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DISSOCIATION OF CARDIOSPECIFIC BIOMARKERS AND LEFT VENTRICULAR SYSTOLIC FUNCTION IN PATIENTS WITH ACUTE LEUKEMIAS

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Abstract

Cardiovascular complications are a significant factor limiting the administration of antitumor therapy in patients with acute leukemias. Traditional assessment of cardiotoxicity is predominantly based on the dynamics of left ventricular ejection fraction (LVEF); however, functional myocardial changes may develop later than biochemical signs of damage. Elevation of cardiac troponin and NT-proBNP with preserved LVEF potentially reflects a subclinical stage of myocardial injury and may be used for earlier risk stratification.

Aim of the study — to assess the frequency and clinical significance of dissociation between cardiospecific biomarkers and LV systolic function in patients with acute leukemias and to determine factors associated with the formation of subclinical cardiac injury.

Materials and methods. The study included 102 patients with acute leukemias aged 18–78 years, mean age 44.8 ± 15.9 years. There were 43 men (42.2%) and 59 women (57.8%). Cardiological evaluation included ECG, transthoracic echocardiography, and determination of troponin T and NT-proBNP. Additionally, molecular genetic variants of SOD2 C14510A, GPX4 C718T, CAT

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G262A, COL1A1 C1997A, EDN1 Lys198Asn, and COMT Val158Met were assessed.

Results. Mean LVEF was $55.9 \pm 7.3\%$, and LVEF reduction $<50\%$ was recorded in 14 (13.7%) patients. At the same time, troponin T >20 ng/L was detected in 29 (28.4%), and NT-proBNP >300 pg/mL in 26 (25.5%) patients. Thus, the frequency of troponin T elevation was 2.07-fold, and NT-proBNP elevation 1.86-fold higher than the frequency of reduced LVEF. These findings indicate the existence of a group of patients in whom biochemical signs of myocardial damage/stress may be detected in the absence of pronounced systolic dysfunction. Among genetic factors, the most pronounced association with the presence of cardiovascular complications was observed for COMT Val158Met: the frequency of the Met allele was 60.94% in patients with complications versus 28.95% in those without; OR=3.83 (95% CI 2.11–6.95).

Conclusion. Isolated assessment of LVEF may be insufficient for the early detection of cardiac injury in patients with acute leukemias. Elevation of troponin T and NT-proBNP occurred approximately twice as often as LVEF $<50\%$. Combined use of echocardiography, cardiospecific biomarkers, and individual predisposition factors may facilitate the detection of a subclinical stage of myocardial damage.

Keywords: Acute leukemia, subclinical myocardial injury, cardiotoxicity, NT-proBNP, troponin T, ejection fraction, cardio-oncology.

Introduction

Modern antitumor therapy has substantially improved outcomes in patients with hematological malignancies. At the same time, cardiovascular complications have become one of the factors capable of limiting treatment intensity, requiring its modification, and adversely affecting prognosis.

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The problem of early diagnosis of myocardial damage occupies a special place. Historically, the cardiotoxicity of antitumor therapy was most often associated with a decrease in LVEF. However, the modern concept of cancer therapy-related cardiovascular toxicity is considerably broader and includes myocardial dysfunction, heart failure, rhythm disturbances, vascular complications, and other forms of cardiovascular damage [1,2]. At the same time, LVEF has an important limitation: its reduction may occur only after a certain degree of cardiomyocyte damage has already developed.

Therefore, methods capable of detecting the pathological process at the preclinical or subclinical stage acquire particular importance.

One such approach is the determination of cardiospecific biomarkers. Cardiac troponins reflect cardiomyocyte damage, whereas BNP and NT-proBNP predominantly characterize hemodynamic stress and increased myocardial wall tension. In cardio-oncology guidelines, their use is considered an additional component of monitoring alongside echocardiography [1–3].

For patients with acute leukemias, interpretation of these indicators is particularly complex.

The cardiovascular system may simultaneously be affected by:

- antitumor agents;
- pronounced anemia;
- systemic inflammation;
- infectious complications;
- hypermetabolism;
- electrolyte disturbances;
- renal dysfunction;
- hemodynamic changes;
- individual genetic predisposition.

Therefore, elevation of biomarkers should not automatically be interpreted as evidence of drug-induced cardiotoxicity. At the same time, their elevation in

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combination with instrumental and clinical changes may identify patients requiring closer follow-up.

In the cohort examined by us, LVEF reduction $<50\%$ was found in 13.7% of patients, whereas troponin T elevation >20 ng/L was observed in 28.4%, and NT-proBNP >300 pg/mL in 25.5%.

This discrepancy served as the basis for the present study.

Aim of the study

To assess the frequency and clinical significance of dissociation between cardiospecific biomarkers and left ventricular systolic function in patients with acute leukemias, and to determine potential clinical and molecular genetic factors associated with subclinical cardiac injury.

Objectives of the study

1. To assess LV systolic function in patients with acute leukemias.
2. To determine the distribution of troponin T and NT-proBNP.
3. To compare the frequency of biomarker elevation with the frequency of LVEF $<50\%$.
4. To characterize clinical and electrocardiographic changes in patients.
5. To formulate the concept of biomarker–echocardiographic phenotypes.
6. To determine the place of genetic factors in early cardiovascular risk stratification.

Materials and methods

The study was conducted at the Republican Specialized Scientific and Practical Medical Center of Hematology, Ministry of Health of the Republic of Uzbekistan. The analysis included 102 adult patients with acute leukemias.

The mean age of patients was 44.8 ± 15.9 years, ranging from 18 to 78 years. There were 43 men (42.2%) and 59 women (57.8%). According to comprehensive

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evaluation, cardiovascular complications were recorded in 64 (62.7%) patients, while they were absent in 38 (37.3%). All patients underwent clinical examination, ECG, and transthoracic echocardiography. Among laboratory markers, troponin T and NT-proBNP concentrations were analyzed.

Echocardiographic examination

The main indicator of systolic function was LVEF. In the overall group, mean LVEF was $55.9 \pm 7.3\%$. Range: 37–68%. LVEF reduction $<50\%$ was recorded in 14 of 102 patients — 13.7%. Consequently, in 88 patients (86.3%) LVEF was $\geq 50\%$. This is an important starting point of the present analysis.

Biomarker study. Troponin T. Median troponin T was 7.6 ng/L. Maximum concentration: 276 ng/L. Troponin T >20 ng/L was detected in 29/102 patients — 28.4%. Thus, a normal value, not exceeding the chosen threshold, was noted in 73 patients (71.6%).

NT-proBNP. Median NT-proBNP was 86.3 pg/mL. Maximum value: 3967 pg/mL. NT-proBNP >300 pg/mL was detected in 26/102 patients — 25.5%. In 76 (74.5%) patients the value did not exceed the chosen threshold.

Results

Dissociation between LVEF and biomarkers. The findings demonstrated a clear difference between the frequency of pronounced systolic dysfunction and the frequency of biochemical changes.

Table 1. Frequency of changes in LVEF and cardiospecific biomarkers

Indicator	n	%
LVEF $<50\%$	14	13.7
Troponin T >20 ng/L	29	28.4
NT-proBNP >300 pg/mL	26	25.5
LVEF $\geq 50\%$	88	86.3

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The ratio of the frequency of troponin elevation to the frequency of reduced LVEF was: $28.4 / 13.7 = 2.07$. For NT-proBNP: $25.5 / 13.7 = 1.86$. Thus, troponin T elevation occurred approximately 2.1-fold, and NT-proBNP elevation 1.9-fold more often than LVEF $<50\%$.

If one relies only on LVEF $<50\%$, signs of pronounced systolic dysfunction are present in every seventh patient.

However, when using the biomarker approach, signs of myocardial damage/stress are found in approximately every third to fourth patient. In a subset of patients, biochemical changes may precede the development of pronounced LVEF reduction.

However, it is fundamentally important here not to draw a statistically incorrect conclusion. From the available aggregated data, it cannot be stated that all 29 patients with elevated TnT or all 26 patients with elevated NT-proBNP had preserved LVEF.

For this, an individual cross-tabulation of indicators is required.

3. Biomarker–echocardiographic phenotypes

For further analysis, it is proposed to divide patients into four fundamentally different phenotypes.

Table 2. Proposed classification

Phenotype	LVEF	TnT/NT-proBNP	Interpretation
I	$\geq 50\%$	normal	low probability of current damage
II	$\geq 50\%$	elevated	subclinical biochemical phenotype
III	$< 50\%$	normal	predominantly functional phenotype
IV	$< 50\%$	elevated	pronounced combined phenotype

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Phenotype II is of the greatest scientific interest. These are patients in whom LVEF is still preserved, but elevation of one or both cardiospecific biomarkers is already present. It is precisely this group that may potentially represent a "window of opportunity" for an early cardioprotective strategy.

Clinical signs. Palpitations were noted in 40 (39.2%) patients.

Chest pain/discomfort — in 40 (39.2%). Dyspnea — in 19 (18.6%).

The high frequency of palpitations corresponds to ECG data, according to which sinus tachycardia was recorded in 33 (32.4%) patients. However, these symptoms must be interpreted with caution. For example, mean hemoglobin in the examined group was only about 86.2 g/L. Consequently, anemia itself could contribute to tachycardia, dyspnea, and increased hemodynamic load.

Electrocardiographic changes

Table 3. Main ECG changes

ECG sign	n	%
Sinus tachycardia	33	32.4
Signs of LVH	28	27.5
Ventricular extrasystole	12	11.8
Supraventricular extrasystole	8	7.8
T-wave inversion	4	3.9
Ischemic changes	2	2.0

These data further demonstrate that the cardiovascular status of patients with acute leukemias cannot be characterized by a single echocardiographic parameter.

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Discussion

The main result of the study is the identified discrepancy between the frequency of biochemical signs of cardiac damage and the frequency of pronounced systolic dysfunction. LVEF $<50\%$ was determined in 13.7% of patients. At the same time, troponin T >20 ng/L was detected in 28.4%, NT-proBNP >300 pg/mL — in 25.5%. Consequently, biomarker changes were recorded approximately twice as often. This result has substantial practical significance. If cardiological monitoring is limited to periodic determination of LVEF alone, a portion of patients with potentially early myocardial damage may remain unidentified. On the other hand, elevation of biomarkers cannot automatically be equated with drug-induced cardiotoxicity. This is especially important in acute leukemias. NT-proBNP may increase under the influence of hemodynamic overload, impaired renal function, infection, and other conditions. Troponin also requires clinical interpretation taking into account concomitant factors.

Therefore, the greatest diagnostic value is represented by the integration of biomarkers with echocardiographic and clinical data.

Conclusions

1. In patients with acute leukemias, a pronounced dissociation was found between the frequency of cardiospecific biomarker elevation and the frequency of pronounced reduction in LV systolic function.
2. LVEF $<50\%$ was found in 14 of 102 (13.7%) patients, with a mean value of $55.9 \pm 7.3\%$.
3. Troponin T >20 ng/L was recorded in 29 (28.4%) patients, which was 2.07-fold higher than the frequency of LVEF $<50\%$.
4. NT-proBNP >300 pg/mL was detected in 26 (25.5%) patients — 1.86-fold more often than reduced LVEF $<50\%$.
5. The findings substantiate the existence of a potentially significant group of patients with biochemical signs of cardiac damage/stress in the absence of

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pronounced systolic dysfunction; the exact size of this group should be established through individual cross-tabulation analysis.

6. Sinus tachycardia was noted in 32.4%, ECG signs of LVH — in 27.5%, ventricular extrasystole — in 11.8%, confirming the need for comprehensive rather than purely echocardiographic assessment.

7. The most promising approach to early risk stratification appears to be the combination of LVEF + TnT + NT-proBNP + clinical factors, while genetic markers may be used as an additional level of personalization after independent validation.

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