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Original article

The Evolution of Imaging Markers in Cardiovascular Evaluation of Patients with Hematological Malignant Neoplasia

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Abstract

Chemotherapy-induced cardiotoxicity is a major cause of morbidity and mortality in cancer survivors. Myocardial dysfunction is one of the most frequent problems of chemotherapy, with highly important unfavorable effects on the prognosis in the short and long term. Its association with malignant pathology influences the compliance with specific oncological therapy and the healing process as well. Therefore, the myocardial dysfunction is becoming a reason for expanded morbidity and even early mortality for this category of patients. Our study demonstrates that cytostatics in the anthracycline class, especially Doxorubicin with a cumulative dose of more than 400 mg/m^2, their association with "targeted" molecular therapies and Cyclophosphamide, along with the co-existence of cardiovascular risk factors such as hypertension and dyslipidemia, can affect longitudinal myocardial mechanics, which can be studied and tracked by decreasing the LSsubendo echocardiographic parameter in the first 12 months of cytostatic treatment. After the 6th dose of chemotherapy, approximately 50% of the patients under study had pathological changes in LSsubendo, and after the 8th treatment this number rose to 88%. In our study we demonstrated that the reduction in GLS between the two evaluated moments, pre-treatment and after 12 months, was influenced by the treatment with anthracyclines, with Doxorubicin administered in a cumulative dose > 400 mg/m^2, with the association of cytostatic classes consisting of: anthracyclines, "targeted" molecular therapies, and cyclophosphamide, and by the coexistence of hypertension and dyslipidemia. Our results on the variation of GLS and LSsubendo at 12 months of the research for patients with hematological neoplasia are consistent with other data in literature, with myocardial deformity parameters changing early during cytostatic specific treatment, thus preceding a decline in LVEF. An early diagnosis of myocardial dysfunction is feasible by using longitudinal deformation criterion (parameters) assessed by 2D speckle tracking echocardiography.

Keywords: **cardiotoxicity, chemotherapy, echocardiography, speckle tracking, parameters.**

1. Introduction

Chemotherapy-induced cardiotoxicity is a major cause of morbidity and mortality in cancer survivors [1]. Myocardial dysfunction is one of the most frequent problems of chemotherapy, with highly important unfavorable effects on the prognosis in the short and long term. Its association with malignant pathology influences the compliance with specific oncological therapy as well as the healing process. Therefore, the myocardial dysfunction is becoming a reason for expanded morbidity and even early on mortality for this category of patients [2].

Anthracyclines are the cornerstone of therapy for a wide range of solid malignant and hematological tumors; however, their use is limited by the risk of chemotherapy-induced cardiotoxicity that leads to cardiomyopathy and heart failure. The incidence of cardiotoxicity in the literature depends on the definition used, the anthracycline dose, the duration of monitoring and the surveillance methods used to identify heart damage. The reported risk of clinical heart failure was about 2% to 4% for low-dose anthracycline treatments, while the incidence of heart damage defined by an abnormal increase in cardiac biomarkers was reported up to 35%. Several mechanisms for anthracycline cardiotoxicity have been proposed, including the harmful effects of oxidative stress and reactive oxygen species and the inhibition of topoisomerase II beta that leads to the death of cardiomyocytes. Furthermore, genetic susceptibility is an emerging field that currently generates active research. The risk factors associated with anthracycline cardiotoxicity include the lifelong cumulative dose, age, previous cardiac dysfunction, and the presence of cardiovascular risk factors, hypertension in particular [3].

Doxorubicin-induced cardiotoxicity is dependent on the dose. Furthermore, the age of the patients plays a role in the

sensitivity of younger patients with a higher risk of cardiotoxicity and heart failure years after the treatment has ended. The exact mechanism responsible for doxorubicin-induced cardiotoxicity is poorly understood and further research needs to be carried out to elucidate the underlying mechanism [4].

The diagnosis of cardiotoxic effects is mainly based on imaging and specific biomarkers. Echocardiography has become the main imaging technique due to its wide availability. In addition to the quantitative determination of left ventricular function using two-dimensional methods, the three-dimensional methods provide better accuracy and lower variability in detecting cardiac dysfunction22. Moreover, the analysis of the global longitudinal strain (GLS) reveals even the subtle changes in the left ventricular function and thus detecting very early damage before the ejection fraction of the left ventricle decreases [5].

Global peak systolic longitudinal tension (GLS) with the help of the speckle tracking echocardiography (STE) has become an important pre-treatment parameter that can independently predict subsequent adverse cardiac events, since these abnormalities typically precede the reduction of left ventricular ejection fraction (LVEF)21. While an absolute measurement of GLS may be informative, an early reduction in GLS of 10%-15% by STE appears to be the most useful metric for prognosis of cardiotoxicity during the treatment [6].

The study of Maria Isabel Camara Planek and collaborators, showed that, in a dose-dependent manner, doxorubicin was associated with subclinical dysfunction of the right ventricle (RV) measured by speckle-tracking echocardiography STE 2D, but without any changes in LVEF, in patients with lymphoma without known underlying heart disease. As far as known, their study is one of the first of its kind to show that the subclinical parameters of RV dysfunction were associated with higher cumulative doses of doxorubicin, even though LVEF was not. Zhao et al.n have recently demonstrated subclinical changes in the parameters of RV function after 6 cycles of chemotherapy with anthracycline [23,24].

2. Materials and Methods

A prospective time series study, interdisciplinary, was performed on 52 patients, consisting of 50% men and 50% women, aged between 24 and 79 years (average age of 40.66 years ± 14.24 years) with hematological malignancies under a cytostatic treatment, found in the evidence of the Oncology and Radiotherapy Clinic of the Municipal Emergency Clinical Hospital Timisoara, addressed to the Ascar Cardiology Clinic in Timisoara for clinical and specialized echocardiographic examination.

Inclusion criteria: age over 18 years; LVEF prior to initiation of cytostatic treatment ≥ 53 %; no antecedents of acute coronary event and/or myocardial revascularization procedure; during inclusion in the study (12 months) no other cause of the decrease in LVEF% was identified, apart from chemotherapy; electrocardiographically all patients were in sinus rhythm; signed informed consent. The exclusion criteria were represented by the patient's refusal to participate in this study, history of coronary heart disease, heart failure (HF) symptoms, pregnancy status, professional sports activity, and LVEF <53% determined by Echo2D. All patients provided their informed written consent to participate in the study. The study was approved by the Ethics Committee of the "Victor Babes" University of Medicine and Pharmacy, from Timisoara.

In the present study, the myocardial dysfunction was defined according to current recommendations (Consensus of Experts for the monitorization of cardiac function during and after cancer therapy published by EACVI and ASE7,8), as symptomatic / asymptomatic reduction of LVEF by ≥ 10% to <53%.

Taking into account the data in the literature and the available recommendations, we considered the appearance of myocardial dysfunction associated with early, subclinical cancer therapy (so patients who are at risk for asymptomatic decrease in FEVS and possibly myocardial dysfunction that manifests clinically), when the parameters of myocardial deformity recorded a relatively decrease in percentage by ≥15% of the initial pre-treatment value [7,8,9].

During the initial evaluation, for each patient several aspects were recorded, such as: age, sex, heredocolateral antecedents or personal pathological history of cardiovascular diseases (CVD), the presence / absence of high blood pressure, diabetes mellitus, dyslipidemia, smoking habit if any, and previous treatments (chemotherapy). The patients were situated in an 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 - increased risk [8].

At the end of the follow-up period, from the observation sheet the following were recorded: the hematological diagnosis, the chemotherapeutic protocol and the number of treatments performed during the follow-up period, and the cumulative dose of anthracycline was individually calculated indexed to the body surface. In our study, the threshold of 400 mg/m^2 for Doxorubicin was used as a risk factor for myocardial dysfunction associated with this therapy [10].

For the acquisition of 2D ultrasonographic datasets, the Vivid S5 ultrasound (GE Healthcare Bio-Sciences Corp, Piscataway, NJ, USA) was used, equipped with probes dedicated to the two-dimensional scanning (M5S) of the heart, and a suitable bed to facilitate the handling of the probe. Both FEVS analysis (performed using Simpson biplane method) and *speckle tracking* data was carried out offline, after the acquisition of echocardiographic images, by applying a different workstation that utilizes the EchoPAC system version 11.0.1 (GE Healthcare Bio-Sciences Corp) program.

In order to avoid the influence of the increased preload on the left ventricle (LV) mechanism, the echocardiographic examination was not done on the day of the cytostatic treatment administration.

Initially, a basic analysis was performed, which included the complete two-dimensional morphological and functional evaluation of all cavities and heart valves. The echocardiographic examination was then continued by using the *speckle tracking* technique.

Patients were examined in left lateral decubitus using the M5S probe. In order to obtain measurements as accurate as possible and to accurately determine the telesystolic and telediastolic timing, the patients were electrocardiographically monitored, adjusting the route in order to obtain well-defined R (or Q) waves. For each section, three consecutive heart cycles were recorded during apnea.

The apical four-chamber view (A4C) and apical two-chamber (A2C) view used for FEVS analysis together with the apical long-axis view (APLAX) used for GLS analysis were captured by minimizing the sector and depth in order to achieve the optimized visualization of the LV walls and a good close up of the endocardium, but especially with the aim of obtaining a minimum frame rate per second (between 70 and 80 Hz) maintaining the same depth throughout the whole the analysis journey, which is an essential criteria for speckle-tracking analysis.

The same was done for the parasternal short-axis (PSAX) view from the mitral valve level, papillary muscles, and apex levels to measure global circumferential strain (GCS) and global radial strain (GRS). Respiratory maneuvers were performed (inhale and exhale for a long time), asking the patient to maintain apnea for a few seconds at the time of optimized visualization of the LV, avoiding its apical shortening during the systole. The obtained images were stored in an external memory and then transferred to the workstation for analysis.

2.1. The Processing of Statistical Data

The statistical analysis was performed using MedCalc statistical software version 12.7.7 (MedCalc Software, Ostend, Belgium). This calculation was based on the reproducibility of the TDI and TSI

determinations, so that the differences of> 5 % between consecutive measurements were statistically significant. The differences between the groups and within the same group before and after the 12 months of follow-up were compared with the help of the associated *t-test*.

3. Results

In our study, the incidence of myocardial dysfunction associated with cytostatic therapy, defined by the decrease of LVEF by more than 10%, below the value of 53% compared to the pre-treatment value, in the case of two-dimensional evaluation, is 15.38%. The changes in myocardial deformity parameters assessed by speckle tracking echocardiography, after 12 months of cytostatic treatment, reached the statistically significant threshold in our study.

Table 1. Descriptive statistics of pre-treatment myocardial deformity parameters (initial) and after 12 months of study.

	GLS		**GLS subendo**		**GLS subepi**		**GCS**		**GRS**	
	Initial	12 months	Initial	12 months	Initial	12 months	Initial	12 months	Initial	12 months
Media	-19,88	-16,49	-24,67	-18,08	-20,74	-16,7	-20,68	-17,22	32,27	28,82
± DS										
Max	-21,9	-18,3	-25,7	-20,5	-21,8	-18,4	-21,9	-19,5	33,5	32,3
Min	-18,8	-15,1	-21,5	-15,8	-18,4	-15,0	-19,4	-15,1	30,7	24,3
N	52	52	52	52	52	52	52	52	52	52
p	p<0,01		p<0,01		p<0,01		p<0,01		p<0,01	

GLS- global longitudinal strain, LSsubendo – subendocardial longitudinal strain, LSsubepi – subepicardial longitudinal strain, GCS – global circumferential strain, GRS – global radial strain, Min.- minimum, Max.-maximum, N-number, DS-standard deviation

Subclinical myocardial dysfunction associated with cancer therapy, diagnosed by a decline of more than 15% of the pre-treatment value of GLS, was observed after the 4th treatment with cytostatics. In 50-75% of cases it developed after the 6th dose of therapy, in the subgroups of patients in treatment with anthracyclines, with Doxorubicin in cumulative dose > 400/m^2, with the association of classes of cytostatics anthracycline, "targeted" molecular therapies, Cyclophosphamide (AMC). The decrease in GLS in the 12 months of the investigation was more remarkable in patients diagnosed with lymphoma non-hodgkin (LNH) and lymphoma hodgkin (LH) than in patients diagnosed with chronic myeloid leukemia (CML), multiple myeloma (MM) or chronic lymphocytic leukemia (CLL).

Subclinical myocardial dysfunction associated with cancer therapy, assessed by lowering GLS by more than 15% of the pre-treatment value, was diagnosed in patients with hypertension and dyslipidemia as early as the 4th session of chemotherapy, but in 50-75% of cases it was noticed after the 6th dose of therapy.

The decrease in the subendocardial longitudinal strain (LSsubendo) was influenced by the treatment with anthracyclines, with Doxorubicin in the cumulative dose > 400/m^2 and by the association of classes of cytostatics represented by: anthracyclines, "targeted" molecular therapies, and Cyclophosphamide, specific to the therapeutic protocol R-CHOP. For patients diagnosed with LNH, there was a statistically important decline in the LSsubendo parameter, compared with those diagnosed with LH, CLL, MM and CML. Myocardial dysfunction associated with cancer therapy, diagnosed by a decrease of more than 15% of the pre-treatment value of LSsubendo, was observed in 50-75% of cases after the 6th dose of therapy for subgroups of patients who received anthracyclines, Doxorubicin in cumulative dose > 400/m^2, with the association of AMC. The decrease in LSsubendo between the two moments, pre-treatment and after 12 months of the investigation, was statistically significant affected by the existence of hypertension and dyslipidemia.

Table 2. Descriptive statistics based on the decrease by more than 15% of the LSsubendo parameter compared to the pre-treatment value associated with monotherapy or combination of AMC cytostatics.

			Censored	
	Total N	Nr of cases	N	%
AMC	33	29	4	12,3%
M	12	1	11	91,67%
AC	7	7	0	0

Ac- anthracycline, AMC- anthracycline, "targeted" molecular therapies, Cyclophosphamide; M- "targeted" molecular therapies, LSsubendo - subendocardial longitudinal strain.

The decrease in the overall circumferential strain was influenced by the treatment with anthracyclines, with Doxorubicin and by the association of cytostatic classes represented by anthracyclines, molecular "targeted" therapies and Cyclophosphamide, particular to the R-CHOP therapeutic protocol. For patients diagnosed with LNH, there was a statistically considerable decline in the GCS parameter, compared with those in patients diagnosed with LH, CLL, MM and CML. Myocardial dysfunction associated with cancer therapy, diagnosed by a decrease of more than 15% of the pre-treatment value of GCS, was observed in 75% of cases after the 6th dose of therapy for the subgroups of patients in treatment with anthracyclines, with Doxorubicin, with the association of AMC. The decrease in GCS between the two moments, pre-treatment and after 12 months from the study was statistically significant influenced by the presence of high blood pressure and dyslipidemia.

The global radial strain GRS and the subepicardial longitudinal strain highlighted changes between the two moments evaluated in our study, but these were not constant, did not have an important magnitude and they appeared in a smaller number, less than 10% of the patients that were included in the present study.

4. Discussion

Anthracyclines are antineoplastic agents with a high efficacy in the treatment of many hematological cancers and solid organs [20]. The clinical impact of Anthracycline-induced cardiac dysfunction increases together with the increase of cancer survival. Anthracycline cardiotoxicity is known as type I cardiotoxicity, characterized by cardiac myocyte death and irreversible heart damage [11].

As for the cytostatics used for specific hematological treatment, more than half of the patients of the studied group were treated with anthracyclines (76.92%), who received Doxorubicin. Many the studied patients also received molecular "targeted" therapies, of which: 52.93% were treated with the chimeric monoclonal antibody Rituximab, 15.39% with tyrosine kinase inhibitor Dasatinib and 15.38% with proteasome inhibitors such as Bortezomib and Carfilzomib (but also with alkylating agents such as Cyclophosphamide (63.46% of the studied patients). Other cytostatics included in the treatment protocols used in our study were: vincristine and fludarabine along with corticotherapy.

A ranking of the cardiovascular risk factors identified in our study shows that the first place is dyslipidemia (55.77%), followed

by hypertension (33%), diabetes (17.31%), heredocolateral antecedent positive for cardio-vascular diseases (14%) and smoking (6%). The global prevalence of hypertension in the general adult population is about 30-45%, about 20% of these being represented by women and 24% by men, data that seem to be constant around the world, regardless of any economic status. More than that, this percentage can even increase to over 60% in the 6th decade of life [12].

In our study, the patients age was between 22 and 79 years old, the average age being 54.9 ± 14.2 years, 75% of the patients being under the age of 65 and only 3.85% over 75 years of age. These data show us that the batch of patients was represented by relatively young subjects, which is consistent with the literature represented by the cohort studies. Studies in Europe led by Cardinale et al. that demonstrated the importance of early detection of myocardial dysfunction associated with anthracycline treatment, between 2010 and 2015, included more than 2500 patients diagnosed with malignant pathologies, with an average age of 53 years [13] and 50 years [14], respectively.

In our study we followed the influence of treatment with cytostatic classes: anthracyclines and molecular "targeted" therapies administered alone, but also in the association of anthracyclines, molecular "targeted" therapies and Cyclophosphamide, on the parameters of myocardial deformity and LVEF, in the 12 months of echocardiographic study that was done in the group of patients. This association of cytostatics is specific to the therapeutic protocol R-CHOP and used in the treatment of LNH, LH and some stages of CLL. Several studies have shown that after the factors of progression of neoplastic diseases, heart damage is the second largest cause of mortality among patients with LNH treated with R-CHOP [15,16].

Using retrospective analysis, Von Hoff et al. [17] demonstrated as early as 1979, that the total cumulative dose of Doxorubicin is a major risk factor for heart failure associated with this type of treatment, with an incidence of 3% for a dose of Doxorubicin of 400 mg/m^2, of 7% for 550 mg/m^2 and even of 18% for the dose of 00 mg/m^2 [17].

In our study, we used the threshold of >400 mg/m^2 for the cumulative dose of Doxorubicin during the 12 months of follow-up and therefore we identified a subgroup of patients composed of 29 subjects at high risk for myocardial dysfunction associated with anthracycline therapy. We focused on observing the decrease in the echocardiographic parameters described in these patients during the 12-month monitoring period.

In conclusion, the studied group has similar characteristics to those described in the literature in terms of demographic and clinical data for patients with hematological neoplasia [18,19].

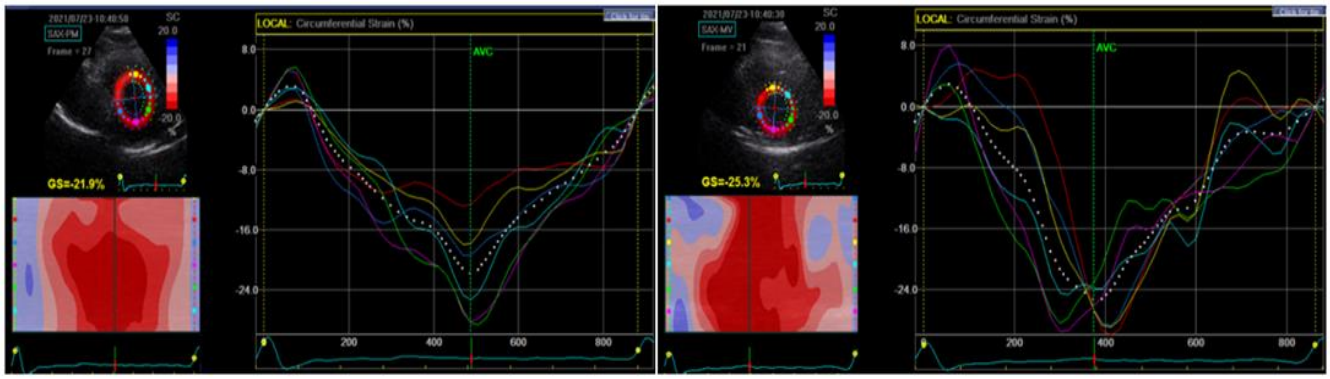

Figure 2. Speckle tracking imaging of the left ventricle circumferential strain, before doxorubicin therapy.

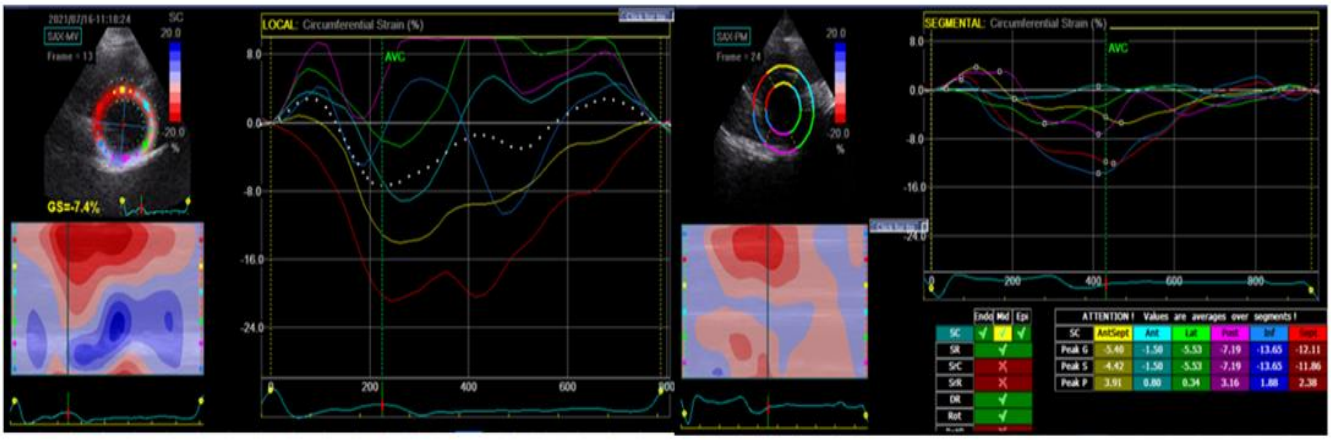

Figure 3. Speckle tracking imaging of the left ventricle circumferential strain, after doxorubicin therapy.

5. Conclusions

Our study demonstrates that the cytostatics in the anthracycline class, especially Doxorubicin with a cumulative dose of more than 400 mg/m^2, as well as their association with "targeted" molecular therapies and Cyclophosphamide, along with the existence of cardiovascular risk factors such as hypertension and dyslipidemia, can affect longitudinal myocardial mechanics, which can be studied and tracked by decreasing the LSsubendo echocardiographic parameter in the first 12 months of cytostatic treatment. After the 6th dose of chemotherapy, approximately 50% of the patients under study had pathological changes in LSsubendo, and after the 8th treatment 88% of them. In our study we demonstrated that the reduction in GLS between the two evaluated moments, pre-treatment and after 12 months, was influenced by the treatment with anthracyclines, with Doxorubicin administered in a cumulative dose > 400 mg/m^2, with the association of cytostatic classes consisting of: anthracyclines, "targeted" molecular therapies, and cyclophosphamide, and by the coexistence of hypertension and dyslipidemia. Our results on the variation of GLS and LSsubendo at 12 months of the research for patients with hematological neoplasia are consistent with the data in the literature, with myocardial deformity parameters changing early during cytostatic specific treatment, thus preceding a decline in LVEF. An early diagnosis of

myocardial dysfunction is feasible by using longitudinal deformation criterion (parameters) assessed by 2D speckle tracking echocardiography.

Ethics approval and consent to participate

Conclusions: Nr. 29/07.12.2015/rev 2022

CECS of UMFVBT concludes, following the analysis of the submitted documentation, that the criteria are met biomedical ethics, from the perspective of general and specific principles regarding research biomedical, being respected the Declaration of Helsinki and the rules of good practice in research on human subjects.

Chairman: Prof. Dr. Alexandra Enache, Primary medical examiner, Graduated in legal sciences

Conflicts of Interest

The authors declares that there is no conflict of interest regarding the publication of this paper.

Authors' contributions

FD performed the speckle tracking measurements, selected patients, and was a major contributor in writing the manuscript. MA performed the echocardiographic examination. II analyzed and interpreted the patient data regarding the hematological disease. FC created a research design. VB was responsible for the statistical part. MCT verified and supervised the entire research. All authors read and approved the final manuscript.

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