GMR
The Original

ANTIOXIDANT DEFENSE GENE POLYMORPHISMS AS MOLECULAR GENETIC PREDICTORS OF CARDIOTOXICITY IN PATIENTS WITH ACUTE LEUKEMIA

Kayumov Abdurakhman Abdumavlyanovich[1], Zokirova Muborakkhon Bobir kizi[2]

[1] Professor, Republican Specialized Scientific and Practical Medical Center of Hematology, Tashkent, Uzbekistan.
[2] PhD, Cardiologist, Republican Specialized Scientific and Practical Medical Center of Hematology, Tashkent, Uzbekistan.

ABSTRACT

Background: Cardiotoxicity remains one of the most important non-hematological complications in patients with acute leukemia receiving anticancer therapy. Oxidative stress plays a central role in myocardial injury, whereas genetic variations in antioxidant defense pathways may influence individual susceptibility to cardiovascular complications. *Objective:* To evaluate the association of SOD2 C14510A, GPX4 C718T, and CAT G262A polymorphisms with cardiotoxicity and cardiovascular complications in patients with acute leukemia. *Methods:* A retrospective observational study included 102 patients with acute leukemia and 97 age- and sex-matched healthy controls. Patients underwent clinical examination, electrocardiography, echocardiography, and assessment of cardiac biomarkers, including troponins and NT-proBNP. Genotyping of SOD2 C14510A, GPX4 C718T, and CAT G262A polymorphisms was performed using real-time polymerase chain reaction. Associations between genetic variants and cardiovascular complications were evaluated using odds ratios (ORs) with 95% confidence intervals (CIs). *Results:* The frequency of the SOD2 A allele was significantly higher in patients with acute leukemia than in healthy controls (34.31% vs. 21.65%; OR=1.90, 95% CI 1.21–2.95; p=0.01). The GPX4 T allele was more prevalent among patients with cardiovascular complications than among those without complications (50.78% vs. 38.16%; OR=1.67, 95% CI 0.92–3.03). Carriers of the CAT A allele demonstrated a tendency toward increased cardiotoxicity risk (OR=2.05), although statistical significance was not achieved. Unfavorable antioxidant gene variants were associated with elevated NT-proBNP and cardiac troponin levels, as well as reduced left ventricular ejection fraction. *Conclusions:* Genetic polymorphisms involved in antioxidant defense contribute to the development of cardiovascular complications in acute leukemia. The SOD2 C14510A polymorphism demonstrated the strongest association with cardiotoxicity and may serve as a promising molecular genetic marker for cardiovascular risk stratification. Comprehensive assessment of SOD2, GPX4, and CAT variants may improve personalized monitoring and prevention strategies in cardio-hematology.

Keywords: Acute leukemia; cardiotoxicity; antioxidant defense; oxidative stress; SOD2; GPX4; CAT.

INTRODUCTION

Acute leukemias are among the most aggressive hematological malignancies and remain a major challenge in modern hemato-oncology. Despite substantial advances in patient management achieved through the introduction of contemporary chemotherapy protocols, targeted therapies, and immunotherapeutic approaches, cardiovascular complications continue to exert a significant impact on prognosis, quality of life, and long-term outcomes in patients who achieve remission of the underlying disease [1,2].

According to the 2022 European Society of Cardiology (ESC) Guidelines on Cardio-Oncology, signs of cardiotoxicity of varying severity are observed in approximately 20–45% of patients receiving potentially cardiotoxic anticancer treatment. In patients treated with anthracyclines, the risk of developing heart failure may reach 26%, whereas subclinical myocardial injury occurs considerably more frequently and often remains undetected during the early stages of follow-up [4].

Recent years have witnessed substantial advances in the understanding of the pathophysiological mechanisms underlying cardiotoxicity. While earlier studies primarily focused on the direct cytotoxic effects of anticancer agents on cardiomyocytes, current evidence highlights the important contribution of oxidative stress, mitochondrial dysfunction, ferroptosis, and genetically determined alterations in antioxidant defense mechanisms.

Excessive generation of reactive oxygen species (ROS) is considered one of the key mechanisms of myocardial injury. ROS overproduction disrupts cellular membrane integrity, damages mitochondria, and triggers programmed cardiomyocyte death [6]. Anthracyclines promote free radical generation through interactions with iron ions and mitochondrial enzymatic systems, leading to enhanced lipid peroxidation, chronic inflammation, and myocardial remodeling [8].

The effectiveness of antioxidant defense largely depends on individual genetic characteristics. In this context, particular attention has been directed toward the genes encoding superoxide dismutase 2 (SOD2), catalase (CAT), and glutathione peroxidase 4 (GPX4), which participate in the sequential detoxification of reactive oxygen species and protect cardiomyocytes from oxidative damage.

The SOD2 (Superoxide Dismutase 2) gene encodes mitochondrial superoxide dismutase, one of the principal enzymes of cellular antioxidant defense. The SOD2 C14510A polymorphism may influence enzyme activity and alter the intensity of free radical oxidation processes. Previous studies have suggested that unfavorable variants of this gene may be associated with increased susceptibility to cancer therapy-related cardiotoxicity.

The CAT (Catalase) gene encodes catalase, an enzyme responsible for the conversion of hydrogen peroxide into water and oxygen. Reduced catalase activity results in hydrogen peroxide accumulation and exacerbation of oxidative stress. Several studies have reported associations between CAT polymorphisms and an increased risk of cardiovascular abnormalities and myocardial remodeling [8].

Particular interest has recently been focused on the GPX4 (Glutathione Peroxidase 4) gene, which is recognized as a key regulator of ferroptosis. GPX4 participates in the detoxification of lipid hydroperoxides and prevents ferroptotic cell death. Experimental and clinical studies indicate that reduced GPX4 activity may play an important role in anthracycline-induced myocardial injury and the development of myocardial dysfunction [7].

Despite growing interest in the genetic mechanisms of cardiotoxicity, evidence regarding the role of antioxidant system gene polymorphisms in patients with acute leukemia remains limited and inconsistent. The distribution of SOD2, CAT, and GPX4 polymorphisms in this patient population, as well as their association with markers of myocardial injury, including troponins, NT-proBNP levels, and echocardiographic parameters, has not been sufficiently investigated.

Therefore, the study of antioxidant defense gene polymorphisms is of considerable scientific and clinical importance. Identification of genetic factors associated with cardiovascular complications may improve early detection of cardiotoxicity, optimize patient monitoring strategies, and facilitate the development of personalized approaches to cardiovascular risk prevention in patients with acute leukemia.

Purpose of the research

To investigate the role of SOD2 C14510A, CAT G262A, and GPX4 C718T polymorphisms in the development of cardiovascular complications in patients with acute leukemia and to evaluate their association with markers of myocardial injury, including NT-proBNP levels, cardiac troponins, and left ventricular ejection fraction.

MATERIALS AND METHODS

This study was conducted at the Republican Specialized Scientific and Practical Medical Center of Hematology. A retrospective, single-center observational study was performed to assess the frequency and structure of cardiotoxic complications in patients with acute leukemia receiving anticancer therapy.

A total of 102 patients with acute leukemia undergoing treatment at the Republican Specialized Scientific and Practical Medical Center of Hematology were enrolled in the study. The control group consisted of 97 apparently healthy individuals matched for age and sex.

According to the presence of cardiovascular complications, patients were divided into two subgroups:

- patients with cardiovascular complications (n = 64);
- patients without cardiovascular complications (n = 38).

All participants underwent clinical evaluation, complete blood count testing, biochemical blood analysis, assessment of cardiac biomarkers (troponin I, troponin T, and NT-proBNP), electrocardiography, and echocardiography.

Molecular genetic analysis included genotyping of the SOD2 C14510A, CAT G262A, and GPX4 C718T polymorphisms using real-time polymerase chain reaction (RT-PCR).

The distribution of genotypes was assessed for compliance with the Hardy–Weinberg equilibrium using the chi-square test. No significant deviations from Hardy–Weinberg equilibrium were observed for any of the investigated polymorphisms ($p > 0.05$).

Statistical analyses were performed using SPSS Statistics version 26.0. Associations between genetic markers and the risk of cardiovascular complications were evaluated by calculating odds ratios (ORs) with 95% confidence intervals (95% CIs). Differences were considered statistically significant at $p < 0.05$.

Table 1. Allele Distribution of the SOD2 C14510A Polymorphism

Allele	Acute Leukemia Patients n=102	Controls n=97	OR	95% CI	p-value
C	134 (65,69%)	152 (78,35%)	0,53	0,34–0,82	0,01
A	70 (34,31%)	42 (21,65%)	1,90	1,21–2,95	0,01

Table 2. Genotype Distribution of the SOD2 C14510A Polymorphism

Genotype	Acute Leukemia Patients	Controls n=97	OR	p-value
CC	43,14%	63,92%	0,45	0,01
CA	45,10%	28,87%	2,02	0,01

Genotype	Acute Leukemia Patients	Controls n=97	OR	p-value
AA	11,76%	7,22%	1,72	0,19

Table 3. Allele Distribution of the GPX4 C718T Polymorphism

Allele	Patients with Cardiovascular Complications (n=64)	Patients without Cardiovascular Complications n=38	OR	95% CI
C	49,22%	61,84%	0,60	0,33–1,09
T	50,78%	38,16%	1,67	0,92–3,03

Table 4. Allele Distribution of the CAT G262A Polymorphism

Allele	Patients with Cardiovascular Complications (n=64)	Patients without Cardiovascular Complications n=38	OR	p
G	82,81%	90,79%	0,49	0,24
A	17,19%	9,21%	2,05	0,24

Table 5. Association Between Antioxidant System Gene Polymorphisms and the Risk of Cardiotoxicity

Gene	Risk Variant	OR	95% CI	p
SOD2	A- **Allele**	1,90	1,21–2,95	0,01
PX4	T- **Allele**	1,67	0,92–3,03	0,08

RESULTS AND DISCUSSION

The present study demonstrated a significant association between antioxidant defense gene polymorphisms and the development of cardiovascular complications in patients with acute leukemia. Among the investigated genetic variants, the SOD2 C14510A polymorphism showed the strongest relationship with cardiotoxicity. The frequency of the A allele was significantly higher in patients with acute leukemia than in healthy controls (34.31% vs. 21.65%; OR=1.90; 95% CI 1.21–2.95; p=0.01), suggesting a potential role of impaired mitochondrial antioxidant protection in myocardial injury.

GPX4 C718T polymorphism was characterized by a higher frequency of the T allele among patients with cardiovascular complications compared with those without complications (50.78% vs. 38.16%; OR=1.67). Although the association did not reach statistical significance, the observed trend may indicate the involvement of ferroptosis-related mechanisms in cardiotoxicity development. GPX4 is a key regulator of lipid peroxide detoxification and cardiomyocyte survival under oxidative stress conditions.

For the CAT G262A polymorphism, carriers of the A allele demonstrated a tendency toward increased cardiovascular risk (OR=2.05). While statistical significance was not achieved, these findings support the biological role of catalase in protecting myocardial tissue against hydrogen peroxide accumulation and oxidative injury.

Importantly, unfavorable genetic variants were associated with elevated levels of NT-proBNP and cardiac troponins, as well as reduced left ventricular ejection fraction. These findings indicate that genetic alterations in antioxidant defense pathways may contribute not only to biochemical evidence of myocardial injury but also to structural and functional cardiac abnormalities.

The results support the concept that oxidative stress represents one of the major mechanisms of cancer therapy-related cardiotoxicity. Identification of genetic markers associated with impaired antioxidant defense may improve cardiovascular risk stratification and facilitate personalized monitoring strategies in patients with acute leukemia.

CONCLUSIONS

The frequency of the A allele of the SOD2 C14510A polymorphism was significantly higher among patients with acute leukemia than in healthy controls (34.31% vs. 21.65%; OR=1.90; 95% CI 1.21–2.95; p=0.01).

The frequency of the T allele of the GPX4 C718T polymorphism reached 50.78% among patients with cardiovascular complications compared with 38.16% among patients without complications, suggesting a possible role of ferroptosis-related mechanisms in cardiotoxicity.

Carriers of the A allele of the CAT G262A polymorphism demonstrated a tendency toward an increased risk of cardiovascular complications (OR=2.05), although the observed differences did not reach statistical significance.

Antioxidant defense gene polymorphisms were associated with higher levels of NT-proBNP and cardiac troponins, as well as a tendency toward reduced left ventricular ejection fraction.

Among the investigated polymorphisms, SOD2 C14510A demonstrated the strongest association with cardiovascular complications and may be considered a promising molecular genetic marker of cardiotoxicity risk.

Comprehensive assessment of SOD2, GPX4, and CAT polymorphisms may improve early identification of patients at increased risk of cardiovascular complications and facilitate personalized cardiovascular monitoring strategies in acute leukemia.

REFERENCES

1. Lyon A.R., López-Fernández T., Couch L.S. et al. 2022 ESC Guidelines on cardio-oncology. *European Heart Journal*. 2022;43(41):4229–4361.
2. Curigliano G., Lenihan D., Fradley M. et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. *Annals of Oncology*. 2020;31(2):171–190.
3. Armenian S.H., Xu L., Ky B. et al. cardiovascular disease among survivors of adult-onset cancer: a community-based retrospective cohort study. *Journal of Clinical Oncology*. 2016;34(10):1122–1130.
4. Herrmann J., Yang E.H., Iliescu C.A. et al. Vascular toxicities of cancer therapies. *Circulation*. 2022;145(18):1356–1371.
5. Kim Y., Moura L.M., Caly D.N. et al. Genetics of cancer therapy-associated cardiotoxicity. *JACC: CardioOncology*. 2022;4(2):143–159.
6. Wallace K.B., Sardão V.A., Oliveira P.J. Mitochondrial determinants of anthracycline cardiotoxicity. *Circulation Research*. 2023;132(4):540–556.
7. Fang X., Wang H., Han D. et al. Ferroptosis as a target for protection against cardiomyopathy. *Proceedings of the National Academy of Sciences of the USA*. 2019;116(7):2672–2680.
8. Chambliss JM, Acosta MA, Kelly JP, et al. *A Polymorphism in the Catalase Gene Promoter Confers Protection Against Severe RSV Bronchiolitis.* Viruses. 2020;12(1):57. doi:10.3390/v12010057.
9. Short N.J., Rytting M.E., Cortes J.E. Acute myeloid leukaemia. *The Lancet*. 2018;392(10147):593–606.

.