Pharmacotherapeutic Options for Philadelphia Chromosome-Positive CML

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Abstract: Chronic myeloid leukemia (CML) is a myeloproliferative disorder of hematopoietic stem cells. Identifying the leading mutation in BCR-ABL that causes CML made it possible to develop a targeted approach against this vastly disseminating disease. The active tyrosine kinase protein of BCR-ABL was effectively blocked with an identified tyrosine kinase inhibitor (TKI), imatinib. Imatinib became the first targeted therapy licensed for patients with chronic-phase CML and its introduction was associated with substantial improvements in response and survival compared with previous therapies. However, drug resistance towards imatinib therapy soon emerged and hence limited the complete eradication of CML in patients receiving imatinib. This is primarily due to the mutations within the ABL kinase domain, and to a lesser degree, due to residual disease after treatment. Nilotinib and dasatinib were soon introduced and showed improved clinical outcomes in patients intolerant and resistant to imatinib treatment. However, the T315I mutant overcame these agents along with imatinib, rendering the treatment ineffective. Exploring the kinase domain of the BCR-ABL protein and identifying key components involved in the signal transduction pathways is crucial towards understanding the disease and developing better strategic approaches towards combating it. In this review, we broadly discuss the current treatment options available against Philadelphia chromosome (Ph) positive BCR-ABL CML.

Keywords: BCR-ABL, tyrosine kinase, imatinib, nilotinib, dasatinib.

INTRODUCTION

Cancer cells have the unique ability to evade the ubiquitous process of programmed cell death (PCD) that is prevalent among all multicellular eukaryotic cells and is necessary for maintaining tissue homeostasis and health. The process now widely known as apoptosis was not familiar until in the last 50 years, when it was identified and termed by John Kerr, Andrew Wyllie, and Alistair Currie [1]. The ability of cancer cells to escape apoptosis gives them the potential to proliferate endlessly. These cancer cells evolve through a multistage process that extends over decades; such process is characterized by the progressive accumulation of mutations and epigenetic abnormalities that result in increased or decreased expression of hundreds of genes [2,3]. It is therefore surprising that despite the extensive disruptive genomic instability of cancer cells, there are patients and experimentally derived systems where only one of the few abnormalities can profoundly inhibit the growth of cancer cells and in some cases also lead to improved survival rates.

Owing to these evidences obtained during the last few decades, it has become clear that most if not all cancers have a genetic origin [4]. One of the most classical examples is that of chronic myeloid leukemia (CML). The discovery of the Philadelphia chromosome and its consistent involvement in CML [5] was the first time that a relationship between a cytogenetic abnormality and malignancy was demonstrated. This review provides an insight into the molecular mechanisms underlying this disease and outlines the current therapeutic options for patients with CML.

CML is a myeloproliferative disorder of the blood stem cells. It is primarily due to a single genetic anomaly where there is a reciprocal chromosomal translocation between the *C-ABL* (Abelson Leukemia virus) oncogene on the chromosome 9 and the *BCR* (breakpoint cluster region) on chromosome 22 [5,6]. The resulting translocation [t(9;22)(q34;q11)] in the *BCR-ABL* gene encodes a fusion tyrosine kinase BCR-ABL protein that is constitutively active, which causes cell-cycle dysregulation and apoptosis as well as affects differentiation and DNA repair [7]. The incidence of CML ranges from 0.6 to 2.0 cases per 100,000 persons per year [8]. The median age of onset was between 45 and 55 years in 2001, but more recently it has been reported to be 66 years, although all age

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groups including children are affected. CML is a malignant clonal disorder of pluripotent hematopoietic stem cells that result in increased myeloid and erythroid cells, platelets in the peripheral blood, and marked myeloid hyperplasia in the bone marrow. Typical symptoms among patients presented with CML include fatigue, anorexia, and weight loss, although 40 percent of all patients remain asymptomatic when they are diagnosed based on abnormal white blood cell count. CML starts from a benign chronic phase to a rapidly progressing flat blast phase within 3 to 5 years. During the blast phase, the cells fail to mature and resemble the myeloblasts or lymphoblasts found in patients with acute leukemia [9].

Depending on the site of breakpoint in the *BCR* gene, the fusion protein can vary in size from 185 kD to 230 kD. Each fusion gene encodes the same portion of the ABC tyrosine kinase but differs in length of the BCR sequence retained at the N-terminal. Typical chronic-phase patients are presented with a 210 kD BCR-ABL protein, whereas patients with Ph-positive acute lymphoblastic leukemia express either a 210 kD or a 190 kD BCR-ABL protein [10]. Cloning of the Ph translocation has led to the development of highly sensitive and specific molecular probes that are valuable tools for monitoring responses to therapy. Quantitative genetic information can be obtained by fluorescence *in situ* hybridization without the need to culture cells [11]. Polymerase chain reaction (PCR) performed on the peripheral-blood RNA is a very sensitive technique and can detect 1 Ph-positive cell expressing the BCR-ABL fusion transcript in 10^5 to 10^6 normal cells [12]. These highly sensitive techniques have allowed for accurate tracking of response to chemotherapeutic treatment in terms of hematologic, genetic, and molecular remissions. A hematologic remission indicates a return of peripheral-blood cell counts and bone marrow morphology to normal, whereas genetic and molecular remissions indicate the disappearance of the Ph chromosome or the BCR–ABL gene, respectively.

MECHANISM OF LEUKEMOGENESIS

A number of evidences indicated that it is the *BCR-ABL* oncogene that is responsible for the induction of leukemia. Transgenic expression of the 190 kD BCR-ABL protein in mice led to the development of leukemia at birth, suggesting that it confers a potent oncogenic signal in hematopoietic cells [13]. Another study confirmed the involvement of *BCR-ABL* gene by introducing the *BCR-ABL* gene into the hematopoietic stem cells of normal mice with infection with a retrovirus, which thereby led to CML [14-16].

Studies performed on the BCR-ABL protein determined the effects of overexpression of BCR-ABL on growth and cellular transformation. The protein was able to transform hematopoietic cells so that their growth and survival *in vitro* became independent of cytokines [17,18]. It can also protect the hematopoietic stem cells from apoptosis and DNA damage from chemotherapy or radiation [18,19]. Biochemical studies demonstrated that the BCR-ABL is a constitutively active tyrosine kinase that is confined to the cytoplasmic compartment. However, the wild-type ABL shuttles between the nucleus and the cytoplasm [20,21]. The constitutively active BCR-ABL protein and its presence in the cytoplasm results in the phosphorylation and activation of numerous substrates of BCR-ABL, thereby activating multiple signal transduction cascades and affecting the growth and differentiation of cells.

Treatment options

CML is pathologically characterized by exhibiting a constitutive kinase activity that drives the survival and proliferation of cells without undergoing apoptosis [22]. Advances made in analyzing the intricate pathways in the pathogenesis of CML continue to uncover the new layers regulating the complex signaling connectivity. The unique and distinct presence of the BCR-ABL in all CML cells, and its evident absence in normal cells, opened the therapeutic potential that became a reality with the discovery of imatinib, a small molecule tyrosine kinase inhibitor (TKI) [23]. The introduction of imatinib changed the original basis of standard care and chemotherapy in patients with CML, with significant increase in patient survival compared to interferon-α, the previous standard for CML treatment [24]. Thus the introduction of small molecule TKIs of BCR-ABL have fundamentally improved the prognosis of CML patients, thereby turning this fatal disease into a treatable one using a molecularly targeted therapeutic approach. The current treatment efforts are focused on optimizing the TKI design and dosing to block all the mutational escape routes of the disease. The current extremes of CML response are the persistence of minimal residual disease (MRD) despite continued TKI therapy and the presence of active disease despite BCR-ABL inhibition. MRD is thought to prevail mainly due to the presence of leukemic stem cells (LSC) that are not fully addicted to the BCR-ABL protein. The advanced stages of CML exhibit substantial degree of BCR-ABL independence,

hence defining a limit for any BCR-ABL targeted approach. Thus, at the center of these disease-eradicating strategies is the pharmacological silencing of BCR-ABL combined with simultaneous inhibition of other crucial targets. Ideally this would lead to the complete wipeout of the disease at all stages ranging from MRD to advanced CML.

Mechanism of action of BCR-ABL TKIs

TKIs can inhibit the constitutively active BCR-ABL tyrosine kinase and reduce the proliferative potential of BCR-ABL positive CML cells [25]. Imatinib, the first identified inhibitor of BCR-ABL tyrosine kinase, is a 2-phenylamino pyridine-based ATP competitive inhibitor that binds to the ABL protein in its inactive conformation and competitively blocks the site for binding ATP, thereby preventing any conformational switch [26]. Imatinib can also inhibit the platelet derived growth factor receptor (PDGFR), Arg and c-kit [23]. There also have been reports suggesting that imatinib could reduce the angiogenesis within the bone marrow along with decreasing the amount of vascular endothelial growth factor (VEGF) in CML patients [27,28]. There was a 97 percent hematological remission and 86 percent complete cytogenic response in newly diagnosed patients with chronic phase that were treated with imatinib, thus making imatinib the first-line therapy for CML patients [29]. However, only chronic phase CML patients responded well to imatinib treatment, while patients with advanced phase relapsed after months or years of treatment with imatinib due to development of resistance [30,31].

Resistance to imatinib treatment validated the need to develop newer BCR-ABL TKIs. Drugs such as nilotinib, having a similar chemical phenylamino-pyrimidine class ATP-competitive group, were designed solely by using the co-crystal structure of imatinib-ABL complex [32]. Nilotinib was later reported as having a much higher affinity for the ABL kinase domain than imatinib, in turn having a higher affinity towards wild-type BCR-ABL. However, it lacks specificity towards the T315I mutant [32-34]. Dasatinib is another non-phenylpyrimidine-based TKI developed as an Src-family kinase inhibitor. Dasatinib is still the only Src/ABL inhibitor that has greater activity against imatinib-resistant or intolerant CML. It is reported to have activity against both the active and inactive conformation of the ABL domain [23,34,35]. Dasatinib inhibits BCR-ABL wild-type and mutant variants that have high levels of imatinib resistance, with the exception of T315I mutation [33].

CLINICAL TRIALS DETERMINING EFFICACY, SAFETY, AND PATIENT COMPLIANCE IN PH POSITIVE CML

Imatinib

Imatinib (STI571) became the first drug approved by the Food and Drug Administration (FDA) for the treatment of Ph positive CML patients. The promising results of two phase II studies in CML-advanced phase and CML-blast crisis patients receiving 600 mg/day of imatinib led to its approval [36,37]. Phase I and II studies with imatinib performed on patients that were intolerant or resistant to recombinant interferon-αhelped determine its safety and efficacy [30,38]. Based on the randomized phase III clinical trials results obtained with imatinib, the FDA approved imatinib 400 mg daily to be used as first-line treatment for patients with chronic CML. The study compared imatinib 400 mg daily with interferon-α in combination with cytosine arabinoside (Ara-C) in about 1000 previously untreated CML-chronic phase patients. The study was named IRIS (International Randomized Study of Interferon and STI571). The estimated complete hematologic response (CHR), major cytogenic response (MCR), and complete cytogenic response (CCR) 19 months after imatinib treatment were 98, 87, and 76 percent, respectively. Follow up results obtained after 5 years showed that the estimated best rates of CHR and CCR were 98 and 87 percent, respectively [24]. In 95 percent of all patients, imatinib was well tolerated, with only 5 percent of patient discontinuing imatinib due to adverse effects. Surprisingly no new adverse effects were reported after long-term use of imatinib [39]. The high rate of patients who crossed over from interferon-α combined with Ara-C arm into the imatinib arm could not allow for the true determination of survival benefit with imatinib versus interferon-α plus Ara-C.

The maximum tolerated dose of imatinib still has not been established, and an initial dose of 400 mg daily orally was standard for adult CML-chronic phase. Several non-randomized studies report higher response in patients receiving 600 or 800 mg imatinib daily [40,41]. A systematic clinical trial with high dose imatinib (800 mg) was compared with the standard dose imatinib (400 mg) in a tyrosine kinase inhibitor optimization and selectivity (TOPS) trial. It was an open, prospective randomized phase III trial involving 476 patients at 103 sites in 19 countries [42]. Patients on high dose imatinib achieved a major molecular response (MMR) at 3 and 6 months, but not at 12 months, when compared to 400 mg/daily imatinib.

Even after enormously high response rates and low relapse rates were achieved with imatinib, there were incidents of patients experiencing imatinib resistance or intolerance. In the IRS study mentioned above, there still remained 38% of patients that did not achieve a CCR during the first 12 months of treatment, and overall there were 13% of patients who did not attain CCR even after 5 years of treatment. There were reports of 3-7% of patients experiencing treatment failure after 3 years of imatinib treatment and a total of 5% of patients who discontinued treatment due to adverse side effects [24]. Thus there still remain several patient populations that require alternate treatments in the case of imatinib failure and intolerance.

Nilotinib

Nilotinib another small molecule TKI was approved by the FDA in 2007 for the treatment of imatinib resistance or intolerance in CML patients. Nilotinib was found to be significantly more effective, with a more favorable safety profile than imatinib, in imatinib-resistant CML patients [43]. The follow up rates for MCR and CCR were 48 and 31%, respectively, in a subsequent phase II trial where nilotinib was administered twice daily at 400 mg, given to 280 imatinib resistant or intolerant patients. Nilotinib showed favorable efficacy profile in CML patients except in the ones harboring the T315I and other resistant mechanisms independent of the BCR-ABL mutations. With mild to moderate adverse effects and a minimal rate of cross-tolerance to imatinib, nilotinib soon became the treatment of choice for CML treatment. Nilotinib showed a rapid and sustainable CHR during a 10-month follow up in 321 patients enrolled in the study with 84 percent rapid and sustained CHR and 59 percent MCR rates. Surprisingly 78% of patients maintained MCR after 24 months. The estimated overall survival rate was 88% at 24 months [44]. A Phase II trial studying nilotinib was conducted, with a median treatment length of 202 days, to evaluate its safety and efficacy in 119 acute phase CML patients that were resistant to imatinib. The rates for HR and MCR were 47 and 29 percent respectively, and the overall survival after 12 months was 79 and 45 percent respectively [45].

Non-hematologic adverse effects reported were mostly mild to moderate in severity. Thrombocytopenia and neutropenia were the most common grade 3 or higher hematologic adverse effects observed among CML patients. Nilotinib had a rapid and sustained response in CML-AP patients who did not respond to imatinib treatment; in total, 137 patients that received nilotinib were studied in a long-term follow-up. The HR and MCR were maintained at 54% and 70% after 24 months and the estimated overall survival at 24 months was 67%. The HR, CHR, MCR, and CCR rates were 56%, 31%, 32%, and 20%, respectively, and the median time to HR was 1 month. Of all, only 9% of patients had to discontinue treatment due to adverse effects [45]. The promising results obtained from the previous study led to nilotinib's approval by the FDA in 2007 for the treatment of Ph positive CML- chronic phase and acute phase patients intolerant or resistant to imatinib.

The administration of nilotinib has also shown positive results in patients with blast phase CML. A phase II study performed on 136 blast phase CML patients undergoing nilotinib therapy showed that the HR, MCR, and CR rates were 21, 40 and 29%, respectively, with overall survival of 42% at 12 months. The results of this study were not accepted by the FDA as being efficacious for the treatment of blast phase CML patients. In another phase II study, nilotinib was being assessed for use as a first-line treatment in previously untreated CML-chronic phase patients. A total of 73% of patients were enrolled and were assessed for a period of 210 days. The CHR rates at 3 and 6 months were 100 and 98% during an ITT (intent-to-treat) analysis and the CCR rates were 78 and 96%, respectively. Nilotinib demonstrated a faster molecular and cytogenic response when compared with imatinib. Of all, only 1 patient harboring the T315I mutation progressed to the accelerated or blast phase after 6 months of treatment [46].

Dasatinib

Dasatinib is an inhibitor of BCR-ABL and Src, and is more potent than imatinib in inhibiting BCR-ABL tyrosine kinases [47]. In a Phase I study, dasatinib (15-240 mg/day) once or twice daily in a 4 week treatment cycle was administered to patients with various phases of CML that could not tolerate or were unresponsive to imatinib treatment [48]. The results obtained from the study indicated that a CHR was achieved in 37 out of 40 CML-chronic phase patients and an MHR in 31 out of 44 CML-acute phase patients. A response was maintained in 95% of patients with chronic phase disease and in 82% of patients with accelerated phase disease after median follow-up periods of more than 12 and 5 months, respectively. Dasatinib at 240 mg was well tolerated, with significant clinical response among

all BCR-ABL genotypes, except for those with a T315I mutation. Thus, phase II studies were carried out with dasatinib, known as the SRC/ABL tyrosine kinase inhibition activity research trials (SRART), which examined the effect of dasatinib in Ph positive CML patients resistant to or intolerant of the adverse effects of imatinib. The results of the clinical study indicated a CHR and MCR were achieved in 90 and 52% of patients respectively. The responses were long lasting, as only 2% of patients achieving a MCR showed further disease progression or mortality. More importantly, impressive results were obtained in patients who were resistant to imatinib treatment. There was a decrease in the BCR-ABL/ABL transcript ratio from 66% at baseline to 2.6% after dasatinib treatment, which induced an MR after 9 months [49]. A median follow up of 15.2 months (treatment duration, 0.1-18.4 months) was performed and the data recorded for a total of 287 patients showed that the CHR was maintained at 91% and the MCR at 59% among the cohort. 52% of the patients were reported as either imatinib intolerant or resistant. Of all the patients, only 7% had disease progression and the disease free progression and overall survival were 90 and 96%, respectively. However, there was a proportion of patients who succumbed to grade 3/4 thrombocytopenia and neutropenia (48 and 49%, respectively), with non hematologic adverse effects being primarily diarrhea (37%), headache (32%), fatigue (31%), dyspnea (30%), and pleural effusion (27%). Pleural effusions were classified as grade 3 in 6% of reported events, with no reports of grade 4 events [50].

A randomized trial was conducted to compare high dose imatinib of 800 mg/daily to imatinib 400-600 mg/day imatinib. 150 patients were randomized 2:1 to receive dasatinib 70 mg twice daily or imatinib 800 mg daily. The median survival of the patients was compared at 15 months. It was observed that dasatinib produced a significantly greater CHR [51] (93 vs. 82%, $p = 0.034$) and MCR (52 vs. 33%, $p = 0.038$) rate compared with 800 mg of imatinib. Higher proportion of patients reached MMR with dasatinib than with imatinib treatment (16 vs. 4%; $p = 0.038$). The patients receiving dasatinib had lower probability of treatment failure and longer progression-free survival. A more recent 2 year follow-up results confirmed the significant progression-free survival and overall survival benefit for dasatinib over imatinib [52].

A trial named START-A aimed at evaluating the safety and efficacy of dasatinib in CML-AP patients with intolerance or resistance to imatinib [53]. Overall, major and complete HR obtained from the study involving 107 patients were 81, 64, and 39%, respectively. A total of 33 and 24% of patients achieved major or complete CR, respectively. There were only 7 patients that relapsed, out of 69 patients that achieved MHR. Overall, 76% of patients were estimated to be alive and were progression-free after 10 months. The study revealed that dasatinib was well tolerated and that imatinib intolerant patients did not discontinue dasatinib treatment on the basis of adverse effects or intolerance. The follow-up data after 14.1 months indicated MCR and CR rates of 39 and 32%, respectively, and MHR and CHR rates of 64 and 45%, respectively, among patients taking dasatinib. The results from the study were consistent irrespective of the BCR-BAL mutation status, having prior stem cell transplantation, or imatinib resistance or intolerance. The 12-month progression-free and overall survival among the patients were 66 and 82%, respectively, [54].

The ability of dasatinib to alleviate CML-blast crisis in patients who are intolerant or resistant to imatinib was evaluated in the START-B and START-L trials, both for myeloid blast crisis, MBC-CML patients lymphoid blast crisis, and LBC-CML patients respectively [55,56]. MHR rates were 34 and 34% and the MCR rates were 31 and 33%, respectively, in the 8- and 12-month follow-up of MBC-CML patients. The median progression-free survival and overall survival were 6.7 and 11.8 months, respectively. In LBC-CML patients, the 8-month and 12-month follow-up results indicated that the MHR rates were 31 and 35%, respectively, and the MCR rates were 50 and 52%, respectively. The median progression-free survival and overall survival were 3.0 and 5.3 months, respectively. The initial approved dose for dasatinib remained at 70 mg twice daily; however, a longer follow-up data from phase I trial of dasatinib showed that once daily dosing in patients resulted in fewer adverse effects [48,49,51]. The results obtained thus lead to phase II dose-optimization trials (designated CA180-034 and CA180-035) in patients resistant to or intolerant of imatinib [56]. In the CA180-034 trial, 670 CML-CP patients with imatinib resistance or intolerance were randomly assigned (1:1:1:1) to four dasatinib treatment groups: 100 mg once daily, 50 mg twice daily, 140 mg once daily, or 70 mg twice daily. Similar efficacy was observed among all four groups after a minimum follow-up of 6 months. The 100 mg once daily dasatinib demonstrated significantly lower rates of toxicity and lower frequencies of dose reductions and/or

interruptions compared to the 70 mg twice-daily regimen. The safety and efficacy of 100 mg dasatinib once daily was recently confirmed [56]. In the CA180-035 trial, 140 mg dasatinib once daily was compared to the 70 mg twice daily dosing in CML acute phase patients with imatinib resistance or intolerance. The median follow-up of 15 months for 140 mg once daily dasatinib demonstrated equal efficacy and improved safety compared to the 70 mg twice daily dosing [57]. The results from the above studies led to the approval by the FDA of dasatinib 100 mg once daily for CML-chronic phase patients and 140 mg once daily for CML-acute phase and CML-blast crisis patients.

RESISTANCE TO TKI

The development of clinical resistance to imatinib has now surfaced in several instances. Acquisition of point mutations in the ABL tyrosine kinase domain that interferes with the binding of imatinib appeared to be the most influential. ABL kinase domain mutations are generally comprised of two categories. The first includes mutations that directly obstruct contact between imatinib and BCR-ABL, such as the gatekeeper mutations T315I or F317L [58]. The second involves mutations that alter the spatial conformation of the BCR-ABL protein by affecting one of the two flexible loops: (1) the P-loop containing the ATP binding pocket, or (2) the activating loop [59-61]. To date, more than 50 ABL kinase domain mutations have been identified. Although the prognostic significance of many of these remains unclear, the T315I mutation has been associated with a particularly adverse outcome, since it disrupts a hydrogen bond critical for binding of the TKI to the ATP-binding site. This mutation has been identified in up to 20% of patients with imatinib-resistant Ph positive CML, and also confers resistance to the second-generation TKIs nilotinib and dasatinib [62].

TREATING IMATINIB RESISTANT CML

Treating imatinib resistant CML often involves the use of high dose imatinib or resolving to alternative TKIs such as nilotinib or dasatinib, and also the use of hematopoietic stem cell transplantation (HCT). Imatinib dose escalation showed improved status, but the improvement was short-lived [63]. A retrospective analysis was performed on 106 newly diagnosed CML-chronic phase patients in the IRIS trial. These patients were initially treated with 400 mg imatinib per day, and then received either 600 or 800 mg daily because of either suboptimal responses or resistance to imatinib. Imatinib dose escalation provided no significant benefit in patients who did not achieve CCR on conventional doses [41,47].

The second-generation TKIs, dasatinib and nilotinib, offer improved potency and a greater likelihood of success in imatinib-resistant patients. As previously stated, many clinical trials have proven the efficacy and safety of dasatinib and nilotinib for the treatment of patients with resistance or intolerance to imatinib [49-51,54,64,65].

Another potential therapeutic option for CML patients who are intolerant to TKIs and harbor the T315I mutation is the allogeneic HCT (AlloHCT). However, it is to be noted that this form of treatment is only reserved for patients that have progressed to advanced forms of CML with unfavorable molecular and cytogenetic disease, since responses to BCR-ABL TKIs are unlikely to be sustained [66]. The updated ELN guidelines recommend AlloHCT for patients in CML-acute phase, blast crisis, or with the T315I mutation, and also for patients who fail or have suboptimal response to second-line TKIs such as nilotinib or dasatinib [67].

Patients who are intolerant or resistant to TKIs with the T315I mutation are also candidates for clinical trials with new investigative drugs, such as the ATP non-competitive ABL TKI, ON012380, the aurora kinase inhibitor, MK-0457, and the p38 MAP kinase inhibitor, BIRB796 [34,68,69]. All of these compounds have been reported to be effective in CML patients with the T315I mutation [70]. With that said, there are a number of treatment options for patients who fail to respond to imatinib. The key is to completely understand the resistance and intolerance profile of the patient in order to optimize therapeutic benefit and avoid unnecessary delays in treatment. Steps such as inquiring about the patient's medical history should be required to avoid any pharmacodynamic and/or pharmacokinetic interactions. Patient's imatinib plasma levels also help to determine compliance with the medication. Mutation analysis can provide additional information regarding the current treatment regimen in use.

PHARMACOKINETIC PARAMETERS

Imatinib is metabolized by cytochrome P450 enzyme CYP3A4 isoform [71,72]. The variance in activity among CYP3A4 enzymes is quite substantial [73], which contributes to variability of imatinib levels among patients. There are also drugs that can alter the

activity of CYP3A4 and hence impact blood concentration of imatinib. For example, drugs that inhibit CYP3A4 may increase, whereas drugs that induce CYP3A4 may decrease plasma levels of imatinib [74]. Further polymorphism studies are mandated to understand the significance of cytochrome P450 enzymes on the plasma levels of imatinib and response to therapy in CML patients. Another important pharmacokinetic factor involved in imatinib-resistance is alpha-1 acid glycoprotein (AGP), which is an acute-phase reactant protein found in the plasma [75,76]. It has been reported that AGP binds imatinib in a 1:1 molar ratio and this could reduce the free concentration of imatinib and attenuate its entry into leukemic cells [75]. However, there is controversy regarding the association of increased AGP levels and imatinib resistance [76].

CONCLUSION

BCR-ABL TKIs have positively changed the treatment landscape of hematological malignancies such as CML. This is primarily attributed to the discovery of predominating Ph positive mutation that drives the disease. Patient survival has drastically improved compared with that of 20 years ago, when treatment was mainly based on mainstream chemotherapeutic agents and stem cell transplantation. However, the challenges today are very different. Resistance and intolerance to imatinib therapy is still quite prevalent among patients. The notorious T315I mutation within the BCR-ABL protein still remains untreatable by several first and second generation TKIs such as imatinib, nilotinib, and dasatinib. Indeed, the diverse and complex body of knowledge e that we have gained in understanding chemotherapeutic failure has provided us with novel strategies to overcome CML disease. It seems pertinent to further explore and determine the resistance mechanisms and to ascertain the resistance profiles of these known BCR-ABL TKIs in order to provide optimal treatment regimens.

CONFLICT OF INTEREST

Authors disclose no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Conceived and designed the concept: AP. Wrote the first draft: AP. Contributed to writing of the manuscript: AP, HZ, DW. Agree with the manuscript and conclusion: AP, HZ, DW, ZSC. Made critical revisions and approved final version: ZSC. All authors reviewed and approved of the final manuscript.

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