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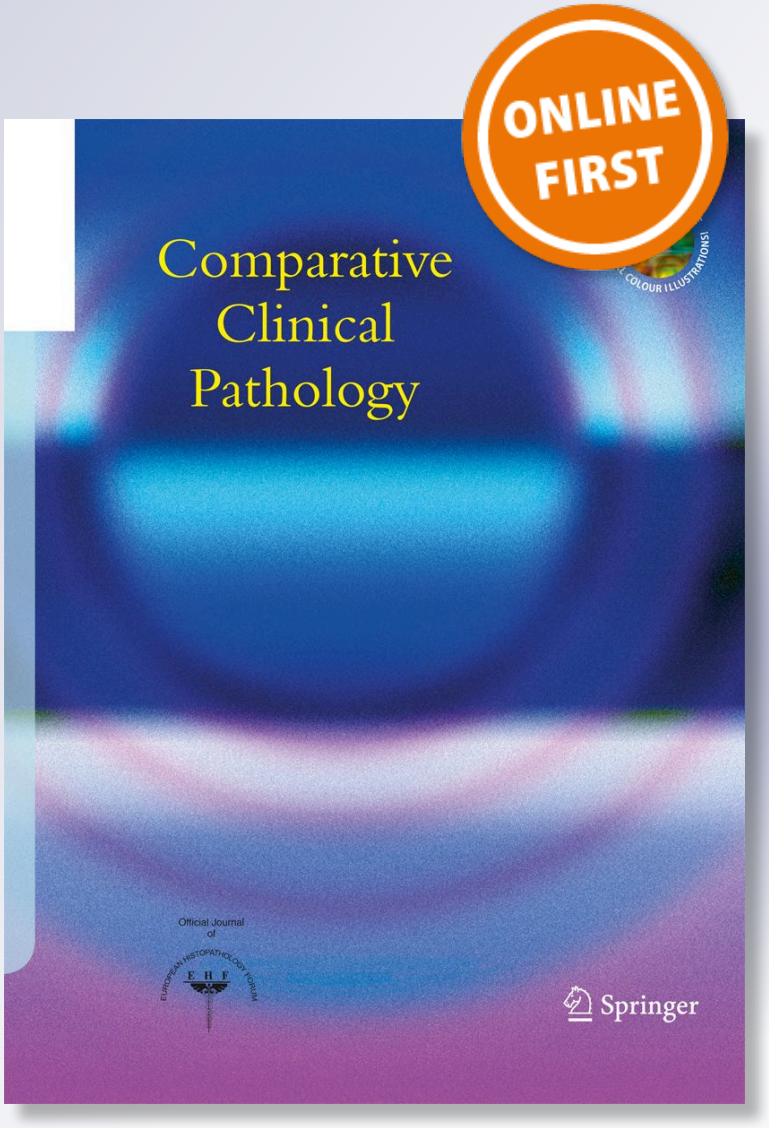

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ORIGINAL ARTICLE

MDR1 polymorphisms (G2677T and C3435T) in B-chronic lymphocytic leukemia

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Abstract The human multidrug resistance (MDR1) gene encodes P-glycoprotein, which affects the pharmacokinetics of many drugs. We investigated whether common MDR1 single-nucleotide polymorphisms (C3435T and G2677T) affect predisposition to B-chronic lymphocytic leukemia (B-CLL). Genotyping was performed in 65 patients with CLL and in 70 controls using polymerase chain reaction—restriction fragment length polymorphism. We observed a higher frequency of carriers of 3435CT gene among B-CLL patients as compared to normal individuals (58.5 vs. 22.9 %, p=<0.001). The genotype 3435CT was associated with B-CLL [odds ratio = 4.8, 95 % confidence interval = 2.3–10.0]. Moreover, patient and control groups did not differ significantly regarding the MDR1 genotype (G2677T). Furthermore, no correlation was shown between the MDR1 (3435 or 2677) genotypes and clinical and laboratory data of patient group. These data indicate that MDR1 C3435T single-nucleotide polymorphism may carry an increased risk of developing B-CLL.

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Keywords MDR-1 gene · Chronic lymphocytic leukemia · Polymerase chain reaction · Single-nucleotide polymorphism

Introduction

B-chronic lymphocytic leukemia (B-CLL) is a hematopoietic neoplasm of B lymphocytes found in the peripheral blood, bone marrow, and/or lymph nodes. It is the most common leukemia of adults (Hermelink et al. 2001). In the World Health Organization classification, chronic lymphocytic leukemia (CLL) is classified as a stage of small lymphocytic lymphoma, a type of B-cell lymphoma, which presents primarily in the lymph nodes (Harris et al. 1997). The etiology of B-CLL is poorly understood though both genetic and environmental factors appear to contribute to leukemogenesis (Houlston et al. 2002). As regards the genetic predisposition, an autosomal dominant mode of transmission was described in some cases with a rare familial subset of B-CLL (Lynch et al. 2002). Considering environmental factors in the pathogenesis of B-CLL, the disease is more frequent in rural areas which may reflect the involvement of agricultural chemicals. Indeed, epidemiological studies in farming communities associate B-CLL with sustained exposure to pesticides (Nanni et al. 1996; Waterhouse et al. 1996; Hatzissabas et al. 1993).

Patients with B-CLL present diverse clinical features, genetic abnormalities, variable responses to treatment, and heterogeneous prognoses (Penna et al. 2011b). Some patients have an aggressive disease requiring early therapy, whereas other patients exhibit a more stable, indolent disease with no benefit from palliative chemotherapy (Dighiero and Binet 2000).

Prognosis of B-CLL is related to clinical staging and cytogenetic findings. The genetic characterization of CLL has made significant progress over the past few years (Stilgenbauer et al. 2002).

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P-glycoprotein (Pgp), encoded by the MDR1 (*ABCB1*) gene, is a 170-kD membrane transporter belonging to the adenosine triphosphate-binding cassette superfamily. Overexpression of Pgp in tumors confers resistance to a wide range of important anticancer agents including anthracyclines, vinca alkaloids, and epipodophyllotoxins by active extrusion of these molecules from neoplastic cells (Ambdukar et al. 1999).

Pgp is highly expressed on the apical (luminal) surface of organs that have excretory functions, such as the bile canalicular membrane of hepatocytes and the renal proximal tubule (Thiebaut et al. 1987), and is significantly expressed on the luminal surface of tissues that serve as barriers, such as the brush border of the small intestine and the capillary endothelial cells of the blood–brain barrier (Schinkel et al. 1996). This characteristic localization enables Pgp to regulate absorption, distribution, and elimination of a wide spectrum of xenobiotics. Additionally, the level of Pgp expression in normal tissues has the potential to affect exposure to environmental carcinogens including several classes of pesticides demonstrated to be substrates of Pgp (Bain and LeBlanc 1996; Lanning et al. 1996; Bain et al. 1997) and to influence the pharmacokinetics of drugs transported by Pgp (Schinkel et al. 1995). Variations in Pgp activity may occur due to genetic alterations, such as single-nucleotide polymorphisms (SNPs), resulting in altered pharmacokinetics of drugs and transporter function, affecting the metabolism of drugs, and influencing the response to therapeutic agents (Jamroziak and Robak 2004).

Previous studies have identified 50 kinds of MDR1 SNPs, including the G2677T SNP at exon 21, which has been found to be the most frequent polymorphism able to affect the function of Pgp (Hoffmeyer et al. 2000). Also, silent C3435T polymorphism in exon 26 may alter the Pgp expression and transport activity (Jamroziak and Robak 2004).

The aim of the present study was to evaluate the role of two MDR1 gene polymorphisms (G2677T polymorphism) in exon 21 and(C3435T polymorphism) in exon 26 as risk factors for development of B-CLL and their relation to the clinical presentation of the patients.

Materials and methods

Human subjects

Peripheral blood samples were collected from 65 B-cell chronic lymphocytic leukemia (CLL group) patients and 70 sex and age matched healthy volunteers (control group). The patients were assessed at their first presentation to the Hematology/Oncology Clinic, El Kasr El Aini Hospital, Cairo University. Their ages ranged from 43 to 84 years, with a median of 60 years, (mean ± SD of 60.5±8.1 years). Forty-eight (73.8 %) patients were males, and 17 (26.2 %) were females with a male-to-female ratio of 2.8:1.0. As regards the control group, their ages ranged from 40 to 78 years, with a median of 60 years (mean ± SD of 58.1±8.3 years). Fifty (71.4 %) patients were males, and 20 (28.6 %) were females.

Diagnosis of CLL was confirmed according to the scoring system for diagnosis of CLL which is based on the expression and staining intensity of five markers (CD5, CD22, CD23, FMC7, and sIg). Diagnosis of CLL requires a score of 4 or 5 and rarely 3 (Matutes et al. 1994). The clinical staging of patients was evaluated according to the modified Rai classification. There were 25 (38.5 %) patients with low risk, 14 (21.5 %) patients with intermediate risk, and 26 (40 %) patients had high risk. The control group geographically and ethnically matched with the patients. The data concerning exposure to carcinogens in patients and controls were not available. The investigation was in accordance with the principles of the Declaration of Helsinki and was approved by the Local Ethical Committee of Cairo University. All subjects enrolled in the study gave informed consent.

Genotyping of C3435T and G2677T MDR1 SNPs

The genotyping of C3435T and G2677T MDR1 SNPs were identified using polymerase chain reaction (PCR)—restriction fragment length polymorphism as described previously (Jamroziak et al. 2002). Briefly, genomic DNA was isolated from the peripheral blood cells using the EZ-10 spin column Blood Genomic DNA Minipreps Kit (Biosystems, CA, USA). The reaction mixture for PCR amplification consisted of a DNA template, 0.5 μM of each primer, for C3435T (forward, 5'-GCT GCT TGA TGG CAA AGA AA-3'; reverse, 5'-ATT AGG CAG TGA CTC GAT GAT GA-3'), and for G2677T (forward, 5'-TGC AGG CTA TAG GTT CCA GG-3'; reverse, 5'-TTT AGT TTG ACT CAC CTT CCC G-3'), 10× PCR buffer, 1.5 mM MgCl2, 0.5 U of *Taq* DNA polymerase, 0.2 mM each dNTP. PCR-grade water was added to a final volume of 20 μl. PCR master mix and specific primers supplied by (Promega Corporation, USA). PCR amplification using a thermocycler (PEQLAB) consisted of initial denaturation at 95 °C for 5 min; 30 cycles of amplifications consist of denaturation at 94 °C for 30 s, annealing at 52 °C for 30 s, and extension at 72 °C for 30 s, followed by final extension at 72 °C for 10 min. A negative control was included in each experiment. The sample was then run in parallel on 2 % agarose gel electrophoresis and visualized on an ultraviolet transilluminator to detect the presence of amplified material. The amplified DNA was digested using (*Ban*I) restriction enzymes (Biolabs, Lyndhurst, NJ, USA, part no. R0118S) and (*Dpn*II) restriction enzymes (Biolabs, part no. R0543S) to study MDR1 G2677T and C3435T polymorphisms, respectively. The amplified product (8 μL) was pipetted

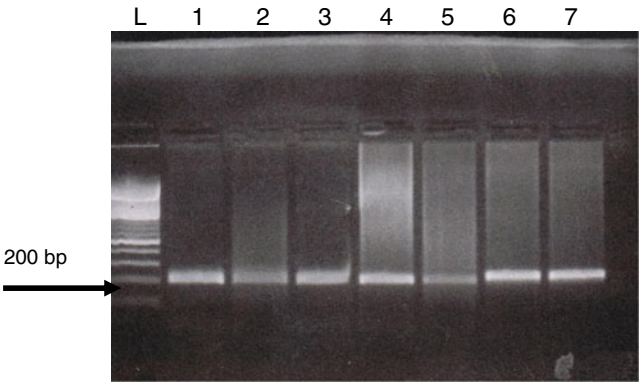

Fig. 1 A representation of the G2677T polymorphism of the MDR1 gene. *L*, ladder (100–1,000 bp). Lanes *1*, *2*, *3*, *4*, *5*, *6*, and *7* represent the wild type of the G2677T genotype of MDR1 gene

in a sterile 0.2-mL Eppendorf tube; then, 1 μL of restriction enzyme and 1 μL of reaction buffer, supplied with the enzyme, were added and then incubated at 37 °C for 4 h. Genotypes were then identified by electrophoresis of DNA fragments generated after digestion (Figs. 1 and 2).

Statistical methods

Data were analyzed using the SPSSwin statistical package version 17 (SPSS Inc., Chicago, IL, USA). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test was used to examine the relation between qualitative variables. For quantitative data, a comparison between two groups was done using Student's *t* test or Mann–Whitney test (nonparametric *t* test) for non-normally distributed data. Odds ratio with 95 % confidence interval was used for risk estimation. A p value< 0.05 was considered significant.

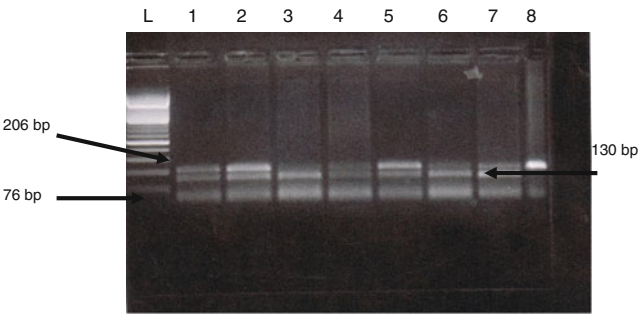

Fig. 2 A representation of the C3435T polymorphism of the MDR1 gene. *L*, ladder (100–1,000 bp). Lanes *1*, *2*, *4*, *5*, *6*, and *7* represent the heterozygous cases of the C3435T genotype of MDR1 gene**.** Lane *3* represents the wild type of C3435T genotype of MDR1 gene. Lane *8* represents undigested band of MDR1 gene

Table 1 Laboratory data of the CLL group

CLL group	Median	Range
Hb (%)	10.9	3.1–14.0
TLC ($\times 10^3/cm^3$)	80	14.8–463.1
ALC ($\times 10^3/cm^3$)	74,124	8,448.0–370,480.0
Platelet count ($\times 10^3/cm^3$)	130	14.0–359.0

Hb (%) hemoglobin concentration, *TLC* total leukocytic count, *ALC* absolute lymphocytic count

Results

Clinical and laboratory data

Regarding the clinical data of the CLL group, 30/65 (46.2 %) patients had hepatosplenomegaly, while 35/65 (53.8 %) had no hepatosplenomegaly. The laboratory data of the CLL group were summarized in Table 1.

Results of MDR1 (C3435T) gene polymorphism in B-CLL patients

There were 38 (58.5 %) cases of the CLL group and 16 (22.9 %) cases of the control group carrying heterozygous 3435CT gene (polymorphic type), while the 3435CC gene (wild type) was present in 27 (41.5 %) cases of the CLL group and 54 (77.1 %) cases of the control group (p=<0.001).The odds ratio was 4.8 (95 % confidence interval = 2.3–10.0), which means that there was a 4.8-fold increased risk for developing CLL in patients carrying the 3435 T allele (Table 2).

Results of MDR1 gene (G2677T) polymorphism in B-CLL patients

The present study revealed that the polymorphic heterozygous gene (2677GT) was present only in 2 (3.1 %) cases of the CLL group and 0 (0 %) cases of control group, while the remaining 63 (96.9 %) cases of CLL group and all 70

Table 2 Comparison between the CLL group and control group as regards MDR1 gene polymorphism (C3435T and G2677T)

		CLL group (65)		Control group (70)		p value
		Count	Percentage	Count	Percentage	
C3435T	Ht	38	58.5	16	22.9	<0.001 HS
	N	27	41.5	54	77.1	
G2677T	Ht	2	3.1	0	0	
	N	63	96.9	70	100	

HS highly significant, *N* normal, *Ht* heterozygous

Table 3 Sex variation between polymorphic type and wild type of the CLL group as regards MDR1 gene polymorphism (C3435T and G2677T)

		CLL group (65)		*p* value
		Males	Females	
C3435T	Ht	27 (56.3 %)	11 (64.7 %)	0.543 NS
	N	21 (43.8 %)	6 (35.3 %)	
G2677T	Ht	2 (4.2 %)	0	
	N	46 (95.8)	17 (100 %)	

NS not significant

(100 %) cases of the control group were carrying the wild gene (2677GG) (Table 2).

Comparison between patients carrying the 3435CT gene (heterozygous type) and those carrying the 3435CC gene (wild type)

It was found that within the 38 heterozygous cases, there were 19 (63.3 %) patients with hepatosplenomegaly and 19 (54.3 %) without hepatosplenomegaly. As regards the 27 patients carrying the wild gene, there were 11 (36.7 %) patients with hepatosplenomegaly and 16 (45.7 %) without hepatosplenomegaly (no statistical significant differences). As regards other clinical data (age and sex) and laboratory data, there was no statistically significant difference between patients carrying the 3435CT gene and those carrying the 3435CC gene (Tables 3 and 4).

Comparison between patients carrying the 2677GT gene (heterozygous type) and those carrying the 2677GG gene (wild type)

The two (4.2 %) heterozygous cases were males, and one (3.3 %) of them was with hepatosplenomegaly. No statistical analysis could be done due to the low number of cases carrying the polymorphic gene (two cases; Table 3).

Discussion

As regards C3435T polymorphism, cytogenetic analysis was successfully done and it revealed that 38/65 (58.5 %) patients of the CLL group vs. 16/70 (22.9 %) of the control group carry this polymorphism. There was a 4.8-fold increased risk for developing CLL in 3435 T allele carriers.

Our results are in accordance with those of Jamroziak et al. (2006) who found that genotypes 3435CT and 3435TT were associated with increased risk of B-CLL in their study on 110 Caucasian B-CLL patients and 201 healthy controls. Additionally, they assessed Pgp activity in malignant lymphocytes of 22 untreated B-CLL patients which was found to be depended on the MDR1 genotype, with the highest Pgp activity in 3435CC homozygotes, intermediate in 3435CT heterozygotes, and lowest in 3435TT homozygotes (p=0.042).

The previous data indicated that the MDR1 C3435T SNP may carry an increased risk of developing B-CLL, possibly by virtue of decreased protection against Pgp substrate carcinogens. The finding of lower Pgp expression and activity in 3435 T allele carriers has been confirmed by several studies in which other tissues including peripheral the blood mononuclear cells and renal parenchyma were examined (Schwab et al. 2003; Fellay et al. 2002; Hitzl et al. 2001), although discrepant results have also been reported (Calado et al. 2002; Illmer et al. 2002).

The functional impact of the C3435T MDR1 SNP remains a point of controversy (Morita et al. 2003; Oselin et al. 2003). Interestingly, Tsimberidou et al. (2003) have presented a rational explanation for the functional effect of MDR1 C3435T**.** The authors have found lower mRNA stability in the carriers of the variant 3435 T allele that is probably caused by altered mRNA secondary structure. Moreover, this functional effect of MDR1 C3435T has not been dependent on linkage disequilibrium with other MDR1 SNPs.

Another explanation is that C3435T polymorphism in exon 26 may alter Pgp expression and transport activity. Consequently, it is likely that specific functional MDR1 haplotypes may result with altered exposure to toxins and drugs, thus influencing predisposition to certain diseases such as

Table 4 Comparison between polymorphic type and wild type of MDR1gene polymorphism (C3435T) within the CLL group as regards clinical and laboratory data

CLL group	Polymorphic type (38)		Wild type (27)		*P* values (NS)
	Range	Median	Range	Median	
Age/years	43–84	80	43–82	62	0.366
Hb (%)	3.1–13.9	12.05	3.6–13.8	10.9	0.654
TLC ($\times 10^3/cm^3$)	14.8–463.1	114.5	16.6–342	80	0.857
ALC ($\times 10^3/cm^3$)	8,448–370,480	164,120	11,620–38,580	74,124	0.979
Platelet count ($\times 10^3/cm^3$)	14–359	186.5	54–359	154	0.203

Hb (%) hemoglobin concentration, *TLC* total leukocytic count, *ALC* absolute lymphocytic count, *NS* not significant

leukemias as well as efficacy or toxicity of pharmacotherapy (Jamroziak and Robak 2004).

The results of the present study did not reveal any significant correlation between the clinical parameters of the patients including age at diagnosis, sex, stage of the disease, CBC results, and patient genotypes. These results were matched with the results of Jamroziak et al. (2006). However, in the former study, the mean age at diagnosis was found to be nearly 3 years lower in carriers of at least one T allele (3435TT or 3435CT genotypes) than in patients homozygous for wild type C allele, although this difference was not statistically significant.

Our results were also supported by that of Qian et al. (2012) who performed a meta-analysis to evaluate the association between C3435T polymorphism and the risk of leukemia with all the case–control studies published before June 2011 according to PubMed. A total of ten case–control studies were included in this analysis. They found that variant genotypes of C3435T (CT/TT) were significantly associated with an increased risk of leukemia, and the association was more significant in B-CLL than in acute leukemia. These findings further provided evidence that the MDR1 C3435T variant may modify the susceptibility to leukemia.

Interestingly, the C3435T MDR1 polymorphism has been associated with a predisposition to other toxin-related diseases including renal tumors, pediatric acute lymphoblastic leukemia, ulcerative colitis, and Parkinson's disease (Jamroziak et al. 2004; Lee et al. 2004).

In the study of Penna et al. (2011b), they found that the C3435T MDR1 polymorphism had no significant correlation with the IgVH gene status or other variables in patients with CLL. Contrary to our study, they found no correlation between the genotype and CLL risk.

Also, in disagreement with our results, Hua-jie et al. (2011) whose aim was to investigate whether common MDR1 (SNPs) (C1236T, C3435T, and G2677T/A) affects predisposition to CLL found comparable allele and genotype frequencies among patients with CLL and controls. Moreover, patient and control groups did not differ regarding MDR1 haplotype distribution, and also, no correlation was shown between the MDR1 1236, 3435, or 2677 genotypes and Binet stage, unmutated immunoglobulin heavy-chain variable region status, CD38 expression, ZAP-70 expression, and p53 deletion. Their results did not support a major influence of MDR1 variants (C3435T) on the risk of CLL, and they stated that these genomic polymorphisms are not associated with clinical prognostic factors in Chinese patients with CLL.

As regards G2677T polymorphism, the genetic analysis was successfully done and revealed that 2/65 (3.1 %) patients of the CLL group vs. 0/70 (0 %) cases of the control group had this polymorphism. The previous results may reflect low incidence of this polymorphism in the studied population.

In disagreement with our results, Penna et al. (2011b) found that the mutant homozygous 2677TT genotype was associated with the occurrence of B-CLL and higher T allele frequency in patients with B-CLL when compared with the control. They also found that for the 2677GT polymorphism, the heterozygous status was associated with higher Hb levels.

On the contrary, Hua-jie et al. (2011) did not support a major influence of MDR1 variants (G2677T) on the risk of CLL and stated that genomic polymorphism was not associated with clinical prognostic factors in Chinese patients with CLL.

In the study of Penna et al. (2011a), analysis of polymorphisms in the MDR1 gene at exon 21 revealed that the 2677 T allele was not a predisposing factor to Richter transformation, while the presence of the wild-type genotype may be associated with a more favorable response to therapy.

The contradictory results may be explained by the fact that allele frequencies of SNPs are population-dependent, and some mutations seem to occur only in selected ethnicities. Interestingly, the TT genotype at 3435 position of MDR1 is present in a quarter of Caucasians, whereas it is rarely observed in Africans (Ameyaw et al. 2001).

The present study had claimed MDR1 (C3435T) polymorphism as a risk factor in B-CLL development that might reflect a serious role of environmental pollutants in the pathogenesis of CLL in the studied population. On the other hand, MDR1 (G2677T) polymorphism seems to be rare in Egypt. Larger-scale studies should be carried on to detect and control different carcinogens and people who are at high risk of developing leukemia in Egypt.

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