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CLINICAL INVESTIGATION

Evaluation of Cardiotoxicity in HER-2-Positive Breast Cancer Patients Treated With Radiation Therapy and Trastuzumab

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Purpose: Trastuzumab is associated with cardiac dysfunction in patients with human epidermal growth factor receptor 2 (HER-2)−positive breast cancer. The current study examines the effect of radiation therapy (RT) on cardiotoxicity in this patient population.

Methods and Materials: The Herceptin Adjuvant (HERA) trial is a phase 3 prospective, randomized clinical trial that established the efficacy of trastuzumab in HER-2−positive breast cancer. The current study is a retrospective analysis of 3321 trial patients treated with trastuzumab, with or without RT. Cardiac function was closely monitored over a median follow-up period of 11 years. The primary endpoint of the current study was to determine the effect of RT on left ventricular ejection fraction (LVEF) and the occurrence of cardiovascular events.

Results: Patients were divided into 3 groups: 1270 patients received trastuzumab and left-sided RT (group 1); 1271 patients received trastuzumab and right-sided RT (group 2); and 780 patients received trastuzumab with no RT (group 3). The incidence of decline in LVEF documented by echocardiography was 9.18%, 8.99%, and 8.80%, respectively, with no significant differences among the 3 groups (P = .073). The incidence of cardiovascular events was low in all groups, with the lowest incidence noted in group 3 (0.62%) followed by group 2 (0.92%) and group 1 (1.08%) (P = .619). Univariate and multivariate competing-risks regression showed that left-sided and right-sided RT delivery did not significantly increase the risk of LVEF decline or cardiovascular events.

Conclusions: Our analysis of the HERA trial suggests that RT does not significantly increase the risk of cardiotoxicity in HER-2−positive breast cancer patients treated with trastuzumab. Continued monitoring of patients is needed to investigate late effects of contemporary treatments for breast cancer patients.

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Introduction

Patients with human epidermal growth factor receptor 2 (HER-2)−positive breast cancer often receive trastuzumab in the adjuvant or preoperative setting as part of their treatment plan.[1,2] Trastuzumab, a monoclonal antibody that antagonizes the HER-2 extracellular domain,[3] decreases locoregional and distant recurrences and is associated with improved overall survival.[4-6]

However, this treatment comes with a side-effect profile that includes cardiotoxicity,[7-9] mainly in the form of declining left ventricular ejection fraction (LVEF), and less commonly congestive heart failure (CHF).[10] An analysis done by de Azambuja et al[11] showed that there is a low incidence of cardiac events associated with trastuzumab in patients with HER-2−positive breast cancer.

Radiation therapy (RT) is an essential component of comprehensive management of HER-2−positive breast cancer.[12] It effectively reduces locoregional recurrence and breast cancer related mortality.[12-15] However, chest RT for breast cancer is known to cause cardiac side effects.[16-20] RT for breast cancer (especially left sided) was shown to increase the incidence of ischemic heart disease due to damage to the coronary vessels,[16] and a modest decline in the LVEF due to damage to the myocardium.[21] To minimize cardiac side effects of RT, modern techniques have been developed to limit the dose to the heart during chest irradiation.[22] One such technique is deep inspirational breath holding (DIBH).[23,24] Another advancement in RT is proton therapy, which has shown lower radiation doses to the heart compared with photons.[23,25-27]

To date, there are no large studies evaluating the additive cardiotoxicity of RT and trastuzumab in patients with HER-2−positive breast cancer. Therefore, the analysis of clinical data from the Herceptin Adjuvant (HERA) trial, which includes 5099 patients who were followed up for more than 10 years, would be ideal to answer this question.[4,6] The current analysis addresses the potential cardiotoxicity of RT in patients with HER-2−positive breast cancer treated with trastuzumab.

Methods and Materials

Study population

This study is a retrospective analysis of data collected in the framework of a prospective clinical trial. Clinical data were collected from the HERA trial, creating a nested cohort of 3321 patients who received trastuzumab with or without RT.[6] Access to the HERA trial data was granted by Vivli.

The full description of the HERA trial is found in the original publication.[6] In brief, the HERA (BIG 1-01/BO16348) trial is an international, intergroup, phase 3 clinical trial that originally aimed at studying the efficacy and safety of trastuzumab in HER-2−positive breast cancer. The trial enrolled 5099 female patients of all ages, with HER-2−positive breast cancer between December 2001 and March 2005. Patients with T4 tumors, supraclavicular nodes, or distant disease were excluded. Patients completed locoregional therapy with surgery with or without adjuvant RT before study entry. Patients completed a minimum of 4 courses of chemotherapy and were assigned randomly into either observation or 1 year or 2 years of trastuzumab in a 1:1:1 ratio. Patients were followed up for a median follow-up of 11 years.[4,6,28]

Figure 1 shows the flow diagram of the nested cohort in the current study. Eligible patients were females with HER-2−positive breast cancer treated with 1 or 2 years of trastuzumab. Patients who were assigned to the observation arm (no trastuzumab) were excluded. In addition, patients who received both left-sided and right-sided RT were excluded. Patients were divided into 3 groups based on the receipt and laterality of RT as follows: group 1 included patients treated

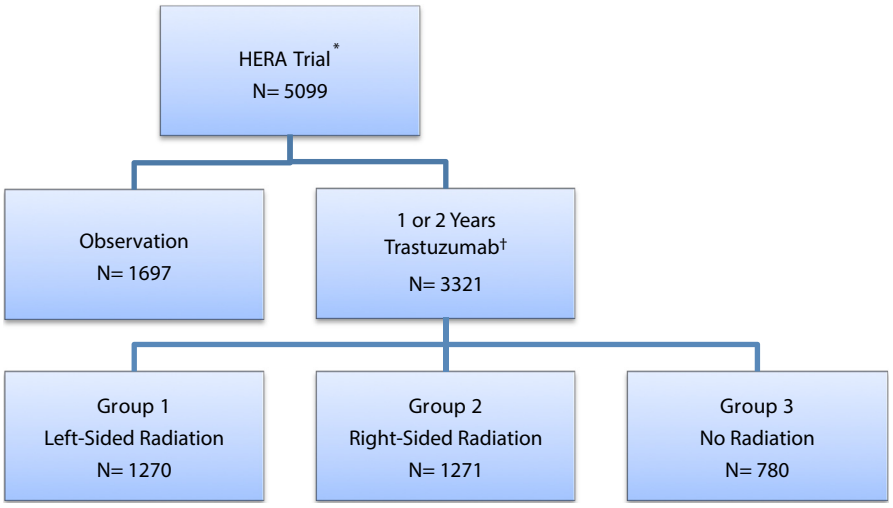

Fig. 1. Flow diagram showing the study's nested cohort within the Herceptin Adjuvant trial. *HERA trial = Herceptin Adjuvant trial. †Excluding patients who received both left-sided and right-sided radiation.

with trastuzumab and left-sided RT (n = 1270); group 2 included patients treated with trastuzumab and right-sided RT (n = 1271); and group 3 included patients who received trastuzumab without RT (n = 780).

Follow-up

All patients adhered to the same schedule of follow-up visits, during which the symptoms, side effects (graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0), and clinical examination findings every 3 months and hematological and chemistry tests every 6 months were recorded for the first 2 years after randomization. Thereafter, clinical and laboratory assessments were scheduled to occur every 6 months for years 3 to 5 and then once each year up to year 10. A yearly chest radiography was required up to year 5 and annual mammography up to year 10. Study visits for individual patients continued for 10 years after randomization with full recording of any breast cancer recurrences, contralateral breast cancer, etc. Adverse events, such as cardiac endpoints, were also collected.[4]

Cardiac monitoring in all 3 groups included clinical assessments and measurements of LVEF by either echocardiography or multiple-gated acquisition scanning at baseline; at months 3, 6, 12, 18, 24, 30, and 36; and annually thereafter up to 10 years from randomization.[4]

Outcomes

This study evaluates the cardiotoxicity of RT in HER-2−positive patients treated with trastuzumab through 2 main endpoints. The first is the decline in LVEF documented by echocardiography, as a decline of at least 10 percentage points from baseline, and to an absolute LVEF less than 50%, similar to prior reports.[11] The other main endpoint is the development of cardiovascular events (CVEs), defined as any form of ischemic heart disease, acute coronary syndrome (ACS), myocardial infarction, or death from ischemic heart disease. Angina and stenting procedures not for ACS were not included. Secondary outcomes included the development of CHF and death due to a CVE.

Statistical analysis

Univariate descriptive analysis was conducted to describe the current cohort. Categorical variables are presented as frequencies and percentages. Continuous variables are presented as mean ± standard deviation. Unadjusted and adjusted competing risks survival regression, based on Fine and Gray's proportional subhazards model, was conducted to measure the association between RT and the development of cardiovascular outcomes, while taking into account the competing risk events, that is, any reason that precludes the occurrence of the outcomes of interest such as death. In particular, for the outcome of CVEs, which includes death attributable to CVE, competing risk events such as death were classified as being attributable to reasons other than CVE. Additionally, cases that refused treatment, discontinued participation, changed treatment, and other related reasons for premature withdrawal were censored. Cases that previously developed the outcomes of interest before the start time of the study were excluded. In competing-risks regression, the cumulative incidence function is reported, which indicates the probability of the event of interest happening before a given time. Study adjustment variables included in the multivariable analysis were dependent on statistical significance in the univariate analyses, as well as based on expert opinion and literature review. Covariates that showed a significant association with $P < .2$ at the bivariate level (ie, unadjusted model) were included in the multivariable model. Statistical significance was set at an alpha of 5% for a 2-sided P value. All statistical analyses were done using STATA 16.1 (StataCorp).

Results

Population characteristics

Of the 5099 patients enrolled in the HERA trial, 3321 patients met the inclusion criteria for the current analysis (Fig. 1). Median follow-up was 11 years. Table 1 presents the baseline characteristics of patients, tumors, and treatments. In our cohort, 1270 patients (38.2%) received left-sided radiation, 1271 patients (38.3%) received right-sided radiation, and 780 (23.5%) patients received no radiation. Mean age was similar among the 3 groups (49.22, 48.71, and 49.55 years for groups 1, 2, and 3, respectively) with a similar percentage of patients older than 55 years of age (28.43%, 26.67%, and 26.28%, respectively). Compared with group 3, patients in groups 1 and 2 had a slightly higher body mass index, larger tumors and received more chemotherapy. The duration of trastuzumab receipt was similar across the 3 groups. RT fractionation data were available on nearly one-half of the subjects. Conventional fractionation was used in most cases (88% in group 1 and 89% in group 2). On the other hand, baseline cardiovascular risk factors such as smoking, hyperlipidemia, hypertension, coronary artery disease, family history of heart disease, and chronic obstructive pulmonary disease were also similar among the 3 groups (Table 1). The groups also had similar baseline LVEF (64.28%, 64.29%, and 64.04%, respectively).

LVEF decline

Table 2 shows the frequency and percentage of patients in each group who developed a decline in LVEF, which was defined similar to prior studies as a decline of at least 10 percentage points from baseline and to an absolute LVEF less than 50%.[11] In group 1, 9.18% developed a LVEF decline,

Table 1 Population characteristics

	Group 1 (left RT), n = 1270 (%)	Group 2 (right RT), n = 1271 (%)	Group 3 (no RT), n = 780 (%)	*P* value
Race				<.001
White	1114 (87.72)	1108 (87.18)	553 (70.90)	
Black	6 (0.47)	4 (0.31)	4 (0.51)	
Asian	2 (0.16)	1 (0.08)	0 (0)	
Other	148 (11.65)	158 (12.43)	223 (28.59)	
Hormone receptor				.037
ER− and/or PR−	609 (48.95)	580 (46.47)	403 (52.34)	
ER+ and/or PR+	635 (51.05)	668 (53.53)	367 (47.66)	
Tumor size, mm				<.001
0-20	543 (43.76)	556 (43.75)	336 (43.08)	
21-50	598 (47.09)	593 (46.66)	411 (52.69)	
>50	129 (10.16)	122 (9.60)	33 (4.23)	
Trastuzumab, years				.543
1	626 (49.29)	649 (51.06)	381 (48.85)	
2	644 (50.71)	622 (48.94)	399 (51.15)	
RT fractionation				.514
Hypofractionated	60 (11.83)	58 (10.45)	-	
Conventional	447 (88.17)	497 (89.55)	-	
Anthracycline therapy	1202 (94.65)	1225 (96.38)	694 (88.97)	<.001
Taxane therapy	365 (28.74)	389 (30.61)	117 (15.00)	<.001
Surgery				<.001
Mastectomy	394 (31.02)	372 (29.27)	520 (66.67)	
BCS	876 (68.98)	899 (70.73)	260 (33.33)	
Smoking	188 (14.80)	167 (13.14)	87 (11.15)	.060
BMI > 30	232 (18.27)	226 (17.78)	109 (13.97)	.030
Age > 55	361 (28.43)	339 (26.67)	205 (26.28)	.480
Diabetes	24 (1.89)	17 (1.34)	18 (2.31)	.218
Hyperlipidemia	53 (4.17)	40 (3.15)	35 (4.48)	.200
Hypertension	202 (15.91)	207 (16.29)	133 (17.05)	.792
Coronary disease Hx	12 (0.94)	6 (0.47)	4 (0.51)	.286
COPD	6 (0.47)	6 (0.47)	4 (0.51)	.979
Family Hx of CHD	215 (16.94)	196 (15.43)	110 (14.10)	.217
Menopause				.489
Postmenopausal	596 (46.93)	579 (45.55)	343 (43.97)	
Premenopausal	175 (13.78)	193 (15.18)	107 (13.72)	
Uncertain	499 (39.29)	499 (39.26)	330 (42.31)	
Mean age (±SD)	49.22 ± 10.20	48.71 ± 10.14	49.55 ± 9.74	.1628
Mean BMI (±SD)	25.84 ± 4.57	25.98 ± 4.82	25.26 ± 4.67	.0029
Mean baseline LVEF (±SD)	64.28 ± 6.29	64.29 ± 6.75	64.04 ± 6.41	.7004

Abbreviations: BCS = breast-conserving surgery; BMI = body mass index; CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease; ER = estrogen; Hx = history; LVEF = left ventricular ejection fraction; PR = progesterone; RT = radiation therapy; SD = standard deviation.

Table 2 Cardiovascular outcomes

	Group 1 (left RT), n = 1270 (%)	Group 2 (right RT), n = 1271 (%)	Group 3 (no RT), n = 780 (%)	*P* value
LVEF decline	94 (9.18)	94 (8.99)	57 (8.80)	.073
CVEs	12 (1.08)	10 (0.92)	4 (0.62)	.619

Abbreviations: CVEs = cardiovascular events; LVEF = left ventricular ejection fraction; RT = radiation therapy.

which was similar to group 2 (8.99%) and group 3 (8.80%) with $P = .073$. Figure 2 depicts the cumulative incidence of a LVEF decline over time for groups 1, 2, and 3.

Table 3 shows the unadjusted and adjusted competing-risks regression with the corresponding coefficients, *P* values, and confidence intervals (CIs) for LVEF decline.

After adjusting for baseline covariates, it was found that groups that received RT (left or right) were both as likely to have LVEF decline as group 3 (no RT) (adjusted hazard ratio [aHR] = 1.02, 95% CI = 0.73-1.42, $P = .906$ for left-sided RT, and aHR = 1.02, 95% CI = 0.73-1.42, $P = .891$ for right-sided RT).

CVEs

Table 2 shows the frequency of CVE and the percentage of patients in each group who developed any CVE, which was defined as a diagnosis of myocardial infarction, ACS, coronary revascularization, or death from ischemic heart disease.[16] The total number of CVE in our cohort was 26, 12 of which happened in group 1 (1.08% of patients), 10 in group 2 (0.92% of patients), and 4 in group 3 (0.62% of patients) with $P = .619$.

Figure 3 demonstrates the cumulative incidence rate of CVE over time for the 3 groups. CVEs were noted to increase steadily throughout the follow-up period. This increase was higher for the group that received left-sided RT than right-sided RT and no RT; however, this difference was not statistically significant ($P = .619$).

Table 3 shows the unadjusted and adjusted competing-risks regression with the corresponding coefficients, *P* values, and CIs for CVE. After adjusting for baseline covariates, it was found that the probability of experiencing CVE is not statistically significant among the 3 groups ($P = .149$ and .452 for groups 1 and 2, respectively)

Discussion

This study aimed at finding whether the addition of RT to trastuzumab significantly increases cardiotoxicity relative to trastuzumab alone in patients with HER-2−positive breast cancer. We found that additional RT does not significantly

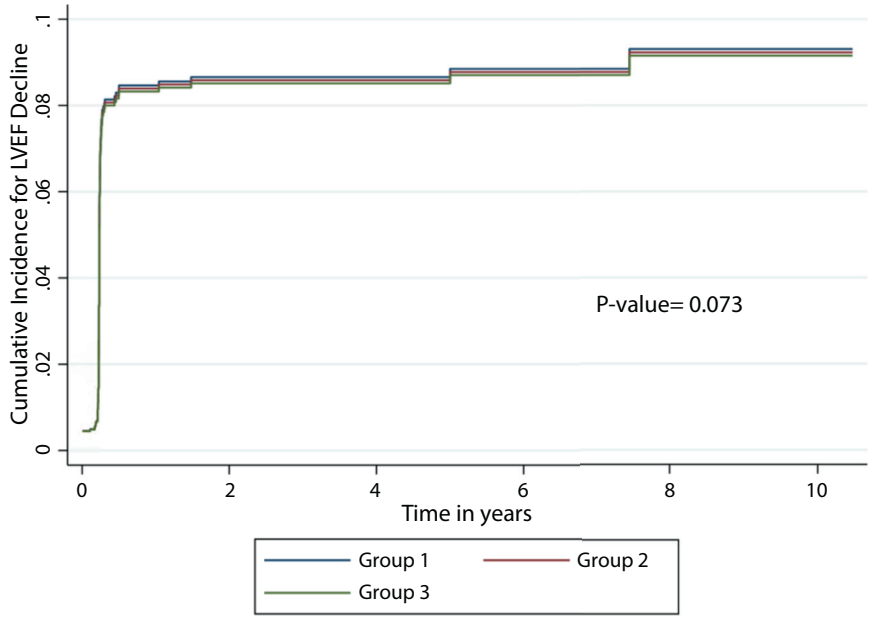

Fig. 2. Cumulative incidence rate of LVEF decline plotted against time (years) for groups 1, 2, and 3 (patients who received left-sided radiation, right-sided radiation, and no radiation, respectively). *Abbreviation:* LVEF = left ventricular ejection fraction.

Table 3 Competing risk analysis for the effect of RT on LVEF drop and CVE

	LVEF decline, HR (95% CI)				CVEs, HR (95% CI)			
	Univariate	*P* value	Multivariate	*P* value	Univariate	*P* value	Multivariate	*P* value
Group 1: left RT	1.05 (0.76-1.46)	0.741	1.02 (0.73-1.42)	0.906	2.25 (0.72-7.02)	0.162	2.32 (0.75-7.28)	.149
Group 2: right RT	1.03 (0.74-1.43)	0.837	1.02 (0.73-1.42)	0.891	1.59 (0.48-5.21)	0.440	1.57 (0.48-5.13)	.452
Group 3: no RT (reference)	-	-	-	-	-	-	-	-

Abbreviations: CI = confidence interval; CVE = cardiovascular event; HR = hazard ratio; LVEF = left ventricular ejection fraction; RT = radiation therapy.

increase the incidence of CVEs or LVEF decline compared with trastuzumab alone.

RT is an essential component of breast cancer therapy. It is part of the standard of care for HER-2−positive breast cancer along with trastuzumab and has proven effective in lowering locoregional recurrence and disease-related mortality.[12-15] Trastuzumab was shown to have cardiac side effects, which include a decline in LVEF and rarely CHF[7-10,29]; however, this cardiotoxicity is generally reversible.[29,30] In addition, RT was shown to have a cardiotoxicity profile[16-20] by 2 different mechanisms: the first is by damaging the myocardial tissue leading to a decline in LVEF,[21] and the second mechanism is by direct damage to the coronary vessels leading to ischemic heart disease (CVE in the current study).[16] Modern techniques in RT, like DIBH and proton therapy, resulted in a decreased radiation dose to the heart and reduced cardiotoxicity in patients receiving chest radiation.[23-27] In contrast, historic studies using older techniques noted a higher incidence of radiation-induced cardiotoxicity.[31,32]

Our analysis is, to our knowledge, the first with a large sample size (3321 patients) and long follow-up to study the cardiotoxicity profile of RT and trastuzumab in treating patients with HER-2−positive breast cancer, taking into account laterality of the primary tumor. In this analysis, we compared patients who received (in addition to trastuzumab) left-sided RT (group 1), right-sided RT (group 2), and no RT (group 3) to determine whether the use and laterality of radiation with trastuzumab cause increased rates of cardiotoxicity. We found that the 3 groups had a similar incidence of LVEF decline. The difference in the outcome was not statistically significant (P = .073). This was similar to what other studies concluded.[1,33-36]

As for the other primary outcome, we also found that there is no statistically significant increase in ischemic heart disease due to RT (P = .619). Other studies have shown that RT causes an increase in the incidence of CVEs when combined with trastuzumab.[37,38] The total number of CVEs in our cohort remained low (26 cases). Of note, another analysis with a relatively large sample size had results similar to our present analysis, whereby RT had no increased risk of ischemic CVEs.[39]

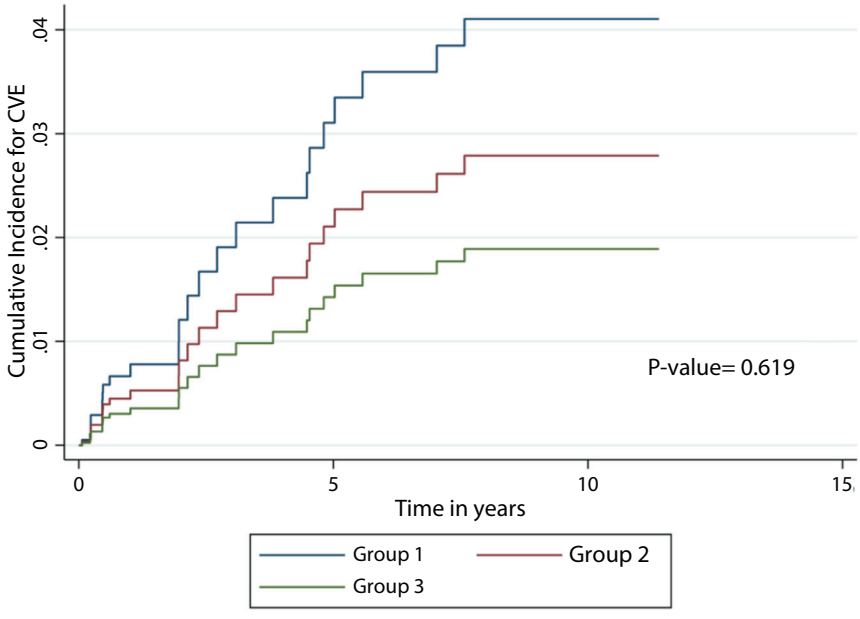

Fig. 3. Cumulative incidence rate of CVEs plotted against time (years) for groups 1, 2, and 3 (patients who received left-sided radiation, right-sided radiation, and no radiation, respectively). *Abbreviation:* CVEs = cardiovascular events.

Groups 1 and 2 in our analysis compared the receipt of left-sided versus right-sided RT to determine whether laterality had any increased risk of cardiovascular outcomes. We found that both groups had no statistically significant difference in the incidence of any of our primary outcomes. The aHR for left-sided radiation was 1.02 (P = .906) and 2.32 (P = .149) for LVEF decline and CVE, respectively. The aHR for right-sided radiation was 1.02 (P = .891) and 1.57 (P = .452) for LVEF decline and CVE, respectively. Other studies have shown consistent results with our findings regarding laterality and LVEF.[1,33,36-38] However, 2 of those studies[37,38] found an increased incidence of CVEs in patients with left-sided compared with right-sided RT, which is in contrast to our findings. This difference might be attributed to differences in populations and the larger sample size in our analysis of the HERA trial, increasing the reliability of our findings.

In our study, we found that there is some cardiotoxicity associated with the concurrent use of RT with trastuzumab in patients with HER-2−positive breast cancer. However, we also found that RT does not significantly increase the cardiotoxicity of trastuzumab, in contrast to the findings in studies of Hodgkin lymphoma, where the addition of systemic chemotherapy increased the incidence of cardiotoxicity after RT.[40,41] This could be attributed to the modern RT methods used in the HERA trial, including 3-dimensional planning and DIBH techniques.[22-27]

The current analysis carries some limitations that are worth noting. First, our study is a retrospective analysis of a prospective clinical trial and thus, is subject to the biases inherent to such studies. The definition of CVE and the limited follow-up period could potentially underestimate the true magnitude of radiation-induced cardiac damage. Another limitation is the use of LVEF to define cardiotoxicity due to its lack of sensitivity. A decline in LVEF does not always mean myocardial damage, and an unchanged LVEF does not exclude myocardial damage.[42-44] Despite those limitations, our study remains the largest, to date, to examine the cardiotoxicity of trastuzumab and RT in the treatment of HER-2−positive breast cancer.

Conclusions

In conclusion, in this secondary analysis of the HERA trial studying patients with HER-2−positive breast cancer, we found that RT does not significantly increase the risk of cardiotoxicity in patients treated with trastuzumab. Continued monitoring of patients is needed to investigate the long-term cardiotoxic effects of modern breast cancer treatments.

References

1. Marinko T, Borstnar S, Blagus R, Dolenc J, Bilban-Jakopin C. Early cardiotoxicity after adjuvant concomitant treatment with radiotherapy and trastuzumab in patients with breast cancer. *Radiol Oncol* 2018;52:204–212.
2. Ponde NF, Zardavas D, Piccart M. Progress in adjuvant systemic therapy for breast cancer. *Nat Rev Clin Oncol* 2019;16:27–44.
3. Hudis CA. Trastuzumab—mechanism of action and use in clinical practice. *N Engl J Med* 2007;357:39–51.
4. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al. 11 Years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: Final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet* 2017;389:1195–1205.
5. Dahabreh IJ, Linardou H, Siannis F, Fountzilas G, Murray S. Trastuzumab in the adjuvant treatment of early-stage breast cancer: A systematic review and meta-analysis of randomized controlled trials. *Oncologist* 2008;13:620–630.
6. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;353:1659–1672.
7. Jawa Z, Perez RM, Garlie L, et al. Risk factors of trastuzumab-induced cardiotoxicity in breast cancer: A meta-analysis. *Medicine (Baltimore)* 2016;95:e5195.
8. Keefe DL. Trastuzumab-associated cardiotoxicity. *Cancer* 2002;95:1592–1600.
9. Zamorano JL, Lancellotti P, Muñoz DR, et al. 2016 ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The task force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J* 2016;37:2768–2801.
10. Perez EA, Rodeheffer R. Clinical cardiac tolerability of trastuzumab. *J Clin Oncol* 2004;22:322–329.
11. de Azambuja E, Procter MJ, van Veldhuisen DJ, et al. Trastuzumab-associated cardiac events at 8 years of median follow-up in the Herceptin Adjuvant trial (BIG 1-01). *J Clin Oncol* 2014;32:2159–2165.
12. Early Breast Cancer Trialists' Collaborative Group (EBCTCG); Darby S, McGale P, Correa C, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: Meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011;378:1707–1716.
13. Fisher B, Costantino J, Redmond C, et al. Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer. *N Engl J Med* 1993;328:1581–1586.
14. Fisher B, Dignam J, Wolmark N, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-17. *J Clin Oncol* 1998;16:441–452.
15. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials. *Lancet* 2005;366:2087–2106.
16. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;368:987–998.
17. Darby SC, McGale P, Taylor CW, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: Prospective cohort study of about 300,000 women in US SEER cancer registries. *Lancet Oncol* 2005;6:557–565.
18. Henson KE, McGale P, Taylor CW, Darby SC. Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer. *Br J Cancer* 2013;108:179–182.
19. Sardar P, Kundu A, Chaterjee S, et al. Long-term cardiovascular mortality after radiotherapy for breast cancer: A systematic review and meta-analysis. *Clin Cardiol* 2017;40:73–81.
20. Taylor CW, Kirby AM. Cardiac side-effects from breast cancer radiotherapy. *Clin Oncol (R Coll Radiol)* 2015;27:621–629.
21. Clasen SC, Shou H, Freedman G, et al. Early cardiac effects of contemporary radiation therapy in patients with breast cancer. *Int J Radiat Oncol Biol Phys* 2021;109:1301–1310.
22. Meattini I, Poortmans PM, Aznar MC, et al. Association of breast cancer irradiation with cardiac toxic effects: A narrative review. *JAMA Oncol* 2021;7:924–932.

23. Mast ME, Vredeveld EJ, Credoe HM, et al. Whole breast proton irradiation for maximal reduction of heart dose in breast cancer patients. *Breast Cancer Res Treat* 2014;148:33–39.
24. Swanson T, Grills IS, Ye H, et al. Six-year experience routinely utilizing moderate deep inspiration breath-hold (mDIBH) for the reduction of cardiac dose in left-sided breast irradiation for patients with early stage or locally advanced breast cancer. *Am J Clin Oncol* 2013;36:24.
25. Ares C, Khan S, Macartain AM, et al. Postoperative proton radiotherapy for localized and locoregional breast cancer: Potential for clinically relevant improvements? *Int J Radiat Oncol Biol Phys* 2010;76:685–697.
26. Lin LL, Vennarini S, Dimofte A, et al. Proton beam versus photon beam dose to the heart and left anterior descending artery for left-sided breast cancer. *Acta Oncol* 2015;54:1032–1039.
27. MacDonald SM, Jimenez R, Paetzold P, et al. Proton radiotherapy for chest wall and regional lymphatic radiation; dose comparisons and treatment delivery. *Radiat Oncol* 2013;8:1–7.
28. Abi Jaoude J, Kayali M, de Azambuja E, et al. De-intensifying radiation therapy in HER-2 positive breast cancer: To boost or not to boost? *Int J Radiat Oncol Biol Phys* 2020;108:1040–1046.
29. Ewer SM. Ewer MS. Cardiotoxicity profile of trastuzumab. *Drug Saf* 2008;31:459–467.
30. Ewer MS, Vooletich MT, Durand J-B, et al. Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. *J Clin Oncol* 2005;23:7820–7826.
31. Cuzick J, Stewart H, Houghton RJ, et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. *J Clin Oncol* 1994;12:447–453.
32. Rutqvist LE, Lax I, Fornander T, Johansson H. Cardiovascular mortality in a randomized trial of adjuvant radiation therapy versus surgery alone in primary breast cancer. *Int J Radiat Oncol Biol Phys* 1992;22:887–896.
33. Bian SX, Korah MP, Whitaker TR, Ji L, Groshen S, Chung E. No acute changes in LVEF observed with concurrent trastuzumab and breast radiation with low heart doses. *Clin Breast Cancer* 2017;17:510–515.
34. Cao L, Cai G, Chang C, et al. Early cardiac toxicity following adjuvant radiotherapy of left-sided breast cancer with or without concurrent trastuzumab. *Oncotarget* 2016;7:1042.
35. Jacob J, Belin L, Pierga JY, et al. Concurrent administration of trastuzumab with locoregional breast radiotherapy: long-term results of a prospective study. *Breast Cancer Res Treat* 2014;148:345–353.
36. Shaffer R, Tyldesley S, Rolles M, Chia S, Mohamed I. Acute cardiotoxicity with concurrent trastuzumab and radiotherapy including internal mammary chain nodes: A retrospective single-institution study. *Radiother Oncol* 2009;90:122–126.
37. Abouegylah M, Braunstein LZ, Alm El-Din MA, et al. Evaluation of radiation-induced cardiac toxicity in breast cancer patients treated with Trastuzumab-based chemotherapy. *Breast Cancer Res Treat* 2019;174:179–185.
38. Nack E, Koffer PP, Blumberg CS, et al. New cardiac abnormalities after radiotherapy inbreast cancer patients treated with trastuzumab. *Clin Breast Cancer* 2020;20:246–252.
39. Halyard MY, Pisansky TM, Dueck AC, et al. Radiotherapy and adjuvant trastuzumab in operable breast cancer: Tolerability and adverse event data from the NCCTG phase III trial N9831. *J Clin Oncol* 2009;27:2638.
40. Aleman BM, van den Belt-Dusebout AW, De Bruin ML, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood* 2007;109:1878–1886.
41. Myrehaug S, Pintilie M, Tsang R, et al. Cardiac morbidity following modern treatment for Hodgkin lymphoma: supra-additive cardiotoxicity of doxorubicin and radiation therapy. *Leuk Lymphoma* 2008;49:1486–1493.
42. Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments: what the cardiologist needs to know. *Nat Rev Cardiol* 2010;7:564.
43. Kaidar-Person O, Zagar TM, Oldan JD, et al. Early cardiac perfusion defects after left-sided radiation therapy for breast cancer: Is there a volume response? *Breast Cancer Res Treat* 2017;164:253–262.
44. Lind PA, Pagnanelli R, Marks LB, et al. Myocardial perfusion changes in patients irradiated for left-sided breast cancer and correlation with coronary artery distribution. *Int J Radiat Oncol Biol Phys* 2003;55:914–920.