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ORIGINAL ARTICLE

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Investigation of MRP1 and ABCG2 Gene Expression in Chronic Myeloid Leukemia (CML) Patients

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ABSTRACT

Background: This study evaluated and compared the quantitative expression of multidrug resistance-associated protein 1 (*MRP1*) and ATP-binding cassette subfamily G member 2 (*ABCG2*), two Multidrug Resistance (MDR) related genes, in 30 CML patients and 27 normal subjects.

Methods: Total RNA was isolated from peripheral blood mononuclear cells (MNCs) using the Trizol reagent. Then cDNAs were synthesized. Gene expression was quantified using Real-Time PCR System. The relative expression of target genes was calculated using the $2^{-\Delta\Delta Ct}$ method.

Results: High expression of *MRP1* and *ABCG2* mRNAs were detected in the patient group. Intra-group comparisons also revealed increased expression of *ABCG2* in Accelerated Phase (AP)-Blastic Crisis (BC) patients compared to Chronic Phase (CP) patients. At the same time, the increased expression of *MRP1* in AP-BC patients was not statistically significant.

Conclusion: Considering the broad spectrum of ATP Binding Cassette (ABC) transporter superfamily substrates, they can play an essential role in cell fate determination. High expression of *MRP1* and *ABCG2* genes can result in the efflux of therapeutic agents and subsequent reduction in their intracellular concentration. This mechanism finally protects cells from the therapeutic effects of medications. On the other hand, these transporters can export growth factors out of the cell. Such exported molecules may have a growth-inducing effect on adjacent cells. These are the possible mechanisms for the participation of *MRP1* and *ABCG2* genes in conferring drug resistance to CML cells.

Keywords: ABCG2, MRP1, CML, Imatinib, Gene expression

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INTRODUCTION:

CML is a malignant disorder of hematopoietic stem cells. Its clinical course is triphasic, initially comprising a Chronic Phase (CP) with variable duration, followed by progression through an Accelerated Phase (AP) and finally Blastic Crisis (BC). The causative event in CML and 25-30% of Acute Lymphocytic Leukemia (ALL) is the *BCR-ABL* fusion that results from t (9; 22) (q34; q11). The new chromosome developed from this translocation is called Philadelphia (Ph) chromosome, and approximately 95% of CML patients are Ph-positive (1).
Nowadays, Imatinib Mesylate is the standard of care for the treatment of CML patients. Imatinib is a tyrosine kinase inhibitor that blocks the activation of *BCR-ABL* tyrosine kinase. Without the function of this oncoprotein, its downstream signaling pathways will be down-regulated. Imatinib has been shown to induce a complete hematologic and cytogenetic response in the majority of CML patients (2).
However, there is a group of patients with primary or secondary resistance to imatinib therapy (3). MDR (multidrug resistance) is a type of resistance mediated through ATP-Binding Cassette (ABC) transporters in malignancies such as CML. ABC transporter superfamily comprises 48 proteins with seven subfamilies based on sequence and structural homology, which are involved in ATP-dependent transportation of a wide variety of xenobiotics, lipids, and metabolic products across the cell membranes (4,5). Overexpression of some members of this superfamily, especially *ABCC1*/*MRP1*, *ABCG2*, and *ABCB1*, has been reported in many different cancers (4,6,7). As efflux pumps, they can export substrates like therapeutic agents out of the target cells, thereby conferring resistance to those agents by reducing drug intracellular levels (8).
In addition to their expression in malignant cells and participation in drug resistance, *MRP1* and *ABCG2* are also expressed in normal cells and play a key role in transporting xenobiotics and preventing cell toxicity (9). Also, *MRP1* and *ABCG2* are involved in tissue defense mechanisms and are essential for protecting cells from damage and death.
We previously investigated *MDR1* genes, efflux transporters, mRNA expression in CML patients. We showed overexpression of *MDR1* as a possible mechanism for CML treatment failure (10). In the present study, we investigated and quantified the expression of two other important transporters, *MRP1*, and *ABCG2* (*BCRP1*), and their possible-association with *MDR1* gene expression in the same population of CML patients.

METHODS:

Peripheral blood samples were obtained from 30 CML cases and 27 healthy individuals (the control group). All participants provided written informed consent before inclusion in the study. The patients and healthy individuals were similar concerning sex and age. CML diagnoses were made based on clinical findings and morphological characteristics of bone-marrow aspirates. Confirming t (9;22) by cytogenetic and PCR methods also helped the diagnosis. The patients were divided into three subgroups of Chronic Phase (CP) (n=16), Accelerated Phase (AP) (n=10), and Blastic Crisis (BC) (n=4). In the CML group, the shortest time to diagnose and initiating Imatinib therapy was one year, while the longest course of the disease was 15 years. Inclusion and Exclusion criteria are shown in **Table 1**.

RNA extraction and cDNA synthesis:

A total of 5-8 ml of peripheral blood was obtained from patients. Mononuclear cells (MNCs) were isolated by Ficoll-Hypaque gradient centrifugation. Total RNA was extracted from 4-6 × 106 cells using Trizol reagent (Invitrogen, Carlsbad, CA); cDNA synthesis was performed using RevertAid™ First Strand cDNA Synthesis Kit (Fermentas, Ontario, Canada) according to the method recommended by the manufacturer with 1μl of total RNA in 20μl reaction mixture [containing 1μl

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Table 1. Inclusion and Exclusion criteria

Inclusion (for patients)	Exclusion (for patients)
All ages and genders	-
Confirmed diagnosis of CML according to clinical, biochemical, morphological, and flow cytometric findings	Confirmed diagnosis of diseases other than CML
t(9;22) positive	t(9;22) negative
The course of the disease (diagnosis, therapy initiation): 1 yr to 15 yrs	-
Patient, parental, or guardians consent	Lack of patient, parental, or guardians consent
Inclusion (for controls)	**Exclusion (for controls)**
All ages and genders	-
Normal CBC counts	Abnormal CBC counts
Absence of disease or infirmity	Existence of any form of the disease
Patient, parental, or guardians consent	Lack of patient, parental, or guardians consent

M-MLV RT (200 u/ µl), 4 µl 1x buffer, 2 µl random hexamer primer (500 ng/µl), 2 µl dNTP mix (10 mmol), 1 µl RNase inhibitor (40 u/µl) and 9 µl DEPC-treated water].

SYBER-Green Real-Time RT-PCR:

Gene expression quantification was done by Fast Start SYBR Green Master Mix (Roche Diagnostics, Mannheim, Germany) and Corbett-Rotor Gene-6000 system (Corbett, Sydney, Australia). The primer sequences for each gene are shown in **Table 2**. Polymerase Chain Reaction (PCR) was performed according to the manufacturer's instructions. Each PCR reaction had 20 µl final volume, containing 10 µl of SYBER-Green PCR Master Mix, 2 µl cDNA, 300 nM of each primer, and 6.4 µl DEPC-treated water. PCR was performed at 95°C for 15 minutes and was followed by 40 cycles of de-

Table 2. Sequences of oligonucleotide primers

Genes	Forward Primer	Reverse Primer
MRP1	GGATCTCTCCAGCCGAAGTCT	GTGATGGGAGCCAGAAGCA
ABCG2	CCAGGTGTGCGTCAGAATCA	GGAGCTACTTAGGCCAGATTTTTG
β-actin	GCTGTGCTACGTCGCCCTG	GGAGGAGCTGGAAGCAGCC

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naturation at 95°C for 15 seconds, annealing at 57°C for 30 seconds, and extension at 60°C for 1 minute. The 2-ΔΔCt method was used to calculate the relative expression of target genes.

Interaction analysis:

The interaction analysis was done using GeneMANIA version 3.5.1, NCBI Gene, and UniProt online databases.

Statistical analysis:

Normal distribution of data was evaluated using Stata software with qnorm program version 11. Data were analyzed by statistical SPSS software (Chicago, IL, SPSS Inc.), version 16. Variables with normal distribution were reported as means and standard deviations. Medians were reported for the variables whose distribution deviated from the normal distribution. Differences between diagnostic subgroups were evaluated using the Kruskal–Wallis test. Comparisons of gene expression levels between CML patients and control group or comparisons of ABC genes expression between the resistant and sensitive groups were performed with the Mann–Whitney test. The correlation between continuous variables was studied with Spearman's rank correlation (rs). All tests were two-tailed, and a 5% significance level was applied.

RESULTS:

MRP1 (ABCC1), ABCG2, and (MDR1) ABCB1 are mainly involved in drug response/transport

Interaction analysis revealed that most of the biological processes and molecular functions found for the target genes are related to drug transportation and drug response (**Figure 1**). The gene networks from GeneMANIA show biological links between MRP1 (ABCC1), ABCG2, and (MDR1) ABCB1.

***MRP1* and *ABCG2* expression in patients and controls**

Expression of *MRP1*, *ABCG2*, and *β-Actin* (the internal control gene), were measured by a reliable and reproducible relative quantification method based on Corbett-Rotor Gene 6000 technology. Standard curves were prepared for target and reference genes. The specificity of amplicons was analyzed by the melting curve and verified by agarose gel electrophoresis.

MRP1 expression was observed in 85% and 70% of patients and control subjects, respectively. *ABCG2* expression was observed in 75% and 60% of patients and control subjects, respectively. By comparing *MRP1* expression in both groups, its high expression levels were observed in patients several times more than in the control subjects. The differences in *MRP1* expression between the two groups were statistically significant (P = 0.026, **Figure 2**). *ABCG2* also demonstrated increased expression in patients compared to control subjects (P = 0.016, **Figure 3**).

***ABCG2* high expression level in AP-BC patients**

Patients were categorized into two groups: the CP group and the AP-BC group to investigate MRP1 and ABCG2 expression in different phases of the disease. We found the *ABCG2* expression to be higher in the latter group than in CP patients, and the difference in this respect was statistically significant (P = 0.001, **Figure 4**). *MRP1* expression was not significantly different between the two groups (P = 0.829, **Figure 5**), although *MRP1* expression in the AP-BC group was higher than in CP patients

Patients' response to treatment

Chronic phase patients responded better to Imatinib than patients at AP and BP phases and showed a more favorable hematologic response. In general, 25% of AP and BP patients demonstrated a hematologic response; whereas, this rate was 90% in CP patients (**Figure 6**). Lack of hematologic response in patients suggested that these patients are at high risk of developing resistance to Imatinib therapy. To this end, we investigate *ABCG2* and *MRP1* expression levels in the two groups of pa-

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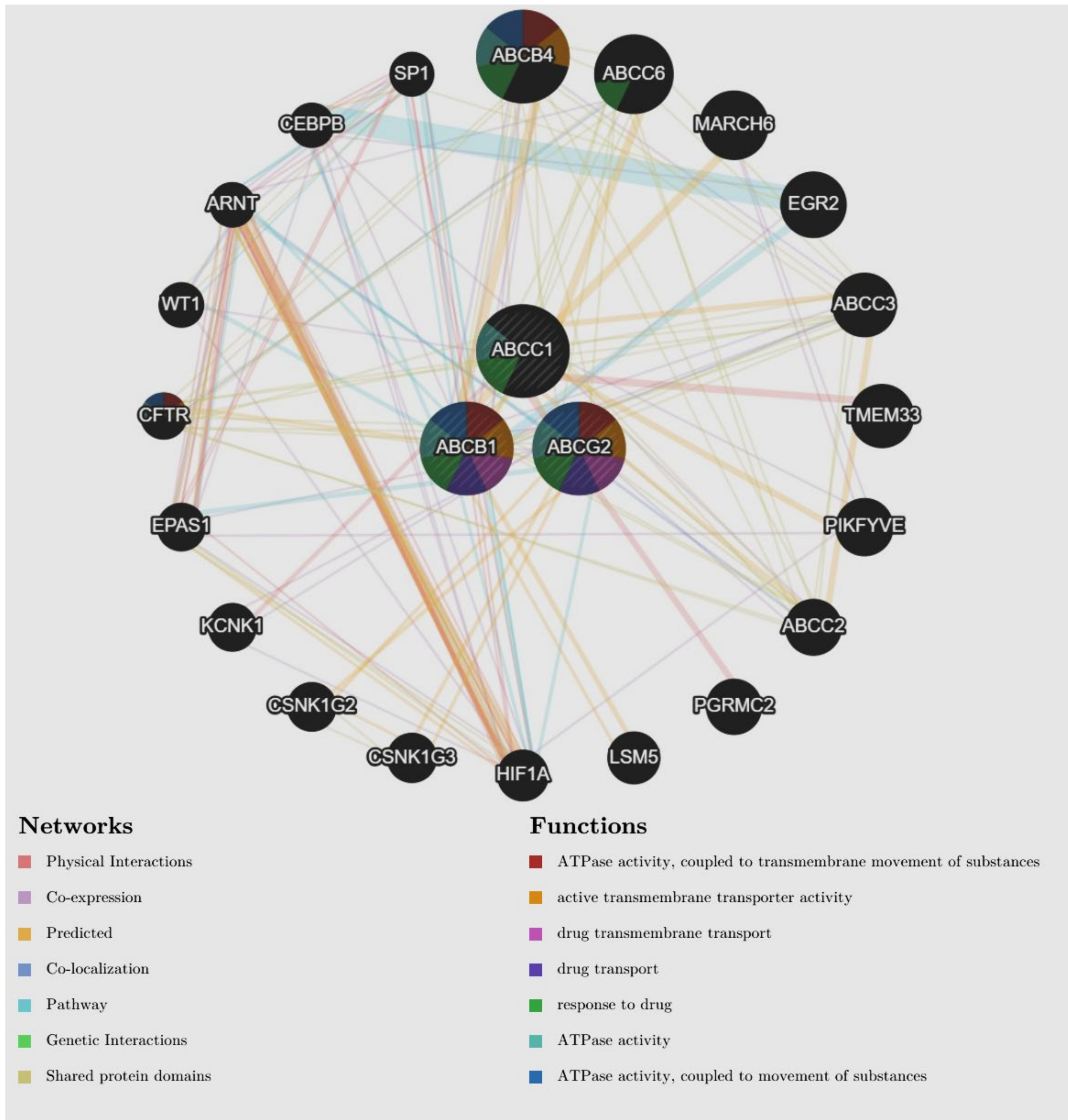

Figure 1. The schema represents the various types of molecular interactions (as colored lines) and functions (as colors within circles) between our investigated genes. Each color demonstrates a type of molecular interaction or function defined within the graph by a color guide. The whole graph produced using the online software, GeneMANIA version 3.5.1. Input genes, including *MRP1* (*ABCC1*), *ABCG2*, and *MDR1* (*ABCB1*), were represented. According to reports produced by the software, the most common function of our target genes is drug response and transmembrane transporter activity.

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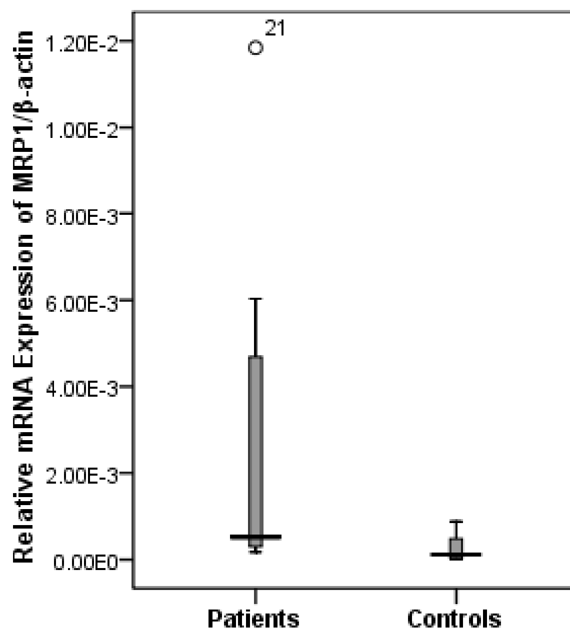

Figure 2. Relative expression of MRP1gene in patients and controls. There were significant differences between the two groups in this respect (P= 0.026).

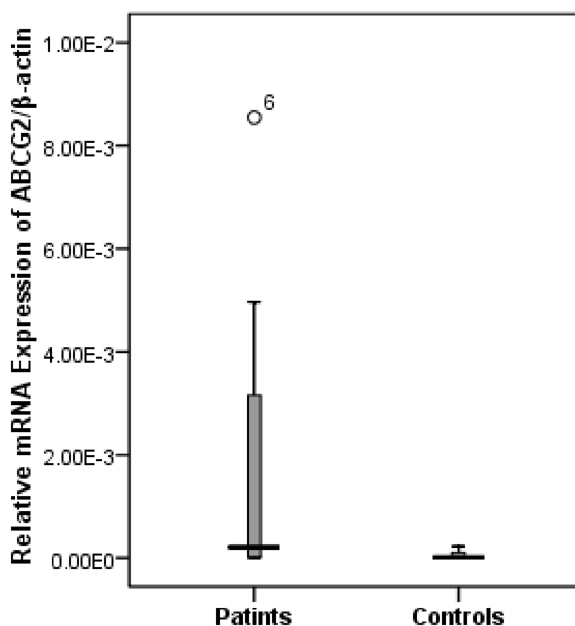

Figure 3. Relative expression of the *ABCG2* gene in patients and controls. There were significant differences between the two groups in this respect (P= 0.016).

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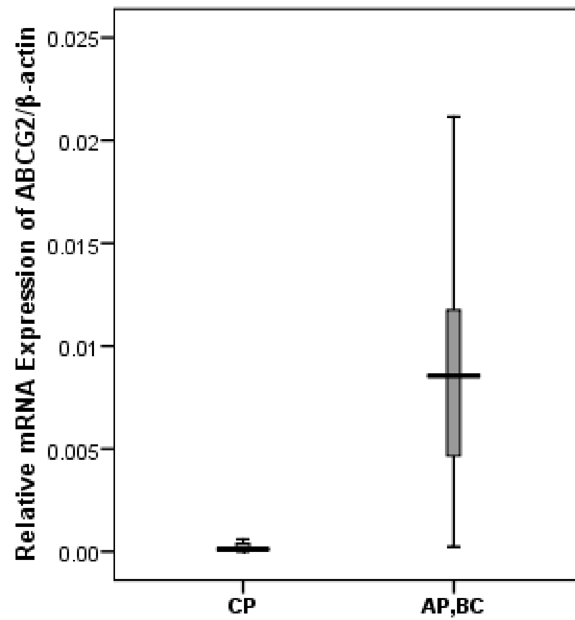

Figure 4. Relative expression of the *ABCG2* gene in the AP, BC phase, and CP patients. The two groups were significantly different in terms of *ABCG2* gene expression (P= 0.001).

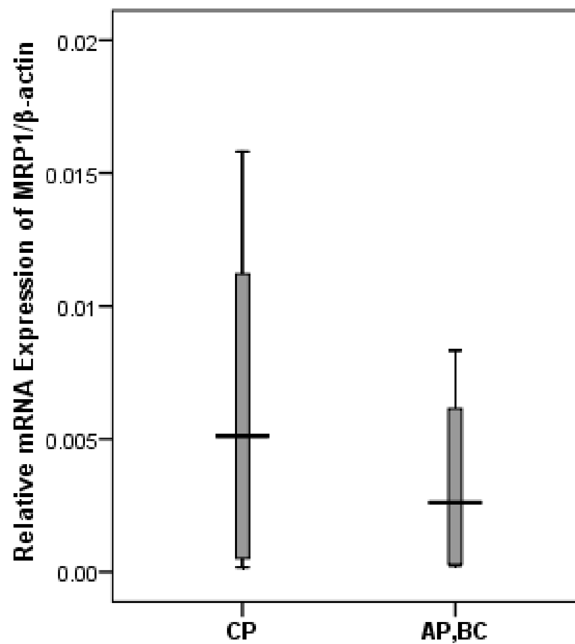

Figure 5. Relative expression of *MRP1* gene in AP, BC phase, and CP patients. The differences between the two groups were not statistically significant (P = 0.829).

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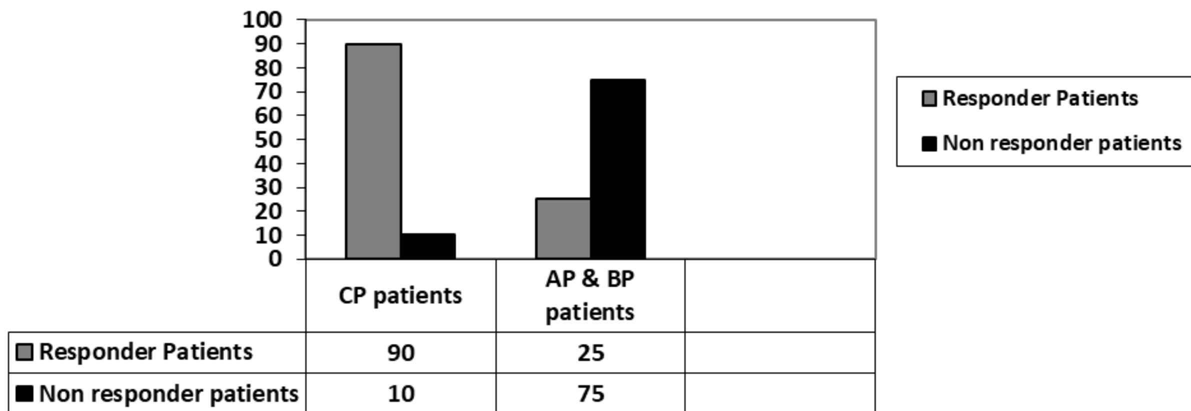

Figure 6. Patients' response to treatment. Twenty-five percent of AP and BP patients demonstrated a hematologic response; whereas, this rate was 90% in CP patients

tients, responsive and non-responsive patients. Our results showed that the responsive group has less expression *ABCG2.* Additionally, the responsive group has less expression of *MRP1* mRNA, but the result was insignificant compared to the non-responsive group (**Figures 7 and 8**).

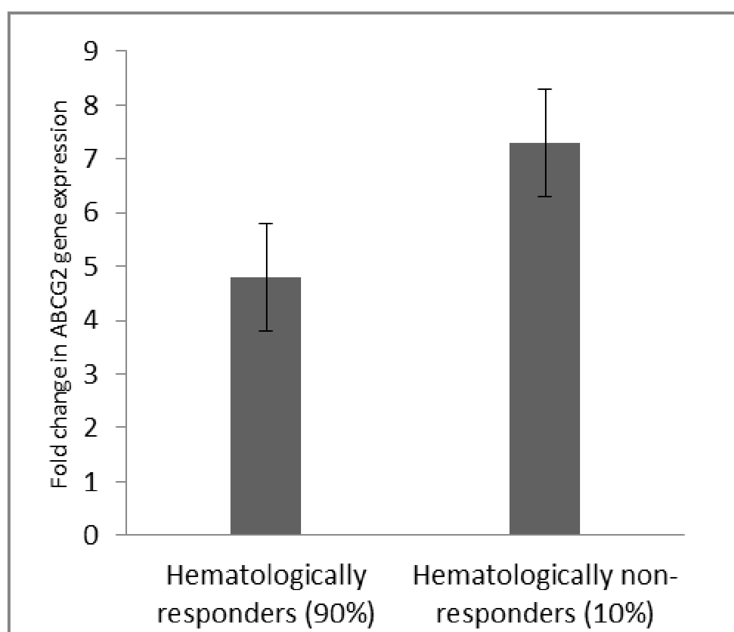

Figure 7. Relative expression of the *ABCG2* gene in hematologically respondent and non-respondent patients with CP. A statistically significant difference was detected between the two groups ($P < 0.05$).

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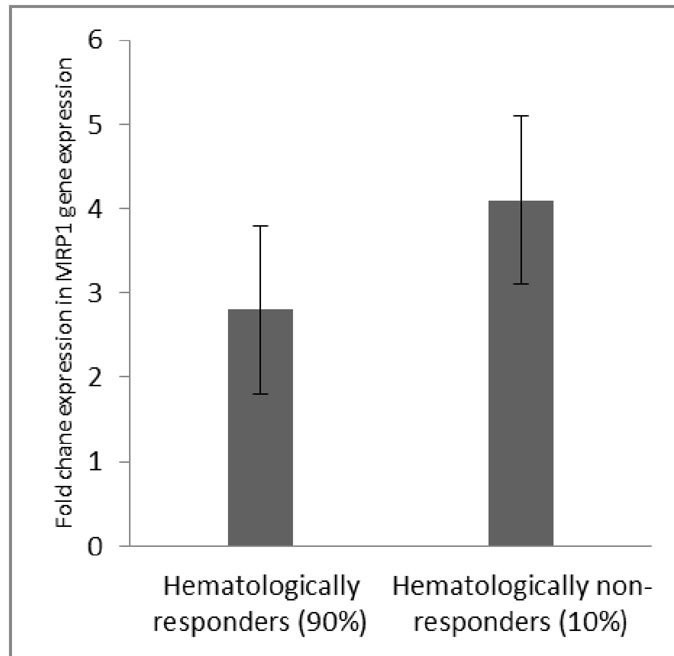

Figure 8. Relative expression of the *MRP1* gene in hematologically respondent and non-respondent patients with CP. Although hematologically responders have less expression of *MRP1* gene in comparison to non-responders, there was not a remarkable difference between the two groups (P > 0.05).

Correlation between *MRP1*, *ABCG2*, and *MDR1*:

Our results demonstrated a positive and significant correlation between *ABCG2* gene expression and expression of other drug resistance genes, including *MRP1* and *MDR1*. Besides, we have found a positive and significant correlation between the expression of *MRP1* and *MDR1* (**Figure 9-11**).

DISCUSSION

The emergence of drug resistance in malignancies, especially leukemia, is an important obstacle in treating these cases (11,12). There are different possible mechanisms involved in developing treatment failure or resistance, mainly to Imatinib Mesylate in CML patients. *BCR-ABL* oncogene amplification, mutations at Imatinib binding site on *BCR-ABL* oncoprotein, additional genetic alterations, and particularly increased expression of multidrug resistance (MDR) proteins are some of the suggested mechanisms conferring drug resistance in CML patients (13-16). Multidrug resistance is caused by a group of transmembrane proteins called ATP binding cassette (ABC) pumps, which can transfer various molecules like drugs to the outside of the cell using energy obtained from ATP hydrolysis (17). This may affect many pharmacokinetic properties of substrates, including drugs, and may result in resistance (9,18,19). ABC transporters, including *MRP1* and *ABCG2*, are found to be upregulated in numerous malignancies. Researches show that overexpression of these genes will lead to MDR in hematologic malignancies (20-22).

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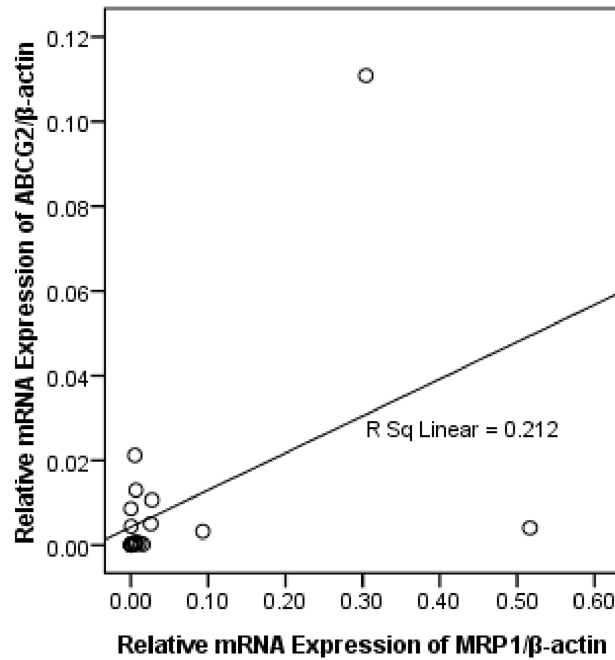

Figure 9. ABCG2 mRNA expression was positively correlated with MRP1expression in PBMCs of CML patients (rs= 0.688, P= 0.002).

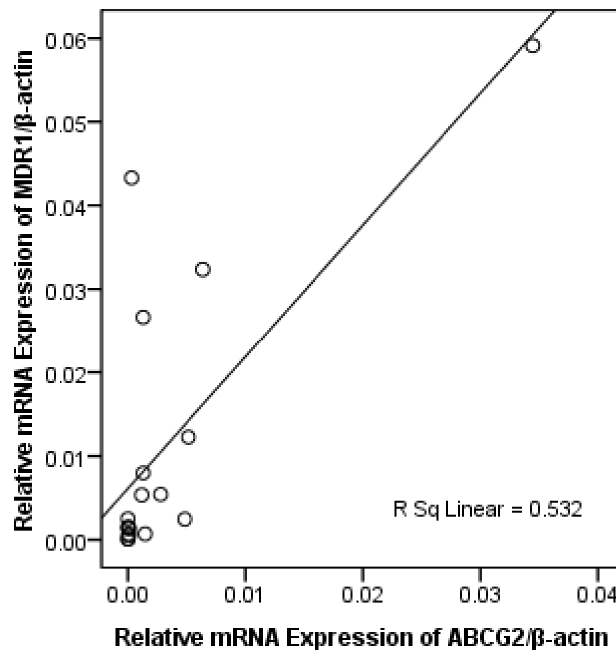

Figure 10. ABCG2 mRNA expression was positively correlated with MDR1expression in PBMCs of CML patients (rs= 0.682, P= 0.002).

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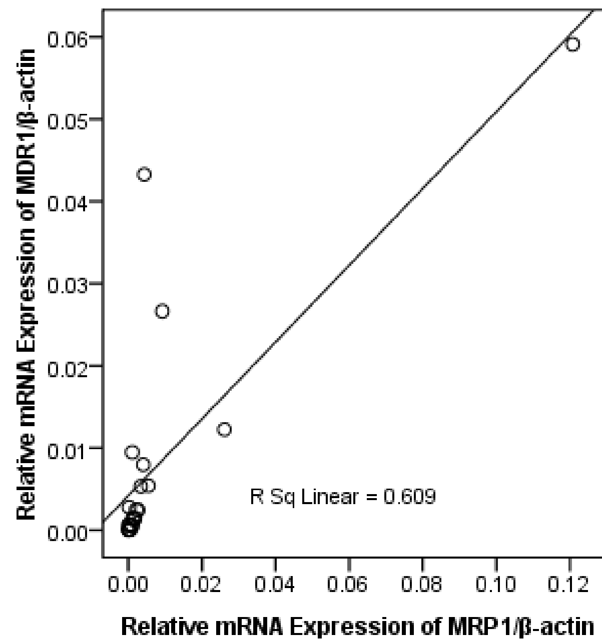

Figure 11. MRP1 mRNA expression was positively correlated with MDR1 expression in PBMCs of CML patients (rs= 0.870, P< 0.001).

They suggest that ABC proteins could be useful for identifying novel treatment for non-responders CML cases, beneficial biomarkers for the leukemia diagnosis, and assessment of treatment response. Also, these proteins could be potential targets for the designing of new therapeutic strategies (21). In this regard, we have evaluated the *MRP1* and *ABCG2* gene expression in patients affected with CML.

We found that MNCs in CML show high levels of *MRP1* and *ABCG2* expression. This phenomenon can induce cell proliferation and cancer progression and contributes to the accumulation of leukemic cells, particularly those with a higher number of drug efflux pumps (ABC transporters) on their membrane (23-27). We also showed that patients with advanced phases of the disease have high *MRP1* and *ABCG2* expression levels. It may play a role in the progression of the disease to AP and BC phases by increased cell resistance to therapy. Lower hematologic responses were observed in these patients. It seems that leukemic cells with a high number of efflux pumps on their surface are less susceptible to therapeutic agents. Besides the efflux of therapeutic agents from the target cells and reduction of intracellular drug levels through *MRP1* and *ABCG2* gene expression, their overexpression may reinforce their physiologic functions that favor cell growth. Transport of various signaling molecules, including growth factors, has been demonstrated as a physiologic function of ABC transporters. Leukotrienes, prostaglandins (PGs), Sphingosine-1phosphate (S1P), Platelet Activating Factor (PAF), cholesterol metabolites, and cyclic nucleotides are other ABC transporters substrates (25,28). Transportation of these molecules by ABC transporters is the only known major efflux mechanism. After their export from the cells, these molecules trigger important signaling pathways. They can induce proliferation, invasion,

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and survival of tumor cells.

MRP1 plays a key role in the export of Prostaglandin E2 (PGE2) and Leukotriene C4 (LTC4) and is an important mediator in tumor biology. Outside the cells, PGE2 and LTC4 can activate their signaling pathways and stimulate target cells (29,30). Associations have been reported between *MRP1* overexpression and tumor differentiation rate, tumor size, and aggressiveness in hepatocellular carcinoma (31) and breast cancer (32). Thus, increased expression of *MRP1* may relate to poor prognosis. There are also reports on the correlation of *ABCC1* increased expression and poor prognosis and poor outcome in neuroblastoma (33). Drug export mediated by *MRP1* in malignant cells might induce cell resistance to anticancer agents and enhance cell survival.

ABCG2 expression has also been shown in hematopoietic cells (34). Its expression in cancer cells and cancer stem cells has also been reported, which plays a crucial role in the emergence of multidrug resistance. *ABCG2* expression was found in CD34+ CML cells as well. It seems that *ABCG2* does not have a key role in normal hematopoiesis. Mice with *ABCG2* deficiency were viable and had a normal number of stem cells (35). *ABCG2* may play a protective role in cells exposed to toxic agents such as chemotherapeutics (36). It has been shown that *ABCG2* is an efflux transporter capable of exporting a wide variety of substrates like Mitoxantrone, Camptothecins, Anthracyclines, Bisantrene, Imatinib, Methotrexate, Flavopiridol, and Epipodophyllotoxins (25,37). Tyrosine Kinase Inhibitors (TKIs), especially Imatinib (38,39), are among the main studied *ABCG2* substrates. High expression of these transporters on the surface of malignant cells can disrupt the balance between cell apoptosis and cell number (40). Our results also showed high expression levels of *ABCG2* in patients at different stages of the disease. High presentation of this efflux pump on the membrane of leukemic cells would facilitate the export of its substrates, especially drugs like Imatinib. Also, we observed an increase in the expression of *ABCG2* with the progression of the disease. Thus, it is possible that increased expression of this efflux pump maintains the leukemic cells and causes subsequent disease progression. In line with our finding, Steinback found a correlation between high *ABCG2* levels and failure to achieve Complete Remission (CR) in AML patients (41). Benderra et al. also found a correlation between *ABCG2* expression, lower CR rate, and shorter survival (42). High levels of *ABCG2* were shown to correlate with Danusertib resistance in CML patients (43).

CONCLUSION

Our study results indicate that high expression of *MRP1* and *ABCG2* is associated with a poor treatment outcome in CML patients. This overexpression results in a reduction of intracellular drug concentration, which per se can protect the cells from the therapeutic effects of medications. On the other hand, the elevated rate of *MRP1* and *ABCG2* efflux pumps accelerates the export of molecules out of the cells where these molecules may play a role in cell growth, proliferation, and survival.

Correlation analysis in our study showed that there is a positive and significant relation between the expressions of *MRP1*, *ABCG2*, and *MDR1*. Also, bioinformatics assessments show that there are biological links between these proteins. This means that in leukemic cells, drug resistance genes upregulate orchestrally to precede progression and escape chemotherapy.

In conclusion, our results show that *MRP1* and *ABCG2* have higher expression in CML patients than the control group. Also, we have found that *MRP1* and *ABCG2* have more elevated expression in CML patients in the AC/BC phase than patients in the Chronic Phase (CP). In this investigation, we have found that CML patients who respond to Imatinib treatment have less expression of *MRP1* and *ABCG2* than non-responders. Besides, we have shown a positive and significant correlation

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between the expression of *MRP1*, *ABCG*, and *MDR1*. These findings suggest that ABC proteins, especially *MRP1* and *ABCG2*, might be helpful targets for diagnosis, treatment, and the assessment of response to the treatment in CML patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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