

CASE PRESENTATION

Identification of the occurrence of cardiotoxic effects by assessing left ventricular dysfunction and vascular remodeling parameters in a patient with acute lymphoblastic leukemia

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Abstract: Therapies for different malignancies are associated with an increased risk of cardiotoxicity. Amongst these drugs, anthracyclines and their analogs are most commonly used as chemotherapy agents but, unfortunately, they increase the incidence of cardiovascular side effects. Cardiovascular side effects induced by chemotherapy are highly associated with the cumulative dose of anticancer drugs. Left ventricular dysfunction followed by cardiac failure are most frequent side effects of chemotherapy. We evaluated here cardiac dysfunction and vascular changes for a young patient without cardiovascular risk factors before, diagnosed with acute lymphoblastic leukemia (ALL), three months after starting chemotherapy and three months after stem cell transplantation. Occurrence of left ventricular dysfunction, without any clinical signs after chemotherapy was reported. Small changes in vascular remodeling parameters have also been identified, which may suggest a more rapid vascular remodeling in patients receiving chemotherapy and radiotherapy.

Keywords: acute lymphoblastic leukemia, chemotherapy, cardiotoxicity, left ventricular dysfunction

Rezumat: Se cunoaște faptul că medicația oncologică se asociază cu risc crescut de cardiotoxicitate. Dintre aceste medicamente antraciclinele și analogii lor sunt cei mai des utilizați ca terapie chimioterapică însă, pe lângă eficiența oncologică dovedită, s-a demonstrat că prezintă o incidență crescută a efectelor adverse cardiovasculare. Efectele adverse cardiovasculare depind de doza cumulativă a citostatice. O complicație frecventă a terapiei citostatice o reprezintă disfuncția ventriculului stâng (DVS) și apariția fenomenelor de insuficiență cardiacă. Scopul acestei prezentări a fost de a evalua posibilitatea apariției disfuncției cardiace și a modificărilor vasculare la o pacientă tânără, fără factori de risc cardiovasculari, diagnosticată cu leucemie acută limfoblastică, la trei luni de la începerea chimioterapiei, respectiv la trei luni după transplantul cu celule stem. Prin rezultatele obținute, s-a observat că poate să apară disfuncție ventriculară stângă, post chimioterapie, fără simptomatologie clinică. Au fost, de asemenea, identificate și mici modificări ale parametrilor de remodelare vasculară, ceea ce poate să sugereze o remodelare vasculară mai accelerată în cazul pacienților ce primesc tratament chimioterapic și radioterapic.

Cuvinte cheie: leucemie acută limfoblastică, chimioterapie, cardiotoxicitate, disfuncție ventriculară stângă

INTRODUCTION

Chemotherapy may induce cardiovascular toxicity¹. Certified side effects of anthracyclines and other cardiotoxic agents could be reduced by the use of cardioprotective drugs, without any decrease of the antineoplastic efficacy^{1,2}. A complete clinical cardiac evaluation of the patient, the identification of the first signs and symptoms of cardiovascular disease, the knowledge of the patient's comorbidities and the treatment of these, as well as the identification of cardiovascular risk factors and their changes seem to be crucial for the identification of the cardiovascular side

effects during and after chemotherapy^{3,4}. Knowing and correctly treating any cardiovascular disease before starting chemotherapy is helpful in preventing possible complications that may occur during such unpleasant treatment. A close collaboration between the oncologist and the cardiologist could prevent the cardiotoxic side effects of chemotherapy and radiotherapy.

CASE PRESENTATION

One year evaluation has been performed for a 23-year-old patient without significant history of cardiovascular or other diseases. This patient with no background

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of previously certified cardiovascular pathology, was diagnosed with acute lymphoblastic leukemia (ALL) with B precursor, CALLA negative BCR-ABL. The patient was admitted to hospital for an intense pain and swelling of right lower limb, asthenia and fatigue.

The patient had pale tegument, mucous membranes and edema at the level of the right lower limb. Clinical examination revealed normal cardiovascular parameters as it follows: SBP/DBP=120/65 mmHg, HR=68 bpm. Electrocardiographic monitoring proved that the patient has a sinus rhythm, intermediate QRS spindle, without terminal phase changes.

By radiography, it has been shown that the heart was within normal limits but the lungs had a slight and diffuse increase of lung interstitium. Deep venous thrombosis has been certified in the right popliteal vein and subcutaneous treatment with low molecular weight heparin has been initiated. Blood count profile, revealed anemia, thrombocytopenia and leukocytosis with high amount of blasts in the peripheral blood. About 92% of bone marrow was infiltrated with lymphoid B-cell precursor cells with a pro-B CALLA negative lymphoblast and a possible presence of the Philadelphia 1 chromosome has been suspected. Molecular biology emphasized the detection and quantification of Bcr - abl Major (p210) and Bcr - abl minor (p190) both of them being positive. Histopathology certified the diagnosis of acute lymphoblastic leukemia with precursor B cells.

The results described advocate for the diagnosis of acute lymphoblastic leukemia with negative CALLA B precursor, possibly positive Philadelphia chromosome. 9 months after the diagnosis was established and chemotherapy was started, allogeneic haematopoietic stem cell transplantation was performed from the unrelated donor.

The patient received anticoagulant treatment with low molecular weight heparin for deep right vein thrombosis and chemotherapy drugs as follows: Daunorubicin total dose of 877.5 mg/m², Adriamycin 525 mg/m², Citarabine in total dose = 188 mg/m², Methotrexate total dose = 4612.5 mg/m², Vincristine total dose = 36 mg/m², Topoisomerase II-topoisomerase inhibitors -VM26 / VPI6 (Teniposide) in the total dose of 2625 mg/m², Alkylating agents -Cyclophosphamide (Imatinib) at a dose of 600 mg/day. The prophylaxis of Cerebral Nervous System with Methotrexate in the total dose of 1635 mg/m², Cytarabine in a total dose of 180 mg/m² and corticotherapy with Dexamethasone in a total dose of 18 mg/m². During the stem

cell transplant, the patient received specific treatment with: Busulfan alkylating agents in the total dose of 864 mg and Corticosteroids with Cyclophosphamide at a total dose of 94g in 28 days. Before bone marrow transplant, the patient followed cranial radiotherapy.

MATERIAL AND METHODS

We used a General Electric Vivid E9 and a 5 MHz transducer for the transthoracic echocardiographic measurements. The patient was monitored by 2D ultrasound, tissue Doppler and Speckle Tracking to assess left ventricular function by calculating LVEF%, S', GLS. LVEF% (left ventricular ejection fraction) was determined by planimetric echocardiographic method in 4 chambers apical section, maximum systolic velocity was measured in the lateral mitral ring (S'), by tissue Doppler imaging (TDI), and by speckle-tracking technique we followed the initial global longitudinal strain (GLS). We also evaluated the following vascular remodeling parameters: Ankle-brachial index (ABI), Intima-Media Thickness (IMT) and pulse wave velocity (PWV) to identify the early appearance of arterial wall damage following chemotherapy.

Pulse wave velocity (PWV) is a method of quantifying aortic rigidity. The patient had PWV analysis done using MedExpert ArteriographTM TL2. This device enabled us to evaluate arterial dysfunction. The principle of the method consists of recording the signals of the pulse wave at the level of the brachial artery which is occluded for several seconds using an inflatable cuff. Using a measuring tape, the distance from the pubic symphysis to the sternal notch is determined. This, alongside other information about the patient (age, height, etc.) is introduced into the computer. PWV is calculated using the distance traveled by the pulse wave in the aorta and the time of travel (RT/2). The measurements are wirelessly transmitted to the computer which then processes the information.

To analyze the intima-media thickness (IMT), the same General Electric Vivid E9 was used, the measurements being done with a 9 MHz transducer. The IMT was determined at the level of the common carotid artery, 1 cm proximal to the carotid bulb.

The ankle-brachial index (ABI) was calculated with the help of a sphygmomanometer and a SONO TRAX Vascular Doppler device. The brachial systolic blood pressure of both arms was determined, and, using the vascular Doppler device, the systolic pressure of the inferior limbs was recorded. This was equivalent to the pressure in the cuff at the moment of the first

Doppler signal being detected in the dorsalis pedis artery. The ratio of systolic pressure of the upper limb to systolic pressure of the lower limb was calculated on both sides, with the greater value being recorded.

These parameters were followed at the beginning of the disease, 3 months after the initiation of chemotherapy and 3 months after stem cell transplantation.

RESULTS

During follow-up, the values of SBP and DBP decreased from the initial recorded value, HR (bpm) increased from the initial recorded value and it was maintained increased also post-transplant, and the body mass index and body surface area decreased during cytostatic therapy, having a slight increase post-transplantation of stem cells.

By evaluating 2D echocardiography, it is observed that at 3 months post chemotherapy, left ventricular shortening fraction has been decreased from the initial value, and then returned to its normal values in 3 months after transplantation. This is also noticeable by MAPSE modification that decreases post-chemotherapy but slightly increased at 3 months post-transplant. LVEDD, LVESD, increased compared to the first

assessment, as well as LVEDV and LVEVS, which were maintained increased post-transplantation.

As in what regards the assessment parameters of the diastolic dysfunction, the E and A waves increased and the E / A ratio decreased from the initial value. By evaluating the tissue Doppler at the level of the mitral lateral ring (TDI-LW), S' wave decreased from the initial value, E' wave increased, and the A' wave and the E/E' ratio decreased from the initial value.

Speckle tracking shows that global longitudinal strain (GLS) decreases at three months post-chemotherapy versus the initial value from -25.2% to -16.5%. Three months after transplantation, GLS begins to increase slightly at a value of -17.9%, but remains low compared to the initial value.

In terms of arterial wall damage, a slight thickening of the IMT in the right carotid artery is observed, the ABI decreased both on the left and on the right compared to the initial value and decreased even more post-transplantation. The PWV was initially 6.5 m/s, which corresponds to the 20 to 30-year-old age percentile, then three months after chemotherapy, the pulse wave velocity increased from the initial value to 7.8 m/s, which corresponds to the 40-50 year old arterial age percentiles, this value being also maintained at three months post-transplant.

Table 1. Comparison between body mass index, heart rate and blood pressure before starting treatment (initial), 3 months from start of chemotherapy and 3 months after transplant

	Initial	3 months from start of chemotherapy treatment	3 months after transplant
BMI(kg/m ²)	20.36	17.1	17,8
Body surface area (m ²)	1.75	1.59	1.62
HR(bpm)	68	100	98
SBP left/right arm (mmHg)	120/115	110/110	100/100
DBP left/right arm (mmHg)	80/75	70/70	60/60

Note: BMI=body mass index, HR=heart rate, SBP=systolic blood pressure, DBP=diastolic blood pressure.

Table 2. Comparison between conventional echo parameters for left ventricular systolic before starting treatment (initial), 3 months from start of chemotherapy and 3 months after transplant

	Initial	3 months from start of chemotherapy treatment	3 months after transplant
IVS (mm)	8	8	9
LVPW (mm)	8	8	9
LVEDD (mm)	30	40	41
LVESD (mm)	18	28	17
LVEF (%)	68	47	53
LVESV (ml)/body surface area	13	24	22
LVEDV (ml)/body surface area	40	45	48
LVFS (%)	40	30	47
MAPSE (mm)	18	11	13

Note: LVFS - left ventricular fractional shortening, IVS - interventricular septum, LVPW - Left ventricular posterior wall, LVEDD - left ventricular end-diastolic diameter, LVESD - left ventricular end-systolic diameter, LVEF - left ventricular ejection fraction, LVEDV - left ventricular end-diastolic volume, LVESV - left ventricular systolic volume, MAPSE - Mitral annular plane systolic excursion.

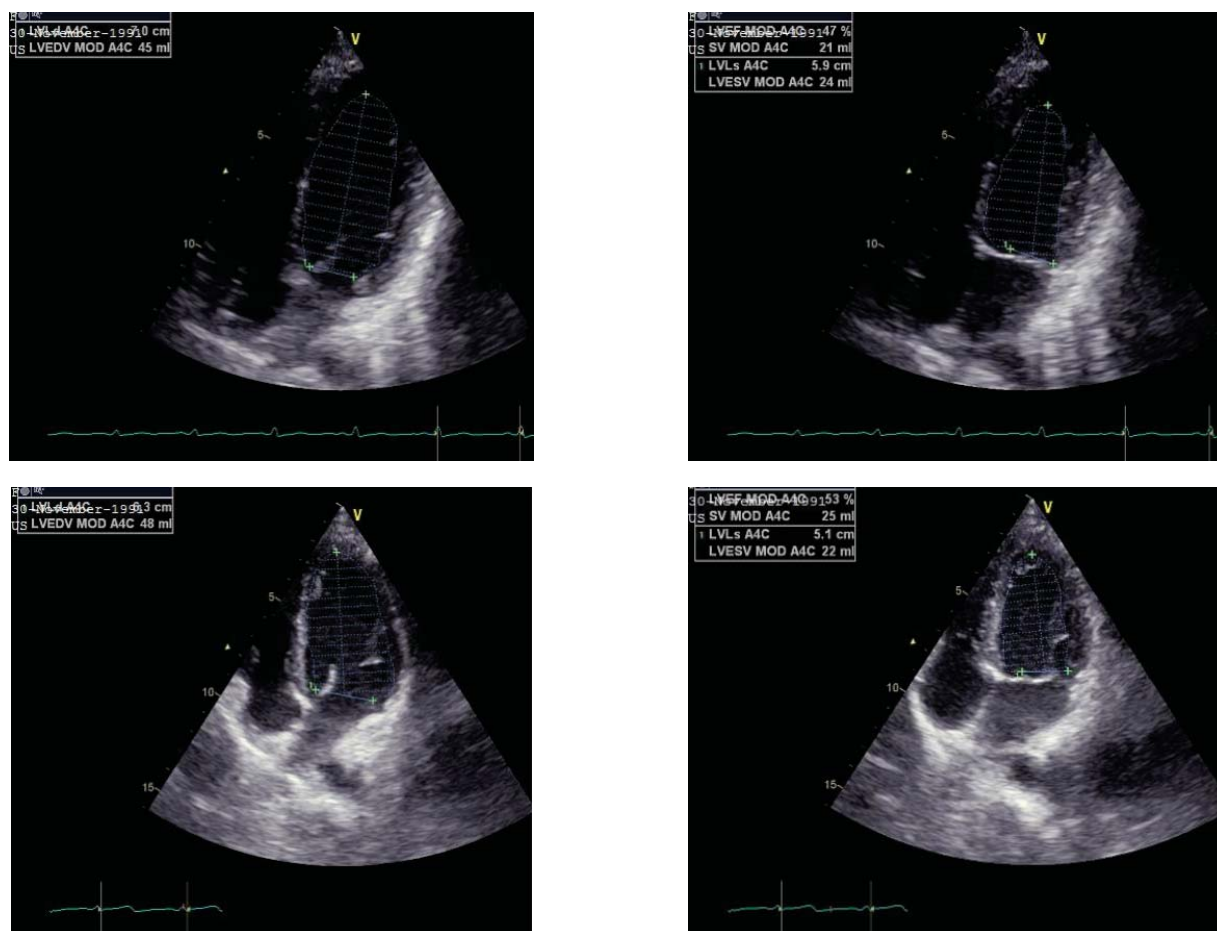


Figure 1. LVEF evaluation in 4 chambers apical section after 3 months from start of chemotherapy and 3 months after transplant.

DISCUSSIONS

By evaluating the periodic echocardiographic of LV cardiac, function in this young patient with ALL, left ventricular ejection fraction was impaired before clinical signs occurred. LVEF decreased by >10% from the initial value, from 68% to 47% at three months after chemotherapy. Several papers showed that a 10% decrease of LVEF post-chemotherapy and this may suggest cardiotoxicity in the absence of any signs of heart failure^{5,6,7}. Cardinal end al. studied anthracycline cardiotoxicity on 2.625 patients and reported that only 9% of the patients showed cardiotoxicity immediately after treatment, and 98% of these patients had clinical manifestations only after the first year of treatment. These results suggest that chemotherapy can induce a constant and progressive alteration of LV function⁸. The incidence of developing LV dysfunction also depends on the chemotherapeutic drug used. Some of them have stronger cardiotoxic effects than others. For the present patient, it has been used anthracyclines certified as having a high potential of developing LV dysfunction for doses over 700 mg/m², in about 18-

48% of cases. Another drug used was Cyclophosphamide with a cardiotoxicity risk of 7-28% and Imatinib with a cardiotoxicity risk of 0.2-2.7%^{5,9}.

Another echocardiographic parameter that can help us in early discovery of cardiotoxicity is GLS. A reduction in GLS >15% compared to the initial value may suggest left ventricular dysfunction^{5,10,11}. In our patient's case, we detected a GLS decrease three months post-chemotherapy of -8.7%. GLS may be a sensitive cardiotoxicity detection parameter, but according to existing data up to now, the chemotherapy treatment should not be interrupted or reduced only if a low GLS value is highlighted, but more parameters are needed⁵.

Kazuaki end al. studied 159 patients treated with chemotherapeutic agents, including anthracyclines. In 52 of the patients (33%) there was a significant change in GLS, and only 14 out of them had low LVEF with >10%, an aspect that suggests cardiotoxicity¹².

Tissue Doppler showed a decrease in S' wave three months after chemotherapy. As some authors have shown, there is a direct relationship between the ma-

Table 3. Comparison between tissue Doppler parameters for left ventricular systolic and diastolic dysfunction before starting treatment (initial), 3 months after chemotherapy and 3 months after transplant

		Initial	3 months from start of chemotherapy treatment	3 months after transplant
Trans mitral flow	E wave(m/s)	0.63	0.72	0.77
	A wave(m/s)	0.44	0.65	0.58
	E/A ratio	1.47	1.11	1.32
TDI - LW	S' wave(cm/s)	18	14	13
	E' wave(cm/s)	9	13	18
	A' wave(cm/s)	9	7	7
	E'/A' ratio	1	1.85	2.57
	E/E' ratio	7.22	5.53	4.27

Note: E: peak early diastolic trans mitral flow velocity, A: peak late diastolic trans mitral flow velocity, TDI-LW - tissue Doppler at the level of the mitral lateral ring, S': peak mitral annulus systolic velocity, E': peak early mitral annular diastolic velocity, A': peak late mitral annular diastolic velocity.

Table 4. Comparison between peak systolic strain parameters in the main three longitudinal views of LV before starting treatment, 3 months from start of chemotherapy and 3 months after transplant

	Initial	3 months from start of chemotherapy treatment	3 months after transplant
GLS-ALX (%)	-25.5	-14.5	-19.4
GLS-A4C (%)	-29	-17.1	-17.1
GLS-A2C (%)	-21.1	-17.8	-17.2
GLS-AVG (%)	-25.2	-16.5	-17.9

Note: ALX: apical long axis, A4C: apical 4-chamber, A2C: apical 2-chamber, views, GLS: global peak systolic strain.

ximum velocity of S' wave and LVEF, especially in patients who do not exhibit kinetic disorders at LV level 13). And in the ESC Position Paper on cancer treatment and cardiovascular toxicity, it has been shown that the decrease of S' wave during the time the patient receives chemotherapy may be an early marker of cytotoxicity⁵.

Katarzyna et al evaluated 35 women with breast cancer using Doppler tissue, who received anthracyclines. They showed that S wave was the only parameter that indicated the left ventricular systolic function

impairment. This decreased during the chemotherapy treatment¹⁴.

In Doppler ultrasound evaluation of carotid arteries, a slight increase by almost 1 mm of the intima-media thickness was observed, compared to the initial evaluation. This may suggest a developing of carotid vascular atherosclerotic disease⁵. Several articles have shown that the risk of developing cerebrovascular disease is doubled after cervical or cranial radiotherapy. Mediastinal and cranial radiotherapy can be associated with increased carotid rigidity and intima-media

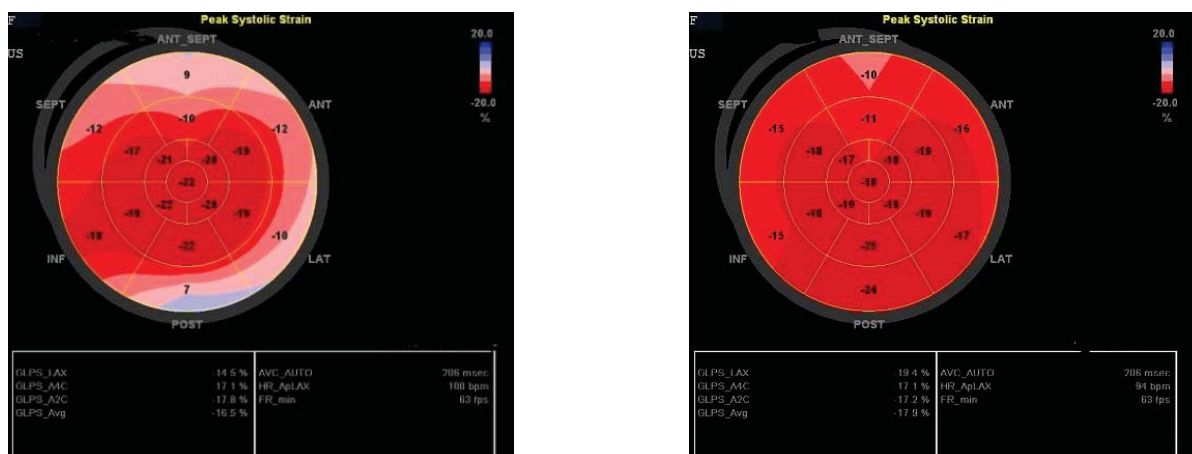


Figure 2. Speckle tracking: GLS 3 months from start of chemotherapy and 3 months after transplant.

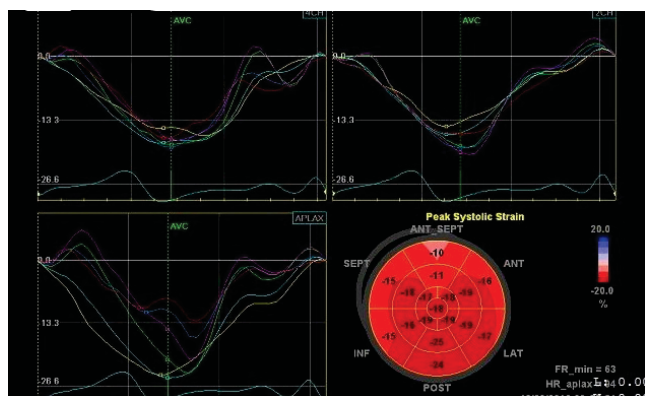


Figure 3. Speckle tracking: GLS 3 months after transplant.

thickness and may lead to accelerated atherosclerosis, and clinical manifestations may occur even 10 years after radiotherapy^{5,15-19}.

Recently, a study including 64 children with ALL treated with antineoplastic drugs revealed the premature appearance of atherosclerotic changes by the increase of IMT for all subjects included in the study. Thus, it has been highlighted that IMT is an important marker of subclinical atherosclerosis identification and a good predictor of cardiovascular and cerebrovascular disease risk for patients previously treated with chemotherapy, radiotherapy or both^{5,20}.

IMT increase observed for our patient may be influenced by the fact that our patient has performed cranial radiotherapy and the risk of cerebrovascular and cardiovascular disease is basically increased due to it and using of chemotherapy treatment.

Other vascular remodeling parameters underwent changes from the initial value, also: the ABI decreased, and PWV increased in the post-transplant evaluation. Alterations of these parameters indicate accelerated atherosclerosis, and may be predictors of possible vascular events that may occur in the future. The fact that the changes of these parameters may be markers that can identify possible vascular events is also shown by Katarzyna and others in their studies that highlighted this possibility on his group of patients¹⁴. Data from

other studies suggests that PWV is a predictor of cardiovascular disease⁵. PWV represents an increase in arterial rigidity. There are studies that have correlated the increase of PWV with strain modifications and LVEF decrease, after treatment with anthracyclines²¹.

Other chemotherapy agents like small molecule tyrosine kinase inhibitors may induce cardiotoxicity by left ventricular dysfunction but also by vascular parameters changes, especially ABI²². There were some studies reporting that ABI changed during and after small molecule tyrosine kinase inhibitors treatment. Kim et al described an increase of atherosclerotic development especially by the development of peripheral arterial disease for patients with chronic myeloid leukemia treated with small molecule tyrosine kinase inhibitors. About 6.3% out of 129 treated patients developed peripheral arterial disease²³. Levato et al also reported that 14.8% out of 82 patients with chronic leukemia developed peripheral arterial disease²⁴. This may support our observation regarding the increase of ABI for our patient, also treated with small molecule tyrosine kinase inhibitors (imatinib).

Anthracyclines used for the treatment of our patient were responsible for the appearance of cardiac disfunction observed 3 month after the beginning of the therapy. Present therapeutic guides highlight that anthracyclines may induce irreversible cardiac dysfunction affecting patients prognosis⁵. In our case, medullary transplant was followed by a complete remission of the disease and also, followed by the recovery of echocardiographic parameters and vascular remodeling most probably due to the lack of chemotherapy after transplant. All together these may be considered a good prognostic factor for the long term follow up

Present study has as the main limit the lack of high-sensitivity troponin I evaluation, this parameter being an important marker for the early detection of post chemotherapy myocardial changes.

Post-treatment assessment should be for as long as possible. In the case presented, the patient will be eva-

Table 5. Intima-media thickness, ankle-arm index and pulse wave velocity, initial, 3 months from start of treatment and 3 months after transplant

	Initial	3 months from start of chemotherapy treatment	3 months after transplant
IMT left CCA (mm)	0.7	0.8	0.8
IMT right CCA (mm)	0.8	0.8	0.9
ABI left	1.12	1.08	1
ABI right	1.23	1.23	0.9
PWV(m/s)	6.5	7.8	8

Note: CCA=common carotid artery; IMT= Intima-media thickness, ABI= ankle-brachial index, PWV= pulse wave velocity.

luated at six months, one year, and then annually after stem cell transplantation, to detect any manifestations of heart failure, valvular, rhythm disorders or vascular manifestations.

CONCLUSIONS

Hematological patients that are about to receive chemotherapy or radiotherapy have to be cardiologically assessed. The better we know the cardiovascular risk factors or the history of the patient's cardiac disease, the faster we will be able to prevent the occurrence of signs of cardiac failure secondary to chemotherapy or radiotherapy.

By tracking echocardiographic parameters, we can detect signs of LV dysfunction long before clinical signs appear, and the quantification of vascular remodeling parameters may provide indications of early atherosclerosis and thus prevent potential cardiovascular events.

Conflict of interest: none declared.

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