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Short Communication

MDR1 Gene Polymorphism and Outcome in Egyptian Chronic Myeloid Leukaemia Patients

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Abstract

We investigated the relation between MDR-1 gene single-nucleotide polymorphisms (SNPs) and treatment outcome in chronic myeloid leukemia (CML) patients. Two groups of patients were included: group 1 (resistant group) consists of 29 CML patients and responsive group (controls, group 2) consists of 25 CML patients of matched age and sex. For all patients, we measured BCR-ABL transcripts percent at diagnosis and 3 months thereafter and MDR-1 gene SNPs (C3435T and G2677T). All patients were followed up for 6 months. We found statistically significant difference in the frequency of C3435T genotype and combined C3435T and G2677T (CC&GG, CT&GT and TT&TT) between both groups as well as in the frequency of mutated type (CT&GT and TT&TT).So, these genotypes may help in early identification of CML patients not responding optimally to therapy and in planning CML individualized therapy. Larger patient population study is still needed to confirm these findings.

INTRODUCTION

Chronic myeloid leukaemia (CML) is a clonal myeloproliferative disorder [1] that represents approximately 15% of all leukaemias diagnosed in adults. It has an incidence of 1–1.5 per 100.000 inhabitants. It had an age of onset at 40–60 years [2]. Imatinib mesylate is a first generation tyrosine-kinase inhibitor (TKIs) that improved CML treatment [3].The second generation TKIs dasatinib and nilotinib are indicated for treating patients resistant or intolerant to first-line therapy and as first-line treatment of CML [4].However, resistance to these TKIs also occurs, and patients proceed to blast crisis, for which existing therapies are limited. Thus, resistance to TKIs is an increasingly important clinical problem [5].

P-glycoprotein (P-gp) is a drug efflux transmembrane protein which is encoded by the ABCB1 multidrug resistance 1 (MDR1) gene. It had the capacity to extrude some drugs from the cells [4]. ABCB1 is expressed in the intestine, liver, kidneys, in the CML stem cells and in the circulating leukocytes of CML patients[4]. Major molecular responses to standard-dose imatinib in CML were associated with *MDR1* gene polymorphisms [6]. Nilotinib seems to be more potent modulators of ABCB1 when compared to imatinib in *in vitro* studies. However, the functional relationship between nilotinib and efflux transporters remains highly controversial and is still under investigation [7] as there is still a high degree of contradiction between in vitro data and clinical evidence [8,9].

About 100 single-nucleotide polymorphisms (SNPs) are located in the coding regions of MDR1 [10].The C3435T polymorphism located in exon 26 is the most SNPs studied in various field of diseases. It is common in all ethnicities; however, its frequency is dependent on racial background [11].3435C> Tpolymorphism is linked to other non-synonymous polymorphism in exon 21 (G2677T) [11].A mechanism on how these SNPs play a role in regulating the P-gp expression remains unclear [11]. However, it has been demonstrated that haplotypes containing the mutated alleles show major structural modifications that result in changes in the conformation of the binding sites and a subsequent decrease in P-gp activity in cell lines [12].

This study was designed to investigate the frequencies of Multidrug resistance 1 gene single-nucleotide polymorphisms (SNPs) C3435T and G2677T among CML patients who are resistant to therapy.

METHODS

Sample

This study included 54 Philadelphia positive CML patients treated at the Haematology Clinic, Alexandria Main University Hospital, between February 2013 and March 2014. The diagnosis of CML was based on standard clinical and laboratory data and confirmed by molecular analysis.All patients were in the chronic

phase. All patients were followed-up for 6 months.Response criteria were that of the European Leukemia Net [13]. Two groups of patients are included according to their response to treatment.Group 1 included 29 CML patients'non-responders to oral nilotinib 400 mg twice daily after imatinib failure (400 mg daily).Patients were considered nilotinib resistant if BCR-ABL>10% at 3 months [14].Their median age at diagnosis was 48 years (range 28-60). 15 were males and 14 were females. Nilotinib and imatinib were provided freely by Egyptian Council of Health. In addition, 25 CML patients of matched age and sex responders to a standard dose of imatinib (400 mg/day) were considered controls (group 2). All had BCR-ABL1 <10% at 3 months of imatinib initiation. Patients were classified according to Sokal risk score [15].

Exclusion criteria: prior therapies with hydroxyurea, interferon-α and cytarabine as well as patients non-compliant or intolerant or developed side effects to treatment.

Data collection

All patients were subjected to complete blood picture, measurement of percent of BCR-ABL1 transcripts at diagnosis by quantitative polymerase chain reaction technique qPCR, as previously described [16] and repeated 3 months thereafter. MDR-1 gene single-nucleotide polymorphisms (SNPs) C3435T and G2677T were performed using polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP).Written consent was taken from all patients. The study was approved by the local Ethics Committee

Measurement of BCR- ABL1 transcripts: Total RNA was extracted from bone marrow or peripheral blood mononuclear cells using RNeasy Midi Kit (Qiagen) and was synthesized into cDNA according to standard procedures in the ipsogen RT kit (Qiagen). RQ-PCR was done on Rotor-gene Q instrument using ipsogen BCR-ABL1 kit (Qiagen). The absolute quantities of BCR-ABL and ABL transcripts in patient specimens were determined by reference to standard curves. RQ-PCR results were reported as a ratio of BCR-ABL/ABL (%) [16].

Analysis of ABCB1 polymorphisms: Genomic DNA was isolated from whole blood by salting out method [17] and used for polymorphic analysis using PCR-RFLP technique.

Analysis of G2677T polymorphism: G2677T polymorphism (at exon 21) was amplified using the following primers sequence (Metabion International AG): forward primer: 5'-TGC AGG CTA TAGGTT CCA GG and reverse primer: 5'-TTT AGT TTG ACT CAC CTT CCC G. The PCR cycling condition was as follow : initial denaturation for 1 cycle at 94°C for 4 minutes followed by 35 cycles at 94°C for 30 seconds, 58°C for 30 seconds and 72°C for 30 seconds, final extension for 1 cycle at 72°C for 10 minutes. The amplified PCR products were digested [18] with Ban I restriction enzyme (Thermo Scientific) for 37°C for 5 minutes.

Analysis of C3435T polymorphism: C3435T polymorphism at exon 26 was amplified using the following primers sequence: forward primer: 5'-TGT TTT CAG CTG CTT GAT GG and reverse primer: 5'-AAG GCA TGT ATG TTG GCC TC.The PCR reaction condition was the same as for G2677Texcept that the annealing temperature was 55°C.The amplified PCR products were digested [18] with (Sau3AI) (Thermo Scientific], then mixed and incubated for 37ºC for 10 minutes.

After digestion, the products were electrophoresed for genotyping. 2677G allele creates site for Ban I enzyme and produces two fragments of 198 bp and 26 bp whereas 2677T allele was identified by single fragment of 224 bp (Figure 1). 3435C allele creates site for Sau3AI and produces two fragments of 158 bp and 39 bp whereas 3435T allele was identified by single fragment of 197 bp (Figure 2). Restriction fragments were visualized after ethidium bromide staining of the agarose gel (Bio Basic INC) with the use of an ultraviolet transilluminator.

Data analysis

All the statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) (version 15.0; SPSS Inc., Chicago, IL, USA). Quantitative data was presented as mean ± standard deviation(SD) and were analyzed using "t" test to compare means of two groups and ANOVA test (F test)to compare means of more than two groups.Least significant difference (LSD) was used when F-value is significant to detect the presence of significance between each 2 groups. Qualitative data such as sex, sokal score, genotype distribution and frequencies in both control and case subjects was presented by percentages and tested by Pearson's Chi Square and Fisher Exact Test according to the categories and cells estimation %. A difference was considered significant if pvalue was less than 0.05 in all analyses.

RESULTS

Baseline characteristics including sex, age, Sokal risk group,

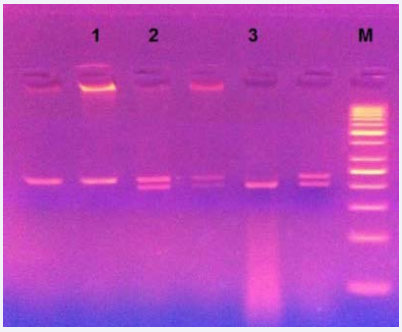

Figure 1 MDR1 (G2677T) polymorphism.
Lane 1: TT (homozygous), lane 2: GT (heterozygous), lane 3: GG (homozygous), M: Marker 50 bp ladder.

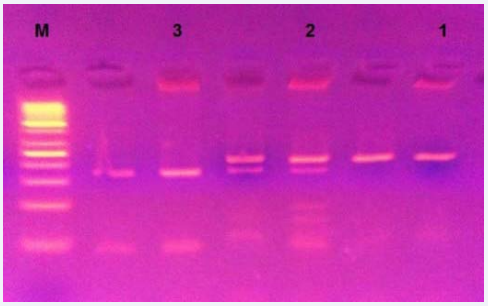

Figure 2 MDR1 (C3455T) polymorphism.
Lane 1: TT (homozygous), lane 2: CT (heterozygous), lane 3: CC (homozygous), M: Marker 50 bp ladder

CBC, percent BCR-ABL1 transcript at diagnosis and after 3 months of initiating therapy of 54 CML patients included are shown in Table 1.

The presented distribution of MDR1 genotypes in both CML groups are shown in Table 2. Eighteen patients (62.07%) with 2677GT and 16 patients (55.1%)with 3435CT in resistant group were high risk according to Sokal score. Tables 3 and 4 show the differences in clinical and laboratory data between wild(3435CC/2677GG)and mutant groups(3435CT/2677GT and 3435TT/2677TT).Wild group (CC & GG) was present in 8 (32%) for group 2 only while mutated group was present in 17 (58.62%)and 11 (44%) in group 1 and 2 respectively (p=0.004). No significant difference in age (p=0.748), sex (p=0.361), pretreatment values of hemoglobin (p=0.227), WBCs (P=0.884), platelet count (p=0.273) or initial BCR-ABL at diagnosis (p=0.967) among the wild and mutant MDR1 genotypes

DISCUSSION

Nilotinib is a second generation TKI with increased potency and improved pharmacological properties compared with imatinib [19].Current data on the role of MDR1 in nilotinib drug efficacy can be summarized as poorly validated [8,9]. Mahon et al. [20] suggested ABCB1 overexpression as a mechanism of resistance to imatinib and nilotinib, whereas Davies et al [21] could not find any substrate interactions between ABC transporters and nilotinib.

A number of single nucleotide polymorphisms (SNP) of the MDR1 gene have been correlated with the P-gp expression [22]. Of those C3435T and G2677T had been particularly investigated. C3435T being the only clearly variant that contributes to different patients' responses to some MDR1 substrates [23] while G2677T is the most common variants in the coding region of MDR [22].

We detected statistically significant difference between the frequency of the MDR13435 CC, CT, and TT genotypes in group 1 (resistant group) compared to group 2 (responders). 3435CT genotype showed the highest frequency (65.52%) in group 1, and 3435 CC (44%) was the highest in group 2.The highest genotype frequency among unrelated Egyptian healthy subjects was 51.50% for 3435CT [24]. Different lifestyles and different levels of exposure to different risk factors may cause inter-individuals heterogeneity [10]. Ethnicity may also play a role. SNP 3435C>T in exon 26 and SNP 2677G>T in exon 21 are among the most frequent ABCB1 gene polymorphism in the Caucasian population [25].

Although C3435T is a silent SNP causing no amino acid change, the literature data often found an association between functional C3435T and cancer outcomes [22].This may be explained by its impact on post-transcriptional modifications of the mRNA, mRNA processingor alteration in the structure of substrate and inhibitor interaction sites [11].

On the other hand, G2677T polymorphism was not a risk

Table 1: Patients' characteristics: clinical and laboratory data.

Parameter	Group 1(n=29)	Group 2(n=25)	Test of sig.	P value
Age (years)	45.17±9.25	51.52±11.21	0.104	0.748
Sex Male Female	 15 14	 10 15	0.742	0.297
Sokal score Low risk Intermediate risk High risk	 - 4 (13.79%) 25 (86.21%)	 2 (8%) 16 (64 %) 7 (28%)	19.134*	0.00
BCR-ABL1 (%) at diagnosis	73.10±21.12	69.16±25.11	1.08	0.303
BCR-ABL1 (%) at 3 months	71.93±21.86	6.40±2.96	58.96*	0.00

Group 1: nilotinib resistant; Group 2: imatinib responders (controls); p is significant if <0.05

Table 2: Distribution of the genotype variants G2677T and C3435T polymorphism among CML groups.

Genotype	Group 1(n=29)	Group 2(n=25)	X2	p value
G2677T	No. (%)	No. (%)	4.496	0.106
GG GT TT	5 (17.27) 21(72.41) 3(10.34)	9 (36) 11(44) 5(20)		
C3435T	No. (%)	No. (%)	6.669*	0.036
CC CT TT	4 (13.79) 19 (65.52) 6 (20.69)	11 (44) 9 (36) 5(20)		
Combined	No. (%)	No. (%)	10.052*	0.007
CC & GG CT & GT TT&TT	14 (48.28) 3 (10.34)	7 (28) 7 (28) 4 (14)		

Group 1: nilotinib resistant; Group 2: responders (controls); p is significant if <0.05

Table 3: clinical data in wild and mutant group.

Parameter	Group 1 (n=29)		Group 2 (n=25)			Test of sig. p value
	Mutated	Others	Wild	Mutated	Others	
No	**17 (58.62%)**	**12 (41.38%)**	**8 (32%)**	**11 (44%)**	**6 (24%)**	**X^2=11.050* P=0.004**
Age (years)	**45.06± 9.68**	**45.33± 9.04**	**45.88±10.89**	**52.18± 10.42**	**57.83± 10.96**	**F=0.104 P=0.748**
Sex						
Male	**7**	**8**	**4**	**5**	**1**	**X^2=4.348**
Female	**10**	**4**	**4**	**6**	**5**	**P=0.361**
Sokal score						
Low				**1**	**1**	
Intermed	**4**		**5**	**6**	**5**	**X^2=19.156* P=0.014**
High*	**13**	**12**	**3**	**4**		

*: Eighteen patients (62.07%) with 2677GT and 16 patients (55.1%) with 3435CT were high Sokal score in resistant group; sig: significance, intermed: intermediate; m: months; Group 1: nilotinib resistant; Group 2: responders (controls); p is significant if <0.05

Table 4: Laboratory data in wild and mutant group.

Parameter	Group 1 (n=29)		Group 2 (n=25)			Test of sig. p value
	Mutated	Others	Wild	Mutated	Others	
Genotype	**CT&GT TT&TT**		**CC & GG**	**CT&GT TT&TT**		
No	**17 (58.62%)**	**12 (41.38%)**	**8 (32%)**	**11 (44%)**	**6 (24%)**	**X^2=11.050* P=0.004**
WBC ($X10^9$/l)	67.12± 61.22	74.56± 34.83	50.695± 24.29	73.14± 56.58	70.898± 76.50	**F=1.328 P=0.273**
Hb (g/dl)	12.19± 2.09	12.33± 1.86	13.38±1.68	12.26± 1.19	11.07± 1.65	**F=1.465 P=0.227**
Platelets ($X10^9$/l)	307.88± 130.06	394.92± 122.46	334.25± 138.25	310.55± 124.48	274.17± 75.81	**F=1.32 P=0.273**
Initial BCR-ABL1 (%)	72.94± 22.54	73.33± 19.90	68± 20.26	71.36± 21.67	66.67± 38.65	**F=0.139 P=0.967**
BCR-ABL1 (%) at 3m	66.24± 23.12	80± 17.84	5.38± 2.97	7.64± 2.20	5.50± 3.73	**F=59.11** P=0.00**

Abbreviations: Sig: Significance, Group 1: Nilotinib Resistant; Group 2: Responders (Controls); p is significant if <0.05; **: LSD showed statistically significant difference between mutated and others in group 2 with wild, mutated and others in group 1

factor for nilotinib resistance in our patients since no significant difference was present between genotype frequencies in both groups.In previous studies, heterozygous 2677GT frequency was increased in haematological poor responders CML patients [26] while, 2677 TT genotype might confer risk to develop CML due to decreased ability to transport carcinogens [27]. In our study, 72.41% (21/29 patients) in group 1 and 44% (11/25 patients) in group 2 had GT genotype. Only 3 (10.34%) in group 1 and 5 patients (20%) in group 2 had TT genotype which may suggest low frequency of this genotype in our patients.

The different effects of SNP G2677T on different drugs may be attributed to the presence of different amino acids at codon 893, leading to increased or decreased plasma concentration of P-gp substrates [26].Other explanation may be the presence of linkage disequilibrium with other functional polymorphisms.

Combined polymorphisms was defined as concurrent two exons polymorphisms whether homozygous wild type, heterozygous mutation or homozygous mutation [11].We found statistically significant increase in combined CT&GT in (48.28%) in group 1 compared with (28%) in group 2. Wild group (CC & GG) was present in 8 patients (32%) of group 2 only while mutated group (CT &GT and TT&TT) was present in 17 (58.62%) and 11 (44%)patients in group 1 and 2 respectively (p=0.004).

Previous *in vitro* and *in vivo* studies suggested that the 3435C>T polymorphism affects protein folding and function when it appears in a haplotype with the 1236C>T and 2677G>T/A polymorphisms [28].Tsai *et al* [29] suggested that the synonymous 3435C>T polymorphism causes the ribosome to pause in the reading of codons, which subsequently affects protein translation.

The inhibition of P-gp with verapamil or PSC833, potent blockers of the pump, led to an improved uptake of nilotinib in LAMA84-rn (nilotinib resistant cell line over-expressing P-gp) [20]. Thus, a study involves combination of these SNPs might be valuable especially in initiating treatment modalities and assessing patients' response to therapy in those receiving P-gp substrate.

CONCLUSIONS

Our data denoted that genotyping of MDR1 gene polymorphism (C3435T and G2677T) might be helpful in planning the individualized therapy of CML patients based on the

genotypes.Testing these findings in a larger patient population with newly diagnosed CML is recommended.

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