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GSTM1 and *GSTP1*, but not *GSTT1* genetic polymorphisms are associated with chronic myeloid leukemia risk and treatment response

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ABSTRACT

Background: Chronic myeloid leukemia (CML) is associated to the *BCR-ABL1* oncogene and can successfully be treated with tyrosine kinase inhibitors (TKIs). However, it remains still under investigation which molecular factors may influence CML risk or varying responses to TKIs. The aim of this study was to assess the role of Glutathione-*S*-transferases (GSTs) genetic polymorphisms in CML susceptibility and TKI clinical outcome.
Materials: Deletion polymorphisms in *GSTM1* and *GSTT1* genes and the single nucleotide polymorphism in *GSTP1* c.319A > G (rs1695; p.105Ile > Val) were genotyped by PCR methods in 141 CML treated patients and 141 sex- and age-matched healthy individuals.
Results: Individual analysis of each GST gene showed no association with CML risk. A trend toward significance (p = 0.07) for a recessive model was found for GSTP1 (OR: 2.04; CI: 0.94-4.4). However, the combined analysis showed that GSTM1-null/GSTP1-GG as well as GSTT1-null/GSTP1-GG were associated with CML development (p = 0.03; OR: 3.54 CI: 1.2-14.57; p = 0.05; OR: 12.65; CI: 1.17-21.5). The relationship with treatment outcome showed that the presence of *GSTM1* gene was significantly linked with an inferior rate of major molecular response (p = 0.048) and poor event free-survival (EFS) (p = 0.02). Furthermore, a group of patients with *GSTP1*-GG genotype were significantly associated with reduced EFS comparing to those carrying other *GSTP1* genotypes (p = 0.049). *GSTP1*-GG genotypes had short time to treatment failure in a group of patients unresponsive to TKIs comparing to other *GSTP1* genotypes (p = 0.03).
Conclusions: This study highlights the significance of *GSTM1* and *GSTP1* polymorphisms on CML susceptibility and response to TKIs in the Argentinean population.

1. Introduction

Tyrosine kinase inhibitors (TKIs), Imatinib (IM), Nilotinib and Dasatinib, inhibits the expression of *BCR-ABL1* fusion gene in chronic myeloid leukemia (CML). First-line treatment with IM has significantly improved quality of life and patients' survival. However, varying responses to IM have been observed [1]. Almost 40% of patients will eventually fail IM treatment and are often treated with second-generation (2G) TKIs such as nilotinib or dasatinib [2,3]. Despite the success of using these agents, failure to 2G TKIs has also been reported [4]. TKIs resistance has been mainly related to point mutations within the *ABL1* kinase domain [5]. There is an increasing body of evidence demonstrating that mechanisms independent of *BCR-ABL1* gene also contribute to TKIs resistance. Germline polymorphisms in genes associated to drug uptake and metabolism have been reported to influence treatment outcome in CML [6]

Pathogenesis of CML is strongly associated to the expression of *BCR-ABL1* fusion oncogene, but the mechanisms which cause this translocation or initiates leukemogenesis remain poorly understood [7,8]. The mechanisms which cause non-random, non-homologous chromosomal translocations in leukemia, although still unknown, may result from misrepair of double-strands breaks

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and mutation in the two major DNA repair pathways, homologous recombination and non-homologous end joining [9]. Ancestral or additional genetic events necessary for CML to develop have long been hypothesized but never really demonstrated [10]. Previous association studies have identified polymorphic variants in various critical genes associated with CML susceptibility, albeit results are still inconsistent [11].

Individual inherited genetic differences related to polymorphism in detoxification enzymes could be an important factor not only in carcinogen metabolism but also in cancer susceptibility [12]. Functional genetic polymorphisms have been described for Glutathione-*S*-transferase (GSTs) genes, a superfamily of phase II metabolizing enzymes. GSTs catalyze the conjugation of reduced glutathione (GSH) to a wide variety of electrophilic compounds in order to make them more soluble enabling their elimination [13]. As a result of this detoxification activity, GSTs protect the cell from DNA damage, genomic instability and cancer development. In addition, as non-enzymatic proteins, GSTs can modulate signaling pathways that control cell proliferation, cell differentiation and apoptosis, among other processes [14,15]. Deletion polymorphisms of *GSTM1* and *GSTT1* genes and the single nucleotide polymorphism in *GSTP1* c.319A > G (rs1695; p.105Ile > Val) lead to the absence or reduced detoxification capacity of the enzyme. Differences in GSTs activity may modify the risk of cancer development and also may impact on the heterogeneous responses to toxic substances or specific therapies [13]. Moreover, GST polymorphisms are known to contribute to inter-individual and ethnic variability in the susceptibility to environmental risk factors, cancer predisposition and drug responsiveness. Several epidemiological studies evaluated the role of GST polymorphisms on CML susceptibility, but conflicting results have been achieved [8]. Moreover, a recent study has assessed the effect of *GSTM1*, *GSTT1* and *GSTP1* polymorphisms on treatment response, but the involvement on CML susceptibility was not evaluated [16]. Therefore, the aim of the present study was investigate, for the first time, the importance of GST genetic polymorphisms in the susceptibility and the response to TKIs in Argentinean patients with CML.

2. Materials and methods

2.1. Study population

Peripheral blood samples were obtained from 141 patients (68 females and 73 males; mean age 51.33 ± 1.33; range 17–85 years) diagnosed with CML and under different TKIs treatment (imatinib, dasatinib, nilotinib) with a mean of follow up of 67.6 months. In particular, 71 patients were in chronic phase and TKIs responders (54 were in optimal response with imatinib, 12 with nilotinib and 5 with dasatinib). In patients failing TKI treatment (n = 70), direct sequencing of the *ABL1* kinase domain of *BCR-ABL1* was carried out. In this group, 25 patients had mutations in the tyrosine kinase domain. The remaining 45 cases, 29 of them were in chronic phase (CP) with suboptimal response either to dasatinib or nilotinib and 16 progressed to accelerated phase/blast phase (AP/BP). *BCR-ABL1* transcripts were measured in whole blood using reverse transcription quantitative PCR (RT-qPCR) with *ABL1* as a reference gene, according to log reduction international scale. Failure to TKI treatment was considered according loss of cytogenetic, hematological responses, confirmed loss of major molecular response, and the presence of *BCR-ABL1* mutations. [17]. Table 1 outlines the main clinical and genetic data available for the patient group considering together the categories of Complete and Partial cytogenetic responses as Major Cytogenetic Response. In addition, 141 sex- and age- matched unrelated healthy individuals without medical history of leukemia or other chronic diseases were analyzed. Patients and controls were Argentineans from Buenos Aires city and surrounding urban areas, and had the same ethnicity. All individuals provided their informed consent according to institutional guidelines. The study was approved by the Institutional Ethical Committee and complies with the International Declaration of Helsinki.

Table 1
Main clinical and genetic data of CML patients.

Clinical Parameters		N (%)[a]
Sokal	High	32 (32)
	Intermediate	32 (32)
	Low	36 (36)
Phase	Chronic	76 (84)
	Accelerated	9 (9.6)
	Blast crisis	9 (9.6)
Treatment outcome	TKIs responders	71 (50.3)
	TKIs non-responders[b]	70 (49.7)
BCR-ABL1 mutation	Yes	25 (36)
	No	45 (64)
Molecular Response	Major/4.5/5.0	63 (45)
	Minor	27 (19)
	Minimal	26 (19)
	Null	23 (17)
Cytogenetic Response	Major[c]	78 (66)
	Minimal	6 (5)
	Minor	20 (17)
	Null	14 (12)
Progression	Yes	16 (14)
	No	110 (86)

[a] Complete data were not available for all patients.
[b] Non-responder patients were considered when at least had one TKI change.
[c] Complete and Partial response were grouped as Major Cytogenetic Response.

2.2. Genotyping

Genomic DNA was isolated using DNAzol (Invitrogen). A multiplex PCR assay using previously published primer pairs was used to amplify *GSTT1* (480 bp) and *GSTM1* (273 bp) genes with β-globin (680 bp) as an internal positive control. *GSTP1* c.313A > G polymorphism was genotyped by RFLP-PCR with *Alw261* restriction enzyme (Thermo Fisher). PCR mix, primer concentrations, cycling conditions and electrophoresis were used as defined earlier [18]. Ten percent (10%) of samples were randomly reanalyzed, yielding identical results.

2.3. Statistical analysis

Statistical analyses were performed using PLINK software and SPSS statistical package (version 15.0) (IBM, SPSS Inc., Chicago, USA). The association between polymorphisms and CML was performed using logistic regression analysis adjusted by age and sex. The estimating of odds ratios (OR) and their corresponding 95% confidence intervals (CIs) were calculated. For *GSTP1* Hardy–Weinberg equilibrium (HWE) was tested using a goodness-of-fit Chi-square test and standard genetic models (additive, recessive and dominant) for disease penetrance were evaluated. For *GSTM1* and *GSTT1* we considered only a recessive model since the PCR-assay does not distinguish between homozygote wild type and heterozygous genotypes. We also assessed combined genetic polymorphisms on CML risk using logistic regression analysis. The Kaplan-Meier method was performed to estimate survival curves, and the log-rank test was used to compare the stratified genotype

Table 2
Study of association between individual GST polymorphisms and CML risk.

Genes	Genotypes/Alleles	CML N = 141(%)	Controls N = 141(%)	Genetic Models	*P*	OR (95%CI)
GSTM1	Present	85 (60.3)	84 (59.6)			
	Null	56 (39.7)	57 (40.4)	*Recessive*	0.83	0.95 (0.56–1.53)
GSTT1	Present	121 (85.8)	117 (83)			
	Null	20 (14.2)	24 (17)	*Recessive*	0.37	0.74 (0.39–1.43)
GSTP1	*AA*	62 (44)	67 (47.5)	*Recessive*	0.07	2.04 (0.94–4.4)
	AG	58 (41)	62 (44)	*Dominant*	0.57	1.15 (0.71–1.8)
	GG	21 (15)	12 (8.5)	*Additive*	0.19	1.26 (0.88–1.82)
	A	182 (65)	196 (70)			
	G	100 (35)	86 (30)	–	0.12	1.32 (0.18–0.93)

subgroups. The following endpoints were undertaken: 1. Time to Major Molecular Response (TMMR): was defined as the first date to achieving the molecular response; 2. Event free survival (EFS): an event was defined as either loss of complete hematologic, cytogenetics or molecular response, progression to AP or BC or death; 3. Time to treatment failure (TTF): an event was considered a change of treatment in patients without molecular or cytogenetic responses during two consecutives studies or intolerance to treatment. All statistical tests were two-sided and values of $p \leq 0.05$ were considered statistically significant.

3. Results

The frequencies of GST polymorphisms are summarized in Table 2. *GSTP1* polymorphism was confirmed to be in HWE for patients and controls (p = 0.22; p = 0.65). To study the association between each GST polymorphism and CML risk, we first tested a recessive genetic model for *GSTM1* and *GSTT1* genes, where the homozygous null genotype has no enzyme activity. Analysis of recessive model showed no significant differences for the individual genotypes of *GSTM1* (p = 0.83; OR: 0.95 CI: 0.56–1.53) and *GSTT1* (p = 0.37; OR: 0.74; CI: 0.39–1.43). Then we tested various genetic models for *GSTP1* gene showing a trend toward significance (p = 0.07) for a recessive model (*AA + GA vs. GG*), in which only the homozygous G genotype would exhibit a reduction of enzyme activity (Table 2).

Given that individual GST genotypes showed no meaningful associations with CML risk, we analyzed the potential joint effect of GST enzymes by logistic regression to screen double or triple combined genotypes considering a recessive model for GSTP1 gene (Table 3). Frequencies of *GSTM1*-null/*GSTP1*-GG as well as *GSTT1*-null/*GSTP1*-GG genotype combinations were significantly increased in patients (5.7% and 5%) respect to controls (2.1%; 0.7%, respectively). This suggest that these combined genotypes are associated with CML development (p = 0.03; OR: 3.54 CI: 1.2–14.57; p = 0.05; OR: 12.65; CI: 1.17–21.5). The analysis of triple GST genotypes combinations, showed a lack of association for the studied group (Table 3).

Three endpoints were undertaken in order to evaluate the association between GSTs polymorphisms and the result of TKIs treatment by Kaplan-Meier plots. No association was found for *GSTT1* polymorphism. Patients carrying *GSTM1*-present genotype were significantly associated with an inferior rate of MMR achievement (p = 0.048) (Fig. 1A). Accordingly, patients with

Table 3
Association analyses between combined GSTs genotypes and CML risk.

Genotypes	Cases N (%)	Controls N (%)	*P*	OR (95% CI)
GSTM1/GSTT1				
M1+/T1+	72 (51.1)	70 (49.6)	0.92	0.97 (0.57–1.65
M1+/T1−	14 (9.9)	15 (10.6)	0.47	0.74 (0.83–1.6)
M1−/T1+	50 (35.5)	48 (34.0)	0.9	0.9 (0.58–1.65)
M1−/T1−	5 (3.5)	8 (5.7)	0.28	0.6 (0.28–1.5)
GSTM1/GSTP1[a]				
M1+/AA + AG	71 (50.4)	76 (53.9)		
M1+/GG	14 (9.9)	9 (6.4)	0.24	1.71 (0.6–4.63)
M1−/AA + AG	48 (34)	53 (37.6)		
M1−/GG	**8 (5.8)**	**3 (2.1)**	**0.05**	**3.54 (1.2–14.57)**
GSTT1/GSTP1[a]				
T1+/AA + AG	106 (75.2)	107 (75.9)		
T1+/GG	14 (9.9)	11 (7.8)	0.47	1.39 (0.57−3.24)
T1−/AA + AG	14 (9.9)	22 (15.6)		
T1−/GG	**7 (5.0)**	**1 (0.7)**	**0.03**	**12.65 (1.17–21.5)**
GSTM1/GSTT1/GSTP1[a]				
M1+/T1+/AA + AG	62 (44)	62 (44)		
M1+/T1+/GG	7 (5.7)	8 (5.7)	0.94	0.96 (0.3–2.99)
M1−/T1+/AA + AG	43 (30.5)	45 (31.2)		
M1−/T1+/GG	7 (5.)	3 (2.1)	0.162	2.7 (0.66–11.85)
M1+/T1−/AA + AG	8 (5.7)	7 (5)		
M1+/T1−/GG	6 (5.0)	8 (5.7)	**0.06**	**9.3 (0.88–10.2)**
M1−/T1−/AA + AG	5 (3.5)	9 (6.4)		
M1−/T1−/GG	1 (0.7)	0	0.99	NA

M1+: *GSTM1* present; M1−: *GSTM1*-null; T1+: *GSTM1*-present; T1−: *GSTT1*-null.
[a] Recessive model was considered for combinations involving *GSTP1*.

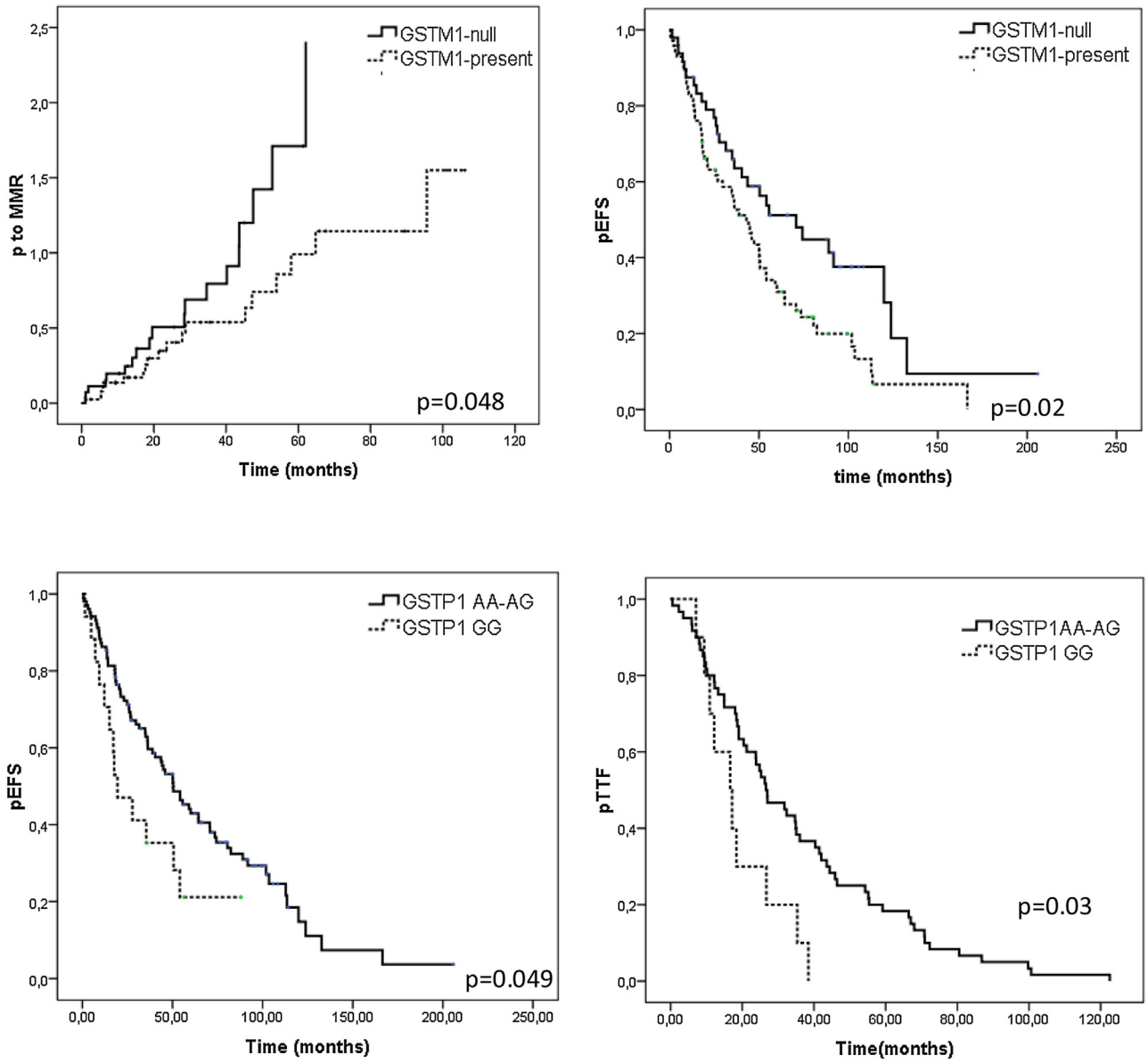

Fig. 1. Kaplan-Meier Log-rank plots stratified according: *GSTM1*-null (solid black line) vs. *GSTM1*-present (dashed black line) and *GSTP1* AA-AG (solid black line) vs. GSTP1 GG (dashed black line). (A) Probability to achieve Major Molecular Response (MMR) (B) y (C) Probability of event free survival during treatment. (D) Probability to time to treatment failure (TTF).

GSTM1-present genotype also exhibited worse EFS than those cases with *GSTM1*-null variant (p = 0.02) (Fig. 1B). Furthermore, a group of patients with *GSTP1*-GG genotype were significantly associated with reduced EFS comparing to those carrying *GSTP1* AA-AG genotypes (p = 0.049) (Fig. 1C). No association was found for TTF analysis considering the entire patients cohort (p > 0.05) (data not shown). Strikingly, when only the group of patients unresponsive to TKIs was considered, individuals with *GSTP1*-GG genotype were most likely to fail treatment compared to cases with *GSTP1* AA + AG genotypes (p = 0.03) (Fig. 1D).

4. Discussion

Studies concerning the importance of GSTs polymorphism on CML are still scarce and remain controversial rather than conclusive. The reasons for these discrepancies might depend on geographic and ethnic variations, among others [19]. Remarkable differences in the pattern of GST frequencies were described worldwide [20]. No studies have evaluated CML patients from Argentina, whose population results of a long-standing process of admixture between several ethnic groups [21]. Thus, we report the influence of GST polymorphisms on CML susceptibility and patients' response in the first case-control study from the Argentinean population.

In our cohort, no significant association was found between the risk to develop CML and *GSTM1* and *GSTT1* polymorphisms. However, a considerable trend toward significance was establish for *GSTP1*, following a recessive model, suggesting a probable involvement of this gene on CML predisposition. In agreement with our findings, previous association studies reported that *GSTM1* gene is not involved on CML susceptibility [22–25]. Similar results were also found in a recent meta-analysis reported with different ethnic populations [8]. Hence, the majority of the epidemiological studies performed to date suggest that *GSTM1* may not be a risk factor for CML development. Contrary to our data, a different scenario was described for *GSTT1*-null genotype, which

has been associated with CML risk in different ethnicities [22,23,26]. Moreover, *GSTT1* deletion, either alone or in association with *GSTM1*-null genotype, increased CML risk in Caucasian, Indian, and Chinese populations [8]. Few studies have evaluated the *GSTP1* polymorphism in CML, demonstrating that *GSTP1*-GG is a predisposing factor to CML susceptibility [19,24]. Accordingly, the combined analysis performed in our study showed that *GSTP1*-GG in combination with *GSTM1*-null or *GSTT1*-null genotypes are significant risk factors for CML development. The finding of a combined role of GST to disease susceptibility is in accordance to the hypothesis that GST genes are involved in the same metabolic pathway with overlapping substrate specificities and that there is also evidence of GST gene interactions [27]. The joint effect of GST variant genotypes found in our and other populations, suggests that combined GST genotypes should be a more appropriate evaluation way for CML risk assessment rather than considering only individual genes.

Polymorphisms in genes encoding drug transporters and metabolizing enzymes may modify drug effectiveness and therefore, can affect therapy response [6]. We have therefore investigated the role of GSTs genetic variability as potential biomarkers of TKIs response. Our results suggest that the presence of the *GSTM1* gene is significantly associated with an inferior rate of MMR achievement and poor EFS. Moreover, patients carrying *GSTP1*-GG genotypes exhibited reduced EFS and TTF comparing to those carrying other *GSTP1* genotypes. Consequently, we demonstrated that patients with *GSTM1*-present and *GSTP1*-GG genotypes may be related with an inferior clinical outcome. However, a recent study reported that absence of the *GSTM1* and *GSTT1* genes is associated with IM failure, and no association was found for *GSTP1* [16]. In contrast, in a case-control study from India, *GSTP1*-GG genotype was more frequently found in patients with accelerated and blast crisis phases, suggesting that this polymorphism might influence in CML progression and therapy response [19].

The underlying pathways explaining the role of GSTs in CML treatment are still unclear; however, variation in the metabolic clearance of the TKIs may not be the reason [16,28]. An alternative explanation may be related to the involvement of *GSTM1* and *GSTP1* in the regulation of cell cycle and apoptosis [29]. *GSTP1* was found to inhibit the c-Jun-N-terminal kinase (*JNK*) through direct protein–protein interactions [15,30,31]. JNK is activated by multiple stimuli, leading to contrary cellular effects such as enhance cell survival and proliferation, as well as apoptosis [15,32]. It has been suggested that elevated levels of GSTP1 sequester and inhibit the activity of JNK and protect tumor cells from apoptosis [30]. On the other hand, GSTM1 interacts with the N-terminal region of ASK1 (apoptosis signaling kinase 1) gene, inhibiting its activity [33]. The dissociation of the GSTM1/ASK1 complex, enables the triggering of ASK1 and the consequent phosphorylation of JNK and p38 leading to apoptosis [30]. It is therefore possible that despite TKIs are not substrates of GSTs, therapy failure associated to the presence of the *GSTM1* gene and *GSTP1*-GG variant genotype may be related to several pathways necessary for the activation of kinases to induce apoptosis.

In conclusion, our study highlights the importance of GSTs variability on CML susceptibility and outcome suggesting that *GSTM1* and *GSTP1*, but not *GSTT1* polymorphisms may be involved on CML pathogenesis as well as with poor TKIs treatment response. Further studies concerning the genetic variability in GSTs may be undertaken in CML in order to define new markers of susceptibility and prognosis to achieve an individualized therapeutic approach based on own genetic background.

Conflicts of interest

Authors declare no conflict of interests.

Authorship contribution

NW performed the experiments, analyzed the data and wrote de manuscript. CF: performed the qRT-PCR and ABL1 mutation analysis. BM, RB, IG and CP: provide the CML samples and clinical data. IL and AF: designed the study and wrote the manuscript.

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References

[1] E. Jabbour, J. Cortes, H. Kantarjian, Treatment selection after imatinib resistance in chronic myeloid leukemia, Target Oncol. 4 (2009) 3–10.
[2] T.P. Hughes, A. Hochhaus, S. Branford, M.C. Müller, J.S. Kaeda, L. Foroni, B.J. Druker, F. Guilhot, R.A. Larson, S.G. O'Brien, M.S. Rudoltz, M. Mone, E. Wehrle, V. Modur, J.M. Goldman, J.P. Radich, IRIS investigators, Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: an analysis from the International Randomized Study of Interferon and STI571 (IRIS), Blood 116 (2010) 3758–3765.
[3] S. Francis, C. Lucas, S. Lane, L. Wang, S. Watmough, K. Knight, J. Bell, M. Kaleel-Rahman, E. Lee, D. O'Brien, N.M. Butt, W. Sadik, L. De Soysa, J.R. Seale, R. Salim, R.E. Clark, A population study showing that the advent of second generation tyrosine kinase inhibitors has improved progression-free survival in chronic myeloid leukaemia, Leuk. Res. 37 (2013) 752–758.
[4] A. Eghtedar, H. Kantarjian, E. Jabbour, S. O'Brien, E. Burton, G. Garcia-Manero, S. Verstovsek, F. Ravandi, G. Borthakur, M. Konopleva, A. Quintas-Cardama, J. Cortes, Outcome after failure of second generation tyrosine kinase inhibitors treatment as first-line therapy for patients with chronic myeloid leukemia, Clin. Lymphoma Myeloma Leuk. 13 (2013) 477–484.
[5] T. Ernst, P. La Rosée, M. Müller, A. Hochhaus, BCR-ABL mutations in chronic myeloid leukemia, Hematol. Oncol. Clin. North Am. 25 (2011) 997–1008.
[6] S. Vaidya, K. Ghosh, C. Shanmukhaiah, B.R. Vundinti, Genetic variations of hOCT1 gene and CYP3A4/A5 genes and their association with imatinib response in Chronic Myeloid Leukemia, Eur. J. Pharmacol. 15 (2015) 124–130.
[7] D.H. Kim, W. Xu, C. Ma, X. Liu, K. Siminovitch, H.A. Messner, J.H. Lipton, Genetic variants in the candidate genes of the apoptosis pathway and susceptibility to chronic myeloid leukemia, Blood 113 (2009) 2517–2525.
[8] H.R. He, X.X. Zhang, J.Y. Sun, S.S. Hu, Y. Ma, Y.L. Dong, J. Lu, Glutathione S-transferase gene polymorphisms and susceptibility to chronic myeloid leukemia, Tumour Biol. 35 (2014) 6119–6125.
[9] J.A. Nickoloff, L.P. De Haro, J. Wray, R. Hromas, Mechanisms of leukemia translocations, Curr. Opin. Hematol. 15 (2008) 338–345.
[10] S. Soverini, C. de Benedittis, M. Mancini, G. Martinelli, Mutations in the BCR-ABL1 kinase domain and elsewhere in chronic myeloid leukemia, Clin. Lymphoma Myeloma Leuk. 15 (2015) S120–8.
[11] H. Bruzzoni-Giovanelli, J.R. González, F. Sigaux, B.O. Villoutreix, J.M. Cayuela, J. Guilhot, C. Preudhomme, F. Guilhot, J.L. Poyet, P. Rousselot, Genetic polymorphisms associated with increased risk of developing chronic myelogenous leukemia, Oncotarget 6 (2015) 36269–36277.
[12] K. Yaya, D. Hind, Q. Meryem, Q. Asma, B. Said, N. Sellama, Single nucleotide polymorphisms of multidrug resistance gene 1 (MDR1) and risk of chronic myeloid leukemia, Tumour Biol. 35 (2014) 10969–10995.
[13] A.L. Hollman, P.B. Tchounwou, H.C. Huang, The association between gene-environment interactions and diseases involving the human GST superfamily with SNP variants, Int. J. Environ. Res. Public Health 13 (2016) E379.
[14] E. Laborde, Glutathione transferases as mediators of signaling pathways involved in cell proliferation and cell death, Cell Death Differ. 17 (2010) 1373–1380.
[15] M. Dusinska, M. Staruchova, A. Horska, B. Smolkova, A. Collins, S. Bonassi, K. Volkovova, Are glutathione S transferases involved in DNA damage signalling? Interactions with DNA damage and repair revealed from molecular epidemiology studies, Mutat. Res. 736 (2012) 130–137.
[16] A. Davies, A. Giannoudis, J.E. Zhang, G. Austin, L. Wang, T.L. Holyoake, M.C. Müller, L. Foroni, P.D. Kottaridis, M. Pirmohamed, R.E. Clark, Dual glutathione-S-transferase-θ1 and -μ1 gene deletions determine imatinib failure in chronic myeloid leukemia, Clin. Pharmacol. Ther. 96 (2014) 694–703.
[17] M. Baccarani, M.W. Deininger, G. Rosti, A. Hochhaus, S. Soverini, J.F. Apperley, F. Cervantes, R.E. Clark, J.E. Cortes, F. Guilhot, H. Hjorth-Hansen, T.P. Hughes, H.M. Kantarjian, D.W. Kim, R.A. Larson, J.H. Lipton, F.X. Mahon, G. Martinelli, J. Mayer, M.C. Müller, D. Niederwieser, F. Pane, J.P. Radich, P. Rousselot, G. Saglio, S. Saußele, C. Schiffer, R. Silver, B. Simonsson, J.L. Steegmann, J.M. Goldman, R. Hehlmann, European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013, Blood 122 (2013) 872–884.
[18] N. Weich, M.C. Nuñez, G. Galimberti, G. Elena, S. Acevedo, I. Larripa, A.F. Fundia, Polymorphic variants of GSTM1, GSTT1, and GSTP1 genes in childhood acute leukemias: a preliminary study in Argentina, Hematology 20 (2015) 511–516.

[19] K. Sailaja, D. Surekha, D.N. Rao, D.R. Rao, S. Vishnupriya, Association of the GSTP1 gene (Ile105Val) polymorphism with chronic myeloid leukemia, Asian Pac. J. Cancer Prev. 11 (2010) 461–464.
[20] S. Karaca, M. Karaca, T. Cesuroglu, S. Erge, R. Polimanti, GSTM1 GSTP1, and GSTT1 genetic variability in Turkish and worldwide populations, Am. J. Hum. Biol. 27 (2015) 310–316.
[21] A. Sau, F. Pellizzari Tregno, F. Valentino, G. Federici, A.M. Caccuri, Glutathione transferases and development of new principles to overcome drug resistance, Arch. Biochem. Biophys. 500 (2010) 116–122.
[22] M. Taspinar, S.E. Aydos, O. Comez, A.H. Elhan, H.G. Karabulut, A. Sunguroglu, CYP1A1, GST gene polymorphisms and risk of chronic myeloid leukemia, Swiss Med. Wkly. 138 (2008) 12–17.
[23] N. Özten, A. Sunguroğlu, M.C. Bosland, Variations in glutathione-S-transferase genes influence risk of chronic myeloid leukemia, Hematol. Oncol. 30 (2012) 150–155.
[24] C. Bănescu, A.P. Trifa, S. Voidăzan, V.G. Moldovan, I. Macarie, E. Benedek Lazar, D. Dima, C. Duicu, M. Dobreanu, CAT, GPX1, MnSOD, GSTM1, GSTT1, and GSTP1 genetic polymorphisms in chronic myeloid leukemia: a case-control study, Oxid. Med. Cell. Longev. 2014 (2014) 875861.
[25] Y. Kassogue, H. Dehbi, M. Quachouh, A. Quessar, S. Benchekroun, S. Nadifi, Association of glutathione S-transferase (GSTM1 and GSTT1) genes with chronic myeloid leukemia, Springerplus 4 (2015) 210.
[26] G. Bhat, A. Bhat, A. Wani, N. Sadiq, S. Jeelani, R. Kaur, A. Masood, B. Ganai, Polymorphic variation in glutathione-S-transferase genes and risk of chronic myeloid leukaemia in the Kashmiri population, Asian Pac. J. Cancer Prev. 13 (2012) 69–73.
[27] F.A. de Lima Marson, C.S. Bertuzzo, R. Secolin, A.F. Ribeiro, J.D. Ribeiro, Genetic interaction of GSH metabolic pathway genes in cystic fibrosis, BMC Med. Genet. 14 (2013) 14–60.
[28] H.P. Gschwind, U. Pfaar, F. Waldmeier, M. Zollinger, C. Sayer, P. Zbinden, M. Hayes, R. Pokorny, M. Seiberling, M. Ben-Am, B. Peng, G. Gross, Metabolism and disposition of imatinib mesylate in healthy volunteers, Drug Metab. Dispos. 33 (2005) 1503–1512.
[29] C.C. McIlwain, D.M. Townsend, K.D. Tew, Glutathione S-transferase polymorphisms: cancer incidence and therapy, Oncogene 25 (2006) 1639–1648.
[30] K.D. Tew, D.M. Townsend, Glutathione-S-transferases as determinants of cell survival and death, Antioxid. Redox Signal. 17 (2012) 1728–1737.
[31] A. Sau, G. Filomeni, S. Pezzola, S. D'Aguanno, F.P. Tregno, A. Urbani, M. Serra, M. Pasello, P. Picci, G. Federici, A.M. Caccuri, Targeting GSTP 1-1 induces JNK activation and leads to apoptosis in cisplatin-sensitive and–resistant human osteosarcoma cell lines, Mol. Biosyst. 8 (2012) 994–1006.
[32] Z. Yin, V.N. Ivanov, H. Habelhah, K. Tew, Z. Ronai, Glutathione S-transferase p elicits protection against H2O2- induced cell death via coordinated regulation of stress kinases, Cancer Res. 60 (2000) 4053–4057.
[33] S.G. Cho, Y.H. Lee, H.S. Park, K. Ryoo, K.W. Kang, J. Park, S.J. Eom, M.J. Kim, T.S. Chang, S.Y. Choi, J. Shim, Y. Kim, M.S. Dong, M.J. Lee, S.G. Kim, H. Ichijo, E.J. Choi, Glutathione Stransferase mu modulates the stress-activated signals by suppressing apoptosis signal-regulating kinase 1, J. Biol. Chem. 276 (2001) 12749–12755.