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The role of TNF-α, Fas/Fas ligand system and NT-proBNP in the early detection of asymptomatic left ventricular dysfunction in cancer patients treated with anthracyclines ☆

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ABSTRACT

Background: Anthracycline-induced cardiotoxicity typically presents as congestive heart failure (CHF). As immuno-inflammatory activation and apoptosis are important mechanisms in the process of heart failure, the use of biomarkers that could detect cardiovascular toxicity before the clinical presentation is of great importance. We studied whether sTNF-a, sTNF-RI, sTNF-RII, Fas/FasLigand system and NT-proBNP associate with early cardiac dysfunction in patients receiving cardiotoxic drugs.
Methods: Two groups of breast cancer patients—group A with metastatic disease under chemotherapy with epirubicin and group B with no residual disease under a less cardiotoxic regimen—as well as healthy women were included in this prospective study. NT-proBNP, sTNF-a, sTNF-RI, sTNF-RII, sFas, sFas-Ligand and left ventricular ejection fraction (LVEF) were determined in all patients before and after the completion of chemotherapy.
Results: In Group A, an increase in sFas levels ($p < 0.001$), a decrease in the sFasL levels ($p = 0.010$), an NT-proBNP increase ($p < 0.001$) and a significant reduction of LVEF ($p < 0.001$) was recorded post-chemotherapy. The decrease in LVEF correlated significantly with the increase in sFas, the decrease in sFasL and the rise in NT-proBNP levels. In Group B, TNF-RI levels were higher ($p = 0.024$) and mean sFas-L levels lower ($p = 0.021$) post chemotherapy with no LVEF drop. Two of group A (7.6%) patients developed symptomatic CHF 12 and 14 months respectively after the end of chemotherapy.
Conclusion: SFas, sFas-L and NT-proBNP correlate with reductions in LVEF and could be used as sensitive biochemical indices for the detection of asymptomatic left ventricular dysfunction in cancer patients under cardiotoxic chemotherapy.

1. Introduction

Anthracyclines have been associated with cardiomyopathy since their introduction in the late 1960s [1]. Anthracycline cardiomyopathy has been described as having three clinical presentations: acute, subacute and late. The acute toxicity is generally minor and reversible ranging from asymptomatic electocardiographic (ECG) changes to rare cases of severe acute myopericarditis [2]. Subacute and late toxicity secondary to anthracycline use typically presents with congestive heart failure (CHF). The classic subacute presentation usually appears from 0 to 231 days with a peak onset of symptoms at 3 months from the last dose [3] whereas the late presentation has been described to occur 5 or more years after the completion of chemotherapy [4]. Asymptomatic cardiac dysfunction is considered to precede symptoms of CHF and consists mainly of systolic rather than diastolic left ventricular dysfunction [5].

Amongst the two widely used anthracyclines, epirubicin is considered to be less cardiotoxic than doxorubicin, and its related cardiotoxicity is closely coupled to the cumulative dose, inducing a life-threatening, slowly progressive deterioration of cardiac function [6]. It has been stated that the risk of cardiotoxicity is less than 1% at doses below 550 mg/m^2 but increases up to 4% at 900 mg/m^2 and 15% at 1000 mg/m^2 [7].

Currently, the main non-invasive diagnostic tool for the detection of anthracycline-related cardiotoxicity is the estimation of left ventricular ejection fraction (LVEF), by means of radionuclide ventriculography or

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2D-echocardiogram. Radionuclide ventriculography is a well validated, established and widely used method for the evaluation of the LVEF that presents high reproductibility and low intraindividual variabilility [8]. In that respect, the endomyocardial biopsy is considered to be the most sensitive and specific method of evaluating anthracycline cardiomyopathy with considerable limitations however due to its invasive nature and the potential of adverse events [9]. Therefore, the identification of new diagnostic indices, such as biomarkers, that could non-invasively detect, well before the onset of clinical symptoms, cardiac dysfunction and cardiovascular toxicity, would be of vital importance for the current clinical practice.

Immuno-inflammatory activation and cardiomyocyte apoptosis have been demonstrated as important pathophysiological mechanisms in the process of heart failure due to any cause but anthracycline-exposure [10]. Circulating plasma levels of the tumor necrosis factor (TNF)-superfamily [TNF-α, TNF Receptors 1 and 2 (TNF-RI, TNF-RII)] and of the apoptosis inhibitor sFas are elevated in heart failure patients and correlate with New York Heart Association (NYHA) class of severity [11,12] and prognosis [13,14]. Finally, the natriuretic peptide NT-proBNP is a well established biomarker of enhanced wall stress and cardiac diastolic and systolic dysfunction, and an independent and strong predictor of heart failure progression [15].

In the present study, we prospectively evaluated the cardiac function and the immuno-inflammatory status of patients with breast cancer (metastatic or not) that received either an epirubicin-based cardiotoxic chemotherapy or a non cardiotoxic regimen. The aim of the study was to assess whether the pro-inflammatory cytokines, the soluble apoptotic Fas/FasLigand system and more established markers of left ventricular dysfunction such as NT-proBNP and LVEF associate with early asymptomatic cardiac dysfunction in patients receiving cardiotoxic drugs.

2. Methods

2.1. Patient population

The study population consisted of forty consecutive female patients with histologically confirmed breast cancer that were included in the study between 08/2001 and 12/2002. All patients were consented and studied in the oncology department of 'Metaxa Oncology Hospital' according to the principles outlined in the Declaration of Helsinki and with the ethical approval of the institution.

Patients were included in the study only if they fulfilled the following criteria: i) absence of any established preexisting heart disease (such as coronary artery disease, arrhythmias, valve disease, hypertensive heart disease and congestive heart failure) on the basis of medical history, clinical examination and diagnostic evaluation, ii) LVEF values above 50% determined by radionuclide ventriculography iii) ECOG (Eastern Oncology Cooperative Group) Performance Status 0,1 and 2, iv) normal renal (serum creatinine < 1.3 mg/dL) and normal or slightly deranged hepatic function (aspartate aminotransferase <80 IU/l or alanine aminotransferase <80 IU/l) and, v) no history of other malignant disease. Exclusion criteria were: administration of chemotherapy and/or hormonal therapy or local radiotherapy 6 months prior to the study.

Tumor-Node-Metastasis (TNM) classification was used in order to determine the stage of the disease. Either total or partial mastectomy with axillary lymphadenectomy was the surgical procedure of choice for all patients. Computed tomography scan was performed in order to identify presence of distal (liver, lung, brain and lymph node) metastases whereas bone metastases were diagnosed by means of X-ray and bone scintigraphy.

Patients were split into two groups (group A and group B) according to the presence of metastatic or advanced disease. Group A patients were those with advanced or metastatic disease whereas group B were patients with no residual disease post-surgery. Group C is an age matched group of healthy women.

2.2. Chemotherapy

Group A patients received a more cardiotoxic chemotherapeutic regimen that was consisted of 6 cycles of epirubicin 80–90 mg/m^2 given as bolus intravenous infusion and paclitaxel 150 mg/m^2 given as an intravenous 3-hourly infusion, on day one. The cycles were repeated every 3 weeks. No patient had previously received any anthracycline-based chemotherapeutic regimen. Left-sided chest wall irradiation was the adjuvant treatment of choice for two (2) patients and right-sided chest wall irradiation for three (3), at least six months prior to their enrolment in the study.

Group B patients received a less cardiotoxic chemotherapy regimen which consisted of docetaxel 75–85 mg/m^2 as well as mitoxantrone 7.5–8.5 mg/m^2 both intravenously as a 1-hour infusion on day one. The cycles were repeated every 3 weeks while the duration of treatment was six cycles.

2.3. Plasma soluble inflammatory and apoptotic markers

Peripheral blood samples were collected before the onset and after the end of treatment, in 10 ml EDTA (2-natrium-ethylenediamine tetra-acetic acid) containing disposable tubes. The samples were centrifuged at 3000 rpm for 7 min, and serum was separated and immediately stored at (−70 °C) until assay. Plasma levels of NT-proBNP were measured before and after chemotherapy by means of an enzyme immunoassay in fmols/ml (BIOMEDICA AUSTRIA), whereas, soluble (s) TNF-a, sTNF receptors I and II, as well as, sFas and sFas ligand, were assayed in duplicate by using commercially available enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, Minnesota) according to the manufacturer's descriptions.

2.4. Radionuclide ventriculography

Radionuclide ventriculography was used to determine LVEF. Therefore, 400 MBq of Tc-99 m-labeled autologous RBCs were injected and acquisition was performed in 6 min with a large-field-of-view gamma camera with a low energy, all-purpose, parallel-hole collimator.

Abnormal values were considered LVEF values below 50%. Significant cardiac toxicity was determined as LVEF decline greater than 10% from baseline level. LVEF was assessed in Group A and B patients before the onset and within one week after the end of chemotherapy. All group A and B patients had normal cardiac function before induction of chemotherapy. Control group C had LVEF levels above 50% and therefore normal ventricular systolic function.

2.5. Cardiac evaluation

Group A and B patients were examined physically before each cycle and were followed up every three months after the end of the chemotherapy. In addition, they were evaluated with a standard 12 lead ECG every three chemotherapy cycles. Bazett's formula ($QTc = QT/\sqrt{RR}$) was used to correct QT time for heart rate (QTc) which was considered prolonged if more than 440 ms.

3. Statistical analysis

Kolmogorov–Smirnov test was used to assess normal distribution. Values are presented as mean (standard error) for normally distributed continuous variables, as median (interquartile range) for skewed variables and as frequency (%) for categorical variables.

For independent group comparisons one-way ANOVA (post hoc Sidak test) or Kruskal Wallis test (post hoc Dunn's test) were used for normally and not normally distributed variables respectively. Correlations between variables were tested by Pearson's or Spearman's correlation coefficients as appropriate. For pair wise comparisons (before and after treatment) the paired *t*-test or the Wilcoxon signed-rank test

Table 1
Baseline characteristics of the 3 groups.

	Group A	Group B	Group C
N	26	14	20
Age (years)	54.5 ± 10.2	56.5 ± 11.6	56.5 ± 16
Clinical status (stage of disease)	Breast cancer, metastatic stages IIIA/IIIB/IV	Breast cancer No residual disease after surgery stages IIA/IIB/IIIA	Healthy
Anti-cancer treatment	Epirubicin/paclitaxel	Docetaxel/mitoxantrone	No treatment
Baseline LVEF	>50%	>50%	>50%
Cardiac evaluation	Clinical examination before each cycle and every three months after the end of treatment. ECG every three chemotherapy cycle	Clinical examination before each cycle and every three months after the end of treatment. ECG every three chemotherapy cycle	No evaluation
Follow-up (median)	62 months (range: 52–78)	62 months (range: 52–78)	No follow-up

Results are presented as means ± SD or percentages. LVEF: left ventricular ejection fraction, ECG: electrocardiogram

was carried out as appropriate. Categorical variables were compared by contingency chi-square test or Fisher exact test.

A p-value <0.05 (2-tailed) was considered statistically significant. Statistical analysis was performed using SPSS software, version 15 (SPSS Inc, Chicago, Illinois).

4. Results

4.1. General demographics and ECG parameters

The study population consisted of 40 breast cancer patients and 20 age-matched female controls. In group A, metastatic sites, prior to treatment, involved the liver ($n = 7$), the lungs ($n = 4$), the bones ($n = 2$), and lymph nodes ($n = 1$). Mean age (SD) of group A ($n = 26$) was 54.4 ± 10.2, of group B ($n = 14$) 53.3 ± 11.7 and of group C ($n = 20$) 54.3 ± 16.6 ($p = 0.803$). Table 1 summarizes all the baseline characteristics.

During the study period no ECG changes were demonstrated in group A and B patients. As regards to QTc time no significant prolongation was recorded in the above groups.

4.2. Baseline (pro-chemotherapy) immuno-inflammatory markers and NT pro BNP across Group A and B patients and healthy controls (group C)

There are significantly increased levels of sFas, TNFa and TNFR1 and a trend for increased levels of TNFR2 amongst group A patients when compared to healthy controls (Table 2). No difference is observed across the three groups (A, B and C) with regards to NT-pro BNP levels (Table 2).

4.3. Immuno-inflammatory markers, NT pro BNP and LVEF pre- and post-chemotherapy in Groups A and B

In Group A patients, there was a significant rise in the mean sFas levels ($p < 0.001$) and a significant decrease in the sFasL levels ($p = 0.010$) post-chemotherapy. There was no significant change in the serum values of sTNF-a, sTNF-RI and sTNF-RII pre and post treatment (Table 3).

Plasma levels of NT-proBNP increased significantly after chemotherapy (283.3 ± 27.2 vs. 158.0 ± 8.4, post- and pre chemo respectively, $p < 0.001$) (Table 3). The LVEF was significantly reduced post chemotherapy (61.6 ± 1.2 vs. 58.0 ± 1.1, $p < 0.001$). The statistical significance of the above comparisons remained after Bonferroni correction for multiple comparisons. Three patients (11.5%) had significant LVEF drop (i.e >10%) post chemotherapy.

In Group B, TNF-RI levels were significantly higher and mean sFas-L levels significantly lower post chemotherapy (Table 3). The increased sFas levels post chemotherapy lost statistical significance when performing Bonferroni correction ($p = 0.028 \times 2 = 0.056$). There was no significant difference amongst the rest biochemical and apoptotic markers including NT-proBNP. The mildly reduced LVEF post chemotherapy also lost statistical significance after Bonferroni correction for multiple comparisons ($p = 0.033 \times 2 = 0.066$). No patients had a significant LVEF drop post chemotherapy.

4.4. Correlations of LVEF reduction with other parameter changes pre- and post-chemotherapy

In group A the decrease in LVEF correlated significantly with the increase in sFas the decrease in sFasL and the rise in NT-proBNP levels. In patients treated with the "low risk" cardiotoxic regimen (Group B) no significant LVEF alterations were recorded after chemotherapy and no association between the LVEF and changes in sFas, sFasL, TNF-α or NT-proBNP levels was demonstrated (Table 4).

4.5. Follow-up

4.5.1. Group A

Two of the 26 (7.6%) of group A patients developed symptomatic congestive heart failure (CHF) 12 and 14 months respectively after the end of chemotherapy. Both patients had to be admitted in hospital for 5 and 7 days respectively. The first patient was found to have an LVEF

Table 2
Baseline immuno-inflammatory parameters and serum NT-proBNP levels in Group A and B patients and healthy controls (Group C).

	Group A	Group B	Group C	*P*-value
sFas (ng/ml)	192.9 (134.0 to 413.7)[a]	152.9 (102.5 to 214.0)	111.3 (92.1 to 131.4)[a]	<0.001
sFas-L (ng/ml)	75.1 (43.1 to 126.3)	79.0 (49.9 to 94.6)	66.1 (50.9 to 77.9)	0.601
TNF-a (ng/ml)	2.0 (1.4 to 3.5)[a]	1.8 (1.0 to 2.6)	1.4 (0.7 to 2)[a]	0.021
TNF-RI (ng/ml)	144.3 (124.9 to 189.8)[a]	110.8 (90.8 to 151.3)	103.9 (78.5 to 119.7)[a]	<0.001
TNF-RII (ng/ml)	238.0 (197.3 to 346.4)	189.1 (166.3 to 252.4)	196.8 (187.8 to 214.6)	0.015
BNP (fmol/ml)	158.0 ± 8.4	189.0 ± 18.2	150.4 ± 15.9	0.163

Results are presented as means ± SE and median (IQR).
BNP: brain natriuritic peptide, TNF: tumor necrosis factor, R: receptor, IQR: interquartile range.
[a] Post hoc $p < 0.05$ between groups as calculated using Dunn's test.

Table 3
Serum inflammatory, antiapoptotic indices and BNP levels as well as estimated LVEF prior and after chemotherapy in Group A (cardiotoxic chemo) and Group B (non cardiotoxic chemo) patients.

	Group A			Group B		
	before Tx	*after Tx*	*P-value*	*before Tx*	*after Tx*	*P-value*
sFas (ng/ml)	308.8 ± 65.1	517.8 ± 91.0	<0.001	171.6 ± 22.5	229.5 ± 25.8	0.028
sFas-L (ng/ml)	86.6 ± 12.6	47.9 ± 8.4	0.010	77.1 ± 33.1	70.0 ± 32.4	0.021
TNF-a (ng/ml)	3.2 ± 0.7	3.6 ± 0.7	0.195	1.8 (1.0 to 2.6)	1.8 (1.3 to 2.6)	0.551
TNF-RI (ng/ml)	165.1 ± 12.6	166.7 ± 10.9	0.883	123.7 ± 11.7	149.5 ± 11.0	0.024
TNF-RII (ng/ml)	270.8 ± 19.2	275 ± 16.1	0.793	219.4 ± 23.0	237.9 ± 16.1	0.444
NT-proBNP (fmol/ml)	158.0 ± 8.4	283.3 ± 27.2	<0.001	189.0 ± 18.2	194.9 ± 19.6	0.529
LVEF	61.6 ± 1.2	58.0 ± 1.1	<0.001	61.7 ± 1.7	59.9 ± 2.0	0.033

Results are presented as means ± SE and median (IQR).
BNP: brain natriuretic peptide, EF: ejection factor, Tx: chemotherapy, TNF: tumor necrosis factor, R: receptor, IQR: interquartile range.

of 40% during hospitalization, while the LVEF presented a drop previously from 65% before chemotherapy to 47% after chemotherapy. An LVEF decline was also shown in the second patient from 70% prior to chemotherapy to 59% after chemotherapy and to 45% while hospitalization. The levels of sFas before and after the completion of chemotherapy increased from 2.32 to 6.7 ng/ml in the first patient and from 17.47 to 22.59 ng/ml in the second patient whereas NT-pro BNP values rose from 152 to 492 fmol/ml and from 153 to 571 fmol/ml respectively.

At 62 months of follow up 2 patients (7.6%) remained free of disease after the initial chemotherapy, 9 patients (34.6%) were still being treated with second and third line chemotherapy, 13 patients died due to metastatic disease and 2 patients were lost from follow-up. With the exception of the 2 above mentioned patients that were hospitalized for HF and the 2 who were lost in follow-up, the rest of the patients were asymptomatic with respect to symptoms related to cardiac dysfunction.

4.5.2. Group B

No patient developed symptoms of congestive heart failure during the follow-up period. Six patients totally remained free of disease whereas other six experienced disease recurrence and were managed with second line chemotherapeutic regimens and 2 were lost from follow-up.

5. Discussion

The present study is the first to show a significant increase in the anti-apoptotic receptor sFas and decrease in the apoptosis inducer sFasL levels, after anthracycline epirubicin chemotherapy in patients with advanced or metastatic breast cancer. Both indices were associated with a significant decrease in LVEF. The cardiotoxicity of epirubicin was also expressed by a significant increase in NT proBNP levels after epirubicin chemotherapy in the same group of advanced breast cancer patients. These increased BNP levels associated significantly with a decrease in the radionuclide ventriculography derived LVEF post chemotherapy.

The concurrent increase of sFas and NT-proBNP levels alongside the LVEF decline just one week after the discontinuation of the potentially cardiotoxic regimen preceded considerably the clinical manifestation of left ventricular dysfunction in Group A. In the clinical setting, although the initial LVEF dropped significantly in 11.5% of group A patients after chemotherapy no symptoms of cardiac dysfunction were reported until several months after the completion of chemotherapy when the cardiotoxicity of epirubicin was expressed as heart failure in 7.6% of group A patients. All the above findings and associations applied only for the category of patients that received the more cardiotoxic regime containing epirubicin but not for any of the patients that were treated with the less cardiotoxic one.

The anthracycline cardiotoxicity is cumulative, dose-related and at sufficiently high dosages can result in congestive heart failure (CHF) and left ventricular (LV) dysfunction. It represents a long term cardiotoxicity—type I cardiotoxicity—induced by cardiomyocyte death either through necrosis or apoptosis [16]. The mechanism of cell death varies with anthracycline concentration with apoptosis occurring at lower and necrosis at higher concentrations [17]. Amongst the several and different mechanisms that have been proposed to explain the toxic effects of anthracyclines on cardiac myocytes, the most important of them are: nuclear DNA damage [18], mitochondrial DNA mutations [19], and changes in phospholipid content and calcium availability [20]. The toxicity that anthracyclines—and mainly doxorubicin—exhibit in cardiomyocytes is attributed to free radical formation caused by their metabolism [21]. The reactive oxygen species that are produced by doxorubicin metabolism in cardiomyocytes subsequently cause cell death through apoptotic pathways [22,23]

Oxidative stress can also occur via induction of nitric oxide synthase, leading to nitric oxide and peroxynitrite formation [24]. This mechanism has been linked to nitration and inactivation of key enzymes in the heart including myofibrillar creatine kinase [25]. In the heart, like other tissue, anthracyclines intercalate into nucleic acids, causing suppression of DNA, RNA and protein synthesis [26]. Impaired synthesis of myofilament proteins, [27], leads to a net negative balance of sarcomeric proteins, a condition we have termed 'cardiac sarcopenia'. In addition anthracyclines induce changes in adrenergic function and adenylate cyclase [28,29], as well as abnormalities in Ca^{2+} handling [30], all critical for the dynamic regulation of cardiac function.

Table 4
Correlations between LVEF change and differences (d) (post chemo − pre chemo) in various parameters.

	NT-proBNP	sFASd	FAS-Ld	TNF-ad	TNFR1d	TNFR2d
Group A						
LVEFd	$r = -0.786$ $p < 0.001$	$r = -0.438$ $p = 0.025$	rho = 0.549 $p = 0.004$	$r = -0.284$ $p = 0.160$	$r = -0.018$ $p = 0.931$	$r = 0.125$ $p = 0.544$
Group B						
LVEFd	$r = 0.107$ $p = 0.716$	$r = -0.277$ $p = 0.338$	$r = 0.313$ $p = 0.276$	rho = −0.132 $p = 0.653$	$r = -0.021$ $p = 0.944$	$r = -0.189$ $p = 0.517$

BNP: brain natriuretic peptide, EF: ejection factor, TNF: tumor necrosis factor, R: receptor, (i.e. IQR: interquartile range).
r = Pearson's correlation.
rho = Spearman's correlation.

Although paclitaxel's cardiac effects are limited to disturbances of cardiac rhythm and conduction, the combination of anthracycline with paclitaxel increases the risk of cardiac dysfunction especially when epirubicin's cumulative dose exceeds 550 mg/m^2 [7,31].

The combination of docetaxel and mitoxantrone has not been associated with deterioration of cardiac function, even in cumulative doses of 100 mg/m^2 and 22 mg/m^2, respectively [32]. The concurrent administration of the two drugs seems to be safe for patients with normal LV function [32], although there have been some studies showing that mitoxantrone may cause cardiac toxic events in a dose dependent manner [33]. Our study did not demonstrate any evidence of cardiotoxicity related to the treatment with mitoxantrone and the combination with docetaxel did not increase that risk.

It has been shown that apoptosis and immune activation are important determinants of both pathogenesis and evolution of heart failure [34,35]. Elevated plasma sFas levels have been demonstrated in chronic heart failure and have also been reported to increase with disease severity and prognosis [12], thus highlighting the pathophysiological role of sFas which has also been implicated in dilated (ischemic and inflammatory) cardiomyopathies [36,37]. A recent study has shown that sFas is an independent risk predictor in advanced HF patients, correlates with BNP and can improve prediction beyond the BNP [14]. In the present study we report an increase in sFas and NT-proBNP levels post chemotherapy in the group of patients who received the more cardiotoxic regimen, despite them not manifesting any heart failure symptoms at that point of time. The higher sFas plasma levels observed in group A patients after chemotherapy, could be indicative of greater tissue and/or cellular injury caused by the 'high risk' cardiotoxic regimen, compared to the 'low risk' one. Increased wall stress in the affected heart ventricles can cause raised BNP production by the myocytes and probably stretch-induced expression of Fas protein [38]. In our previous study we demonstrated NT-pro BNP elevation after cardiotoxic chemotherapy with epirubicin in female patients with advanced breast cancer [39].

With regards to the two patients that later developed CHF after receiving epirubicin, they both exhibited LVEF decrease associated with sFas and NT-proBNP rise after chemotherapy. The increased immuno-inflammatory markers in group A at baseline confirm the well known effects of metastatic/advanced cancer on the immune system [40,41]. However this baseline difference did not affect our results as we were focusing on post chemo differences rather than absolute values.

Our study is the first one to demonstrate a significant change in the apoptotic markers sFas and sFas-L after the administration of epirubicin-based cardiotoxic chemotherapy. Moreover the association between the change of sFas and sFas-L and the LVEF decline is a novel finding. A limitation of our study is the small number of patients which reflects the difficulty in consenting patients with cancer to participate in a research project that involves further blood tests and diagnostic procedures.

Given that all three, the anti-apoptotic marker sFas, the apoptosis inducer sFas-L and the wall stress indicator NT-proBNP, correlate with reductions in LVEF, the above biochemical indices could be used in the near future either independently or even synergistically for the detection of early stages of LV (diastolic and/or systolic) dysfunction. Future studies might disclose additive diagnostic and prognostic value of sFas, sFas-L, and NT-proBNP for the detection of early asymptomatic LV dysfunction in this sensitive category of cancer patients. Establishing reliable and sensitive diagnostic indices for the early detection and treatment of the asymptomatic LV dysfunction in this group of patients is of great importance, as it facilitates adjustment of chemotherapy, reduces the risk from cardiac disease and limits the comorbidities that could aggravate the already compromised quality of life of the cancer survivors.

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