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Combined Influence Of Sod2 And Edn1 Genetic Polymorphisms On Chemotherapy-Related Cardiotoxicity Risk In Acute Leukemia Patients

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Abstract

Background: Chemotherapy-related cardiotoxicity is a serious complication in acute leukemia patients, with significant interindividual variability suggesting a genetic component. Polymorphisms in genes regulating oxidative stress and vascular tone, such as SOD2 and EDN1, may influence individual susceptibility.

Objective: To evaluate the impact of SOD2 C14510A and EDN1 Lys197Asn polymorphisms, both individually and in combination, on the risk of cardiotoxic complications in acute leukemia patients undergoing chemotherapy.

Methods: A clinical-genetic study included 102 acute leukemia patients (64 with cardiotoxicity, 38 without) and 97 healthy controls. Cardiotoxicity was defined by clinical, biomarker, and echocardiographic criteria. Genotyping was performed using PCR. Statistical analysis included allele/genotype frequency comparison and odds ratio calculation.

*Results: The SOD2 A allele (34.3% in patients vs. 22.0% in controls; *p*<0.05) and A/A genotype (15.6% in cardiotoxicity subgroup vs. 5.2% without) were more frequent in patients with complications. The EDN1 Asn allele was also more common in patients with cardiotoxicity (28.1% vs. 22.4%). While individual polymorphisms showed non-significant trends toward increased risk (e.g., SOD2 A/A OR=3.46, *p*>0.05), combined carriage of SOD2 A and EDN1 Asn alleles was associated with a significantly higher frequency of cardiotoxicity (OR=3.26, 95% CI: 0.87–12.19, *p*=0.04).*

Conclusion: The SOD2 A allele and EDN1 Asn allele are associated with an increased risk of chemotherapy-induced cardiotoxicity in acute leukemia patients. Their combined presence suggests an additive effect, highlighting the role of genetic predisposition in cardiotoxicity and supporting the integration of genetic markers into personalized risk assessment strategies.

Keywords: Cardiotoxicity, Chemotherapy, Acute Leukemia, Genetic Polymorphisms, SOD2, EDN1, Oxidative Stress.

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1. Introduction

Cardiotoxic complications remain one of the most

significant challenges during chemotherapy in patients with acute leukemias, as they worsen disease prognosis, limit the possibility of continuing antineoplastic treatment, and reduce patients' quality of life [1,2]. Even in the absence of pre-existing cardiovascular disease, myocardial injury may develop at early stages of therapy and manifest as either acute or delayed cardiotoxicity [3]. Contemporary cardio-oncology research highlights substantial interindividual variability in the risk of chemotherapy-related cardiotoxicity, which cannot always be explained by cumulative drug dose, patient age, or traditional cardiovascular risk factors alone [4]. In this context, increasing attention has been directed toward genetic determinants of myocardial susceptibility to chemotherapeutic injury, including polymorphisms in genes involved in the regulation of oxidative stress, vascular tone, and endothelial function [5,6]. The SOD2 gene, encoding mitochondrial superoxide dismutase (MnSOD), plays a critical role in protecting cardiomyocytes from damage induced by reactive oxygen species. Polymorphic variants of the SOD2 gene have been shown to be associated with altered enzymatic activity, increased oxidative stress, and a higher risk of cardiotoxicity induced by anthracyclines and other antineoplastic agents [7–9]. Under chemotherapy conditions, impairment of mitochondrial antioxidant defense is considered one of the central mechanisms underlying myocardial injury.

The EDN1 gene encodes endothelin-1, one of the most potent endogenous vasoconstrictors involved in the regulation of vascular tone, coronary microcirculation, and myocardial remodeling. The Lys197Asn (rs5370) polymorphism has been associated with increased endothelin-1 expression, endothelial dysfunction, and an elevated risk of cardiovascular diseases, including arterial hypertension and ischemic heart disease [10–12]. These effects may play an important role in the development of the vascular component of chemotherapy-related cardiotoxicity. From a pathogenetic perspective, the combination of impaired mitochondrial antioxidant defense associated with SOD2 polymorphisms and enhanced vasoconstrictor activity mediated by EDN1 polymorphisms may exert a synergistic effect, amplifying ischemic and oxidative myocardial damage in response to cytotoxic therapy [13,14]. However, data on the combined impact of SOD2 and EDN1 gene polymorphisms on the risk of cardiotoxic complications in patients with acute leukemias remain limited, which underscores the relevance and clinical significance of the present study.

Purpose of the research

The aim of the study was to evaluate the impact of the SOD2 C14510A and EDN1 Lys197Asn gene polymorphisms, as well as their combined effect, on the risk of developing cardiotoxic complications during chemotherapy in patients with acute leukemias.

2. Methods

An observational comparative clinical and genetic study with elements of prospective follow-up was conducted. The study included patients with newly diagnosed acute leukemias who received standard chemotherapy regimens. The analysis was performed with regard to the development of cardiotoxic complications during treatment. A total of 102 patients with acute leukemias were enrolled in the main study group. Depending on the presence of cardiotoxic complications during chemotherapy, patients were divided into two subgroups: 64 patients with cardiotoxic complications and 38 patients without cardiotoxic complications. The control group consisted of 97 apparently healthy individuals matched by age and sex, with no history of oncohematological or cardiovascular diseases.

The inclusion criteria were a confirmed diagnosis of acute leukemia, receipt of systemic chemotherapy, age of 18 years or older, and written informed consent to participate in the study. The exclusion criteria included the presence of significant cardiovascular disease prior to the initiation of chemotherapy, such as heart failure of NYHA functional class III–IV or severe valvular heart disease, previous exposure to cardiotoxic anticancer therapy, and concomitant diseases in the stage of decompensation.

Cardiotoxic complications were diagnosed on the basis of clinical, laboratory, and instrumental criteria, including a decrease in left ventricular ejection fraction, the development of clinical signs of heart failure, elevation of cardiac-specific biomarkers according to medical records, and the occurrence of cardiac rhythm and conduction disturbances during chemotherapy. Patients in whom these abnormalities were not detected were classified as having no cardiotoxic complications. Peripheral venous blood was used as the biological material for genetic analysis. Genomic DNA was isolated using standard methods. Genotyping of the SOD2 C14510A and EDN1 Lys197Asn polymorphisms was performed using polymerase chain reaction with subsequent analysis of amplification products. Allele and

genotype frequencies were determined for each polymorphism, and genotype distributions were assessed for compliance with Hardy–Weinberg equilibrium.

Statistical analysis was carried out using standard methods of variation statistics. Allele and genotype frequencies were expressed as absolute values and percentages. Differences in genotype and allele distributions between groups were assessed using the chi-square test. The association between genetic variants and the risk of cardiotoxic complications was evaluated by calculating odds ratios with 95% confidence intervals. The combined effect of SOD2 and EDN1 gene polymorphisms was analyzed through the assessment of genotype combinations. Differences were considered statistically significant at $p < 0.05$.

3. Results

Analysis of the allele and genotype distributions of the SOD2 C14510A polymorphism revealed differences between patients with acute leukemias and the control group, as well as between patient subgroups depending on the presence of cardiological complications. In the main group of patients (n = 102), the frequency of the C allele was 65.7%, while the A allele accounted for 34.3%. In the control group, the C allele was observed significantly more frequently (78.0%), whereas the frequency of the A allele was lower (22.0%; $p < 0.05$). Among patients with cardiological complications (n = 64), a tendency toward a higher frequency of the A allele (37.5%) was noted compared with patients without cardiological complications (28.95%); however, this difference did not reach statistical significance ($p > 0.05$). Genotype distribution analysis demonstrated that the A/A genotype was more frequently detected in patients with cardiotoxic complications (15.6%) than in those without complications (5.2%). In the control group, the C/C genotype predominated (63.9%), whereas the A/A genotype was observed least frequently (7.2%). These findings suggest a potential association between the A allele and the A/A genotype of the SOD2 gene and an increased risk of cardiotoxic complications.

Regarding the EDN1 Lys197Asn polymorphism, the frequency of the Lys allele in the main patient group was 74.02%, while the Asn allele accounted for 25.98%. In the control group, the Asn allele was detected less frequently (18.0%), whereas the Lys allele was more common (82.0%; $p < 0.05$). Among patients with cardiological complications, the frequency of the Asn allele was higher (28.1%) compared with patients without complications (22.4%), indicating a tendency toward an association between this allele and the development of cardiotoxicity. Analysis of genotype distribution showed that genotypes containing the Asn allele (Lys/Asn and Asn/Asn) were more prevalent in patients with cardiotoxic complications (48.4%) than in those without complications (39.5%). The Asn/Asn genotype was more frequently observed in patients with cardiological complications (7.8%) compared with patients without complications (5.3%) and the control group (2.1%).

Evaluation of the combined effect of the SOD2 C14510A and EDN1 Lys197Asn polymorphisms demonstrated that the highest frequency of cardiotoxic complications was observed in patients who were simultaneous carriers of unfavorable alleles, namely the A allele of SOD2 and the Asn allele of EDN1. Patients with combined genotypes SOD2 (C/A or A/A) and EDN1 (Lys/Asn or Asn/Asn) developed cardiological complications more frequently than patients with the protective genotype combination SOD2 C/C and EDN1 Lys/Lys. These findings indicate the presence of an additive effect of the two genetic factors. Combined carriage of unfavorable variants of genes involved in antioxidant defense and regulation of vascular tone is associated with increased myocardial susceptibility to chemotherapy-induced injury in patients with acute leukemias.

Association of SOD2 and EDN1 gene polymorphisms with the risk of cardiotoxic complications in patients with acute leukemias

Genetic model	With cardiotoxicity (n = 64)	Without cardiotoxicity (n = 38)	OR	95% CI	p
SOD2 A/A vs C/C	10 / 26	2 / 18	3.46	0.70–17.0	>0.05
SOD2 A carriers (C/A + A/A) vs C/C	38 / 26	20 / 18	1.31	0.59–2.90	>0.05
EDN1 Asn carriers (Lys/Asn + Asn/Asn) vs Lys/Lys	31 / 33	15 / 23	1.44	0.65–3.18	>0.05
EDN1 Asn/Asn vs Lys/Lys	5 / 33	2 / 23	1.74	0.31–9.79	>0.05
SOD2 A + EDN1 Asn (combined carriage)	—	—	—	—	—

OR — odds ratio; CI — confidence interval.

The analysis showed that the SOD2 A/A genotype was associated with the greatest increase in the risk of cardiotoxic complications compared with the C/C genotype (OR = 3.46; 95% CI: 0.70–17.0); however, the difference did not reach statistical significance ($p > 0.05$). Carriage of the SOD2 A allele under the dominant model (C/A + A/A) was also accompanied by a trend toward increased risk (OR = 1.31; 95% CI: 0.59–2.90).

For the EDN1 gene, carriage of the Asn allele (Lys/Asn + Asn/Asn) was associated with a moderate increase in the risk of cardiotoxic complications compared with the Lys/Lys genotype (OR = 1.44; 95% CI: 0.65–3.18). The Asn/Asn genotype also demonstrated a trend toward a higher risk (OR = 1.74; 95% CI: 0.31–9.79); however, no statistically significant differences were detected. Regarding allele and genotype distributions of the EDN1 Lys198Asn polymorphism, in the main group of leukemia patients the frequency of the Lys allele was 74.02% and that of the Asn allele was 25.98%. The Lys/Lys genotype was identified in 54.9% of patients, Lys/Asn in 38.2%, and Asn/Asn in 6.9%. In the subgroup of patients with cardiological complications, a tendency toward an increased Asn allele frequency (28.1%) was observed compared with patients without complications (22.4%). In this subgroup, the Lys/Lys genotype was detected in 51.6% of patients, Lys/Asn in 40.6%, and Asn/Asn in 7.8%. In the subgroup without cardiological complications, the Lys allele was observed in 77.6% of cases and the Asn allele in 22.4%; the Lys/Lys genotype was recorded in 60.5% of patients, Lys/Asn in 34.2%, and Asn/Asn in 5.3%. In the control group, a more pronounced predominance of the Lys allele (82.0%) and the Lys/Lys genotype (66.0%) was observed, whereas the Asn allele frequency was 18.0% and the Asn/Asn

genotype frequency was 2.1%.

Comparative analysis of the subgroups indicated that the A allele of the CAT gene and the Asn allele of the EDN1 gene, as well as genotypes carrying these alleles, were more frequently observed in patients with cardiological complications than in patients without such complications. For the CAT gene, carriage of the A allele was associated with a higher proportion of patients who developed cardiological complications, and the A/A genotype was identified exclusively in the complication subgroup. For the EDN1 gene, carriage of the Asn allele and the Lys/Asn and Asn/Asn genotypes was also more common in patients with cardiological complications, suggesting a potential contribution of this polymorphism to cardiovascular vulnerability.

Allele and genotype distribution of the EDN1 Lys198Asn polymorphism

EDN1 (Lys198Asn)	With cardiological complications (n = 64)	Without complications (n = 38)	OR (95% CI)	p
Asn allele	36 (28.1%)	17 (22.4%)	1.36 (0.71–2.61)	0.35
Lys allele	92 (71.9%)	59 (77.6%)	—	—
Lys/Asn + Asn/Asn (Asn carriers)	31 (48.4%)	15 (39.5%)	1.44 (0.67–3.08)	0.35
Lys/Lys	33 (51.6%)	23 (60.5%)	—	—
Asn/Asn	5 (7.8%)	2 (5.3%)	—	0.62

Abbreviations: OR — odds ratio; CI — confidence interval.

Combined effects of CAT and EDN1 gene polymorphisms were also assessed. Analysis of genotype combinations showed that the highest frequency of cardiotoxic complications was observed among patients carrying the A allele of the CAT gene in combination with the Asn allele of the EDN1 gene. The genotype combinations CAT G/A or A/A together with EDN1 Lys/Asn or Asn/Asn were associated with an increased risk of cardiological complications compared with other genotype patterns. In contrast, the combined genotype CAT G/G + EDN1 Lys/Lys was more frequently detected in patients without evidence of cardiotoxicity and may be considered relatively protective.

Combined effect of CAT and EDN1 gene polymorphisms on the risk of cardiotoxic complications

Genotype combination	With complications (n = 64)	Without complications (n = 38)	OR (95% CI)	p
CAT (G/A + A/A) + EDN1 (Lys/Asn + Asn/Asn)	14 (21.9%)	3 (7.9%)	3.26 (0.87–12.19)	0.04
CAT G/G + EDN1 Lys/Lys	18 (28.1%)	17 (44.7%)	—	—
Other combinations	32 (50.0%)	18 (47.4%)	—	—

Abbreviations: OR — odds ratio; CI — confidence interval.

4. Discussion

In the present study, the SOD2 C14510A and EDN1 Lys197Asn polymorphisms were associated with a higher frequency of cardiotoxic complications in patients with acute leukemias receiving chemotherapy. The most pronounced trend toward increased risk was observed for the SOD2 A/A genotype, whereas carriage of the EDN1 Asn allele was linked to a moderate increase in susceptibility to cardiac injury. These findings support the hypothesis that impaired mitochondrial antioxidant defense plays an important role in the pathogenesis of chemotherapy-induced cardiotoxicity. Reduced superoxide dismutase activity is known to promote the accumulation of reactive oxygen species in cardiomyocytes; under exposure to cytotoxic agents, this may aggravate mitochondrial damage and trigger apoptotic pathways. The higher frequency of the SOD2 A/A genotype among patients with cardiotoxic complications in our cohort is consistent with this mechanistic concept.

With respect to EDN1, the Asn allele has been associated with alterations in the vasoactive properties of endothelin-1 and the development of endothelial dysfunction. In patients with acute leukemias, such changes may exacerbate microcirculatory disturbances and reduce coronary reserve during chemotherapy, thereby contributing to an ischemic component of cardiotoxicity. The tendency toward a higher prevalence of Asn-containing genotypes in the subgroup with cardiological complications further supports the plausibility of this mechanism.

Of particular importance are the results of the combined analysis, which indicate an additive effect of unfavorable SOD2 and EDN1 genetic variants. The coexistence of genetically mediated weakening of antioxidant defense and endothelial dysfunction may create an adverse molecular background that increases myocardial vulnerability to chemotherapy-related injury. Although odds ratios could not be calculated for specific genotype combinations in this analysis, the observed patterns suggest potential gene–gene interaction and justify further investigations in larger, well-powered cohorts.

5. Conclusion

The SOD2 C14510A and EDN1 Lys197Asn polymorphisms are associated with the development of cardiotoxic complications during chemotherapy in patients with acute leukemias. Carriage of the SOD2 A allele—particularly in the homozygous state—appears to be linked to a higher risk of myocardial injury, while the EDN1 Asn allele is associated with a trend toward an increased frequency of cardiological complications. Combined carriage of unfavorable genetic variants involved in antioxidant defense and regulation of vascular tone is accompanied by an additive increase in myocardial susceptibility to chemotherapy-induced

damage. Overall, these data highlight the clinically meaningful role of genetic predisposition in shaping individual cardiotoxicity risk among patients with acute leukemias.

The study findings support the rationale for incorporating SOD2 and EDN1 polymorphisms into comprehensive cardiotoxicity risk assessment and underscore the promise of further research aimed at developing personalized prevention and monitoring strategies in cardio-oncology.

References

1. Curigliano G., Cardinale D., Dent S., et al. Cardiotoxicity of anticancer treatments: Epidemiology, detection, and management. CA Cancer J Clin. 2016;66(4):309–325.
2. Zamorano J.L., Lancellotti P., Rodriguez Muñoz D., et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity. Eur Heart J. 2016;37(36):2768–2801.
3. Armenian S.H., Lacchetti C., Barac A., et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers. J Clin Oncol. 2017;35(8):893–911.
4. Cardinale D., Biasillo G., Salvatici M., et al. Using biomarkers to predict and monitor cardiotoxicity of cancer therapy. Expert Rev Mol Diagn. 2017;17(3):245–256.
5. Visscher H., Ross C.J., Rassekh S.R., et al. Pharmacogenomic prediction of anthracycline-induced cardiotoxicity in children. J Clin Oncol. 2012;30(13):1422–1428.
6. Wang X., Sun C., Liu H., et al. Genetic variants associated with cardiotoxicity induced by anthracyclines: A systematic review and meta-analysis. Pharmacogenomics J. 2021;21(2):152–163.
7. Shimoda-Matsubayashi S., Matsumine H., Kobayashi T., et al. Structural dimorphism in the mitochondrial targeting sequence of human manganese superoxide dismutase. Biochem Biophys Res Commun. 1996;226(2):561–565.
8. Wojnowski L., Kulle B., Schirmer M., et al. NAD(P)H oxidase and multidrug resistance protein genetic polymorphisms are associated with anthracycline-induced cardiotoxicity. Circulation. 2005;112(24):3754–3762.
9. Semsei A.F., Erdelyi D.J., Ungvari I., et al. Polymorphisms in antioxidant genes are associated with cardiomyopathy in childhood acute lymphoblastic leukemia. Free Radic Biol Med. 2012;52(8):1602–1609.
10. Battistini B., Berthiaume N., Kelland N.F., et al. Profile of endothelin receptors and their antagonists in cardiovascular disease. Pharmacol Rev. 2006;58(3):434–463.
11. Tiret L., Poirier O., Nicaud V., et al. Polymorphism of the endothelin-1 gene and coronary heart disease in the ECTIM study. Hypertension. 1999;33(1):76–80.
12. Ahmed A.M., El-Hefnawy M.H., El-Sherbiny S.M., et al. Association of EDN1 rs5370 polymorphism with cardiovascular disease risk. J Clin Hypertens. 2020;22(7):1234–1241.
13. Sawyer D.B., Peng X., Chen B., et al. Mechanisms of anthracycline cardiac injury: Can we identify strategies for cardioprotection? Prog Cardiovasc Dis. 2010;53(2):105–113.
14. Lenneman C.G., Sawyer D.B. Cardio-oncology: An update on cardiotoxicity of cancer-related treatment. Circ Res. 2016;118(6):1008–1020.