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Strain-oriented strategy for guiding cardioprotection initiation of breast cancer patients experiencing cardiac dysfunction

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Aims This study assessed the impact of the strain-guided therapeutic approach on cancer therapy-related cardiac dysfunction (CTRCD) and rate of cancer therapy (CT) interruption in breast cancer.

Methods and results We enrolled 116 consecutive female patients with HER2-positive breast cancer undergoing a standard protocol by EC (epirubicine + cyclophosphamide) followed by paclitaxel + trastuzumab (TRZ). Coronary artery, valvular and congenital heart disease, heart failure, primary cardiomyopathies, permanent or persistent atrial fibrillation, and inadequate echo-imaging were exclusion criteria. Patients underwent an echo-Doppler exam with determination of ejection fraction (EF) and global longitudinal strain (GLS) at baseline and every 3 months during CT. All patients developing subclinical (GLS drop >15%) or overt CTRCD (EF reduction <50%) initiated cardiac treatment (ramipril+ carvedilol). In the 99.1% (115/116) of patients successfully completing CT, GLS and EF were significantly reduced and *E*/e′ ratio increased at therapy completion. Combined subclinical and overt CTRCD was diagnosed in 27 patients (23.3%), 8 at the end of EC and 19 during TRZ courses. Of these, 4 (3.4%) developed subsequent overt CTRCD and interrupted CT. By cardiac treatment, complete EF recovery was observed in two of these patients and partial recovery in one. These patients with EF recovery re-started and successfully completed CT. The remaining patient, not showing EF increase, permanently stopped CT. The other 23 patients with subclinical CTRCD continued and completed CT.

Conclusion These findings highlight the usefulness of 'strain oriented' approach in reducing the rate of overt CTRCD and CT interruption by a timely cardioprotective treatment initiation.

Keywords breast cancer • cancer therapeutics related cardiac dysfunction • global longitudinal strain • ejection fraction • heart failure

Introduction

Nowadays, cancer therapy (CT) progressively prolongs survival in oncologic diseases. Nevertheless, it may expose patients to life-threatening complications involving cardiovascular system. Thus, cardiotoxicity may become one of the main determinants of quality of life impairment and mortality in this specific population.[1,2] Anti-cancer drugs can lead to several adverse cardiovascular effects, such as arterial hypertension, myocardial ischaemia, thromboembolic complications, arrhythmias, and conduction disturbances.[3] However, the most frequent and clinically relevant form of cardiotoxicity corresponds to a dilated and hypokinetic cardiomyopathy leading to overt heart failure (HF).[4] Cancer therapy-related cardiac dysfunction (CTRCD) can be due to different kinds of treatment: anthracyclines

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provoke a dose-cumulative myocardial damage with irreversible cellular necrosis (Type I cardiotoxicity), while other agents, such as trastuzumab (TRZ), lead to a non-dose-related but reversible cardiac impairment (Type II cardiotoxicity).[5–7] The sequential or concurrent use of these two different types of agents may increase myocardial injury and CTRCD is often the result of the combined detrimental effect of the two therapies.[7]

A timely initiation of cardioprotective treatment for CTRCD is pivotal to continue the ongoing CT till completion and reduce the risk of overt HF. Cardiac treatment of CTRCD is currently guided by 2D echocardiographic evaluation of left ventricular (LV) ejection fraction (EF).[8] However, EF is affected by several limitations including its load-dependence, the need of geometric assumption for its calculation and, above-all, its substantial biological (day-to-day) variability that makes subtle changes often doubtful and questionable.[9] As an alternative, global longitudinal strain (GLS), easily obtainable by speckle tracking echocardiography, has shown optimal feasibility and temporal reproducibility and its changes may precede EF reduction in the general population and in oncologic patients as well.[10]

The lack of definite results on clinical outcomes produced by a GLS-oriented strategy, i.e. the impact of a strain-guided cardioprotective therapy initiation on the development of overt HF, makes this innovative approach not ready yet for addressing the decision-making in this clinical setting. Accordingly, the present study was designed to assess the impact of the strain-oriented therapeutic approach in reducing the development of overt CTRCD and the rate of CT interruption in breast cancer patients.

Methods

Study population

After their informed consent was collected, 116 consecutive female patients with diagnosis of HER2-positive breast cancer were enrolled in the Oncologic Clinic of Federico II University Hospital. The approval by the Ethical Committee of Federico II University Hospital was obtained. Patients with coronary artery disease, overt HF, primary cardiomyopathies, haemodynamically significant valvular heart disease, permanent or persistent atrial fibrillation, congenital heart disease, and inadequate echocardiographic imaging before starting CT therapy were excluded. The presence of cardiovascular risk factors including arterial hypertension, diabetes mellitus, dyslipidaemia, and smoke habit was collected in individual patients.

All patients underwent a standard transthoracic echo-Doppler study at baseline before the start of CT and every 3 months during the therapy. Blood pressure was measured in supine position by a cuff sphygmomanometer (average of three measurements) at the end of each exam.

Cancer therapy protocol

Patients underwent a CT standard protocol defined as EC [anthracycline epirubicine (90 mg/m^2) + cyclophosphamide (600 mg/m^2)] for four cycles, with an inter-cycle interval of 21 days. At the end of EC, CT continued with the administration of paclitaxel (80 mg/m^2) in combination with TRZ (4 mg/kg for the first week and then 2 mg/kg weekly for 11 cycles), followed by paclitaxel (80 mg/m^2) + TRZ (6 mg/kg) for 13 cycles (inter-cycle pauses of 21 days).

A complete echo-Doppler exam was performed at baseline, after EC completion, and every 3 months during and at the end of the remaining CT. If overt CTRCD was suspected (decrease in EF >10 percentage points, to a value below 50% according to the 2016 American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI) Expert Consensus on the role of cardiac imaging in adult cancer patients),[5] a repeated echocardiographic exam was performed within 2–3 weeks to confirm the finding. When two consecutives evaluation showed overt CTRCD, we referred to the oncologist to determine whether discontinuation of anti-cancer drugs was needed (i.e. in presence of cardiac symptoms), as recommended.[8] Of those who interrupted the anti-cancer drug administration, only the ones with full recovery (EF recovery to baseline values) or partial recovery (EF recovery above 50% but below baseline values) re-started the planned CT protocol. Patients with a GLS reduction >15% from baseline, independently on EF values, were diagnosed to have a subclinical CTRCD.[5] Noteworthy, in our established protocol all patients developing CTRCD (either overt or subclinical) initiated a cardioprotective treatment with angiotensin-converting enzyme (ACE)-inhibitors (ramipril) and beta-blockers (carvedilol), at a maximal tolerated dosage, as recommended.[8]

Echo Doppler exam

Standard echo-Doppler exam including speckle tracking echocardiography of apical views were performed by a Vivid E9 ultrasound machine (GE Healthcare, Horten, Norway), using a 2.5 MHz transducer with harmonic capability.

Two-dimensional and Doppler exams were performed according to the standards of our laboratory.[11,12] LV analysis was quantified in agreement of 2015 recommendations of the ASE and the EACVI[13] and the EACVI standardization of the echo report.[14] Two-dimensional echo derived EF was calculated from LV end-diastolic and end-systolic volumes (from apical four- and two-chamber views) computed by the modified Simpson rule. Relative wall thickness and LV mass were obtained by 2D guided M-mode imaging or directly from 2D longitudinal long-axis view. LV mass was indexed for height powered to 2.7.[15] Left atrial volume was indexed for body surface area.[16] Transmitral Doppler inflow and pulsed Tissue Doppler were recorded in apical four-chamber view to analyse LV filling pattern (transmitral *E*/*A* ratio and *E* velocity deceleration time), and the average of early diastolic velocities (e′) of septal and lateral mitral annulus was used to calculate the *E*/e′ ratio.[16]

Speckle tracking echocardiography procedures were performed according to the standards of our laboratory.[11,12] LV longitudinal deformation was recorded on 2D images of three consecutive cardiac cycles from the three apical (long-axis, four- and two-chamber) views at an approximately equal heart rate. An interactive software of a dedicated workstation (Echopac BT13 version, GE) allowed to automatically trace the endocardial-cavity interface, with possible, subsequent manual adjustment, and rejection of segments of poor imaging quality. Each of the three apical images was automatically divided into six myocardial segments. Peak negative longitudinal strain was measured from six segments in each of the three apical views and GLS was computed as the average of individual peak strain before aortic valve closure. Reproducibility of speckle tracking echo in our laboratory has been previously reported.[17] GLS was considered in absolute value according to Chamber Quantification recommendations.[13]

Statistical analysis

Statistical analysis was performed by SPSS package, release12 (SPSS Inc., Chicago, IL, USA). Data are presented as mean value ± standard deviation. Descriptive statistics were obtained by one factor ANOVA (Bonferroni *post hoc* intergroup analysis) and χ^2 distribution with computation of exact *P*-value by Monte Carlo method and inter-group *post hoc* (Bonferroni test) comparison. The null hypothesis was rejected at two-tailed $P < 0.05$.

Results

Figure 1 summarizes the behaviour of our overall breast cancer population through the entire study duration. The characteristics of the study population are shown in *Table 1*. In the overall population, 27.6% patients ($n = 32$) were hypertensive (22 treated with antihypertensive drugs including ACE-inhibitors, angiotensin II receptor blockers, beta-blockers, and calcium channel antagonists), and 19.8% ($n = 23$) overweight.

During the follow-up, no patient had an episode of atrial fibrillation, whereas effort dyspnoea was observed in four patients during TRZ treatment. The 99.1% (115/116) of the patients successfully completed CT. In this group, GLS ($P < 0.0001$) and EF ($P < 0.002$) were both reduced and E/e' ratio increased ($P = 0.028$) at TRZ end in comparison with baseline (*Table 2*).

Combined subclinical and overt CTRCD was diagnosed in 27 of the 116 patients (23.3%) (*Figure 1A*). The individual characteristics of these 27 patients are summarized in *Table 3*. Among eight hypertensive patients, six received antihypertensive treatment at baseline (data not in table). By comparing baseline echo parameters of patients with and without CTRCD, no significant difference of EF was observed whereas GLS was slightly higher ($P < 0.02$) in CTRCD group. The prevalence of hypertensive patients assuming antihypertensive drugs was comparable between the two groups (66.7% and 75% in the CTRCD and non-CTRCD groups, respectively, $P = 0.66$).

All 27 CTRCD patients started cardioprotective treatment with ramipril (average daily dose 7.8 ± 2.5 mg) and carvedilol (average daily dose 10.3 ± 3.1 mg), without referring any significant side effect. Four of these patients (3.4%) subsequently developed overt CTRCD and, based on cardiac symptoms, i.e. effort dyspnoea, and EF reduction 'below 50%' (in at least two repeated echo exams), interrupted CT at variable TRZ cycle timing, after oncologic consultation (*Figure 1B*). Worthy of note, in all these patients GLS was reduced by >15%. One of these patients did not show any EF increase (in two repeated echo exams within 3 weeks and, subsequently, after 1 month) and, being still symptomatic for effort dyspnoea, definitely stopped CT after oncologic consultation; a complete EF recovery to baseline values induced by cardioprotective treatment was observed in two patients, and a partial recovery in the remaining one (*Figure 1C*). The three patients showing EF recovery had also a concomitant GLS recovery (*Figure 2*) and could re-start the programmed CT protocol till completion.

The remaining 23 patients (19.8%) developed subclinical CTRCD (GLS drop >15%), 8 at the end of EC and 19 during TRZ courses, and—thanks to cardiac treatment—continued and successfully completed the TRZ cycles, without any interruption because they did not progress towards overt CTRCD. *Table 4* compares the echo data obtained at baseline, CTRCD onset and the end of CT of the 23 patients developing subclinical CTRCD. Both EF and GLS were reduced at CTRCD onset compared to baseline (both $P < 0.0001$), whereas significantly improved at the time of CT completion in

Table 1 Clinical characteristics of the overall study population at baseline

Variables	Mean ± SD	Range
Age (years)	52.5 ± 12.1	24–77
Body mass index (kg/m^2)	26.1 ± 4.6	16.8–40.1
Systolic BP (mmHg)	125.8 ± 15.2	90–170
Diastolic BP (mm/Hg)	78.4 ± 8.5	50–110
Heart rate (bpm)	72.8 ± 11.4	50–109

BP, blood pressure; SD, standard deviation.

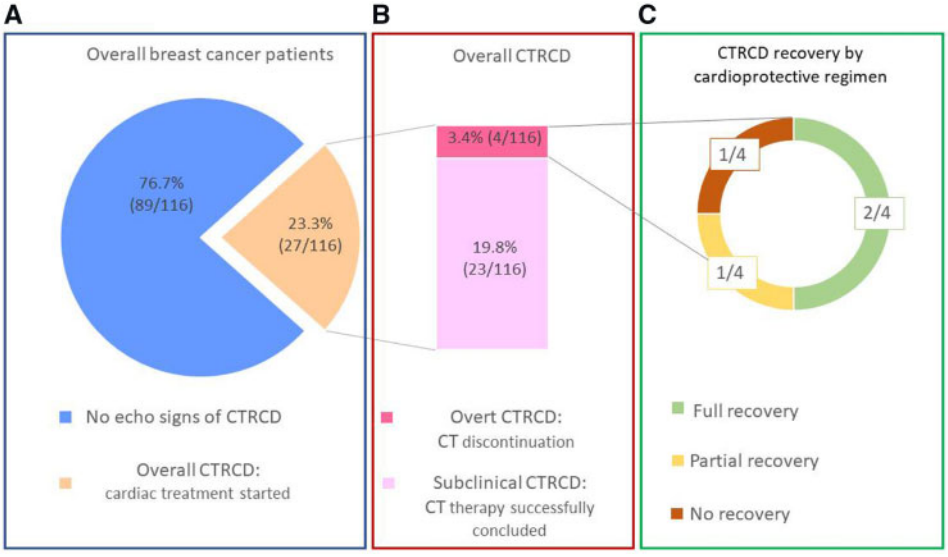

Figure 1 Picture of the study population. (*A*) Overall breast cancer population, (*B*) CTRCD (both subclinical and clinical) population, and (*C*) CTRCD recovery after cardioprotective regimen. CTRCD, cancer therapy-related cardiac dysfunction.

Table 2 ANOVA comparison of echocardiographic parameters at baseline, at end EC, and at TRZ completion in patients without CTRCD ($n = 89$)

Variables	Baseline	End EC	End TRZ
Relative wall thickness	0.32 ± 0.05	0.32 ± 0.06	0.33 ± 0.04
LV mass index (g/m$^{2.7}$)	33.2 ± 8.2	34.1 ± 8.2	35.0 ± 8.2
LV EF (%)	63.4 ± 3.9	62.1 ± 4.3	61.4 ± 4.0[a]
LV GLS (%)	22.0 ± 2.4	21.0 ± 2.5	20.2 ± 4.8[b]
Transmitral *E/A* ratio	1.11 ± 0.4	1.10 ± 0.3	1.10 ± 0.4
E velocity DT (ms)	210.1 ± 44.4	207.8 ± 48.1	211.8 ± 46.0
E/e′ ratio	7.5 ± 2.4	7.9 ± 2.4	8.9 ± 2.7[c]
LAVi (ml/m^2)	26.4 ± 6.6	27.1± 5.9	26.1 ± 6.0

CTRCD, cancer therapy-related cardiotoxicity; DT, deceleration time; EF, ejection fraction; End EC, end epirubicine + cyclophosphamide; End TRZ, end trastuzumab; GLS, global longitudinal strain; LAVi, left atrial volume index; LV, left ventricular.
[a]$P < 0.002$ between baseline and end of anticancer therapy.
[b]$P < 0.0001$ between baseline and end of anticancer therapy.
[c]$P = 0.028$ between baseline and end of anticancer therapy.

comparison with both baseline and time of CTRCD onset. *Figure 3* depicts a clinical case of a patient who developed subclinical CTRCD with a significant GLS drop, but successfully recovered both GLS and EF at the end of TRZ thanks to cardiac treatment.

Discussion

Our study demonstrates that in a population of HER2-positive breast cancer patients undergoing adjuvant therapy: (i) the use of GLS allows to identify subclinical CTRCD when EF is still normal, with a prevalence of 23.3% (27/116); (ii) all the 23 patients developing subclinical CTRCD without progression towards overt HF were able to complete CT without interruption, thanks to the help of cardioprotective treatment; (iii) among the four patients developing subsequent overt CTRCD, three could complete CT with an adequate cardioprotective treatment; (iv) in the subgroup of patients without CTRCD (76.7%) a reduction in EF and GLS and an increase in *E/e′* ratio was detected at the end of CT in comparison with baseline.

Nowadays, the methodology for early diagnosing subclinical CTRCD in cancer patients remains controversial. Cardinale *et al.*

Table 3 Clinical characteristics of the patients developing subclinical and overt CTRCD

Patient	Age	BMI	Smoke	HTN	Dyslipidaemia	DM 2	CTRCD onset	Baseline EF (%) and GLS (%)	CTRCD EF(%) and GLS (%)	End TRZ EF (%) and GLS (%)
1	56	23.9	0	0	1	0	2 TRZ	60–23.4	60–18.4	60–20.6
2	64	24.3	1	0	1	0	1 TRZ	63–25.1	59–20.9	60–19.1
3	54	24.8	1	1	0	0	End EC	60–28.4	60–23.9	68–25
4	68	35.2	0	0	1	0	9 TRZ	59–21.1	60–17.2	65–20.3
5	45	22.1	0	0	0	0	End EC	65–23	67–19.0	59–17.8
6	60	25.7	0	0	1	0	End EC	65–23	60–19	64–17.8
7	56	25.5	1	0	1	0	End EC	64–24.6	58–20.5	60–19.3
8	24	24.3	1	1	0	0	End EC	69–24.8	62–20.1	66–22.1
9	47	19.1	0	0	1	0	1 TRZ	70–21.8	57–17.5	58–17.7
10	64	32.5	0	0	0	0	End EC	65–26.2	65–20.9	61–21.9
11	49	19.5	0	0	1	0	End EC	65–27.7	68–22.5	58–18.6
12	48	27.8	1	0	1	0	1 TRZ	67–20.7	65–16	58–20.6
13	73	29.1	1	1	0	0	End EC	64–22.7	59–18.7	58–22
14	46	22.3	0	0	1	0	1 TRZ	72–24.3	62–20.4	59–21.2
15	73	31.2	0	1	1	0	3 TRZ	65–23.2	48–14.3	
16	45	37.0	0	0	1	0	4 TRZ	67–23.4	60–17.0	61–22.7
17	28	21.0	0	0	0	0	6 TRZ	67–23.2	58–16.7	60–22.7
18	62	30.4	0	0	1	0	1 TRZ	58–20.0	51–16.5	60–18.0
19	58	26.6	1	0	1	0	5 TRZ	60–21.4	49–14.7	
20	55	24.3	1	1	0	0	6 TRZ	65–27.1	50–16.4	
21	65	23.2	0	0	1	0	6 TRZ	68–22.5	52–17.3	58–22.0
22	58	25.4	0	0	0	0	2 TRZ	65–20.0	57–17.0	64–23.2
23	46	21.6	1	1	1	0	9 TRZ	60–18.2	38–11.9	
24	54	24.5	1	0	0	0	1 TRZ	60–19.9	56–14.2	60–18.9
25	54	29.3	0	1	0	0	5 TRZ	62–19.6	61–15.5	64–19.5
26	62	32.0	0	0	1	1	11 TRZ	58–19.2	53–15.1	61–19.7
27	50	27.8	0	1	0	0	8 TRZ	65–20.8	57–17.5	59–17.9

BMI, body mass index; DM 2, diabetes mellitus type 2; EC, epirubicine + cyclophoshamide; EF, ejection fraction; GLS, global longitudinal strain; HTN, arterial hypertension; LV, left ventricular; TRZ, trastuzumab.

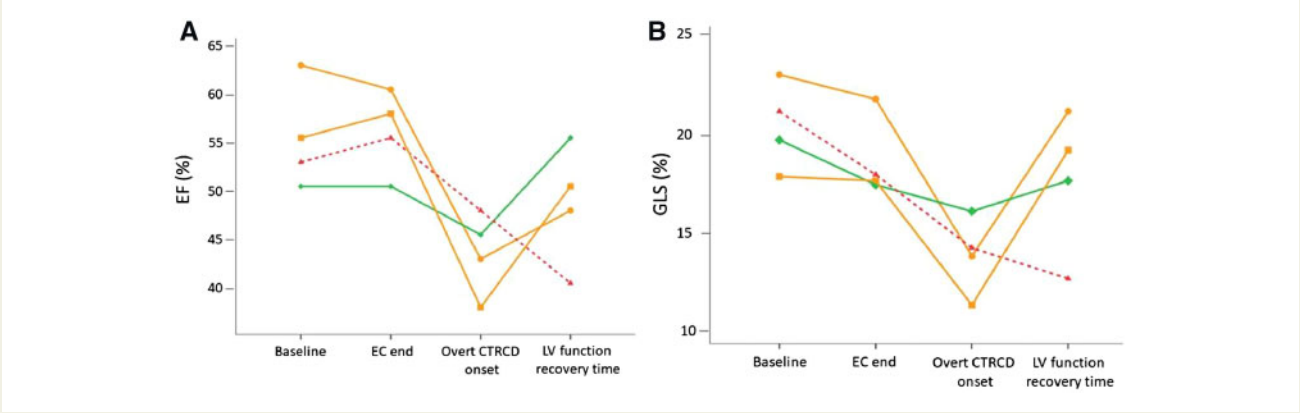

Figure 2 Behaviour of EF (*A*) and GLS (*B*) at EC end, at the time of overt CTRCD onset (during TRZ) and at the time of LV function recovery in the individual patients developing overt CTRCD. Solid green lines indicate patients with full LV function recovery thanks cardioprotective regimen (at 60 and 95 days, respectively); solid orange lines indicate patient with partial LV function recovery thanks cardioprotective regimen (at 120 days). Dotted red lines indicate patient without LV function recovery (after 51 days after interrupting CT) and forced to permanently stop CT. CTRCD, cancer therapy-related cardiac dysfunction; EC, epirubicine + cyclophosphamide; EF, ejection fraction; GLS, global longitudinal strain; LV, left ventricular.

Table 4 ANOVA comparison of echocardiographic parameters at baseline, at end EC, and at TRZ completion in patients with subclinical CTRCD ($n = 23$)

Variables	Baseline	End EC	End TRZ
Relative wall thickness	0.31 ± 0.04	0.29 ± 0.04	0.32 ± 0.04
LV mass index (g/m$^{2.7}$)	35.8 ± 9.1	40.2 ± 8.3	39.4 ± 10.2
LV EF (%)	62.8 ± 3.5[a]	53.0 ± 6.0[b]	60.7 ± 2.0[c]
LV GLS (%)	22.9 ± 2.9[a]	17.8 ± 2.9[b]	20.3 ± 2.3[c]
Transmitral *E*/*A* ratio	0.93 ± 0.4	0.94 ± 0.4	1.0 ± 0.3
E velocity DT (ms)	230.4 ± 42.7	206.6 ± 41.5	208.4 ± 43.9
E/*e*′ ratio	8.4 ± 2.1	9.1 ± 2.9	8.3 ± 2.5
LAVi (mL/m^2)	24.5 ± 7.6	29.1 ± 9.9	29.0 ± 6.5

CTRCD, cancer therapy-related cardiotoxicity; DT, deceleration time; EC, epirubicine + cyclophoshamide; EF, ejection fraction; GLS, global longitudinal strain; LAVi, left atrial volume index; LV, left ventricular; TRZ, trastuzumab.
[a]$P < 0.0001$ baseline vs. CTRCD onset.
[b]$P < 0.004$ CTRCD onset vs. end of anticancer therapy.
[c]$P = 0.002$ baseline vs. end TRZ.

successfully demonstrated the possibility of identifying subclinical CTRCD by using troponin I. An early troponin I increase predicted subsequent EF reduction and outcomes (mainly HF) in patients undergoing anthracyclines or adjuvant therapy, thus addressing initiation of cardioprotective treatment with ACE inhibitors.[18–22] This strategy is limited by the need of serial troponin I assessment and by the lack of a defined troponin I threshold for diagnosis of CTRCD onset. An alternative is currently represented by EF monitoring. In a recent study, the EF determination at baseline and every 3 months during CT and the initiation of cardioprotection in case of overt CTRCD (=EF decrease >10 absolute points, and <50%), led to a full recovery of LV systolic function (EF increase to baseline value) or at least to a partial recovery (EF increase >5 absolute points and >50%) in 71% of the patients.[21] The main limitation of EF corresponds to its temporal (day-to-day) variability which is suboptimal (greater than 10%)[9] and does not allow to attribute a definite clinical value to its changes.

In the present study, we applied the GLS strategy suggested by the ASE/EACVI Expert Consensus to identify subclinical CTRCD[5] and timely started cardioprotection. The superior feasibility[23] and reproducibility (inter-exam variability of about 6%) of GLS in comparison with EF (about 10%)[24] is well-known and allows a friendly use of this parameter in the oncologic setting.[25] Moreover, LV longitudinal dysfunction testified by GLS precedes EF reduction, being particularly useful in the preclinical stages of several cardiac diseases,[26,27] including CTRCD.[28,29] Accordingly, the European Society of Cardiology has recently promoted the possibility of monitoring GLS changes during CT.[8] A GLS drop >15% from baseline is a concrete variation to predict HF in cancer patients undergoing concurrent TRZ and anthracycline therapy, independently on baseline EF.[30] Changes of GLS appear to parallel the increase of troponin I values as an expression of myocardial cell damage, both being predictive of overt CTRCD in cancer patients.[30] By embracing this concept, even when GLS remains widely normal, i.e. >19%, the occurrence of its drop of at least 15% during CT should be considered clinically relevant to identify a subclinical cardiac damage and start cardioprotective regimen.[5,8]

To the best of our knowledge, this is the first study to demonstrate that in a population of HER2-positive breast cancer patients undergoing CT the GLS-based approach and the consequent and timely initiation of cardioprotection with concomitant ACE-inhibitors and beta-blockers, may have a clear impact on the onset of subsequent overt HF and on CT withdrawn. A previous non-randomized observational study by Negishi *et al.*[31] has similarities but also clear differences with our study. By applying a GLS decrease ≥11% to detect subclinical LV dysfunction and initiate cardioprotective therapy with beta-blockers at discretion of clinician, an improvement of both

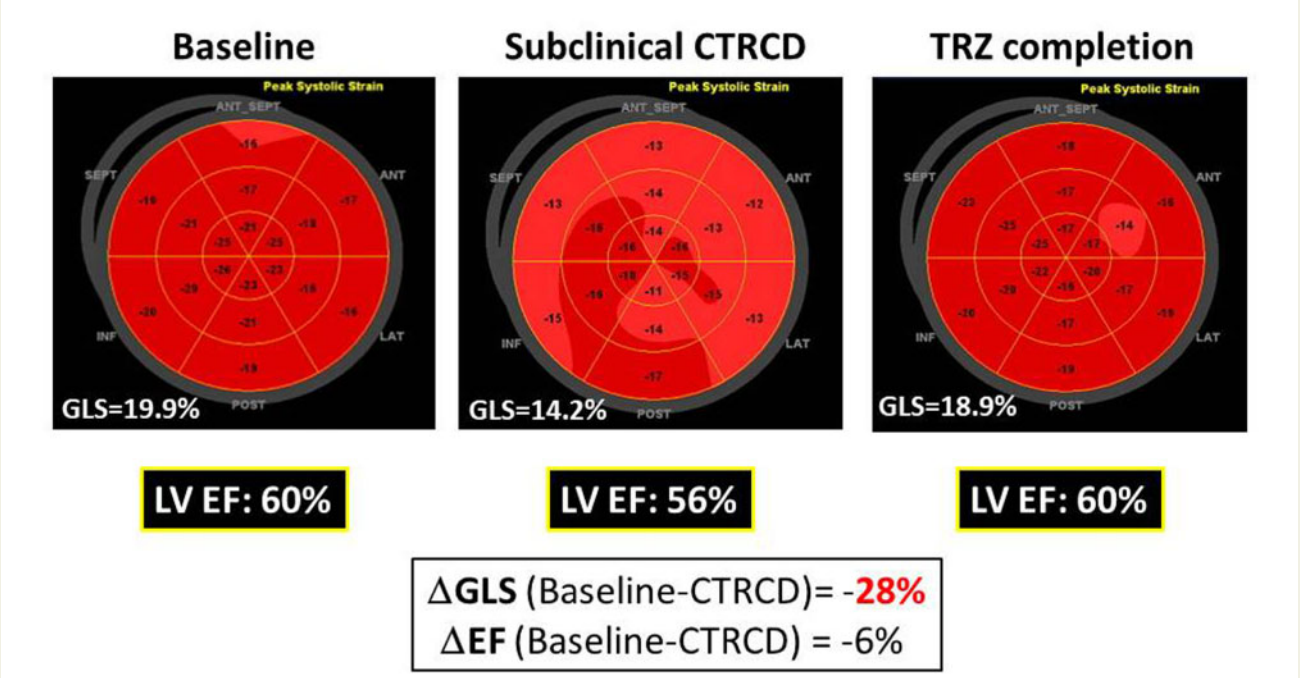

Figure 3 Clinical case of a patients developing subclinical CTRCD at the XI TRZ cycle but completing successfully TRZ thanks the timely cardioprotective treatment. Bull's eyes of GLS at baseline (left), at the time of subclinical CTRCD (mid), and at cancer therapy completion (right). CTRCD, cancer therapy-related cardiotoxicity; EF, ejection fraction; GLS, global longitudinal strain; TRZ, trastuzumab.

EF and GLS was found in the beta-blocker group but not in the non-beta-blocker group. In the present study, we used a GLS drop >15%—as suggested by ASE and EACVI[5]—and a combined cardioprotective regimen with beta-blockers and ACE-inhibitors.

It is noteworthy that, by applying this strategy, the incidence of overt CTRCD (3.4%) was substantially lower than that reported in other recent investigations (from 7% to 34%).[21,32] Most importantly, all the 23 patients developing subclinical CTRCD without progression towards overt HF were able to complete CT without interruption, also obtaining an almost complete recovery of both GLS and EF thanks to the cardioprotective regimen. The strain-oriented approach provided a positive impact even in the four patients (3.4%) developing subsequent overt HF (overt CTRCD) since two out of four patients showed a full recovery (EF increase to baseline value), and one patient showed at least a partial recovery (EF increase >5 absolute points and >50%). The remaining patient, not showing any EF recovery and being symptomatic, was forced to permanently interrupt CT. Combined all together, these results demonstrate that the application of this innovative approach may allow to accomplish CT in almost the totality (96.5%) of cancer patients.

An ancillary but important observation is also represented by the fact that in the remaining 76.7% of patients not developing subclinical or overt CTRCD, significant changes of both LV systolic (reduction of EF and GLS) and diastolic function (increase of E/e' ratio) were detectable at the end of CT in comparison with baseline. This finding demonstrates a global detrimental cardiac effect of CT on LV function in the setting of breast cancer and highlights the need of careful monitoring LV function even after the CT completion.

Study limitations

The main limitation corresponds to the lack of a head-to-head comparison between 'standard LV EF' vs. 'GLS-based' guidance in addressing cardioprotective therapy in the cancer setting. Accordingly, the 'true' impact of strain-oriented cardiac therapy on GLS and LVEF recovery or on the withdrawal of chemotherapy cannot be definitively established by our findings. Moreover, similarly to EF, GLS is a load-dependent parameter and has a variability which prevents to attribute an absolute clinical value to its fluctuations during follow-up. Nevertheless, the day-to-day variability of GLS is much lower than the one presented by EF[24] and, based on evidences,[30] a GLS decrease >15% from baseline is a cornerstone of ASE/EACVI Expert Consensus on imaging evaluation of adult patients during and after CT.[5] The 'Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes' (SUCCOUR) trial is an ongoing international multicentric prospective randomized controlled trial that aims to analyse the different aspects of the two approaches (GLS vs. EF) in the diagnosis and management of oncologic patients at high risk of cardiotoxicity.[33] The results of this trial will probably provide definitive insights to put GLS in first line for surveillance of CTRCD. Another possible limitation corresponds to the absence of biomarker monitoring, very challenging to obtain in the outpatients referring to our University Hospital because of organizational procedures. Although its role remains controversial in this clinical setting,[8] troponin I has been successfully used to detect subclinical CTRCD and predict subsequent development of overt HF.[18–20] It could also have been very innovative to verify if GLS could anticipate the increase of NT-proBNP or BNP values compared to the behaviour

of LVEF. However, the role of atrial peptides is not well-established for defining the routine surveillance of high-risk patients in the European position statement of cancer treatments and cardiovascular toxicity.[8] Of note, BNP levels predicted overt CTRCD in some studies but not in others.[30,34,35] Finally, the inter-vendor variability and technical requirements of GLS are intrinsic to the strain technology.[8,28] Although recent studies have demonstrated a good concordance of GLS among different vendors,[24] its measurement remains vendor-specific.[36] Accordingly, serial assessment of GLS during CT should performed using the same vendor machine.

Conclusion

Our study puts a spotlight on the 'GLS-oriented' approach in detecting CTRCD and its prompt treatment, a matter that both cardiologists and oncologists will have to be aware of in the future years. This strategy may effectively prevent overt and irreversible HF and avoid the possible subsequent interruption of CT, with clear negative reflections on cancer progression end relapse. Ongoing and future studies could open new horizons and possibly even define the lowest value of GLS to be considered as clinically relevant.

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IMAGE FOCUS

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Aorta-right atrium tunnel: an unexpected diagnosis

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An asymptomatic 52-year-old woman was referred for the evaluation of a 4/6 continuous murmur in the right parasternal border. Patient had no relevant family history of congenital heart disease. The electrocardiogram showed sinus rhythm and the echocardiogram revealed a round, vascular communication from the left aortic sinus (LAS) to the right atrium (RA), with continuous turbulent flow on Doppler evaluation. Additionally, a cardiac computed tomography angiography was performed for better delineation of coronary and extra-cardiac anatomy. 3D volume rendered reconstructions showed a large and tortuous 'tunnel-like' structure arising from the LAS, coursing posteriorly to the aortic root and terminating in the roof of the RA, just inferior and medial to the superior vena cava junction (*Panel A*). The left anterior descending (LAD) and the circumflex (LCX) arteries arose independently from the proximal portion of the tunnel. Cardiac magnetic resonance imaging with phase-contrast cine (PC-MRI) showed non-dilated right ventricle (RV), right ventricular outflow tract (RVOT) or main pulmonary artery (MPA) and there were no signs of pressure or volume overload (*Panels B–E* and Supplementary data online, *Video S1*). The Qp:Qs ratio assessed by PC-MRI was 1.8 (*Panels F–I*). The shunt volume assessed by in-plane PC-MRI was 37 mL, and this result was comparable to the difference between the pulmonary (PA) and aortic (Ao) flow (Qp–Qs = 40 mL). Once the patient was asymptomatic and there were no signs of right overload, we decided to manage the patient conservatively with close follow-up.

Aorta-RA tunnel (ARAT) is an extremely rare congenital anomaly. To the best of our knowledge, this is the oldest patient diagnosed with ARAT to be reported in the literature.

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.