Role of Antioxidant Gene Polymorphisms in Risk and Prognosis of Chronic Myeloid Leukemia

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Abstract

Introduction: We aimed to investigate the possible role of antioxidant enzyme polymorphisms CAT -21A/T (rs7943316), CAT -262C/T (rs1001179), GPX1 -198C/T (rs1050450), MPO -463G/A (rs2333227), GSTM1 (rs366631) & GSTT1 (rs17856199) with susceptibility to chronic myeloid leukemia (CML) and their association with tyrosine kinase inhibitor (TKI, imatinib) response. Methods: Six single nucleotide polymorphisms (SNPs) in antioxidant enzyme genes were genotyped in a total of 325 samples, of which 125 were from CML patients and 200 from healthy controls. The SNPs were correlated with various confounding variables like BCR-ABL1 levels and tyrosine kinase domain mutation status in CML patients. Results: Genotyping results revealed statistically significant associations with CAT-21A/T (p=0.037) and GPX1 -198C/T (p=<0.0001) polymorphisms with risk of CML. No associations were observed between CAT-262C/T, MPO -463G/A, GSTM1 & GSTT1 polymorphisms and CML. The CAT-21A/T polymorphism conferred 2.95 folds increased risk of CML under co-dominant model (p=0.024) and 2.51 folds risk under dominant models (p=0.05). In addition, the haplotypes of CAT-21A/T and -262C/T polymorphisms, ATCC and ATCT conferred higher incidence of CML risk by 2.67 times (p=0.05) and 2.99 times (p=0.045). The GPX1 -198C/T polymorphism conferred significantly increased risk of CML under co-dominant model [CC vs CT (p=<0.0001), CC vs TT (p=<0.0001)] and dominant models [CC vs CT+TT (p=<0.0001)]. The heterozygous GPX1 CT genotype frequency significantly elevated in poor molecular responders (p=0.005) and TKD mutation carriers (p=0.114) as compared to respective groups. Conclusions: Our results suggest that the reduced activity of antioxidant enzymes caused by the CAT-21A/T and GPX1-198C/T polymorphisms might contribute to increased risk of CML. In addition, the GPX1-198C/T polymorphism was associated with poor molecular response and acquired TKD mutations. Hence, the present study indicates that defective antioxidant defense system might have a strong influence on CML susceptibility and TKI (imatinib) response through oxidative stress.

Keywords: Chronic Myeloid leukemia- Imatinib- Resistance- Antioxidant genes- polymorphism
malignancies [6-9]. Antioxidant enzymes such as catalase (CAT), manganese superoxide dismutase (MnSOD), glutathione peroxidase 1 (GPX1), myeloperoxidase (MPO) and glutathione-S-transferases (GSTs) balance ROS levels and defend cells against oxidative stress. Most of these antioxidant enzymes are highly polymorphic. Genetic variations of these antioxidant enzymes with altered enzymatic activity may contribute to the imbalance of ROS production and scavenging [10-11]. The activity of several antioxidant enzymes was noted to be reduced in CML patients [12]. Several studies demonstrated that polymorphisms in antioxidant enzymes (CAT, MnSOD, GPX1, MPO & GSTs) might be associated with susceptibility to various solid tumors [13-15] and hematological malignancies [16-20].

Hence, the present study aimed to investigate the possible role of polymorphisms in antioxidant enzyme polymorphisms: Catalase (CAT) -21A/T & -262C/T, Glutathione peroxidase 1 (GPX1) -198C/T, Myeloperoxidase (MPO) -463G/A, deletion of Glutathione S-Transferase M1 & T1 (GSTM1 & GSTT1) with susceptibility to chronic myeloid leukemia and their association with TKI (imatinib) response.

Materials and Methods

The present study included 325 samples, out of which 125 are from CML patients and 200 were from age & gender matched controls without a family history of any cancer. The inclusion criteria for patients included Ph+ve CML cases with confirmed diagnosis, on TKI treatment and TKI refractory cases regardless of age, gender or race. The study was approved by the institutional ethics committee and an informed consent was obtained from patients participating in the study. Blood samples (6mL in EDTA vacutainer) were collected from both CML patients and controls. Genomic DNA was extracted from blood samples using non-enzymatic rapid salting-out method. The purity & concentration of DNA samples were checked on Nanodrop1000 and further these DNA samples were subjected for analysis of SNPs in antioxidant enzyme genes.

Genotyping of antioxidant gene SNPs

Genotyping of CAT-21A/T (rs7943316), CAT-262C/T (rs1001179), GPX1 (-198C/T rs1050450) and MPO (-463G/A rs2333227) was performed by PCR-RFLP (polymerase chain reaction - restriction fragment length polymorphism) method. The null/deletion polymorphism in GSTM1 & GSTT1 genes (rs366631 & rs17856199) were performed by multiplex polymerase chain reaction followed by agarose gel electrophoresis. The primers used for amplification and restriction enzymes for RFLP analysis are listed in Table 1. The CAT-21A/T & -262C/T, GPX1 (-198C/T) and MPO (-463G/A) polymorphism were determined by digesting the PCR amplified products with HinfI, Smal, Apad and SstII restriction enzymes (Table 1).

Statistical analysis

Chi square and multivariate analysis tests were calculated to test the significance of genotype association with the occurrence of CML and its prognosis. All the p values were two sided and the level of significance was taken as p < 0.05. Statistical analyses were performed using the GraphPad Prism software version 6.0 (San Diego, CA) and online VassarStats software. Haplotype and pairwise linkage disequilibrium was calculated using Haplovie version 4.2 and cox regression analysis by SPSS version 22 software.

Results

Baseline characteristics (Table 2)

The demographic and clinical characteristics of CML patients are presented in Table 2. The median age at diagnosis of CML was 42 years (range 12 to 89 years) and a male preponderance was observed with a male to female ratio of 1.6:1. Of the 125 patients, 102 cases presented in chronic phase, 13 in accelerated phase and 10 in blast crisis phase of CML.

Prognostic scores like Sokal, Hasford, and EUTOS (European Treatment Outcome Study) were calculated for all patients using baseline hematological variables [21]. With Sokal risk scoring, 37.6% of patients had low risk and 62.4% had intermediate + high risk. With respect to Hasford risk score, 39.2% had low risk and 60.80% had intermediate + high risk. When EUTOS risk scores were considered, 72.0% of patients were presented with low risk and 28% with high EUTOS risk. Majority of patients were on imatinib (IM) treatment, nearly 42.4% of patients received higher IM doses (600mg/ 800mg), 16.8% on IM standard dose (400mg), 16.0% on other drugs (2nd generation TKIs or on clinical trials), 16.8% deceased and 8% are newly diagnosed.

Median follow-up of these patients for a period of 40 median months revealed that 20.8% had optimal response to imatinib and 79.02% of patients lost response which might be either due to loss of complete hematological response (CHR), complete cytogentic response (CCyR), major molecular response (MMR) or presence of TKD mutations.

Correlation with CAT-21A/T polymorphism (Table 3)

The CAT-21A/T genotyping results revealed that heterozygous AT genotype frequency was observed to be significantly increased in CML patients compared to controls (p=0.037). This polymorphism was significantly associated with increased risk of CML. With respect to molecular response, homozygous TT genotype and T allele frequencies were elevated in non-responders i.e., patients having higher BCR-ABL1 expression levels (44.70%, 0.705) compared to responders i.e., patients having lower levels (35.0%, 0.625) (p=0.259). Heterozygous AT genotype frequency was found to be slightly increased in TKD mutation carriers (p=0.571) and in deceased group of patients (p=0.548) when compared to respective groups. No differences were found with either of the prognostic risk scores: Sokal, Hasford or EUTOS.

The CAT-21A/T polymorphism showed statistically significant association with risk of CML and conferred
Table 1. Primer Sequences used for Analysis of Polymorphisms in Anti oxidant Enzyme Genes

| Gene | SNP | Primer sequence | Product size | Restriction enzyme |
|------|-----|-----------------|--------------|-------------------|
| CAT  | -21A/T | 5'- AATCAGAAGGCACTCCTCCC-3' | 250bp | HinfI |
|      | (rs7943316) | 5'- TCCTGAGGACACAGTGTAAC-3' | 185bp | SmaI |
| CAT  | -262C/T | 5'- AGAGCCCTGCCCAGCCGGCACG-3' | 222bp | Apal |
|      | (rs1001179) | 5'- TAAGAGCTGAGAAAGCATAGCT-3' | 350bp | SstI |
| GPX  | -198C/T | 5'- TCCAGACCATTGACATCGAG-3' | 299bp | |
|      | (rs1050450) | 5'- AATCAGAAGGCAGTCCTCCC-3' | 219bp | |
| MPO  | -463G/A | 5'- CGGTATAGGCAACAATGGTGAG-3' | 480bp | |
|      | (rs2333227) | 5'- TAAGAGCTGAGAAAGCATAGCT-3' | 350bp | |
| GSTM1| Deletion | 5'- GAACCTCCTGAAAGCTGTAACG-3' | 219bp | |
|      | (rs366631) | 5'- GACTCCTGAAAGCTGTAACG-3' | 219bp | |
| GSTT1| Deletion | 5'- TCCAGACCATTGACATCGAG-3' | 480bp | |
|      | (rs17856199) | 5'- TAAGAGCTGAGAAAGCATAGCT-3' | 350bp | |
| Beta globin | | 5'- ACACAACTGTGTTCACTAGC-3' | 299bp | |

Haplotype analysis of the CAT gene (Table 6)

The haplotype analysis of the CAT gene polymorphisms (-21A/T and -262C/T) were performed and represented in Table 6. The haplotypes ATCC and ATCT conferred higher incidence of CML risk by 2.67 times (OR=2.678, 95% CI: 1.058-5.992, p=0.05), whereas overdominant model (AT vs AA+TT) was found to be protective against CML (OR=0.632, 95% CI: 0.404-0.994, p=0.060) (Table 4).

Correlation with CAT -262C/T polymorphism (Table 5)

There was no significant difference observed between cases and controls (p=0.711), molecular response (p=0.865) and presence or absence of TKD mutations (p=0.708) with CAT-262C/T polymorphism. This polymorphism was not associated with risk of CML. Whereas the homozygous CC genotype and C allele frequencies were found to be elevated in the deceased group (71.42%, 0.857) compared to those patients on follow-up (50.0%; 0.711) (p=0.139). The prognostic risk scores were not associated with this polymorphism.

Correlation with MPO -463G/A polymorphism (Table 9)

The MPO -463G/A polymorphism demonstrated no significant association between cases and controls (p=0.494), nor with either of the confounding variables like molecular response (p=0.465), TKD mutation status (p=0.392), present status (p=0.767) and prognostic risk scores.

Correlation with GSTM1 & GSTT1 null/deletion polymorphism (Table 10)

No significant association observed with GSTM1 null polymorphism between cases and controls, molecular response, presence or absence of TKD mutations. Whereas GSTM1 presence genotype (M1) was found to be elevated in deceased group (80.95%) compared to those on follow-up (66.34%) (p=0.392), present status (p=0.767) and prognostic risk scores.

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Haplotype, Linkage Disequilibrium (LD) and Cox Regression analysis:
The haplotype and pairwise epistasis among six SNPs did not reveal any significant association, hence data not presented. The linkage disequilibrium (LD) analysis revealed that the two CAT -21A/T (rs1001179) and CAT -262 C/T (rs7943316) exhibited high LD (D'=0.9). Since the two SNPs are located on chromosome 1, the observed significant LD might be attributed to the physical proximity. None of the other SNP combinations showed significant LD with D'<0.5 (Figure 1). Cox regression analysis of SNPs with BCR-ABL1 levels revealed no significant association.

Discussion
In the present study, we investigated the association of the genetic variations of the antioxidant enzymes: CAT (-21A/T, rs7943316 & -262C/T, rs1001179), GPX1 (-198C/T, rs1050450), MPO (-463G/A, rs2333227) and GSTM1 (rs366631) & GSTT1 genes (rs17856199) with susceptibility to CML and their correlation with imatinib (TKI) response.

Our results revealed statistically significant association of CAT -21A/T (p=0.037) and GPX1 -198C/T (p<0.0001) polymorphisms with the risk of CML. No significant associations were observed between CAT -262C/T (p=0.711), MPO -463G/A (p=0.494), GSTM1 and GSTT1 null/deletion polymorphisms (p=1; p=0.193) and CML. Catalase is an endogenous antioxidant enzyme involved in ROS neutralizing pathways and prevents
Two polymorphisms: CAT -21A/T with altered gene expression pattern [23] and CAT -262C/T with lower CAT enzyme activity [24] may alter ROS detoxification and increase oxidative stress, implicating oxidative DNA damage and modulating disease risk [25]. In the present study, the CAT -21A/T polymorphism was significantly associated with increased risk of CML (p=0.037).

The stratified genotyping results with various confounding variables revealed that the homozygous variant TT genotype increased in non responders (p=0.259) and the heterozygous AT genotype frequency in TKD mutation carriers (p=0.571) and in deceased (p=0.548) group of patients. In addition, the codominant model (AA vs AT) (p=0.024) and dominant models (combined AT and TT genotypes) (p=0.05) presented significant association with increased risk of CML when compared with AA homozygote. Whereas Liu et al (2016)
reported an increased cancer risk with recessive model and homozygote model [26]. This indicates that variant T allele with lower catalase activity and thus increased levels of ROS may contribute to genomic instability and increased risk of cancer. Earlier studies reported no significant associations with the risk of colorectal cancer [27], gastric cancer (GC) and hepatocellular carcinoma (HCC) [13].

In our study, we found no evidence of the CAT -262 C/T polymorphism with CML risk or its association with confounding variables. Our results are in accordance with earlier studies that reported no significant association with cDNA microarray analysis.
Table 10. Genotyping of GSTM1 & GSTTI Deletion Polymorphism

| Genotype frequencies | T1          | T0          | p value | M1          | M0          | p value | Total |
|----------------------|-------------|-------------|---------|-------------|-------------|---------|-------|
| CML cases            | 97 (77.6%)  | 28 (22.4%)  | 0.193   | 86 (68.8%)  | 39 (31.2%)  | 1       | 125   |
| Controls             | 168 (84.0%) | 32 (16.0%)  |         | 136 (68.0%) | 64 (32.0%)  |         | 200   |
| BCR-ABL1 levels < 10%| 35 (87.5%)  | 5 (12.5%)   | 0.111   | 27 (67.5%)  | 13 (32.5%)  | 1       | 40    |
|                      | 62 (72.94%) | 23 (27.05%) |         | 59 (69.41%) | 26 (30.58%) |         | 85    |
| TKD mutations        |             |             |         |             |             |         |       |
| Presence             | 27 (90.0%)  | 3 (10.0%)   | 0.105   | 22 (73.33%) | 8 (26.66%)  | 0.698   | 30    |
| Absence              | 70 (73.68%) | 25 (26.31%) |         | 64 (67.36%) | 31 (32.63%) |         | 95    |
| Present status       |             |             |         |             |             |         |       |
| Follow-up            | 80 (76.92%) | 24 (23.07%) | 0.92    | 69 (66.34%) | 35 (33.65%) | 0.289   | 104   |
| Deceased             | 17 (80.95%) | 4 (19.04%)  |         | 17 (80.95%) | 4 (19.04%)  |         | 21    |

risk of hepatocellular carcinoma [28], breast cancer [29], and gastric cancer [30]. Previous other studies showed significant increased risk of cervical cancer [15], breast cancer [31], hepatocellular carcinoma [32] and prostate cancer [33]. Whereas others reported that -262C/T polymorphism was a protective factor with respect to chronic myeloid leukemia [19] and hepatocellular carcinoma susceptibility [14-17].

GPX1 is a key enzyme of the antioxidative system that detoxifies peroxide radicals and lipid hydroperoxides. The -198C/T (Pro200Leu) polymorphism in GPX1 is associated with reduced enzyme activity [34-35]. Previous studies reported that higher GPX1 activity is required to counterbalance the ROS levels and related damage occurring during initiation or progression of the cancer [36-39]. We observed statistically significant association of the homozygous variant TT genotype with CML risk (p<0.0001). The stratified results of confounding variables presented the significant association of GPX1 -198 C/T polymorphism with poor molecular response (p=0.005) and acquired TKD mutations (p=0.114). In addition, the codominant (CC vs CT and CC vs TT) and dominant (CC vs CT+TT) models conferred increased risk of CML when compared with CC homozygote (p=<0.0001). Our results were in accordance with others findings on breast cancer [39-41], bladder cancer [42] and lung cancer [43]. This indicates that the variant Leu allele with reduced enzyme activity might increase ROS levels thereby induced oxidative DNA damage and increased susceptibility to cancer. Whereas other studies failed to find an association of GPX1 -198C/T polymorphism with the risk of CML [19], breast cancer [44-45] and prostate cancer [46].

Glutathione S-transferases (GSTs) are involved in detoxification of a wide range of carcinogens and ROS thereby offering protection against oxidative DNA damage. GST enzymes are polymorphic, which may contribute to the inter-individual variability in the response to oxidative stress suggesting its role in carcinogenesis and risk for cancer. In the present study, the GSTM1 and GSTTI null/deletion polymorphisms were not associated with risk of CML. Our results are similar with earlier studies on CML [20]. Previous studies on the GSTTI null polymorphism reported positive association with risk of CML [47-50] and AML [20]. Earlier studies on GSTM1 null polymorphism showed no association the risk of CML [50], AML [51] and breast cancer [52]. Myeloperoxidase (MPO) is an endogenous oxidant enzyme that activates carcinogens [53]. A single nucleotide polymorphism in the promoter region of the MPO gene, G-463A (rs2333227) has been associated with reduced mRNA expression and transcriptional activity and subsequent decreased metabolic activation of procarcinogens [54]. In the present study, no evidence of MPO -463G/A polymorphism with the risk of CML was observed. Our results were in accordance with earlier studies on ALL [55], AML [56] and breast cancer [57]. Whereas others reported that the A allele with reduced MPO activity and ROS production has been associated with decreased risk of breast cancer [58], lung cancer [59] and prostate cancer [60].

In conclusion, our results suggest that the reduced activity of antioxidant enzymes caused by the CAT-21A/T and GPX1-198C/T polymorphisms might contribute to increased risk of CML. In addition, the GPX1-198C/T polymorphism was associated with poor molecular response and acquired TKD mutations. Hence, the present study indicates that defective antioxidant defense system might have a strong influence on CML susceptibility and TKI (imatinib) response through oxidative stress.

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Conflicts of interest

There are no conflicts of interest.
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