

THE ROLE OF BETABLOCKERS IN LOWERING THE RISK OF CHEMOTHERAPY-INDUCED HEART FAILURE IN BREAST CANCER

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Abstract

Anthracyclines and molecular targeted therapy, pharmacologic agents currently used in breast cancer, are potentially cardiotoxic, leading to cardiac dysfunction, and even to overt heart failure. This paper reviews the art of protecting the heart in breast cancer recipients of chemotherapy with betablockers. The main mechanism of anthracycline induced cardiotoxicity is the oxydative stress, occurring in mitochondrial arena. Recent trials supporting β -blockers cardioprotection in this particular population of patients are discussed. As a result of these studies, betablockers are, along with renin-angiotensin-aldosterone antagonists, statins, and dexrazoxane, the most cardioprotective drugs. The paper also covers some methods (biomarkers, imaging), integrating the sphere of prevention with those of monitoring and treatment. The trials outcomes are illustrated by curves, plots, histograms, tables, etc.

Keywords: chemotherapy-induced cardiotoxicity, breast cancer, betablockers.

1. INTRODUCTION

The heart is a target of injury for many drugs; particularly, cardiotoxic agents are prominent in cancer treatment. As part of the multimodal treatment of locally advanced breast cancer (BC), chemotherapy is currently employed. Cardiologists are increasingly faced with new cardiac disorders related to drug toxicities, as survival of cancer patients continues to improve. The patients being treated for BC are vulnerable, because they usually present several cardiovascular risk factors and/or asymptomatic cardiac disease, that could be aggravated by chemotherapy. Finding agents that limit cardiotoxicity, without decreasing the antineoplastic activity of chemotherapeutics is critical.

This paper reviews the art of protecting potential „broken” hearts with betablockers (BB) in BC recipients of chemotherapeutic agents (Nohria, 2013).

2. MATERIALS AND METHODS

The compounds used in chemotherapy of BC are quite varied in structure and mechanism of action. The oxidative stress is supported by most experimental data as the etiology of anthracycline-induced cardiotoxicity. Anthracyclines seem to reduce the activity of respiratory chains and to compromise the function of, either the adenine nucleotide translocator, or the voltage-dependent anion channel, or both; these proteins are important in ATP generation and transport from mitochondria to cytosol, where it is used for several cellular functions. In addition, by doxorubicin

binding, the activity of bivalent cations (Ca^{2+} , Mg^{2+} , Cu^{2+} , Zn^{2+}) decreases, with subsequent mitochondrial damage and energy depletion.

A pathway of anthracycline-induced cardiac dysfunction/death is proposed in figure 1 (Heide et al., 2007).

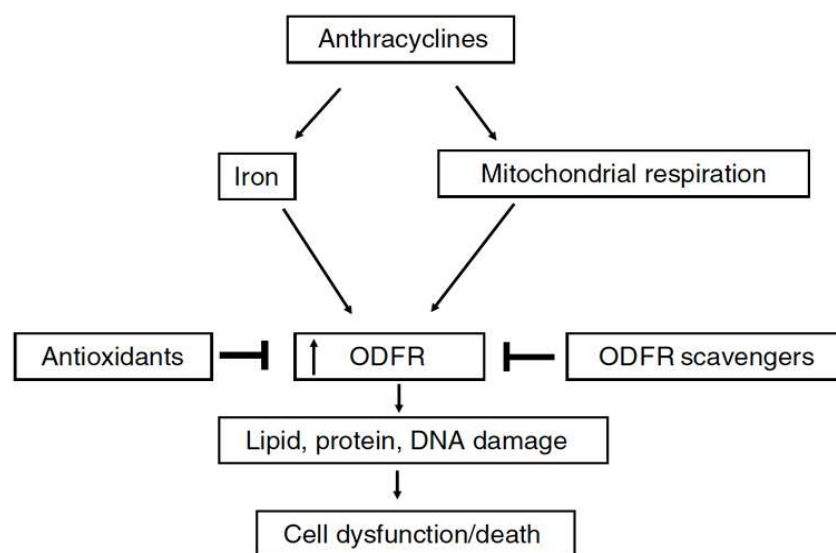


Figure 1. Proposed pathway of anthracycline-induced cardiac dysfunction/death. ODFR = oxygen-derived free radicals (Heide et al., 2007)

There are two types of chemotherapy related cardiac dysfunction (Table 1).

Table 1. Clinical features distinguishing type I and type II CRCD (Ewer & Ewer, 2010)

Type I CRCD (model: doxorubicin)	Type II CRCD (model: trastuzumab)
Cellular death	Cellular dysfunction
Typical anthracycline biopsy changes noted	No typical anthracycline biopsy changes
Cumulative dose-related	Not cumulative dose-related
Permanent damage, mostly non-reversible	Generally reversible
Direct effects on myocytes	Vascular dysfunction

To achieve cardioprotection, it seems rationale to test firstly drugs used for HF treatment, like BB, angiotensin converting enzyme inhibitors / angiotensin receptor blockers, and diuretics; then, other drugs currently used in cardiology, like HMG-CoA-reductase-inhibitors (statins), or calcium channel blockers; last, but not least, other drugs, e. g. dexrazoxane, already well experienced in oncology.

Just before focusing on these pharmacological classes, let us take an at-a-glance perspective on the constellation of trials published in this field. In figure 2, we tried to link two pharmacologic issues: the cardiotoxic chemotherapeutic drugs that could induce cardiac dysfunction / HF (top), with the cardioprotective drugs (bottom). On every arrow is mentioned the trial first author's name.

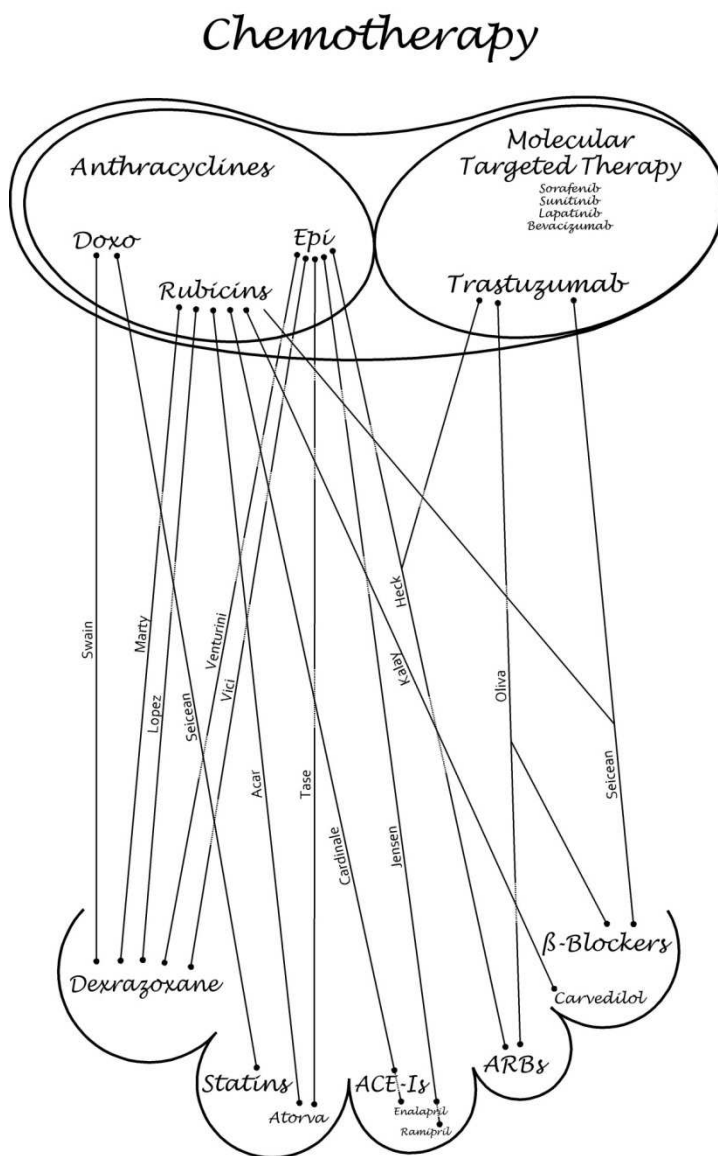


Figure 2. Linking cardiotoxic to cardioprotective drugs in BC chemotherapy recipients

There are several cardioprotective arguments for BB.

3. RESULTS AND DISCUSSIONS

Although the use of cardioprotective agents has been suggested, to the best of our knowledge, the first study of continuous use of BB during anthracycline and trastuzumab treatment has been published recently (Seicean, 2013). The hypothesis was if continuous incidental use of BBs is protective against HF. From a pool of 920 consecutive patients with BC, of age 52.3+/-11.0 years, with normal ejection fraction (EF) before receiving trastuzumab and anthracyclines between 2005 and 2010, the authors compared 106 patients on continuous BBs during BC treatment with 212 matched patients from the same pool with similar characteristics, but not on continuous BBs. During a median follow-up of 3.2+/-2.0 years, 32 incident HF admissions were found, and 28 non-

cardiac, cancer-related deaths occurred before any incidental HF. Coincidental, the continuous use of BBs was associated with lower incidence of HF in patients with BC (hazard ratio 0.2; 95% confidence interval, 0.1-0.5; $p=0.003$). According to this observational study, BBs may be cardioprotective in BC patients treated with anthracyclines or trastuzumab.

Figure 3 illustrates the impact of uninterrupted use of BBs during cancer therapy in patients with BC on trastuzumab and anthracycline therapy, not only addressing the risk of new HF, but also taking into account of the competing risk of cancer-related mortality. BBs seem to be significantly protective with hazard ratios for HF of 0.2 (95% confidence interval [CI], 0.1–0.7); $P=0.008$ and estimated cumulative incidence of 0.25 ($P<0.0005$) over a 5-year period. Other covariates found to be associated with lower risks of incident HF in this cohort were age, being a lifetime non-smoker, and coincidental use of statins.

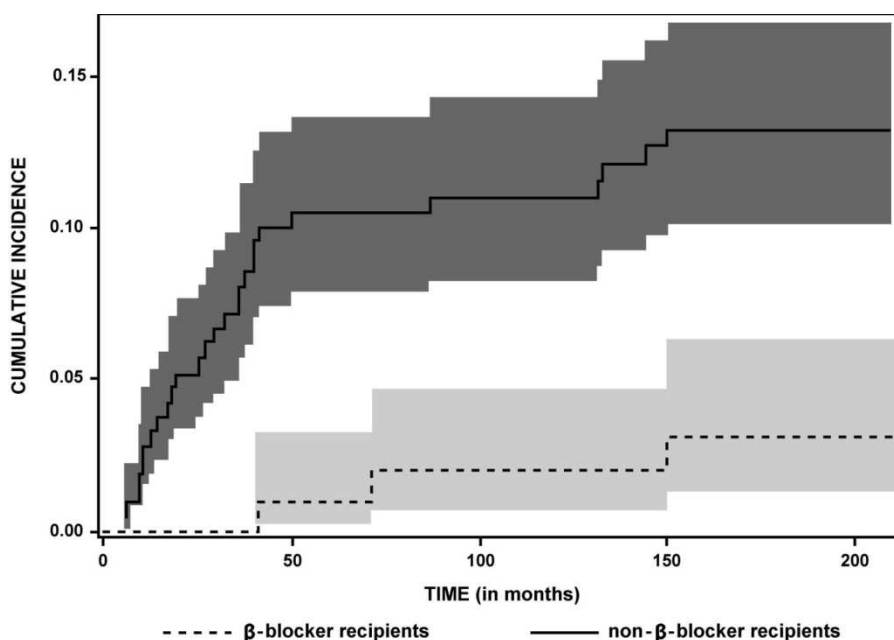


Figure 3. An estimate of cumulative incidence, plotted as step function to display differences in new HF risk between patients with BC on BBs therapy and other patients with BC (Seicean, 2013)

Trastuzumab showed a significant risk for cardiotoxicity, independent of anthracycline therapy with a HR of 9.5 (95% CI, 3.9–23.1); $P<0.0001$, when compared with patients only on anthracycline treatment (Fig. 4). The cumulative incidence of HF occurrence at 3 years was 19.6% (95% CI, 16.8–22.4) in patients on trastuzumab therapy compared with 1% (95% CI, 0.9–1.4) in counterparts not on trastuzumab. The baseline LV measurement was also associated with new HF events (HR, 3.4 [95% CI, 1.5–7.9]; $P=0.004$ per unit).

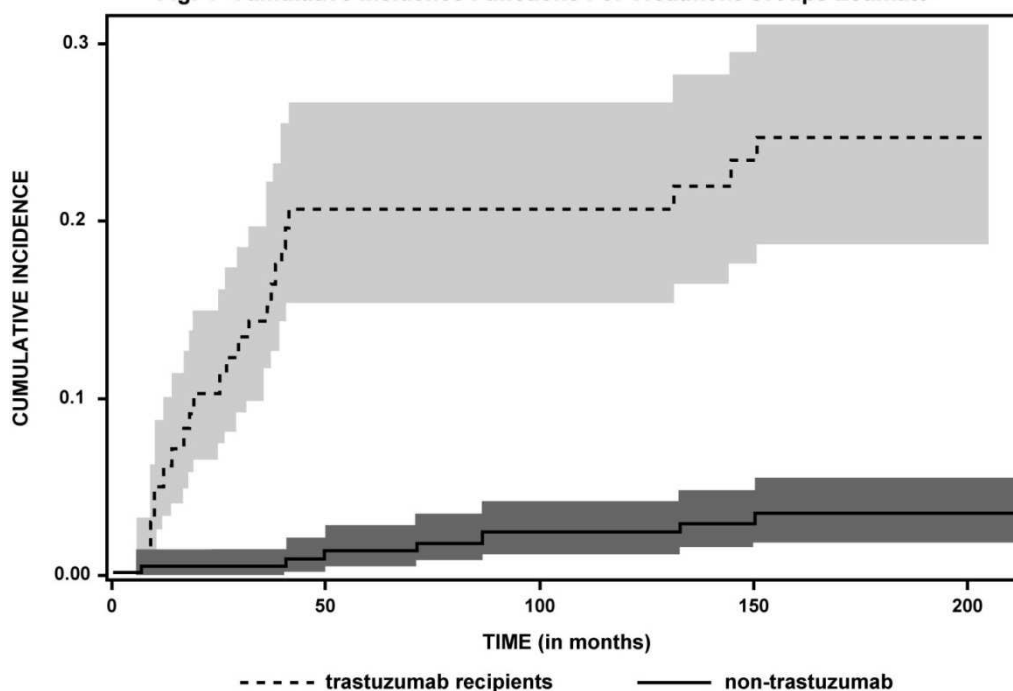


Figure 4. An estimate of cumulative incidence, plotted as step function to display differences in new HF risk between patients with BC on trastuzumab therapy and patients with BC on anthracycline (Seicean, 2013)

Even though the authors do not specify the mean dose or type of BBs, the current study suggests that BBs may cardioprotect the subjects treated with anthracycline or trastuzumab chemotherapy. It seems that the low rates of anthracycline-mediated cardiotoxicity may reflect the BBs cardioprotective effect. Conversely, the high incidence of cardiomyopathy in trastuzumab-treated patients suggests that BBs provide lower cardioprotection with trastuzumab versus anthracyclines. Carvedilol, a non-selective β and α_1 -adrenergic antagonist with antioxidant properties, has been shown to reduce anthracycline-induced cardiotoxicity, by reducing oxidative stress and apoptosis. Methodologically, 25 patients in whom anthracycline therapy was planned were randomized in a carvedilol 12,5 mg/day group, and a placebo one. By the end of six months of follow-up, one patient from the carvedilol group and four from the control group died. The control LVEF (left ventricular ejection fraction) was under 50% in one patient in carvedilol group and in 5 patients in placebo group. The mean EF in carvedilol group was similar at baseline and control echocardiography (70.5 vs. 69.7, respectively; $p = 0.3$). In contrast, the mean LVEF in the control group was significantly lower in control echo (68.9 vs. 52.3; $p < 0.001$) (figure 5).

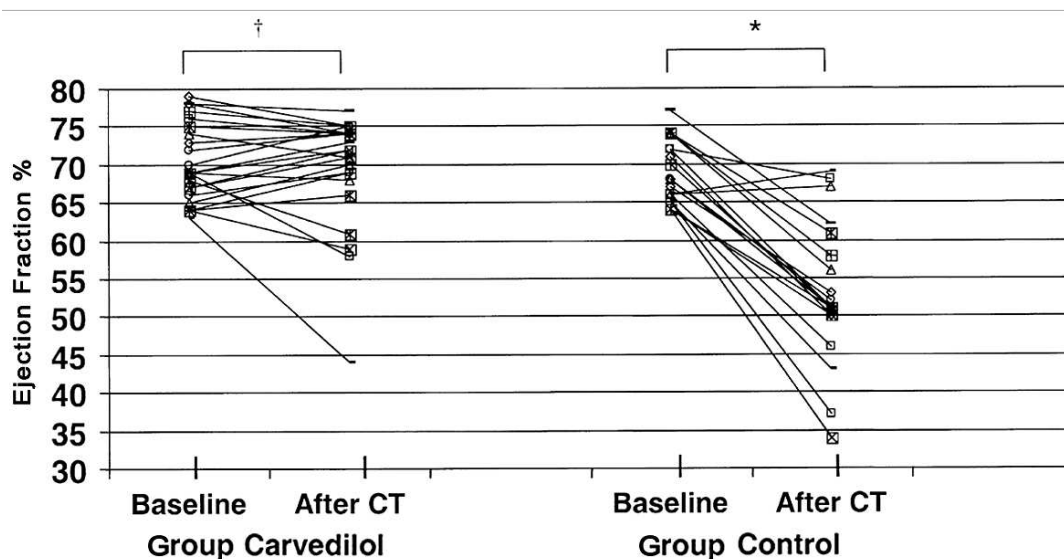


Figure 5. Individual systolic data at baseline and after chemotherapy (CT) in the two groups: carvedilol $p = 0.3$ vs. control $p < 0.001$ (Kalay, 2006)

In a Doppler study, whereas E velocities in the carvedilol group decreased, E velocities and E/A ratios were significantly reduced inside the control group. (figure 6)

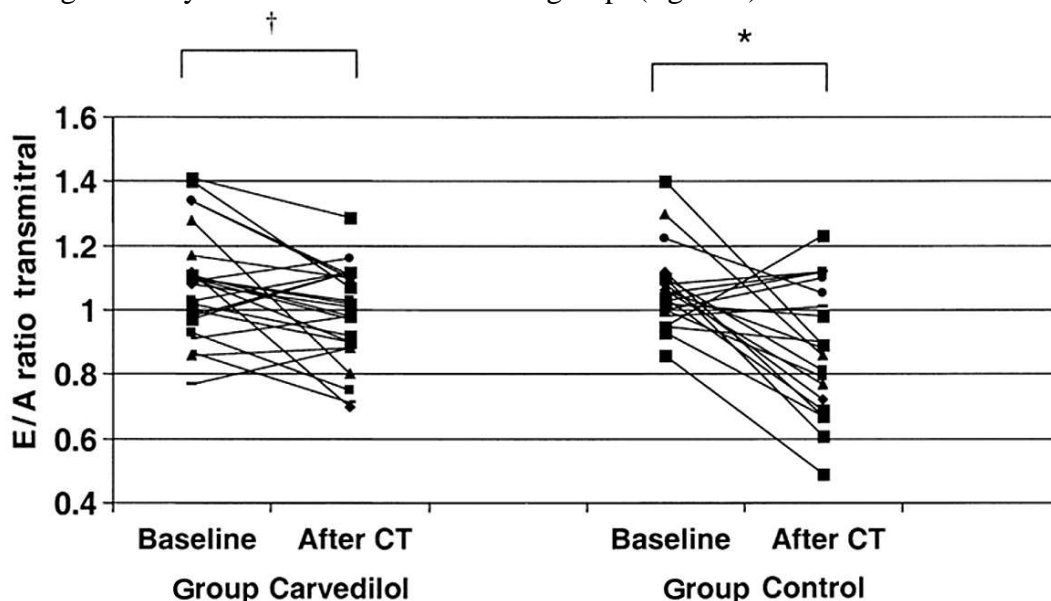


Figure 6. Individual change in mitral early/late diastolic flow (E/A) ratio before and after chemotherapy (CT) in the two groups: carvedilol $p < 0.02$ vs. control $p = 0.23$ (Kalay et al., 2006)

Obviously, the prophylactic use of carvedilol in patients receiving anthracyclines may protect both systolic and diastolic LV functions.

Nebivolol, a β_1 selective antagonist with NO-dependent vasodilatory properties, has been shown to decrease oxidative stress, reduce markers of myocardial injury, and improve LV function when co-administered with anthracyclines (De Nigris et al., 2008).

Taking into consideration the diversity of BBs, the class effect concept is not applicable here. Pharmacologically, in animal individuals exposed to anthracyclines, β_1 and β_2 activation seems to be cardiotoxic and, respectively, cardioprotective. This cardioprotective effect of β_2 receptor activation seems to attenuate the mitochondrial dysfunction observed with anthracyclines. These data suggest that β_1 selective antagonists could provide higher protection against anthracycline-induced cardiomyopathy versus non-selective BBs. However, an analysis of human cancer subjects registry data suggests that β_2 -blockade limits BC specific mortality. That's why, a net effect of β_1 versus β_2 blockade in preventing cancer-related cardiotoxicity remains unclear.

As opposite arguments, we can mention two.

Firstly, in COMBO cohort study authors observed an increased risk to BC recurrence with BBs use (HR = 1.29; 95% CI, 1.01-1.64), compared with non-users. (Boudreaux et al., 2014)

Secondly, the concomitant use of ACE-Is/angiotensin receptor blockers (ARBs) and BBs during the first trimester of adjuvant trastuzumab therapy was correlated with the stage of arterial hypertension, as well as with the decrease in LVEF, whereas the same combo therapy is associated with a recovery of LVEF during months 3-12 of adjuvant trastuzumab therapy (Oliva et al., 2012).

Other drugs that could lower the risk of chemotherapy-induced HF in BC are renin-angiotensin-aldosterone antagonists, HMG-CoA-reductase inhibitors and dexrazoxane.

4. CONCLUSIONS

BB as cardioprotective drugs administered before chemotherapy could prevent cardiotoxicity and subsequent HF. Preventative treatment with BB seems to have quite similar efficiency against cardiotoxicity as dexrazoxane, statin or angiotensin antagonists. Once this approach accepted, after additional conclusive clinical trials, it might enable chemotherapy recipients to reduce subsequently the cardiac-related morbi-mortality (Kalam et al., 2013).

In a similar manner to athletes training to become „fit for fight” and perform at their peak, BB appear to be a necessary component for BC chemotherapy recipients to get ready to battle in the clinical arena.

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