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Use of Beta-Antagonists for Cardioprotection during Chemotherapy in Oncology Patients

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USE OF BETA-ANTAGONISTS FOR CARDIOPROTECTION DURING CHEMOTHERAPY IN ONCOLOGY PATIENTS

by

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Abstract

Over the years, oncologists are better able to fight cancer and have increased cancer survival, but we are also finding out that these lifesaving therapies can affect the heart and other parts of the body in a negative way. Chemotherapy is excellent at destroying cancer cells, but it also causes collateral damage to other healthy cells as well. There are certain chemotherapeutic agents that are known to cause cardiotoxicity. Currently we are monitoring the heart function of the patients who are receiving these cardiotoxic drugs prior to starting the chemotherapy as well as during and after treatment. However, there are currently no recommendations for what can be done to prevent the cardiotoxicity. The intention of this scholarly review is to look into the benefits and compelling results in adrenergic beta-antagonists and HMG-CoA-reductase inhibitors to reduce the risk of cardiotoxicity during chemotherapy in oncology patients. The goal of this paper is to look at the research and hopefully conclude that either beta-blockers or statins are a reliable option to prevent chemotherapy-induced cardiotoxicity. An extensive literature review was performed and at this time, there are no concrete benefits of using either a beta-blocker or a statin to reduce chemotherapy-induced cardiotoxicity. In the research that has been done, there is some evidence of using these agents to protect the heart. More long-term studies need to be conducted as well as more precise inclusion terms need to be used, such as the exact chemotherapy regimen or the particular cardioprotective medication that is used in the study. At this time, recommendations to prevent chemotherapy-induced cardiotoxicity remains inconclusive.

Keywords: cardiotoxicity, heart failure, beta-blockers, cardio protection, HMG-CoA-reductase inhibitors, cancer, neoplasms

INTRODUCTION

Over the years, oncologists are better able to fight cancer and have increased cancer survival, but we are also finding out that these lifesaving therapies can affect the heart and other parts of the body in a negative way. Since chemotherapy is not able to target just the tumor, there is collateral damage to other cells throughout the body. This off-target destruction can have external signs such as nausea, vomiting, and hair loss. In addition, there is also silent internal damage being done, sometimes to the heart and blood vessels. These injuries can appear immediately while receiving chemotherapy or at times the damage may not surface for years after treatment. There are not a lot of research studies available to look at what options can be done to protect the healthy cells from the effects of the chemotherapy. This is important to consider because of the negative effects that are being caused by the chemotherapy. The benefit of finding a cardioprotective agent for this population could help save the hearts and lives of many oncology patients.

One of the most well known and most studied chemotherapeutic agents that is associated with adverse cardiac events are anthracyclines, such as doxorubicin. Anthracyclines are often used to treat adult malignancies such as breast cancer, sarcoma, lymphoma, or gynecological cancer. For many years, anthracycline-based chemotherapy has caused cardiotoxicity, attributing mostly to the creation of oxygen free radicals causing oxidative stress. More recent research has revealed that the mechanism for anthracycline cardiotoxicity is due to DNA damage from disruption. There are other chemotherapeutic agents associated with cardiotoxic side effects, which include, taxanes (paclitaxel, docetaxel), alkylating agents (carboplatin, cisplatin), small molecule tyrosine kinase inhibitors (lapatinib, imatinib), and trastuzumab which is a monoclonal antibody that is directed at the human epidermal growth factor receptor-2 (HER2). Clinical

manifestations of cardiotoxicity include many disorders, ranging from mild transient arrhythmias and heart failure to possibly deadly conditions such as myocardial infarction or ischemia and cardiomyopathy.

The intention of this scholarly review is to look into the benefits and compelling results of adrenergic beta-antagonists in reducing the risk of cardiotoxicity during chemotherapy in cancer patients. The goal is to look at the research and hopefully conclude that beta-blockers are a reliable option for heart protection during antineoplastic treatment.

Statement of the Problem

It is known that certain chemotherapeutic agents have the potential to lead to cardiac damage, but there is no known method to protect the heart cells from this potent drug. Monitoring for damage prior to starting the chemotherapy treatment, during the course of treatment, and following the completion of treatment is already being done for patients that are receiving chemotherapeutic agents known to cause cardiotoxicity. Methods to prevent this myocardial damage are still being researched. In particular, research is being done to look at the benefit of using beta-blockers or statins to prevent chemotherapy-induced cardiotoxicity. Adrenergic beta-antagonists or HMG-CoA-reductase inhibitors may be the answer to cardiotoxic protection for adults who are receiving cardiotoxic chemotherapy.

Research Question

In adult oncology patients, do either adrenergic beta-antagonists or HMG-CoA-reductase inhibitors reduce the risk of cardiotoxicity in patients receiving chemotherapy?

Methodology

In this review, three databases were searched including Dynamed Plus, PubMed with and without MeSH, and the Cochrane Database of Systematic Reviews. A variety of key terms were

used when searching. The PubMed database was used in which a search was conducted using MeSH, the keywords used were neoplasms [MeSH], cardiotoxicity [MeSH], heart failure [MeSH], beta-blockers [MeSH], and HMG-CoA-reductase inhibitors [MeSH]. A PubMed keyword search was also completed in which the search terms beta-blockers, HMG-CoA-reductase inhibitors, cancer, cardiotoxicity, and cardioprotection were used. Dynamed Plus was used to find the symptoms of cardiotoxicities from chemotherapeutic agents and beta-blockers for heart failure were searched. The final database that was examined was the Cochrane Database of Systematic Reviews. In this last database, the search was conducted using the key terms cancer, beta-blockers, cardioprotection, cardiotoxicity, and heart failure. The inclusion criteria were as follows: the studies were written in the English language, the studies involved adult male and/or female patients who were being treated with chemotherapy that had a risk for cardiotoxicity, and the research was published between 2008 and 2018. This article is not a systematic review encompassing all published articles of chemotherapy induced cardiotoxicity.

LITERATURE REVIEW

Etiology, prevalence, and outcomes of cardiotoxicity in adult patients receiving chemotherapy.

The review article by Babiker et al. (2018) states that chemotherapy is very effective at treating cancer, but it also causes toxicity. Cardiac toxicity or cardiac damage has been related to many cytotoxic agents including; anthracyclines, anthraquinolones, antimetabolites, antimicrotubules, vinca alkaloids, and tyrosine-kinase inhibitors. This article refers to chemotherapy-induced cardiotoxicity (CIC) as a term that refers to toxicity that affects the heart from antineoplastic drugs. Chemotherapy-induced cardiotoxicity can present itself in many ways

that include heart failure, left ventricle ejection fraction decline, hypertension, acute coronary syndrome, atrial fibrillation or other forms of arrhythmias. The article estimates a 1-5% range for an occurrence of symptomatic clinical heart failure from using one of the treatment modalities listed above with an asymptomatic decrease in left ventricular function ranging from 5-20%. Cardiotoxicity related to doxorubicin therapy is unusual in adults at cumulative doxorubicin doses less than 300 mg/m^2, and the rate of heart failure is approximately 7-26% at 550 mg/m^2 and at a rate of 18-48% at a cumulative dose of 700 mg/m^2. Due to the potential of heart failure, there is a maximum lifetime cumulative dose of anthracyclines that is recommended. The recommended cumulative lifetime dose is 400-550 mg/m^2 for adults. New chemotherapy drugs continue to arrive on the market that exhibit their own cardiotoxic complications. It is important to evaluate each patient receiving chemotherapy for risk factors of developing cardiotoxicity and monitor patients throughout their treatment course for the first signs and symptoms of cardiotoxicity. If cardiotoxicity is noticed, the cardiac event should be treated immediately to prevent further heart damage. There are several guidelines available for management of cardiotoxicity related to chemotherapy, but there are limited studies on pharmacologic intervention for prevention. Another limitation seen is that there is no consistency in the different studies in how heart failure or cardiotoxicity is defined. Additionally, prior to starting chemotherapy, the patients can have diverse levels of heart function, therefore making it difficult to say whether or not their previous heart condition advanced due to natural progression or because of chemotherapy they received.

The literature review by Chang et al. (2018) states that patients with cancer are living longer and survival rates have increased over the years. Cardiotoxic effects are becoming recognized more often and some institutions have initiated cardio-oncology to the

multidisciplinary team that is providing care to cancer patients. Asymptomatic systolic or diastolic heart failure are the most common signs of chronic cardiotoxicity in cancer survivors. This makes close monitoring an essential step not only just during treatment but afterwards as well. Doxorubicin, daunorubicin, and mitoxantrone cause dose-dependent cardiomyopathy and congestive heart failure. These antineoplastic agents work by cross-linking topoisomerase IIα to DNA, leading to DNA injury, increased reactive oxygen species, apoptosis, mitochondrial injury, and programmed cell death. Trastuzumab is a targeted antibody that targets Her2/neu in some breast cancers, but it also has toxic effects on the heart and potentially even makes anthracycline heart damage worse. This article touches on the multiple mechanisms that are at the root of cardiotoxicity. If these mechanisms are mastered, healthcare providers will better be able to prevent and treat chemotherapy-induced cardiotoxicity. A major barrier to finding more answers regarding which survivors are more at risk for developing cardiotoxicity are limited to studies with small sample sizes. Until more studies are completed that involve a larger number of participants, there will be a gap in the understanding of chemotherapy-induced cardiotoxicity.

This review by Nathan et al. (2016) looks at pediatric and adult cancer patients separately to discuss cardiac outcomes in cancer survivors which survivors are at risk for developing cardiomyopathy, it reviews prevention and treatment of cancer therapeutic-related cardiac dysfunction (CTRCD) and looks at cardiac surveillance in cancer survivors. The article states that cancer recurrence is the primary cause of mortality early in the survivorship period, but cardiac and pulmonary disease are responsible for a larger proportion of premature deaths over time in this population. The article states that more than 60% of adults and 80% of children with cancer will turn into long-term survivors. Adults that are treated with trastuzumab for cancer are at increased risk for developing cardiomyopathy, which is usually reversible. In cases where

patients were treated with trastuzumab, 12% developed cardiotoxicity within 5 years and patients who relieved trastuzumab plus anthracycline therapy, 20% developed cardiotoxicity within 5 years. The review paper reviewed research studies and papers pertinent to the subject at hand. This paper looks at a seminal study where congestive heart failure was observed in 88 (2.2%) of 3,941 patients that were given doxorubicin, which was usually seen around 23 days (mean of 30 days) after the last dose of chemotherapy was given. The cumulative doxorubicin dose seems to be the best predictor of heart failure with a median dose of 390 mg/m^2 in the patients who developed heart failure and 180 mg/m^2 in those patients who did not develop heart failure. In patients who received greater than 400 mg/m^2, the incidence of congestive heart failure was 3%, 7% in those patients that received 400-550 mg/m^2, and 18% in patients who received doses greater than 550 mg/m^2. However, these numbers could be underestimated due to lack of image-based assessment of subclinical left ventricular dysfunction and limited follow-up. More research is being done on cardiovascular health of cancer survivors, but there are still many unanswered questions. It is still not clear which cancer patients are at increased risk of developing cardiac disease and what type of surveillance, including imaging, should be completed on this population. There is also uncertainty about what the best primary and secondary preventions strategies are for cardiac disease in cancer survivors. Another seen limitation is that cancer survivors have a variety of comorbid health conditions such as cancer recurrence, second malignant neoplasms, and other complications, such as osteoporosis, related to their treatment course, all impacting cardiac health and treatment options that are available.

In a review by Volkova et al. (2011), the authors discuss the pathogenesis and incidence of anthracycline-induced cardiotoxicity plus methods to detect, prevent, and treat the condition. Since the 1950s when anthracycline drugs such as doxorubicin originated, they have since been

used to treat of a variety of solid organ tumors and hematologic malignancies, including leukemia, lymphoma, breast cancer, lung cancer, multiple myeloma and sarcoma. The authors looked at a retrospective analysis where over 4,000 patients who were receiving doxorubicin developed clinical signs and symptoms of congestive heart failure. Heart failure prevalence seemed to increase at a high cumulative dose of anthracycline therapy. Other studies showed that there were changes in left ventricle ejection fraction (LVEF) with anthracycline chemotherapy, especially at higher cumulative doses (Table 1). Many of these changes were asymptomatic with only moderate cardiotoxicity and the LVEF seemed to stabilize with discontinuation of anthracycline therapy. Cardiotoxicity caused from chemotherapy can be characterized into two different categories. Type I cardiotoxicity is caused by cardiomyocyte death through necrosis or apoptosis and is not reversible. Type II cardiotoxicity is caused by dysfunction of cardiomyocytes and can be reversed. The cardiotoxic effect from anthracycline therapy is related to free radical formation caused by doxorubicin metabolism. It appears that cardiomyocytes are more sensitive to the oxidative stress than other cells. Even tumor cells are not damaged by the oxidative stress of anthracycline therapy unless given at very high doses. Anthracycline chemotherapy remains a great option to help treat a variety of cancers, but it is imperative to be aware of the side effects of the therapy, including cardiotoxicity. Being aware of patients that may be at higher risk (Table 2) of developing cardiotoxicity and monitoring all patients on this therapy is important in order to catch the complication early and treat the cardiotoxicity immediately. In order to do this effectively, there is benefit to close collaboration with oncology and cardiology specialties. However, it is still unknown which factors increase the likelihood of a patient developing cardiac damage and to what extent. Researchers are limited by patients having

different past medical histories, varying cancer diagnoses, and diverse treatment types and dosages.

Prevention of chemotherapy-induced cardiotoxicity with the use of HMG-CoA-reductase inhibitors

This article by Sharalaya et al. (2018) addresses strategies to prevent chemotherapy-induced cardiotoxicity. Several years ago, dose-dependent anthracycline-based chemotherapy regimens were linked to cardiotoxicity. Since that time, new regimens have become available that are more selective and more mechanism-based, but they have also been found to have negative cardiac effects. This article included a study that looked at patients (n = 40) undergoing anthracycline-based chemotherapy. The mean ejection fraction for the group that received the statin was unchanged before and after chemotherapy (61 +/- 8% versus 63 +/- 9%, p = 0.14) but was lower in the control group (63 +/- 7% versus 55 +/- 10%, p < 0.0001). Another study that was included in this article looked at anthracycline-based chemotherapy in female breast cancer patients (n = 628). This study showed that patients who received statins, 4 patients (6%) compared to the 27 patients (13%) in the control group, had a lower incidence of heart failure. In conclusion, it is important to prevent cardiotoxicity related to chemotherapy, especially since cancer survivorship is increasing. There is limited data on this topic due to small patient numbers and only using short-term follow up in these studies. There has been an influx of cardio-oncology teams starting in recent years which will hopefully enable larger multicenter randomized controlled trials on chemotherapy-induced cardiotoxicity. Research is limited due to the different antineoplastic regimens that can potentially cause cardiotoxicity.

Anthracyclines and trastuzumab chemotherapeutic agents increase the risk for breast cancer patients to develop heart failure during their treatment or in the years following

completion of treatment. The review done by Upshaw (2018) looks at the risk of cardiac disease in a variety of therapies used to treat breast cancer, including anthracycline chemotherapy. The author compares therapeutic strategies that could potentially reduce the risk of cardiotoxicity during chemotherapy in breast cancer patients. The paper mentions that in some randomized control trials, dexrazoxane has been proven to significantly reduce the risk of cardiotoxicity in anthracycline chemotherapy by inhibiting DNA topoisomerase IIb-anthracycline mediated ds DNA breaks as well as reducing the formation of free radicals. Studies looking at the role of neurohormonal therapy, such as angiotensin-converting-enzyme inhibitors and beta-blockers, show promising results in reducing cardiotoxicity by evaluating troponin values and left ventricle ejection fraction. Statins may also reduce cardiotoxicity with anthracycline therapy by decreasing oxidative stress by evaluating LVEF changes. The article looks at animal model data, a small randomized-control trial, and observational data related to cardioprotection during anthracycline therapy. These studies show that statin therapy may reduce the risk of cardiotoxicity during anthracycline chemotherapy. A limitation of the dexrazoxane therapy to reduce cardiotoxicity is that the studies use patients who received high cumulative anthracycline doses who also had metastatic disease, but no studies have looked at how this works in patients with early breast cancer. There are several unknown questions that need to be answered regarding this topic such as if all patients treated with anthracycline chemotherapy should receive prophylactic treatment to prevent cardiotoxicity as well as what the prognosis and long-term consequences are of LFEF reduction. These studies use a variety of different prophylactic measures to prevent cardiotoxicity. Even when looking at one class of medications, different medications were used, making it difficult to say which class or which drug is best at preventing chemotherapy induced cardiotoxicity.

The Preventing Anthracycline Cardiovascular Toxicity with Statins (PREVENT) trial is currently in phase 2 of the trial with an estimated completion date of 2020. The objective of this study is to determine if atorvastatin 40 mg by mouth daily decreases the change of developing cardiotoxicity in women who are receiving anthracycline-based chemotherapy for stage I-III breast cancer. Inclusion criteria for this study includes: patients with a newly diagnosed stage I-III female breast cancer, patients who are scheduled to receive adjuvant chemotherapy with an Anthracycline agent, have a LVEF greater than 50% (most recent within the last 5 years), being between the ages of 30 to 80 years old, have a prior chemotherapy regiment not containing anthracyclines is allowed, patient is able to hold breath for 15 seconds, ECOG 0 or 1, and prior cancers are allowed if no evidence of disease in the last 5 years. The women (n = 250) will participate in a double-blind, placebo-controlled, randomized clinical trial of 0 or 40 mg of atorvastatin daily. Magnetic resonance imaging (MRI) will be used to accurately measure LVEF. This is the first systematic collection of data of the mechanism and time course by which heart failure evolves in patients that are receiving anthracycline-based chemotherapy for female breast cancer. In conclusion of the current trial, the hope is to prove that the use of affordable statins, such as atorvastatin, will exhibit cardioprotective properties and improve the survival in breast cancer patients.

Doxorubicin chemotherapy can lead to cardiotoxicity due to the intense cardiac oxidative stress and inflammation. Statins, or 3-Hydroxy-3-methylglutaryl coenzyme (HMG-CoA-reductase inhibitors), work through anti-inflammatory and antioxidative mechanisms. This study by Riad et al. (2009) looks at whether or not fluvastatin pretreatment can attenuate doxorubicin-induced cardiotoxicity. In this study, eight to ten-week-old C57BL/10 mice were randomly divided into three groups (n = 6 per group). Two of the groups received doxorubicin at a dose

that had been shown to be cardiotoxic and the third group was given saline. Four days prior to starting the regimen, one of the doxorubicin groups were given 100 mg/kg/day fluvastatin and the other doxorubicin group was given saline. The third group without doxorubicin, the placebo group, received no further treatment. Systolic function was measured by left ventricle end-systolic pressure and dP/dt max as a marker of left ventricle contractility. Using dP/dtmin and the end-diastolic-pressure-volume relationship, diastolic pressure was measured. Global cardiac function was measured by stroke volume, heart rate, and cardiac output. Results of the study showed that five days following the doxorubicin administration, untreated mice displayed significantly impaired systolic (LVP, −29%; d*P*/d*t*max, −45%; $P < 0.05$), diastolic (d*P*/dtmin, −44%; stiffness, +275%; $P < 0.05$), and global left ventricle function (SV, −61%; HR, −18%; CO, −68%; $P < 0.05$) versus the placebo group. Therefore, Raid's group concluded that using a statin, such as fluvastatin, to pretreat patients receiving doxorubicin therapy helps to prevent cardiotoxicity. There are limitations to this study, the first being that this study was done in mice instead of humans. More research would need to be completed to ensure that pretreatment with a statin would beneficial for patients receiving doxorubicin chemotherapy. It would also be important to consider if statin treatment would counteract with the oncological effect of doxorubicin. Another limitation to this study was the small sample size. There was only a total of 18 mice used in the study with 6 mice in each group. In order to formulate recommendations for the use of statins for cardioprotection in doxorubicin chemotherapy, a larger sample size would be more beneficial to compare results to.

Mechanism of action of adrenergic beta-antagonists

Gorre et al. (2010) wrote a paper focusing on the mechanism of action of beta-blockers and share their analysis on how beta-blockers should be used in cardiovascular pathology. Beta-

blockers influence the heart by decreasing spontaneous depolarization of pacemakers which causes prolongation of sinus node cycle length, atrioventricular refractory period, and atrioventricular conduction times. Beta-blockers that fall into the first-generation category are known as non-selective agents, while second-generation agents bind more to B1-receptors instead of B2-receptors. The article continues to discuss the various properties of beta-blockers and the mechanism of action in regard to hypertension, heart failure, and other indications for beta-blockers.

Prevention of chemotherapy-induced cardiotoxicity with the use of beta-blockers

Avila et al. (2018) conducted a randomized double-blind control study to assess the role of carvedilol, a beta-blocker, in preventing anthracycline chemotherapy cardiotoxicity. There were 192 Her2-negative breast cancer patients with normal LVEF. The patients received either carvedilol or placebo throughout their course of anthracycline chemotherapy treatment. The primary endpoint was prevention of a greater than or equal to 10% reduction in LVEF at the six month point with secondary outcomes of carvedilol effects on B-type natriuretic peptide, troponin I, and diastolic dysfunction. In review of the primary endpoint, 14 patients (14.5%) in the carvedilol group and 13 patients (13.5%) in the placebo group ($p = 1.0$) reached this goal. In review of secondary outcomes, the B-type natriuretic peptide and LVEF did not have a significant difference between groups. There was a significant difference between the groups with a lower troponin I seen in the carvedilol group ($p = 0.003$). There was also a lower incidence of diastolic heart failure found in the carvedilol group ($p = 0.039$) when compared to the control group. Therefore, carvedilol did not affect early onset of LVEF reduction, but the carvedilol did have a significant reduction in troponin levels and diastolic dysfunction. The authors identified several limitations to the study. The first limitation was that the study was

conducted in one single cancer center, but it did include a representative sample of breast cancer patients. Another limitation that was noted by the authors was that the incidence of early onset cardiotoxicity was lower than expected (13.5% to 14.5%) which could decrease the statistical power to study carvedilol effects. Due to primary endpoints not being met, the secondary endpoints must be carefully studied to make sure it is interpreted correctly. Using carvedilol for chemotherapy-induced cardiotoxicity may not benefit left ventricular function, but due to the Troponin I result, carvedilol may be of assistance for myocardial injury prevention. Another limitation that can be seen in this study is that the population is based solely on breast cancer patients at one cancer center using one chemotherapeutic agent. There are several chemotherapeutic agents used that can lead to cardiotoxicity used to treat not only breast cancer, but other forms of cancer as well.

Beheshti et al. (2016) led a randomized control study using 70 female breast cancer patients that were planning to receive doxorubicin chemotherapy. There were 70 female patients enrolled in the study and 30 of the females were randomly selected to receive 6.25 mg of carvedilol daily throughout chemotherapy. The remaining 40 females received a placebo as the control group. Left ventricular ejection fraction and strain/strain rate measured by echocardiography were evaluated in all participants one week before and one week after chemotherapy. Results showed that the case group showed no significant decrease in strain/strain rate parameters following intervention; however, there was a significant decrease in the control group (all p values <0.001). The study also showed that the mean differences of strain parameters in the case group were significantly less than the control group and also the strain-rate parameters. This study shows that doxorubicin-induced cardiotoxicity can be reduced with carvedilol prophylaxis. Initially 90 patients were enrolled in the study, 45 in each group. There

were 20 patients that were terminated due to poor compliance and inaccessibility. The GE Healthcare Vivid-7 ultrasound system was used throughout the study. Limitations include that this system did not allow for evaluation of global, radial, and circumferential strain and strain rate. Cardiotoxicity can appear weeks to even years following the use of a cardiotoxic chemotherapeutic agent. This study had no long-term follow up with its participants to monitor cardiac function after initial chemotherapy treatment.

A systematic review and metanalysis was completed by Yun et al. (2015) to determine the efficacy of beta-blockers and angiotensin antagonists to prevent left ventricular dysfunction and cardiac events in cancer patients receiving anthracycline chemotherapy. The authors searched PubMed, EMBASE, and Cochrane databases up to July 2015 for relevant articles that were limited to trials comparing the efficacy of cardioprotective agents with control groups in adult patients over 18-years-old that were treated with anthracycline-based chemotherapy. Anthracycline-based chemotherapy regimens are common therapy options for patients with breast cancer as well as lymphomas. This chemotherapy regimen has been shown to cause chemotherapy-induced cardiotoxicity. The results of the author's analysis showed an association of angiotensin antagonists and beta-blocker therapy with high post-chemotherapy LVEF of 64.03% compared with 57.48% for control treatment. Experimental agents such as beta-blockers and ACE inhibitors, were seen to be more beneficial on LVEF preservation when the accumulative dose of anthracycline therapy was higher. The point estimate for the relative rate of cardiac dysfunction was lower in the experimental arm, the difference was not statistically significant. The benefit of experimental agents on LVEF preservation was prominent in those given a higher accumulative dose of anthracyclines. In the author's final analysis, the use of angiotensin antagonists and beta-blockers during treatment with high accumulative dose

anthracycline therapy was beneficial. The use of these agents was associated with better VFEF preservation. They concluded that there is some support for using these cardioprotective agents with a high accumulation dose of anthracycline chemotherapy in cancer patients. The authors observed several limitations in their systematic review and metanalysis. One limitation that was noted was that there were different beta-blockers used in different studies, some of which were selective and some of which were non-selective. Another limitation was that in one study, LVEF was not assessed at baseline and at twelve months, but was assessed at one, three, six, and twelve months after chemotherapy plus when it was clinically indicated. Obtaining a pre-chemotherapy and post-chemotherapy LVEF is a guideline set forth by the National Comprehensive Cancer Network. This information serves as an indicator of cardiovascular reserve capacity in those patients who receive cardiotoxic chemotherapy. This systematic review and metanalysis only assessed studies that looked at preventing early-onset (defined as 6-12 months after chemotherapy) and not long-term cardiotoxic effects following chemotherapy. There are several areas that need further research in order to make concrete recommendations. Follow up was limited to a maximum of one year in all of the studies that were reviewed Cumulative incidence of anthracycline-induced cardiotoxicity will continue to increase over time, much longer than one year. Therefore, these studies are not able to review the benefit of these cardioprotective agents in late-onset cardiotoxicity following administration of anthracycline chemotherapy. The exact medications used were not reported in the analysis. Instead a broad class of medication were listed for cardiotoxicity prevention, but in order to make recommendations on exact drug and does to prevent chemotherapy induced cardiotoxicity, researchers much focus and report which exact medication and dose was used so outcomes and recommendations can be consistent.

DISCUSSION

It is well known that certain chemotherapy agents, such as anthracycline-based regimens, can cause cardiotoxicity that can be seen in multiple forms such as arrhythmias, heart failure, or cardiomyopathy. These effects can be seen throughout the course of chemotherapy or they can be seen months or even years following the completion of chemotherapy. In the current research that is published, it is difficult to make concrete practice recommendations because of the various chemotherapeutic agents that are used in the studies and the different methods of evaluation of cardiac damage varies from study to study.

HMG-CoA-reductase inhibitors protect the heart through anti-inflammatory and antioxidative mechanisms and have the potential to protect the heart from chemotherapy-induced cardiotoxicity. In the article by Sharalaya et al. (2018) and the article by Upshaw (2018), there is evidence that points to the use of HMG-CoA-reductase inhibitors being beneficial to prevent chemotherapy-induced cardiotoxicity. The studies in these papers have many limitations such as small sample size and using only short-term follow-up. There is still a lot of research that needs to be done before any further recommendations can be made. The PREVENT trial has an estimated completion date of 2020 and will hopefully provide more conclusive results on whether or not statins should be used to prevent chemotherapy-induced cardiotoxicity.

Adrenergic beta-antagonists effect the heart by reducing spontaneous depolarization of pacemakers to cause continuation of sinus node cycle length, atrioventricular refractory period, and atrioventricular conduction times, Gorre et al. (2010). Due to the mechanism of action of this class of medication, it is thought that it may be of benefit to prevent chemotherapy-induced cardiotoxicity and research is being done to determine if this is true. Avila et al. (2018) reports that the beta-blocker carvedilol may reduce diastolic heart failure and lower troponin I values

leading to a decreased incidence of myocardial injury. The metanalysis by Yun et al. (2015) shows that beta-blockers and ACE inhibitors may help preserve left ventricle ejection fraction in patients who are receiving the cardiotoxic anthracycline chemotherapy. This could be related to cardioprotective factors or it could be anthracycline dose dependent. Unfortunately, the research that has been done on beta-blockers and chemotherapy-induced cardiotoxicity is inconclusive. Different beta-blockers and different cardiotoxic chemotherapeutic agents were used in the various studies that have been completed.

In conclusion, the use of any pharmacological therapy to reduce chemotherapy-induced cardiotoxicity cannot yet be recommended. There is evidence that points to both HMG-CoA-reductase inhibitors and adrenergic beta-antagonists to be beneficial for cardioprotection; however, until there is further research completed that looks at specific chemotherapeutic agents, specific statins or beta-blockers, and long-term studies looking at heart function, no specific recommendations may be made to prevent chemotherapy-induced cardiotoxicity.

APPLICATION TO CLINICAL PRACTICE

Anthracycline chemotherapy along with some other antineoplastic drugs such as taxanes, alkylating agents, small molecule tyrosine kinase inhibitors, and trastuzumab may lead to cardiotoxicity presenting as arrhythmias, heart failure, ischemic injury, or cardiomyopathy. In research studies and in clinic practice, the oncology patients that are recommended to receive these therapies are having their cardiac function monitored, often before, during, and after treatment. Unfortunately, there are no recommendations for prevention of chemotherapy-induced cardiotoxicity at this time.

In studying the review articles above, it is common for oncology patients that are on cardiotoxic regimens to be referred to cardiology to test the heart function before starting therapy and follow heart function during and after therapy. Echocardiograms or MUGA (multiple-gated acquisition) scans are the studies of choice to assess and monitor cardiac function, but other laboratory values such as troponin I may be used as well to assess cardiac function.

Until further research is done regarding the use of beta-blocks or statins for prevention of chemotherapy-induced cardiotoxicity, monitoring the patient's cardiac function is very important. Healthcare providers need to be aware of the cardiotoxic effects that may result during or following antineoplastic therapy. Even though cardiac monitoring may start under the direct care of the patient's oncologist, it is important for primary care providers to be aware of the side effects of these chemotherapeutic agents and assess these patients in the clinic with these side effects in mind. Whether a patient is just starting their chemotherapy regimen or is five years post-treatment, all healthcare providers should make sure to do a thorough cardiac exam to rule out any residual damage from the chemotherapy.

Figures

Table 1.

Dose related risk of doxorubicin-induced congestive heart failure by Volkova et al. (2011).

Cumulative Dose (mg/m^2)	Patients with CHF (%)
150	0.2
300	1.6
450	3.3
600	8.7

Table 2.

Factors associated with increased risk of anthracycline-induced cardiotoxicity by Volkova et al. (2011).

Age >65 years of <4 years
Female gender
Hypertension
Pre-existing cardiac disease
Mediastinal radiation
Treatment with cyclophosphamide, paclitaxel, or trastuzumab
Cumulative anthracycline dose
Higher individual anthracycline doses

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