2019

Use of Beta-antagonists or HMG-CoA Reductase Inhibitors for Cardioprotection During Chemotherapy in Oncology Patients

Nicole Streich
University of North Dakota

Use of beta-antagonists or HMG-CoA reductase inhibitors for cardioprotection during chemotherapy in oncology patients

UND School of Medicine & Health Sciences
University of North Dakota

Nicole Streich, PA-S

Department of Physician Assistant Studies, University of North Dakota School of Medicine & Health Sciences

Abstract

Over the years, oncologists are better able to fight cancer and have increased cancer survival, but we are also finding 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. 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-antagonists or hmg-CoA reductase 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.

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. 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-antagonists 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 these drugs. 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-antagonists or hmg-CoA reductase 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?

Literature Review

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

- Cardiac toxicity has been related to many cytotoxic agents including; anthracyclines, anthraquinolones, antimetabolites, antimicrotubules, vinca alkaloids, and tyrosine-kinase inhibitors, Babiker et al. (2018). There is no consistency in how heart failure or cardiotoxicity is defined and there was varying degrees of heart function prior to starting therapy.
  - ❑ 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.
- Asymptomatic systolic or diastolic heart failure are the most common signs of chronic cardiotoxicity in cancer survivors, Chang et al. (2018). This makes close monitoring an essential step not only just during treatment but afterwards as well. Study limited by small sample size.
- 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, Nathan et al. (2016) Limitations include varying comorbid health conditions.
- Volkova et all (2011) reported that heart failure prevalence seems to increase at a high cumulative dose of anthracycline therapy. Research is limited due to patients having different medical histories, varying cancer diagnoses, and diverse treatments. Table used to compare cumulative doxorubicin dose and percentage of patients with CHF.

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

- Patients (n = 40) undergoing anthracycline-based chemotherapy with mean EF for the statin group 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), Sharalaya et al. (2018). Limited by small sample size and no long-term follow-up.
  - ❑ Anthracycline-based chemotherapy in female breast cancer patients (n = 628). This study showed that patients who received HMG-CoA reductase, 4 patients (6%) compared to the 27 patients (13%) in control group had a lower incidence of heart failure, Sharalaya et al. (2018).
- Upshaw (2018) compared several medications to reduce chemotherapy induced cardiotoxicity. Most showed promise, including beta-antagonists and HMG-CoA reductase inhibitors. This study was limited by using various medications in one specific class.
- Riad et al. (2009) looked if fluvastatin pretreatment can attenuate doxorubicin-induced cardiotoxicity. The study was done in mice, not humans.
  - ❑ Results of the study showed that five days following the doxorubicin administration, untreated mice displayed significantly impaired systolic (LVP, −29%; d*P*/dtmax, −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.

Mechanism of action of adrenergic beta-antagonists

- Beta-antagonists influence the heart by decreasing spontaneous depolarization of pacemakers which causes prolongation of sinus node cycle length, atrioventricular refractory period, and atrioventricular conduction times, Gorre et al. (2010).

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

- Carvedilol to prevent anthracycline chemotherapy cardiotoxicity using 192 Her2-negative breast cancer patients with normal LVEF, Avila et al. (2018). Study only looked at breast cancer patients in one cancer center.
  - ❑ Carvedilol did not affect early onset of LVEF reduction, but the carvedilol did have a significant reduction in troponin levels and diastolic dysfunction.
- Carvedilol 6.25 mg daily throughout chemotherapy in female breast cancer patients that were planning to receive doxorubicin chemotherapy, Beheshti et al. (2016). Study did not include any long term follow-up.
  - ❑ There was a significant decrease in the control group (all p values <0.001). The mean differences of strain parameters in the case group were significantly less than the control group and also the strain-rate parameters.
  - ❑ Doxorubicin-induced cardiotoxicity can be reduced with carvedilol prophylaxis.
- Efficacy of beta-antagonists and angiotensin antagonists to prevent left ventricular dysfunction and cardiac events in cancer patients receiving anthracycline chemotherapy, Yun et al. (2015). No long-term follow-up. Exact medications used were not reported.
  - ❑ 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-antagonists and ACE-I, were seen to be more beneficial on LVEF preservation when the accumulative dose of anthracycline therapy was higher.

Discussion

Chemotherapy agents can cause cardiotoxicity that can be seen 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.

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.
- Evidence may show that these may be beneficial to prevent chemotherapy-induced cardiotoxicity, Sharalaya et al. (2018) and the article by Upshaw (2018).

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).
- Carvedilol may reduce diastolic heart failure and lower troponin I values leading to a decreased incidence of myocardial injury, Avila et al. (2018).
- beta-antagonists and ACE inhibitors may help preserve left ventricle ejection fraction in patients who are receiving the cardiotoxic anthracycline chemotherapy, Yun et al. (2015). This could be related to cardioprotective factors or it could be anthracycline dose dependent.

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. Until there is further research completed that looks at specific chemotherapeutic agents, specific hmg-CoA reductase or beta-antagonists, and long-term studies looking at heart function, no specific recommendations may be made to prevent chemotherapy-induced cardiotoxicity.

Applicability 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.
- Cardiac function is monitored before, during, and after treatment. Unfortunately, there are no recommendations for prevention of chemotherapy-induced cardiotoxicity at this time.
- 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.
- Until further research is done regarding the use of beta-antagonists or HMG-CoA reductase inhibitors 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. It is important for providers to be aware of the side effects of these chemotherapeutic agents and assess these patients with these side effects in mind. Whether a patient is just starting their chemotherapy regimen or is five years post-treatment, providers should make sure to do a thorough cardiac exam to rule out any residual damage from the chemotherapy.

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

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

References

Avila, M.S., Ayub-Ferreira, S.M., Wanderley, M.R., Cruz, F.D., Brandao, S.M., … Bocchi, E.A. (2018). Carvedilol for prevention of chemotherapy-related cardiotoxicity. *Journal of the American College of Cardiology, 71(20), 2281-2290.* http://dx.doi.org/10.1016/j.jacc.2018.02.049

Babiker, H.M., McBride, A., Newton, M., Boehmer, L.M., Drucker, A.G., L.M., Gowan, M., … Hollands, J.M. (2018). Cardiotoxic effects of chemotherapy: A review of both cytotoxic and molecular targeted oncology therapies and their effect on the cardiovascular system. *Critical Reviews in Oncology/Hematology,* 126, 186-200. http://dx.doi.org/10.1016/j.critrevonc.2018.03.014

Beheshti, A.T., Toroghi, H.M., Hosseini, G., Zarifian, A., Shandiz, F.H. & Fazlinezhad, A. (2016). Carvedilol administration can prevent doxorubicin-induced cardiotoxicity: A double bind randomized trial. *Cardiology,* 134(1), 47-53.

Csapo, M., Lazar, L. (2014). Chemotherapy-induced cardiotoxicity: pathophysiology and prevention. *Clujul Medical.* 87(3): 135-142.

Chang, V.Y. & Wang, J.J. (2018). Pharmacogenetics of chemotherapy-induced cardiotoxicity. *Current Oncology Reports,* 20(7). http://dx.doi.org/10.1007/s11912-018-0696-8

Gorre, F., & Vandekerckhove, H. (2010). beta-antagonists: Focus on mechanism of action which beta-blocker, when and why? *Acta Cardiologica,* 65(5), 565-570. http://dx.doi.org/10.1080/AC.65.5.2056244

Hundley, G. MD. (2013). Preventing anthracycline cardiovascular toxicity with hmg-CoA reductase (PREVENT). *U.S. National Library of Medicine.* ClinicalTrials.gov Identifier: NCT01988571

Nathan, P.C., Amir, E., & Abdel-Qadir, H. (2016). Cardiac outcomes in survivors of pediatric and adult cancers. *Canadian Journal of Cardiology,* 32(7), 871-880. http://dx.doi.org/10.1016/j.cjca.2016.02.065

Riad, A., Bien, S., Westerman, D., Becher, P.M., Loya, K., Landmesser, U., … Tschope, C. (2009). Pretreatment with statin attenuates the cardiotoxicity of doxorubicin in mice. *Cancer Research,* 69(2), 695-699. http://dx.doi.org/10.1158/0008-5472.CAN-08-3076

Sharalaya, Z., & Collier, P. (2018). Prevention of cardiotoxicities with traditional and novel chemotherapeutic agents. *Current Heart Failure Reports,* 15(4), 260-269. http://dx.doi.org/10.1007/s11897-018-0400-1

Upshaw, J.N. (2018). Cardio-oncology: Protecting the heart from curative breast cancer treatment. *Gland Surgery,* 7(4), 350-365. http://dx.doi.org/10.21037/gs.2017.11.09

Volkova, M. & Russell III, R. (2011). Anthracycline cardiotoxicity: Prevalence, pathogenesis and treatment. *Current Cardiology Reviews.* 7(4), 214-220. http://dx.doi.org/10.2174/157340311799960645

Yun, S., Vincelette, N.D., & Abraham, I. (2015). Cardioprotective role of beta-antagonists and angiotensin antagonists in early-onset anthracyclines-induced cardiotoxicity in adult patients: A systematic review and meta-analysis. *Postgraduate Medical Journal,* 91(1081), 627-633.