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RESEARCH ARTICLE

Association of *GSTM1*, *GSTT1* and *GSTP1* Ile105Val polymorphisms with clinical response to imatinib mesylate treatment among Malaysian chronic myeloid leukaemia patients

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Abstract. The detoxifying activity of glutathione *S*-transferases (GST) enzymes not only protect cells from the adverse effects of xenobiotics, but also alters the effectiveness of drugs in cancer cells, resulting in toxicity or drug resistance. In this study, we aimed to evaluate the association of *GSTM1*, *GSTT1* and *GSTP1* Ile105Val polymorphisms with treatment response among Malaysian chronic myeloid leukaemia (CML) patients who everyday undergo 400 mg of imatinib mesylate (IM) therapy. Multiplex polymerase chain reaction (multiplex-PCR) was performed to detect *GSTM1* and *GSTT1* polymorphisms simultaneously and polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis was conducted to detect the *GSTP1* Ile195Val polymorphism. On evaluating the association of the variant genotype with treatment outcome, heterozygous variant (AG) and homozygous variant (GG) of *GSTP1* Ile105Val showed significantly a higher risk for the development of resistance to IM with OR: 1.951 (95% CI: 1.186–3.209, $P = 0.009$) and OR: 3.540 (95% CI: 1.305–9.606, $P = 0.013$), respectively. Likewise, *GSTT1* null genotype was also associated with a significantly higher risk for the development of resistance to IM with OR = 1.664 (95% CI: 1.011–2.739, $P = 0.045$). Our results indicate the potential usefulness of GST polymorphism genotyping in predicting the IM treatment response among CML patients.

Keywords. *GSTM1*; *GSTT1*; *GSTP1*; chronic myeloid leukaemia; imatinib mesylate; single-nucleotide polymorphism.

Introduction

Chronic myeloid leukaemia (CML) accounts for 20% of all cases of leukaemia (Baccarani *et al.* 2015). This clonal myeloproliferative disorder (Karkucak *et al.* 2012) is characterized by the increased levels of leukocytes, splenomegaly, myeloid hyperplasia in bone marrow and also increased levels of mature myeloid cells in peripheral blood (Sawyers 1999; Kabarowski and Witte 2000; O'Dwyer *et al.* 2002). In CML, a breakpoint cluster region-Abelson (BCR-ABL) oncogene with markedly increased tyrosine kinase activity is generated from the Philadelphia (Ph) chromosome translocation t(9;22)(q34;q11). An increasing knowledge and advancement of technology in understanding the abnormal activity of the BCR-ABL protein had led to the designing and emergence of targeted therapies such as tyrosine kinase inhibitors (TKIs) for Ph chromosome positive CML. Imatinib mesylate (IM) is the first used molecularly targeted TKI drug (Druker *et al.* 1996) and still remains the gold standard for CML treatment. Despite having shown to produce superior results, up to 33% of CML patients develop resistance to IM. Apart from mutations and amplifications of the BCR-ABL gene, also pharmacokinetic variability accounts for development of drug resistance among patients. It is now becoming increasingly clear that variations in genes involved in transport, binding and metabolism of IM affect the pharmacokinetics of drugs and may be important determinants of pharmacokinetic variability.

The xenobiotic metabolizing enzymes play important role in the metabolism of drugs including chemotherapeutic drugs. Many of these enzymes are genetically polymorphic. Polymorphisms in genes encoding drug metabolizing enzymes can vary in their enzymatic activity and can play important role in pharmacokinetic variability, potentially modifying treatment response and resistance or drug-related toxicity (Weinshilboum 2003). Glutathione *S*-tranferases (GSTs) are one of the phase II drug metabolizing enzymes super family, which are ubiquitous, multifunctional and play an important role in cellular detoxification, and also in protecting macromolecules from being attacked by the reactive electrophiles (Strange *et al.* 2001). Of the eight classes of GSTs, the most commonly studied genes are *GSTM, GSTT* and *GSTP* and several types of allelic variations are identified in them. Polymorphisms occurring within these genes are associated with an increased risk of cancer and diverse response to treatment (Zmorzyński *et al.* 2015).

GSTμ (GSTM) subfamily coded by 100-kb gene cluster is located on chromosome 1p13.3 and arranged in the order of 5′-GSTM4-GSTM2-GSTM1-GSTM5-GSTM3-3′ (Pearson *et al.* 1993; Landi 2000). *GSTM1* consists of eight exons, size range from 36 to 112 bp, whereas introns vary from 87 to 2641 bp (Parl 2005). *GSTM1* is embedded and flanked in between two identical 4.2 kb regions with extensive homologies. *GSTM1* null allele emerges by homologous recombination of 4.2 kb repeats on right and left of *GSTM1* gene, resulting in deletion of 16 kb region containing whole sequence of *GSTM1*. Deletion commonly involves both the alleles resulting in *GSTM1*−/− and can be technically assessed by PCR assay which will be characterized as null genotype or *GSTM1*−/− when PCR product is absent.

There are two genes (*GSTT1* and *GSTT2*) existing in theta-class GST gene cluster (GSTθ) subfamily, separated by about 50 kb, located on chromosome 22q11.2 (Coggan *et al.* 1998; Whittington *et al.* 1999; Landi 2000). The *GSTT1* has five exons with size range from 88 to 195 bp and introns with size range from 205 to 2363 bp (Parl 2005). The *GSTT1* is present in a region between two 18 kb extensive homology, which has more than 90% homologies called HA3 and HA5. HA3 and HA5 share 100% identity of 403-bp sequence. Null deletion of *GSTT1* emerges from the homologous recombination of 403 bp repeats on the left and right of *GSTT1*, which result in 54-kb deletion of whole sequence of *GSTT1*. This null deletion involves only *GSTT1* and does not include *GSTT2* (Coggan *et al.* 1998).

Glutathione *S*-transferase P1 (*GSTP1*) which belongs to the pi (π) class gene family, is located on chromosome 11q13 (Autrup 2000), spans ~2.48 kb and consists of seven exons (Morrow *et al.* 1989; Bora *et al.* 1997). Two polymorphisms are reported and identified in this gene. The first one is A–G polymorphism in exon 5 at nucleotide 313. This polymorphism leads to substitution of amino acid isoleucine (Ile) by valine (Val) at amino acid position 105 (Ile105Val) (Ali-Osman *et al.* 1997; Watson *et al.* 1998; Sailaja *et al.* 2010). The other polymorphism of this gene is C–T transition at nucleotide 341, which leads to amino acid substitution of alanine by valine at codon 114 in exon 6 (Ala114Val) (Ali-Osman *et al.* 1997; Hayes *et al.* 2005; McIlwain *et al.* 2006).

Genetic variations may result in a decreased intracellular enzyme concentration, a dysfunctional protein and may also alter the structure of enzyme, which later leads to changes in the function of the enzyme. Therefore, polymorphisms that decrease the activity of GSTs are associated with an increased risk of cancer development and may also be associated with the phenomenon of drug resistance (Traverso *et al.* 2013). It was hypothesized that polymorphisms in *GSTM1*, *GSTT1* and *GSTP1* may be involved in variation of IM metabolism and thus, contributing to interindividual variation of IM response in CML patients. The current study was designed to test the above hypothesis.

Materials and methods

Subject recruitment

In the present study, 278 CML patients (including 132 IM good responders and 146 IM resistant) were successfully recruited from few hospitals in Malaysia which includes Hospital Universiti Sains Malaysia (HUSM), Universiti Kebangsaan Malaysia Medical Centre (PPUKM), Sime Darby Medical Centre, Hospital Raja Perempuan Zainab II (HRPZII) Kota Bharu, Hospital Pulau Pinang, Penang, Hospital Raja Permaisuri Bainun, Ipoh and Hospital Umum Sarawak (HUS) and Miri. Only Philadelphia (Ph) chromosome positive CML patients who were treated with 400 mg IM for at least 12 months and were negative for BCR-ABL mutation and amplification were recruited. This study was initiated after getting ethical approval from Research and Ethics Committee of Universiti Sains Malaysia (ethical numbers USMKK/PPP/JEPeM [244.3.(4)] and USMKK/PPP/JEPeM [264.3.(8)]) and Ministry of Health Malaysia (NMRR-10-1207-7183).

Multiplex-PCR analysis for detection of GSTM1 and GSTT1 null deletion

Three millilitres of peripheral blood was collected from study subjects (CML patients) after getting their written informed consent. Genomic DNA was extracted using commercialized kit, QIAGEN QIAamp DNA Blood Mini kit (Qiagen, Hilden, Germany), followed by amplification of targeted gene. Multiplex polymerase chain reaction (multiple-PCR) was used for the detection of null allele in both *GSTM1* and *GSTT1* simultaneously. Three pairs of primers were used simultaneously in which *β-globin* served as a control (table 1). PCR mixture was prepared

Table 1. Primer sequences for multiplex PCR reaction.

Gene	Primer sequence	Primer length (bp)	Product size (bp)	References
GSTT1	F: 5′-TTCCTTACTGGTCCTCACATCTC-3′	23	459	Shahpudin *et al.* (2011)
	R: 5′-TCACCGGATCATGGCCAGCA-3′	20		
GSTM1	F: 5′-GAACTCCCTGAAAAGCTAAAGC-3′	22	219	Ateş *et al.* (2005)
	R: 5′-GTTGGGCTCAAATATACGGTGG-3′	22		
β-GLOBIN	F: 5′-CAACTTCATCCACGTTCACC-3′	20	260	Ateş *et al.* (2005)
	R: 5′-GAAGAGCCAAGGACAGGTAC-3′	20		

in total volume of 20 μL including 2× HotStarTaq *Plus* Master Mix, 0.1 μM of each forward and reverse primers for *GSTM1*, *GSTT1* and *β-globin*, RNase-free water and DNA template. Conditions used for multiplex-PCR were initial denaturation at 95°C for 5 min, followed by 30 cycles of the following steps: denaturation at 94°C for 1 min, annealing at 55.5°C for 1 min and extension at 72°C for 1 min and final extension at 72°C for 10 min. To determine the success of PCR analysis, 3% agarose gel was used. Null deletion was detected when no band appeared at specific region.

Genotyping of GSTP1 polymorphism (Ile105Val)

Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used in amplification and detection of *GSTP1* polymorphism. One set of primers were used to amplify 433 bp targeted gene which were 5′-GTAGTTTGCCCAAGGTCAAG-3′ (forward) and 5′-AGCCACCTGAGGGGTAAG-3′ (reverse). PCR mixture was prepared in a total of 25 μL which consisted of 1× PCR buffer, 1 μM of $MgCl_2$, 0.22 μM of dNTPs, 0.4 μM of each primers, 1 U of Go*Taq* DNA polymerase and deionized water. PCR cycles consisted of an initial denaturation at 95°C for 2 min, followed by 30 cycles of 3 steps: denaturation at 94°C, annealing at 57°C and extension at 72°C for 45 s each respectively, and final extension of 72°C for 5 min. PCR product was electrophoresed on 2% agarose gel to check the success of amplification. PCR products of all samples were cut using *Bsm*BI enzyme with incubation period for 1 h at 55°C. The outcome of RFLP analysis was observed in presence of three different band sizes 433, 327 and 106 bp on 3% agarose gel. A homozygous wild type produced only one band at 433 bp, a heterozygous variant produced three bands at 433, 327 and 106 bp and a homozygous variant produced two bands at 327 and 106 bp.

Following the genotyping, a few samples from each of different genotype category were randomly selected for direct sequencing to confirm that the designed primers amplified the correct targeted sequence of the candidate gene. Samples were sent to the commercial company, First BASE Laboratories Sendirian Berhad (Kuala Lumpur, Malaysia).

Statistical analysis

The genotype frequencies of the studied single-nucleotide polymorphisms (SNPs) were determined. The difference in genotype frequencies of the SNPs between IM good responders and IM resistant group of CML patients were compared using the χ^2 test. The association of genotypes with CML response was determined using the binary logistic regression analysis and deriving odds ratio (OR) with 95% confidence interval (CI). Statistical tests were two-sided and $P < 0.05$ was considered as statistically significant.

Results

In this study, we successfully recruited 278 CML patients (132 IM good responders and 146 IM resistant) who were undergoing imatinib mesylate treatment. Mutiplex-PCR was able to successfully amplify the three pairs of primers for detection of null (deletion) genotypes of *GSTM1* and *GSTT1* (figure 1). PCR-RFLP performed using *Bsm*BI enzyme correctly cut the targeted region on sequence of *GSTP1* as shown in figure 2.

The distribution of genotype frequencies of the SNPs studied among the two groups of CML patients are provided in table 2. Frequency of *GSTM1* wild-type genotype was higher in good response group as compared to resistant group, whereas null genotype was higher in resistant group as compared to response group, but was not statistically significant. *GSTT1* wild type was significantly higher in good response as compared to resistant group. In contrast, null genotype of *GSTT1* was significantly higher in resistant group as compared to response group. For *GSTP1*, our results showed that AA (Ile) genotype was significantly higher in IM good responders as compared to the IM resistant CML patients (58.3% versus 39.7%; $P = 0.002$). However, heterozygous variant (AG) and homozygous variant (GG) genotypes were significantly higher, 49.3 and 11.0% in IM resistant CML patients, respectively, as compared to the IM good responders, which were 37.1 and 4.6%, respectively.

The results on the association of polymorphic genotypes with IM response are provided in table 2. Although,

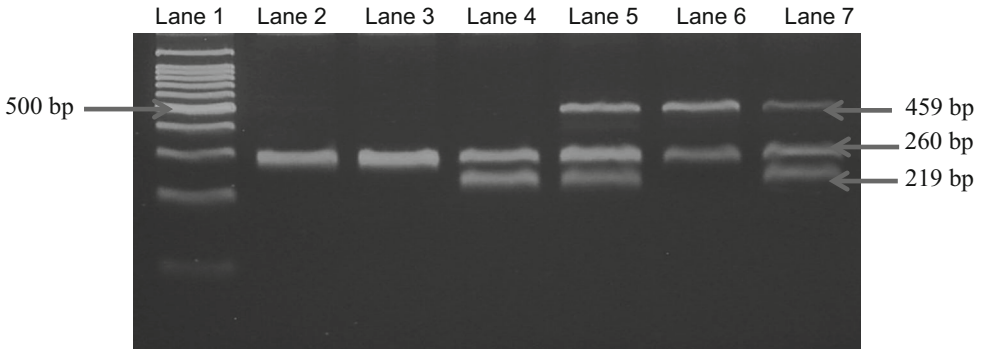

Figure 1. Gel electrophoresis picture showing multiplex-PCR analysis of *GSTT1* and *GSTM1*. Lane 1 represents 100 bp ladder. Lanes 2 and 3 show only one band present at 260 bp (represent deletion of *GSTT1* and *GSTM1*). Lane 4 shows two bands present at 260 bp for *β-globin* and 219 bp for *GSTM1* (indicates deletion of *GSTT1*). Lanes 5 and 7 show presence of three bands at 459 (*GSTT1*), 260 (*β-globin*) and 219 bp (*GSTM1*), representing presence of both genes. Lane 6 shows presence of two bands at 459 (*GSTT1*) and 260 bp (*β-globin*) indicating deletion of *GSTM1*.

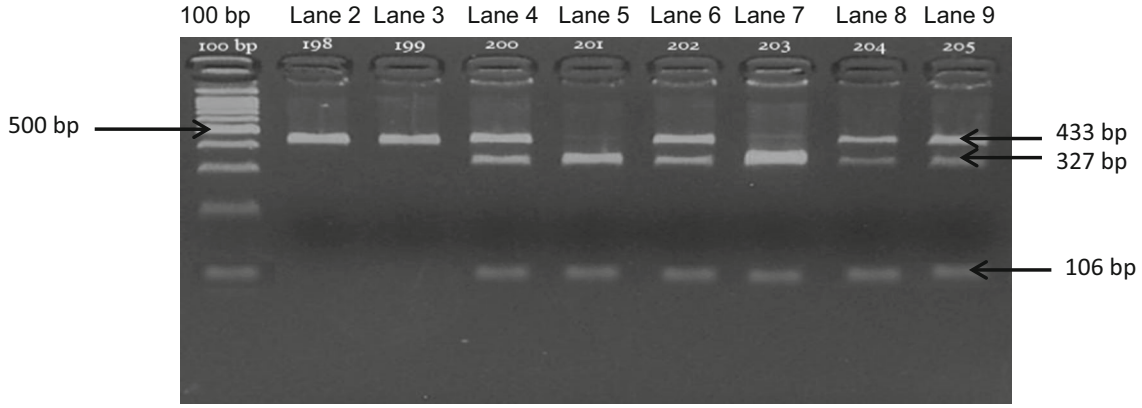

Figure 2. Gel electrophoresis picture showing RFLP analysis of *GSTP1*. Lane 1 represents 100 bp ladder. Lanes 2 and 3 show homozygous wild type (AA); lanes 4, 6, 8 and 9 show heterozygous variant (AG) and lanes 5 and 7 show homozygous variant (GG).

Table 2. Genotype frequencies and risk association of *GSTM1*, *GSTT1* and *GSTP1* Ile105Val polymorphism with IM response in CML patients.

Genotypes	Resistance ($n = 146$) (%)	Good response ($n = 132$) (%)	P *	OR	95% CI	P #
GSTM1						
Present	57 (39.0)	45 (34.1)	0.392	1.000	Reference	–
Null	89 (61.0)	87 (65.9)		0.808	0.495–1.318	0.393
GSTT1						
Present	86 (58.9)	93 (70.5)	**0.044**	1.000	Reference	–
Null	60 (41.1)	39 (29.5)		1.664	1.011–2.739	**0.045**
GSTP1						
Ile/Ile	58 (39.7)	77 (58.3)	**0.002**	1.000	Reference	–
Ile/Val	72 (49.3)	49 (37.1)	**0.041**	1.951	1.186–3.209	**0.009**
Val/Val	16 (11.0)	6 (4.6)	**0.048**	3.540	1.305–9.606	**0.013**

P value < 0.005 (statistically significant) are in bold; OR, odds ratio; CI, confidence interval; #' simple logistic regression.

GSTM1 null genotype showed lower risk for the development of IM resistance, it was statistically not significant (OR: 0.808, 95% CI: 0.495–1.318, $P = 0.393$). On the contrary, *GSTT1* showed significantly higher risk for development of IM resistance with OR value 1.664 (95% CI: 1.011–2.739, $P = 0.045$). Regarding the association of *GSTP1* Ile105Val with development of resistance to IM, heterozygous variant showed 1.951-fold higher risk for resistance development (95% CI: 1.186–3.209, $P = 0.009$) and homozygous variant showed 3.540-fold higher risk for

Table 3. Risk association of combined genotype of *GSTM1*, *GSTT1* and *GSTP1* polymorphisms with IM response in CML patients.

Combined genotypes		Resistance ($n = 146$) (%)	Good response ($n = 132$) (%)	OR	95% CI	*P*
GSTM1	*GSTT1*					
Present	Present	36 (24.7)	33 (25.0)	–	–	–
Null	Null	39 (26.7)	27 (20.5)	1.324	0.670–2.616	0.419
Present	Null	21 (14.4)	12 (9.1)	1.604	0.684–3.761	0.277
Null	Present	50 (34.2)	60 (45.4)	0.764	0.418–1.396	0.382
GSTM1	*GSTP1*					
M1(+/+)	Ile/Ile	28 (19.2)	23 (17.4)	–	–	–
M1(+/+)	Ile/Val	23 (15.8)	17 (12.9)	1.111	0.482 – 2.561	0.804
M1(+/+)	Val/Val	6 (4.1)	5 (3.8)	0.986	0.266 – 3.649	0.983
M1(−/−)	Ile/Ile	29 (19.9)	53 (40.1)	**0.449**	**0.220–0.917**	**0.028***
M1(−/−)	Ile/Val	50 (34.2)	33 (25.0)	1.245	0.615–2.520	0.543
M1(−/−)	Val/Val	10 (6.8)	1 (0.8)	8.214	0.978–69.007	0.052
GSTT1	***GSTP1***					
T1(+/+)	Ile/Ile	49 (37.1)	38 (26.0)	–	–	–
T1(+/+)	Ile/Val	40 (30.3)	40 (27.4)	1.289	0.701–2.372	0.414
T1(+/+)	Val/Val	4 (3.0)	7 (4.8)	2.257	0.615–8.276	0.220
T1(−/−)	Ile/Ile	27 (20.5)	20 (13.7)	0.955	0.466–1.956	0.900
T1(−/−)	Ile/Val	10 (7.6)	32 (21.9)	**4.126**	**1.805–9.433**	**0.001***
T1(−/−)	Val/Val	2 (1.5)	9 (6.2)	**5.803**	**1.184–28.445**	**0.030***

$P > 0.05$ (statistically not significant); OR, odds ratio; CI, confidence interval.
* P value < 0.005 (statistically significant) and are in bold.

development of resistance to IM (95% CI: 1.305–9.606, $P = 0.013$).

Polymorphisms which did not show a significant association with IM response when acting individually, an association could still be possible when the genotypes of these different polymorphisms are combined. Thus, we investigated the combination of *GSTM1* versus *GSTT1*, *GSTM1* versus *GSTP1* and *GSTT1* versus *GSTP1* and their association with IM response and the results are presented in table 3. Combination of both *GSTM1* and *GSTT1* deleted genes (*GSTM1* and *GSTT1* null genotypes) and combination of *GSTM1* present and *GSTT1* null genotypes showed higher OR values indicating higher risk for development of IM resistance, but the values were statistically not significant ($P = 0.419$ and 0.277). Similarly, combination of null *GSTT1* versus *GSTP1* Ile/Val and null *GSTT1* versus *GSTP1* Val/Val showed significantly higher OR value (OR values of 4.126 and 5.803), which represent higher risk for IM resistance development for carriers of these combination genotypes. In contrast, combination of null *GSTM1* versus *GSTP1* Ile/Ile showed lower OR value, thereby indicating a protective role in IM resistance development for carriers of such genotype combinations.

Discussion

Drug metabolizing enzymes are involved in the activation and/or detoxification of cytotoxic drugs. Genetic variation in genes encoding the drug metabolizing enzymes could explain interpatient variability in drug response, and could be crucial and basal determinants for treatment response assessment. Polymorphisms can result in lack of enzymatic activity and reduced detoxification role for GSTs. Few studies have reported associations of GST polymorphisms with the efficacy and toxicity of cancer chemotherapy and have also been implicated in resistance to some anticancer drugs (Tew 1994; Hayes and Strange 1995; Ban *et al.* 1996). However, reports on the association of polymorphisms in GSTs with response to IM are limited. To the best of our knowledge, this is the first study to determine the association of genetic variations in *GSTP1*, null deletion in both *GSTM1* and *GSTT1* with clinical response to IM in CML patients from Malaysia.

The present study evaluated the association of genetic variation in *GSTM1* and *GSTT1* with IM treatment outcome. Both *GSTM1* and *GSTT1* showed higher frequency of wild-type genotype in IM response group, whereas the frequency of null genotype was higher among IM resistant group of CML patients. However, the difference in frequency of *GSTM1* was statistically not significant between the two groups, whereas *GSTT1* frequency showed significant difference between the two groups (IM resistant group and IM good response group). Regarding the susceptibility to IM failure, *GSTT1* null deletion genotype showed 1.6-fold higher risk in development of resistance to IM. This result was concurrent with a study by Ovsepyan *et al.* (2014) among Russian CML patients. Ovsepyan *et al.* (2014) found that carriers of null deletion of *GSTT1* genotype showed 3.3-fold higher risk in failure of achieving cytogenetic response with 95% CI: 0.7–14.47 with $P = 0.013$.

The risk of IM treatment failure for those with combined carriership of deletion of *GSTT1* and *GSTM1* was also

evaluated. Our study found that carriers of null genotypes of both *GSTT1* and *GSTM1* were higher in IM resistant group as compared to those with good response group, with higher OR values although statistically not significant. This result was concurrent with the result reported by Ovsepyan *et al.* (2014). In the present study, lack of statistical significance may be attributed to the small sample size. According to Ovsepyan *et al.* (2014), the high risk in failure of high cytogenetic response (HCR) after 12 months of imatinib therapy among carriers of *GSTM1* and *GSTT1* null deletion genotypes could be due to higher incidence in mutations of tumour cells because of less deactivation of exogenous and endogenous genotoxicants, which then lead to promoting the emergence of resistant clones insensitive to imatinib therapy in a daily dose of 400 mg (Ovsepyan *et al.* 2014). Thus, combined carriership of null deletion of *GSTM1* and *GSTT1* has been implicated as a risk factor for CML progression which then leads to failure of imatinib therapy. This result also highlights the probable significance of gene–gene interactions for the risk of CML progression.

In this present study, frequency of heterozygous variant (AG) of *GSTP1* was significantly higher in IM resistant group as compared to the IM good response group with P value = 0.041. In addition, homozygous variant (GG) also showed elevation in frequency of IM resistant group as compared to the IM good response group with P value = 0.048. We also evaluated the association of genotype pattern of *GSTP1* Ile105Val with response to imatinib mesylate and found that carriage of heterozygous variant and homozygous variant genotypes were associated with higher risk for development of resistance towards IM with OR 1.951 (95% CI: 1.186–3.209, P = 0.009) and OR 3.540 (95% CI: 1.305–9.606, P = 0.013), respectively. Among Indian CML patients, Sailaja *et al.* (2010) also had shown results in response to IM in terms of haematological response which indicated elevation in frequency of combined genotypes in cytogenetic poor (41.6%) and minor (53.7%) responders as compared to major (38.51%) responders. Sailaja *et al.* (2010) suggested that *GSTP1* Ile105Val polymorphism with reduced *GSTP1* enzyme activity might induce abundance of intermediate metabolites in the body and initiate additional mutation which delays response rates towards treatment and also favours disease progression.

In addition, we also determined the risk of IM treatment failure for combination of *GSTP1* Ile105Val genotype with *GSTM1* deletion, as well as *GSTT1* deletion to strengthen the finding of this study. In the *GSTM1* null and *GSTP1* genotype combination analysis, the *GSTM1* null / *GSTP1* Ile105Ile genotypes combination showed significant lower risk for development of resistance to IM with P value of 0.028. However, when association of combination genotype of *GSTT1* and *GSTP1* with IM response was assessed, higher risk to IM resistance development was observed among carriers of *GSTT1* null / *GSTP1* Ile105Val and *GSTT1* null / *GSTP1* Val105Val combination genotypes and the associations were statistically significant. We could not compare our data with other reports as no other reports are available on combination genotype analysis.

Due to the dual role of activation and detoxification, the specific mechanism through which GSTs modify the response to IM treatment cannot be explained accurately. According to Traverso *et al*. (2013), GSTs can combine with mitogen-activated protein kinases (MAP/MAPK) (Traverso *et al.* 2013). As a result of this, apoptosis-inducing MAP kinases are blocked and cannot be activated by compounds with anticancer properties. However, the interplay of genetic and cellular environment factors cannot be underestimated, while exploring the clinical impact of GST in IM therapy and this remains an issue to be explored.

In conclusion, the present study showed that CML patients with carriage of heterozygous and homozygous variant genotypes of *GSTP1* Ile105Val and *GSTT1* null, have a higher risk for development of resistance to IM. Hence, genetic variation in GST super family genes could be considered as pharmacogenetic markers to predict the treatment outcome for imatinib mesylate among CML patients.

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