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CHEMOTHERAPY-INDUCED ECHOCARDIOGRAPHY CHANGES IN HEPATOCELLULAR CARCINOMA PATIENTS

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Abstract

Introduction. Cardiovascular diseases (CVD) still remain a major health problem, occupying a leading position in the structure of morbidity and mortality. The incidence of comorbidities increases with age and when CVD is added to cancer, it becomes a major healthcare problem.

The aim. To identify earlier echocardiographic changes in myocardial dysfunction in patients with hepatocellular carcinoma without cardiovascular disease receiving targeted therapy along or in combination with transcatheter arterial embolization (TACE).

Materials and methods. In this prospective study, 73 patients undergoing targeted therapy by sorafenib and targeted therapy by sorafenib + TACE (doxorubicin) for hepatocellular carcinoma, underwent serial echocardiograms pre- and 6 months during therapy. Left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) and global longitudinal strain (GLS) of the left ventricle. The mean values of the listed echocardiography parameters were assessed both within groups over time and between groups of patients receiving different treatment protocols. The nonparametric method U Mann-Whitney (between groups) and Wilcoxon criterion (within group) were used for samples with irregular distribution. Student's t-test was used for parameters with normal distribution. Statistically significant differences were considered at $p<0.05$.

Results. Baseline left ventricular ejection fraction (LVEF) before targeted therapy along and targeted therapy + TACE was 61,6±4,4% vs 58,2±3,9% respectively. LVEF, LVEDV and LVESV there were no statistically significant changes in ejection fraction within 6 months from the start of therapy. However, we found a statistically significant decrease in GLS: -14,2±2,9 and -14,8±2,2, p=0,044 in both groups after 6 months targeted therapy; -20,1±2,6 and -14,2±2,9, p=0,029 in target therapy along group in dynamics after 6 months of therapy; -20,4±2,0 and -14,8±2,2, p=0,036 in target therapy + TACE group in dynamics after 6 months of therapy.

Conclusion. GLS can be used to determine preclinical myocardial systolic dysfunction in patients undergoing anticancer therapy.

Keywords: *hepatocellular carcinoma, cardiotoxicity, echocardiography, myocardium.*

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Резюме

ЭХОКАРДИОГРАФИЧЕСКИЕ ИЗМЕНЕНИЯ, ВЫЗВАННЫЕ ХИМИОТЕРАПИЕЙ, У ПАЦИЕНТОВ С ГЕПАТОЦЕЛЛЮЛЯРНОЙ КАРЦИНОМОЙ

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Введение. Сердечно-сосудистые заболевания (ССЗ) остаются одной из главных проблем здравоохранения, занимая ведущее место в структуре заболеваемости и смертности. Частота сопутствующих заболеваний увеличивается с возрастом, и когда ССЗ сочетаются с раковыми заболеваниями, это создает серьезные проблемы для здравоохранения.

Цель. Целью данного исследования было выявление ранних эхокардиографических изменений миокардиальной дисфункции у пациентов с гепатоцеллюлярной карциномой (ГЦК), не имеющих предшествующих сердечно-сосудистых заболеваний, которые получали таргетную терапию как в монотерапии, так и в комбинации с трансартериальной химиоэмболизацией (ТАХЭ).

Материалы и методы. В данном проспективном исследовании участвовали 73 пациента с ГЦК, которые получали таргетную терапию сорафенибом или комбинацию сорафениба и ТАХЭ (доксорубицин). Пациентам выполняли серию эхокардиографического исследования до начала лечения и через 6 месяцев после старта лечения. Оценивались параметры: фракция выброса левого желудочка (ФВЛЖ), конечный диастолический объем левого желудочка (КДО ЛЖ), конечный систолический объем левого желудочка (КСО ЛЖ) и глобальную продольную деформацию левого желудочка (GLS). Для статистической обработки использовались непараметрический критерий Манна-Уитни (для сравнения групп), критерий Уилкоксона (для анализа внутри групп) и t-тест Стьюдента для параметров с нормальным распределением, при этом статистически значимыми считались различия при $p<0,05$.

Результаты. Исходная ФВЛЖ до начала лечения сорафенибом составила 61,6 ± 4,4% в группе сорафениба и 58,2 ± 3,9% в группе сорафениб + ТАХЭ. Через 6 месяцев не было статистически значимых изменений ФВЛЖ, КДО ЛЖ и КСО ЛЖ в обеих группах. Однако было выявлено статистически значимое снижение (GLS): -14,2 ± 2,9 и -14,8 ± 2,2 в группе комбинированной терапии ($p=0,044$); -20,1 ± 2,6 и -14,2 ± 2,9 в группе сорафениб ($p=0,029$); -20,4 ± 2,0 и -14,8 ± 2,2 в группе сорафениб + ТАХЭ ($p=0,036$).

Вывод. Глобальная продольная деформация может быть использована для выявлени доклинической миокардиальной систолической дисфункции у пациентов, проходящих противоопухолевую терапию.

Ключевые слова: *гепатоцеллюлярная карцинома, кардиотоксичность, эхокардиография, миокард.*

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Түйіндеме

ГЕПАТОЦЕЛЛЮЛЯРЛЫ КАРЦИНОМАСЫ БАР НАУҚАСТАРДАҒЫ ХИМИОТЕРАПИЯ ӘСЕРІНЕН ТУЫНДАҒАН ЭХОКАРДИОГРАФИЯЛЫҚ ӨЗГЕРІСТЕР

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Кіріспе. Жүрек-қан тамырлары аурулары (ЖҚА) денсаулық сақтаудың негізгі мәселерлерінің бірі бола отырып, ауру мен өлім құрылымында жетекші орын алады. Қосымша жүретін аурулардың жиілігі жас ұлғайған сайын артады және ЖҚА қатерлі ісікпен біріктірілгенде, бұл денсаулық сақтау үшін елеулі мәселелер қаупін тудырады.

Мақсаты. Бұл зерттеудің мақсаты монотерапияда да, трансартериялық химиоэмболизациямен (ТАХЭ) біріктірілуде де мақсатты терапия алған алдыңғы жүрек-қан тамырлары аурулары жоқ гепатоцеллюлярлық карциномасы (ГЦК) бар емделушілерде миокард дисфункциясының ерте эхокардиографиялық өзгерістерін анықтау болды.

Материалдар мен әдістер. Осы проспективті зерттеуге сорафенибпен мақсатты терапия немесе сорафениб пен ТАХЕ (доксорубицин) комбинациясын алған 73 ГЦК бар пациенттер қатысты. Пациенттерге емдеу басталғанға дейін және емдеу басталғаннан кейін 6 айдан кейін бірқатар эхокардиографиялық зерттеулер жүргізілді. Келесі параметрлер: сол қарыншаның шығарылу (аластау) фракциясы (LVEF), сол қарыншаның соңғы диастолалық көлемі (LVEDV), сол қарыншаның соңғы систолалық көлемі (LVESV) және сол қарыншаның глобалды бойлық деформациясы (GLS) бағаланды. Статистикалық өңдеу үшін Манна-Уитнидің параметрлік емес критерийі (топтарды салыстыру үшін), Уилкоксон критерийі (топтар ішіндегі талдау үшін) және Стьюденттің қалыпты үлестірім параметрлері үшін t тесті қолданылды, $p<0,05$-тегі айырмашылықтар статистикалық маңызды болып саналды.

Нәтижелер. Бастапқы сол қарыншаның шығарылу (аластау) фракциясы (LVEF) сорафенибпен емдеуді бастамас бұрын сорафениб тобында 61,6 ± 4,4% және сорафениб + TAXE тобында 58,2 ± 3,9% құрады. 6 айдан кейін екі топта да LVEF, LVEDV, және LVESV статистикалық маңызды өзгерістер болған жоқ. Алайда, статистикалық маңызды төмендеу (GLS) анықталды: аралас терапия тобында -14,2 ± 2,9 және -14,8 ± 2,2 (p=0,044); сорафениб тобында -20,1 ± 2,6 және -14,2 ± 2,9 (p=0,029); сорафениб + TAXE тобында -20,4 ± 2,0 және -14,8 ± 2,2 (p=0,036).

Қорытынды. Ісікке қарсы терапияны қабылдап жатқан науқастарда клиникаға дейінгі миокардтың систолалық дисфункциясын анықтау үшін глобалды бойлық деформацияны қолдануға болады.

Түйінді сөздер: *гепатоцеллюлярлық карцинома, кардиоуыттылық, эхокардиография, миокард.*

Дәйексөз үшін:

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Introduction

Despite the rapid development of cardiology and cardiac surgery, cardiovascular diseases remain a major problem, causing significant harm to the health of the global population [7, 10]. Kazakhstan is no exception, and cardiovascular diseases occupy a leading position in the structure of morbidity and mortality. Despite of the measures on prevention and treatment the general cardiovascular morbidity (CVD) for the expired years of the XXI century in the Republic of Kazakhstan has increased by 2,5 times, from 6775,6 on 100 thousand population in 2001 up to 16982,9 in 2022 [26]. The first registered CVD in adults (18 years and older) during these years has increased from 1841,3 (2001) to 4378,6 (2020) per 100 thousand population, including arterial hypertension (AH) from 614,0 to 2138,9, ischemic heart disease (IHD) from 321,5 to 604,2 and cerebrovascular disease (CVD) from 210,3 to 433,7 respectively. The growth of CVDs, along with other factors, to some extent is due to the increase in life expectancy. The vast majority of CVDs are in the elderly and old age, and they are more likely to have comorbid diseases. Approximately 80% of elderly people have three or more diseases [2, 13, 27], which significantly increases mortality, so with two or more diseases it reaches 82% [15, 21].

The above-mentioned circumstances become especially relevant when CVD is combined with oncopathology [4, 5, 8, 28]. The analysis by K.C. Stoltzfu et al.[8] of 7529481 lethal outcomes of cancer patients showed that in 5,24 % of the causes were the heart diseases and mortality rate from CVD made 10,61/10000 man-years, and the standardized coefficient was 2,24 (95% CI: 2,23-2,25). The authors noted that the risk of CVD mortality increases with age and increases in cancer survivors over time. Here, it should be noted that first-diagnosed cancer morbidity in Kazakhstan, over the past 20 years has decreased from 195.9 (2001) per 100,000 population to 94.2 (2020), also significantly decreased mortality from 134.4 to 75.0 respectively.

Every year, the oncology field is developing more and more, with minimally invasive surgery using targeted chemotherapy drugs, such as hepatic artery chemoembolization (TACE), and new classes of pharmaceutical groups appearing for the treatment of cancer patients. Unfortunately, the use of antitumor drugs leads to the development of cardiotoxicity, worsening the quality of life of patients and the survival prognosis [14].

Echocardiography is a key noninvasive method for the early detection of cardiotoxicity in patients receiving potentially cardiac-damaging therapies. This method allows for the assessment of structural and functional changes in the myocardium, which can appear long before the development of clinical symptoms. Determining the ejection fraction and global longitudinal strain (GLS) helps detect subclinical reductions in cardiac contractility. Regular echocardiographic monitoring allows for timely treatment adjustments, reducing the risk of heart failure progression.

Due to its high availability and safety, echocardiography remains the primary tool for monitoring cardiac function during chemotherapy and other potentially cardiotoxic treatments.

For two years we have providing a project of identification early potential CVD complications in patient with HCC. The main **aim** is to identify earlier echocardiographic changes of myocardial dysfunction in patients with liver cancer without concomitant cardiovascular diseases that developed during chemotherapy and chemotherapy in combination with transcatheter arterial embolization (TACE).

Materials and methods. The result of the article is a subanalysis in a prospective study performed under grant from the Ministry of Education and Science of the Republic of Kazakhstan (Individual Registration Number AP19176025). The study was approved by the Ethical Commission of NJSC Astana Medical University (No. 21 from 09/2023). This subanalysis included 73 patients over 18 years of age with hepatocellular carcinoma who were followed from October 2023 to November 2024 at the clinical site of Astana Medical University. Patient selection was carried out using a continuous method, including patients with histologically verified hepatocellular carcinoma without cardiovascular diseases. Before inclusion in the study, all patients signed informed consent. They were divided into two groups depending on the chemotherapy method: targeted therapy with sorafenib (Nexavar, Bayer, Germany) at a dose of 800 mg per day (n=29) or targeted therapy with TACE doxorubicin (Zuvidox, OncoAce, India) at a dose of 50 mg (n=44). We monitored the echocardiographic parameters of patients before the start of therapy and 6 months after the start of therapy.

Exclusion criteria included patients under 18 years of age, those with metastatic liver cancer, cardiovascular diseases, other types of malignancies, any intraventricular conduction abnormalities, heart rhythm disturbances, ejection fraction less than 50% and a glomerular filtration rate (GFR) less than 30 mL/min.

All patients underwent serial 2DE studies (GE Ultrasound System, Vivid E95, GE Healthcare, Milwaukee, WI) before and 6 months after initiation of chemotherapy. Dedicated apical 2- and 4-chamber images were obtained for measurement of bi-plane left ventricular ejection fraction (Simpson method). For measurement of GLS apical 4-, 3-, and 2-chamber images of the LV were obtained for 3 cardiac cycles at high frame rates (40 to 80 frames/s) Peak systolic GLS was measured using EchoPAC version 202 (AFI, GE). The following measurements were taken: left ventricular ejection fraction (LV EF,%), left ventricular end-diastolic volume (LVEDV, ml/m²) and left ventricular end-systolic volume (LVESV, ml/m²) corrected for body surface area and global longitudinal strain (GLS) of the left ventricle [16, 24].

Statistical analysis was performed using the statistical package SPSS, version 26 (IBM, USA). The nonparametric method U Mann-Whitney (between groups) and Wilcoxon criterion (within group) were used for samples with irregular distribution. Student's t-test was used for parameters with normal distribution. Statistically significant differences were considered at $p<0.05$. Data are presented as median, 25th and 75th percentiles, mean and standard deviation; binary variables are presented as frequencies in absolute values and percentages.

Results

Table 1 shows the characteristics of patients suffering from hepatocellular carcinoma. In the targeted therapy group, 38% were women, in the targeted therapy with TACE group, 47%. The average age was 58±10.7 and 60±8.2, respectively. There were no differences in general clinical laboratory parameters between the two subgroups and the data did not go beyond the reference values; the ejection fraction parameters were also within the normal range. Surgical treatment was low in both subgroups and amounted to 27% and 32%. There was no difference in blood pressure between the groups, while heart rate was slightly higher in the group of patients receiving targeted therapy with TACE - 69 bpm vs 73 bpm in targeted therapy with TACE (Table 1).

Table 1.

Characteristics of patients on targeted and targeted therapy with TACE.

Indicator	Targeted therapy along (n =29)	Targeted therapy + TACE (n=44)	p
Female gender, people (%)	11 (38%)	21 (47%)	0,467
Age, years old	58±10,7	60±8,2	0,782
Duration of disease, months	12,6±4,6	7,6±3,3	0,037
Hemoglobin, g/l	122,4±20,6	118,3±13,4	0,487
Potassium, μmol/L	4,16±1,1	3,89±0,82	0,140
Glucose, mmol/L	5,4±1,8	5,2±2,4	0,422
Creatinine, μmol/L	76,4±17,4	88,9±13,9	0,067
Systolic blood pressure, mm Hg	128±13	130±12	0,251
Diastolic blood pressure, mm Hg	84±10	79±12	0,540
Rest heart rate, beats per min	69±8	73±8	0.049
Operative treatment, people (%)	8 (27%)	14 (32%)	0,019

Echocardiographic parameters showed no differences between the two groups and were within normal range before starting therapy. Echocardiographic parameters of the targeted therapy and targeted therapy with TACE are summarized in Table 2.

Table 2.

Echocardiographic parameters of patients in both groups before starting therapy.

Indicator	Targeted therapy along (n =29)	Targeted therapy + TACE (n=44)	p
LV EF, %	61,6±4,4	58,2±3,9	0,299
LVEDV, ml/m2	56,5±7,4	55,7±8,0	0,058
LVESV, ml/m2	22,9 ±3.2	23,1±3,1	0,082
GLS, %	-20,1±2,6	-20,4±2,0	0,199

After 6 months, we performed a follow-up Echocardiogram. LV EF, as well as end-diastolic and LVEDV and LVESV values, were within normal ranges, while the GLS index began to statistically significantly decrease in both groups, decrease to -14,2±2,9 in targeted therapy group and -14,8±2,2 in targeted therapy with TACE ($p=0.044$) (Table 3).

Table 3.

Echocardiographic parameters of patients in both groups after 6 months targeted therapy.

Indicator	Targeted therapy along (n =29)	Targeted therapy + TACE (n=44)	p
LV EF, %	60,1±4,4	59,4±4,1	0,061
LVEDV, ml/m2	56,2±7,1	56,7±7,8	0,091
LVESV, ml/m2	22,6 ±3.5	21,9±3,7	0,086
GLS, %	-14,2±2,9	-14,8±2,2	0,044

We also compared echocardiographic parameters within groups using different treatment protocols. A statistically significant reduction in GLS was observed in the targeted therapy along group 6 months after the start of therapy (-20,1±2,6 vs -14,2±2,9, p=0,029) (Table 4).

Table 4.

Echocardiographic parameters of patients in the targeted therapy group along in dynamics after 6 months of therapy.

Indicator	Targeted therapy along (n =29)	Targeted therapy along after 6 months (n=29)	p
LV EF, %	61,6±4,4	60,1±4,4	0,312
LVEDV, ml/m2	56,5±7,4	56,2±7,1	0,074
LVESV, ml/m2	22,9 ±3.2	22,6 ±3.5	0,09
GLS, %	-20,1±2,6	-14,2±2,9	0,029

In patients of the target group + TACE, a statistically significant decrease in GLS was also observed, amounting to -20,4±2,0 before the start of therapy and -14,8±2,2 (p=0,036) after 6 months from the start of therapy (Table 5).

Table 5.

Echocardiographic parameters of patients in the target therapy + TACE group in dynamics after 6 months of therapy.

Indicator	Targeted therapy + TACE (n=44)	Targeted therapy + TACE after 6 months (n=44)	p
LV EF, %	58,2±3,9	59,4±4,1	0,061
LVEDV, ml/m2	55,7±8,0	56,7±7,8	0,095
LVESV, ml/m2	23,1±3,1	21,9±3,7	0,084
GLS, %	-20,4±2,0	-14,8±2,2	0,036

Discussion

The problem of cardiotoxicity in cancer patients is increasingly attracting the attention of the medical community. Cardiovascular disease plays a significant role in the administration of cardiotoxic antitumor therapy. In cardiac patients receiving chemotherapy, the risk of developing complications increases severalfold [17,18]. According to *Morris P.G. et al*. [22], the presence of arterial hypertension in patients receiving trastuzumab was 1.89 times higher than in those receiving trastuzumab. There is accumulated experience and data of long-term observation of cancer survivors, which shows various complications - from myocardial dysfunction, myocardial remodelling and reduced contractility to potentiation of arrhythmogenesis with influence on all types of cells of the cardiac conduction system. The cardiotoxic effect of chemotherapy can be manifested by a wide range of Echocardiography changes, including reduction of left ventricular ejection fraction, increase LVEDV, LVESV and GLS reduction. [1, 12, 26].

Baseline LVEF and GLS levels are recommended for all patients undergoing TTE before initiating cardiotoxic anticancer therapy to stratify the risk of anticancer drugs and identify significant changes during treatment. Most often, left ventricular injury is a consequence of cardiotoxicity in patients undergoing anticancer therapy. Changes in loading conditions frequently occur during chemotherapy (eg, volume gain due to intravenous fluid administration, volume loss due to vomiting or diarrhea, changes in blood pressure and heart rate due to pain or stress) and can affect cardiac volume, LVEF, and GLS quantification. Echocardiography is undoubtedly the primary noninvasive and reproducible method. However, visible changes, such as increased LVEDV and LVESV, which characterize a decrease in left ventricular ejection fraction, are usually irreversible.

It's important to remember that a normal left ventricular ejection fraction does not rule out damage and decreases as heart failure progresses. However, the left ventricular ejection fraction is a reliable test for the early detection of left ventricular systolic dysfunction. But it is important to remember that strain measurements may vary between different equipment, so it is recommended to perform serial GLS measurements for each patient using the same device/software.

The most important in identifying cardiotoxicity is its early, reversible detection [27]. Undoubtedly, GLS determination is the primary noninvasive method for the early detection of left ventricular systolic myocardial dysfunction [25, 29]. Yes, GLS has some limitations: high software requirements, an experienced physician, a normal heart rate, and sinus rhythm. However, these should not be a limitation in identifying myocardial dysfunction in cancer patients [28].

Bellinger A. M. et al. reported that anthracyclines cause cardiomyocyte death, leading to irreversible myocardial damage [3]. The extent of this damage depends on the total dose of the anticancer drug. Additionally, anthracyclines can cause cardiac rhythm and conduction disorders in 16-36% of cancer patients. While our study did not detect reduced ejection fraction, we observed differences in GLS after 6 months of therapy.

Our results are supported by studies conducted in cancer patients. A study by *Gonzalez-Manzanares et al.* identified of patients on antitumor therapy in patients with acute leukemia subclinical decrease in GLS before changes in left ventricular ejection fraction [9]. Another study by *Niemelä J. et al.* demonstrated that patients with different malignancies had abnormal LV longitudinal strain and 70% of patients had normal LV ejection fraction [23].

Our subanalysis demonstrated a stable decrease in the GLS level, both within the group of patients with target therapy along (-20.1±2.6 vs. -14.2±2.9, p=0.029) and with target therapy + TACE (-20.4±2.0 vs. -14.8±2.2, p=0.036), as well as with the appointment of group therapy under different treatment protocols (-14.2±2.9, -14.8±2.2, p=0.044).

Unfortunately, our study has several limitations. The quality of documentation remains inconsistent. Some

missing data regarding the frequency of therapy and periods when the patient was off treatment may introduce some errors. Although echocardiography in our study was performed directly by the researchers, extrapolating these results to all patients likely has some limitations. All cases for both medical examination and medical history collection were intentionally selected, which may have introduced some bias.

Conclusion

According to *Felker G.M.* (2000), fibrotic focal changes dominated in myocardial histopreparations in patients receiving traditional chemotherapy with taxanes and anthracyclines, possibly as a consequence of cardiomyocyte apoptosis during therapy with these chemotherapy drugs [6]. The appearance of clinical symptoms such as chronic Heart Failure requires a long period of time and irreversible changes on echocardiography, such as a decrease in the LV EF. Thus, the inclusion of GLS in diagnostic and treatment protocols for patients with oncological diseases helps to identify cardiotoxicity at early stages and prevent the development of left ventricular systolic dysfunction [11, 24].

In patients with HCC without cardiovascular pathology, comparison between the groups of targeted therapy along and targeted therapy + TACE, as well as observation within the groups in dynamics for 6 months after the start of therapy showed a decrease in GLS. The GLS has proven to be a valuable diagnostic parameter for predicting subclinical cardiac dysfunction and predicting future significant decline in LVEF in cancer patients. The results highlight the importance of careful monitoring of Echocardiographic characteristics during targeted chemotherapy without or with TACE, especially given the potential risk of adverse cardiovascular events. Our findings significantly contribute to the accumulating evidence on chemotherapy-induced Echo changes in HCC patients. This necessitates comprehensive cardiac monitoring and personalized treatment strategies for this vulnerable population.

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