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Review Article

A Review of the Genetic Variants Affecting Efficacy and Adverse Effects of the Standard of Care Treatment in Patients with Chronic Myelogenous Leukemia

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Abstract

Chronic myelogenous leukemia (also called CML or chronic granulocytic leukemia) is a disorder in which the bone marrow generates many white blood cells. There is no recognized etiology for CML in most individuals. Only a few known risk factors for CML development have been identified related to exposure to specific chemicals. It is distinguished by a cytogenetical irregularity comprising a reciprocal translocation between the long arms of chromosomes 22 and 9 [t (9;22)]. CML treatment entails taking a variety of drugs and undertaking additional therapies, all of which can cause unpleasant side effects. In this manuscript, we have sifted through the literature and compiled studies investigating various gene variants affecting the efficacy and adverse effects of the standard of care treatment in CML. Our study shows some promising candidate genes that may be used as a predictor of certain adverse effects of CML treatment. Recommendations are made to employ these genetic variants in clinical medicine.

Keywords: Chronic myelogenous leukemia, adverse effects, efficacy, genetic variants, Philadelphia chromosome, Gleevec

Introduction

Chronic myelogenous leukemia (also called CML or chronic granulocytic leukemia) is a disorder in which the bone marrow generates many white blood cells. CML is a slow-developing blood and bone marrow disease that generally affects people between their forties to sixties and infrequently occurs in youngsters (N.C.I. NIH 2022,March 25). Relocation t(9;22) (q34;q11), which results in the development of the Philadelphia (Ph) chromosome and the *BCR-ABL1* fusion gene, is present in CML, a myeloproliferative illness (Quintás-Cardama and Cortes 2009). CML is split into three stages: chronic phase (CP), accelerated phase (AP), and blast phase (BP). Chronic indicates that fewer than 10% of the blood and bone marrow blasts are present. Blasts are immature white blood cells that can last for several years. The AP of CML is defined by the presence of 10 to 19 percent blasts in both the blood and bone marrow or more than 20 percent basophils in the peripheral blood, in most individuals. In the blast phase (also called blast crisis (BC), there are 20 percent or more blasts in the blood or bone marrow (Cancer.Net 2018). CP of CML develops to the AP and then to the BC (Goldman and Melo 2001). 20% to 25% of people

may acquire BC without passing through the intermediate AP. (Baccarani et al. 2013). Regarding gene expression profiling, the transition from CP to advanced stages has been defined as a two-step process rather than a three-step approach. A halt of differentiation and apoptosis, alterations in cell linkage, triggering of signaling pathways, and a change toward turning on the representation of genes associated with the nucleosome are all observed during the transition from CP to AP (Radich et al. 2006).

The condition usually appears between the ages of 45 and 55, and most patients are asymptomatic at the time of diagnosis, which is often established following routine blood testing. The progression of CML follows a biphasic or triphasic pattern. Most cases (85%) are identified in the asymptomatic CP stage when the cells are primarily differentiated, modestly invasive, and still functioning. Fatigue, weight loss, stomach fullness, bleeding, purpura, splenomegaly, leukocytosis, anemia, and thrombocytosis are all common symptoms at the time of diagnosis (Stefan Faderl et al. 1999b).

Epidemiology of CML

CML has a global yearly incidence rate of 0.87 per 100,000, increasing with age to 1.52 in individuals over 70. A minor masculine preponderance exists (Hoffmann et al. 2015). The incidence of CML in Asia is lower than in Western countries (Au et al. 2009). CML cases grew somewhat globally from 31,752 in 1990 to 34,179 in 2017, while the age-standardized incidence rate (ASIR) reduced dramatically from 0.75 per 100,000 people in 1990 to 0.43/100,000 people in 2017 (Ning et al. 2020).

Risk Factors

There is no recognized etiology for CML in most individuals. Only a few known risk factors for CML development have been identified related to exposure to specific chemicals. Long-term exposure to high quantities of benzene and other organic solvents, for instance, is a risk factor for CML. Exposure to high-dose radiation (such as being a survivor of an atomic bomb blast or nuclear reactor accident) increases the risk of getting CML. It is unclear how significant the increase will be, but most doctors attempt to keep a patient's radiation exposure as low as possible(A.c. society 2018 ,June 19).

Pathophysiology

CML is a disorder in which hematopoietic stem cells are involved. It is distinguished by a cytogenetical irregularity comprising a reciprocal translocation between the long arms of chromosomes 22 and 9 [t (9;22)], Philadelphia (Ph1) chromosome first time explained by Nowell and Hungerford as shown in figure 1. The translocation reposition an oncogene called *ABL* from the long arm of chromosome 9 to a specific cut-off point cluster region (*BCR*) in the long arm of chromosome 22 (Druker et al. 2001; H. Kantarjian et al. 2002; Merx et al. 2002; H.M. Kantarjian et al. 2003). Genetic sequences on Chromosome 22 (*BCR* gene) are joined with sequences translocated from chromosome 9 *ABL* gene). This fusion gene produces an aberrant protein that acts as a tyrosine kinase. This Tyrosine Kinase is involved in signal transduction and activates pathways inside the afflicted cells that lead to malignancy. Tyrosine kinases govern cell division by transferring a phosphate group from ATP to intracellular proteins (Hassan et al. 2015). JAK/STAT, PI3K/AKT, and RAS/MEK pathways that impact cell proliferation, survival, apoptosis inhibition, and transcription factor activation are affected (S. Faderl et al. 1999a).

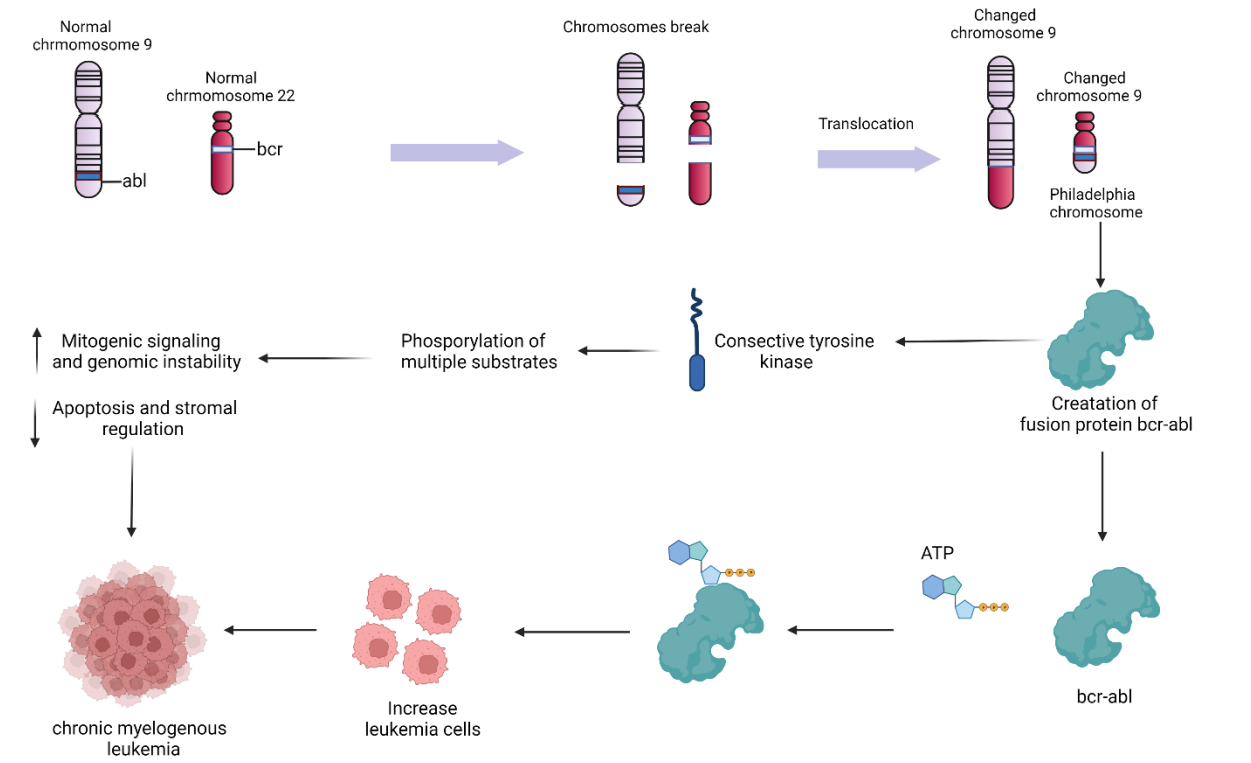

Figure 1: The figure illustrates some of the important steps in the pathogenesis of CML.

Major Challenges in the CML

CML treatment entails taking a variety of drugs and undertaking additional therapies, all of which can cause unpleasant side effects. Tyrosine kinase inhibitors **(**TKIs) are medications used as a type of targeted treatment to treat a variety of cancers. TKIs, such as Gleevec can alter the rhythm of the heart. Another side effect linked to TKIs is depression. Patients may also experience depression related to their cancer in general, and the drugs could worsen (healthline 2020,March 06). Imatinib causes fluid to build up around the eyes, feet, and abdomen (belly). Fluid build-up around the lung (called a pleural effusion) is a significant Dasatinib side effect that can develop. Nilotinib can alter the cardiac rhythm, resulting in a condition known as prolonged QT syndrome (A.C. Society 2022a)**.** Ponatinib can cause severe blood clots, liver, and heart problems, including liver and heart failure, which can be severe and may lead to death (ICLUSIG® 2022, 05). Chemotherapy, in addition to killing cancer cells, can harm healthy cells. Chemotherapy treatment used for CML can cause hair loss, low blood cell counts, skin problems, and fertility problems (C.C. Society 2022b), low white blood cell counts (leukopenia), low blood platelet counts (thrombocytopenia), low red blood cell counts (A.C. Society 2018, June 19). Chemotherapy has a severe side effect; tumor lysis syndrome (when many leukemia cells are destroyed, a large amount of cell waste accumulates in the blood. It can harm kidneys, heart, and neurological system) and can damage many **o**rgans **(**this can include damage to the kidneys, liver, testicles, ovaries, heart, or lungs) as shown in figure 2 (Center 2022).

Role of Pharmacogenetics

Several researchers have investigated the effect of genetic influence on the response of therapy in CML. Genetic variation is an important determinant of the therapeutic response and

adverse effects while treating any disease (Figure 3). Here we compiled, reviewed, and discussed important genetic variants of certain genes that are associated with the therapeutic response and/or adverse effects of the standard of care in CML.

ATP binding cassette subfamily G member 2 (*ABCG2*)

The *ABCG2* gene is part of the ATP-binding cassette family, which comprises genes that provide commands for constructing proteins that help transport chemicals throughout cell membranes. Urate results from some metabolic activities that occur naturally in the body. A study in which *ABCG2* Single nucleotide polymorphisms 34G>A, 421C>A, 623T>C, 886G>C, 1574T>G and 1582G>A were examined in K562 cells by retroviral gene transfer. SNPs 421C>A, 623T>C, 886G>C, and 1574T>G raise the efficacy of studied TKIs (imatinib, CGP74588, dasatinib, and nilotinib), indicating that these SNPs might influence TKI pharmacokinetics in vivo, according to findings (Skoglund, Boiso Moreno, et al. 2014). Another study demonstrated that *ABCG2* rs2231142 GG genotype is linked with a decreased risk of molecular remission. MDR-transporters SNPs may appreciably impact the accomplishment and failure of molecular response in CML patients treated with nilotinib is also concluded (Loscocco et al. 2021). The *ABCG2 C421A* polymorphism was shown to be substantially linked with the greater major molecular response (MMR) in individuals taking imatinib according to a meta-analysis (Jiang et al. 2017). In another study, it is revealed that transport molecules for drugs *SLC22A1* and *ABCG2* have no association with bosutinib efflux (Redaelli et al. 2015; Skoglund, Moreno, et al. 2014).

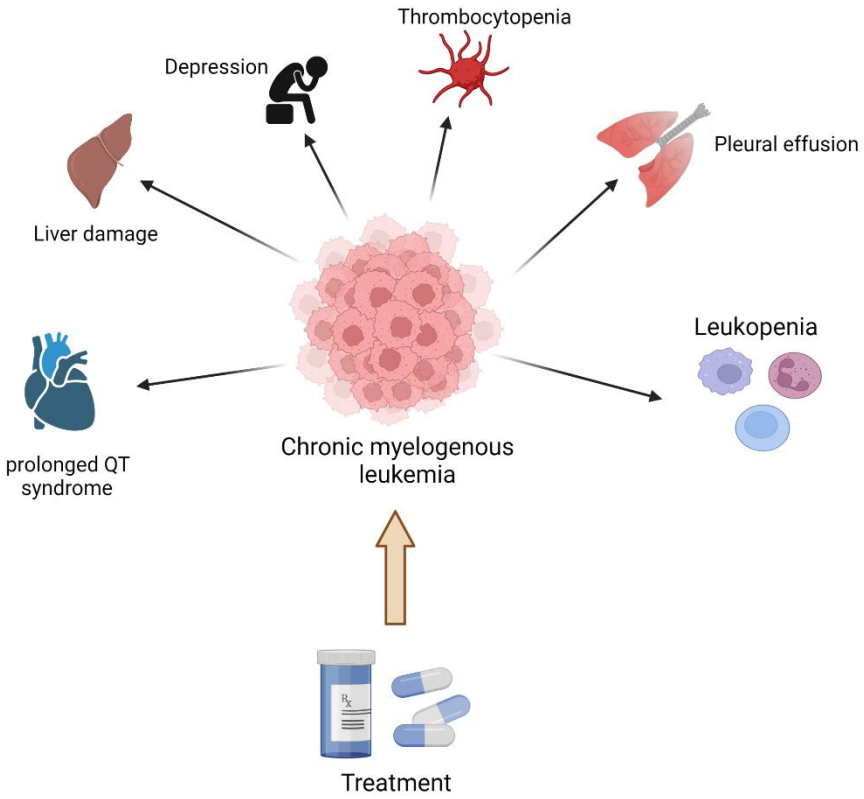

Figure 2: This figure shows some of the major challenges faced while treating CML patients.

Cytochrome P450, family 3, subfamily A, member 4,5 (*CYP3A5, CYP3A4*)

In adults, *CYP3A4* and *CYP3A5* are the two most valuable drug-metabolizing enzymes in the *CYP3A* subfamily, involve in the majority of clinical drug metabolism (Rendic 2002). *CYP3A4* and *CYP3A5* account for 30-50 percent of total P450 in the liver (Lin et al. 2002; Kuehl et al. 2001). Polymorphisms of *CYP3A4*18* (rs28371759) are common in Malaysian CML patients, according to a study it is demonstrated that *CYP3A4*18* has no association with response to Imatinib therapy while there *CYP3A5*3* has an association with imatinib (Maddin et al. 2016).

Cytochrome P450, family 1, subfamily A, polypeptide 1 (*CYP1A1*)

CYP1A1 is a kind of protein, (Kawajiri 1999) in humans that is encoded by the *CYP1A1* gene (Nelson et al. 2004). *CYP1A1* is a member of the cytochrome P450 superfamily of enzymes (Smith et al. 1998). In the Indian population, researchers looked at the risk factors linked with the *CYP1A1*2C* [rs1048943;A>G] polymorphism in CML patients, The AG genotype of the *CYP1A1*2C* polymorphism was found to have a protective effect against CML with imatinib patients (Lakkireddy et al. 2015).

Glutathione S-Transferase Mu 1, P1 & Theta (*GSTM1, GSTP1, GSTT1*)

GSTM1 is involved in the detoxification of metabolites of carcinogens found in the environment, such as cigarette smoke. There is some evidence to show that persons with common variants in these genes are more susceptible to a variety of malignancies (Web 2019 , September 01). *GSTT1* belongs to a protein family that catalyzes the conjugation of reduced glutathione to a wide range of electrophilic and hydrophobic molecules (NCBI NIH 2022,July 18). *GSTP1* is a polymorphic gene that encodes active, functionally distinct *GSTP1* variant proteins that are considered to have a role in xenobiotic metabolism and cancer susceptibility (NCBI NIH 2022, July 03). The impact of GSTs variability on CML susceptibility was highlighted in the research, and the results revealed that *GSTM1* and *GSTP1* polymorphisms, but not *GSTT1* polymorphisms, may be implicated in CML pathogenesis (Weich et al. 2016). According to recent research, individuals with *GSTP1* AA/AG genotypes alone and in conjunction with *GSTT1* null genotypes acquire cytogenetic response of imatinib faster, however, patients with *GSTP1*-GG and *GSTMI* positive genotypes may take longer to achieve imatinib cytogenetic response. (Delmond et al. 2021). A meta-analysis of CML patients showed that G allele carriers with *GSTP1* Ile105Val polymorphism had significantly worse responses to imatinib treatment (Lee et al. 2020).

Solute Carrier Organic Anion Transporter Family Member 1A2 (*SLCO1A2*)

The cellular absorption of a wide range of endogenous substrates, as well as medicines and xenobiotics, is mediated by the organic anion-transporting polypeptide 1A2 (*OATP1A2*) (gene symbol, *SLCO1A2*). *OATP1A2* is found in a variety of organs, including small intestine epithelial cells' apical membranes (Eloranta et al. 2012). The *SLCO1A2* 1105G>A/1032G>A genotype (P = 0.075) and the *SLCO1A2* 361GG genotype (P = 0.005) genotypes were shown to impact Imatinib clearance in CML patients. Findings showed that *OATP1A2* transports imatinib in intestinal cells and targets CML cells and that *SLCO1A2* polymorphisms have a major impact on imatinib pharmacokinetics (Y Yamakawa, Hamada, Shuto, et al. 2011). In the Canadian population, the GG genotype at *SLC22A1* (rs683369) was substantially related to a high incidence of loss of response and treatment failure with Imatinib (Kim et al. 2009). G allele carriers of *SLC22A1* C480G and A allele carriers of G1222A were substantially related to imatinib resistance in a study of Malaysian patients (Makhtar et al. 2018).

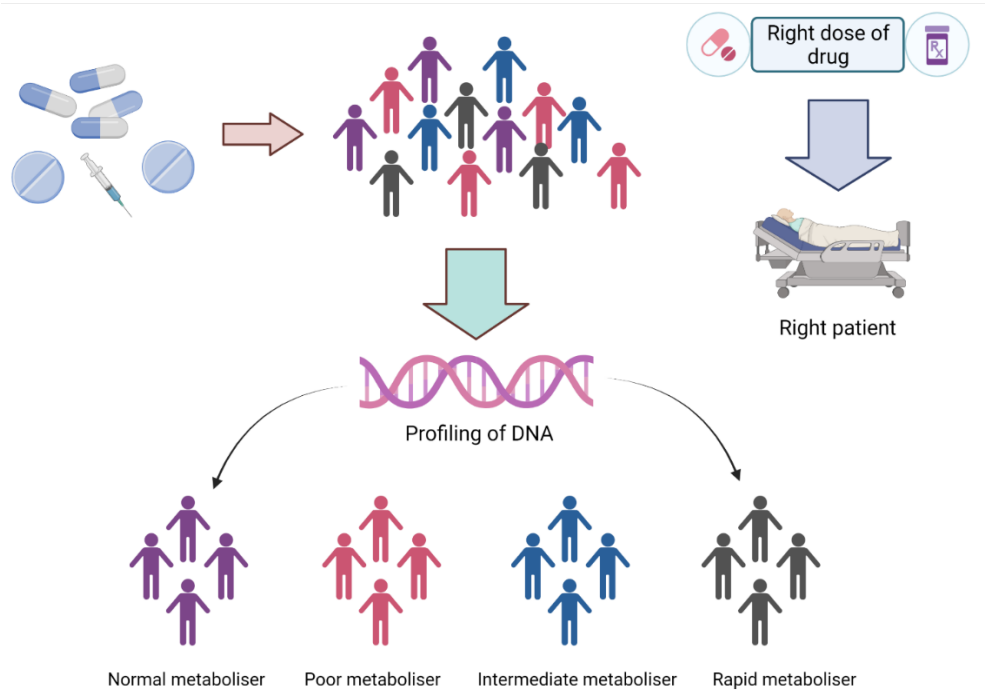

Figure 3. The figure illustrates that genetic variation is an important determinant of a drug reaching the right patient at the right time with right dose.

Solute carrier organic anion transporter family member 1B3 (SLCO1B3), ATP-BINDING CAS-SETTE, SUBFAMILY B, MEMBER 1 (ABCB1), and organic cation uptake transporter (*OCT1*)

Organic anion-transporting polypeptide 1B3 (*OATP1B3*), also called *SLCO1B3*, is a protein produced by the *SLCO1B3* gene. *OATP1B3* is an influx transporter with a 12-transmembrane domain. The transporter is normally found in the liver and is responsible for the absorption of large, non-polar medicines and hormones from the portal vein (NCBI NIH 2022, July 07). The *ABCB1* gene produces the P-glycoprotein transmembrane transporter, which removes a variety of xenobiotic substances from cells. *ABCB1* is found in the plasma membranes of many different cells and organs, including the endothelium of the blood-brain barrier (BBB) (Seo et al. 2020). *OCT1* is the main transporter of organic cationic medicines into hepatocytes, as well as several positively charged endogenous substances (Hyrsova et al. 2016). *OCT1* is primarily responsible for imatinib uptake, but dasatinib uptake is unaffected by *OCT1* (Giannoudis et al. 2008). A study revealed that SNPs of the influx transporter *SLCO1B3* 334TT and the efflux transporter *ABCB1* 3435CC have an association with clearance (decrease) of imatinib treatment in CML patients (Yuji Yamakawa, Hamada, Nakashima, et al. 2011). The 1236CC genotype was substantially related to improved responsiveness to imatinib in the Asian population based on a study of ABCB1 c.1236C4 > T polymorphism. The *ABCB1* c.3435C > T polymorphism was linked to a better imatinib response, whereas the 3435 T allele was linked to a poorer imatinib response (Zheng et al. 2015). According to a meta-analysis, the *ABCB1* C1236T polymorphism is linked to an increased risk of imatinib resistance, but the *ABCB1* G2677T and C3435T polymorphisms had no link to imatinib resistance (Zu et al. 2014). It is also found in a study that the *SLCO1B3* 334TT genotype shows association with a high risk of failure of cytogenic response and also revealed that the *SLCO1B3* 334GT/GG genotype is

associated with cytogenetic response (Nair et al. 2017). The *SLCO1B3* 699GG and 344TT genotypes were shown to be strongly related to improved imatinib response in a Brazilian investigation (de Lima et al. 2015). *ABCB1* 1199G>A SNP impacts the action of tested TKIs (imatinib, nilotinib, and dasatinib), according to research The *ABCB1* 1199A variation is linked to increased *ABCB1* efflux activity, especially toward imatinib and dasatinib (Géraldine Dessilly, Elens, et al. 2016). A study revealed that there is no association between *ABCB1, ABCG2, or OCT1* with imatinib-induced thrombocytopenia in CML patients (Francis et al. 2015). *OCT1* and *ABCB1* polymorphisms did not affect Nilotinib's clinical effectiveness or toxicity (Galimberti et al. 2017). In a study, *ABCB1* polymorphism is investigated to Imatinib in CML patients and revealed that *ABCB1* 1236CT/2677GT/3435CT haplotype has an association with MMR to imatinib in CML patients (Vivona et al. 2012). Another study investigated the *ABCB1* SNPs polymorphism association with TKIs (imatinib, nilotinib, Dasatinib, and ponatinib) anti-proliferative and intracellular accumulation in transinfected HEK293 and K562 cells and revealed that wild-type *ABCB1* exports imatinib more efficiently than 1236T-2677T-3435T variant protein and it is also reported that *ABCB1* polymorphisms have a weak association with activity of nilotinib, dasatinib and ponatinib(G. Dessilly, Panin, et al. 2016)

Xeroderma pigmentosum, complementation group C (*XPC*)

XPC is a protein that is encoded by the *XPC* gene in humans. In nucleotide excision repair, XPC is involved in the identification of bulky DNA adducts (NCBI NIH 2022, July 07). In a recent study SNPS on nucleotide excision repair (NER) genes (*ERCC2-ERCC8*, *RPA1-RPA3*, *LIG1*, *RAD23B*, *XPA*, *XPC*) were investigated and it is revealed that wild-type haplotype (499C-939A) was associated with a better response to imatinib after Haplotype analysis of *XPC* (Guillem et al. 2010).

Nuclear Receptor Subfamily 1 Group I member 2 (*NR1I2*)

Various endogenous and xenobiotic substances bind to and activate this nuclear receptor. Multiple genes involved in the metabolism and secretion of potentially hazardous xenobiotics, medicines, and endogenous substances are activated by this transcription factor. *NR1I2* belongs to the nuclear receptor superfamily, members of which are transcription factors characterized by a ligand-binding domain and a DNA-binding domain (GeneCards 2017). A study showed that polymorphisms of *ABCB1*, *ABCG2*, and *CYP3A4* did not influence bosutinib plasma concentrations (Cmin), however, polymorphism of *NR1I2* influenced Cmin of bosutinib in Japanese patients (Maiko Abumiya et al. 2018).

Multidrug resistance (MDR) gene

The overexpression of a class of membrane proteins termed P-glycoproteins (P-gps) generated by the *MDR* gene family causes MDR, which is a key impediment in cancer treatment for many human malignancies (Ling 1997). The expression of P-gps encoded by the *MDR1* gene is associated with the emergence of the MDR phenotype in cancer cells (Kuo et al. 2002). A meta-analysis study revealed that *MDR1* polymorphisms (G2677T) are associated with the response of imatinib therapy and concluded that it might be useful in response prediction to therapy with imatinib in patients with CML (Elghannam et al. 2014). Another study found that *MDR1* and *CYP3A5* genetic variants had a substantial impact on plasma trough levels and imatinib treatment response in CML patients (Harivenkatesh et al. 2017). *MDR1* has impact on several drugs pharmacokinetics. *MDR1* has an impact on several drugs pharmacokinetics. *MDR1* SNPs polymorphism in CML patients

treated with imatinib is investigated and revealed a significant correlation of the SNPs polymorphisms with imatinib efficacy. Imatinib resistance was statistically associated with one of the haplotypes (2677A-1236C genotype)(Ni et al. 2011).

Bcl-2-like protein 11

Bcl-2-like protein 11, called BIM, is a protein that is encoded by the *BCL2L11* gene in humans. (Hsu, Lin, and Hsueh 1998; O'Connor et al. 1998). The BCL-2 protein family includes the protein expressed by this gene. Members of the *BCL-2* family create hetero- or homodimers and operate as anti- or pro-apoptotic regulators engaged in a wide range of cellular functions (NCBI NIH 2022, July 18). A Meta-analysis showed that BIM deletion does not show significant results and is not associated with TKI resistance (Xu et al. 2017).

Uridine diphosphate-glucuronosyltransferase (*UGT1A1*)

The *UGT1A1* gene is one of a group of genes that supply instructions for producing UDP-glucuronosyltransferases (UGTs). These enzymes perform a chemical reaction called glucuronidation, in which a compound called glucuronic acid is attached (conjugated) to one of several different substances. The protein produced from the *UGT1A1* gene called the bilirubin uridine diphosphate glucuronosyltransferase (bilirubin-UGT) enzyme, is the only enzyme that glucuronidated bilirubin, a substance produced when red blood cells are broken down. This enzyme converts the toxic form of bilirubin (unconjugated bilirubin) to its nontoxic form (conjugated bilirubin), making it able to be dissolved and removed from the body (MedlinePlus 2012 , February 01). The influence of *UGT1A1* polymorphism and nilotinib plasma trough concentration on nilotinib-induced hyperbilirubinemia was investigated and revealed that patients who acquire *UGT1A1**6/*6 and *6/*28 genotypes (poor metabolizers) have a significantly high proportion with hyperbilirubinemia. It is also suggested to avoid nilotinib-induced hyperbilirubinemia it may beneficial to reduce the initial dose of nilotinib to 300-400 mg/day for *UGT1A1* poor metabolizers (M. Abumiya et al. 2014). Another study association between severe toxicity and *UGT1A1* polymorphisms (*6 and *28) investigated and suggest that variant allele *6 has an association with severe toxicity of nilotinib (QTC interval prolongation and hyperbilirubinemia) (Shibata et al. 2014).

Conclusions

Conventional therapy for CML provides symptomatic relief attained through several different strategies. Despite of the significant efficacy of the existing therapies, the anticipated therapeutic outcome is not always achieved in all patients. On the other hand, a non-trivial fraction of the patients experiences significant adverse effects. At the moment there is no reliable way to predict treatment response in patients; hence pharmaceutical companies are restricted to 'one size fits all' approach while developing therapeutic agents. However, this perspective for drug development in CML does not benefit all patients.

The studies reviewed in this manuscript show that this approach may lead to detrimental effects in many CML patients. Despite many environmental and pharmacokinetic factors fostering this heterogeneity, a major contributor 'genetic variation' is often ignored. In order to reduce risk of such adverse events, incorporation of pharmacogenomics into clinical practice would be a wise choice. The main goal of pharmacogenomics is to identify the genetic factors accountable for variable drug efficacy among the individuals, consequently predict drug response and facilitate personalized medicine. This approach ultimately lowers the cost of health care, patient's treatment duration as well as drug induced complications, thus enhance treatment

safety. Besides it can also lower the risk of failures and cost in clinical trials by selecting only those patients who are eligible to respond drug therapy. In this manuscript, we reviewed important studies conducted to identify influence of genetic variations on variable response to CML treatments. However, the data obtained so far show associations with certain genetic variants while the functional role of genetic variants is generally ambiguous as these were underpowered and small-scale studies. There is need to upgrade these researches in order to reap benefit from them by adding in clinical practice. Furthermore, novel disease modifying drugs for treatment of CML also needed, so as to have more treatment options for personalized medicines based on pharmacogenomic signature of individuals.

Conflict of Interest

The authors declare that they have no competing interests.

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Study Approval

NA

Consent Forms

NA

Authors Contribution

AU and FA conceptualized the study, SAM and SSUH did literature search, helped with analysis and writing the first draft, FA supervised the whole project and wrote the final manuscript.

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