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PROGNOSTIC VALUE OF NATRIURETIC PEPTIDE AND TROPONIN T IN PATIENTS WITH ACUTE MYELOBLASTIC LEUKEMIA

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Abstract. **Background***: Early detection of myocardial injury in acute myeloblastic leukemia (AML) is crucial for preventing irreversible cardiovascular complications.*

Objective*: To assess the prognostic value of the natriuretic peptide NT-proBNP and cardiac troponin T in detecting chemotherapy-induced cardiotoxicity in AML patients.*

Methods*: A prospective observational study involved 58 AML patients undergoing polychemotherapy. These patients underwent specialized biochemical and instrumental diagnostic evaluations. Results: All AML patients showed signs of cardiovascular dysfunction during polychemotherapy. This was reflected in a significant increase in NT-proBNP levels after treatment (from 30.39±2.9 to 320.0±2.9 pg/mL, p<0.05). Additionally, troponin T levels rose markedly (97.8±2.9 ng/L versus 18.2±2.7 ng/L in the control group, p<0.05), correlating with clinical symptoms resembling acute coronary syndrome.*

Conclusion*: NT-proBNP and troponin T are sensitive biomarkers for the early detection of chemotherapy-induced cardiotoxicity in patients with AML.*

Keywords: *Acute myeloblastic leukemia, cardiotoxicity, polychemotherapy, NT-proBNP, troponin T, cardiovascular complications, left ventricular ejection fraction, myocardial ischemia, prognosis of toxic myocardial injury.*

Annotatsiya: **Kirish:** *O‘tkir mieloblast leykemiyada (OML) miokard shikastlanishini erta aniqlash yurak-qon tomir tizimi asoratlarining oldini olishda muhim ahamiyatga ega.*

Maqsad: *OML bilan kasallangan bemorlarda ximioterapiya natijasida yuzaga kelgan kardiotoksiklikni aniqlashda NT-proBNP natriyuretik peptidi va yurak troponin T biomarkerlarining prognostik ahamiyatini baholash.*

Uslublar: *Tadqiqotda poliximioterapiya olayotgan 58 nafar OML bemori ishtirok etdi. Ular maxsus biokimyoviy va instrumental diagnostika usullari yordamida tekshiruvdan o‘tkazildi.*

Natijalar: *Barcha OML bemorlarida poliximioterapiya davrida yurak-qon tomir faoliyatining buzilishi kuzatildi. Bu NT-proBNP darajasining ahamiyatli oshishi bilan namoyon bo‘ldi (davolanishdan oldin 30.39±2.9 pg/mL dan keyin 320.0±2.9 pg/mL gacha, p<0.05). Bundan tashqari, troponin T darajasi sezilarli darajada oshdi (nazorat guruhiga nisbatan*

97.8±2.9 ng/L va 18.2±2.7 ng/L, p<0.05) va bu holat o‘tkir koronar sindromga o‘xshash klinik belgilar bilan bog‘liq edi.

Xulosa: *NT-proBNP va troponin T OML bemorlarida ximioterapiya bilan bog‘liq kardiotoksiklikni erta aniqlash uchun sezgir biomarkerlardir.*

Kalit so‘zlar: *O‘tkir mieloblast leykemiya, kardiotoksiklik, poliximioterapiya, NT-proBNP, troponin T, yurak-qon tomir asoratlari, chap qorinchadan chiqarish fraksiyasi, miokard ishemiyasi, toksik miokard shikastlanishi prognozi.*

Аннотация. **Актуальность:** *Ранняя диагностика поражения миокарда при остром миелобластном лейкозе (ОМЛ) имеет решающее значение для предотвращения необратимых сердечно-сосудистых осложнений.*

Цель: *Оценить прогностическую значимость натрийуретического пептида NT-proBNP и сердечного тропонина Т в выявлении химиотерапевтически индуцированной кардиотоксичности у пациентов с ОМЛ.*

Методы: *Проспективное обсервационное исследование включало 58 пациентов с ОМЛ, получавших полихимиотерапию. У всех участников проводились специализированные биохимические и инструментальные методы диагностики.*

Результаты: *У всех пациентов с ОМЛ на фоне полихимиотерапии наблюдались признаки сердечно-сосудистой дисфункции. Это проявлялось достоверным повышением уровня NT-proBNP после лечения (с 30,39±2,9 до 320,0±2,9 пг/мл, p<0,05). Кроме того, уровень тропонина Т также значительно увеличился (97,8±2,9 нг/л против 18,2±2,7 нг/л в контрольной группе, p<0,05), что коррелировало с клиническими симптомами, напоминающими острый коронарный синдром.*

Заключение: *NT-proBNP и тропонин Т являются чувствительными биомаркерами для раннего выявления химиотерапевтически индуцированной кардиотоксичности у пациентов с острым миелобластным лейкозом.*

Ключевые слова: *острый миелобластный лейкоз, кардиотоксичность, полихимиотерапия, NT-proBNP, тропонин Т, сердечно-сосудистые осложнения, фракция выброса левого желудочка, ишемия миокарда, прогноз токсического поражения миокарда.*

INTRODUCTION:

There is a steady global trend toward an increase in the number of diagnosed malignant neoplasms, particularly those affecting the hematopoietic and lymphatic systems [2,6]. Pharmacological therapy- especially polychemotherapy- has also evolved with the advancement of oncological diseases and diagnostic methods. However, this progress has been accompanied by a growing incidence of adverse effects. One of the most frequent complications is cardiomyocyte damage, which has led to the emergence of the concept of chemotherapy-induced cardiotoxicity.

Recently, oncohematologists have increasingly focused on early predicting and preventing cardiological complications associated with chemotherapy [10,3,11]. Modern diagnostic approaches for assessing cardiotoxic effects in oncohematological patients include

echocardiography and the measurement of cardiac biomarkers (troponin I or T and natriuretic peptides such as BNP and NT-proBNP) before and during polychemotherapy[9].

According to the guidelines of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI), the primary criterion for chemotherapy-induced cardiotoxicity associated with symptoms of heart failure is a decrease in left ventricular ejection fraction (LVEF) by 10% or more, provided that the LVEF falls below [8].

The implementation of troponin-level assessment systems has significantly enhanced the specificity of diagnosing not only acute myocardial infarction but also myocardial cell injury resulting from the toxic effects of chemotherapy. Cardiac troponin (cTn) is a protein complex composed of three subunits: troponin T anchors the troponin complex to the actin filament, troponin C serves as the calcium-binding component, and troponin I inhibits actin-myosin interaction in the absence of adequate calcium ions [7]. Since cardiac troponins I (cTnI) and T (cTnT) are structural components of the myocardial contractile apparatus and are expressed almost exclusively in the heart, they exhibit high specificity as biomarkers of cardiomyocyte dysfunction. In patients with acute myeloblastic leukemia (AML), polychemotherapy (PCT) involves the use of several classes of pharmacological agents, including anthracyclines, alkylating agents, antimetabolites, antimicrotubule agents, monoclonal antibodies, low-molecular-weight tyrosine kinase inhibitors, and proteasome inhibitors. The selection and dosing of these agents are determined on an individual basis. Anthracycline-induced cardiotoxicity is classified as type I, which is considered irreversible and results from cardiomyocyte death. The extent of myocardial damage in such cases is dose-dependent, correlating with the cumulative dose of the drug. In contrast, trastuzumab-induced cardiotoxicity is categorized as type II, which is potentially reversible and mediated by mitochondrial and protein-related damage. This type of cardiotoxicity is not dose-dependent[4]. Once symptoms of heart failure become clinically apparent, the prognosis significantly worsens. According to the literature, the two-year survival rate in such cases is less than 50%. While the cardiotoxic effects of anthracyclines have been extensively studied in patients receiving high cumulative doses, cardiovascular changes in patients treated with lower cumulative doses remain insufficiently explored.

Following troponin, the second most crucial cardiotoxicity biomarker is brain natriuretic peptide (BNP). BNP exists in several molecular forms depending on its site of synthesis:

1. **Atrial natriuretic peptide (ANP)** *is synthesized predominantly in the atria, with significantly lower expression in the ventricles. It has also been identified in the brain, anterior pituitary, kidneys, and lungs.*
2. **Brain natriuretic peptide (BNP)** *is produced mainly in the ventricular myocardium, with smaller amounts synthesized in the atria and brain.*
3. **C-type natriuretic peptide (CNP)** *is primarily secreted by vascular endothelial cells and, to a lesser extent, by the brain and epithelial cells of the renal tubules and collecting ducts.*

Materials and Methods:

A total of 58 patients were examined, including 32 men and 26 women, aged 46 to 63 years (median age of 51). All patients were hospitalized at the Scientific and Practical Medical Center of Hematology, in the Hematology Departments I and II. The diagnosis of acute myeloid leukemia (AML) was established based on clinical complaints, such as severe weakness, body-wide hemorrhagic manifestations, frequent nosebleeds, and gingival hyperplasia. Patients with a complete blood count (CBC) showed signs of thrombocytopenia and hyperleukocytosis. Additionally, bone marrow analysis revealed the presence of blast cells, which enabled the formulation of a preliminary diagnosis. The final clinical diagnosis was confirmed through phenotyping, fluorescence in situ hybridization (FISH) analysis, and flow cytometry.

Subsequently, patients underwent polychemotherapy (PCT) by national clinical protocols, with cytostatic drug dosages adjusted individually based on body weight. The treatment began with induction therapy. The selected antitumor agents were azacitidine or decitabine ± venetoclax. Azacitidine was administered at 75 mg/m² subcutaneously or intravenously for days 1–7 (alternatively, days 1–5 plus days 8–9), or decitabine at 20 mg/m² intravenously for days 1–5. Venetoclax was given with dose escalation: 100 mg on day 1, 200 mg on day 2, and 400 mg orally once daily from day 3 to 28. After 28 days, if bone marrow analysis showed less than 5% blast cells, the next phase — consolidation — was initiated, which included six cycles of the selected chemotherapy regimen. At the time of therapy initiation, no cardiovascular symptoms or abnormalities were identified in the patients. According to the literature, azacitidine is associated with the following cardiovascular side effects: arterial Hypotension, atrial fibrillation, heart failure, cardiac arrest, cardiomyopathy, and orthostatic Hypotension. Possible cardiac side effects of azacitidine include **Tachycardia (***rapid heartbeat***)**, **Hypotension (***low blood pressure***)**, **Dyspnea** *(sometimes related to cardiac or pulmonary insufficiency)*, **Edema** *(which may be a sign of heart failure)*, **Chest pain**, *and rare cases,* **heart failure or myocardial ischemia**. *Decitabine, a hypomethylating agent used in the treatment of acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), can also cause cardiotoxic effects. According to a review published in the journal Clinical Oncohematology, decitabine may be associated with the development of myocarditis, peripheral edema, Hypotension, chest discomfort, myocardial ischemia, and even cardiac arrest (E.N. Parovichnikova; E.I. Emelina, G.E. Gendlin, I.G. Nikitin).[5]*

For the diagnosis and monitoring of these conditions, electrocardiography (ECG), 24-hour Holter monitoring, and echocardiography are recommended, as well as the measurement of cardiac biomarkers such as troponin I and NT-proBNP. Special attention should be paid to patients with cardiovascular risk factors (E.I. Emelina, G.E. Gendlin, I.G. Nikitin). Studies have shown that venetoclax does not significantly affect the QTc interval, indicating a low arrhythmogenic potential. In a clinical trial involving 176 patients who received up to 1200 mg of venetoclax per day, there was no QTc prolongation or other significant electrophysiological changes in the heart. However, when venetoclax was used in combination therapy with other agents, such as ibrutinib, an increased frequency of severe cardiovascular adverse events was observed (T.E. Bialik). Study results: At the time of admission, out of 58 patients, 9 had a previously diagnosed ischemic heart disease (IHD) with stable exertional angina class II, and these patients also had baseline chronic heart failure (CHF) class II according to NYHA, with preserved ejection fraction. The ESC 2019 guidelines established the diagnosis. In 7 out of 58 patients, grade 2 arterial hypertension was diagnosed, and blood pressure was well controlled on

antihypertensive therapy. These patients were taking medications from the following classes: beta-blockers, ACE inhibitors, and calcium channel blockers. No cardiovascular complaints were reported.

Biomarker levels were assessed twice during the initiation of chemotherapy. The first measurement of troponin and NT-proBNP levels was performed before chemotherapy when the patients had no cardiovascular symptoms. The second measurement was conducted after the completion of induction polychemotherapy (PCT) and at the start of the consolidation phase, specifically on day 10 following the second cycle of PCT. The control group consisted of 22 conditionally healthy individuals. The first phase included the evaluation of NT-proBNP, troponin T, and ECG before the initiation of chemotherapy. The second phase was carried out after administration of cytostatic agents according to the induction and consolidation protocols, specifically on day 10 of therapy following the start of the second PCT cycle. This phase also included the assessment of the biomarkers above and instrumental diagnostics such as ECG and echocardiography (EchoCG). This time frame was chosen explicitly for cardiovascular system diagnostics, as patients most commonly begin reporting discomfort in the heart region and dyspnea during the early consolidation phase following high-dose induction chemotherapy.

The material was the venous blood of the studied cyclone activator test tubes, and the serum concentration of NT-proBNP was determined using enzyme-linked immunosorbent assay (ELISA) with commercial test systems "IBL" and "Biochemmak" (Germany). The troponin T level was determined using the electrochemiluminescence immunoassay (ECLIA) method on a COBAS e 402 analyzer (USA). In addition, standard electrocardiography (ECG) was performed at a paper speed of 50 mm/sec using a 12-channel "Carewell" ECG device, and echocardiographic examinations (EchoCG) were carried out with a MyLABX6 ultrasound system (Italy). The left ventricular ejection fraction (LVEF) was assessed using Simpson's method by the ASE Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[1]

Statistical analysis was done using the software package "Statistica 8.0" (StatSoft). All values are presented as the mean ± standard error of the mean (M±m). The results were considered statistically significant at $p<0.05$.

Results:

Analysis of the clinical and laboratory-instrumental manifestations of cardiovascular complications revealed that such complications were observed in 100% of all patients with acute myeloblastic leukemia (AML) included in the study at various stages of intensive polychemotherapy (PCT).

The rationale for cardiovascular system evaluation was based on patients' complaints. The most common and earliest symptoms included intensified or irregular heartbeats, progressive dyspnea during physical exertion or at rest, and retrosternal chest pain lasting up to 20 minutes, radiating to the left arm and relieved by 0.5 mg of nitroglycerin.

In all patients with acute myeloblastic leukemia (AML) included in the study, NT-proBNP concentrations increased during polychemotherapy (PCT). Statistically significant differences were observed between NT-proBNP levels before and after chemotherapy. The concentration of this peptide increased significantly in patients following the completion of the main cytostatic

chemotherapy regimen. Additionally, cardiac chamber dilatation in this group of patients was associated with a marked increase in NT-proBNP values, confirming its role as a potential biomarker of myocardial dysfunction. E.D. Teplyakova and M.O. Yegorova reportedly conducted this study.

Parameter	Healthy individuals (n=52)	AML patients before PCT (n=58)	AML patients after PCT (remission induction, n=58)
NT-proBNP, pg/mL	*6,14±2,7*	*30,39±2,9**	*320,0±2,9**

Note: * – *statistically significant differences compared to the control group (p<0.05)*

Analysis of troponin T levels showed that baseline troponin T concentrations were within the normal range and did not differ significantly from those of the relatively healthy control group included in the study. However, elevated troponin T levels have been observed in patients who reported cardiovascular complaints after a course of cytostatic chemotherapy.

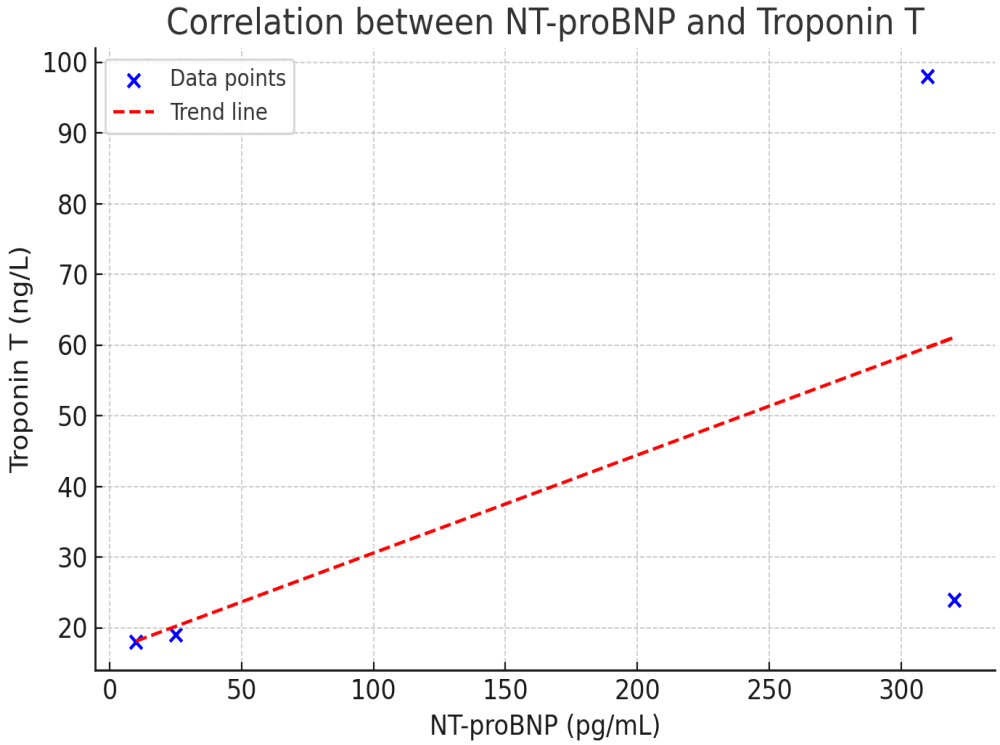
Parameter	Healthy individuals (n=52)	AML patients before PCT (n=58)	AML patients after PCT (remission induction, n=47)	AML patients after PCT with cardiovascular symptoms (n=11)
Troponin T, ng/L	*18.2±2,7*	*19.7±2,9**	*23.8±2,7*	*97.8±2,9**

Note: * – *statistically significant differences compared to the control group (p<0.05)*

Elevated troponin levels in patients with leukemia may be associated with various factors, including direct myocardial injury, anemia, hypoxia, thromboembolic complications, and side effects of chemotherapy (E.N. Parovichnikova).

Alexander Dietl demonstrated that significantly elevated troponin T (TnT) levels in patients with acute coronary syndrome (ACS) are associated with acute exacerbations of comorbid COPD upon hospital admission, the development of acute myocardial infarction (AMI), and deterioration of spirometric parameters. It has also been shown that in patients without AMI, TnT levels during COPD exacerbation are significantly higher than in the stable phase of the disease (B.G. Iskenderov, N.V. Berenstein, T.V. Lokhina, A.V. Zaitseva). To date, chemotherapy remains one of the most reliable and well-established methods for treating malignant tumors and hematologic diseases (O.V. Krikunova). When comparing laboratory data on troponin T levels, a correlation was found with ECG results indicating ischemic changes. In 47 patients, the mean troponin T level reached the upper limit of normal.

The dynamics of troponin and NT-proBNP concentration changes during high-dose polychemotherapy suggest that these biomarkers may indicate cardiotoxicity (V.O. Sarzhevsky, D.S. Kolesnikova, V.Ya. Melnichenko).



✅ **Pearson correlation coefficient:** *r = 0.62*

📉 **p-value:** *p = 0.38*

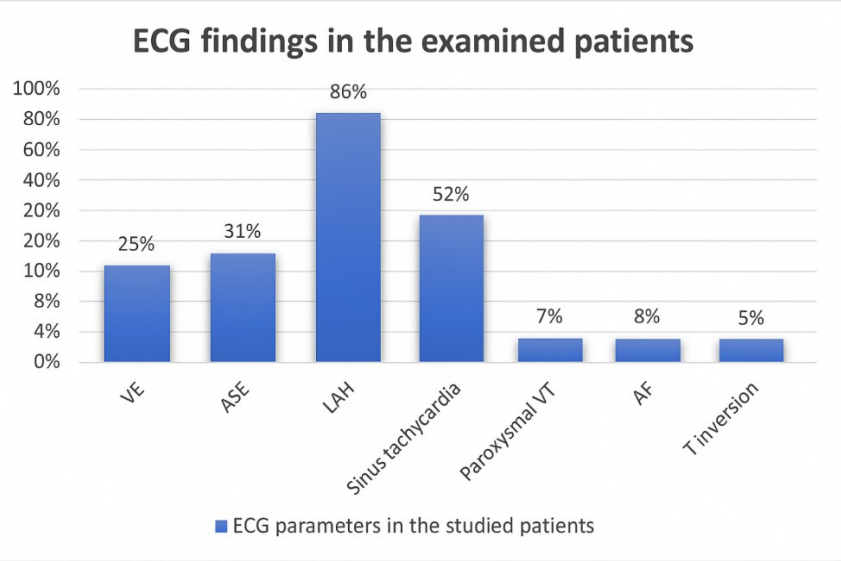
Interpretation:

- A moderate positive correlation was observed between NT-proBNP and troponin T levels.

- However, p > 0.05 indicates that this correlation is not statistically significant (which is expected given the small number of data points — only four groups).

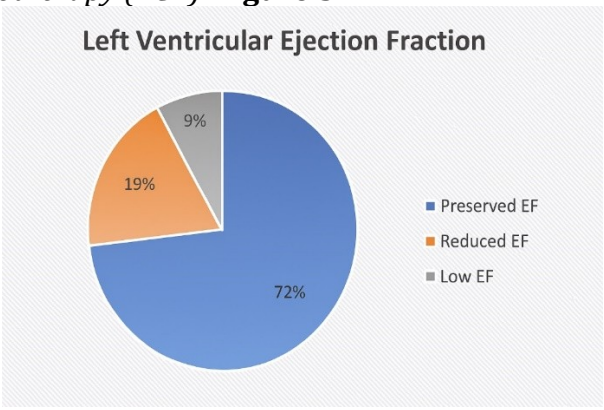
Prior to chemotherapy, no significant complaints or critical abnormalities were detected on electrocardiography (ECG) or echocardiography (EchoCG). However, signs of left ventricular hypertrophy (LVH) were recorded in 67% of patients.

*Figure 2 presents the frequency of electrocardiographic changes observed in patients with AML after completing a course of polychemotherapy***.**



According to ECG data recorded during polychemotherapy (PCT), the following abnormalities were identified among patients: premature ventricular contractions (PVCs) were observed in 25% of patients, non-sustained ventricular tachycardia (NSVT) in 31%, and ECG signs of left ventricular hypertrophy (LVH) in 86%. Sinus tachycardia with an average heart rate of 102 bpm was found in 52% of patients. Paroxysmal tachycardia occurred in 6%, and newly diagnosed atrial fibrillation (AF) was observed in 7% of cases. The most common patient complaints included dyspnea, a sensation of strong or irregular heartbeats, and retrosternal chest pain. T-wave inversion in chest leads was observed in 8% of cases, while ST-segment depression was noted in 3%. Given the patients' complaints, all of them underwent urgent ECG with rhythmogram, followed by a recommendation for planned 24-hour Holter monitoring.

Prevalence of Echocardiographic Changes in the Assessment of Left Ventricular Ejection Fraction (LVEF) by the Simpson Method in Patients with Acute Myeloblastic Leukemia Following a Course of Polychemotherapy (PCT). **Figure 3.**



According to echocardiographic (EchoCG) data, after a course of cytostatic chemotherapy, preserved left ventricular ejection fraction (LVEF >56%) was observed in 42 patients (72%). Moderately reduced LVEF (approximately 50%) was found in 11 patients, while severely reduced LVEF (around 46%) was observed in 5 patients. Additionally, the average echocardiographic measurements revealed an end-diastolic dimension (EDD) of 4.8 cm, End-

systolic dimension (ESD) of 2.5 cm, Interventricular septum (IVS) of 1.3 cm, Posterior wall (PW): 1.3 cm Left ventricular mass (LVM): 200 g Mitral regurgitation (MR): grade 1–2 Tricuspid regurgitation (TR): grade 1 Aortic regurgitation (AR): not observed (grade 0)

Conclusion:

An increase in serum NT-proBNP levels in patients with acute myeloblastic leukemia (AML) may indicate potential myocardial injury and the development of heart failure or cardiomyopathy. In this group of patients, a marked increase in ECG abnormalities and cardiovascular complaints was also observed, suggesting the onset of cardiotoxic effects likely caused by cytostatic therapy. Elevated troponin T levels in patients with ECG changes support the hypothesis that myocardial damage may be the result of selective toxic effects of polychemotherapy.

Although new cytostatic treatment regimens yield positive results in terms of the primary disease, many patients experience worsening comorbid conditions, especially those with pre-existing cardiovascular diseases.

Therefore, further studies are needed on a larger cohort of patients with careful consideration of comorbidities. Monitoring troponin levels in this patient population has prognostic value and should be implemented early in the primary therapy. A panel of biomarkers, such as NT-proBNP and troponin T, may be helpful in early detecting myocardial dysfunction.

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