HHS Public Access

Author manuscript

*Med Oncol*. Author manuscript; available in PMC 2017 January 22.

Published in final edited form as:

*Med Oncol*. 2016 July ; 33(7): 82. doi:10.1007/s12032-016-0797-x.

# Anthracycline- and trastuzumab-induced cardiotoxicity: a retrospective study

**Yasmin Hamirani**[1], **Ibrahim Fanous**[1], **Christopher M. Kramer**[1], **Andrew Won**[1], **Michael Salerno**[1], and **Patrick Dillon**[1]

[1]UVA Division of Hematology/Oncology, University of Virginia, UVA Box 800716, Charlottesville, VA 22908, USA

## Abstract

Some chemotherapeutic agents cause cardiotoxic effects including reduction in left ventricular ejection fraction (LVEF) and occasionally congestive heart failure. Anthracyclines and HER2 monoclonal antibodies are common offenders, but clinical practice data on LVEF changes, risk factors and acute recovery is lacking. We retrospectively examined the electronic medical record at an academic medical center for receipt of anthracyclines and/or trastuzumab from 2000 to 2013 in cancer patients. Patient characteristics and serial LVEF assessments were collected. Patients with and without LVEF decline were analyzed by univariate and multivariate analysis. A total of 549 patients were identified with anthracycline/trastuzumab use and 216 had multiple LVEF assessments. Only 27 of the 216 patients who had multiple LVEF assessments at multiple occasions suffered a clinically significant LVEF fall (12.5 %), and symptomatic CHF was rare (0.5 %). Compared to unaffected patients, those with a fall in LVEF were more likely to have hypertension, hyperlipidemia or coronary artery disease (CAD). Concomitant trastuzumab and anthracycline use was a risk factor (36 vs 9.5 % for anthracycline alone, $p < 0.001$). The median time from start of chemotherapy to reduced LVEF was 202 days (5–3008). On multivariate analysis, hypertension and use of trastuzumab remained independent predictors of LVEF fall. Acute recovery in LVEF was observed in 44 % of patients. LVEF changes from cancer therapies are frequent and hard to predict. Hypertension, hyperlipidemia and CAD are associated with LVEF decline. Acute recovery of LVEF is observed in those experiencing treatment-related cardiotoxicity. Attention to timely interruption of cardiotoxic chemo is recommended.

### Keywords

Anthracyclines; Trastuzumab; Cardiotoxicity; Ejection fraction; Recovery

✉Patrick Dillon, Pmd5b@hscmail.mcc.virginia.edu.

**Compliance with ethical standards**

**Research involving human participants** Institutional Review Board approval of this retrospective database review was obtained from the University of Virginia.

**Conflict of interest** The authors disclose no conflict of interest related to this work.

## Introduction

The use of anthracyclines and trastuzumab sometimes leads to cardiotoxic effects. Chemotherapy-related cardiomyopathy may happen immediately after the first dose or as late as several years after treatment. Immediate pericarditis–myocarditis syndrome, chronic progressive congestive heart failure and late-onset cardiotoxicity presenting years after the treatment course ends, have been reported [1].

Risk factors that may increase the likelihood of cardiotoxicity include cumulative dose, administration schedule, extremes of age, gender, African American ethnicity, combinations with other drugs, concurrent cardiovascular disease, diabetes, hypertension, tobacco abuse and obesity [2, 3]. There have been many attempts to mitigate against anthracycline-induced cardiotoxicity. Examples include angiotensin-converting enzyme inhibitors, beta blockers, liposomal and other nanoparticle anthracycline delivery systems, novel anthracycline analogues and cardioprotective agents such as dexrazoxane [4]. Despite technologic improvements, cardiotoxic effects of cancer therapies persist and impact upon patient quality of life and suitability for treatment.

To better address the rates of cardiotoxicity in a real-world clinical setting in the modern treatment era and to better assess the potential contributory risk factors, we initiated a study of all cancer patients receiving anthracyclines or trastuzumab therapy and analyzed their changes in cardiac function as well as their baseline risk factors.

## Methods

The study is a retrospective study examining data in the electronic medical record at an academic cancer center in central Virginia. The study was performed with institutional review board approval. The electronic medical record was queried for anthracyclines and/or trastuzumab use from 2000 to 2013. A total of 549 patients had LVEF assessments around the time of chemotherapy. A total of 221 patients had more than one assessment of LVEF. Five of those 221 patients were treated for coronary artery syndromes around the time of chemotherapy and were excluded from further analysis to avoid confounding. Therefore, a total of 216 patients had at least one pretreatment and one posttreatment assessment of ejection fraction. A clinically significant decline in LVEF was defined per standard criteria as a 10 % change from baseline and a final LVEF below 50 %. A non-clinically significant LVEF decline was defined as a drop of 10 %, but a final LVEF >50 % [5, 6]. Symptomatic heart failure was defined by NYHA classification [7]. Anthracyline equivalent dose was calculated per the Children’s Oncology Group standard (idarubicin/doxorubicin ratio of 5:1) [8]. Kruskal–Wallis test and Fisher’s exact test were utilized to estimate the difference between groups, and logistic regression model was used to predict a decline in the LVEF. IBM SPSS version 22.0 (Armonk, NY, IBM Corp) was used for statistical analysis.

## Results

There were 549 cancer patients who had any LVEF assessment and a subset of 216 patients with LVEF assessments at multiple time points (2–8 LVEF assessments with a mean of 3.5 assessments). A total of 27 patients (12.5 %) experienced a clinically significant decline in

the ejection fraction after chemotherapy (as defined above). The other 185 patients (86.6 %) did not experience a clinically significant decline in LVEF (Table 1) although a few had asymptomatic LVEF declines without a final LVEF below 50 %. Notably, for the 27 patients experiencing clinically significant decline in LVEF, only one went on to develop symptomatic NYHA class III or IV heart failure, resulting in a symptomatic heart failure rate of 0.5 % in this mixed population of leukemia, lymphoma, sarcoma and breast cancer patients. In the 216 patients that we assessed at multiple occasions, the mean EF change from baseline was −4 %. The mean change for the clinically significant decline population was −20 % (Table 2).

An assessment of the risk factors in this population reveals that more patients with a fall in ejection fraction had hypertension, hyperlipidemia, coronary artery disease and preexisting systolic or diastolic dysfunction in univariate analysis. Patients who received both trastuzumab and an anthracycline had a slightly higher incidence of a clinically significant decline in the LVEF as compared to anthracyclines alone (36 % vs 9.5 % $p = 0.001$). On multivariate analysis, hypertension and the use of trastuzumab remained independent predictors of ejection fraction decline.

In this cohort, the median time difference (days) between start of chemotherapy/trastuzumab and reduced EF was 202 days (5–3008). The median anthracycline dose in the group of patients experiencing an LVEF decline was 240 mg/m$^2$ (75–375 mg/m$^2$). The trastuzumab-only population was patients with breast cancer treated with taxane plus trastuzumab regimens. Only two of those patients (13 %) experienced LVEF declines. In the small subset of patients receiving liposomal doxorubicin, there was only one patient out of 15 who experienced a LVEF decline (6.7 %).

## Discussion

Anthracyclines and trastuzumab are well-known cardiotoxins; however, the rates of symptomatic and asymptomatic changes in LVEF vary among different patient populations and in different clinical trials. Much of the data available comes from select patients meeting eligibility criteria for clinical trial participation. This current retrospective study attempts to assess the real-world implications and outcomes of anthracycline and trastuzumab use. As such, this is one of the few studies examining risk factor associations with LVEF decline in a general cancer population [9, 10].

We observed a clinically significant LVEF decline rate of 12.5 % of the study population that had LVEF assessments at multiple occasions. This is higher than other contemporary studies [11]. Likewise, we observed associations of hypertension, hyperlipidemia, CAD and systolic/ diastolic heart failure with the endpoint of clinical LVEF decline. In multivariate analysis, hypertension was the only statistically significant cardiac risk factor associated with LVEF decline. This corroborates some studies, although there remains a degree of uncertainty in the literature about the roles of other factors such as smoking, diabetes, coronary artery disease and hyperlipidemia. We conclude that the presence of preexisting hypertension, as observed in our study and others, may be the most useful clinical predictor for future LVEF decline (59 % of hypertension patients suffered LVEF decline) [2]. It is also

clinically relevant that 12 % of the patient population getting multiple LVEF assessments had preexisting heart failure of any degree. Forty-four percent of those high-risk patients had further clinically significant LVEF drop from their baseline. These data suggest that in the real-world experience, oncologists often may be compelled to give cardiotoxic drugs to patients with underlying cardiac disease.

In this retrospective study, none of the 27 cases of clinically significant LVEF decline involved patients with high cumulative doses of either anthracycline or trastuzumab. One explanation may be that the practice pattern since the 1990s has been to limit the lifetime doses of anthracyclines. For trastuzumab-treated patients, cardiotoxicity may occur independent of the cumulative dose [12], and this study lends support to that conclusion.

Cardiac recovery has been reported in some cases of anthracycline-induced cardiotoxicity. “ Acute recovery” can be classified as “ partial acute recovery” if the LVEF improved by >5 % or the LVEF improved to >50 %. “ Complete acute recovery” is defined as LVEF recovery to the baseline value. Complete acute recovery occurs most often after stopping the cardiotoxic agent and starting heart failure therapy [13]. In this study, we observed acute recovery in 12 of the 27 patients with LVEF declines; 5 of these cases had complete recovery and 7 had partial recovery. This is congruent with other studies observing LVEF stabilizations and acute recoveries after discontinuation of the offending agent [6, 14, 15].

The limitations of this study include the retrospective design, the size and the heterogeneity of the cancer diagnoses. The strength of a heterogeneous analysis is that it provides real clinical practice experience with use of these agents in a real-world patient population with significant degrees of comorbidity. Many of these patients would never have been included in clinical trials. Indeed, the slightly higher rate of clinically significant LVEF declines in this population as compared to recent prospective trials suggests that in a population with a high index of cardiac disease and risk factors, that cardiotoxicity of chemotherapy may be underappreciated. It is also possible that the 12.5 % incidence of LVEF decline in this study could be an overestimate since many patients receiving chemotherapy did not undergo serial LVEF assessment and were not captured in the denominator for this analysis.

Despite the slightly high incidence of clinically significant LVEF decline, it is encouraging that only one patient went on to develop symptomatic heart failure. Overall, the cardiac safety of anthracycline/trastuzumab therapy appears good in the last decade. Clinician education and cardiac monitoring have been emphasized between the oncology and cardiology communities. Further, there is a better understanding of the action of anthracyclines on cardiomyocytes [14, 16] and a large body of literature on rates of symptomatic CHF from anthracyclines/trastuzumab (rates of CHF may be as high as 10 %) [14, 17, 18]. Simultaneously, the detection of chemotherapy-related cardiotoxicity has improved. Myocardial strain imaging by echocardiography, magnetic resonance imaging and quantitative radionuclide angiocardiography are widely available. Blood biomarkers remain within the realm of research tools currently [16, 19].

## Conclusion

Anthracyclines and HER2-targeted antibodies can cause cardiotoxic effects. There are many risk factors that may increase the likelihood of these effects [20]. Hypertension, hyperlipidemia and CAD were univariate predictors of LVEF decline, while only hypertension was significant in multivariate analysis. The 12.5 % prevalence rate of LVEF reduction in the anthracycline-using study population that had LVEF assessments at multiple occasions suggests that it remains important for clinicians to recognize and assess for changes in cardiac function in any patients treated with anthracyclines or HER2-targeted antibody therapies. Furthermore, the findings of acute recovery in this report and others highlight the potential reversibility of cardiac toxicity in some patients and the importance or early detection. Furthermore, the recent reports from the (MANTICORE) and (PRADA) trials add support to the growing field of early cardioprotection with ACE inhibitors and beta blockers [21, 22].

## References

1. Jones RL, Swanton C, Ewer MS. Anthracycline cardiotoxicity. Expert Opin Drug Saf. 2006; 5(6): 791–809. [PubMed: 17044806]
2. Reinbolt RE, et al. Risk factors for anthracycline-associated cardiotoxicity. Support Care Cancer. 2016; 24(5):2173–2180. [PubMed: 26563179]
3. O'Donnell PH, Dolan ME. Cancer pharmacoethnicity: ethnic differences in susceptibility to the effects of chemotherapy. Clin Cancer Res. 2009; 15(15):4806–4814. [PubMed: 19622575]
4. Hale JP, Lewis IJ. Anthracyclines: cardiotoxicity and its prevention. Arch Dis Child. 1994; 71(5): 457–462. [PubMed: 7826122]
5. Shakir DK, Rasul KI. Chemotherapy induced cardiomyopathy: pathogenesis, monitoring and management. J Clin Med Res. 2009; 1(1):8–12. [PubMed: 22505958]
6. de Azambuja E, 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(20):2159–2165. [PubMed: 24912899]
7. Russell SD, et al. New York Heart Association functional class predicts exercise parameters in the current era. Am Heart J. 2009; 158(4 Suppl):S24–S30. [PubMed: 19782785]
8. Feijen EA, et al. Equivalence ratio for daunorubicin to doxorubicin in relation to late heart failure in survivors of childhood cancer. J Clin Oncol. 2015; 33(32):3774–3780. [PubMed: 26304888]
9. Schwartz RG, et al. Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy. Seven-year experience using serial radionuclide angiocardiography. Am J Med. 1987; 82(6):1109–1118. [PubMed: 3605130]
10. Plana JC, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2014; 27(9):911–939. [PubMed: 25172399]
11. Tan TC, Scherrer-Crosbie M. Cardiac complications of chemotherapy: role of imaging. Curr Treat Options Cardiovasc Med. 2014; 16(4):296. [PubMed: 24519487]
12. Mutlu H, Coskun HS. Is there any cumulative dose for trastuzumab? J Oncol Pharm Pract. 2015; 21(6):468–470. [PubMed: 24903272]
13. Cardinale D, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation. 2015; 131(22):1981–1988. [PubMed: 25948538]
14. Volkova M, Russell R. Anthracycline cardiotoxicity: prevalence pathogenesis and treatment. Curr Cardiol Rev. 2011; 7(4):214–220. [PubMed: 22758622]
15. Lotrionte M, et al. Review and meta-analysis of incidence and clinical predictors of anthracycline cardiotoxicity. Am J Cardiol. 2013; 112(12):1980–1984. [PubMed: 24075281]

16. Bristow MR, et al. Doxorubicin cardiomyopathy: evaluation by phonocardiography, endomyocardial biopsy, and cardiac catheterization. Ann Intern Med. 1978; 88(2):168–175. [PubMed: 626445]
17. Armenian SH, et al. Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol. 2015; 16(3):e123–e136. [PubMed: 25752563]
18. Hershman DL, Shao T. Anthracycline cardiotoxicity after breast cancer treatment. Oncol Williston Park. 2009; 23(3):227–234.
19. Jiji RS, Kramer CM, Salerno M. Non-invasive imaging and monitoring cardiotoxicity of cancer therapeutic drugs. J Nucl Cardiol. 2012; 19(2):377–388. [PubMed: 22351492]
20. Rochette L, et al. Anthracyclines/trastuzumab: new aspects of cardiotoxicity and molecular mechanisms. Trends Pharmacol Sci. 2015; 36(6):326–348. [PubMed: 25895646]
21. Pituskin E, et al. Rationale and design of the multidisciplinary approach to novel therapies in Cardiology Oncology Research Trial (MANTICORE 101–Breast): a randomized, placebo-controlled trial to determine if conventional heart failure pharmacotherapy can prevent trastuzumab-mediated left ventricular remodeling among patients with HER2+ early breast cancer using cardiac MRI. BMC Cancer. 2011; 11:318. [PubMed: 21794114]
22. Gulati G, et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 × 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. Eur Heart J. 2016; 37(21):1671–1680. [PubMed: 26903532]

**Table 1**

Patient characteristics and univariate relationships

| | Total population *N* = 216 | No EF decline *N* = 185 | EF decline >10 % *N* = 27 | *p* value |
|---|---|---|---|---|
| Type of cancer | | | | |
| Breast | 82 (38 %) | 71 (38 %) | 11 (41 %) | 0.001 |
| Sarcoma | 91 (42 %) | 85 (46 %) | 6 (22 %) | |
| Leukemia | 42 (19 %) | 33 (18 %) | 9 (33 %) | |
| Lymphoma | 1 (0.5 %) | 0 | 1 (3.7 %) | |
| Age (years) | 39 (2–45) | 39 (22.5–44.5) | 39 (27–45) | 0.59 |
| Gender—female | 139 (65 %) | 119 (64 %) | 20 (74 %) | 0.47 |
| Comorbid conditions | | | | |
| Diabetes | 54 (25 %) | 47 (25 %) | 7 (26 %) | 1 |
| Hypertension | 75 (35 %) | 59 (32 %) | 16 (59 %) | 0.008 |
| Hyperlipidemia | 47 (22 %) | 35 (19 %) | 12 (44 %) | 0.005 |
| Coronary artery disease | 16 (7.4 %) | 11 (6 %) | 5 (18 %) | 0.03 |
| Radiation treatment | 100 (46 %) | 89 (48 %) | 11 (40 %) | 0.68 |
| Smoking | 57 (26 %) | 51 (28 %) | 6 (22 %) | 0.81 |
| Hx of systolic/diastolic heart failure (prior to chemo) | 25 (12 %) | 13 (7 %) | 12 (44 %) | 0.001 |
| Imaging modality | | | | |
| TTE | 96 (44 %) | 85 (46 %) | 11 (41 %) | |
| MUGA | 118 (55 %) | 104 (56 %) | 14 (52 %) | 0.028 |
| Stress MIBI | 1 (0.5 %) | 0 | 1 (3.7 %) | |
| TEE | 1 (0.5 %) | 0 | 1 (3.7 %) | |
| Baseline imaging | | | | |
| Median EF (%) | 60 (58–63) | 60 (59–63) | 60 (56–61) | 1 |

**Table 2**

LVEF outcome measures

| | **Total population** ***N*** **= 216** | **No EF decline** ***N*** **= 185** | **EF decline >10 %** ***N*** **= 27** | ***p*** **value** |
|---|---|---|---|---|
| Absolute EF change from baseline | −4 % (+16 to −42 %) | −2 % (−9 to +16 %) | −20 % (−11 to −42 %) | <0.001 |
| Median days between start of chemo and decline in EF <50 % | | | 202 (5–3008) | |
| Therapies | | | (% with EF drop) | |
| 1. Anthracyclines only | 178 | 161 | 17(9.5 %) | 0.012 |
| 2. Anthracycline and Trastuzumab | 22 | 14 | 8 (36 %) | 0.002 |
| 3. Trastuzumab only | 16 | 14 | 2 (13 %) | n/a |
| Type of anthracycline | | | (% with EF drop) | |
| Doxorubicin | 144 | 129 | 15 (10 %) | 0.19 |
| Idarubicin | 27 | 21 | 6 (22 %) | 0.11 |
| Daunorubicin | 23 | 19 | 4 (17 %) | 0.50 |
| Liposomal doxorubicin | 15 | 14 | 1 (6.7 %) | <0.001 |
| Epirubicin | 2 | 2 | 0 | 1 |