

**Cardiotoxicity secondary to breast cancer chemotherapy**Shivanshan Pathmanathan<sup>1</sup>, Jasotha Sanmugarajah<sup>1,2,3</sup>, Selvanayagam Niranjan<sup>1,2,3</sup>

1. Gold Coast University Hospital, Southport, QLD, Australia

2. Griffith University, Southport, QLD, Australia

3. Bond University, Robina, QLD, Australia

Corresponding authors: Shivanshan Pathmanathan, Selvanayagam Niranjan

Email: Shivvyp89@gmail.com/Selvanayagam.Niranjan@health.qld.gov.au

## Abstract

**Abstract:** Survival rates of breast cancer, have increased with improving chemotherapy and radiation therapy. The use of anthracyclines and trastuzumab have become the cornerstones in the treatment of breast cancer in both an adjuvant and metastatic therapeutic protocols. However, the adverse effects of both agents include cardiotoxicity, particularly left ventricular dysfunction, which limits their use. This article aims to review the initial evaluation of patients prior to receiving cardiotoxic chemotherapy and the monitoring of cardiotoxicity during and post therapy. This article also aims to describe the management of patient who develop cardiotoxicity.

**Introduction**

Survival rates of breast cancer patients have improved, with five-year survival currently estimated to be 90% in comparison to 72% in the 1960's. There are a number of reasons for the improved survival, which include improved screening methods, surgical techniques, radiotherapy and chemotherapy<sup>(1)</sup>. Unfortunately, several chemotherapy agents that are used in the management of breast cancer are cardiotoxic, limiting their use. Cardiotoxicity secondary to chemotherapy include diverse pathological entities encompassing arrhythmias, hypertension, perimyocarditis, myocardial ischaemia and left ventricular dysfunction.

Anthracyclines and human epidermal growth factor 2 (Her2) agents are commonly prescribed in the management of breast cancer, in both an adjuvant and metastatic setting. Common anthracyclines used include doxorubicin and epirubicin, while Her2 agents include trastuzumab, lapatinib and pertuzumab. The prolonged use of anthracyclines and trastuzumab is limited by left ventricular dysfunction. Anthracyclines lead to irreversible myocardial injury via several mechanisms including the production of oxygen free radicals, increase in oxidative stress and lipid peroxidation. It also binds to the topoisomerase-II (Top2) enzyme which triggers cell death in cancer cells but also in myocardial tissue<sup>(2,3)</sup>. Toxicity secondary to anthracyclines can be divided into 3 categories. Firstly, acute presentation with arrhythmias, left ventricular dysfunction or a peri-myocarditis, occurring in approximately 3% of treated patients<sup>(4)</sup>.

Secondly as subacute cardiomyopathy, defined as reduction in left ventricular ejection fraction (LVEF) within one year of treatment occurring in 1.6 to 2.1%. Lastly as chronic cardiomyopathy, where the onset is greater than 1-year post treatment and occurs in 1.6 to 5% of the population<sup>(5)</sup>. On the contrary, some patients that are treated with trastuzumab will have a loss of contractility of the myocardium or a 'stunned' myocardium, in the absence of damage to the myocytes. Therefore, contractility can return when the drug is withheld, as evidenced by improvement in LVEF<sup>(6)</sup>. There is a certain percentage of patients who will have persistent cardiomyopathy suggesting permanent damage<sup>(7)</sup>. The rate of left ventricular dysfunction is variable for trastuzumab; ranging from 2% to 7% when used as monotherapy, and up to 27% when used in conjunction with anthracyclines and cyclophosphamide<sup>(8)</sup>.

This article is an overview that aims to discuss the initial evaluation, risk factors, monitoring and management of patients who have left ventricular dysfunction secondary to chemotherapy.

**Initial Evaluation:**

Initial history should determine potential cardiac risk factors including hyperlipidaemia, hypertension, smoking, coronary artery disease, heart failure, arrhythmias, valvular heart disease and diabetes. Risk factors specific for different chemotherapy regimens should also be explored as described below. A thorough cardiac examination including vital signs and body mass index (BMI) should be performed.



Investigations should include a baseline electrocardiogram (ECG), which may indicate evidence of cardiac dysfunction such as conduction abnormalities, prior myocardial infarction, left ventricular hypertrophy or prolonged corrected QT interval (QTc). A baseline echocardiogram should be completed in patients at an increased risk of cardiac disease or who have known cardiac disease for the evaluation of systolic and diastolic function<sup>(9)</sup>. This is controversial in patients with no risk factors, as there is an expectation of a normal result, and rarely changes management<sup>(10)</sup>. Lastly, the chemotherapy regimen and the associated specific cardiac side effects should be understood before treatment is started<sup>(9)</sup>.

### Risk Factors

There are a number of factors that increase the risk of cardiotoxicity of anthracycline agents. Lefrak et al and Swain et al showed that the incidence of left ventricular dysfunction increased with cumulative doses of anthracycline (Table 1)<sup>(11,12)</sup>. As a result, maximum lifetime cumulative dose of doxorubicin is generally limited to between 400mg/m<sup>2</sup> and 550mg/m<sup>2</sup><sup>(11,12)</sup>. Concurrent use of anthracyclines with both trastuzumab and taxanes potentiate left ventricular dysfunction at lower doses. The maximum doxorubicin dose is limited to 300mg/m<sup>2</sup> in these regimens<sup>(13)</sup>. Other risk factors include extremes of age, prior radiation therapy to the chest, bolus administration rather than infusion, female gender, hypertension, diabetes and prior coronary artery disease<sup>(5)</sup>.

Risk factors for patient receiving trastuzumab include pre-existing cardiac dysfunction (reduced LVEF), older age, elevated BMI, and hypertension<sup>(5)</sup>. Based on the above risk factors, risk prediction models for heart failure and cardiomyopathy post adjuvant trastuzumab therapy have been formulated. However they have not been externally validated and are not used in clinical practice currently<sup>(7,14)</sup>. There are no such models for anthracycline based chemotherapy.

### Early detection of Left Ventricular Dysfunction secondary to chemotherapy

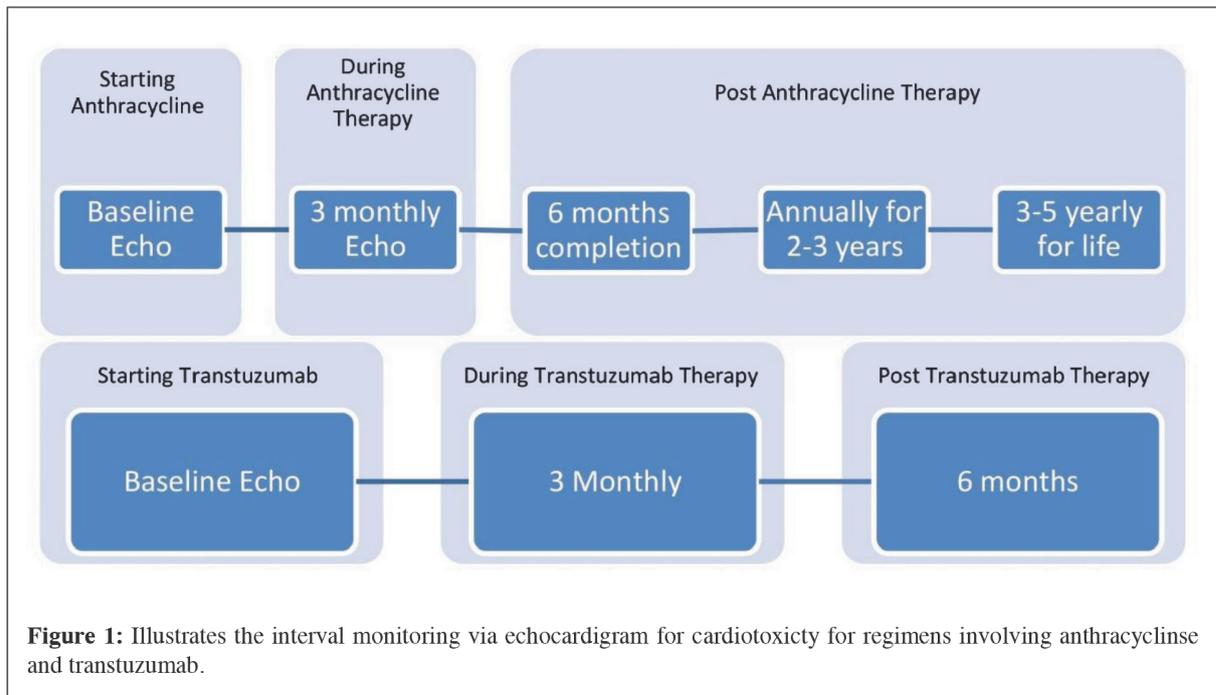
The detection of left ventricular dysfunction is most commonly completed through the frequent monitoring of LVEF via either echocardiography or multi-gated acquisition scanning (MUGA). There is currently no evidence based guidelines describing the intervals at which imaging should be performed. However, recommendations have been made via the European Medical Oncology Society (ESMO). It defines cardiotoxicity a reduction in LVEF greater than 10% to below 55%, or symptomatic heart failure<sup>(5)</sup>.

Trastuzumab is commonly continued for 12 months in the adjuvant setting. Monitoring via echocardiography should be performed at 3, 6, 9 and 12 months during this time, and then again 6 months' post completion<sup>(5,9)</sup>. In the metastatic setting, monitoring can be less vigorous, with evaluation to be done when symptomatic. The duration of anthracycline therapy varies between the different adjuvant chemotherapy regimens. Current recommendations suggest 3-monthly echocardiography during chemotherapy. After cessation of chemotherapy, it is recommended that asymptomatic patients have imaging 6 months post conclusion of treatment, and then annually for 2 or 3 years before changing to 3 to 5 year intervals for life<sup>(5)</sup>. Figure 1 illustrates an echocardiography schedule during and post completion of both chemotherapy agents.

Nevertheless, a limitation of using echocardiography as a marker for cardiotoxicity is that it is relatively insensitive in detecting early toxicity, as a certain amount of myocardial damage must occur before a reduction in LVEF is noticed. Moreover, it is dependent on image quality, assumption of LV geometry, and load dependency, as well as having a significant test-retest variation.

Dose of Doxorubicin	Incidence of cardiotoxicity
400 mg/m <sup>2</sup>	3-5%
550 mg/m <sup>2</sup>	7-26%
700 mg/m <sup>2</sup>	18-48%

Table 1: Showing the increased risk of cardiotoxicity associated with increasing doses of anthracyclines



**Figure 1:** Illustrates the interval monitoring via echocardiogram for cardiotoxicity for regimens involving anthracycline and trastuzumab.

Even though 2D methods are more commonly used, 3D echocardiography has been shown to offer greater reproducibility of LVEF. More sensitive methods include multiple-gated acquisition (MUGA), which would reduce variability, but expose the patient to radiation. MRI is the gold standard for evaluating left ventricular volumes, but is not routinely available and is expensive<sup>(5,15)</sup>. Additionally, an ideal situation would be the identification of cardiotoxicity before a drop in LVEF is found.

Speckle-tracking strain imaging measures the deformation of the myocardium. More specifically the global longitudinal strain (GLS) has shown to be a reproducible and accurate marker of the above<sup>(16)</sup>. It has shown the ability to detect subclinical myocardial dysfunction, with a drop in GLS 3 months after of initiation of chemotherapy predicting future cardiotoxicity with a sensitivity of 78 to 79% and a specificity of 79 to 82%<sup>(15,17)</sup>. A relative percentage drop of greater than 15% from baseline of GLS is suggestive of subclinical LV dysfunction<sup>(16)</sup>. The above methods are promising but are yet to be integrated into routine clinical practice, with 2D echocardiography remaining the mainstay for monitoring cardiotoxicity. Other markers of cardiotoxicity have been investigated to determine patients at high risk of left ventricular dysfunction. Elevated troponins during chemotherapy and particularly, persistent elevation post completion of chemotherapy have been considered as an early marker of myocardial injury.

One analysis looking at 703 patients receiving anthracyclines showed increased incidence of cardiac events, including heart failure and acute pulmonary oedema, in those with elevated troponins. It also showed an asymptomatic decline in the LVEF of patients who had a transient elevation in troponins during chemotherapy, and in particular those patients who had persistent troponin elevation one-month post chemotherapy<sup>(18)</sup>. Although troponin elevation was suggestive of future cardiotoxicity, one study of 81 patients indicated its specificity was only 48%<sup>(17)</sup>. As a result, the use of troponin to detect subclinical cardiotoxicity and influence further management has not yet been characterised and is not routinely used as a marker. Despite this, if troponin is noted to be elevated, more frequent monitoring of LVEF has been suggested in this subgroup, with 3 monthly echocardiography for 1 year post chemotherapy, followed by 6 monthly echocardiography for the next 5 years<sup>(5)</sup>.

### Management

LVEF is regularly monitored during chemotherapy to assess for cardiotoxicity. With regards to anthracyclines, the ESMO guidelines currently recommend that if there is a drop in LVEF below 50% during therapy, the medication should be withheld and re-evaluated in 3 weeks. In the case of improvement in LVEF, chemotherapy can be restarted. In the case of ongoing deterioration, heart failure medications should be initiated, with more frequency clinical and echocardiographic examination.



If the LVEF drops below 40%, chemotherapy should be ceased and alternative options discussed<sup>(5)</sup>. Due to the reversible nature of the left ventricular decline in trastuzumab, a continuation and discontinuation protocol can be used to prolong the duration of therapy. When the ejection fraction drops below 40% or 10% below baseline, treatment can be withheld for 3 weeks and the LVEF re-evaluated. If there is improvement, the patient can be re-initiated on therapy. If the ejection fraction remains below 40%, treatment should be ceased<sup>(5)</sup>.

Patients who are symptomatic or asymptomatic with a depressed ejection fraction while on chemotherapy should be treated in accordance to the American Heart Failure Guidelines. It is recommended that these patients should be initiated on angiotensin converting enzyme inhibitors (ACEi) and beta-blockers. If required, they should also have diuretics added to mitigate fluid retention and considered for spironolactone, nitrates, hydralazine or digoxin based on the indications<sup>(19)</sup>. There are no known interactions between these agents and anthracyclines and trastuzumab<sup>(9)</sup>.

It should also be noted that other causes of heart failure must be excluded before attributing the cause to the chemotherapeutic agents.

Even though most trials evaluating the efficacy of ACEi and beta-blockers in heart failure excluded patients on cardiotoxic chemotherapy from their studies, there is evidence that these drugs are effective in this subgroup. Cardinal et al. trial evaluated the use of enalapril to prevent a drop in LVEF in patients who had elevated troponin secondary to anthracycline therapy (high risk patients). The trial comprised of 473 patients, with 114 patients showing increased troponin who were subsequently randomised into either receiving enalapril (56 patients) or placebo (58 patients). It showed all 56 patients treated with enalapril had preserved LVEF at 1 year, while 43 percent of patients who received placebo, had a significant drop in LVEF (greater than 10% to an LVEF of less than 50%<sup>(20)</sup>). As a result, ESMO guidelines suggest the initiation of enalapril when troponin leaks are present during therapy<sup>(5)</sup>.

A second trial, which observed patients who had a reduced LVEF of less than 45% secondary to anthracyclines, showed an improvement in the systolic function in 42% of these patients when treated with ACEi and Beta-blockers (defined as a 10% absolute increase to greater than 50%), and

a partial response in a further 13% (defined as a 10% absolute increase to less than 50%). Also, it was found that there was an improved rate of response to cardiac medication if started within 2 months of chemotherapy cessation.<sup>(21)</sup> Therefore, the close monitoring of ejection fraction and early initiation of ACEi and beta-blockers are important. Angiotensin receptor blockers (ARB's) are also associated with similar outcomes. The long term benefit of enalapril remains questionable, with a small retrospective study of childhood survivors of cancer showing an improvement in LVEF for up to 6 years, after which the left ventricular function began to deteriorate despite therapy<sup>(22)</sup>. This needs to be further evaluated with prospective trials.

Beta-blockers, ACEi and ARBs have showed promising results in the primary prevention of anthracycline induced cardiotoxicity when evaluated in randomised controlled trials. Four trials examined the use of carvedilol, nebivolol and a combination of metoprolol and carvedilol respectively against a placebo arm. Most recently, Avila et al performed a prospective randomised double blinded placebo controlled trial examining the effect of carvedilol as a primary prophylactic therapy for anthracycline induced cardiotoxicity in 200 patients with HER 2 negative breast cancer. The study did not show a significant difference in LVEF between both groups at 6 months. However, there was reduction in troponin levels, the clinical significance of which is not certain and also a reduction in LV end diastolic dimensions which may suggest a beneficial effect on cardiac remodelling<sup>(23)</sup>. Kalay et al, and Kaya et al, studies showed that patients managed with beta-blockers or ACEi had preserved ejection fraction at 6 months, whilst the placebo arm showed statistically significant drops in ejection fraction<sup>(24,25)</sup>. On the contrary, a trial which followed up patients for 31 months, looking at enalapril, metoprolol and placebo, showed no statistically significant difference between patients treated actively in comparison to placebo, with regards to the incidence of left ventricular dysfunction<sup>(26)</sup>. As a result, the use of these medications in the prevention of left ventricular dysfunction needs to be further evaluated. A meta-analysis of the above studies suggested that patients treated with ACEi and beta-blockers had a greater LVEF in comparison to those who did not (64.03% v 57.48% p = 0.03)<sup>(27)</sup>. The heterogeneity of the studies did not allow the meta-analysis to make firm conclusions and recommended further investigation to confirm the findings.



## Conclusion

Left ventricular dysfunction associated with anthracyclines and trastuzumab remains a key issue in the management of breast cancer. Cardiotoxicity of these agents is currently being monitored via regular echocardiography during and post completion of chemotherapy. The use of global longitudinal strain and troponin levels are being investigated further to assess their utility in determining subclinical cardiotoxicity. Current management includes cessation of the culprit agent and introduction of ACEi and beta-blockers. ACEi and beta-blockers are not routinely used in the primary prophylaxis of chemotherapy induced cardiotoxicity.

**Conflicts of Interest:** Nil

## References

1. *Breast Cancer in Australia*. 2016 [cited 2016 30/1]; Available from: <http://canceraustralia.gov.au/affected-cancer/cancer-types/breast-cancer/breast-cancer-statistics#source-tables>.
2. Chatterjee, K., et al., Doxorubicin cardiomyopathy. *Cardiology*, 2010. 115(2): p. 155-62.
3. Vejpongsa, P. and E.T. Yeh, Prevention of anthracycline-induced cardiotoxicity: challenges and opportunities. *J Am Coll Cardiol*, 2014. 64(9): p. 938-45.
4. Wojnowski, L., et al., NAD (P)H oxidase and multidrug resistance protein genetic polymorphisms are associated with doxorubicin-induced cardiotoxicity. *Circulation*, 2005. 112(24): p. 3754-62.
5. Curigliano, G., et al., Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. *Ann Oncol*, 2012. 23 Suppl 7: p. vii155-66.
6. Ewer, M.S. and S.M. Lippman, Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. *J Clin Oncol*, 2005. 23(13): p. 2900-2.
7. Romond, E.H., et al., Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol*, 2012. 30(31): p. 3792-9.
8. Berardi, R., et al., State of the art for cardiotoxicity due to chemotherapy and to targeted therapies: a literature review. *Crit Rev Oncol Hematol*, 2013. 88(1): p. 75-86.
9. Jahangir, E., et al., Risk assessment and management of anthracycline and HER2 receptor inhibitor-induced cardiomyopathy. *South Med J*, 2015. 108(2): p. 71-8.
10. Jeyakumar, A., et al., Routine cardiac evaluation in patients with early-stage breast cancer before adjuvant chemotherapy. *Clin Breast Cancer*, 2012. 12(1): p. 4-9.
11. Lefrak, E.A., et al., A clinicopathologic analysis of adriamycin cardiotoxicity. *Cancer*, 1973. 32(2): p. 302-14.
12. Swain, S.M., F.S. Whaley, and M.S. Ewer, Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer*, 2003. 97(11): p. 2869-79.
13. Seidman, A., et al., Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol*, 2002. 20(5): p. 1215-21.
14. Ezaz, G., et al., Risk prediction model for heart failure and cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. *J Am Heart Assoc*, 2014. 3(1): p. e000472.
15. Nolan, M.T., et al., Chemotherapy-related cardiomyopathy: a neglected aspect of cancer survivorship. *Intern Med J*, 2014. 44(10): p. 939-50.
16. Liu, J., et al., Contemporary Role of Echocardiography for Clinical Decision Making in Patients During and After Cancer Therapy. *JACC Cardiovasc Imaging*, 2018. 11(8): p. 1122-1131.
17. Sawaya, H., et al., Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. *Circ Cardiovasc Imaging*, 2012. 5(5): p. 596-603.
18. Cardinale, D., et al., Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. *Circulation*, 2004. 109(22): p. 2749-54.
19. Yancy, C.W., et al., 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*, 2013. 62(16): p. e147-239.
20. Cardinale, D., et al., Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation*, 2006. 114(23): p. 2474-81.



21. Cardinale, D., et al., Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol*, 2010. 55(3): p. 213-20. 1.
22. Lipshultz, S.E., et al., Long-term enalapril therapy for left ventricular dysfunction in doxorubicin-treated survivors of childhood cancer. *J Clin Oncol*, 2002. 20(23): p. 4517-22.
23. Avila, M.S., et al., Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity: The CECCY Trial. *J Am Coll Cardiol*, 2018. 71(20): p. 2281-2290.
24. Kalay, N., et al., Protective effects of carvedilol against anthracycline-induced cardiomyopathy. *J Am Coll Cardiol*, 2006. 48(11): p. 2258-62.
25. Kaya, M.G., et al., Protective effects of nebivolol against anthracycline-induced cardiomyopathy: a randomized control study. *Int J Cardiol*, 2013. 167(5): p. 2306-10.
26. Georgakopoulos, P., et al., Cardioprotective effect of metoprolol and enalapril in doxorubicin-treated lymphoma patients: a prospective, parallel-group, randomized, controlled study with 36-month follow-up. *Am J Hematol*, 2010. 85(11): p. 894-6.
27. Yun, S., N.D. Vincelette, and I. Abraham, Cardioprotective role of beta-blockers and angiotensin antagonists in early-onset anthracyclines-induced cardiotoxicity in adult patients: a systematic review and meta-analysis. *Postgrad Med J*, 2015. 91(1081): p. 627-33.