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Lack of Association of Multidrug Resistance Gene-1 Polymorphisms with Treatment Outcome in Chronic Myeloid Leukemia Patients Treated with Imatinib

Yaya Kassogue*♦, Hind Dehbi *, Meryem Quachouh, Asma Quessar**, Said Benchekroun**, Sellama Nadifi***

**Genetics and Molecular Pathology Laboratory, Medical School of Casablanca, Hassan II University, Casablanca, Morocco*
***Department of Onco-Hematology, Ibn Rochd University Hospital, Casablanca, Morocco*

Abstract

Background: Despite the impressive results obtained with imatinib, inadequate response or resistance are observed in certain patients. It is known that imatinib is a substrate of a multidrug resistance gene (*MDR1*). Thus, interindividual genetic differences linked to single nucleotide polymorphisms in *MDR1* may influence the metabolism of imatinib. The present study has aimed to examine the impact of *MDR1* polymorphisms on the hematologic and cytogenetic responses in 70 chronic myeloid leukemia patients who received imatinib.

Methods: We used a polymerase chain reaction followed by restriction fragment length polymorphism to identify different profiles of 1236C>T, 2677G>T and 3435C>T in *MDR1*.

Results: The distribution of the three SNPs in responders and poor responders did not show any particular trend ($P>0.05$). The T allele was slightly higher in responders, but not significantly regardless of the type of SNP (40.3% vs. 33.8% for 1236C>T; 25% vs. 14.7% for 2677G>T and 33.3% vs. 22% for 3435C>T). The dominant model showed a similar trend ($P>0.05$). Diplotypes composed by the T allele in different exons were frequent in responders. Haplotype analysis showed that 1236C-2677G-3435C was slightly higher in poor responders (60.02%) compared to responders (50.42%). However, 1236T-2677T-3435T was frequent in responders (16.98%) compared to poor responders (13.1%). Overall, none of the haplotypes were associated with IM response in our cohort (global haplotype association test, $P=0.39$).

Conclusion: The identification of 1236C>T, 2677G>T and 3435C>T polymorphisms may not be advantageous to predict imatinib response for our chronic myeloid leukemia patients.

Keywords: *MDR1* polymorphisms, Chronic myeloid leukemia, Imatinib mesylate

♦Corresponding Author:
Yaya Kassogue, MD, PhD
Genetics and Molecular Pathology Laboratory, Medical School of Casablanca, 19 Rue Tarik Ibnou Ziad, BP. 9154
Morocco
Tel: +212629083348
Email: kassoy2@yahoo.fr

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Introduction

Chronic myeloid leukemia (CML) is a malignant proliferation of hematopoietic cells due to the presence of a specific cytogenetic marker t (9; 22) (q34; q11) or molecular marker (BCR-ABL fusion gene).[1,2] It is well established that utilization of imatinib (IM) mesylate (Gleevec), a selective tyrosine kinase, as first-line treatment in the management of CML results in better hematologic, cytogenetic and molecular responses.[3,4] It is known that IM induces apoptosis in malignant cells by selectively inhibiting expression of the BCR-ABL fusion gene.[5,6] Notwithstanding these remarkable results obtained with IM in CML patients, the drug appears to be disappointing for some patients who spend more time to achieve a desirable response or show resistance.[4] Resistance of leukemic cells to IM can be explained by mutation/amplification of the BCR-ABL domain or overexpression by a multi-drug resistance gene (*MDR1*).[7,8] In addition, changes in IM bioavailability related to inherited individual genetic differences in the enzymes that metabolize IM have been cited as factors that affect treatment outcome.[9-12] The *MDR1* gene on chromosome 7q21.12 is composed of 28 exons and encodes for the P-glycoprotein (P-GP) of a 170-kDa protein, known as a transmembrane protein.[13] P-GP, a member of ATP-binding cassette transporters (ABCB1), is implicated in the transport and elimination of IM.[14-16] Therefore, single nucleotide polymorphisms (SNP) in the *MDR1* gene that affect the expression of P-GP may be useful factors to explain individual differences in terms of therapeutic response to IM. More than 50 SNPs have been identified in the *MDR1* gene.[17,18] However, the most common SNPs represented by 1236C>T (exon 12; rs1128503, Gly412Gly), 2677G>T (exon 21; rs2032582, Ala893Ser/Thr), and 3435C>T (exon 26; rs1045642, Ile1145Ile) are associated with IM response in CML patients.[9,19,20] Additionally, it has been reported that stratification of these three SNPs in haplotype groups may be important for a better estimate of the functional value of *MDR1*, especially at the clinical level.[21] To the best of our knowledge, there are no data on the pharmacogenetic aspects of CML in relation to *MDR1* polymorphisms in the Moroccan population. Thus, we have undertaken the present study to investigate the impact of 1236C>T, 2677G>T, and 3435C>T polymorphisms on IM response in order to understand the differences in therapeutic response observed in CML patients.

Materials and Methods

Patients

The present study enrolled 70 CML patients with a median age of 40.3 years (range: 18-74 years) at the time of diagnosis. All patients were confirmed to have the reciprocal translocation t (9;22) (q34; q11). The patients were in the chronic phase and followed in the Department of Onco-Hematology of Ibn Rochd University Hospital, Casablanca, Morocco from 2010 to 2014. Each patient received a daily oral dose of 400 mg of Imatinib. The initial dose was increased to 600 or 800 mg per day for patients who failed to achieve a complete hematologic response (CHR) at 3 months, a major cytogenetic response (MCyR) at 6 months, or a complete cytogenetic response (CCyR) at 12 months. Hematologic and cytogenetic responses were described previously.[22] Patients who reached CCyR at 18 months were considered responders and those without CCyR at this time point were classified as poor responders. The protocol of the present study was approved by the local Ethics Committee. All participants accepted and signed the informed consent. DNA extraction was performed with 4 ml of peripheral blood collected from each patient through the salting out method.[23]

Genotyping of MDR1 polymorphisms

The identification of different profiles of 1236C>T, 2677G>T and 3435C>T polymorphisms was performed by using polymerase chain reaction-restriction fragment length polymorphism. The forward and reverse primers used to identify 1236C>T, 2677G>T and 3435C>T as well as the detailed technical aspects were described in our previous paper.[24] Negative

Table 1. Genotypic and allelic distribution of 1236C>T, 2677G>T and 3435C>T single nucleotide polymorphisms (SNPs) according to gender, hematologic and cytogenetic responses.

	Female N (%)	Male N (%)	*P*-value	No CHR N (%)	CHR N (%)	*P*- value	No CCyR N (%)	CCyR N (%)	*P*- value
C1236T			0.8			0.80			0.72
CC	17 (41.5)	14 (48.3)		4 (36.4)	27 (45.8)		16 (47.1)	15 (41.7)	
CT	16 (39)	10 (34.5)		5 (45.4)	21 (35.6)		13 (38.2)	13 (36.1)	
TT	8 (19.5)	5 (17.2)		2 (18.2)	11 (18.6)		5 (14.7)	8 (22.2)	
Alleles		0.6	0.8			0.49			
C	50 (61)	38 (65.5)		13 (59.1)	75 (63.6)		45 (66.2)	43 (59.7)	
T	32 (39)	20 (34.5)		9 (40.9)	43 (36.4)		23 (33.8)	29 (40.3)	
G2677T			1			0.17			0.19
GG	25 (60.5)	20 (64.3)		5 (45.5)	40 (67.8)		24 (70.6)	21 (58.4)	
GT	12 (31.6)	10 (35.7)		6 (54.5)	16 (27.1)		10 (29.4)	12 (33.3)	
TT	3 (7.9)	0 (0)		0 (0)	3 (5.1)	0 (0)			3 (8.3)
Alleles			0.5			0.39			0.14
G	62 (77.5)	50 (83.3)		16 (72.7)	96 (81.4)		58 (85.3)	54 (75)	
T	18 (22.5)	10 (16.7)		6 (27.3)	22 (18.6)		10 (14.7)	18 (25)	
C3435T			0.6			0.16			0.33
CC	21 (51.2)	18 (62.1)		5 (45.5)	34 (57.6)		21 (61.8)	18 (50)	
CT	15 (36.6)	8 (27.6)		6 (54.5)	17 (28.8)		11 (32.3)	12 (33.3)	
TT	5 (12.2)	3 (10.3)		0 (0)	8 (13.6)		2 (5.9)	6 (16.7)	
Alleles			0.5			1			0.18
C	57 (69.5)	44 (75.9)		16 (72.7)	85 (72)		53 (78)	48 (66.7)	
T	25 (30.5)	14 (24.1)		6 (27.3)	33 (28)		15 (22)	24 (33.3)	

CHR: Complete hematologic response; CCyR: Complete cytogenetic response (responders).

control (tube without DNA) was used in all reactions and did not show any amplification after electrophoresis on agarose gel stained with ethidium bromide.

Statistical analysis

Data analysis was performed by using the statistical package SPSS version 16 (SPSS Inc., Chicago, IL, USA). Fisher's exact test was used to estimate the difference between the distribution of genotypes and IM response. Due to the lack of difference in the Fisher exact test, odds ratio (OR) with confidence interval (CI) at 95% was not calculated for genotypes and alleles. SNPStats was used to test the Hardy-Weinberg equilibrium between observed and expected alleles, to estimate the haplotype distribution, and finally to assess their association with IM response.[25] A $P<0.05$ (two-sided) was considered significant.

Results

In the present study, we explored the effect of the three most common SNPs in the *MDR1* gene on treatment outcome of 70 CML patients treated with IM. Of the 70 patients, 36 (51.4%) obtained CCyR (responders), while 34 (48.6%) patients failed to reach CCyR (poor responders).

The distribution of genotypes and alleles of 1236C>T, 2677G>T and 3435C>T polymorphisms with respect to gender, hematologic and cytogenetic responses are summarized in Table 1. The overall genotype distributions were 44.3% (1236CC), 37.1% (1236CT), and 18.6% (1236TT) in exon 12. In exon 21 the frequencies were 64.3% (2677GG), 31.4% (2677GT), and 4.3% (2677TT). The overall frequencies in exon 26 were 55.7% (3435CC), 32.9% (3435CT), and 11.4% (3435TT). The genotype and allele frequencies did not deviate

Table 2. Distribution of complete versus incomplete cytogenetic responders according the dominant model.

	No CCyR N (%)	CCyR N (%)	*P*-value
1236 C>T			
CC	16 (51.6))	15 (48.4)	0.8
CT+TT	18 (46.2)	21 (53.8)	
2677 G>T			
GG	21 (51.2)	20 (48.8)	0.45
GT+TT	10 (40)	15 (60)	
3435 C>T			
CC	21 (53.8)	18 (46.2)	0.35
CT+TT	13 (41.9)	18 (58.1)	

CCyR: Complete cytogenetic response

from the Hardy-Weinberg equilibrium.

The genotypic and allelic frequencies of the three SNPs were comparable between men and women (P>0.05). This finding remained valid for the hematologic and cytogenetic responses between responders and poor responders (P>0.05). Statistically, the three SNPs did not influence IM response. However, the T allele was slightly higher in responders, regardless of the type of polymorphism (40.3% vs.33.8% for 1236C>T; 25% vs. 14.7% for 2677G>T and 33.3% vs. 22% for 3435C>T).

In Table 2, the dominant model showed that the T allele was more pronounced in responders compared to poor responders, however this result was not statistically significant.

In Table 3, the distribution of diplotypes in responders and poor responders showed no particular trend in IM response. However, we noted that diplotypes composed mainly by the T allele were observed in responders. We found a moderate linkage disequilibrium (LD) with P<0.001 between the three SNPs. The D' values at loci 1236C>T/2677G>T, 1236C>T/3435C>T and 2677G>T/3435C>T were 0.72, 0.67 and 0.86, respectively.

As shown in Table 4, the frequency of the haplotype 1236C-2677G-3435C (CGC) was slightly higher in poor responders (60.02%) compared to responders (50.42%). However, the haplotype 1236T-2677T-3435T (TTT) was slightly higher in responders (16.98%) compared to poor responders (13.1%). Overall, the T allele in haplotype compositions was more frequent in responders, however there was no significant effect of haplotype on IM response and the global association test with IM response had a *P*-value of 0.39.

Discussion

In the post-genomic era, genetic information determines individuals' health, disease and therapeutic response. Research on genes such as *MDR1*, which is known to participate in the metabolism of numerous medications and various xenobiotics, can be helpful for predicting treatment outcome. Although many studies have investigated the impact of the three most common polymorphisms in the *MDR1* gene on treatment outcome of patients undergoing IM treatment, the results are conflicting.[9,19,20,26]

In the current study, 1236C>T, 2677G>T and 3435C>T SNPs did not influence hematologic and cytogenetic responses in our cohort. However, we observed a non-significantly higher frequency of the T allele in responders in all three SNPs. The dominant model which compared heterozygous plus mutant homozygote to wild type homozygous showed no particular effect in terms of IM response. Similar results were obtained by Vivona et al. when SNPs were analyzed separately.[26] In contrast to our findings, Elghannam et al. reported that homozygous for the T allele in exon 21 was associated with hematologic and cytogenetic responses.[27] Maffioli et al. also found that patients who carried the homozygous 3435CC in exon

Table 3. Distribution of main diplotypes from different exons according to imatinib (IM) response.

Diplotypes	No CCyR N (%)	CCyR N (%)	*P*-value
1236CC/2677GG	16 (53.3)	14 (46.7)	
1236CT/2677GT	8 (50)	8 (50)	0.7
Other 10 (41.7)	14 (58.3)		
1236CC/3435CC	15 (53.6)	13 (46.4)	
1236CT/3435CT	8 (57.1)	6 (42.9)	0.4
Other	11 (39.3)	17 (60.7)	
2677GG/3435CC	20 (60.6)	13 (39.4)	
2677GT/3435CT	8 (50)	8 (50)	0.071
Other	6 (28.6)	15 (71.4)	
1236TT/2677TTa	0 (0)	2 (100)	
1236TT/3435TTa	1 (25)	3 (75)	
2677TT/3435TTa	0 (0)	3 (100)	

a: Minor diplotye; CCyR: Complete cytogenetic response

26 had higher exposure to primary failure of IM treatment, while the 2677TT genotype was a protective factor.[19] However, Ni et al. demonstrated that cytogenetic resistance was higher in patients who were carriers of 1236TT or 3435TT/CT.[28] The distribution of diplotypes in responders and poor responders in our study showed that diplotypes composed mainly of the T allele were virtually observed in responders. Recently, Vine et al. reported that polymorphisms in *MDR1* could not explain IM failure when the IM level was controlled.[29]

We previously demonstrated[24] that haplotype analysis showed a moderate LD between the three SNPs. However, it has been reported that haplotype analysis rather than separate analysis of SNPs is the best way to understand the functional value of polymorphisms in the *MDR1* gene; this may explain the contradictory results.[21] In our cohort, we have observed that the haplotype CGC was slightly higher in poor responders compared to responders, whereas the haplotype TTT was slightly higher in responders. In our observation of the haplotypes' compositions, we noticed that the T allele appeared to be more represented in responders, however this was not significant. Dulucq et al. demonstrated that the CGC haplotype was not associated with any major molecular response (MMR).[9] On the other hand, Deenik et al. reported that patients with 1236CC were associated with MMR while patients who carried 3435TT and 2677TT showed no association with MMR.[30] Vivona et al. reported that patients who carried the haplotype 1236CT-2677GT-3435CT were better candidates to reach MMR.[26] The analysis of various studies from different authors have shown conflicting results when SNPs in the *MDR1* gene were considered separately or in haplotype. It is known that the frequencies of the *MDR1* gene vary widely around the world in different populations.[31] However, this variability might not explain these discrepancies in terms of IM response through different studies in different populations. Therefore, other gene-gene interactions with *MDR1*, such as cytochrome P450 enzymes might explain this variability in IM response.

Conclusion

We have investigated the effect of 1236C>T, 2677G>T and 3435C>T SNPs in the *MDR1* gene on the hematologic and cytogenetic responses of newly diagnosed CML patients who received IM. Based on our findings, the 1236C>T, 2677G>T and 3435C>T SNPs of the *MDR1* gene when analyzed separately, in diplotype, or in haplotype did not influence IM response in our cohort, even when the T allele was slightly more frequent in

Table 4. Haplotype distribution of *MDR1* polymorphism in responders and poor responders according to cytogenetic responders from exons 12, 21 and 26.

Haplotypes	No CCyR (%)	CCyR (%)	OR (95% CI)	*P*-value
CGC	63.02	50.42	Ref.	-
TTT	13.1	16.98	1.52 (0.57-4.04)	0.41
TGC	13.31	9.9	0.83 (0.29-2.41)	0.74
TGT	5.81	8.82	1.77 (0.47-6.63)	0.4
CGT	3.16	5.86	2.22 (0.35-14.04)	0.4
TTC	1.61	4.57	4.17 (0.38-46.18)	0.25
TTC	0	1.67	-	-
CTC	0	1.78	-	-

Global haplotype association *P*-value: 0.39; CCyR: Complete cytogenetic response

responders.

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Conflict of interest

No conflict of interest is declared.

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