Review Article

Beta-Blocker Attenuates Cardiotoxicity Related Anthracycline Usage

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To summarize the recent trials and studies of the role of beta-blocker on the treatment for cancer patients treated with anthracycline to decrease morbidity and mortality rate. Good management of cancer will result in large numbers of cancer survivors. On the other hand, cancer therapy also has side effects, one of which is cardiotoxicity. Cardiotoxicity could reduce therapy effectiveness, hence, increase disease progression and mortality rate. Anthracyclines is one of the chemotherapy agents with cardiotoxicity as a side effect. Beta-blocker has the ability to reduce cardiotoxicity due to anthracyclines usage.

Keywords: Beta-blocker; Cardiotoxicity; Anthracyclines

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Cancer therapy has been proved to increase the life expectancy significantly worldwide. Cardiovascular side effect or cardiotoxicity has been a major problem in most of the cancer therapy. Before starting chemotherapy by an agent with potential cardiotoxicity, clinicians must perform pre-chemotherapy evaluation by doing electrocardiography and echocardiography[1,2].

Cancer patients who needed cardiotoxicity agents would have their cardiovascular reserve reduced, and the effect results in signaling cascades that promote undesired cancer cell proliferation and would not protect cardiomyocyte and endothelial cells[2].

Cancer therapy with cardiotoxic agents were in three classes as, anthracyclines, ErbB2 inhibitor trastuzumab, and vascular endothelial growth factor (VEGF) signaling pathway inhibitor sunitinib and sorafenib[2].

Kalam et al did a systematic review and meta-analysis of the evidence from randomized trials and observational studies from 14 published articles. They studied a prophylactic pharmacological intervention on prevention of the left ventricular dysfunction and heart failure in patients that underwent chemotherapy with anthracycline as compared to patients with normal ejection fraction (EF) and no history of heart failure. From this study, they have concluded that prophylactic treatment with dexrazoxane, beta-blocker, statin, or angiotensin antagonists have similar efficacies to reduce cardiotoxicity related to anthracycline[3].

Beta-blocker has role in reducing cardiotoxicity related to anthracyclines and the mortality related with this problem[1,2], The present review focused on anthracyclines induced cardiotoxicity and the benefit of beta-blocker.

Mechanisms of cancer-therapy-induced cardiomyocyte injury

Anthracyclines are a double-stranded DNA breaks and free-radical agents. These effects could lead to intracellular accumulation of mutated proteins, resulting in endoplasmic reticulum stress. This agent could accelerate the ubiquitin-proteinase system for protein removal. When this condition is excessive, it can induce caspases cascade activation that leads to cell death. Anthracyclines can also lead to cardiomyocyte injury via the induction of autophagy. Autophagy is a mechanism that can damage the proteins and have organelles removed and then, recycled during stress. It also promotes cell death. Evidence has shown that autophagy has

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a role in doxorubicine induced cardiomyopathy. Anthracyclines exposure results in induction of autophagy activity in cardiomyocytes, by means of increases cytotoxicity. There is strong evidence that histone deacetylase inhibition (HDACi) is an instrument in stress-induced maladaptive autophagy in cardiac myocytes. HDACi promotes autophagy in tumor cells[1,2].

Anthracyclines usage is limited by dose-dependent toxicity. A retrospective study in adults suggest that the incidence of congestive heart failure due to doxorubicin was 1.7% at a cumulative dose of 300 mg/m², 4.7% at 400 mg/m², 15.7% at 500 mg/m², and 48% at 650 mg/m². Anthracyclines target topoisomerase II (Top2), binding to both DNA and Top2 to form complexes that trigger apoptosis. Anthracyclines enter the cells and the quinone moiety will turn to redox cycling, resulting in free radicals through enzymatic pathway via the mitochondrial respiratory chain, and non-enzymatic pathway involving direct interactions between anthracyclines and intracellular iron. It results in impaired mitochondrial function, cellular membrane damage, and cytotoxicity. Toxin hydroxyl radicals from anthracycline-iron complexes act as cytotoxic messengers. The enzyme nitric oxide synthase also plays a role in the generation of anthracycline-mediated reactive nitrogen species and decreases nitrosative stress. Top2a, which overexpressed in proliferating cancer tissues and Top2b, which expressed in adult mammalian cardiomyocytes, are targets of anthracyclines. Cardiomyocytes from wild-type mice will show abnormalities in p53 tumor suppressor gene, b-adrenergic signaling, and apoptotic pathways. Doxorubicin prolonged exposure in wild-type cardiomyocytes with comparison to Top2b/D cardiomyocytes show bad alterations in the expression of genes that regulate mitochondrial function, biogenesis, and oxidative phosphorylation including downregulation of peroxisome proliferator-activated receptor c coactivator-1 a and -1 b. Peroxisome proliferator-activated receptor c coactivator-1 a is a regulator of oxidative metabolism and expressed in the heart. The GTPase Rac 1 is a regulator of DNA damage after Top2 inhibition by anthracyclines. Rac 1 is a subunit of NADPH oxidase and used for activation and reactive oxygen species (ROS) generation. Cardiomyocyte-specific Rac 1 deletion in animal model of doxorubicin exposed lead to reduced ROS formation, attenuated apoptosis, and improved myocardial function. Anthracyclines affect the population of cardiac progenitor cells, which leads to an impaired response to pathologic stress and injury repair[1,2].

Beta-blocker therapy may attenuate anthracycline induced cardiotoxicity via several mechanisms

Beta blocker reduces mortality in systolic heart failure patients and are used for cardiotoxicity related anthracycline. The exact mechanism is still unclear. Researchers hypothesized for certain beta-blockers such as carvedilol, nebivolol, or alprenolol, that they inhibit beta adrenergic receptor mediated G protein-coupled receptor signaling and beta-adrenergic receptor recruitment of beta-arrestin and transactivation of ErbB1 or epidermal growth factor receptor. Beta-arrestin had cardioprotective effects for long term cathecolamine stimulation and activation prosurvival signaling via the ErbB receptor pathway. Carvedilol in animal study could reduce oxidative stress including ischemia reperfusion injury and dilated cardiomyopathy related anthracycline. Carvedilol prevents doxorubicin-induced mitochondrial respiration alterations and changes in capacity of mitochondrial calcium. Beta blocker prevents myocardial calcium overload. In a randomized controlled trial, patients with anthracycline initiation and carvedilol showed reduce in low ventricular EF decline and reduce alterations in diastolic function. In another randomized controlled study, patients with breast cancer had been initiated seven days before anthracycline-based chemotherapy and continued for six months also had nebivolol in their therapy. Compared with the controls (n=18), patients treated with nebivolol (n=27) had attenuation of left ventricular ejection fraction (LVEF) decline at six months[4,5].

Salehi et al evaluated the protective effect of carvedilol in cardiomyopathy caused by anthracyclines in patients suffering from breast cancer and lymphoma. In this clinical trial, patients that underwent chemotherapy were randomly divided into three groups. The first group received placebo and the second and third groups received, respectively, 12.5 mg and 25 mg of carvedilol 24 hours before starting the study. The patients then underwent echocardiography and tissue Doppler to look for cardiomyopathy. After four months, the efficacy of carvedilol was evaluated. Sixty-six patients were evaluated. No significant difference was observed among the groups in terms of mortality, age, gender, type of malignancy, chemotherapy regimen, and cumulative dose of doxorubicin and epirubicin. No

statistically significant differences were observed between control and case groups considering the frequency of systolic cardiomyopathy (p=0.284) or the frequency of diastolic cardiomyopathy (p=0.284). Salehi et al concluded that carvedilol at a daily dose of 12.5 mg had a protective effect against diastolic disorder and at a daily dose of 25 mg had a protective effect against both systolic and diastolic disorders[6].

Kalay et al studied the protective effect of carvedilol in anthracycline-induced cardiomyopathy. The researchers enrolled 25 patients in carvedilol and control groups. In the carvedilol group, 12.5 mg once-daily oral carvedilol was given for six months. The patients were evaluated with echocardiography before and after chemotherapy. LVEF and systolic and diastolic diameters were calculated. At the end of six months of follow-up, one patient in the carvedilol group and four in the control group had died. Control EF was below 50% in one patient in the carvedilol group and in five in the control group. The mean EF of the carvedilol group was similar at baseline and control echocardiography at 70.5 versus 69.7 (p=0.3), but in the control group, the mean EF at control echocardiography was significantly lower at 68.9 versus 52.3 (p<0.001). Both systolic and diastolic diameters were significantly increased compared with basal measures in the control group. In the Doppler study, E velocities in the carvedilol group decreased, E velocities and E/A ratios were significantly reduced in the control group. The conclusion was that prophylactic use of carvedilol in patients receiving anthracycline may protect both systolic and diastolic functions of the left ventricle[7].

Kaya et al with small, prospective, and double-blind study, randomly assigned 45 consecutive patients with breast cancer and planned chemotherapy to receive nebivolol 5 mg daily (n=27), or placebo (n=18). Echocardiographic measurements and N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels were obtained at baseline and at 6-month of chemotherapy. The results showed both studied groups had comparable echocardiographic variables and NT-pro-BNP levels at baseline. At 6-month, the left ventricular end-systolic (LVESD) and end-diastolic diameters (LVEDD) increased in the placebo group as LVESD was 29.7±3.4 to 33.4±4.5 mm and LVEDD was 47.2±3.8 to 52.0±4.6 mm (p=0.01 for both). However, they remained unchanged in the nebivolol group as LVESD was 30.4±3.5 to 31.0±3.6 mm (p=0.20) and LVEDD was 47.0±4.4 to 47.1±4.0 mm (p=0.93). The placebo group also had lower LVEF than the nebivolol group at 57.5±5.6% versus 63.8±3.9% (p=0.01) at 6-month. NT-pro-BNP level remained static in the nebivolol group with 147±57 to 152±69 pmol/L (p=0.77), while it increased in the placebo group with 144±66 to 204±73 pmol/L (p=0.01). Prophylactic use of nebivolol treatment may protect the myocardium against anthracycline-induced cardiotoxicity in breast cancer patients[8].

Screening for risk factors and preventive of cardiac events

Patients should be assessed for pre-existing cardiac risk factors before starting therapy with anthracyclines. Multiple risk factors cardiotoxicity related anthracycline were cumulative of anthracyclines, dosing schedules, previous anthracyclines therapy, radiation therapy, and co-administration of potentially additional cardiotoxic agents. Risk factors in patients were age, obesity, smoking, and pre-existing cardiovascular disease or cardiac risk factors such as hypertension, diabetes, and dyslipidemia. Early use of beta-blockers in the course of the disease shows increased efficacy in the prevention of adverse cardiac events. There is evidence that pre-treatment can reduce in decrease of EF seen with high-dose chemotherapy. The long-term efficacy and tolerability of this strategy deserves to be tested in a clinical trial. However, it should be remembered that beta-blockers are not preventing myocyte apoptosis, the underlying mechanism of anthracycline toxicity. They are improving the heart's compensatory mechanisms, and thus, it is not an antidote, allowing higher doses of anthracycline to be given. If appropriate, patients should also be advised of ways to reduce their cardiac risk through stop smoking, lipid and blood pressure lowering, increased exercise, and losing weight[9-11].

Dose limitation and schedule modification

Anthracycline cardiotoxicity potential can be minimized by keeping the total lifetime cumulative dose of doxorubicin below the recommended threshold. It is generally recommended that the lifetime dose be less than 550 mg/m² for doxorubicin and 900 mg/m² for epirubicin. This approach will result in discontinuation of anthracycline administration to some patients who might gain further benefit from therapy[12,13].

Exposure to peak levels of anthracyclines maybe an important factor in the pathogenesis of anthracycline cardiotoxicity. Since converting bolus injections of anthracycline into prolonged infusions has been reported to be less cardiotoxic, it has been proposed that a potential strategy to decrease the risk

of anthracycline-induced cardiotoxicity is infusion over several hours. Replacing bolus administration of anthracycline with slow infusion, however, remains controversial. Current good practice is to give a bolus via a fast-flowing saline infusion due to the increased risk of extravasation or tissue necrosis with vesicants. For infusing anthracyclines longer than 24 hours, there is the potential to use small infusion devices via a central line. This would reduce the risk of extravasation, but would potentially increase the risk of infections, costs of chemotherapy, and nursing time to set up and flush the line weekly. Additional costs of the procedure and chest X-rays to check line position would also need to be considered. In most cases, prolonged infusions are not recommended as a strategy to reduce cardiotoxicity associated to anthracyclines[14,15].

Conclusion

Anthracyclines remain an important class of drugs in the treatment of cancer, but also a problematic chemotherapeutic agent with cardiotoxic effects. Close monitoring of the patients is essential to reduce the risk of anthracycline-induced cardiotoxicity, as using early implementation of cardioprotective therapies, especially in those individuals at increased risk of developing left ventricular dysfunction after therapy with anthracyclines. Beta-blockers such as carvedilol and nebivolol have been proven to reduce cardiotoxicity related anthracyclines as chemotherapy agents. Reducing the cardiotoxic effects of these agents while improving the oncologic benefits of the therapy could be increased by close collaboration between the oncologist and cardiologist.

What is already known on this topic?

Anthracyclines is one of chemotherapy agents with cardiotoxicity as side effect. Beta-blocker can reduce cardiotoxicity due to anthracyclines usage.

What this study adds?

The authors provided novel summary of the recent trials and studies that strengthen the role of beta-blocker in reducing cardiotoxicity due to anthracyclines usage.

Conflicts of interest

The authors declare no conflict of interest.

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