Influence of MDR1 and CYP3A5 Genetic Polymorphisms on Egyptian Chronic Myeloid Leukemia Patients Receiving Imatinib

Short title: *MDR1 and CYP3A5 Genetic Polymorphisms on CML Receiving Imatinib*

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Abstract

Background: In individuals with chronic myeloid leukemia (CML), imatinib (IM) has increased long-term survival rates and clinical outcomes; nonetheless, resistance to IM has been noted.

Aim of the Work: Was to study the prevalence and influence of Ex12 C1236T (rs1128503), Ex26 C3435T (rs1045642) and Ex21 G2677T/A (rs2032582) in MDR1 gene as well as A6986G (rs776746) in CYP3A5 gene polymorphisms among Egyptian CML patients on IM and to define their role in disease outcome and prognosis of CML.

Subjects and Methods: One hundred and thirty Egyptian CML patients as well as 60 age and sex matched normal controls were included. The genetic polymorphisms were determined by PCR-RFLP.

Results: CYP3A5 A6986G (rs776746) homozygous (GG) variant and the mutant G allele were linked to a higher risk of developing CML (p-value 0.019, 0.002, OR 2.901, 2.158 and 95%CI 1.188-7.082, 1.341-3.473 respectively). The presence of homozygous (GG) variants and the mutant G allele linked to a higher risk of developing IM resistance (p-value 0.033, 0.012, OR 4.386, 2.192 respectively). The MDR1 gene Ex21 G2677T (rs2032582) (GT, TT) genotypes, the heterozygous (GT) genotype and the mutant T allele were associated with increased risk of developing CML (p-value 0.004, 0.002, 0.043, OR 2.480, 2.985, 1.637 and 95%CI 1.325-4.640, 1.488-5.986, 1.016-2.635 respectively). Moreover, MDR1 gene polymorphisms were not linked to the risk of developing IM resistance in CML patients.

Conclusion: CYP3A5 gene polymorphisms may be involved in IM resistance, while MDR1 gene polymorphisms have no role in developing IM resistance.

Key Words: Chronic myeloid leukemia, imatinib mesylate, MDR1 gene, CYP3A5 gene, genetic polymorphism, PCR-RFLP.

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Introduction

Chronic myeloid leukemia(CML) is a myeloproliferative tumor that is distinguished by the unchecked proliferation of bone marrow stem cells with pluripotency [1]. The disease is characterized by the existence of a reciprocal t(9;22) (q34;q11.2), also referred to as the Philadelphia (Ph) chromosome, which produces a BCR-ABL fusion gene and protein. BCR-ABL requires constitutive tyrosine kinase function and is required for the disease to develop [2].

Imatinib (IM) mesylate is the first logically created small molecule for tumor targeted treatment of CML. IM prevents kinase activation and signal transmission by specifically targeting and blocking the phosphorylation of the BCR-ABL1 fusion protein's tyrosine kinase domain [3-5]. Even while IM is quite effective, a significant percentage of patients do not experience the best possible therapeutic outcome, and some of them eventually become resistant to IM [6].

The active metabolite CGP74588 is produced when IM is broken down by the microsomal enzymes CYP3A4 and CYP3A5 [7]. The MDR1 (ABCB1) gene codes for P-glycoprotein (Pgp), which IM is a substrate of. Pgp is essential for the growth of resistance to IM and other anticancer medications [8-10].

After receiving chemotherapy for cancer, human tumor cells overexpressed the ATP-dependent transmembrane transporter MDR1, which was linked to resistance to multiple medications. It is important for drug-drug interactions and ADME (absorption, distribution, metabolism, and excretion) mechanisms [11]. One of the hypothesized causes for resistance to IM is over-expression of the MDR1 gene, which decreases the accessibility of IM inside tumor cells by increasing Pgp functioning [8].

The hydroxylation of endogenous hormones, the bio-activation of certain Geno toxicants, and the absorption of over 50% of therapeutically utilized medications are all mediated by the CYP3A subfamily of the human cytochrome P450 (CYP). The degree at which CYP3A substrates, including IM, are metabolized and eliminated could be impacted by genetic variations in CYP3A function. CYP3A4 and CYP3A5 are the primary mediators of IM metabolism [12].

CYP3A4/5 catalysis the main pathway in the CYP mechanism, which contributes to the oxidative processing of IM. An intron 3 single-nucleotide polymorphism (SNP) (6986A4G; CYP3A5*3)has a significant association with CYP3A5 expression, indicating that germ line CYP3A5 SNPs could affect IM trough amount and the effectiveness of medications, despite the fact that few prevalent CYP3A4 polymorphisms have been found to have an in vivo impact upon the enzyme's function [12].

Polymorphisms in the MDR1 and CYP3A5 genes may be the cause of the notable inter-individual variation observed in IM metabolism and transport. The accessibility of IM within tumor cells may be impacted by these polymorphisms, which could result in an insufficient treatment response [13].

The aim of the present work was to study the prevalence of C1236T (rs1128503), C3435T (rs1045642) and G2677T/A (rs2032582) in MDR1 gene as well as A6986G (rs776746) in CYP3A5 gene polymorphisms among CML patients on IM and to explore the influence of MDR1 and CYP3A5 genetic polymorphisms on patients receiving IM, after 12 months of beginning the treatment and its relation with various clinical, laboratory findings, disease outcome and prognosis of CML patients.

Patients and Methods

Patients

This prospective study involved 130 Egyptian patients with Philadelphia chromosome-positive chronic-phase CML from the National Cancer Institute, Cairo University, along with 60 age and gender matched normal healthy controls. All patients provided their written informed participation concent. The study was approved by the Ethical Committee of Kasr Al-Ainy School of Medicine, Cairo University, Cairo, Egypt and was conducted according to the ethics guidelines of the Declaration of Helsinki.

Methods

All patients underwent a comprehensive evaluation that included a detailed medical history, clinical examination for splenomegaly, signs of anemia, and bleeding manifestations. Laboratory investigations involved a complete blood count, bone marrow examination, cytogenetic and molecular studies using quantitative RT-PCR for BCR-ABL1, along with serum LDH and uric acid assessments. CML diagnosis followed WHO criteria, indicated by persistent leucocytosis and confirmed through detection of BCR-ABL1. Bone marrow examination was essential for karyotype analysis and morphological evaluation, confirming less than 10% blasts in the chronic phase [14].

Special tests analysed the expression of C1236T, C3435T, and G2677T/A in the MDR1 gene, as well as A6986G in the CYP3A5 gene, using PCR-RFLP in peripheral blood samples from CML patients on IM therapy and followed-up [13].

Genotyping of MDR1 and CYP3A5 by PCR-RFLP analysis:

Two millilitres of venous blood were collected from each patient and control participant using sterile EDTA vacutainer tube and stored at -20°C. The salting out procedure was used to extract DNA from the blood [15], include column purification using the Gene JET Genomic DNA Purification Mini Kit and Proteinase K digestion (Thermo Scientific, Waltham, MA, USA) according to the manufacturer instructions. Followed by Polymerase Chain Reaction (PCR); amplification of the extracted DNA by using specific primers for MDR1 gene (C1236T, C3435T, G2677T/A) and CYP3A5 gene (A6986G) variants, then genotyping analyses and enzymatic digestion by

specific restriction enzyme (Thermo scientific, Massachusetts, USA) as shown in Table (1) for each gene of the amplified DNA using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique was performed for all patients and controls according to the method described by Harlvenkatesha et al. [13], The digested fragments were separated on 4% agarose gel electrophoresis and visualized by ethidium bromide staining under a UV transilluminator.

Evaluation of response to IM

All CML patients were monitored for one year while receiving a daily dose of 400 mg IM to assess responsiveness to IM treatment. Follow-up assessments included real-time quantitative polymerase chain reaction (RQ-PCR) to quantify BCR-ABL1 transcript levels, and complete blood picture to evaluate haematological parameters throughout the treatment period. Monitoring was carried out every three months until a major molecular response (MMR) or better was achieved, after which assessments were performed every three to six months, in accordance with the guidelines established by the European Leukemia Net [5]. Patients exhibiting a response were classified as responders when BCR-ABL1 levels were less than 1% on the International Scale (IS), whereas those with levels greater than 1% were categorized as non-responders (failure)[5].

Statistical Analysis

The data was coded and entered using the statistical program for the social sciences (SPSS) version 25 (IBM Corp., Armonk, NY, USA). Means, standard deviations, medians, range have been employed to summarize quantitative data, whereas frequencies (counts) and percentages (%) were used to summarize categorical data. The non-parametric Mann-Whitney and Kruskal-Wallis analyses were used to compare quantitative variables. Using the Chi square ($\chi 2$) test, categorical results were compared. Logistic regression was used to get the odds ratio (OR) with 95% confidence intervals. P-values below 0.05 were regarded as statistically significant.

Results

This study included 130 Egyptian chronic-phase CML patients aged ranged from 20 to 66 years, with a mean age of 37.2 ± 11.9 years and a median age of 34.5 years, they were 67 males (51.5%) and 63 females (48.5%). Sixty age and gender matched healthy subjects were also included as a control group, ages varied from 20 to 64 years, with a median of 35 years and a mean of 37.7 ± 11.4 years, 31 males (52%) and 29 females (48%). The demographic, clinical, laboratory characteristics and prognosis among CML patients are presented in table (2).

Table (3) shows the genotype and allele frequency of CYP3A5 A6986G (rs776746) and MDR1 G2677T/A (rs2032582), C1236T (rs1128503) and C3435T (rs1045642) genes variants among CML patients and the control group. For the CYP3A5 gene A6986G (rs776746), CML patients exhibited a higher prevalence of mutant genotypes (90%) compared to the control group (80%) with 2.2-fold increased risk of CML, and with significant differences in allele frequencies for A (21% in patients vs. 37% in controls) and G (79% in patients vs. 63% in controls), yielding p-values of 0.048 and 0.002, respectively. For MDR1 gene Ex21 G2677T (rs2032582), CML patients had a significant higher frequency of mutant genotypes (62%) compared to controls (40%), and it indicated a substantial risk, with GT or TT mutations conferring a 2.5-fold increased risk of CML (p-value 0.004), the heterozygous GT variant a 2.9-fold increase (p-value 0.002), and the mutant allele T a 1.6-fold increase in risk (p-value 0.043). While other MDR1 variants revealed no significant differences in genotype or allele distributions between the two groups and they were not identified as risk factors for CML. Moreover, combined gene polymorphisms were not associated with an elevation of the risk of developing CML (p-value 0.604).

The relationship of the different genotypes (wild, heterozygous and homozygous) of CYP3A5 and MDR1 polymorphisms with the demographic, laboratory data and the response of imatinib in CML patients were studied. There was no significant difference between the different groups (p-value >0.05).

Comparison between responder and non-responder groups of the CML patients as regards demographic, laboratory characteristics and prognosis are shown in table (4). There was a significant difference found between the 2 groups regarding sex prevalence, serum LDH, alkaline phosphatase, BCR-ABL by FISH and RT-PCR after 3, 6, 12 months with p-value <0.05, as Responder group included more males (62%), lower serum LDH and alkaline phosphatase, and lower BCR-ABL by FISH and RT-PCR than non-responders. Whereas no

significant difference was found regarding age and the other laboratory data with p-value > 0.05.

Table (5) displays that the responders had a higher prevalence of the wild CYP3A5 rs776746 genotype (AA) at 16% compared to 4.5% in non-responders, with significant differences in allele frequencies (A allele: 28% in responders vs. 15% in non-responders; G allele: 72% in responders vs. 85% in non-responders, $p<0.05$), and the CYP3A5 gene A6986G (rs776746) polymorphism was identified as a significant risk factor, with homozygous (GG) carriers exhibiting a 4.3-fold increased likelihood of developing IM resistance ($p=0.033$), and the presence of the mutant allele G correlating with a 2.19-fold increased risk ($p=0.012$). Conversely, MDR1 variants showed no significant differences in genotype distributions or allele frequencies between the two groups, and they were not found to significantly contribute to the risk of IM resistance. Overall, the CYP3A5 A6986G polymorphism was correlated with treatment response, while the MDR1 gene polymorphisms did not demonstrate any associations with response to treatment in CML patients, indicating that only the CYP3A5 polymorphism plays a notable role in this context.

Haplotype analysis in responders and non-responders CML patients are illustrated in Table (6). Despite the variations which are obvious in haplotype distribution between the two groups, statistical analysis indicated no significant differences, with a p-value of 0.372.

Discussion

A primary treatment for CML involves TKIs like IM, which inhibit the ATP binding site of the BCR-ABL1 protein, blocking the phosphorylation of proteins that drive cell proliferation and inhibit apoptosis [17]. However, despite its efficacy, many patients do not achieve optimal therapeutic responses, and some develop resistance to IM over time [18].

IM is metabolized by the microsomal enzymes CYP3A4 and CYP3A5 into the active metabolite CGP74588 and its efflux is mediated by the transporters MDR1 and MDR2 [19]. And it was reported that MDR1 and CYP3A5 genes polymorphisms might be responsible for the marked inter-individual variations in the pharmacokinetics of IM among CML. These polymorphisms can affect the availability of IM inside the tumor cells, leading to inadequate therapeutic response [13].

In the present study of CML patients, a high percentage exhibited mutations in the CYP3A5 A6986G polymorphism, with a significant prevalence of the homozygous GG genotype (68%) compared to the control group (47%). Most patients were mutants (90%), while the wild type (10%) was less common. The distribution of the A and G alleles showed a greater frequency of the G allele (79%) among CML patients than in controls, indicating a notable difference in genotype distribution between the two groups**.** This was in consistency with Bedewy and El-Maghraby [20] who reported that CYP3A5 wild (AA) form was the least frequent (26.9%), while the mutants (73%) were the most frequent; heterozygous (AG) was (41%) and the homozygous GG (32%), the G allele was the most frequent (70%) and the A allele was the least frequent (30%). Also Maddin et al. [12] found that the wild genotype (AA) was 30% and the mutants were 70%; 46% of them were heterozygous (AG) and 24% were homozygous (GG), but found that the frequency of A allele (53%) was higher than the G allele (47%).

Furthermore, our study found that the homozygous CYP3A5 GG genotype and the mutant G allele are associated with an increased risk of developing CML. The CYP3A5 polymorphism may lead to heightened expression of the mutant allele, potentially causing the accumulation of endogenous steroids or xenobiotics in tissues, which could induce genotoxicity and elevate susceptibility to CML. This was in concordance with the study done by Sailaja et al. [11] who found a significant increase in the homozygous GG genotype and mutant G allele frequency among CML patients compared to healthy controls. This suggests that reduced CYP3A5 expression linked to the mutant allele may lead to the accumulation of endogenous steroids or xenobiotics, potentially increasing the risk for CML development. On the contrary, Liu et al. [21] reported no association between CYP3A5 polymorphism and myeloid leukemia risk. This discrepancy may arise from differences in populations and sample sizes across studies.

In CML responder patients, the majority exhibited mutant genotypes for the CYP3A5 A6986G polymorphism, with a notable presence of both heterozygous (24%) and homozygous variants (60%). The G allele (72%) was more prevalent than the A allele (28%). While, non-responder patients showed more predominance of mutant genotypes (95.5%), with a higher frequency of the G allele (85%) compared to the A allele (15%). This trend suggests a potential association between polymorphism and patient response to treatment. So our current study highlights that homozygous (GG) genotype and mutant G allele of CYP3A5 A6986G increase the risk of IM resistance by 4.4 and 2.19 fold, respectively, due to impaired metabolic activity,

as evidenced by Park et al.[22]. Contrarily, Harivenkatesh et al. [13] found that CML patients with the GG genotype exhibited higher IM levels and better responses, while those with the AA genotype experienced treatment failures due to lower IM plasma levels. Maddin et al. [12] similarly reported that patients with AG and GG genotypes had reduced resistance risk. Also, Natarajan et al. [19] reported AA, AG, GG in 43%, 45%, 56% without cytogenetic relapse and 57%, 55%, 44% with cytogenetic relapse, respectively.

The current study assessed the distribution of MDR1 gene polymorphisms among CML patients and a control group, revealing a higher prevalence of mutant genotypes and alleles in the patient group for Ex21 G2677A, Ex21 G2677T, Ex26 C3435T, and Ex12 C1236T variants compared to controls, who exhibited more wild-type genotypes. These results of MDR1 gene polymorphisms distribution were similar to earlier report by Ali and Elsalakawy [23].

Our study found that certain MDR1 gene polymorphisms, specifically Ex21 G2677A and Ex26 C3435T, do not act as risk factors for CML, whereas the Ex21 G2677T genotype (GT, TT) significantly increases 2 fold CML risk. Additionally, the presence of the heterozygous GT type and the mutant T allele also correlates with heightened risk. These genetic variants will change the expression, efflux, substrate specificity and mRNA stability of P-gp in MDR1 gene leading to leukemia development [24].

Nevertheless, Ma et al. [25] found a significant correlation between adult leukemia (CT+TT vs. CC: OR 2.77, 95%CI 1.05-7.31) and CML (CT vs CC: OR 1.71, 95%CI 1.05-2.80) in their study's subgroup examination based on relevant ethnicity, age, and leukemia type. Their meta-analysis suggested that the MDR1 C1236T polymorphism would increase vulnerability to adult leukemia and CML. This could be explained by different sample sizes used and different populations.

The distribution of MDR1 gene polymorphisms in CML responders and non-responders was noted largely similar across various variants in our study. Both groups exhibited comparable patterns in the Ex21 G2677A, Ex21 G2677T, Ex26 C3435T, and Ex12 C1236T polymorphisms, with similar frequencies of wild and mutant genotypes. Overall, despite some differences in specific patterns, the genetic profiles of responders and non-responders were largely alike across the analyzed polymorphisms. The findings from Ali and Elsalakawy [23] on the distribution of gene polymorphisms in patients with optimal response and primary failure showed similar patterns for G2677T, C3435T, and C1236T variants, with distinct proportions of genotypes observed in both groups. Thus, in contrast to the results of our investigation, Natarajan et al. [19] differentiated between patients with and without cytogenetic relapse, revealing varying distributions of the same MDR1 polymorphisms. Specifically, they reported differences in the frequency of genotypes associated with cytogenetic relapse for G2677T/A, C3435T, and C1236T, highlighting that certain alleles were more prevalent in patients experiencing relapse compared to those without. Overall, these studies emphasize the complex relationship between MDR1 gene polymorphisms and treatment outcomes in CML.

Furthermore, MDR1 SNPs (G2677T/A, C3435T, and C1236T) do not act as risk factors for IM resistance in our CML patients, although they affect drug transport protein functions. Supporting this, Rinaldi et al. [26] reported no association between MDR1 C1236T polymorphism and IM response, while Angelini et al. [27] found a significant correlation between the C3435T variant and complete molecular response and Hari venkatesha et al. [13] concluded that certain MDR1 polymorphisms significantly influenced therapeutic response. Additional studies by Maffioli et al. [28] and Dulucq et al. [29] identified other MDR1 specific genotypes associated with treatment outcomes. Overall, discrepancies across studies may stem from differences in ethnic backgrounds and lifestyle factors, as suggested by Abdul-Razaq et al. [30].

In conclusion, the CYP3A5 A6986G (rs776746) and MDR1 G2677T (rs2032582) polymorphisms may play roles in the pathophysiology and development of CML in Egypt, whereas other MDR1 polymorphisms (G2677A, C3435T, and C1236T) do not contribute to CML development. Additionally, the CYP3A5 A6986G polymorphism may be linked to IM resistance, while the other MDR1 variants are not associated with resistance. Therefore, the CYP3A5 A6986G polymorphism could serve as a predictive molecular marker for prognosis and disease outcomes in CML patients, highlighting its significance for assessing both risk and prognosis in the condition. Further research on these polymorphisms should be conducted with a larger cohort of CML patients to better understand their impact on the disease's development, severity, and prognosis.

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Table (1): Primer sequence and restriction enzymes used in PCR-RFLP reaction in CYP3A5 and MDR1gene polymorphisms

Polymorphism		Primer sequence (5'-3')	Restriction enzymes	Fragment size
MDR1 (rs1128503)	**C1236T**	F: 5′-TAT CCT GTG TCT GTG AAT TGC C-3′	HaeIII (cat.#FD0154)	35, 62, 269 bps
		R: 5′-CCT GAC TCA CCA CAC CAA TG-3′		35, 62, 97, 269 bps
				97, 269 bps
MDR1 (rs1045642)	**C3435T**	F: 5′- TGT TTT CAG CTG CTT GAT GG-3′	Sau3AI (cat.#FD0784)	39, 158 bps
		R: 5′-AAG GCA TGT ATG TTG GCC TC-3′		39, 158, 197 bps
				197 bp

MDR1 G2677A	F: 5′-TGC AGG CTA TAG GTT CCA GG -3′	BsrI	220 bp
(rs2032582)	R: 5′-GTT TGA CTC ACC TTC CCA G-3′	(cat.#FD0884)	14, 206, 220 bps
			14, 206 bps
MDR1 G2677T	F: 5′-TGC AGG TA TAG GTT CCA GG-3′	BanI	26, 198 bps
(rs2032582)	R: 5′- TTT AGT TTG ACT CAC CTT CCC G-3′	(cat.#FD1004)	29, 198, 224 bps
			224 bp
	F: 5′-CAT CAG TTA GTA GAC AGA TGA-3′		20, 125, 148 bps
· **CYP3A5A6986G (rs776746)**	R: 5′- GGT CCA AAC AGG GAA GAA ATA-3′	SspI (cat.#FD0774)	20, 125, 148, 168 bps
			125, 168 bps

Polymorphism	**Primer sequence (5'-3')**	**Restriction enzymes**	**Fragment size**
	F: 5′-TAT CCT GTG TCT GTG AAT TGC C-3′		35, 62, 269 bps
MDR1 C1236T (rs1128503)	R: 5′-CCT GAC TCA CCA CAC CAA TG-3′	HaeIII (cat.#FD0154)	35, 62, 97, 269 bps
			97, 269 bps

	F: 5′- TGT TTT CAG CTG CTT GAT GG-3′		39, 158 bps
MDR1 C3435T (rs1045642)	R: 5′-AAG GCA TGT ATG TTG GCC TC-3′	Sau3AI (cat.#FD0784)	39, 158, 197 bps
			197 bp
MDR1 G2677A	F: 5′-TGC AGG CTA TAG GTT CCA GG -3′	BsrI	220 bp
(rs2032582)	R: 5′-GTT TGA CTC ACC TTC CCA G-3′	(cat.#FD0884)	14, 206, 220 bps
			14, 206 bps
MDR1 G2677T	F: 5′-TGC AGG TA TAG GTT CCA GG-3′	BanI	26, 198 bps
(rs2032582)	R: 5′- TTT AGT TTG ACT CAC CTT CCC G-3′	(cat.#FD1004)	29, 198, 224 bps
			224 bp
	F: 5′-CAT CAG TTA GTA GAC AGA TGA-3′		20, 125, 148 bps
. **CYP3A5A6986G (rs776746)**	R: 5′- GGT CCA AAC AGG GAA GAA ATA-3′	SspI (cat.#FD0774)	20, 125, 148, 168 bps
			125, 168 bps

Polymorphism	**Primer sequence (5'-3')**	**Restriction enzymes**	**Fragment size**

	F: 5′-TAT CCT GTG TCT GTG AAT TGC C-3′		35, 62, 269 bps
MDR1 C1236T (rs1128503)	R: 5′-CCT GAC TCA CCA CAC CAA TG-3′	HaeIII (cat.#FD0154)	35, 62, 97, 269 bps
			97, 269 bps
	F: 5′- TGT TTT CAG CTG CTT GAT GG-3′		39, 158 bps
MDR1 C3435T (rs1045642)	R: 5′-AAG GCA TGT ATG TTG GCC TC-3′	Sau3AI (cat.#FD0784)	39, 158, 197 bps
			197 bp
MDR1 G2677A	F: 5′-TGC AGG CTA TAG GTT CCA GG -3′	BsrI	220 bp
(rs2032582)	R: 5′-GTT TGA CTC ACC TTC CCA G-3′	(cat.#FD0884)	14, 206, 220 bps
			14, 206 bps
MDR1 G2677T	F: 5′-TGC AGG TA TAG GTT CCA GG-3′	BanI	26, 198 bps
(rs2032582)	R: 5′- TTT AGT TTG ACT CAC CTT CCC G-3′	(cat.#FD1004)	29, 198, 224 bps
			224 bp
· **CYP3A5A6986G (rs776746)**	F: 5′-CAT CAG TTA GTA GAC AGA TGA-3′	SspI (cat.#FD0774)	20, 125, 148 bps

	R: 5′- GGT CCA AAC AGG GAA GAA ATA-3′		20, 125, 148, 168 bps
			125, 168 bps

Polymorphism	Primer sequence (5'-3')	Restriction enzymes	Fragment size
MDR1 C1236T (rs1128503)	F: 5′-TAT CCT GTG TCT GTG AAT TGC C-3′	HaeIII (cat.#FD0154)	35, 62, 269 bps
	R: 5′-CCT GAC TCA CCA CAC CAA TG-3′		35, 62, 97, 269 bps
			97, 269 bps
MDR1 C3435T (rs1045642)	F: 5′- TGT TTT CAG CTG CTT GAT GG-3′	Sau3AI (cat.#FD0784)	39, 158 bps
	R: 5′-AAG GCA TGT ATG TTG GCC TC-3′		39, 158, 197 bps
			197 bp
MDR1 G2677A	F: 5′-TGC AGG CTA TAG GTT CCA GG -3′	BsrI	220 bp

(rs2032582)	R: 5′-GTT TGA CTC ACC TTC CCA G-3′	(cat.#FD0884)	14, 206, 220 bps
			14, 206 bps
MDR1 G2677T	F: 5′-TGC AGG TA TAG GTT CCA GG-3′	BanI	26, 198 bps
(rs2032582)	R: 5′- TTT AGT TTG ACT CAC CTT CCC G-3′	(cat.#FD1004)	29, 198, 224 bps
			224 bp
	F: 5′-CAT CAG TTA GTA GAC AGA TGA-3′		20, 125, 148 bps
. **CYP3A5A6986G (rs776746)**	R: 5′- GGT CCA AAC AGG GAA GAA ATA-3′	SspI (cat.#FD0774)	20, 125, 148, 168 bps
			125, 168 bps

Polymorphism	**Primer sequence (5'-3')**	**Restriction enzymes**	**Fragment size**
	F: 5′-TAT CCT GTG TCT GTG AAT TGC C-3′		35, 62, 269 bps
MDR1 C1236T (rs1128503)		HaeIII (cat.#FD0154)	
	R: 5′-CCT GAC TCA CCA CAC CAA TG-3′		35, 62, 97, 269 bps

			97, 269 bps
	F: 5′- TGT TTT CAG CTG CTT GAT GG-3′		39, 158 bps
MDR1 C3435T (rs1045642)	R: 5′-AAG GCA TGT ATG TTG GCC TC-3′	Sau3AI (cat.#FD0784)	39, 158, 197 bps
			197 bp
MDR1 G2677A	F: 5′-TGC AGG CTA TAG GTT CCA GG -3′	BsrI	220 bp
(rs2032582)	R: 5′-GTT TGA CTC ACC TTC CCA G-3′	(cat.#FD0884)	14, 206, 220 bps
			14, 206 bps
MDR1 G2677T	F: 5′-TGC AGG TA TAG GTT CCA GG-3′	BanI	26, 198 bps
(rs2032582)	R: 5′- TTT AGT TTG ACT CAC CTT CCC G-3′	(cat.#FD1004)	29, 198, 224 bps
			224 bp
	F: 5′-CAT CAG TTA GTA GAC AGA TGA-3′		20, 125, 148 bps
. **CYP3A5A6986G (rs776746)**	R: 5′- GGT CCA AAC AGG GAA GAA ATA-3′	SspI (cat.#FD0774)	20, 125, 148, 168 bps
			125, 168 bps

Polymorphism	**Primer sequence (5'-3')**	**Restriction enzymes**	**Fragment size**

	F: 5′-TAT CCT GTG TCT GTG AAT TGC C-3′		35, 62, 269 bps
MDR1 C1236T (rs1128503)	R: 5′-CCT GAC TCA CCA CAC CAA TG-3′	HaeIII (cat.#FD0154)	35, 62, 97, 269 bps
			97, 269 bps
	F: 5′- TGT TTT CAG CTG CTT GAT GG-3′		39, 158 bps
MDR1 C3435T (rs1045642)	R: 5′-AAG GCA TGT ATG TTG GCC TC-3′	Sau3AI (cat.#FD0784)	39, 158, 197 bps
			197 bp
MDR1 G2677A	F: 5′-TGC AGG CTA TAG GTT CCA GG -3′	BsrI	220 bp
(rs2032582)	R: 5′-GTT TGA CTC ACC TTC CCA G-3′	(cat.#FD0884)	14, 206, 220 bps
			14, 206 bps
MDR1 G2677T	F: 5′-TGC AGG TA TAG GTT CCA GG-3′	BanI	26, 198 bps
(rs2032582)	R: 5′- TTT AGT TTG ACT CAC CTT CCC G-3′	(cat.#FD1004)	29, 198, 224 bps
			224 bp

	F: 5′-CAT CAG TTA GTA GAC AGA TGA-3′		20, 125, 148 bps
. **CYP3A5A6986G (rs776746)**	R: 5′- GGT CCA AAC AGG GAA GAA ATA-3′	SspI (cat.#FD0774)	20, 125, 148, 168 bps
			125, 168 bps

Polymorphism	**Primer sequence (5'-3')**	**Restriction enzymes**	**Fragment size**
MDR1 C1236T (rs1128503)	F: 5′-TAT CCT GTG TCT GTG AAT TGC C-3′	HaeIII (cat.#FD0154)	35, 62, 269 bps
	R: 5′-CCT GAC TCA CCA CAC CAA TG-3′		35, 62, 97, 269 bps
			97, 269 bps
MDR1 C3435T (rs1045642)	F: 5′- TGT TTT CAG CTG CTT GAT GG-3′	Sau3AI (cat.#FD0784)	39, 158 bps
	R: 5′-AAG GCA TGT ATG TTG GCC TC-3′		39, 158, 197 bps
			197 bp
MDR1 G2677A	F: 5′-TGC AGG CTA TAG GTT CCA GG -3′	BsrI	220 bp

(rs2032582)	R: 5′-GTT TGA CTC ACC TTC CCA G-3′	(cat.#FD0884)	14, 206, 220 bps
			14, 206 bps
MDR1 G2677T	F: 5′-TGC AGG TA TAG GTT CCA GG-3′	BanI	26, 198 bps
(rs2032582)	R: 5′- TTT AGT TTG ACT CAC CTT CCC G-3′	(cat.#FD1004)	29, 198, 224 bps
			224 bp
	F: 5′-CAT CAG TTA GTA GAC AGA TGA-3′		20, 125, 148 bps
· **CYP3A5A6986G (rs776746)**	R: 5′- GGT CCA AAC AGG GAA GAA ATA-3′	SspI (cat.#FD0774)	20, 125, 148, 168 bps
			125, 168 bps

Polymorphism	**Primer sequence (5'-3')**	**Restriction enzymes**	**Fragment size**
MDR1 C1236T (rs1128503)	F: 5′-TAT CCT GTG TCT GTG AAT TGC C-3′	HaeIII (cat.#FD0154)	35, 62, 269 bps
	R: 5′-CCT GAC TCA CCA CAC CAA TG-3′		35, 62, 97, 269 bps
			97, 269 bps

	F: 5′- TGT TTT CAG CTG CTT GAT GG-3′		39, 158 bps
MDR1 C3435T (rs1045642)	R: 5′-AAG GCA TGT ATG TTG GCC TC-3′	Sau3AI (cat.#FD0784)	39, 158, 197 bps
			197 bp
MDR1 G2677A	F: 5′-TGC AGG CTA TAG GTT CCA GG -3′	BsrI	220 bp
(rs2032582)	R: 5′-GTT TGA CTC ACC TTC CCA G-3′	(cat.#FD0884)	14, 206, 220 bps
			14, 206 bps
MDR1 G2677T	F: 5′-TGC AGG TA TAG GTT CCA GG-3′	BanI	26, 198 bps
(rs2032582)	R: 5′- TTT AGT TTG ACT CAC CTT CCC G-3′	(cat.#FD1004)	29, 198, 224 bps
			224 bp
	F: 5′-CAT CAG TTA GTA GAC AGA TGA-3′		20, 125, 148 bps
· **CYP3A5A6986G (rs776746)**	R: 5′- GGT CCA AAC AGG GAA GAA ATA-3′	SspI (cat.#FD0774)	20, 125, 148, 168 bps
			125, 168 bps

Polymorphism	Primer sequence (5'-3')	Restriction enzymes	Fragment size
MDR1 C1236T (rs1128503)	F: 5′-TAT CCT GTG TCT GTG AAT TGC C-3′	HaeIII (cat.#FD0154)	35, 62, 269 bps
	R: 5′-CCT GAC TCA CCA CAC CAA TG-3′		35, 62, 97, 269 bps
			97, 269 bps
MDR1 C3435T (rs1045642)	F: 5′-TGT TTT CAG CTG CTT GAT GG-3′	Sau3AI (cat.#FD0784)	39, 158 bps
	R: 5′-AAG GCA TGT ATG TTG GCC TC-3′		39, 158, 197 bps
			197 bp

MDR1 G2677A	F: 5′-TGC AGG CTA TAG GTT CCA GG -3′	BsrI	220 bp
(rs2032582)	R: 5′-GTT TGA CTC ACC TTC CCA G-3′	(cat.#FD0884)	14, 206, 220 bps
			14, 206 bps
MDR1 G2677T	F: 5′-TGC AGG TA TAG GTT CCA GG-3′	BanI	26, 198 bps
(rs2032582)	R: 5′-TTT AGT TTG ACT CAC CTT CCC G-3′	(cat.#FD1004)	29, 198, 224 bps
			224 bp
· **CYP3A5A6986G (rs776746)**	F: 5′-CAT CAG TTA GTA GAC AGA	SspI (cat.#FD0774)	20, 125, 148 bps

		TGA-3′ R: 5′-GGT CCA AAC AGG GAA GAA ATA-3′		
			20, 125, 148, 168 bps	
			125, 168 bps	

Polymorphism		Primer sequence (5'-3')	Restriction enzymes	Fragment size
MDR1 (rs1128503)	**C1236T**	F: 5′-TAT CCT GTG TCT GTG AAT TGC C-3′ R: 5′-CCT GAC TCA CCA CAC CAA TG-3′	HaeIII (cat.#FD0154)	35, 62, 269 bps 35, 62, 97, 269 bps 97, 269 bps
MDR1 (rs1045642)	**C3435T**	F: 5′- TGT TTT CAG CTG CTT GAT GG-3′ R: 5′-AAG GCA TGT ATG TTG GCC TC-3′	Sau3AI (cat.#FD0784)	39, 158 bps 39, 158, 197 bps 197 bp
MDR1 G2677A (rs2032582)		F: 5′-TGC AGG CTA TAG GTT CCA GG -3′ R: 5′-GTT TGA CTC ACC TTC CCA G-3′	BsrI (cat.#FD0884)	220 bp 14, 206, 220 bps 14, 206 bps
MDR1 G2677T (rs2032582)		F: 5′-TGC AGG TA TAG GTT CCA GG-3′ R: 5′- TTT AGT TTG ACT CAC CTT CCC G-3′	BanI (cat.#FD1004)	26, 198 bps 29, 198, 224 bps 224 bp

• **CYP3A5A6986G (rs776746)**	F: 5′-CAT CAG TTA GTA GAC AGA TGA-3′ R: 5′- GGT CCA AAC AGG GAA GAA ATA-3′	SspI (cat.#FD0774)	20, 125, 148 bps 20, 125, 148, 168 bps 125, 168 bps

Table (2): The CML patients' characteristics.

Item	CML patients (No.130)
Age (years)	
Median (Range)	34.5 (20 – 66)
Mean ± SD	37.2 ± 11.9
Gender (No, %)	
Male	67 (51.5%)
Female	63 (48.5%)
Clinical data (no, %)	
Hepatomegaly	0 (0%)
Splenomegaly	130 (0%)
Lymphadenopathy	0 (0%)
Laboratory data	
Hb (g/dl)	
Median (Range)	9.7 (4.8 - 14.2)
WBCs ($x10^3$/µl)	
Median (Range)	177.5 (12 – 644)
Platelets ($x10^3$/µl)	
Median (Range)	309.5 (38- 961)
LAP score	
Median (Range)	5 (0 - 20)
BMA cellularity (No, %)	
Hypercellular	53 (41%)
Marked hypercellular	77 (59%)
BM Blasts (%)	
Median (Range)	2 (0 - 5)
Cytogenetic studies of BCR-ABL by FISH (%)	
Median (Range)	90 (25 -100)
LDH (U/L)	
Median (Range)	588.5 (300 -1800)
Uric acid (mg/dL)	
Median (Range)	4.6 (2.3 -10.7)
Alkaline phosphatase (U/L)	
Median (Range)	106.5 (54–439)
Prognosis: No (%)	
Responders	63 (48.5%)
Non responders	67 (51.5%)

Table (3): Genotypes and allele frequency of CYP3A5 and MDR1 genes variants among CML patients and the control group.

Polymorphism (No., %)	CML patients (No.130)	Control group (No.60)	P value	OR	95% CI
CYP3A5 gene A6986G (rs776746) by Sspl					
Wild AA	13(10%)	12 (20%)	-	-	-
Mutant AG, GG	117 (90%)	48 (80%)	0.048	2.250	0.958-5.283
Hetero AG	29 (22%)	20 (33%)	0.556	1.338	0.508-3.529
Homo GG	88 (68%)	28 (47%)	0.019	2.901	1.188-7.082
A	55 (21%)	44 (37%)	-	-	-
G	205 (79%)	76 (63%)	0.002	2.158	1.341-3.473
MDR1 gene Ex21 G2677A (rs2032582) by BSR1					
Wild GG	91 (70%)	44 (73%)	-	-	-
Mutant GA, AA	39 (30%)	16 (27%)	0.638	1.179	0.595-2.336
Hetero GA	38 (29%)	16 (27)	0.693	1.148	0.578-2.281
Homo AA	1 (1%)	0 (0%)	1.000	-	-
G	220 (85%)	104 (87%)	-	-	-
A	40 (15%)	16 (13%)	0.600	1.182	0.633-2.208
MDR1 gene Ex21 G2677T (rs2032582) by BAN1					
Wild GG	49 (38%)	36 (60%)	-	-	-
Mutant GT, TT	81 (62%)	24 (40%)	0.004	2.480	1.325-4.640
Hetero GT	65 (50%)	16 (27%)	0.002	2.985	1.488-5.986
Homo TT	16 (12%)	8 (13%)	0.428	1.469	0.567-3.805
G	163 (63%)	88 (73%)	-	-	-
T	97 (37%)	32 (27%)	0.043	1.637	1.016-2.635
MDR1 gene Ex26 C3435T (rs1045642) by Sau3AI					
Wild CC	48 (37%)	24 (40%)	-	-	-
Mutant CT, TT	82 (63%)	36 (60%)	0.684	1.045	0.608-2.133
Hetero CT	66 (51%)	28 (47%)	0.626	1.179	0.609-2.280
Homo TT	16 (12%)	8 (13%)	1.000	1.000	0.375-2.664
C	162 (62%)	76 (63%)	-	-	-
T	98 (38%)	44 (37%)	0.848	1.045	0.668-1.636

MDR1 gene Ex12 C1236T (rs1128503) by HaeIII	48 (37%)	20 (33%)			
Wild CC	82 (63%)	40 (67%)			- 0.449-
Mutant CT, TT	64 (49%)	24 (40%)	- 0.631	- 0.714	1.627 0.551-
Hetero CT	18 (14%)	16 (27%)	0.768 0.081	1.111 0.469	2.241 0.200-
Homo TT					1.099
C	160 (61.5%)	64 (53%)	- 0.131	- 0.714	
T	100 (38.5%)	56 (47%)			- 0.461- 1.106

Table (4): Comparison between responder and non-responder groups of the CML patients as regards demographic, laboratory data, BCR-ABL by RT-PCR after IM treatment.

Items	Responders (No.63)	Non-responders (No.67)	P value
Age			
Median (Range)	35 (20 -65)	34 (20-66)	0.682
Mean±SD	37.8 + 12.8	36.6+11.1	
Gender (No, %)			
Male	39(62%)	28(42%)	0.002
Female	24 (38%)	39(58%)	
Laboratory data			
Hb (g/dl) Median (Range)	9.9 (6.8-13.6)	9.6 (4.8-14.2)	0.391
WBCs ($x10^3$/µl) Median (Range)	180 (12-533)	172 (14-644)	0.798
Platelets ($x10^3$/µl) Median (Range)	280 (91-917)	318 (38-961)	0.522
LAP score Median (Range)	5 (0-15)	5 (0-20)	0.829
BMA cellularity (No, %)			
Hypercellular	23 (36.5%)	30 (45%)	0.338
Marked hypercellular	40 (63.5%)	37 (55%)	
BM Blasts (%) Median (Range)	2 (0-5)	2 (0-5)	0.355
LDH (U/L) Median (Range)	453 (304-1062)	809 (300-1800)	< 0.001
Uric acid (mg/dL) Median (Range)	4.8 (2.3-10.7)	4.5 (2.7-8.9)	0.557
Alkaline phosphatase (U/L) Median (Range)	93 (54-439)	117 (56-340)	0.021
Cytogenetic studies of BCR-ABL by FISH (%) Median (Range)	85 (25 -100)	90 (35 -100)	0.020
BCR-ABL by RT-PCR after 3 months (% IS) Median (Range)	5 (0.02-250)	25.9 (0.5-310)	< 0.001
BCR-ABL by RT-PCR after 6 months (% IS)	0.4 (0-16)	14 (0.3-223)	< 0.001

Median (Range)			
BCR-ABL by RT-PCR after 12 months (% IS) Median (Range)	0.1 (0-1)	18 (1.10-277)	< 0.001

Table (5): Genotypes and allele frequency of CYP3A5 and MDR1 genes variants among responder and non-responder groups of the CML patients.

Polymorphisms (No., %)	Responders (No. 63)	Non-responders (No. 67)	P value	OR	95% CI
CYP3A5 gene A6986G (rs776746) by Sspl			-	-	-
Wild AA	10 (16%)	3 (4.5%)	0.03	4.025	1.053-15.381
Mutant AG, GG	53 (84%)	64 (95.5%)	0.133	3.111	0.707-13.689
Hetero AG	15 (24%)	14 (21%)	0.033	4.386	1.129-17.044
Homo GG	38 (60%)	50 (74.5%)			
			-	-	-
A allele	35 (28%)	20 (15%)	0.012	2.192	1.186-4.053
G allele	91 (72%)	114 (85%)			
MDR1 gene Ex21 G2677A (rs2032582) by BSR1			-	-	-
Wild GG	44 (70%)	47 (70%)	0.969	0.985	0.465-2.087
Mutant GA, AA	19 (30%)	20 (30%)	0.919	1.040	0.487-2.220
Hetero GA	18 (28.5%)	20 (30%)	1.000	---	---
Homo AA	1 (1.5%)	0 (0%)			
				-	-
G allele	106 (84%)	114 (85%)	-	0.930	0.474-1.824
A allele	20 (16%)	20 (15%)	0.832		
MDR1 gene Ex21 G2677T (rs2032582) by BAN1			-	-	-
Wild GG	25 (40%)	24 (36%)	0.650	1.179	0.579-2.398
Mutant GT, TT	38 (60%)	43 (64%)	0.498	1.293	0.615-2.720
Hetero GT	29 (46%)	36 (54%)	0.716	0.810	0.260-2.522
Homo TT	9 (14%)	7 (10%)			
			-	-	-
G allele	79 (63%)	84 (63%)	0.998	1.001	0.605-1.654
T allele	47 (37%)	50 (37%)			

MDR1 gene Ex26 C3435T (rs1045642) by Sau3AI					
Wild CC	24 (38%)	24 (36%)	-	-	-
Mutant CT, TT	39 (62%)	43 (64%)	0.78	1.10	0.541-
Hetero CT	33 (52.5%)	33 (49%)	8	3	2.249
Homo TT	6 (9.5%)	10 (15%)	1.00	1.00	0.475-
			0	0	2.103
C allele	81 (64%)	81 (60%)	0.38	1.66	0.523-
T allele	45 (36%)	53 (40%)	8	7	5.314
			-	-	-
			0.52	1.17	0.712-
			3	8	1.947
MDR1 gene Ex12 C1236T (rs1128503) by HaeIII					
Wild CC	23 (36.5%)	25 (37%)	-	-	-
Mutant CT, TT	40 (63.5%)	42 (63%)	0.92	0.96	0.474-
Hetero CT	31 (49.5%)	33 (49%)	4	6	1.970
Homo TT	9 (14%)	9 (14%)	0.95	0.97	0.463-
			6	9	2.071
C allele	77 (61%)	83 (62%)	0.88	0.92	0.311-
T allele	49 (39%)	51 (38%)	0	0	2.719
			-	-	-
			0.89	0.96	0.586-
			1	6	1.592

Table (6): Haplotype analysis in responder and non-responder CML patients.

Haplotype analysis (No., %)	Responders (No. 63)	Non-responders (No. 67)	P value
GCC	62 (49%)	70 (52.5%)	0.372
GCT	12 (9.5%)	5 (4%)	
GTC	5 (4%)	7 (5%)	
GTT	0 (0%)	2 (1.5%)	
TCC	6 (5%)	3 (2%)	
TCT	1 (1%)	3 (2%)	
TTC	4 (3%)	3 (2%)	
TTT	36 (28.5%)	41 (31%)	