Review Article

Narrative review—cardiotoxicity in patients with early-stage breast cancer who received locoregional radiotherapy and trastuzumab

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Background and Objective: Considering that patients with human epidermal growth factor receptor 2 (HER2)-positive early-stage breast cancer (EBC) are routinely treated with adjuvant trastuzumab for at least 1 year, adjuvant radiotherapy (RT) and trastuzumab are frequently concurrently administered after surgery or completion of chemotherapy to avoid delay in achieving locoregional control with RT and because trastuzumab hypothetically enhances the radiosensitivity of cancer cells. However, treatment with trastuzumab alone has been demonstrated to result in cardiac events (CEs) in certain patients. Therefore, possible parameters for detecting CEs in patients with HER2-positive EBC concurrently treated with RT and trastuzumab need to be identified, especially in patients undergoing left-sided RT. In this review article, we summarize the incidence of CEs, defined as conditions characterized by decreased left ventricular ejection fraction (LVEF), in patients with HER2-positive EBC treated with concurrent trastuzumab and RT in prospective and retrospective studies.

Methods: A literature survey was performed in the publicly available PubMed database. We searched for articles reporting on the association between acute or chronic CEs and concurrent treatment with trastuzumab and RT in HER2-positive EBC patients. We reviewed eligible English-language articles published between January 2005 and December 2022.

Key Content and Findings: Although CEs related to breast cancer treatment rarely occur, with an incidence ranging from 1.0% to 2.5%, a mean heart dose (MHD) of >4 Gy, internal mammary node (IMN) irradiation, and left-sided RT using conventional techniques are risk factors for the development of CEs in patients concurrently treated with trastuzumab and RT. Several reports have shown that in addition to decreased LVEF, new cardiac abnormalities such as diastolic dysfunction, arrhythmias, and myocardial and valvular abnormalities may be associated with CEs in patients concurrently treated with trastuzumab and left-sided RT. However, in some studies, trastuzumab administration did not increase the risk of CEs in patients who underwent RT using modern techniques, which caused a relatively lower MHD compared with conventional RT techniques.

Conclusions: Long-term follow-up of CEs and prospective assessment of new parameters for the early detection of CEs are warranted in HER2-positive EBC patients concurrently treated with trastuzumab and

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left-sided or IMN irradiation using modern techniques.

Keywords: Cardiotoxicity; radiotherapy (RT); trastuzumab; breast cancer

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Introduction

Background

Breast cancer is a major cause of cancer-related morbidity worldwide (1). Several studies have demonstrated that breast-conserving surgery (BCS) followed by adjuvant radiotherapy (RT) provides similar clinical outcomes, including locoregional recurrence (LRR) and overall survival (OS) rates, to mastectomy in patients with early-stage breast cancer (EBC) (2-4). In high-risk postmastectomy patients, adjuvant locoregional RT reduces LRR, leading to better OS than in the absence of RT (5,6). The analysis of the Early Breast Cancer Trialists' Collaborative Group demonstrated that the use of RT decreased the absolute LRR rate by 18.1% and the absolute breast cancer mortality rate by 9.35% at 10 years in 1772 women who underwent axillary dissection and had at least four positive nodes (5). However, in patients with left breast cancer undergoing BCS or mastectomy, adjuvant left whole-breast RT, left chest wall irradiation, or left internal mammary node (IMN) irradiation may cause cardiac events (CEs), including ischemic heart disease, pericarditis, and valvular disease, in the long-term follow-up (7-9).

In a study of 936 patients with breast cancer who experienced major coronary events, including myocardial infarction, coronary revascularization, or death from ischemic heart disease, and a paired control group of 1205 patients with breast cancer without CEs, Darby *et al.* found that the incidence of major coronary events was significantly associated with the mean heart dose (MHD) from RT (10). In their analysis, the heart dose from RT was estimated by reconstructing the conventional tangential-field plans using modern RT planning, and the rate of major coronary events was found to increase with increasing MHD at a rate of 7.4% per Gy. This study indicated that close follow-up of CEs after the completion of RT is recommended in patients with breast cancer because CEs can occur up to 20 years after RT exposure. However, Darby *et al.* analyzed a long period of diagnosis (between 1958 and 2001), during which most patients underwent RT using conventional techniques. As computed tomography-based planning, in which the heart is routinely blocked, was not performed for most patients, some patients may have received a higher RT dose to the heart, especially postmastectomy patients who underwent RT using the conventional electron technique (10). Therefore, CEs resulting from left-sided RT may have been overestimated in the above-mentioned study (10), as modern RT techniques can avoid exposing the heart to radiation.

Over the past few decades, invasive breast cancer has been molecularly classified into different subtypes according to gene expression profiles and their association with clinical outcomes (11,12). Four subtypes of breast cancer have been proposed based on the expression patterns of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), as assessed using immunohistochemistry and fluorescence *in situ* hybridization techniques (13-16). Accordingly, breast cancer is categorized into the following four subtypes: luminal A/B [hormone receptor (HR)$^+$/HER2$^-$, HR$^+$ (ER$^+$ and/or PR$^+$)], luminal HER2 (HR$^+$/HER2$^+$), HER2 (HR$^-$/HER2$^+$), and triple negative (HR$^-$/HER2$^-$) (13-17).

On the basis of the unique biological significance of HER2 signaling in the molecular pathogenesis of breast cancer (18,19), the administration of trastuzumab, a HER2-targeting antibody, has been demonstrated to provide better progression-free survival and OS in the adjuvant setting for patients with HER2-positive EBC in four large randomized trials [Breast International Group 01-01 (HERA), National Surgical Adjuvant Breast and Bowel Project (NSABP)-B31, North Central Cancer Treatment Group N9831, and Breast Cancer International Research Group-006] (20-22). However, the use of trastuzumab alone in patients with metastatic breast cancer has been reported to be associated with cardiac dysfunction (23). In the HERA trial, which compared the outcomes of patients with HER2-positive EBC among three groups (observation, 1-year trastuzumab, and 2-year trastuzumab), Cameron *et al.* reported that the 10-year disease-free survival (DFS) rate in the observation, 1-year trastuzumab, and 2-year trastuzumab groups was 63%, 69%, and 69%, respectively (24). Furthermore,

Cameron *et al.* revealed that the occurrence rate of the primary cardiac endpoint [defined as cardiologist-confirmed New York Heart Association class III/IV toxicity, at least 10% decrease in left ventricular ejection fraction (LVEF) compared with baseline, LVEF <50%, or cardiac mortality] in the observation, 1-year trastuzumab, and 2-year trastuzumab groups was 0.1%, 1%, and 1%, respectively (24). These findings indicate that the administration of trastuzumab for 1 year after chemotherapy for HER2-positive breast cancer improves long-term DFS and rarely causes cardiotoxicity (24).

Rationale and knowledge gap

Considering that patients with HER2-positive breast cancer are routinely treated with adjuvant trastuzumab, adjuvant RT is frequently concurrently administered with trastuzumab to avoid delay in RT treatment and to take advantage of the potential of trastuzumab to increase the radiosensitivity of cancer cells (25-27). Among patients with HER2-positive EBC with positive axillary lymph nodes or with high-risk clinicopathological features but without positive axillary lymph nodes after surgery, the joint analysis of two randomized trials (NSABP-B31 and N9831) demonstrated that those who received doxorubicin plus cyclophosphamide followed by paclitaxel and trastuzumab followed by trastuzumab had better DFS and OS than those who received doxorubicin plus cyclophosphamide followed by paclitaxel plus trastuzumab (21). Although this article summarizes the potential cardiotoxicity resulting from concurrent RT and trastuzumab in patients with HER2-positive EBC, a proportion of these patients had been treated with an anthracycline-based regimen in the neoadjuvant and adjuvant settings before RT. In contrast to anthracycline-induced cardiac dysfunction that manifests as irreversible myocardial damage (also called sequential high stress-induced type 1 cardiotoxicity), trastuzumab-induced cardiac dysfunction (also called low stress-induced type 2 cardiotoxicity) shows transient and reversible recovery after the discontinuation of trastuzumab (28-30). Therefore, the relationship between cardiotoxicity and concurrent RT and trastuzumab therapy should be interpreted with caution, especially for patients previously treated with an anthracycline-based regimen.

Objective

To examine CEs that may result from left breast or left chest wall RT and IMN RT concurrently administered with trastuzumab, we reviewed studies describing the relationship between the occurrence of CEs, including ischemic heart disease, valvular disease, and congestive heart failure (CHF), and RT doses to the heart, coronary arteries, and ventricles. We present this article in accordance with the Narrative Review reporting checklist (available at https://tro.amegroups.com/article/view/10.21037/tro-22-18/rc).

Methods

Most patients with HER2-positive EBC are treated with anthracycline-containing regimens in the neoadjuvant and adjuvant settings. Considering that the combination of anthracyclines and trastuzumab may increase the risk of cardiotoxicity, trastuzumab has been administered alone, in combination with taxanes, or concurrent with RT after anthracycline-containing regimens (28-30). Because anthracyclines induce a dose-dependent and dose-accumulative cardiotoxicity, in this way, data should be interpreted carefully in patients with HER2-positive EBC who received RT with concurrent trastuzumab.

We searched the PubMed database for English-language articles of prospective and retrospective studies describing the relationship between CEs and concurrent treatment with trastuzumab and RT for HER2-positive EBC. In addition, the use of chemotherapy regimens with doxorubicin or epirubicin in these patients were included in this review process, particularly, accumulated-dose information. This review article summarizes the CEs reported in selected articles published between January 2005 and December 2022. We used the following key terms for the literature search: “LVEF”, “CHF”, “ischemia”, “diastolic function”, “myocardial abnormality”, “valvular abnormality”, “breast cancer”, “HER2-positive”, “early-stage”, “trastuzumab”, “radiotherapy”, “regional lymph node”, “left side”, “taxanes”, “doxorubicin”, and “epirubicin”. This review article provides information on CEs, doses, and schedules of trastuzumab administration, doses and fractions of RT, irradiated fields, and RT techniques.

Herein, we summarize the incidence of CEs, defined as conditions characterized by decreased LVEF, in patients with HER2-positive EBC concurrently treated with trastuzumab and RT in prospective and retrospective studies. In addition to decreased LVEF, we also briefly assessed ischemic heart disease, CHF, diastolic dysfunction, myocardial abnormalities, valvular abnormalities, and MHD in patients concurrently treated with locoregional RT and trastuzumab. The results of prospective and

retrospective studies on LVEF-related CEs and non-LVEF-related CE parameters in patients with HER2-positive EBC concurrently treated with locoregional RT and trastuzumab are described below.

Key content and findings

CEs resulting from concurrent trastuzumab and left breast RT in randomized trials and prospective studies

Halyard *et al.* investigated cardiac adverse effects in patients with HER2-positive breast cancer who participated in the N9831 clinical trial. Their results revealed that among 1,938 patients, of whom 1,418 (73.2%) underwent adjuvant RT and 450 (23.2%) did not undergo RT, the cumulative incidence of CEs (defined as symptomatic CHF, definite cardiac death, or probable cardiac death) was significantly higher in patients who received adjuvant doxorubicin plus cyclophosphamide followed by weekly paclitaxel followed by sequential trastuzumab or those who received doxorubicin plus cyclophosphamide followed by paclitaxel plus trastuzumab followed by sequential trastuzumab than in those who received doxorubicin plus cyclophosphamide followed by paclitaxel (31). In addition, their results revealed that RT concurrently used with trastuzumab did not affect the risk of CEs, as the cumulative incidence of CEs in the doxorubicin plus cyclophosphamide-paclitaxel-trastuzumab arm was similar between the RT and no RT groups (2.7%). In contrast, in the concurrent chemotherapy and trastuzumab arm (doxorubicin plus cyclophosphamide-paclitaxel plus trastuzumab-trastuzumab), the cumulative incidence of CEs in the RT and no RT groups was 1.7% and 5.9%, respectively. Notably, the 3-year incidence of CEs did not differ between the left-sided and right-sided RT groups. However, the median follow-up of patients was short (3.7 years), during which CEs may not have yet occurred. After a long-term follow-up (9.2 years) of patients included in the N9831 trial, Advani *et al.* reported that the cumulative incidence of 6-year CEs in the doxorubicin plus cyclophosphamide-paclitaxel, doxorubicin plus cyclophosphamide-paclitaxel plus trastuzumab, and doxorubicin plus cyclophosphamide-paclitaxel plus trastuzumab-trastuzumab arms was 0.6%, 2.8%, and 3.4%, respectively (32). In patients who received trastuzumab-containing regimens in the N9831 trial, older age, LVEF <65%, and hypertension were risk factors for the development of CEs. However, RT was not associated with the occurrence of CEs in univariate analysis. The incidence of CEs in the N9831 trial may be lower during a follow-up period of <10 years because CEs can occur after 10 years from RT exposure (33).

Procter *et al.* analyzed CEs in patients included in the observation and 1-year adjuvant trastuzumab arms of the HERA trial. Their results revealed that the proportion of patients with significantly decreased LVEF was higher in the trastuzumab group than in the observation group (3.6% *vs.* 0.6%) at a median follow-up of 3.6 years (34) (*Table 1*). However, the proportion of patients with severe CHF was not different between the trastuzumab and observation arms (0.8% *vs.* 0%). Among 73 patients with severe CHF or significantly decreased LVEF, 59 (81%) patients in the trastuzumab arm had recovered cardiac function. In the HERA trial, RT was used in 72.7% of patients in the 1-year trastuzumab arm and in 75.3% of patients in the observation arm.

Caussa *et al.* prospectively analyzed the cardiotoxicities in patients with EBC treated with concurrent adjuvant trastuzumab and RT by assessing LVEF before RT, immediately after RT, and 4–6 months after RT (35). In their study, IMN irradiation was performed in 88 of 106 (83%) patients (chest wall irradiation was mainly performed using the electron technique) and anthracycline-based adjuvant chemotherapy was administered to 92% of patients. Among the 106 total patients, 6 developed grade ≥2 left ventricular systolic dysfunction (LVSD), including 4 patients with reversible symptomatic CEs and 2 patients with asymptomatic CEs, after a median follow-up of 28 months (range, 14–60 months) (*Table 1*).

In a French single-center prospective study that assessed clinical outcomes and impaired LVEF (LVEF <55%, as evaluated using echocardiography or myocardial scintigraphy) in patients with HER2-positive EBC concurrently treated with adjuvant trastuzumab (administered every 3 weeks) and RT, Jacob *et al.* reported that 26 (8.4%) patients had impaired LVEF [grade 1, n=17; grade 2, n=7; grade 3, n=2; according to Common Terminological Criteria for Adverse Events (CTCAE) version 3.0] after the completion of RT (36) (*Table 1*). Importantly, among these 26 patients, 20 showed LVEF recovery, with a median time to recovery of 13.1 months (range, 0.7–43.4 months) after RT completion. In this prospective study, 193 patients underwent whole-breast RT (50 Gy in 25 fractions; 182 patients also received a tumor-bed boost of 16 Gy in 8 fractions) and 115 patients underwent chest wall RT (50 Gy in 25 fractions). Irradiation of the locoregional field (46 Gy in 23 fractions), including

Table 1 CEs reported in patients with EBC who received concurrent trastuzumab and locoregional RT

Authors	Number of RT[†]	Median follow-up	LVEF	CHF
Halyard *et al.* (31)	522	3.7 y	No report	AC-T-H: 2.7%
	413			AC-TH-H: 1.7%
Procter *et al.* (34)	1,682 (72.7% RT)	3.6 y	Decrease 3.6%	Severe CHF 0.8%
Caussa *et al.* (35)	106	28 m	≥ Gr 2 decrease 5.6%	No report
Jacob *et al.* (36)	308	52 m	Gr 1 to 3 8.4% (IMN RT: 73.7%)	1.0%
Belkacémi *et al.* (37)	146	16 m	≥ Gr 2 decrease 10%	HERA criteria
				Impairment: 6%
Shaffer *et al.* (38)	95	15 m	Mean absolute decrease: 4%	4.5%
Meattinii *et al.* (39)	95	4.3 y	Median decrease: 7%	1.1%
Cao *et al.* (40)	64	LVEF: 6.7 m	Gr 1: 7.8%	0%
		Cardiac function: 26 m		
Bian *et al.* (41)	Rt sided RT: 41	45 m	Mean absolute decrease 5.6%	0%
	Lt sided RT: 47		Mean absolute decrease 3.1%	
Sayan *et al.* (42)	Hypofractionated	36 m	Gr 1: 7%	0%
	RT: 41			
	Conventional RT	32 m	Gr 1: 5%	
	RT: 100			
Grela-Wojewoda *et al.* (43)	Total: 130	N/A	Gr 2: 7.7%	0%
	RT: 102			

[†], number of RT: the number of patients who were evaluated for CEs after receiving concurrent trastuzumab and RT. Grade 1 LVEF alteration: 50%≤ LVEF <60%; grade 2 LVEF alteration: 40%≤ LVEF <50%, according to the Common Terminology Criteria for Adverse Events version 3.0. HERA criteria: LVEF declined by ten points or more compared to baseline, or LVEF strictly below 50%. CEs, cardiac events; EBC, early-stage breast cancer; RT, radiotherapy; LVEF, left ventricular ejection fraction; CHF, congestive heart failure; y, years; m, months; AC, doxorubicin and cyclophosphamide; T, paclitaxel; H, trastuzumab; IMN, internal mammary node; Gr, grade; HERA, Breast International Group 01-01; Rt, right side; Lt, left side; N/A, not available.

supraclavicular and IMN irradiation, was performed in 227 of 308 (73.7%) patients who underwent RT. In addition, concurrent trastuzumab and RT resulted in a 4-year locoregional control rate of 95% and an OS rate of 98%, and the treated breast site (left-sided RT, P=0.655) and IMN irradiation (P=0.213) were not associated with impaired LVEF in univariate analysis. These results indicate that concurrent treatment with trastuzumab and locoregional RT results in a lower incidence of CEs and reversible LVEF reduction after a median follow-up of >4 years.

CEs resulting from concurrent trastuzumab and left breast RT in retrospective studies

Belkacémi *et al.* performed a retrospective analysis of 146 patients with stage II–III HER2-positive breast cancer who received weekly (23%) or three-weekly trastuzumab, among whom 103 (71%) patients underwent IMN RT in addition to adjuvant breast or chest wall RT. In this study, 10% of patients had ≥ grade 2 decreased LVEF (40%≤ LVEF <50%, according to CTCAE version 3.0) and 6% of patients had impaired LVEF (LVEF decrease of ≥10% from baseline or LVEF strictly <50%, according to the HERA criteria) (37) (*Table 1*). Further multivariate analysis showed that weekly trastuzumab administration was a prognostic factor for LVEF reduction (P=0.04 based on CTC version 3.0, P=0.004 based on the HERA criteria). However, irradiation of regional sites, including the supraclavicular fossa or the IMN area, was not associated with CEs.

In another study that investigated CEs in patients treated

with adjuvant trastuzumab with (n=44) or without (n=11) RT, Shaffer *et al.* observed that left-sided IMN RT did not increase the occurrence of LVEF impairment; however, 11 (18.6%) patients discontinued trastuzumab (5 patients underwent left-sided RT) because of decreased LVEF after a short median follow-up of 15 months (38) (*Table 1*). Although this study did not mention the percentage decrease in LVEF, the mean LVEF was reported to have increased from 46%±5.3% to 56%±6.2% after the discontinuation of trastuzumab. Three patients developed clinical CHF; however, none of them underwent left-sided RT (38). Meattini *et al.* analyzed 95 patients with stage I–III HER2-positive breast cancer treated with concurrent trastuzumab (administered every 3 weeks) and RT. They reported that 58 (61.1%) patients had LVEF dysfunction, with a median LVEF decrease from baseline of 10% at the end of trastuzumab administration and 7% at the last follow-up, during a median follow-up of 4.3 years (39) (*Table 1*). However, in this study, 48 patients (50.5%) underwent left-sided RT, 29 patients (30.5%) underwent electron beam RT of the chest wall, and only 1 patient underwent IMN RT. The chest wall electron technique, especially left-sided irradiation, has been reported to be potentially associated with a 10% incidence of LVSD.

Cao *et al.* analyzed 45 patients with HER2-positive EBC treated with RT and a trastuzumab-based regimen after BCS and mastectomy, and further investigated the association between the MHD from RT and acute CEs [defined according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0] in these patients (44). They reported that among 24 patients who underwent left-sided RT, the MHD was significantly higher in patients with CEs [a significant decrease in LVEF (>10%), defined as ≥ grade 1] than in those without CEs (10.14 *vs.* 6.27 Gy, P=0.03). All patients were treated with doxorubicin-based regimens, and the baseline toxicity was similar between patients who underwent left-sided RT and those who underwent right-sided RT. In addition, the MHD from left-sided and right-sided RT was 6.92 and 3.27 Gy, respectively. Furthermore, the same group retrospectively analyzed the changes in LVEF, according to NCI-CTC version 2.0, in 64 patients concurrently treated with trastuzumab and RT and 73 patients treated with RT alone. They reported that the incidence of grade 1 LVEF dysfunction (asymptomatic decrease in LVEF by at least 10% but < 20% from baseline) was 7.8% in the combination arm and 4.1% in the RT alone arm (P=0.473) (40) (*Table 1*). Furthermore, multivariate analysis revealed that the IMN RT field was significantly correlated with LVEF dysfunction in patients treated with concurrent trastuzumab and left-sided RT. In addition, the MHD and absolute value of V10 (heart volume receiving a dose of at least 10 Gy) in the left ventricle were significantly associated with the development of left ventricular dysfunction (40).

Bian *et al.* retrospectively assessed the association between LVEF and heart dose from RT among 88 patients with HER2-positive EBC treated with concurrent trastuzumab and breast or chest wall RT, and reported that doxorubicin therapy (P=0.013) and left-sided RT (P=0.088) were two important factors that affected the changes in LVEF (41). In their study, patients who underwent left-sided RT had a mean LVEF change of –3.1% (lowest posttreatment LVEF minus baseline LVEF) and those who underwent right-sided RT had a mean LVEF change of –5.6%, whereas the MHD from RT in patients who underwent left-sided and right-sided RT was 3.6% and 1.1%, respectively (P<0.001) (*Table 1*). In addition, the percentage heart volume that received at least 5 or 10 Gy did not correlate with the changes in LVEF. These findings indicate that when the MHD from RT was <4 Gy, reduction in LVEF or heart RT dose was not associated with the use of left-sided RT.

In a retrospective analysis of 3,321 patients with HER2-positive EBC included in the HERA trial (trastuzumab for 1 or 2 years, with and without RT), Bachir *et al.* observed that the occurrence of cardiotoxicity (defined as a 10% decrease in LVEF or an absolute LVEF value of <50%, as assessed using echocardiography) did not differ among patients who underwent left-sided RT (9.18%), those who underwent right-sided RT (8.99%), and those who did not undergo RT (8.8%) (P=0.073) (45). In addition, cardiovascular events, defined as conditions characterized by a diagnosis of acute myocardial infarction, were rare in all three groups, with an incidence of <1.1% in all groups. This result is in line with two previous reports that showed that left-sided RT was not associated with an increased risk of LVEF impairment in patients treated with trastuzumab (38,41). A possible reason for this finding is that most patients who participated in the HERA clinical trial underwent RT using the three-dimensional technique.

In patients with EBC, several randomized trials have demonstrated that hypofractionated whole-breast irradiation results in similar LRR and OS rates to conventional whole-breast irradiation (46-49). In addition, RT-related potential adverse effects, such as rib fracture, pulmonary fibrosis, breast shrinkage, breast tightening, and cosmesis issues, did not differ between hypofractionated and conventional RT

in patients with EBC according to meta-analyses of several randomized trials (46-49). However, hypofractionated RT resulted in less acute skin radiation toxicity, breast pain, edema, and telangiectasia compared with conventional fractionated RT. With regard to the cardiotoxicities reported in the aforementioned randomized trials and meta-analyses, only two randomized trials (START A and B trials) analyzed cardiac ischemia in patients who underwent bilateral or left-sided RT and showed no differences between conventional fractionated RT and hypofractionated RT after 5 years of follow-up (47). Haviland *et al.* analyzed 4,452 patients who participated in the START A and B trials and reported that hypofractionated RT was not different from conventional fractionated RT in terms of the occurrence of ischemic heart disease after a median follow-up of 9.3 years (50). However, most patients who participated in the START A and B trials were treated with endocrine therapy, whereas a few patients were treated with chemotherapy or combined chemotherapy and endocrine therapy, but not with trastuzumab.

Considering the increasing use of hypofractionated RT as a routine clinical method for patients with EBC, including HER2-positive EBC, assessment of the relationship between cardiotoxicity and concurrent trastuzumab and hypofractionated RT, especially left-sided RT, is warranted in these patients. However, only a few retrospective studies have investigated this issue. For example, Bonzano *et al.* retrospectively analyzed the occurrence of cardiotoxicity (defined according to CTCAE version 3) in 52 patients who underwent different hypofractionated RT regimens concurrent with trastuzumab and reported that grade 2 cardiotoxicity occurred in 2 of 15 (13%) patients who received 46 Gy in 20 fractions, 0 of 16 (0%) patients who received 39 Gy in 13 fractions, and 1 of 21 (5%) patients who received 35 Gy in 10 fractions after a median follow-up of 5 years (51). Sayan *et al.* investigated whether changes in LVEF, as assessed using echocardiography or multiple-gated acquisition (MUGA) scanning before and every 3 months during trastuzumab administration, differed between 41 patients who underwent hypofractionated RT and 100 patients who underwent conventional fractionated RT (42). Among them, 3 (7%) and 5 (5%) patients who underwent hypofractionated and conventional fractionated RT, respectively, showed a significant asymptomatic decrease in LVEF (P=0.203), defined as an absolute decrease in LVEF of ≥10% below the lower limit of normal or ≥16% from the baseline value (*Table 1*). However, no patient (either in the hypofractionated or conventional fractionated RT group) developed symptomatic CHF.

In a subgroup of analysis of 727 patients treated with hypofractionated whole-breast RT, De Santis *et al.* reported that patients who received chemotherapy (an anthracycline and a taxane, followed by cyclophosphamide, methotrexate, and fluorouracil) and trastuzumab (n=51) had a significantly higher risk of grade ≥1 CEs than those who received chemotherapy alone (n=125) (15.7% *vs.* 7.9%) (52). The association between trastuzumab administration and concurrent use of hypofractionated RT, particularly left-sided RT and IMN RT, in patients with HER2-positive EBC needs to be further investigated.

Non-LVEF-related CE parameters in patients treated with concurrent trastuzumab and RT

LVEF is the most commonly assessed parameter to detect CEs in patients with breast cancer treated with chemotherapy or RT; however, few studies have examined other CE parameters in patients treated with concurrent trastuzumab and RT (53,54). Considering that LVEF dysfunction may not be a sensitive parameter for detecting minor cardiac damage, some studies have suggested that left ventricular diastolic dysfunction (LVDD) may serve as an early sign of CEs in cancer patients treated with chemotherapy (55,56). In a retrospective study investigating the association between LVDD and heart dose from RT in patients with EBC who had normal baseline left ventricular diastolic function and underwent RT with or without concurrent trastuzumab, Cao *et al.* reported that LVDD, defined as E (maximum early diastolic mitral flow velocity)/Em (early diastolic mitral annular velocity) ≥15, occurred in 11 of 29 (37.9%) patients who were treated with concurrent trastuzumab and left-sided RT, 8 of 25 (32%) patients who were treated with concurrent trastuzumab and right-sided RT, and in 12 of 61 (19.7%) patients who were treated with left-sided RT alone (57). In a further analysis of the RT dose to the left ventricle in patients who were treated with concurrent trastuzumab and left-sided RT, Cao *et al.* observed that the mean dose, minimum dose reaching relative volume levels ranging from 15% to 70% (D15–D70), and relative heart volume receiving dose levels ranging from 3 to 7 Gy (V3–V7) were higher in patients who developed LVDD than in those who did not (P<0.05) (57). In another study that investigated LVDD (using echocardiography) and LVSD (using MUGA scanning) in patients treated with a trastuzumab-based therapy, Klein *et al.* observed that LVDD can be detected before the

development of LVSD (58). These findings suggest that LVDD may serve as a sensitive parameter for predicting the subsequent development of LVSD in patients with EBC treated with concurrent left-sided RT and trastuzumab and that the RT dose to the left ventricle may be associated with the development of LVDD in these patients.

Yu *et al.* analyzed the systolic and diastolic functions of the left ventricle and the levels of circulating high-sensitivity troponin I (hsTnI) before RT, immediately after RT, and 6 months after RT in patients with HER2-positive EBC treated with an anthracycline-based therapy, trastuzumab, and RT using modern techniques, including conformal three-dimensional RT and intensity-modulated RT. They observed that the MHD was not different between patients who underwent left-sided RT and those who underwent right-sided RT [1.8±1.5 (n=26) *vs.* 1.1±1.3 Gy (n=21)] (59). Furthermore, although decreased LVEF was observed, left ventricular diastolic function was not reduced in the post-RT echocardiographic examination compared with the pre-RT level. However, the changes in LVEF and LVDD were not different between 6 months after RT and before RT. The median hsTnI levels also decreased after RT when compared with before RT [before RT *vs.* after RT: 5.7 (3.0–8.7) *vs.* 3.7 (2.0–5.9) pg/mL]. These findings suggest that early LVDD rarely occurs in patients concurrently treated with trastuzumab and RT using modern techniques.

Abouegylah *et al.* retrospectively analyzed the relationship between RT dose to the cardiac organs (including the heart, each heart chamber, and the left anterior descending artery) and CEs (including cardiac ischemia, arrhythmias, heart failure, wall motion abnormalities, and LVEF dysfunction) in 202 patients treated with trastuzumab and RT. They observed that left-sided RT was significantly associated with the occurrence of arrhythmias (14.2% *vs.* <1%, P<0.001) and cardiac ischemia [10/106 (9.4%) *vs.* 1/96 (0.1%), P=0.011] (53). Abouegylah *et al.* also showed that equivalent uniform doses to the left ventricle (P=0.037), right ventricle (P=0.023), and left anterior descending artery (P=0.049) were significantly associated with a >10% decrease in LVEF in these patients (53). These findings indicate that in addition to decreasing the LVEF, concurrent treatment with left-sided RT and trastuzumab may increase the risk of arrhythmias and ischemia.

In addition to assessing LVEF dysfunction (>10% decrease in LVEF) using echocardiography and MUGA scanning, Nack *et al.* investigated new cardiac abnormalities, including myocardial abnormalities (atrial or ventricular dilation, hypertrophy, hypokinesis, and impaired relaxation) and valvular abnormalities (thickening or stenosis of the valve leaflets) in 110 patients treated with trastuzumab and RT using modern techniques (60). In their analysis, left-sided RT was significantly associated with the risk of new cardiac abnormalities, including myocardial and valvular abnormalities, compared with right-sided RT, whereas the incidence of LVEF dysfunction in patients who underwent left-sided RT (9.6%) was not significantly different from that in patients who underwent right-sided RT (2.1%) (P=0.207). Notably, an MHD of >2 Gy was significantly associated with new cardiac abnormalities, and the MHD from left-sided and right-sided RT was 3.13 and 0.45 Gy, respectively. In addition to the MHD, the percentage of heart volume that received at least 20, 30, or 40 Gy was significantly associated with new cardiac abnormalities (60).

López-Sendón *et al.* prospectively analyzed the incidence of cardiotoxicity, defined as new or worsening myocardial damage or ventricular dysfunction, in 865 patients who received anticancer therapy and underwent regular echocardiographic follow-ups according to three parameters, including biomarkers, left ventricle dysfunction (LVD), and symptomatic heart failure, revealed that 31.6% of the patients had mild cardiotoxicity [abnormal high-sensitivity troponin T and N-terminal brain natriuretic propeptide (NT-proBNP) levels but LVEF ≥50%], 2.8% had moderate cardiotoxicity (left ventricular dysfunction with an LVEF of 40–49%), and 3.1% had severe cardiotoxicity (LVEF ≤40% or symptomatic heart failure) after a median follow-up of 24 months (61). In their study, anthracyclines caused mild (33.8%), moderate (2.7%), and severe (3.1%) cardiotoxicity in 731 patients, whereas the use of anti-HER2 agents resulted in mild (37.3%), moderate (5.6%), and severe (0.6%) cardiotoxicity in 177 patients. However, anthracyclines and anti-HER2 agents caused mild (38.6%), moderate (6.4%), and severe (0.7%) cardiotoxicity in 140 patients. These results indicate that in addition to LVEF evaluation, the assessment of biomarkers is useful in monitoring cardiac function in patients treated with highly cardiotoxic anticancer therapies, such as anthracyclines and trastuzumab. Assessment of the blood markers (high-sensitivity troponin T and NT-proBNP) may help physicians in monitoring cardiotoxicity in patients with EBC who were concurrently treated with trastuzumab and RT.

Grela-Wojewoda *et al.* assessed the association of biomarkers, including NT-proBNP, creatine kinase-MB (CK-MB), and myoglobin, and clinical factors with cardiotoxicity in 130 patients with EBC treated with adjuvant trastuzumab (102 patients treated with RT and 128 patients treated with

anthracyclines) and reported that trastuzumab therapy was withheld in 24 (18.5%) patients (14 patients discontinued and 10 patients resumed trastuzumab therapy) (43). Among them, 10 patients (7.7%) experienced cardiotoxicity, defined as a >10% decrease in LVEF or an absolute LVEF value of <50% (*Table 1*). In their analysis, the use of RT was significantly associated with decreased LVEF, whereas the NT-proBNP, CK-MB, and myoglobin levels did not correlate with the occurrence of cardiotoxicity in the studied patients.

Incidence of cardiotoxicity in patients treated with concurrent trastuzumab plus pertuzumab and RT

In a retrospective study of 55 patients with HER2-positive EBC treated with pertuzumab and trastuzumab combined with locoregional RT at a biological equivalent dose of at least 40 Gy (median dose of 50 Gy), Aboudaram *et al.* observed that the mean difference in LVEF between after RT and before chemotherapy was –2.43% (62). In their study, most patients received taxane-based chemotherapy regimens (70.2%) and 14.5% patients received epirubicin. None of the patients had a >10% decrease in LVEF or an absolute LVEF value of <55% after RT, and left-sided and right-sided RT did not differ in terms of LVEF reduction.

Zhang *et al.* analyzed cardiotoxicity, defined as a >10% decrease in LVEF at follow-up when compared with the baseline value, in 420 patients with HER2-positive EBC treated with trastuzumab alone or trastuzumab with pertuzumab. They reported that 67 (15.9%) patients had cardiotoxicity; however, most patients had no symptoms of cardiac failure (63). In their analysis, older age, history of coronary heart disease, use of left chest wall RT, and sequential anthracycline therapy were significantly associated with the incidence of cardiotoxicity in the studied patients.

Conclusions

According to prospective and retrospective studies that investigated the administration of trastuzumab concurrently with adjuvant RT in patients with HER2-positive EBC, left-sided RT or IMN RT may cause more CEs (defined according to LVEF) than right-sided RT or trastuzumab alone. MHD remains an important parameter that is significantly associated with LVEF reduction. However, the reported incidence of CEs should be interpreted with caution because of the diverse follow-up periods and different RT techniques used in the above-mentioned studies. Modern RT techniques, such as intensity-modulated RT, volumetric-modulated arc therapy, and deep-inspiration breath-hold technique, result in lower RT doses to the heart (including MHD and V10) and a relatively lower incidence of CEs than conventional RT techniques (64). However, it is difficult to conclude that the concurrent use of modern RT techniques and trastuzumab therapy can truly decrease cardiotoxicity and that new parameters such as LVDD, arrhythmias, and myocardial and valvular abnormalities are better CE parameters than LVEF. More systematic reviews focusing on the relationship between cardiotoxicity and LVEF, LVDD, MHD, V10, and myocardial and valvular abnormalities in patients with HER2-positive EBC concurrently treated with trastuzumab and RT using modern techniques, especially IMN irradiation and left-sided RT, are warranted.

Although many studies have suggested that LVEF is a surrogate indicator of cardiac function, some cardiac abnormalities resulting from concurrent treatment with trastuzumab and RT may not be reflected by LVEF changes. Several studies have demonstrated that LVDD may precede LVEF dysfunction, and the development of arrhythmias and myocardial and valvular abnormalities may correlate with the RT dose to the heart. These factors can serve as new parameters for monitoring CEs in patients treated with concurrent trastuzumab and RT. Further prospective studies and long-term clinical follow-up of these new cardiac parameters, in addition to LVEF, are warranted in patients with HER2-positive EBC concurrently treated with RT using modern techniques and trastuzumab. Moreover, further studies on new HER2-targeting agents, such as pertuzumab, trastuzumab emtansine and trastuzumab deruxtecan, are required.

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Footnote

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