Alteration of circulating miRs expression profile in cardiac dysfunction patients associated with cancer treatment

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INTRODUCTION

Improved prognosis and life expectancy in cancer patients, as consequence of major therapeutic advances carried out in lasts years, has highlighted cardiotoxic side effects of chemotherapy. Preserve functional capacity requires early detection of cardiotoxic events. Recent systematic review reported that most useful predictor of chemotherapy-induced cardiotoxicity is an early reduction in global longitudinal strain (GLS).
Given its circulating stability peripheral blood, microRNAs (miRs) are being assessed as biomarkers of cardiovascular diseases. Likewise, several studies showed selective miRs regulation after chemotherapy treatment in patients or animal models. We sought to assess changes in miRs expression profile in breast cancer patients with altered GLS, to identify a biomarker of subclinical carditoxicity.

METHODS AND RESULTS

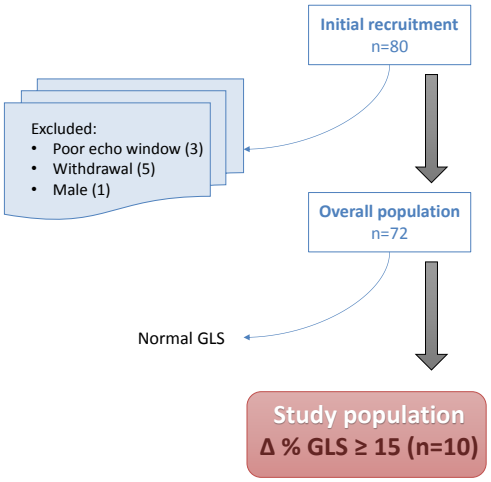

Fig. 1. Workflow. A cohort of 80 breast cancer patients were recruited consecutively at Complejo Hospitalario Universitario de Santiago de Compostela. After follow up, patients with poor echocardiographic window, those who withdrew informed consent and male patients were excluded. Overall population was classified based on the presence/absence of subclinical cardiotoxicity considering biochemical and echocardiographic parameters during treatment. Study population was selected based on the variation of the GLS with respect to the baseline. Clinical data of the overall vs study population (baseline and follow up) are represented in Table 1.

	Overall	Impaired GLS	
	Baseline (n=72)	Baseline (n=10)	Follow up (n=10)
Age, years	52±11	52±8,3	
BMI, kg/m²	27±5	26±4	27±5
Systolic pressure, mmHg	129±17,3	129±18,4	124±14,2
Diastolic pressure, mmHg	74±14,2	78±19	77±9,8
Heart rate, bpm	74±12,4	78±12,9	73±8,3
CVD risk factors			
Menopause	27 (39)	2 (20)	
Smoker	12 (17)	3 (30)	
Previous CVD	3 (4)	-	
Hypertension	14 (20)	-	
Diabetes	3 (4)	-	
Hyperlipidemia	8 (11)	-	
Cardioprotective treatment			
ACEi	13 (18)	-	-
Beta-blocker	6 (9)	-	-
Statins	10 (14)	-	4 (40)
Echocardiographic parameters			
LVEF, %	67±5	66±4	64±4
GLS, %	-22±6	-23,6±1,3	-18,9±1,5
Biochemistry			
NT-proBNP (pg/mL)	57±45	47±25	51±17
us-TnI (ng/mL)	4,2±2,9	3,67±1,2	6,36±3,7
Chemotherapy			
Docetaxel	-	-	10 (100)
Trastuzumab	-	-	4 (40)
Fluorouracil	-	-	10 (100)
Epirubicin	-	-	10 (100)
Cyclophosphamide	-	-	10 (100)
Radiotherapy	-	-	8 (80)

Table 1. Data are **n (%)** or **mean±SD**

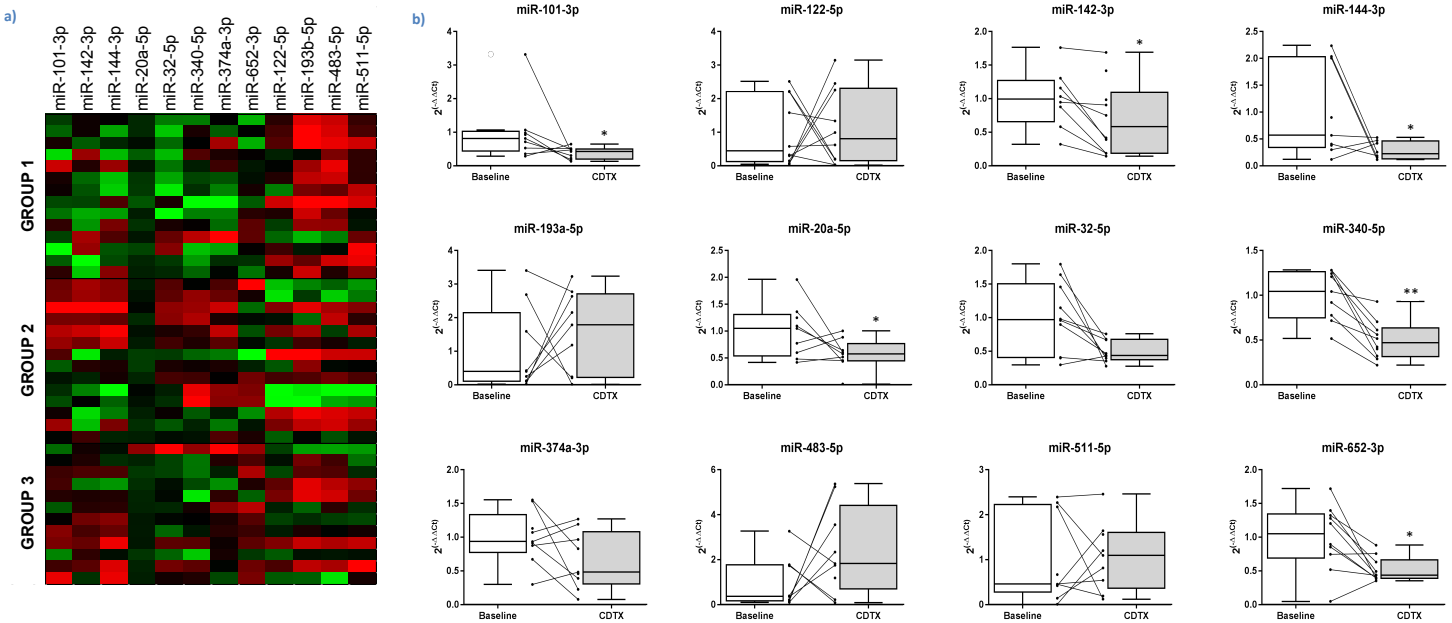

Fig 2. miRs expression study. Total miRs where isolated from peripheric blood plasma. **a)** Heatmap showing the expression profile of circulating miRs obtained by Next Generation Sequencing (RNAseq) using Illumina technology at baseline group (1), detection of decrease of GLS group (2) and control group (3). **b)** Sequencing data were validated by TaqMan qPCR in baseline group vs. decrease of GLS group (CDTX), which show differential expression of 6 miRs significatively: **hsa-miR-101-3p, hsa-miR-142-3p, hsa-miR-144-3p, hsa-miR-20a-5p, hsa-miR-340-5p** and **hsa-miR-652-3p.** Data are represented as Boxplot and whiskers. Statistical significance * $p < 0.05$ and ** $p < 0.005$ vs. control.

CONCLUSIONS

The comparative study of expression profile in those patients that meet subclinical cardiotoxicity criteria exhibit a differential profile of miRs expression after chemotherapy treatment. Our results show an alteration in circulating miRs profile in patients with decreased GLS and suggest that these changes could be useful as potential biomarkers of early detection of cardiotoxicity.

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