Effects of *ABCG2* C421A and *ABCG2* G34A genetic polymorphisms on clinical outcome and response to imatinib mesylate, in Iranian chronic myeloid leukemia patients

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Abstract

Background: Chronic myeloid leukemia (CML) is a multifactorial clonal myeloid neoplasm that mainly arises from the Philadelphia chromosome. Even though imatinib mesylate (IM) is considered the gold standard for first-line treatment, a number of CML patients have shown IM resistance that can be influenced by many factors, including pharmacogenetic variability. The present study examined whether two common single nucleotide polymorphisms (SNPs) of *ABCG2* (G34A and C421A) contribute to IM resistance and/or good responses.

Material and methods: A total of 72 CML patients were genotyped with high-resolution melting (HRM) and restriction fragment length polymorphism-polymerase chain reaction (RFLP-PCR). We also determined the cytogenetic and hematological response, as evaluable factors for measuring response to imatinib.

Results: In the current study, we explored the relationship between the different variants of *ABCG2* G34A and C421A and clinical response to imatinib among CML patients. There were no statistically significant differences between genotypes of C421A and G34A and allele frequencies among the resistant and responder groups, with response to IM ($P > 0.05$). Also, we found no statistically significant association between genotypes and cytogenetic and hematological responses.

Conclusion: This is the first study to investigate the association between genotypes of the G34A and C421A SNPs and the outcome of IM treatment in Iranian population. As a whole, genotyping of these SNPs is unhelpful in predicting IM response in CML patients.

Keywords: BCR-ABL, CML, Drug resistance, Pharmacogenetics, Philadelphia chromosome

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Background

Chronic myeloid leukemia (CML) is a multifactorial clonal myeloid neoplasm originating from malignant hematopoietic stem cells [1–3] with an approximate incidence of one to two per 100,000 adults worldwide [4]. The reciprocal translocation (t (9; 22) (q34; q11)) resulting in the Philadelphia (Ph) chromosome formation is pivotal to the pathogenesis of CML [8]. The ensuing oncoprotein named breakpoint cluster region- abelson (BCR-ABL) is an active tyrosine kinase

triggering many downstream signaling pathways such as RAS, RAF, JUN kinase, MYC, and STAT, consequently increasing proliferation, apoptosis prevention, mutation accumulation, and genomic instability [2, 4, 5].

CML treatment prior to the 2000s was confined to nonspecific drugs such as busulfan, hydroxyurea, and interferon-alpha (IFN-α) [6]. Alternative therapies, including allogeneic stem cell transplantation (allo-SCT), are also available but come with health risks and mortality [4]. Imatinib mesylate (IM), used to treat a variety of cancers and is a selective tyrosine kinase inhibitor (TKI), is known to be the gold standard of first-line treatment for Philadelphia chromosome-positive CML [7, 8]. The death rate in CML patients has been dropped since the introduction of IM in 2000 [9]. Inactive (closed) form of BCR-ABL is bound by IM, which prevents ATP binding [10]. Following this interaction, the subsequent phosphorylation and activation of downstream pathways are inhibited, resulting in apoptosis promotion of leukemic cells, and inhibiting leukemogenesis [11–13]. In line with the results of recent studies, IM significantly improved CML patients' clinical outcomes and prognoses. However, despite its remarkable efficacy, cancer treatment is hampered in some cases by primary or acquired resistance to IM and severe side effects [11, 14–19]. Increasing the dose of IM from 400 to 800 mg/day or switching to second-generation tyrosine kinase inhibitors such as dasatinib or nilotinib is recommended when there is no adequate response to IM or treatment fails [20].

IM resistance can be attributed to BCR-ABL-dependent and BCR-ABL-independent mechanisms [21, 22]. Mutations in BCR-ABL's tyrosine kinase domain, which is the most common cause of resistance, and overexpression of the BCR-ABL protein are examples of BCR-ABL-dependent mechanisms [15, 22–26]. BCR-ABL-independent causes can include activation of downstream oncogenic pathways, alterations of apoptosis-related genes, and IM pharmacokinetics (IM blood and/or intracellular levels), which are mostly still unknown [27–31].

CML patients' drug response and IM pharmacokinetics are influenced by efflux and influx transporters, such as ABCB1, ABCG2, and OCT1 (SLC22A1) [32–38]. There has been evidence that genetic polymorphisms in such genes lead to transporter function alteration and affect IM response [21, 39]. Previous studies have analyzed the association between *ABCG2* (ATP-binding cassette subfamily G member 2) polymorphisms and pharmacokinetic inter-individual variations, along with the efficacy and toxicity of drugs [40–42]. To date, more than 80 *ABCG2* single nucleotide polymorphisms (SNPs) have been detected in various populations via direct DNA sequencing [43, 44]. The two common *ABCG2* variants are G34A (V12M, rs2231137) and C421A (Q141K, rs2231142), which are located on exon 2 and 5, respectively [21, 41, 45]. In this study, we investigated the relationship between these two SNPs and the IM response/resistance among Iranian CML patients.

Material and methods
Study subjects
The study involved 72 Ph-positive CML patients (37 females and 35 males) receiving 400 mg IM (Gleevec, STI571 (signal transduction inhibitor 571), and CGP57148B) daily for at least three months. Before participation in this study, these patients with chronic phase CML were diagnosed by the Department of Hematology, Omid Hospital (Isfahan, Iran). Written informed consent was obtained from all patients, and peripheral blood samples were collected in EDTA-containing tubes. Participants taking IM metabolism-interfering drugs, such as Phenobarbital and Phenytoin, were excluded. At the time of diagnosis, Philadelphia chromosome and BCR-ABL fusion mRNA presence were confirmed, respectively, by cytogenetic analysis and RT-PCR technique. Table 1 summarizes the demographic and clinical characteristics

Table 1 Demographic and clinical characteristics of study subjects

	Responder	Resistant
Age (year (mean ± SD))	50.27 ± 12.72	46.39 ± 11.27
Gender (number (%))	Male: 21 (48%)	Male: 14 (50%)
	Female: 23 (52%)	Female: 14 (50%)
WBC (× 10^3 cell/μL)	Primary: 125.53 ± 241.75	Primary: 820.97 ± 773.31
	Secondary: 810.9 ± 765.05	Secondary: 774.53 ± 566.89
Plt (× 10^5/μL)	Primary: 2.5070 ± 1.7844	Primary: 2.0548 ± 1.2716
	Secondary: 2.5196 ± 1.4656	Secondary: 1.9325 ± 9.2211
Hb (g/dL)	Primary: 12.6 ± 2.39	Primary: 12.9 ± 1.76
	Secondary: 12.6 ± 2.26	Secondary: 12.8 ± 1.60

of patients. This study was approved by the Yazd University of Medical Sciences local Ethics Committee (IR.SSU.MEDICINE.REC.1398.091).

Clinical assessment

The guidance for evaluation of clinical response and ordinary follow-up of patients were chased as given in "European Leukemia Net: guideline for managing CML patients". Bone marrow morphology and cytogenetic studies were utilized for early diagnosis of patients and definition of the phase of the disease at the time of clinical demonstration. The primary treatment prescribed was 400 mg of IM [46].

The response to the drug was evaluated at regular intervals. For this reason, hematological (WBC count $< 10 \times 10^9$/L; basophils $< 5\%$; an absence of myelocytes, promyelocytes, or myeloblasts in peripheral blood; platelet counts $< 450 \times 10^9$/L) and molecular (BCR-ABL1/ABL1 $\leq 0.1\%$) response every 3 months, and the cytogenetic (0% Ph + meta phases) response at 6 months was assessed [47, 48].

An indication of resistance can be determined by a lack of complete hematological response at 3 months, complete cytogenetic response (0% Ph-positive metaphases) at intervals of 12 months and (MMR) major molecular response (BCR-ABLIS $\leq 0.1\%$) at 18 months [47].

In this study, CML patients were followed up at an interval of 6 months. During this period, hematological, cytogenetic, and molecular responses were evaluated.

DNA extraction and SNP genotyping

Genomic DNA was extracted from peripheral blood lymphocytes using the PrimePrep Genomic DNA isolation kit (Genet Bio, Korea) based on the manufacturer's protocol. Qualitative and quantitative assessments of the isolated DNA were examined utilizing electrophoresis on 2% agarose gel and Thermo Scientific NanoDrop 2000 Spectrophotometer, respectively.

The G34A polymorphism was genotyped utilizing the allelic discrimination assay by High-Resolution Melting (HRM) technique (Rotor Gene-6000, Corbett Research, Sydney, Australia). PCR was performed in a final volume of 20 µL PCR mixture using HOT FIREPol® EvaGreen® HRM Mix (Solis BioDyne, Estonia). The HRM conditions were as follows: one cycle of 95 °C for 12 min to activate HOT FIREPOL DNA polymerase; 40 cycles of 95 °C for 15 s, 58 °C for 20 s, 72 °C for 20 s; and a HRM step from 76 to 86 °C rising at 0.2 °C with 2-s hold time after each step. The results were analyzed by Q 5plex HRM software V.2.3.4. Having found no feasible 80–100-bp primers, PCR–RFLP-based genotyping using the BseMI enzyme was designed to genotype the C421A polymorphism. After amplification DNA fragments by PCR, they were cut by 2 units of restriction enzyme BseMI for 16 h at 55 °C. Then, DNA fragments created after digestion run on a 3% agarose gel. Electrophoresis of these fragments could distinguish the genotypes based on fragments length. Primer sequences were designed using GeneRunner software. Primer sequences were as follows: Forward 5′AGGATGATGTTGTGATGGGC3′, Reverse 5′TGACCCTGTTAATCCGTTCG3′ for C421A and Forward 5′ GTTGTGCCTGTCTTCCCAT 3′, Reverse 5′ TCGACAAGGTAGAAAGCCAC 3′ for G34A. We randomly sequenced 10% of the samples using the ABI 3730XL automatic sequencer (Applied Biosystems, USA) to confirm results.

Statistical analysis

Data analysis was performed using SPSS software package version 26 (SPSS Inc., Chicago, IL, USA). The Chi-square test and independent samples t-test were used to assess the differences between demographics and response/resistance to IM. Then, the binary logistic model was exploited to calculate odds ratios (ORs) and 95% confidence intervals (CIs). We also performed Wilcoxon analysis and paired *T*-test to find out whether genotypes were associated with hematological responses. A *P* value lower than 0.05 was considered statistically significant.

Results

Table 1 lists the demographic and clinical characteristics of study participants. There was no statistically significant difference between the response to treatment and age ($P = 0.179$) or sex ($P = 0.851$). Furthermore, neither C421A ($P = 0.146$, $P = 0.170$) nor G34A ($P = 0.235$, $P = 0.398$) genotype and allele frequencies provided any statistically significant association with response to IM (Tables 2, 3).

A hematologic index (Hb, WBC, and Plt count) analysis was also performed to find out how well the drug altered responder and resistant patients' hematologic profiles. Comparing the primary and secondary responses before and after drug intake, no significant relationship between drug use and hematological index was revealed, according to the data provided in Table 4. Moreover, genotypes did not significantly affect hematologic outcomes (WBC, Plt, and Hb count) (Table 5) and cytogenetic response (Table 6).

Discussion

Two types of *ABCG2* variants, C421A and G34A, have been extensively studied in order to predict the IM response among CML patients. However, the results were noticeably contrasting. We compared the distribution of *ABCG2* C421A and *ABCG2* G34A polymorphism

Table 2 C421 and G34A genotype frequencies in the responder and resistant groups

SNP	Genotype	Responder (%)	Resistant (%)	OR	(95% CI)	*P*
C421A	CC	33 (75.0)	25 (89.3)	1.00		
	CA	11 (25.0)	3 (10.7)	2.78	(0.70–11.02)	0.146
G34A	GG	17 (38.6)	7 (25.0)	1.00		
	AG	27 (61.4)	21 (75.0)	1.89	(0.66–5.39)	0.235

Table 3 C421 and G34A allele frequencies in the responder and resistant groups

SNP	Allele	Responder (%)	Resistant (%)	OR	(95% CI)	*P*
C421A	C	77 (87.5)	53 (94.6)	1.00		
	A	11 (12.5)	3 (5.4)	0.396	(0.11–1.49)	0.170
G34A	G	61 (69.3)	35 (62.5)	1.00		
	A	27 (30.7)	21 (37.5)	1.356	(0.67–2.74)	0.398

Table 4 The comparison of hematological response between patients with different genotypes

SNP	WBC ($\times 10^3$ cell/μL)			Plt ($\times 10^5$/μL)			Hb (g/dL)		
	Primary*	Secondary**	*P*	Primary	Secondary	*P*	Primary	Secondary	*P*
C421A /CC	135.000 ± 257.711	779.868 ± 510.220	0.710	2.30831 ± 1.39946	2.33890 ± 1.21186	0.390	12.74 ± 2.14	12.71 ± 2.08	0.746
C421A /CA	116.820 ± 131.619	109.390 ± 145.113	0.124	1.70200 ± 4.0608	1.93400 ± 2.8648	0.299	13.69 ± 2.84	13.93 ± 2.23	0.387
G34A /AG	123.875 ± 232.534	743.583 ± 462.148	0.817	2.19658 ± 1.27317	2.22916 ± 1.10475	0.476	12.93 ± 2.27	12.95 ± 2.09	0.916
G34A /GG	781.800 ± 757.694	903.108 ± 100.914	0.209	2.60041 ± 2.13952	2.41554 ± 1.65904	0.764	12.39 ± 1.90	12.37 ± 1.84	0.930

*Before drug intake

**After drug intake

Table 5 The comparison of hematological response between responder and resistant groups

Index	Responder*			Resistant**		
	Primary***	Secondary****	*P*	Primary	Secondary	*P*
WBC ($\times 10^3$ cell/μL)	168.950 ± 345.076	704.900 ± 278.401	0.110	776.413 ± 661.808	775.800 ± 578.235	0.236
Plt ($\times 10^5$/μL)	2.63250 ± 1.59091	2.69400 ± 1.29271	0.978	1.81066 ± 9.45490	1.89733 ± 9.79390	0.946
Hb (g/dL)	12.19 ± 2.22	12.25 ± 2.18	0.806	12.66 ± 1.40	12.62 ± 1.28	0.724

*WBC $< 10 \times 10^9$/L/ platelet $< 450 \times 10$9/L/ an absence of myelocytes, promyelocytes, or myeloblasts in peripheral blood

**WBC and platelet counts have not returned to normal, there are immature cells seen in blood

***Before drug intake

****After drug intake

Table 6 The comparison of cytogenetic response between different genotype groups

Polymorphism	Genotype	(CCyR)*	(Non-CyR)**	*P*
C421A	CA	6 (54.5%)	5 (45.5%)	0.737
	CC	19 (45.2%)	23 (54.8%)	
G34A	AG	18 (48.6%)	19 (51.4%)	0.774
	GG	7 (43.8%)	9 (56.2%)	

*Complete cytogenetic response (0% Ph + metaphases on cytogenetic analysis)

**Non-cytogenetic response

genotypes among responding and resistant CML patients treated with IM. According to our results, these SNPs did not show significantly different distributions between the two groups. Between the genotypes C421A and G34A of *ABCG2* and the IM response, no statistically significant association could be established [47]. Also, *ABCG2* C421A was not effective in reaching an optimal response to IM treatment [49, 50]. In comparison with *ABCG2* C421A polymorphism, *ABCG2* G34A polymorphism has a contradictory effect on IM response [51]. In study

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carried out in 2016, *ABCG2* is not involved in forecasting optimal molecular responses after IM consumption [52]. In the present study, no information on patients' molecular responses was available.

Furthermore, we found that the frequencies of these alleles were insignificantly different between these two groups and were not found to be risk factors for resistance. Our results are in disagreement with some studies that the *ABCG2* polymorphism is associated with response to IM [2, 21, 53].

The association of each SNP genotype of *ABCG2* G34A and C421A with hematological responses (WBC, Hb, and Plt counts) was also examined. IM is effective in the hematological response since BCR-ABL protein is effective in proliferation of blood cells (myeloid), and BCR-ABL is IM's target, although according to Table 4, hematological indices did not vary significantly between the groups with different genotypes and drug therapy with IM did not significantly influence primary or secondary hematological response. In this regard, similarly results from study of CML patients in western of Iran showed no statistically significant correlation between *ABCG2* C421A and hematological response (Hb, WBC, and Plt counts) [2]. The disconnection needs to be confirmed by further investigation.

Several studies have shown that the association between SNPs genotypes and cytogenetic response is more important for evaluating drug response than the relationship between SNPs genotypes and hematological response. According to our findings, no statistically significant relationship was found between G34A and C421A variants and cytogenetic response in both groups. Similarly, no significant correlation for *ABCG2* C421A has been reported [21, 54]. Also, no statistically significant association has been observed between cytogenetic response and SNP genotype of *ABCG2* C421A and G34A, which is consistent with some previously published research [47].

Conclusion

To sum up, our study reveals that *ABCG2*/C421A and *ABCG2*/G34A polymorphisms are insignificantly associated with the optimal response rate to IM and cytogenetic/hematologic response and cannot be used as a predictive marker for optimal response/primary failure in CML patients receiving IM. Nevertheless, our study is the first that investigates the association between hematologic index among responder and resistant groups, as well as the association between these indexes and drug consumption. Our study had some restrictions such as not checking the molecular response test. In addition, the statistical population of the present study for assessing the relationship between response to treatment and combined SNPs was small. Therefore, additional studies with larger and different populations for evaluating the relationship between *ABCB1*, *SLC22A1*, *CYP3A4*, and *CYP3A5* polymorphisms and response/resistance to IM are suggested.

Author contributions
NN contributed significantly to the preparation of this study by collected samples from Sayed Al-Shohada Hospital, designing the protocol of work, contributing to practical part of the study, and writing and editing the manuscript. VM, ZK, and MK contributed to collect samples from Sayed Al-Shohada Hospital and provide patients' data. Also, ZK contributed to practical part of the study, especially PCR–RFLP technique. EZ, EA, and FZ edited the manuscript, and analyzed and interpreted the patient data. SK was primarily responsible for the writing of the manuscript. All authors have read and approved the manuscript.

Availability of data and materials
The data that support the findings of this study are available on request from the corresponding author.

Declarations

Ethics approval and consent to participate
This research was approved by the Yazd University of Medical Sciences Local Ethics Committee, and informed written consent was taken from every participant in the study; the committee's reference number is IR.SSU.MEDICINE.REC.1398.091.

Consent for publication
Consent to publish from the patient had been taken.

Competing interests
The authors declare that they have no competing interests.

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