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RESEARCH ARTICLE

Genetic Predictors of Chemotherapy-Induced Cardiotoxicity in Leukemia: The Role of Sod2 And Comt Polymorphisms

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Abstract: Chemotherapy-induced cardiotoxicity remains a major clinical challenge in patients with leukemias, contributing to reduced treatment tolerability and adverse long-term cardiovascular outcomes. Oxidative stress and neurohumoral dysregulation are key mechanisms underlying myocardial injury, while genetic variability may partly explain interindividual differences in susceptibility. This study aimed to evaluate the association of SOD2 (Val16Ala, rs4880) and COMT (Val158Met, rs4680) polymorphisms with the risk of cardiotoxic complications in leukemia patients receiving anticancer therapy. A total of 102 patients were stratified into subgroups with (n = 64) and without (n = 38) cardiological complications; 97 healthy individuals served as controls. Genotyping was performed using polymerase chain reaction with restriction fragment analysis. The SOD2 A allele showed a moderate association with cardiotoxicity, particularly for the homozygous A/A genotype (OR = 3.33; p = 0.12). In contrast, the COMT A (Met) allele demonstrated a strong and statistically significant association with cardiological complications (OR = 3.82; 95% CI: 1.97–7.42; p < 0.001), and the A/A genotype was associated with more than a fourfold increase in risk (OR = 4.45; p = 0.008). Combined analysis revealed a dose-dependent additive effect: carriage of two or more unfavorable alleles was associated with a more than fourfold increase in cardiotoxicity risk (OR = 4.22; p = 0.009). These findings support the role of pharmacogenetic factors in myocardial susceptibility and highlight the potential value of integrating SOD2 and COMT genotyping into personalized cardiovascular risk stratification strategies in leukemia patients.

Key words: Chemotherapy-induced cardiotoxicity; leukemia; SOD2 Val16Ala; COMT Val158Met; oxidative stress; catecholamine metabolism; pharmacogenetics; gene–gene interaction; myocardial injury; cardiovascular risk stratification.

INTRODUCTION

Cardiotoxic complications of anticancer therapy remain one of the most significant causes of reduced treatment tolerability and poorer long-term outcomes in patients with oncohematological diseases, including acute leukemias. Current clinical guidelines emphasize that cardiovascular events may occur both during chemotherapy and months or even years after its completion, which necessitates a systematic approach to risk assessment, monitoring, and prevention throughout all stages of treatment [1–3]. The pathogenesis of chemotherapy-induced myocardial injury is multifactorial and involves oxidative stress, mitochondrial dysfunction, disruption of intracellular homeostasis, and activation of programmed cardiomyocyte death. In anthracycline-related cardiotoxicity, evidence indicates that the major injury pathways largely converge on mitochondrial impairment and redox imbalance, which helps explain both early and delayed clinical manifestations [4,5].

At the same time, accumulating data demonstrate marked interindividual variability in cardiotoxicity risk even among patients receiving similar treatment regimens, supporting the need to identify additional predictors, including molecular genetic markers

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[1–3]. In this context, investigating genetic variants related to antioxidant defense and endothelial regulation of vascular tone may have practical value for refining risk stratification models and developing personalized monitoring strategies for patients with acute leukemias [1–5].

One of the key candidate genes is SOD2, which encodes mitochondrial superoxide dismutase. The functional Val16Ala (rs4880) polymorphism affects the import of the enzyme into mitochondria and its antioxidant activity. Studies by Shimoda-Matsubayashi et al. (2018) and subsequent reviews by Bast et al. (2019) have shown that reduced SOD2 activity is associated with increased tissue vulnerability to oxidative damage, including in the myocardium, making this gene a meaningful marker of potential cardiotoxicity risk.An equally important role may be played by the COMT gene, which encodes catechol-O-methyltransferase, an enzyme involved in the inactivation of catecholamines. The Val158Met (rs4680) polymorphism leads to decreased enzymatic activity, which is accompanied by higher catecholamine levels and enhanced sympathetic stimulation. As reported by Lachman et al. (1996), Tunbridge et al. (2020), and Stein et al. (2018), this polymorphism has been associated with alterations in vascular tone, endothelial function, and cardiovascular regulation, potentially amplifying the cardiotoxic effects of anticancer drugs.

Despite the accumulating evidence, most studies focus on individual genes and do not account for their potential combined effects. Reviews by Leong et al. (2022) and Henriksen (2023) emphasize the scarcity of data on the joint contribution of genes involved in antioxidant defense and catecholamine metabolism to cardiotoxicity in oncohematological patients. Evidence is particularly limited for patients with leukemias, highlighting the need for further research in this area.

Purpose of the research

To evaluate the association of SOD2 and COMT gene polymorphisms with the risk of developing cardiotoxic complications in patients with leukemias, and to determine their prognostic value for cardiovascular risk stratification.

METHODS

A total of 102 patients with leukemias receiving anticancer therapy were enrolled in the study. Depending on the presence of cardiological complications, patients were divided into two subgroups: those with cardiological complications (n = 64) and those without cardiological complications (n = 38). The control group included 97 apparently healthy individuals matched by age and sex, with no history of oncohematological or cardiovascular diseases.

Inclusion criteria were a confirmed diagnosis of leukemia, receipt of anticancer therapy, and written informed consent to participate. Exclusion criteria comprised previously diagnosed severe cardiovascular diseases, congenital cardiomyopathies, and acute infectious conditions at the time of examination.

Cardiological complications were diagnosed based on clinical assessment as well as electrocardiographic and echocardiographic examinations. The presence of rhythm and conduction disturbances, signs of systolic and diastolic myocardial dysfunction, changes in blood pressure, and clinical symptoms of heart failure were evaluated. The diagnostic criteria for cardiotoxicity were in accordance with current European Society of Cardiology recommendations.

Peripheral venous blood samples were collected into EDTA tubes. Genomic DNA was isolated from peripheral blood leukocytes using a standard method with commercial DNA extraction kits according to the manufacturer's instructions. DNA concentration and purity were assessed spectrophotometrically.

Genotyping of the SOD2 Val16Ala (rs4880) polymorphism was performed by polymerase chain reaction (PCR) followed by restriction fragment analysis using real-time PCR-based amplification. Target DNA fragments were amplified using specific primers. The resulting PCR products were digested with the appropriate restriction endonuclease and separated by agarose gel electrophoresis, with

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RESEARCH ARTICLE

visualization under ultraviolet illumination. Genotypes were determined based on the characteristic sizes of restriction fragments.

The COMT Val158Met (rs4680) polymorphism was genotyped using an analogous real-time PCR approach. After amplification of the target genomic region with specific primers, PCR products underwent enzymatic digestion, and genotypes were identified by electrophoretic separation of DNA fragments.

For genotyping quality control, a subset of samples was reanalyzed in a blinded manner; the reproducibility of results was 100%.

Statistical analysis was performed using standard software packages. Allele and genotype frequencies were calculated by direct counting. The Hardy–Weinberg equilibrium (HWE) was assessed using the χ^2 test. Comparisons of allele and genotype frequencies between groups were conducted using the χ^2 test or Fisher's exact test, as appropriate. Associations between genetic variants and the risk of cardiological complications were evaluated by calculating odds ratios (ORs) with 95% confidence intervals (95% CIs). Differences were considered statistically significant at $p < 0.05$.

RESULTS

In the control group, genotype distributions of the SOD2 and COMT polymorphisms were consistent with Hardy–Weinberg equilibrium ($p > 0.05$), indicating sample representativeness and the absence of systematic genotyping errors. No significant deviations from Hardy–Weinberg equilibrium were observed in the patient cohort.

In the patient group, the SOD2 A allele was more frequent among individuals with cardiological complications (37.5%) than among those without complications (28.95%). Allelic analysis demonstrated a trend toward increased risk of cardiotoxic complications in A-allele carriers (OR = 1.47; 95% CI: 0.78–2.77; p = 0.23). Genotype-based analysis showed a more pronounced association for the homozygous A/A variant: the A/A genotype was detected in 15.6% of patients with cardiological complications and in only 5.2% of patients without complications. Carriage of the A/A genotype was associated with more than a threefold increase in the odds of cardiotoxic complications (OR = 3.33; 95% CI: 0.69–16.0; p = 0.12). Overall, the SOD2 polymorphism demonstrated moderate prognostic relevance, most evident for the homozygous A/A variant.

For the COMT Val158Met polymorphism, statistically significant differences in allele distribution were observed between patient subgroups. The A (Met) allele was significantly more frequent among patients with cardiological complications (60.9%) compared with those without complications (28.9%). Allelic analysis showed that carriage of the A (Met) allele was associated with a significantly increased risk of cardiotoxic complications (OR = 3.82; 95% CI: 1.97–7.42; $p < 0.001$). Genotype analysis confirmed these findings: the A/A (Met/Met) genotype was identified in 34.4% of patients with complications and in only 10.6% of those without complications. Carriage of this genotype was associated with more than a fourfold increase in the odds of cardiological complications (OR = 4.45; 95% CI: 1.39–14.2; p = 0.008).

Comparative analysis indicated that the COMT polymorphism exhibited a stronger association with cardiotoxic complications than the SOD2 polymorphism. While SOD2 showed only a trend toward increased risk, the most robust and statistically significant effects were observed for the A allele and the A/A genotype of COMT. In the combined analysis of unfavorable genetic variants, patients carrying the SOD2 A allele together with the COMT A (Met) allele had a higher risk of developing cardiotoxic complications compared with patients without these variants. The highest risk was observed in individuals with the combined homozygous genotype pattern SOD2 A/A + COMT A/A, suggesting an additive effect of the studied genetic factors.

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Table 1. Allele distribution of SOD2 and COMT genes in leukemia patients according to the presence of cardiotoxic complications

Gene	Allele	With cardiological complications, n (%)	Without cardiological complications, n (%)	OR	95% CI	p
SOD2	C	80 (62.5)	54 (71.1)	—	—	—
	A	48 (37.5)	22 (28.9)	1.47	0.78–2.77	0.23
COMT	G (Val)	50 (39.1)	54 (71.1)	ref	—	—
	A (Met)	78 (60.9)	22 (28.9)	3.82	1.97–7.42	<0.001

Table 2. Association of COMT (Val158Met) genotypes with the risk of cardiotoxic complications

Genotype	With cardiological complications, n (%)	Without cardiological complications, n (%)	OR	95% CI	p
G/G (Val/Val)	8 (12.5)	20 (52.6)	ref	—	—
G/A (Val/Met)	34 (53.1)	14 (36.8)	6.07	2.20–16.8	<0.001
A/A (Met/Met)	22 (34.4)	4 (10.6)	4.45	1.39–14.2	0.008

Table 3. Comparative prognostic significance of SOD2 and COMT polymorphisms

Gene	Unfavorable variant	OR	95% CI	p	Prognostic significance
SOD2	A (allele)	1.47	0.78–2.77	0.23	moderate
SOD2	A/A	3.33	0.69–16.0	0.12	moderately high
COMT	A (Met)	3.82	1.97–7.42	<0.001	high
COMT	A/A (Met/Met)	4.45	1.39–14.2	0.008	very high

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Table 4. Combined effect of SOD2 and COMT polymorphisms on the risk of cardiotoxic complications

Number of unfavorable alleles	With cardiotoxicity (n = 64)	Without cardiotoxicity (n = 38)	OR	95% CI	p
0 (SOD2 C/C + COMT G/G)	18 (28.1%)	20 (52.6%)	ref	—	—
1 (SOD2 A or COMT A)	27 (42.2%)	13 (34.2%)	2.31	1.01–5.27	0.046
≥2 (SOD2 A + COMT A)	19 (29.7%)	5 (13.2%)	4.22	1.39–12.8	0.009

The combined analysis demonstrated a pronounced dose-dependent effect of genetic risk. In patients carrying one unfavorable allele, the risk of cardiotoxic complications increased more than twofold (OR = 2.31; p = 0.046), whereas carriage of two or more unfavorable alleles was associated with more than a fourfold increase in risk (OR = 4.22; p = 0.009) compared with the reference group.

DISCUSSION

The present study evaluated the role of SOD2 and COMT gene polymorphisms in the development of cardiotoxic complications in leukemia patients receiving anticancer therapy. The results support the hypothesis that genetic factors contribute to interindividual susceptibility of the myocardium to cytotoxic injury and highlight the potential of a pharmacogenetic approach in cardio-oncology.

Of particular interest are the findings of the exploratory combined analysis, which revealed a dose-dependent effect of accumulating unfavorable alleles of the SOD2 and COMT genes. In patients carrying two or more unfavorable genetic variants, the risk of cardiotoxic complications increased more than fourfold compared with the reference group. This observation suggests an additive interaction between antioxidant and neurohumoral mechanisms in the pathogenesis of cardiotoxicity and underscores the value of an integrated genetic assessment. These findings have important clinical implications. In the setting of anticancer therapy, patients with an unfavorable genetic profile may represent a high-risk subgroup requiring intensified cardiovascular monitoring, early detection of subclinical myocardial changes, and potentially the use of cardioprotective strategies. Incorporating SOD2 and COMT genotyping into personalized risk assessment algorithms may help reduce the incidence of severe cardiotoxic complications and improve long-term treatment outcomes.

Several limitations should be acknowledged. The exploratory nature of the combined analysis, the conditional risk-stratification model, and the relatively small sample size limit the generalizability of the results. In addition, potentially relevant factors such as cumulative chemotherapy dose, pre-existing cardiovascular disease, and biomarkers of myocardial injury were not included in the analysis. Therefore, these findings should be considered preliminary and require confirmation in larger prospective studies.

Overall, the present study supports that COMT and SOD2 polymorphisms contribute to individual predisposition to cardiotoxic complications in leukemia patients. The most pronounced contribution to cardiotoxicity risk was observed for COMT, whereas SOD2 appeared to act as a modifying factor that may amplify the damaging effects of oxidative stress. Combined analysis of these genes represents a promising direction for further research and for the development of personalized approaches in cardio-oncology.

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CONCLUSION

SOD2 and COMT gene polymorphisms make a meaningful contribution to individual susceptibility to cardiotoxic complications in leukemia patients receiving anticancer therapy. The strongest prognostic value was demonstrated for the COMT Val158Met polymorphism: carriage of the A (Met) allele—and particularly the A/A (Met/Met) genotype—was associated with a substantial increase in the risk of cardiological complications. In contrast, the SOD2 polymorphism showed a moderate effect and likely acts as a modifying factor that amplifies oxidative stress–mediated myocardial injury.

The exploratory combined analysis revealed an additive effect of unfavorable SOD2 and COMT genetic variants, characterized by a dose-dependent increase in cardiotoxicity risk. These findings support the promise of an integrated pharmacogenetic approach for cardiovascular risk stratification and justify further prospective studies aimed at implementing personalized strategies for prevention and monitoring of cardiotoxic complications in clinical practice.

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