib was still in the early stages of development, it was reported that *BCR::ABL1* might escape inhibition via substitution of threonine for isoleucine at position 315 (T315I), which was the first identified mutation associated with drug resistance [20]. Later, however, it was shown that, considering the disease course, the sooner the TKI treatment is started, the lower the relapse rate and the degree of genetic instability responsible for mutation acquisition. In other words, although TKI-resistant mutations continue to be a problem in patients with accelerated-phase CML (AP-CML) and blast-phase CML (BP-CML), they are considerably less common in patients with CP who are appropriately treated with TKIs as early as possible. Being the target of a key mutation (T315I), Threonine 315 residue was subsequently named 'the gatekeeper' residue because of its strategic placement in the ATP-binding pocket, which allows it to regulate the accessibility of the pocket. While in contact with imatinib, the hydroxyl group of the amino acid threonine 315 binds to the inhibitor via a hydrogen bond, and the side chain at position 315 allosterically regulates the inhibition of the inhibitor's binding to hydrophobic regions adjacent to the ATP-binding site. Thus, imatinib binding is eliminated [21,22].

Imatinib failure can also result from mutations in the P-loop, such as G250E or Y253H, which impair imatinib binding, or in the activation loop, such as H396R, which prevents the activation loop from being closed [23]. Additional *BCR::ABL1* mutations in CML patients have been found by our team, including the E459K mutation, which manifested in one patient with a poor response to TKI [24].

Dasatinib, nilotinib, and/or bosutinib have activity against the majority of imatinib-resistant mutants, except T315I. Although the development of a TKI active against the T315I mutant has proven challenging, ponatinib (AP24534), a third-generation TKI and a pan *BCR::ABL1* inhibitor, seems to induce potent and durable responses in CML patients, regardless of their mutational status. It binds to the ATP binding domain without requiring the formation of a hydrogen bond with the mutation T315I. Ponatinib was tested in the PACE clinical trial in patients with the T315I mutation or who are resistant/intolerant to either dasatinib or nilotinib. Findings from PACE show that major molecular response (MMR) is achieved in 56% of CP patients with the T315I mutation. Nevertheless, the presence of this mutation necessitates an increase in the ponatinib dose, and a proportion of patients might ultimately develop ponatinib-resistance. Therefore, it is crucial to categorize patients in accordance with their *BCR::ABL1* mutation pattern to select the most effective TKI for treatment.Conflicting results have been reported regarding the involvement of many of the discovered *BCR::ABL* Kinase Point Mutations in TKI resistance [25]. This makes it challenging to identify the most appropriate treatment course for each patient, which further emphasize the need for continued research in this area to improve the effectiveness of treatment options for CML patients. This will not only help to identify the mutations responsible for resistance but also enable the development of new therapies and treatment strategies that target these mutations effectively. The most common *BCR::ABL1* mutations and how they affect individuals with CML's responsiveness to TKIs are shown in Table S2. Our group previously documented *BCR::ABL1* mutation and additional chromosomal abnormalities in CML patients [26,27].

2.2.1.2. Amplification of BCR::ABL1 oncogene.

BCR::ABL1 dependent mechanisms of resistance include amplification or overexpression of the *BCR::ABL1* oncogene. High *BCR::ABL1* transcript levels in the advanced stage have been reported to be linked to TKI resistance [28,29], mainly because *BCR::ABL* overexpression can impair TKI binding [30], and thus lead to elevated kinase activity [20,31]. Despite the increased rate of amplification per cell division, it is more common to identify point mutations in a clinical context, mainly because overexpression of *BCR::ABL1* promotes cell injury [32].

2.2.2. BCR::ABL1 -Independent TKI resistance mechanisms

Besides alterations in *BCR::ABL1*, it is plausible that resistance occurs independently of the kinase, which may involve mechanisms related to genomic instability, epigenetic alterations, overexpression of multidrug resistance (MDR) proteins involved in the efflux of anticancer drugs, activation of survival pathways, and interactions with the LSC microenvironment.

2.2.2.1. Impact of drug metabolism.

Pharmacogenetic variants in cytochrome P450 enzymes have been linked to TKI resistance CML. TKIs are cytochrome P450 substrates, namely CYP3A4 and CYP3A5 [33] (Table S3). Consequently, it is reasonable to predict drug–drug interactions with a broad variety of drugs to occur, resulting in the activation or inhibition of TKI metabolism. These treatments include rifampicin, anticonvulsants, and herbal remedies, all of which are known to activate certain cytochrome P450 enzymes. As a consequence of increased TKI metabolism, the desired TKI plasma concentration is reduced, resulting in chemoresistance [34]. Imatinib, for example, is both a moderate CYP3A4 inhibitor and a substrate [35. Imatinib is converted by CYP3A4 to the active but less cytotoxic metabolite CPG74588 [36]. Autoinhibition of CYP3A4 leads to the identification of a second elimination route, CYP2C8, which is involved in the hepatic clearance. Furthermore, CYP3A4 and CYP3A5 enzyme activity have been demonstrated to be greater in CML patients who achieve full molecular remission compared to poor responders . Because the potency of the significant metabolite CGP74588 is equivalent to that of imatinib, CYP3A and its products have demonstrated therapeutic significance in imatinib-treated-CML patients [37].

In the presence of pharmacogenetic differences, enzyme activity may be restricted or enhanced, which may have an impact on TKI metabolism. The most clinically significant polymorphisms include CYP3A4*20 and CYP3A4*22, both of which may result in a reduction of up to 20% of enzyme activity [38,39]. CYP3A4 and CYP3A5 have a high degree of sequence similarity, and their substrate spectra overlap [40]. The major variations of CYP3A5 include nonfunctional CYP3A5*3, CYP3A5*6, and CYP3A5*7, which vary in their expression patterns across ethnicities [38]. Patients with CML who have known CYP3A4 polymorphisms may have decreased TKI metabolism, resulting in greater side effects, but their response to TKI may be enhanced. However, there is contradictory evidence regarding the significance of CYP450 variations in TKI responsiveness.

Contrary to expectations of an enhanced imatinib response in the presence of a non-functional protein, multiple investigations have shown that CYP3A5*3-harbouring patients had a worse response to the drug [41]. On the other hand, a link between imatinib therapy and greater complete cytogenetic response rates has been observed in some populations, including Asians [42]. Although the relationship between the TKI response and many metabolism-related

genetic variants has not been fully established, some evidence suggests that CYP2C8*2 and CYP3A4*7 play a role in alterations in imatinib levels in homozygous carriers [43,44]. Table S4 summarizes the major genetic variations in cytochrome P450 enzymes and their relevance to TKI response in CML.

CYP3A4 interactions have a more significant impact on the development of adverse events or the inability to react to TKIs [45]. A consequence of this is that genotyping and measuring cytochrome P450 activity or function are no longer routinely performed in clinical practice [45]. Therefore, strong CYP3A4 inducers should be avoided when beginning the imatinib treatment [45]. Patients who must be co-administered with a strong CYP3A4 inducer should have their imatinib dosage raised by ∼50%, and their clinical response should be closely monitored. Because the concomitant treatment of imatinib and strong CYP3A4 inducers may result in a reduction in overall exposure to IM, alternative agents should be investigated [46]. A substantial increase in imatinib exposure may occur when imatinib is administered concurrently with strong CYP3A4 inhibitors, on the other hand. Imatinib will raise the plasma levels of medicines that are metabolized by CYP3A4. As a result, care should be used when giving imatinib in conjunction with CYP3A4 substrates that have a limited therapeutic window. Patients should be given LMWH instead of warfarin when imatinib is administered, because warfarin is metabolized by CYP2C9 and CYP3A4, and because imatinib interacts with medications metabolized by CYP2D6 and has a limited therapeutic window. Other factors such as patients' adherence, it was found that high rate of TKIs failure is explained by poor adherence [47,48].

2.2.2.2. Impact of drug transporters. There is evidence that drug transporters contribute to drug resistance by either decreasing drug concentrations inside cells or limiting a drug's bioavailability in certain tissues. Many drug efflux transporters and drug importers have been linked to TKI resistance in CML (Table S3, S4).

The efflux proteins belonging to the ATP-binding cassette (ABC) superfamily are represented by 49 genes, of which some ABC members are associated with CML, among other diseases [49]. Particularly, members of the ABCB, ABC subfamilies (Table S4).

In recent years, ABCB1 has emerged as one of the most extensively researched drug transporters, with pharmacogenetic variants being investigated in considerable depth (Table S3, S4). The ABCB1/pump P-glycoprotein (Pgp) was first described by Juliano and Ling [50], as a 170-kDa cell surface glycoprotein which showed a membrane permeability barrier 'function' in drug-resistant cells. Studies have shown that Pgp, play an important role in drug efflux, by pumping out a wide range of substrates, including TKIs [51]. It is conceivable that TKI responsiveness will be enhanced by loss-of-function mutations or variants with lower protein function, resulting in decreased efflux ability. Notwithstanding, 40 years after the discovery of Pgp [52], there is still no solid confirmation regarding the role of ABCB1/Pgp in drug resistance. Most importantly, ongoing controversy surrounds the relevance of *ABCB1* polymorphisms in the development of TKI resistance among CML patients, with no compelling evidence that *ABCB1* variants may be utilized as predictive biomarkers in pharmaceutical therapy. As a result, we believe it is important to review the pre-clinical approaches involving ABCB1 expression, activity, and genetic variants in CML to better understand the role of ABCB1 transporters in TKI resistance among CML patients in a clinical context. While P-gp inhibitors can help overcome drug resistance, they can also significantly increase the toxicity of P-gp substrate cytotoxics [53]. Thus, studying TKI-transporter interactions may assist in discovering elusive TKI resistance mechanisms, guide the creation of combination scheduling trials, or reduce undesirable side effects].

Additionally, ABCG2 is a drug efflux transporter and is extensively expressed in hematopoietic precursors and stem cells. ABCG2 is a stem cell factor that is highly expressed in hematopoietic precursors and stem cells. Several studies have shown that ABCG2 is linked to the development of leukaemia [54]. In regard to changing the transport capacity of the protein, *ABCG2* polymorphisms are addressed in the same manner as *ABCB1* polymorphisms are discussed to alter the protein's transport capacity. One of the most essential variants is 34G > A (V12M, exon 2, rs2231137), and the other is 421C > A (V12M, exon 2, rs2231137) (Q141K, rs2231142) (Table S3). The homozygous 34G > A mutation, which results in an amino acid switch from valine to methionine, has been associated to a greater response to imatinib, perhaps due to decreased *ABCG2* expression . Evidence on the effects of 421C > A, which is believed to change the conformation of the ATP binding domain remains inconsistent. The expression of the variant was shown to decrease imatinib bioavailability in some studies, while others indicated that it had no impact on imatinib pharmacokinetics in vivo [55–57]. Nonetheless, Jiang and colleagues suggested that this variation might be utilized to predict imatinib response in individuals with chronic lymphocytic leukaemia [58]. The −15,622C > T promoter SNP (rs7699188) has also been linked to lower BCRP expression in a number of tissues, including the liver, suggesting that imatinib clearance from the cell is reduced [59]. Additional *ABCG2* variants were examined, but they did not affect TKI clearance or responsiveness, as previously reported []. As a result, there is no apparent connection

between pharmacogenetic polymorphisms and imatinib response for either *ABCB1* or *ABCG2*, and further study is required to determine their relevance in drug resistance [44]. Many studies have revealed that the expression of *ABCB1* and *ABCG2* in drug resistance seems to be dose-dependent. Following imatinib cessation, ABCG2 expression in peripheral blood leukocytes was shown to be a good predictor of treatment-free remission. More study is needed to establish the effect of ABC transporter polymorphisms on neoplastic disorders like CML. In our investigation, there was no significant pattern of AGP and PGP expression, regardless of whether the patient responded to or was resistant to medication. AGP and PGP levels were not linked with resistance in our CML patient group, which was unanticipated [60–62].

Some TKIs are believed to be transported into tumor cells via the organic cation transporter 1 (OCT1/SLC22A1), found on the surface of tumor cells. Although there are contradicting data regarding the significance of OCT1 in CML, some studies have demonstrated overexpression of OCT1 in patients with imatinib resistance [63], while others have shown that OCT1 is not regulated [64,65]. It was found that OCT1 expression and activity may be used as a predictive predictor for long-term imatinib response in patients with CML [66]. However, no evidence that OCT1 variation impacts imatinib response in various clinical studies is available to date [66].

2.2.2.3. Impact of protein-tyrosine phosphatases. Among the TKI resistance mechanisms, there has been a growing body of evidence regarding the mutual interplay between protein-tyrosine phosphatases (PTP) receptor type γ (*PTPRG*) and *BCR::ABL1* [67]. Our group previously documented that the expression level of *PTPRG* was considerably higher among optimal TKI responders compared to non-responders. Also, we reported that the protein level of *PTPRG* is drug dependent [68], suggesting that approaches aiming at enhancing *PTPRG* expression/activity might benefit CML patients [69,70].

Our team also identified an antagonistic relationship between β-catenin and *PTPRG* in CML cells [71,72]. Our findings showed that *PTPRG* can dephosphorylate β-catenin, causing cytosolic instability and protein degradation. Furthermore, we found that increased β-catenin expression is associated with DNA (cytosine-5)-methyl transferase 1 (DNMT1) over-expression, whereas its inhibition or down-regulation is associated with PTPRG re-expression [71,72]. Furthermore, we found that *PTPRG* plays a role in controlling *BCR::ABL1* and β-catenin phosphorylation in primary human CML samples. These findings suggest a regulatory loop involving *PTPRG* and β-catenin, the imbalance of which alters the kinetics of the CML [73]. In addition, we recently studied the impact of *PTPRG* SNPs on TKI response prediction [68,74]. We discovered three novel SNPs (c.1602 1603insC, c.85 + 14412delC, and c.2289-129delA). Compared to responders and healthy persons, these SNPs had significantly different genotypes and allele frequencies in CML patients who failed imatinib therapy [74,75]. Other phosphatases have been reported to be involved in CML pathogenesis [76].

2.2.2.4. Epigenetic alterations. Epigenetic factors play a role in regulating gene expression. There has been growing body of evidence that aberrant DNA methylation plays a key role in CML progression. Our group previously reported that methylated CpG sites were dramatically increased in CML patients compared to healthy subjects, suggesting the potential involvement of CpG methylation sites in the molecular processes leading to CML. These results support the hypothesis that CML etiology may involve a combination of factors, not only the *BCR::ABL1* translocation [73,77].

Furthermore, microRNA expression and epigenetic control may have a role in the pathogenesis of CML and treatment resistance. The presence of TKIs in CML patients' blood samples has been found to affect the microRNA expression pattern. Furthermore, the global microRNA expression pattern appears to vary between responding and non-responding CML patients [78–80]. In addition, it has been reported that the dysregulation of some microRNAs, such as miR-203 or −30a/e, may lead to an altered TKI response [81–83]. Even if *BCR::ABL1* is not active, microRNAs such as miR-144/451 or miR-212/ABCG2 may be engaged in regulating several downstream target genes in the signaling cascade, thus contributing to drug resistance []. As a result, it has been debated whether microRNA expression may be utilized for monitoring TKI therapy response [84].

2.2.2.5. Alternative pathways. The activation of the *BCR::ABL1* fusion protein has been reported to trigger the PI3KAkt, JAK-STAT, and MAPkinase signaling pathways, among others, leading to enhanced cell proliferation, antiapoptotic signaling, alterations in cell motility, and changes in stromal cell adhesion [85]. Many of the signaling proteins in these pathways function as *BCR::ABL1* activation-dependent oncogenes. When different stimuli activate these pathways in cancer cells, such as WNT/ β-catenin signaling in leukemic stem cells or JAK2 activation by external stimuli, the tumor cell becomes at least partially independent of *BCR::ABL1*, potentially facilitating therapy failure or low response rates. Many signaling system adaptations come not just from mutations downstream of *BCR::ABL1* or in alternate signaling pathways but also from changes in gene transcription. Autophagy activates or reactivates proliferative pathways such as hedgehog and PI3K/Akt signaling. Discovering and combining

critical signaling pathways to design an optimal target to overcome resistance and cause synthetic lethality, particularly in leukemic stem cells, is a significant issue. TKIs promote mutations, clonal evolution, and selection, all of which contribute to the progression of CML. Still, they also promote TKI resistance and, as a result, the alteration of treatment regimens, given that TKIs must be taken for the rest of one's life. In most subjects who failed to respond to imatinib, switching to newer generation TKIs in compliance with the recommendations resulted in positive outcomes.

2.2.2.6. TKIs and leukemic Stem Cells (LSCs). CML leukemic stem cells (LSCs) represent a low-frequency subpopulation of leukaemia cells that are able to self-renew and are drug-resistant. Although they seem to express *BCR::ABL1*, they can escape the TKIs effect and increase the chances of relapse [86], even after *BCR::ABL1* activity has been shut down, and thus posing as a *BCR::ABL1* -independent TKI resistance mechanism [87–90]. To overcome quiescence and induce an LSC-free state, combined strategies to target LSCs are currently being evaluated, such as the combination of the anti-TNFα antibody infliximab (IFX) with TKIs, to induce the susceptibility of LSC to TKIs [91] and the combination of the CXCR4 antagonist BKT140 with TKIs to overcome the protective effect of bone marrow milieu [90]. CML LSCs can also be targeted through signaling pathways such as Wnt/b-catenin by C82, Hedgehog by LDE225, JAK/STAT by Pioglitazone, among others. Moreover, LSCs could be targeted via BCL-2 and P53 modulation, targeting lysosomal mediated autophagy by hydroxychloroquine or Lys05. Epigenetic targeting by EZH2 histone methyltransferase inhibitor and targeting LSCs via surface markers are potential strategies to achieve LSC treatment-free remissions [90].

3. Future strategies

3.1. Discontinuation of TKI Therapy in CML

TKI-treated CML patients have a relative survival rate that is on par with the general population [92]. Although TKI therapy is generally safe and effective, there may be certain risks associated with long-term use of these medications. Patients regularly encounter low-grade, persistent adverse events that are common but may have an effect on their overall health. Additionally, late adverse effects such arterio-thrombotic events [93] and the potential elevated risk of second malignancies identified in some [93] reports are becoming more recognized. The financial burden that prolonged TKI treatment places on patients and society is another factor that is becoming more significant [94]. Several studies have been conducted to determine if TKIs may be safely discontinued in individuals who have established long-term deep molecular responses or patients with less deep but stable remission [95–99]. Currently, only patients with at least 5 years of therapy, 2 years of deep molecular response, no past history of resistance or suboptimal/warning response, no hematopoietic stem cell transplantation with a typical *BCR::ABL1* transcript, and aged ≥ 18 years may be considered for treatment discontinuation [100]. Many aspects, however, still remain unaddressed, such as how to more accurately identify individuals who will have deep molecular responses and treatment-free remission, and if these people should be deemed 'cured'? How can we help more patients experience deep molecular response so they will be ready to try a treatment-free remission trial? Moreover, the effects of gradual treatment withdrawal and whether it's feasible in patients with less deep but stable remission is a promising strategy but requires further investigation [99,101,102].

3.2. TKI dose individualization

Drug personalization is an ultimate goal for doctors to reach; the aim is to tailor patient therapy to optimize efficacy and decrease toxicity. There are currently several ways of individualization such as therapeutic drug monitoring, population pharmacokinetics, selecting antibiotics according to bacterial culture sensitivity, and pharmacogenomics. Nowadays, building simulation models using pharmacometrics science provides a great tool for health care workers to integrate information from different domains into one model to make medical decisions. Different techniques are currently used to personalize TKI dose in clinical practice [103].

Currently, the most common tool for dose individualization is therapeutic drug monitoring (TDM) [103]. TDM is involved in measuring drug levels in biological fluids at steady to improve patient care. TDM has been shown to be useful in predicting the efficacy of imatinib in CML [104]. Multiple studies have shown that imatinib (Trough level) 1,000 ng/mL is currently considered a target to reach. This level (1000 ng/mL) in CML patients is considered a guarantee for a higher chance of attaining a complete cytogenetic response and reaching MMR. Nevertheless, further research is needed to determine its validity with other TKIs [105,106].

Moreover, pharmacogenetics (PGx) is important for dose personalization in cancer patients. Worldwide, there are few organizations responsible for guideline development and release, such as the French National Network of Pharmacogenetics (RNPGx) and the Clinical Pharmacogenetics Implementation Consortium (CPIC). Currently, more than 10 chemotherapy drugs have

clinical PGx guidelines, but TKI is not one of them. Although there are different pharmacogenetic variants that influence TKI efficacy and toxicity, clinical PGx guidelines are still not available for TKI due to contradicting data [107,108].

In addition to PGx and TDM, other dose personalization techniques are evolving, such as pharmacometrics or population pharmacokinetics models (PPK). It has been previously reported that there is variation in imatinib disposition after administration of the standard dose [109–113]. The patients' characteristics that may impact the interindividual imatinib variability were identified by those studies [109–113]. Those reported variables included chronic imatinib exposure, genetic polymorphisms, age, and weight. Population pharmacokinetics models can identify the different variables that affect patient drug response variability [109–113]. A recent study on the Nigerian population reported wide variability in the imatinib area under the curve and clearance compared to other studies done on different populations [113]. The genetic and Pk results can help optimize patients' imatinib doses. Most importantly, they will be a powerful tool in describing those variabilities if combined in one mathematical model [114]. After building the model, it can predict the patient optimized dose.

3.3. Gene editing

Over the past few years, gene editing techniques, particularly CRISPR/Cas9 have gained considerable attention in the context of leukaemia [115–120]. CRISPR/Cas9 system was reported to successfully silence the *BCR::ABL1* oncogene, reversing its tumor-promoting function [119]. In addition, in a CML xenograft model, subcutaneous injection of edited single cell derived clones failed to develop tumors [119]. These findings suggest that CRISPR/Cas9 technology could serve as a successful promising new therapeutic option for CML patients who experience TKI resistance. However, it should be noted that studies on CML specifically are limited, and further research is needed. A precision medicine approach utilizing clinically validated biomarkers and population health analyses would aid in the successful implementation of gene therapy for CML [121–123]. Figure 4 illustrates the comparison between TKI therapy and gene therapy for CML, where gene therapy can eradicate the oncogene at the genome level and replenish the bone marrow niche with corrected LSCs, enabling regular hematopoiesis.

Conclusion

Despite considerable advances in CML treatment with the development of TKIs, many patients acquire TKI resistance, some progress to blast crisis, and the majority relies on TKI therapies for long-term disease management. Current strategies to overcome TKIs resistance have mostly focused on increasing the potency and specificity of drugs that target *BCR::ABL1* or overcoming resistance caused by mutations in the *BCR::ABL1* oncogene. This strategy, however, may be less successful in many CML patients who acquire resistance despite effective *BCR::ABL1* suppression with TKIs, i.e. *BCR::ABL1* -independent resistance

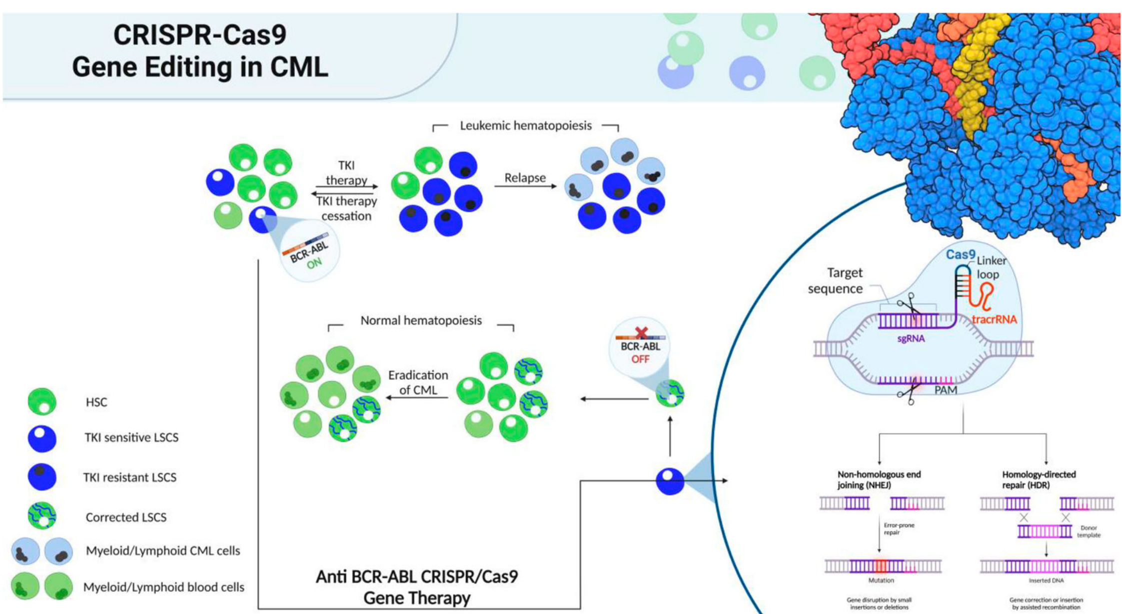

Figure 4. Gene therapy vs conventional therapy for CML. Conventional therapy based on tyrosine kinase inhibitors (TKI) effectively silences *BCR::ABL1* in leukemic stem cells (LSCs). Because there are still cells that are *BCR::ABL1* positive after treatment has ended, recurrence is possible. Recurrence of the disease may result from the emergence of TKI-resistant LSCs during therapy. However, the oncogene would be eradicated at the genome level via anti- *BCR::ABL1* gene therapy. Corrected LSCs could replenish the bone marrow niche, enabling regular hematopoiesis. Figure was created with BioRender.com.

mechanisms. To enhance treatment results in such individuals, novel therapeutic options, such as combining TKIs with other therapeutics that target *BCR::ABL1* independent pathways, may be required. A combined therapy strategy might eliminate LSCs, maximizing treatment-free remission in CML and improving sensitivity to TKIs in patients who are currently unresponsive to TKIs. Furthermore, CML patients who fail TKIs without evidence of kinase domain mutations should be screened for alternative mechanisms of resistance that can activate alternative survival pathways in order to determine an appropriate therapeutic approach. Most importantly, novel therapeutic strategies such as gene editing techniques need to be further explored in the context of CML as potential therapeutic strategies.

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