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Treatment of mild asymptomatic cardiotoxicity in early-stage HER 2-positive breast cancer. Is it justified?

Tratamiento de la cardiotoxicidad leve asintomática en cáncer de mama HER2 positivo precoz. ¿Está realmente justificado?

To the Editor,

The definition of cancer therapy-related cardiac dysfunction (CTRCD) has changed in recent years. At present, CTRCD is classified as mild when troponin is elevated or when there is > 15% change in global longitudinal strain (GLS) from baseline with left ventricular ejection fraction (LVEF) ≥ 50%, moderate when LVEF drops 10 points and is 40% to 49%, and severe when LVEF drops below 40%.[1] The recently published Guidelines on Cardio-Oncology[2] recommend starting beta-blockers and angiotensin-converting enzyme inhibitors (ACEIs) in cases of mild CTRCD to prevent progression to moderate-to-severe CTRCD, as a class IIa recommendation with level of evidence B.[2]

In this study, the incidence of CTRCD was measured in a cohort of patients with early HER2-positive breast cancer (eHER2-bc). Likewise, the study investigated the predictive value of high-sensitivity troponin I (hsTnI) and GLS for the appearance of moderate-to-severe CTRCD, as well as their potential as tools to aid in the decision to start cardioprotective treatment.

Between May 2018 and May 2021, 95 consecutive patients with eHER2-bc were enrolled in the study at a tertiary medical center. The exclusion criteria were baseline LVEF < 50%, the presence of heart disease possibly leading to impaired LVEF during follow-up, and prior chemotherapy. Clinical and echocardiographic follow-up were performed at baseline and every 3 months until treatment completion. The biplanar Simpson method was used to analyze LVEF, and mean regional GLS was obtained by 2-, 3-, and 4-chamber analyses. Additionally, hsTnI was measured during each treatment cycle and was considered positive when above the laboratory's reference threshold (> 40 ng/L). If CTRCD was present, then cardiac magnetic resonance imaging (cMRI) was also performed. Native T_1- and T_2-weighted values were obtained from the average value of the 16 short-axis segments in the T_1- and T_2-weighted mapping sequences. Extracellular volume was calculated based on the T_1-weighted mapping sequences before and after contrast administration. As per protocol, treatment was started with ACEIs or beta-blockers only in cases of moderate-to-severe CTRCD.

Table 1 lists the patients' baseline characteristics. Sequential treatment was given with anthracyclines and anti-HER2 therapy to 48.4% of patients, while anti-HER2 therapy without anthracyclines was given to the other 51.6%. During follow-up (mean, 13.6 months), symptomatic CTRCD did not appear in any patients. Nevertheless, the incidence of asymptomatic CTRCD was 60%: mild in 53 patients (55.8%), moderate in 3 (3.2%), and severe in 1 (1.1%). The mean time to CTRCD diagnosis was 162.1 days. In all, 3 patients experienced cancer progression, and 1 patient died from a noncardiovascular cause. In the bivariate analysis, cardiovascular risk factors and the use of dual anti-HER2 blockade with pertuzumab were not associated with the development of CTRCD. In the multivariate models adjusted for age, hypertension, dyslipidemia, diabetes, and use of pertuzumab, the only factor associated with CTRCD was the use of anthracyclines (odds ratio = 7.78; 95% confidence interval, 2.55-27.08; $P < .001$).

A total of 37 (38.9%) patients exhibited hsTnI elevation and 36 (37.9%) had > 15% change in GLS; 16 patients had both abnormalities. However, only 4 (4.2%) patients had moderate-to-severe CTRCD. Table 1 shows the distribution of the TnI, GLS, and LVEF abnormalities based on whether or not anthracyclines had been given. Table 2 lists the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of hsTnI and > 15% change in GLS in predicting the appearance of moderate-to-severe CTRCD. While the sensitivity, specificity, and PPV were poor for hsTnI and GLS, the NPV was 95.1% and 99%, respectively. In contrast, only 1 of 4 patients with moderate-to-severe CTRCD had hsTnI elevation, and although all also exhibited > 15% change in GLS, this change was not documented until moderate-to-severe CTRCD was diagnosed.

In keeping with the results of the Cardiotox registry,[3] our eHER2-bc cohort also showed a high incidence of mild CTRCD in the form of increased hsTnI and abnormal GLS, whereas the incidence of moderate-to-severe CTRCD was low (4.2%). As in other series,[4] the added value of hsTnI and GLS came mainly from their high NPV for predicting moderate-to-severe CTRCD,

Table 1
Differential characteristics of patients with eHER2-bc according to the development of CTRCD and the cancer therapy received

	Total sample (n = 95)			Patients with anthracycline-based treatment (n = 46)			Patients on non-anthracycline-based treatment (n = 49)		
	No CTRCD, n = 38	CTRCD, n = 57	*P*	No CTRCD, n = 7	CTRCD, n = 39	*P*	No CTRCD, n = 31	CTRCD, n = 18	*P*
Baseline characteristics									
Age, y	55.2 ± 14.1	51.6 ± 11	.28	51.5 ± 11.7	49.5 ± 11.1	.92	56 ± 14.6	56.1 ± 9.7	.87
Smoking	11 (29)	15 (26.3)	.87	3 (42.9)	13 (33.3)	.75	8 (25.8)	2 (11.1)	.38
BMI	25.5 ± 5.5	25.7 ± 5	.58	27.1 ± 6.5	24.8 ± 3.6	.38	25.2 ± 5.3	27.7 ± 6.7	.18
Hypertension	11 (29)	7 (12.3)	.05	2 (28.6)	3 (7.7)	.15	9 (29)	4 (22.2)	.75
Diabetes mellitus	5 (13.2)	4 (7)	.48	2 (28.6)	1 (2.6)	.06	3 (9.7)	3 (16.7)	.66
Dyslipidemia	9 (23.7)	10 (17.5)	.61	2 (28.6)	5 (12.8)	.57	7 (22.6)	5 (27.8)	.74
Baseline therapy									
ACEIs or ARBs	2 (5.3)	2 (3.5)	1	0	1 (2.6)	1	2 (6.5)	1 (5.6)	1
Beta-blockers	1 (2.6)	1 (1.8)	1	0	1 (2.6)	1	1 (3.2)	0	1
Statins	1 (2.6)	2 (3.5)	1	0	0	1	1 (3.2)	2 (11.1)	.71
Baseline echocardiographic data									
LV end-diastolic diameter	42.3 ± 4.8	42.9 ± 4.6	.52	42.3 ± 3.7	42.1 ± 4.9	.98	42.3 ± 5	44.6 ± 3.5	.11
LV end-systolic diameter	28.3 ± 3.8	27.7 ± 3.8	.34	29.1 ± 3.9	27.4 ± 3.9	.29	28.1 ± 3.9	28.4 ± 3.7	.91
Left atrium, cm^2	16.3 ± 3.6	16.5 ± 3.3	.82	16.9 ± 2.8	15.9 ± 3.2	.34	15.8 ± 3.9	17.7 ± 3.1	.18
TAPSE, mm	21.2 ± 3.5	21.9 ± 3.4	.39	22.3 ± 2.7	22 ± 3.4	.62	21 ± 3.7	21.6 ± 3.4	.52
Mean baseline GLS	−21.4 ± 2.2	−22.1 ± 2.4	.21	−21.2 ± 1.1	−22 ± 2.3	.36	−21.5 ± 2.4	−22.3 ± 2.6	.02
Baseline E/e'	7 ± 2.6	7 ± 1.8	.78	7 ± 1.9	7.1 ± 1.7	.85	7 ± 2.7	6.9 ± 2.1	.98
E/e' > 15	1 (2.6)	2 (3.5)	1	0	0		1 (3.2)	2 (11.1)	.55
Baseline LVEF, %	61.4 ± 3.3	62.1 ± 4	.47	58.7 ± 1.4	62.2 ± 3.6	.02	62 ± 3.2	61.9 ± 4.8	.61
Baseline biomarkers									
High-sensitivity troponin I, ng/L	3.4 ± 0.8	4.8 ± 3.8	.16	3 ± 0	5 ± 4.3	.10	3.5 ± 0.9	4.2 ± 2	.54
Oncologic variables									
Tumor stage			.34			.24			.31
I	10 (26.3)	5 (8.8)		0	2 (5.1)		10 (9.7)	3 (16.7)	
II A	16 (42.1)	30 (52.6)		2 (28.6)	21 (53.8)		14 (29)	9 (50)	
II B	8 (21.1)	13 (22.8)		1 (14.3)	9 (23.1)		7 (12.9)	4 (22.2)	
III A	1 (2.6)	4 (7)		1 (14.3)	3 (7.7)		0	1 (5.6)	
III B	1 (2.6)	2 (3.5)		1 (14.3)	2 (5.1)		0	0	
III C	2 (5.3)	3 (5.3)		2 (28.6)	2 (5.1)		0	1 (5.6)	
Chemotherapy									
Anthracyclines	7 (18.4)	39 (68.4)	< .001	7 (100)	39 (100)	1	0	0	
Doxorubicin	4 (10.5)	19 (33.3)	.02	4 (57.1)	19 (48.7)	1			
Liposomal doxorubicin	1 (2.6)	2 (3.5)	1	1 (14.3)	2 (5.1)	.39			
Adriamycin	2 (5.3)	20 (35.1)	.001	2 (28.6)	20 (51.3)	.42			
Cyclophosphamide	7 (18.4)	39 (68.4)	< .001	7 (100)	39 (100)	1	0	0	
Taxanes									
Docetaxel	14 (36.8)	14 (24.6)	.25	0	3 (7.7)	1	14 (45.2)	11 (61.1)	.36
Paclitaxel	24 (63.2)	44 (77.2)	.16	7 (100)	37 (94.9)	1	17 (54.8)	7 (38.9)	.37

Table 1 *(Continued)*
Differential characteristics of patients with eHER2-bc according to the development of CTRCD and the cancer therapy received

	Total sample (n = 95)			Patients with anthracycline-based treatment (n = 46)			Patients on non-anthracycline-based treatment (n = 49)		
	No CTRCD, n = 38	CTRCD, n = 57	*P*	No CTRCD, n = 7	CTRCD, n = 39	*P*	No CTRCD, n = 31	CTRCD, n = 18	*P*
Carboplatin	14 (36.8)	11 (19.3)	.1	0	0		14 (45.2)	11 (61.1)	.38
Pertuzumab	26 (68.4)	51 (89.5)	.01	7 (100)	37 (94.9)	1	19 (61.3)	14 (77.8)	.35
Radiotherapy									
Mean cardiac dose	1.94 ± 1.8	1.97 ± 1.8	.91	1.55 ± 1	1.98 ± 1.7	.68	2 ± 1.9	1.9 ± 2	.76
Follow-up: biomarkers and echocardiogram									
High-sensitivity troponin I elevation	0	37 (37.6)		0	35 (89.7)		0	2 (11.1)	
High-sensitivity troponin I peak	10.2 ± 10.7	123.8 ± 179.1	< .001	27.3 ± 14.7	139.9 ± 132.7	.001	6.5 ± 4.5	84.6 ± 261.7	.17
> 15% change in GLS	0	36 (63.2)		0	20 (51.3)		0	16 (88.9)	
Worse GLS	−20 ± 2	−18.7 ± 2.1	.002	−20.2 ± 1.5	−19 ± 1.9	.08	−20 ± 2.1	−18 ± 2.5	.01
LVEF < 50%	0	4 (7)		0	1 (2.6)		0	3 (16.7)	
Worse LVEF, %	59.5 ± 2.9	57.1 ± 5.5	.02	58.1 ± 3.3	57.6 ± 3.6	.76	59.7 ± 2.8	55.9 ± 8.2	.18

ACEIs, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; CTRCD, cancer therapy-related cardiac dysfunction; GLS, global longitudinal strain; LV, left ventricle; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion.
Data are expressed as No. (%) or mean ± standard deviation.

whereas the value of sensitivity, specificity, and PPV was slight. Although we consider that the presence of mild CTRCD warrants close cardiologic follow-up,[5] none of the 53 patients in our series who had mild CTRCD progressed to moderate-to-severe CTRCD during follow-up despite not starting ACEI or beta-blocker therapy. On the other hand, only 1 of 4 patients with moderate-to-severe CTRCD had previously had mild CTRCD and, therefore, the other 3 would have had no indication for this treatment. Last, 38.2% of cMRIs performed on patients with mild CTRCD were entirely normal, and no abnormalities were observed in the mapping parameters of T_1- or T_2-weighted sequences or in extracellular volume. Although these results are limited by the small sample size, they indicate that the risk of progression to moderate-to-severe CTRCD in these patients with normal cMRI is likely low, even without cardioprotective therapy. Consequently, cMRI could be useful as an additional marker when deciding whether or not to start cardioprotective therapy in patients with mild CTRCD.

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AUTHORS' CONTRIBUTIONS

G. Oristrell and I. Ferreira-González have contributed to the text of the article and the statistical analyses. M. Arumí and S. Escrivá-de-Romaní have contributed in the inclusion of patients in the study. F. Valente and G. Burcet have contributed to the performance of echocardiograms and cMRIs on patients included in the study.

CONFLICTS OF INTEREST

The authors state that they have no conflict of interests regarding this project.

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Table 2
Sensitivity, specificity, and positive and negative predictive value of hsTnI and GLS for the development of moderate-to-severe CTRCD

	Moderate-to-severe CTRCD			
	Sensitivity	Specificity	Positive predictive value	Negative predictive value
hsTnI +	0.25 (0.01-0.81)	0.60 (0.50-0.71)	0.03 (0.01-0.13)	0.95 (0.91-0.97)
> 15% change in GLS	1 (0.40-1)	0.65 (0.54-0.75)	0.09 (0.05-0.13)	0.99 (0.95-1)
> 15% change in GLS + hsTnI +	0.25 (0.01-0.81)	0.84 (0.74-0.90)	0.23 (0.05-0.64)	0.85 (0.76-0.91)

CTRCD, cancer therapy-related cardiac dysfunction; GLS, global longitudinal strain; hsTnI, high-sensitivity troponin I.

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Quality control of cardiovascular risk in hospitalized diabetic patients in cardiology services

Grado de control del riesgo cardiovascular del paciente diabético hospitalizado en los servicios de cardiología

To the Editor,

The 2019 European Society of Cardiology (ESC) guidelines on diabetes, prediabetes, and cardiovascular disease introduced the concept of cardiovascular (CV) risk as the basis for treating patients with diabetes and restratified it into 3 risk categories: moderate, high, and very high.[1] Patients at high or very high risk should be treated with diabetes drugs with proven CV benefit, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and glucagon-like peptide 1 (GLP-1) receptor agonists.[2] A need for greater participation by cardiologists in diabetes management has also been identified.[2]

The aim of the study was to evaluate the profile of patients with diabetes admitted to cardiology units. The study was divided into 2 phases. In the first phase, we analyzed preadmission data for patients with diabetes to assess CV risk according to the 2019 ESC guideline categories[1] and prescription rates of statins, high-potency statins, SGLT2 inhibitors, and GLP-1 receptor agonists. In the second phase, we analyzed cardiology admission data to assess newly diagnosed diabetes, hemoglobin A_{1c} (HbA_{1c}) and proteinuria determination during admission, and treatment optimization at discharge.

Under a confidentiality agreement, the Ministry of Health of the Principality of Asturias (one of Spain's autonomous communities) was asked to furnish a list of hospital discharges for patients admitted to cardiology units over 3 consecutive months in 2019 (minimum stay, 4 days). Information on the study variables was obtained from hospital discharge reports.[3]

Using the R software program, we calculated descriptive statistics for patients with and without diabetes and analyzed treatments prescribed to patients with diabetes. Comparisons were made using the chi-square or Fisher exact test for categorical variables and the Kruskal-Wallis or Mann-Whitney U tests for numerical variables. Posthoc Benjamini-Hochberg correction was applied to variables with a P value $< .05$.

Of the 1200 patients selected, 127 were excluded due to incomplete discharge reports.[3] The final sample thus comprised 1073 patients from 5 hospitals serving a population of 901 339 people (88.4% of the total population in Asturias). In total, 29.9% of the study population had diagnosed diabetes and 75% of these had a very high CV risk prior to admission. The baseline characteristics of the sample are summarized in table 1. A number of differences were observed between patients with and without diabetes and between patients with diabetes at very high CV risk and those with diabetes at high or moderate CV risk. Of note, almost half of the patients (48.5%) were on statins prior to admission, and the rate was significantly higher in those with diabetes (67%). When admitted, 76% of patients with diabetes and very high CV risk were on statins (high-potency in 50% of cases). SGLT2 inhibitors had been prescribed to 7.9% of patients with a very high CV risk and in 7.5% of those with a high or moderate risk. Analysis of prehospital glycemic control showed that 25.5% of patients had an HbA_{1c} level $< 7\%$ and 54.8% a low-density lipoprotein (LDL) cholesterol level < 100 mg/dL.

According to the discharge reports, 19 patients were newly diagnosed with diabetes during hospitalization, that is, 2.5% of all patients without diabetes at baseline. HbA_{1c} was measured in 45.5% of patients, and the differences between those with and without diabetes were nonsignificant. LDL cholesterol was measured in 70.7% of the patients overall and in 68.2% of those with diabetes. The respective percentages for proteinuria determination were 7% and 9.3%.

Changes to diabetes and lipid-lowering treatments noted on the discharge reports of patients with diabetes are shown in figure 1. There was a slight but significant increase in the percentage of patients prescribed SGLT2 inhibitors (from 8.1% to 11.1%, $P = .039$). No changes were observed in GLP-1 receptor agonist prescriptions. On analyzing the use of diabetes drugs with IA recommendations for patients at very high CV risk[1] and excluding contraindications (type 1 diabetes, renal function according to 2019 summary of product characteristics, and body mass index precluding reimbursement for GLP-1 receptor agonists), we observed that just 16.1% of patients eligible for SGLT2 inhibitors and 21.3% of those eligible for GLP-1 receptor agonists had been prescribed these drugs. The increase in the use of statins is more striking. Changes in