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Research Article

ANALYSIS OF CARDIOVASCULAR RISK FACTORS AND SPECKLE-TRACKING PARAMETERS IN PATIENTS WITH MALIGNANT HEMATOLOGICAL DISEASES

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ABSTRACT

The study aimed to identify the post-chemotherapy variation of myocardial deformation parameters evaluated by speckle-tracking echocardiography and their evolution in the cardiovascular evaluation of patients with hematological malignancies. Furthermore, the study of the post-chemotherapy variation of these parameters, according to classic cardiovascular risk factors, contributes to better risk stratification of the myocardial dys-function associated with cancer therapy. We describe the changes over 12 months of myocardial de formation study, evaluated by speckle-tracking echocardiography, and the relationship between changes in echo cardio-graphic parameters and cardiovascular risk factors. We report that 13.46% of patients in the study had positive cardiovascular here docolateral antecedents, 32.69% were diagnosed with HTA (17 patients), 17.31% with di-abetes (9 patients), 55.77% with dyslipidemia (29 patients), and 5.77% were active smokers (3 patients). The decreased GLS between the two moments, pre-chemotherapy and at 12 months was statistically significant, influenced by hypertension and dyslipidemia. Early myocardial dysfunction associated with cancer therapy in hypertensive patients and those with dyslipidemia, diagnosed by decreased GCS by more than 15% of the pre-chemotherapy value, was reported in 50–75% of cases after the sixth course of therapy. The global radial systolic strain GRS showed changes between the two moments evaluated in our study, but these were not constant, they did not have a significant magnitude, and they only appeared in a small number—under 10% of the studied patients.

Keywords: cardiotoxicity; chemotherapy; echocardiography speckle tracking; cardiovascular risk factors.

INTRODUCTION

Echocardiography is the most frequently used method in the assessment of cardiac function. Conventional measurements such as left ventricular (LV) ejection fraction are of limited utility to detect changes over time; hence, more sensitive methods are required. Strain—as a measure of myocardial deformation—carries incremental information on the change in the LV shape during the cardiac cycle[1]. Strain imaging may detect subtle alterations in cardiac function [2]. Advances in oncology therapy have increased cancer patient survival rates [3]. Numerous anticancer therapies (i.e., anthracyclines, HER-2-targeted therapies, immune checkpoint inhibitors, radiotherapy, tyrosine kinase inhibitors, MEK and RAF inhibitors, multiple myeloma therapies) cause cardiac toxicity, leading to cardiac (systolic and diastolic) dysfunction and heart failure over time [17]. Therefore, cancer patients are exposed to the damaging effects of cancer therapeutic-related cardiac dysfunction (CTRCD), which represents a significant cause of morbidity and mortality [4, 5]. This complication may result in cancer treatment discontinuation and compromise cancer control or its cure [6]. Additionally, chemotherapy-related heart failure (HF) often has a worse prognosis than many cancers, with mortality as high as 60% within 2 years [4].

Considering the literature, some risk factors associated with cardiac toxicity of anthracycline treatment are [14]: cumulative dose; female sex; age >65 years or<18 years; concomitant/previous use of mediastinal radiotherapy, alkylating agents, immunotherapy, "targeted" molecular therapy treatments, hypertension, or genetic factors.

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Several risk factors predispose cytostatic treatment patients tocardiotoxicity. The spectrum of cardiac side effects varies depending on the antineoplastic agent, dose, and chemotherapy regimen used. Cumulative doses, infusion rate, and pre-existing cardiac disease are important risk factors associated with cardiotoxicity [15]. Cardiotoxicity factors associated with the taxanes (TAK-sayn) drug are age, hypertension, diabetes, and chest radiotherapy [16]. Recognizing the risk factors, we hope doctors will choose the most optimal, safe, and suitable treatment for each patient's specific needs.

GLS (global longitudinal strain) with spectral tracking evaluation has become a cornerstone for detecting and quantifying subtle changes in LV function [18]. Furthermore, the up-to-the-minute ESC Guidelines on cardio-oncology[19] highlight the importance and need of assessing and evaluating the GLS for the early detection of oncology treatment's cardiotoxicity [20].

The study aimed to identify the post-chemotherapy variation of myocardial deformation parameters evaluated by speckle-tracking echocardiography and their evolution in the cardiovascular evaluation of patients with hematological malignancies. Furthermore, studying the post-chemotherapy variation of these parameters, according to classic cardiovascular risk factors, contributes to better risk stratification of the myocardial dysfunction associated with cancer therapy. Therefore, we present a description of the changes in the 12 months of myocardial deformation parameters evaluated by speckle-tracking echocardiography and the analysis of the relationship between these changes in the studied echocardiographic parameters and the presence of cardiovascular risk factors.

MATERIALS AND METHODS

Type of study: prospective, interdisciplinary. The study was conducted between November 2019 and September 2021 on 52 patients with hematological malignancies under cytostatic treatment. Patients were hospitalized at the Oncology and Radiotherapy Clinic of the Timișoara Municipal Emergency Clinical Hospital and addressed to the As car Cardiology Clinic in Timișoara for a specialized clinical and echocardiographic examination [26]. Patients were 50% men and 50% women, aged 24–79 yr (mean age 40.66 ± 14.24yr). More than half were <65 years old (75%, 39 patients), 11 were 65–75 yr (21.15%), 2 (3.85%) were> 75 yr [26].

For the initial assessment, each patient shared the following: age, sex, hereditary or personal pathological history of CVD, presence/absence of HTA, diabetes, dyslipidemia, smoking habit, previous treatments (chemotherapy). The patients were classified based on the age category, depending on the risk of adverse cardiac events associated with cancer therapy: <65 years—low risk, 65–74 years—intermediate risk, and >75 years—high risk [7]. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using a sphygmomanometer (Riester RIE1350) before chemotherapy and at the 12-month follow-up. The value of SBP and DBP was recorded as the average of two measurements after a 5min rest in a supine position. In our study, we defined myocardial dysfunction according to current recommendations (Expert Consensus for monitoring cardiac function during and after cancer therapy published by EACVI and ASE[8,9]) as the symptomatic/asymptomatic reduction in LVEF by ≥10% up to <53% [26].

For capturing the 2D ultrasonographic data sets, the Vivid S5 ultrasound machine was used (GE Healthcare Bio-Sciences Corp., Piscataway, NJ, USA), equipped with probes dedicated for two-dimensional scanning (M5S) of the heart and an appropriate bed to facilitate the handling of the probe. Analysis of LVEF with the Biplane Simpson Method and the speckle-tracking data was performed offline after the data capture of the echocardiographic images, using a separate workstation that uses the Echo PAC program system version 11.0.1 (GE Healthcare Bio-Sciences Corp).

Statistical analysis was performed using the statistical software MedCalc version 12.7.7 (MedCalc Software, Ostend, Belgium). This calculation was based on reproducibility of TDI and STI determinations, such that >5% differences between consecutive measurements were statistically significant. Continuous data were expressed as mean ± standard deviation and significant as a percentage. Differences between groups and within the same group before and after the 12-month follow-up were compared by the associated *t*-test. Statistical values of $p<0.05$ were considered significant [26].

RESULTS

We report that 13.46% of the patients in the study had positive cardiovascular heredocolateral antecedents, 32.69% were diagnosed with HTA (17 patients), 17.31% with diabetes (9 patients), 55.77% with dyslipidemia (29 patients), and 5.77% were active smokers (3 patients).

From the cancer therapy point of view, this was mainly composed of the following classes of cytostatics: anthracyclines (Doxorubicin and Daunorubicin), alkylating agents (Cyclophosphamide), and molecularly targeted therapy represented by: monoclonal antibodies (Rituximab), tyrosine kinase inhibitors (Dasatinib), and proteasome inhibitors (Carfilzomib and Bortezomib).

Longitudinal deformation: global longitudinal strain (GLS)

Gender and age did not represent risk factors in the GLS decrease during the 12 months of study. Hence, the echocardiographic parameter GLS decreased during the study period without preferences between the two sexes, $p=0.421$ (Table 1).

Table 1. Variation of the global longitudinal strain (GLS) range before chemotherapy (1) and at 12 months of study (2) based on gender.

GLS		Average	*p*
M	1	−20.2	0.243
	2	−16.78	0.237
F	1	−19.63	0.324
	2	−16.23	0.345

GLS, global longitudinal strain; *p*, standard error; M, male; F, female.

We analyzed the changes in GLS echocardiographic parameter during the study period based on the age categories and risk degrees, but obtained similar results—GLS varied regardless of the age category ($p=0.973$, Table 2).

Table 2. Variation of the global longitudinal strain (GLS) before chemotherapy (1) range and at 12 months of study (2) according to age.

GLS		Average	*p*
<65 years	1	−20.03	0.543
	2	−17.46	0.567
65–75 years	1	−19.8	0.365
	2	−17.1	0.368
>75 years	1	−18.9	−213
	2	−16.35	0.243

GLS, global longitudinal *strain*; *p*, standard error.

Table 3presents the pre-chemotherapy and 12-month GLS values for the subgroups of patients associated with HTA, dyslipidemia, DM, smoking, and positive cardiovascular here docolateralantecedents. In our study, the decrease in GLS during the studied period was influenced by the presence of HTA ($p=0.02$) and dyslipidemia ($p=0.036$).

Table 3. Descriptive statistics of GLS pre-chemotherapy (initial) and at 12 months of follow-up according to the presence of classic cardiovascular risk factors.

			Average	*p*
HTA	YES	initial	−19.86	0.205
		at 12 months	−16.25	0.224
	NO	initial	−19.3	0.238
		at 12 months	−17.7	0.261
Dyslipidemia	YES	initial	−19.81	0.185
		at 12 months	−16.26	0.211
	NO	initial	−19.58	0.289
		at 12 months	−17.83	0.325
DM	YES	initial	−19.26	0.166
		at 12 months	−16.7	0.208
	NO	initial	−20.02	0.433
		at 12 months	−17.83	0.540
Smoking	YES	initial	−19.9	0.171
		at 12 months	−15.2	0.210
	NO	initial	−19.74	0.473
		at 12 months	−15.31	0.386
CHA+	YES	initial	−20.47	0.166
		at 12 months	−16.06	213
	NO	initial	−19.68	0.362
		at 12 months	−16.6	0.364

GLS, global longitudinal *strain*; HTA, arterial hypertension; DM, diabetes mellitus; CHA+, positive cardiovascular here docolateralantecedents; *p*, standard error; YES, presence of disease; NO, absence of disease.

Here, 67.5% of patients with HTA had a decreased GLS by more than 15% compared to the initial value in the 12 months of the study. After six courses of cytostatics, patients without HTA had the same variation of GLS in the 12 months of follow-up after the eighth course of chemotherapy (Table 4).

Table 4. Descriptive statistics according to the decreased GLS by more than 15% compared to the pre-chemotherapy value and the presence of HTA.

			Censored	
	Total N.	**No of Cases**	**N**	**%**
Without HTA	35	3	32	91.42%
With HTA	17	10	7	37.5%

HTA, arterial Hypertension; GLS, global longitudinal *strain*; N, number of patients.

The GLS decreased by more than 15% compared to pre-chemotherapy in 75% of studied patients with dyslipidemia and in only 22% of patients without dyslipidemia (Table 5).The subgroup of patients with dyslipidemia had a significantly greater risk for GLS decline over the 12-month follow-up: $p<0.001$.

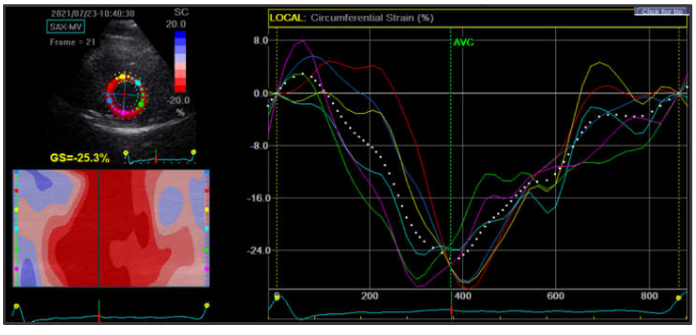
Table 5. Descriptive statistics according to the variation of the global longitudinal strain by more than 15% compared to the pre-chemotherapy value and the presence of dyslipidemia.

			Censored	
	Total N.	**No of Cases**	**N**	**%**
Without Dyslipidemia	23	5	18	78%
With Dyslipidemia	29	21	8	25%

N, number of patients.

In conclusion, between the demographic and cardiovascular risk factors, the GLS changes between the two moments, pre-chemotherapy and at 12 months of the study, were influenced by hypertension and dyslipidemia.

Subclinical myocardial dysfunction associated with cancer therapy was diagnosed in patients with hypertension and dyslipidemia in 50–75% of cases after the sixth course of therapy. In the subgroup of patients without HTA and dyslipidemia, subclinical myocardial dysfunction was diagnosed after the eighth course of cytostatics.



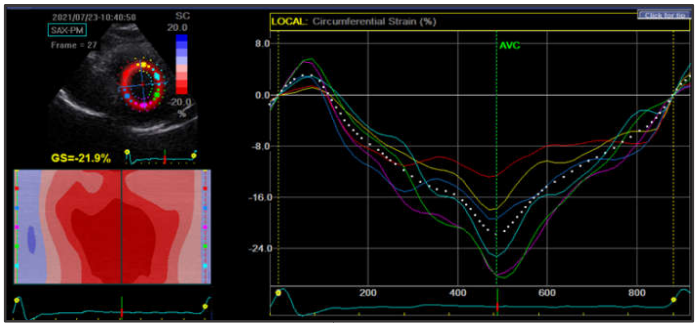


Figure 1. Speckle tracking imaging of the left ventricle circumferential strain before doxorubicin therapy in a patient with HTA.

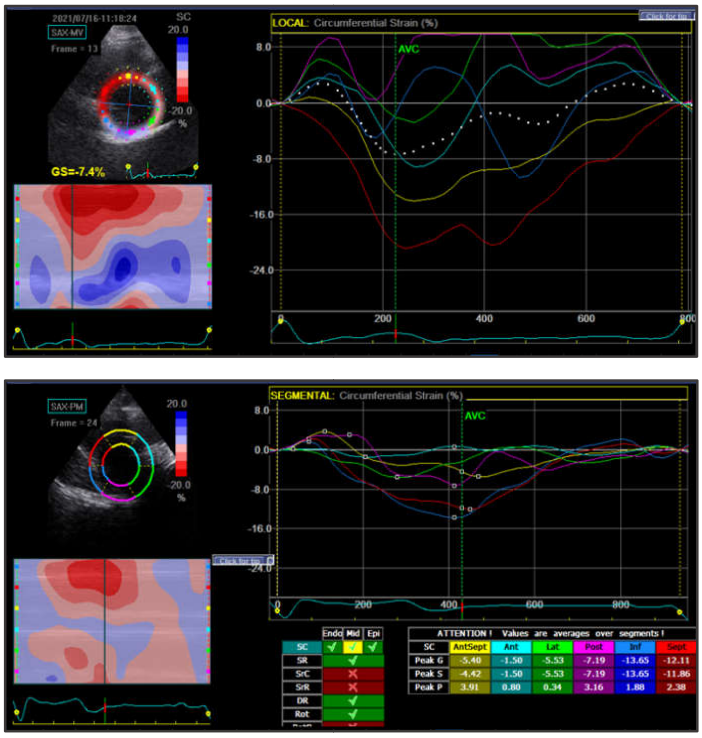


Figure 2. Speckle tracking imaging of the left ventricle circumferential strain after doxorubicin therapy in a patient with HTA.

Global Circumferential Strain—GCS

Gender and age did not represent risk factors in the GCS decrease during the 12 months of the study. Hence, GCS decreased without preference between sexes ($p=0.830$, Table 6). We analyzed the decrease in GCS according to the age categories and the degree of risk, but obtained similar results—GCS varied regardless of age ($p=0.853$, Table 7).

Table 6. Variation of global circumferential strain (GCS) pre-chemotherapy (1) and at 6 months of study (2) based on gender.

GCS		**Average**	***p***
M	1	−21.15	−213
	2	−17.51	0.256
F	1	−20.91	0.347
	2	−16.61	0.389

GCS, global circumferential strain; p, standard error; M, male; F, female.

Table 7. Variation of global circumferential strain (GCS) pre-chemotherapy(1) and at 6 months of study (2) according to age category.

GCS		Average	*p*
<65 years	1	−21.22	0.654
	2	−17.02	0.687
65–75 years	1	−21.3	0.341
	2	−16.9	0.328
>75 years	1	−19.55	0.521
	2	−17.15	0.523

GCS, global circumferential strain; p, standard error.

Table 8 shows the GCS values before chemotherapy and after 12 months of study for patients with HTA, dyslipidemia, DM, smoking, and positive cardiovascular heredocolateral antecedents.

Table 8. Descriptive statistics of GCS pre-chemotherapy (initial) and at 12 months of follow-up according to the presence of classic cardiovascular risk factors.

			Average	*p*
HTA	YES	initial	−21.91	0.35
		at 12 months	−16.81	0.38
	NO	initial	−21.12	0.30
		at 12 months	−17.22	0.32
Dyslipidemia	YES	initial	−21.89	0.44
		at 12 months	−16.12	0.55
	NO	initial	−21.23	0.28
		at 12 months	−17.35	0.35
DM	YES	initial	−20.37	0.67
		at 12 months	−17.3	0.95
	NO	initial	−21.16	0.26
		at 12 months	−16.99	0.37
Smoking	YES	initial	−21.2	0.84
		at 12 months	−17.2	0.58
	NO	initial	−20.94	0.26
		at 12 months	−17.09	0.37
CHA+	YES	initial	−21.27	0.78
		at 12 months	−16.5	0.57
	NO	initial	−20.93	0.26
		at 12 months	−17.16	0.36

GCS, global circumferential strain; HTA, arterial hypertension; DM, diabetes mellitus; CHA+, positive cardio vascular heredocolateralantecedents; *p*, standard error.

Here, 70.58% of patients with HTA had adecrease of > 15% over the initial GCS parameter compared to only 5.71% of patients without HTA in whom the same event was observed (Table 9). In 50–75% of patients with HTA and adecrease of > 15% of GCS, this was observed after six courses of cytostatics, and in patients without HTA, the same “event” was observed after eight courses of chemotherapy.

Table 9. Descriptive statistics for a decrease of > 15% compared to the pre-chemotherapy GCS parameter and the presence of HTA.

			Censored	
	Total N.	No of Cases	N	%
Without HTA	35	2	33	94.29%
With HTA	17	12	15	29.42%

HTA, arterial hypertension; N, number of cases.

The probability that the GCS echocardiographic parameter will decrease by more than 15% from the initial value during the 12 months of study was higher for hypertensive patients, $p<0.001$.

Moreover, 68.96% of patients with dyslipidemia showed a decrease of > 15% compared to the pre-chemotherapy GCS, and only 22% of patients without dyslipidemia observed the same event (Table 10).

Table 10. Descriptive statistics according to the decrease of more than 15% from the pre-chemotherapy GCS value and the presence of dyslipidemia.

			Censored	
	Total N.	No of Cases	N	%
Without Dyslipidemia	23	5	18	78%
With Dyslipidemia	29	20	9	31.04%

Most patients with dyslipidemia (75%), in whom we observed adecrease of > 15% from the pre-chemotherapy GCS value, were on their sixth course of chemotherapy. In the group without dyslipidemia, 25–50% of patients who recorded the event were on their eighth course of cytostatics. In conclusion, cardiovascular risk factors influence the decrease inthe GCS echocardiographic parameter between the two moments analyzed in our study, pre-chemotherapy and after 12 months of study, reaching the threshold of statistical significance in hypertensive and patients with dyslipidemia.

Subclinical myocardial dysfunction associated with cancer therapy assessed by a decrease of > 15% of the initial GCS echocardiographic parameter in patients with hypertension and dyslipidemia was reported in 75% of cases after the sixth course of therapy. For cases without HTA and dyslipidemia, subclinical myocardial dysfunction with cancer therapy was assessed by the GCS parameter after the eighth course of cytostatics.

Global Radial Strain (GRS)

The decrease in GRS during the 12-month study was not influenced by classic cardiovascular risk factors: HTA (p=0.548), dyslipidemia (p=0.581), DM (p=0.769), CHA+ (p=0.515), or smoking (p =0.634).

DISCUSSION

GLS has been proposed as a valuable tool for early detection [21] of changes in contractile function (right or left) based on its simplicity and repeatability (with automated measurement being superior to conventional).Therefore, it is recommended in all patients before initiation, as well as during and after potentially cardiotoxic oncologic therapies, to stratify risk and identify major changes of cardiac damage [22]. Combining this method with biomarker evaluation of cardiac damage (i.e., troponins, BNP) or overload can augment the accuracy of GLS assessment, as well as patients’ liability of developing cardiovascular complications[23–25]. Cancer treatment-related cardiotoxicities have emerged as an unintended consequence of evolving therapies and improved cancer-related survival, and CVD risk factors have been shown to potentiate cardiotoxicity [10].A ranking of the cardiovascular risk factors identified in our study shows dyslipidemia (55.77%) followed by HTA (33%), DM (17.31%), CHA-positive cardiovascular heredocolateralantecedents (14%), and smoking (6%). The widespread presence of HTA in the general adult population is approximately 30–45%[11], with~20% being women and 24% men; these values are relatively constant globally, regardless of economic status. Moreover, this percentage can increase to >60% in the sixth decade of life [11].In our study, subjects ranged between 22 and 79 years, with an average age of 54.9 ± 14.2 years; 75% of

patients were <65 yr. and only 3.85% were >75 yr. The patients were relatively young, consistent with the specialized literature represented by cohort studies. The European studies by Cardinale *et al.,* between 2010 and 2015 included over 2500 patients diagnosed with malignant pathologies, with average ages of 53 years [12] and 50 years [13]; both argued the importance of early myocardial infarction dysfunction diagnosis associated with anthracycline therapy.

CONCLUSIONS

The decreased GLS between pre-chemotherapy and at 12 months was statistically significantly influenced by hypertension and dyslipidemia. Subclinical myocardial dysfunction associated with cancer therapy, assessed by a > 15% decrease in GLS, was diagnosed in patients with hypertension and dyslipidemia as early as the fourth course of cytostatics. However, in 50–75% of cases, this was observed after the sixth course of therapy. For subgroups of patients not associated with HTA and dyslipidemia, early myocardial dysfunction associated with cancer therapy diagnosed by GLS assessment was observed after the eighth course of cytostatics.

The decrease in GCS between the two moments, pre-chemotherapy and at 12 months of study was statistically significantly influenced by hypertension and dyslipidemia. Early myocardial dysfunction associated with cancer therapy in patients with hypertension and dyslipidemia, diagnosed by adecrease in GCS by more than 15% of the pre-chemotherapy value, was reported in 50–75% of cases after the sixth course of therapy.

The GRS global radial strain showed changes between the two moments evaluated in our study, but these were not constant, did not have a significant magnitude, and appeared in a small number—under 10% of the studied patients.

Author Contributions: F.D. wrote the manuscript and analyzed and interpreted the patient data regarding hematological disease, performed the speckle tracking measurements. T.M. and I.I. selected patients. M.A. performed the echocardiographic examination. F.C. and A.A. created the research design. D.M. and V.B. were responsible for the statistical analysis. M.C.T. verified and supervised the research. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement: Following the analysis of the submitted documentation, the criteria met biomedical ethics from the perspective of general and specific principles regarding biomedical research, respecting the Declaration of Helsinki and the rules of good practice in research on human subjects. The Ethics Committee is the Scientific Research Ethics Committee at the University of Medicine and Pharmacy “Victor Babes” Timisoara Nr. 29/07.12.2015/rev 2022; Chairman: Prof. Dr. Alexandra Enache, Primary medical examiner, Graduate in legal sciences.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish this paper

Conflicts of Interest: The authors declare no conflict of interest regarding the publication of this paper.

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