Among a panel of polymorphisms in genes related to oxidative stress, CAT-262 C>T, GPX1 Pro198Leu and GSTP1 Ile105Val influence the risk of developing BCR-ABL negative myeloproliferative neoplasms

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Objectives: To analyze the relationship between six polymorphisms in genes related to oxidative stress, namely CAT-262 C>T, MnSOD Ala16Val, GPX1 Pro198Leu, GSTM1 and GSTT1 null genotypes, and GSTP1 Ile105Val, and the occurrence of BCR-ABL negative myeloproliferative neoplasms (polycythemia vera, essential thrombocythemia, and primary myelofibrosis).

Methods: We genotyped for these polymorphisms 328 patients with a known mutation status for JAK2 V617F, MPL and CALR, and 363 controls, using molecular genetics assays.

Results: The CAT-262 C>T and GPX1 Pro198Leu polymorphisms were seen significantly less frequently, while the GSTP1 Ile105Val polymorphism was seen significantly more frequently in patients with BCR-ABL negative myeloproliferative neoplasms, regardless of the molecular sub-type (e.g. JAK2 V617F or CALR mutated).

Discussion and conclusion: Our study provides evidence that variation in genes related to oxidative stress might modulate the risk of developing BCR-ABL negative myeloproliferative neoplasms.

Keywords: BCR-ABL negative myeloproliferative neoplasms, Oxidative stress, Genetic polymorphisms

Introduction

Polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) are the three classical BCR-ABL negative myeloproliferative neoplasms (MPN). They are characterized by the acquisition of specific somatic mutations (JAK2, MPL or CALR) in most of the cases. The JAK2 46/1 haplotype and the TERT rs2736100 (A>C) SNP are constitutional genetic variations consistently associated with the occurrence of MPN.

A recent genome-wide association study performed by Tapper et al. on a large cohort of MPN patients revealed interesting findings. The authors found significant associations between JAK2 rs12339666 and MECOM rs2201862 SNPs, and JAK2 V617F-negative MPN, whereas HBS1L/MYB rs9376092 and TERT rs2736100 SNP achieved genome-wide significance when including JAK2 V617F-positive cases.

The CAT-262 C>T polymorphism has been associated with variations in expression of the catalase.
Lower levels of catalase lead to increased levels of hydrogen peroxide. The CT heterozygotes and the TT homozygotes have higher levels of catalase than the CC homozygotes.\(^5\) Superoxide dismutases are essential in detoxifying the superoxide free radicals. Manganese superoxide dismutase (MnSOD) acts as the primary mitochondrial antioxidant enzyme. The polymorphism Ala16Val, affecting the mitochondrial targeting sequence of SOD2, has been associated with MnSOD activity, which is higher in the Ala/Ala homozygotes.\(^6\) The meta-analysis published by Wang et al.\(^7\) showed a positive association between this polymorphism and prostate cancer risk, and breast cancer risk in premenopausal women who had low consumption of antioxidants. The glutathione peroxidase 1 (GPX1) catalyzes the reduction of organic peroxides using the glutathione as a reducing substrate. The most characterized polymorphism of the GPX1 gene, Pro198Leu, probably reduces the enzymatic activity of the GPX. A recent meta-analysis revealed a positive association between this polymorphism and bladder, but not prostate cancer.\(^8\) The glutathione-S-transferases (GST) are enzymes involved in phase II drug metabolic reactions, conjugating the electrophilic substances with glutathione. They detoxify a wide range of carcinogens, toxins, and drugs. GSTM1, GSTT1, and GSTP1 are the most extensively studied GST. Their genes present variations decreasing or even abolishing their activities: null alleles in the case of GSTM1 and GSTP1, and the Ile105Val substitution in the case of GSTP1.\(^9\) These three polymorphisms have been extensively studied in a plethora of cancers, including some of the hematological ones, yielding various conclusions. A very large recent meta-analysis revealed positive associations between both GSTM1 and GSTT1 null genotypes and various cancers, mostly of epithelial origin, but also acute lymphoblastic leukemia, in both Caucasian and Asian populations.\(^10\)

Exposure to benzene and/or petroleum products has been shown to increase the risk of developing MPN.\(^11\) We might expect that exposure to other environmental factors could modulate the risk of developing MPN. The detoxification of most of these compounds supposes the involvement of proteins related directly or indirectly to oxidative stress, such as catalase, GPX1, and glutathione S-transferases M1, T1, and P1. Here we aimed to assess whether common polymorphisms of these genes are linked to the occurrence of the classical BCR-ABL negative MPN—PV, ET, and PMF.

**Material and methods**

**Patients and controls**

The study enrolled 328 patients—140 with PV, 140 with ET and 48 with PMF. The patients were diagnosed between 1985 and 2014 in several hematology centers—Cluj-Napoca (‘Ion Chiricuţă’ Cancer Institute), Tîrgu-Mureş (First Haematology Clinic), and Bucharest (Colentina Hospital). Their diagnosis was reviewed according to the 2008 WHO classification of myeloid neoplasms. Their principal demographic and biological features, including the specific somatic mutations displayed (JAK2 V617F, MPL, CALR), are presented in Table 1.

The study also included a group of 363 controls. They were enrolled from the same geographic regions as the patients. These individuals were free of any malignancies and were age and sex matched to the patients.

The study was reviewed and approved by the Ethics Committees of the Universities of Medicine and Pharmacy from Cluj-Napoca and Tîrgu-Mureş. Written consent regarding genetic testing was also obtained from all the participants to the study.

**Genotyping procedures**

All the genotyping procedures were performed on genomic DNA obtained from peripheral blood withdrawn on EDTA, using commercially available kits [Wizard Genomic DNA Purification Kit (Promega, Madison, WI, USA) and Quick-gDNA MiniPrep Kit (ZymoResearch, Irvine, CA, USA)]. The JAK2 V617F, MPL, and CALR status had already been assessed in all patients, using PCR-based assays, as previously described.\(^12\)-\(^14\)

The CAT-262 C>T, MnSOD Ala16Val, GPX1 Pro198Leu and GSTP1 Ile105Val polymorphisms were genotyped by PCR-RFLP assays, as previously described.\(^15\)-\(^18\) GSTM1 and GSTT1 null genotypes were assessed by a multiplex PCR assay, as previously described.\(^19\)

**Statistical analysis**

All the tests were performed using the SPSS version 21 software (Chicago, IL, USA). The distribution of

| Feature                  | PV group \(N = 140\) | ET group \(N = 140\) | PMF group \(N = 48\) |
|--------------------------|-----------------------|----------------------|-----------------------|
| Male sex; \(n\) (%)      | 85 (60.7)             | 54 (38.6)            | 24 (50)               |
| Age at diagnosis (years); median (range) | 62 (27–87) | 58 (22–84) | 63.5 (44–84) |
| Splenomegaly; \(n\) (%) | 74 (52.9)             | 34 (24.1)            | 48 (100)              |
| Major thrombosis; \(n\) (%) | 47 (33.6) | 30 (21.4) | 2 (4.2)               |
| JAK2 V617F mutation; \(n\) (%) | 121 (86.4) | 75 (53.6) | 23 (47.9) |
| MPL mutations; \(n\) (%) | –                    | 2 (1.4)              | 2 (4.2)               |
| CALR mutations; \(n\) (%) | –                    | 41 (29.3)            | 12 (25)               |
| Triple-negative status; \(n\) (%) | –                    | 22 (15.7)            | 11 (22.9)             |
qualitative variables between different groups was compared using the chi-square and Fisher’s exact test, whenever appropriate. For variables that achieved statistical significance, OR (odds ratio), and 95% CI (confidence interval) were calculated. Variables that achieved statistical significance in univariate analysis were included in a binary logistic regression, in order to establish their independent influence. The level of statistical significance was set at 0.05.

Results

Distribution of the polymorphisms in MPN patients and controls

All the polymorphisms analyzed were distributed in patients and controls according to the Hardy–Weinberg equilibrium (data not shown).

The CT and TT genotypes of the CAT-262 C>T polymorphism were seen in 134 patients with MPN (40.9%) and 185 controls (51%) (dominant model: OR = 0.66; 95% CI = 0.49–0.89; P-value = 0.003). The association was also significant when analyzing the TT genotype alone (recessive model: OR = 0.49; 95% CI = 0.25–0.95; P-value = 0.03, respectively). The same significant difference was also observed when comparing the T and C allele frequencies (T versus C allele: OR = 0.70; 95% CI = 0.55–0.90; P-value = 0.005). When analyzing the distribution of the CAT-262 C>T polymorphism in each MPN entity, the CT and TT genotypes were seen significantly less frequently in PMF patients (25%) than in controls (51%) (OR = 0.32; 95% CI = 0.16–0.63; P-value = 0.001). This association remained significant also when comparing the allele frequencies – the T allele had a frequency of 14.6% in patients and 29.3% in controls (OR = 0.70; 95% CI = 0.55–0.90; P-value = 0.005). In PV and ET patients, although the CT + TT genotypes, and the T allele of the CAT-262 C>T polymorphism had lower frequencies than in controls, this finding did not reach statistical significance (P-value > 0.05 in both models – dominant and recessive).

In the case of GPX1 Pro198Leu polymorphism, 265 patients with MPN (80.8%), and 328 controls (90.4%) had the Pro/Leu or Leu/Leu genotype (dominant model: OR = 0.44; 95% CI = 0.28–0.70; P-value < 0.001). The association was also significant when analyzing the Leu/Leu genotype alone (recessive model: OR = 0.47; 95% CI = 0.28–0.78; P-value = 0.004, respectively). Also the Leu allele had a lower frequency in patients with MPN than in controls (OR = 0.79; 95% CI = 0.64–0.98; P-value = 0.03). The association remained significant when analyzing the GPX1 Pro198Leu in PV and PMF groups (P-value < 0.05 for both diseases in both models – dominant and recessive). However, when analyzing only the ET group, the statistical significance was lost (P-value > 0.05 in both models – dominant and recessive).

The Ile/Val and Val/Val genotypes of the GSTP1 Ile105Val polymorphism were seen in 157 patients with MPN (47.8%) and 113 controls (31.1%) (dominant model: OR = 2.03; 95% CI = 1.48–2.77; P-value < 0.001). Also when analyzing the Val/Val homozygous genotype alone, it was seen significantly more frequent in patients with MPN than in controls (recessive model: OR = 2.72; 95% CI = 1.41–5.26; P-value = 0.003). Also the Val allele had a higher frequency in patients than in controls (OR = 1.83; 95% CI = 1.42–2.36; P-value < 0.001). The association remained positive when analyzing each disease in part (PV, ET, and PMF, P-values < 0.05 for all these comparisons, in both models – dominant and recessive).

The other three polymorphisms analyzed – MnSOD Ala16Val, GSTM1 and GSTT1 null genotypes, had similar frequencies in MPN patients (in the whole cohort and in each entity – PV, ET, and PMF) and controls (P > 0.05 for all these comparisons, for both models: dominant and recessive).

The detailed distribution of the six polymorphisms in patients and controls is presented in detail in Table 2.

Seventy-nine patients (24.1%) had major thrombosis. The six polymorphisms analyzed had similar frequencies in patients with and without thrombosis (P-value > 0.05 for all these comparisons). One hundred and fifty-six patients (47.6%) had splenomegaly. None of the six polymorphisms was enriched in patients with splenomegaly compared to those without (P > 0.05 for all these comparisons). Also the values of the laboratory parameters (hematocrit, hemoglobin, white blood cells and the platelets) were linked to none of the six polymorphisms analyzed (P-values > 0.05 for all these comparisons).

Distribution of the polymorphisms in MPN patients stratified after the somatic mutation status (JAK2 V617F, CALR, MPL and triple-negative)

We analyzed then the distribution of the six polymorphisms in MPN patients, taking into account the type of somatic mutation displayed. All the six polymorphisms (CAT-262 C>T, MnSOD Ala16Val, GPX1 Pro198Leu, GSTP1 Ile105Val, GSTM1, and GSTM1 null genotypes) had a similar distribution in JAK2 V617F-mutated (219 patients) and non-mutated (109 patients) MPN patients (P-values > 0.05 for all these comparisons). We performed a similar analysis on CALR mutations, which characterized a part of the patients with ET and PMF (53 patients versus 135 non-CALR patients in the combined ET+PMF group). All the six polymorphisms
analyzed had a similar distribution in CALR and non-CALR ET and PMF patients (P-value > 0.05 for all polymorphisms in both models – dominant and recessive).

The triple-negative status (absence of JAK2 V617F, MPL or CALR mutations) characterized 33 patients with ET and PMF. The six polymorphisms analyzed shared similar frequencies between the triple-negative patients and the ones with JAK2 V617F, MPL or CALR mutations (P-value > 0.05 for each polymorphism). However, the combined null genotype for both GSTM1 and GSTT1 polymorphisms was seen more frequently in the triple-negative group (24.2% versus 7.1%, OR = 3.82; 95% CI = 1.4–10.3; P-value = 0.009).

In a multivariate regression model, CAT-262 C>T, GPX1 Pro198Leu, and MnSOD Ala16Val polymorphisms remained independently associated with BCR-ABL negative MPN, in both dominant and recessive models (P-value < 0.05 for each of the three polymorphisms).

**Discussion**

The CAT-262 C>T, GPX1 Pro198Leu, and MnSOD Ala16Val polymorphisms were rarely investigated in relationship with the hematological malignancies. To our best knowledge, the relationship between these polymorphisms and BCR-ABL negative MPN has never been assessed previously. Lightfoot et al. analyzed the CAT-262 C>T, GPX1 Pro198Leu, and MnSOD Ala16Val polymorphisms in 928 patients with non-Hodgkin’s lymphoma and 1446 controls. They observed a similar distribution of the CAT-262 C>T and MnSOD Ala16Val polymorphisms in patients and controls. However, the heterozygous and homozygous genotypes of the GPX1 Pro198Leu were seen more frequently in patients than in controls (OR = 1.25; 95% CI = 1.05–1.48; P-value = 0.01).20 We recently shown that the heterozygous genotype for the CAT-262 C>T polymorphism is protective against chronic myeloid leukemia.21 In the present study, we show that the heterozygous and homozygous variant genotypes of the CAT-262 C>T polymorphism are protective against BCR-ABL negative MPN. This finding could be explained by the fact that the activity of the catalase is higher in individuals with CT or TT genotypes. On the other hand, higher levels of catalase mean lower levels of hydrogen peroxide, which is able to promote cancerogenesis by increasing the oxidative stress.5

Wang et al. analyzed 13 SNPs in 10 genes related to oxidative stress, among which GPX1 Pro198Leu and MnSOD Ala16Val polymorphisms in 1172 cases with non-Hodgkin lymphoma and 982 controls. In the case of MnSOD Ala16Val, the Ala/Ala genotype was seen more frequently in cases than in controls (OR = 1.3, 95% CI = 1.0–1.6, P = 0.01). The GPX1 Pro198Leu polymorphism had no effect on the occurrence of non-
Hodgkin lymphoma.\textsuperscript{22} In a recent study performed on chronic myeloid leukemia, we demonstrated no effect of the \textit{MnSOD} Ala16Val and \textit{GPX1} Pro198Leu polymorphisms in relation with the occurrence of this entity.\textsuperscript{21} However, in the present study, we found a protective effect of the homozygous Pro/Pro genotype of the \textit{GPX1} Pro198Leu polymorphisms in the whole cohort of patients with \textit{BCR-ABL} negative MPN. This finding is quite intriguing, if we take into account that the Leu allele probably reduces the activity of the GPX, which could increase the oxidative stress, promoting the cancerogenesis.

The \textit{GSTP1} Ile105Val, \textit{GSTTI}, and \textit{GSTMI} polymorphisms were not previously analyzed in relationship with all three classical \textit{BCR-ABL} negative MPN (PV, ET, and PMF). There is only a study that assessed the relationship between the \textit{GSTM1} and \textit{GSTTI} null genotypes and PV, published by Naffa \textit{et al}.\textsuperscript{23} They included 61 patients with PV and 70 controls and found a positive association between the \textit{GSTM1} null genotype and PV (OR = 3.38; 95\% CI = 1.63–7.01; \textit{P}-value = 0.001).\textsuperscript{23} On the other hand, we failed to demonstrate an association between \textit{GSTM1} and \textit{GSTTI} null genotypes and the occurrence of PV, ET, and PMF. However, we observed significantly higher frequencies of the \textit{GSTP1} Ile105Val polymorphisms not only in patients with PV, but also in patients with ET and PMF. In fact, the \textit{GSTP1} Ile105Val polymorphism conferred the highest risk of developing all three types of \textit{BCR-ABL} negative MPN, among the six polymorphisms we analyzed in this study. This might suggest a link between the occurrence of \textit{BCR-ABL} negative MPN and an imbalance in phase II metabolic reactions, induced by the \textit{GSTP1} Ile105Val polymorphism.

We found significant correlations between \textit{CAT}-262 C>T, \textit{GPX1} Pro198Leu and \textit{GSTP1} Ile105Val SNPs and the development of MPN. None of these SNPs were found in the genome-wide association study performed by Tapper \textit{et al}.\textsuperscript{4} on a larger cohort of patients. There are several possible reasons explaining this discrepancy: first, we chose to target common, known variants in genes involved in oxidative stress. These variants have non-specific, general consequences at multiple levels, by producing imbalances in the oxidative stress status. These imbalances could promote cancerogenesis, in general. As such, they could be positively linked to various hematological and non-hematological cancers, as shown by different studies. Another possible explanation would be the fact that genome-wide association studies don’t cover all the SNPs from the genome. The different sample size of the cohort analyzed in this study represents another aspect that should be taken into account.

In conclusion, we provide evidence that polymorphisms in oxidative stress related genes might modulate the risk of developing \textit{BCR-ABL} negative MPN. We found a protective effect in case of \textit{CAT}-262 C>T and \textit{GPX1} Pro198Leu polymorphisms and a risk effect in case of \textit{GSTP1} Ile105Val. We consider these findings warrant further research on other cohorts of patients with MPN.

\textbf{Acknowledgements}
This study would have not been possible without the help of our friend and colleague, Dr Andrei Cucuianu. Unfortunately, he passed away while the study was in progress.

\textbf{Disclaimer statements}
\textbf{Contributors} All authors listed in this paper fulfill the criteria justifying their position as authors.

\textbf{Funding} This study was supported by an Internal Research Grant of the University of Medicine and Pharmacy Tirgu-Mureş, Romania, to CB (Project no. 19/11.12.2013).

\textbf{Conflicts of interest} No conflicts-of-interest.

\textbf{Ethics approval} The study received ethical approval from the Ethics Committee of the ‘Iuliu Hatieganu’ University of Medicine and Pharmacy.

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