Among Adult Cancer Survivors Treated With Anthracycline Chemotherapies, Concurrent Statin Therapy May Reduce Their Decline in Left Ventricular Dysfunction

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Among Adult Cancer Survivors Treated With Anthracycline Chemotherapies, Concurrent Statin Therapy May Reduce Their Decline in Left Ventricular Dysfunction

Abstract

Background:

Anthracycline chemotherapies are used to treat a wide variety of malignancies. A study by Von Hoff et al showed that 2.2% of patients previously treated with anthracycline chemotherapy were later diagnosed with heart failure. A more recent study by Smain, et al, showed that 26% of patients receiving higher doses of anthracycline were later diagnosed with heart failure. Statins have been shown to have properties that may allow them to be cardioprotective. Animal research performed by Henninger et al suggests that statin therapy is beneficial for reducing anthracycline-related cardiotoxicity in mice. It also lends evidence supporting the theory that, among adult cancer survivors treated with anthracycline chemotherapies, statin therapy may reduce their decline in left ventricular dysfunction, which is the aim of this systematic review.

Methods:

An exhaustive search using MEDLINE-Ovid, ClinicalKey, and Web of Science was performed using the terms: statin, anthracycline, and heart failure. Studies were excluded if they were review articles, opinion-based articles, animal studies, published over five years ago, or written in a language besides English. Articles were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria.

Results:

Three studies met criteria and were used in this systematic review. A randomized controlled trial by Acar et al found that the mean reduction in left ventricular ejection fraction (LVEF) was significantly lower in the statin group than the control group (P < 0.0001). A retrospective observational study by Seicean et al found that only four cases of heart failure requiring hospitalization occurred in the group receiving statin therapy, as opposed to 23 cases in the control group (P = 0.03; HR: 0.3). Another retrospective observational study by Chotenimitkhun et al showed a statistically significant, linear, dose-response relationship between the amount of statin given daily and the decline in LVEF (P = 0.02).

Conclusion:

Overall, the quality of evidence supporting the use of statin therapy concurrently with anthracycline treatment is low. However, the data from these studies is significant and warrants further investigation. Statins are generally well tolerated medications and benefits have been shown to occur with less than one year of therapy. The evidence would argue that the benefits of using statins concurrently and for six months following anthracycline chemotherapy outweigh the risks unless otherwise contraindicated.

Degree Type

Capstone Project

Degree Name

Master of Science in Physician Assistant Studies
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Among Adult Cancer Survivors Treated With Anthracycline Chemotherapies, Concurrent Statin Therapy May Reduce Their Decline in Left Ventricular Dysfunction

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A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
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Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Mariah McGaffey grew up in Beaverton, Oregon. She attended Oregon State University where she earned a Bachelor of Science in Exercise and Sport Science and a Minor in Chemistry. During her undergraduate years, Mariah worked part time as a lab assistant and a CNA at a local nursing home and skilled nursing facility. After graduation, she stayed in Corvallis and continued her work as a CNA at Good Samaritan Regional Medical Center on an Oncology floor.
Abstract

Background:

Anthracycline chemotherapies are used to treat a wide variety of malignancies. A study by Von Hoff et al showed that 2.2% of patients previously treated with anthracycline chemotherapy were later diagnosed with heart failure. A more recent study by Smain, et al, showed that 26% of patients receiving higher doses of anthracycline were later diagnosed with heart failure. Statins have been shown to have properties that may allow them to be cardioprotective. Animal research performed by Henninger et al suggests that statin therapy is beneficial for reducing anthracycline-related cardiotoxicity in mice. It also lends evidence supporting the theory that, among adult cancer survivors treated with anthracycline chemotherapies, statin therapy may reduce their decline in left ventricular dysfunction, which is the aim of this systematic review.

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Keywords: Heart Failure, anthracycline, chemotherapy, statins
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To my family: Thank you for supporting me in everything I do. I would never have made it this far in life without your love and encouragement.

To my friends: Thank you for always being willing to listen and encourage me through the difficult moments. I could not have accomplished what I have without your support.
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Table I: Quality Assessment of Reviewed Articles

List of Abbreviations

LVEF...............................................................Left Ventricular Ejection Fraction
HR......................................................................Hazard Ratio
CI.......................................................................Confidence Interval
CAD.................................................................Coronary Artery Disease
CMRI.............................................................Cardiovascular Magnetic Resonance Imaging
Among Adult Cancer Survivors Treated With Anthracycline Chemotherapies, Concurrent Statin Therapy May Reduce Their Decline in Left Ventricular Dysfunction

BACKGROUND

Anthracycline chemotherapies are commonly used to treat a wide variety of hematological malignancies, sarcomas, and breast cancers.¹ This class of chemotherapeutic agents has many U.S. Boxed Warnings, including severe cardiotoxicity.² It is unclear why anthracycline is so cardiotoxic. A number of theories such as oxidative stress and accumulation of free superoxide anion radicals are still being explored.³ A retrospective study by Von Hoff et al⁴ conducted in 1979 showed that 2.2% of patients previously treated with 364-390 mg/m² of anthracycline chemotherapy were later diagnosed with heart failure. This study also showed a dose-response relationship between the amount of anthracycline given and the percent of patients diagnosed with heart failure.⁴ A more recent retrospective study by Swain et al⁵ conducted in 2003 studied patients who had received higher doses of anthracycline (550 mg/m²). Among the participants in this study, 26% were diagnosed with heart failure.⁵ This side effect of anthracycline is associated with significant morbidity and mortality. It has been shown that 33% of patients who have taken anthracycline chemotherapy and experienced a decreased left ventricular ejection fraction (LVEF) do not return to their baseline LVEF.¹ Studies have also shown that heart failure may have as low of a survival rate as 57% at 18 months after diagnosis.⁶

Statins are beneficial for serum cholesterol reduction, but they also have antioxidative and anti-inflammatory properties.⁷ As one of the theorized mechanisms for anthracycline-induced cardiotoxicity is oxidative stress, more research was performed to investigate statin use among this unique population. Animal research performed by Henninger et al⁸ suggests that statin therapy is beneficial for reducing anthracycline-related cardiotoxicity in mice. This new
research has further prompted scientists to explore the potential benefits of statin therapy. It also lends evidence supporting the theory that, among adult cancer survivors treated with anthracycline chemotherapies, statin therapy may reduce their decline in left ventricular dysfunction, which is the aim of this systematic review.

METHODS

An exhaustive literature search using MEDLINE-Ovid, ClinicalKey, and Web of Science was performed using the terms: statin, anthracycline, and heart failure. Studies were required to be published within the past five years and written in English. Studies were excluded if they were review articles, opinion-based articles, or animal studies. Articles were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria.

RESULTS

The above search resulted in 10 total articles, which were then screened for relevance. Three articles were found that met the inclusion criteria. One of these articles is a randomized controlled trial\(^9\) and the other two are retrospective observational studies\(^{10,11}\). See Table I.

Acar et al

This randomized control trial\(^9\) was designed to test the effect of statin therapy on patients receiving anthracycline chemotherapy. Its primary endpoint was impairment in LVEF utilizing echocardiogram measurements. This study included 40 participant, 20 of whom were randomly selected to be given 40 mg/day of atorvastatin during chemotherapy and for the six months following. The other 20 patients in the study were placed in a control group that did not receive statin therapy. Echocardiograms were performed on each patient both before and six months
after receiving anthracycline chemotherapy. Each echocardiogram was read by two separate cardiologists who were blinded to all patient identifiers.  

The study excluded patients who had a history of chemotherapy, radiotherapy, heart failure or left ventricular dysfunction, coronary artery disease (CAD), or with moderate-to-severe valvular disease. It also states that none of the patients were taking other medications that could alter cardiac function.

A two-sample t test was used to compare mean changes in LVEF between the statin group and the control group after chemotherapy. Within the statin group, no difference was found between baseline LVEF (61.3% ± 7.9%) and six month follow up LVEF (62.6% ± 9.3%). However, the control group experienced a significant decrease in LVEF from 62.9% ± 7.0% to 55.0% ± 9.5% LVEF at six months. The mean reduction in LVEF was significantly lower in the statin group than the control group (P < 0.0001).

Seicean et al

This retrospective observational study identified 628 women within the Cleveland Clinic Health System who had been newly diagnosed with breast cancer and received anthracycline chemotherapy. From this group, 67 patients were identified as being on statin therapy. The study matched these patients 1:2 to 134 controls by propensity score matching. The primary endpoint of this study was new-onset heart failure requiring hospitalization after initiation of anthracycline chemotherapy. They collected this data through an EMR review of each patient included in the study.

This study excluded patients who had other neoplasms, kidney or heart transplants, heart failure, chronic pulmonary disease, hypertrophic cardiomyopathy, valvular heart disease, aortic aneurism, or who were on dialysis prior to their diagnosis of breast cancer.
The Wilcoxon rank sum and Pearson’s chi-square test were used when comparing the characteristics of patients treated with statins against those who were not treated with statins. Due to matching the 67 patients on statin-therapy to the controls, the two groups were of similar age, race, social determinants of health, smoking habits, body measurements, Charlson score, cancer-related treatment, and follow up time. However, patients taking statins were more likely to have hypertension and be taking medication with potentially cardioprotective qualities, such as ACE inhibitors and beta-blockers.  

This study showed that only four cases of heart failure requiring hospitalization occurred in the group receiving statin therapy, as opposed to 23 cases in the control group. The cardioprotective effect of statins was significant when using a nested Cox proportional hazards model (HR: 0.3; 95% CI: 0.1-0.9; p = 0.03).  

**Chotenimitkhun et al**  

This retrospective observational study identified 51 participants from the Comprehensive Cancer Center at Wake Forest Health Sciences with breast cancer, leukemia, or lymphoma who had been treated with anthracycline chemotherapy. Among this group, 14 patients were receiving statin therapy and 37 patients were not. This study also subdivided the statin group into patients taking high-dose statins (40-80 mg/day) and those taking low-dose statins (10-20 mg/day). The primary endpoint of this study was impairment in LVEF. This was measured through cardiovascular magnetic resonance imaging (CMRI) measurements by blinded personnel taken before and six months after treatment with anthracycline chemotherapy.  

The study excluded patients who were receiving radiation therapy during their course of anthracycline chemotherapy. A two-sample t test was used to compare the statin group to the control group. This study showed that those receiving high-dose statin (40-80mg) actually had an
increase in LVEF. However, those receiving low-dose statin therapy (10-20mg) had a 3.4% ± 4% decrease in LVEF and patients not receiving statin therapy had a 9.2% ± 3% decrease in LVEF (P = 0.02). This study also found a statistically significant, linear, dose-response relationship between the amount of statin taken and the decline in LVEF (P = 0.006).

DISCUSSION

Acar et al

The article by Acar et al\(^9\) is a randomized controlled trial that has both strengths and limitations. Among the studies included in this review, this study is the only one where patients were randomly allocated to the statin and the control group. Also, within the statin group, the amount and duration of statin therapy was consistent. The statin and control groups were similar in regard to age, sex, cancer diagnosis, and chemotherapeutic treatment. Also, unlike either of the observational studies, none of the patients on statin therapy were taking other medications that could alter cardiac function and skew the study’s results.\(^9\)

This study also had limitations. It had a very small sample size, with only 20 patients allocated to each group. It also had a very short follow up of six months following each patient’s anthracycline chemotherapy treatment. Another limitation is that patients in the control group were not receiving a placebo. However, this had minimal effect on the results of the study since the primary outcome was LVEF read from echocardiograms; a minimally subjective endpoint.\(^9\)

Overall, even with some limitations, the results of this study are significant. No significant difference in mean LVEF was appreciated in the statin group (P=0.144). The control group, however, showed a significant decline in LVEF (P<0.0001). Although this study was small, it did not lose any participants during the follow-up process, which adds to its credibility and decreases its risk of bias. Also, the short duration of the study would be more likely to under-
estimate the decline in patient’s LVEF because anthacycline cardiotoxicity most often occurs within one year of the last medication dose given. There is a chance that the study missed the more subtle decline in LVEF experienced by patients with a more delayed or more mild response to their anthracycline treatment. This article’s quality of evidence is technically categorized as moderate (see Table I). Due to the quality and significance of the study’s findings, clinicians should weigh this evidence carefully during their decision making process.

Seicean et al

The retrospective observational study by Seicean et al was strengthened by the larger group of patients involved (201 total). The researchers also matched patients on statin therapy to those in the control group 1:2. Therefore, the groups were similar in regards to prognostic factors. The primary outcome chosen in this study was also more specific and clinically significant than the primary outcomes in the other two studies. Secean et al chose to study heart failure requiring hospitalization as opposed to studying LVEF, which would show the more subtle declines in cardiac function.

The main limitation of this study is that patients in the statin group were more likely to be receiving ACE inhibitors and beta-blockers. These are medications which have also been hypothesized to be cardioprotective. The researchers were unsure if they were able to adequately adjust for this factor in their research. For this reason, the article’s quality of evidence is categorized as “very low”. (See Table I)

Even with a reduction in evidence quality, the results of this study were significant. It showed a hazard ratio of 0.3 and a P value of 0.03, which means that there was a 70% reduction in heart failure hospitalization rate among patients on statin therapy. Also, similar to the study by Acar et al, this study may under-estimate the cardioprotective effects of statin therapy because it
did not count the number of patients diagnosed with heart failure in outpatient settings or declines in LVEF found on echocardiogram.\textsuperscript{10}

\textbf{Chotenimitkhun et al}

The retrospective observational study by Chotenimitkhun et al\textsuperscript{11} is categorized as very low quality of evidence (see Table I). It is limited by a very small number of participants, 51 total and only 14 receiving statin therapy. Also, the group receiving statin therapy was not matched to the control group. Therefore, the patients receiving statin therapy were older and more likely to have diabetes, hypertension, and hyperlipidemia. Similarly to the study by Seicean et al,\textsuperscript{10} the patients taking statins were also more likely to be taking other potentially cardioprotective medications.\textsuperscript{11}

The main strength of this study is that the endpoint of LVEF is objective. Also, the cardiologists reading the echocardiograms were blinded to all patient identifiers.\textsuperscript{11}

Arguably, the most interesting part of this study is that a statistically significant, linear dose-response was found between the amount of statin given and the cardioprotective effects seen on echocardiogram (\(P = 0.006\)). The study also found a significant decline in LVEF among the patients not receiving statins (\(P = 0.02\)). Although the quality of evidence is very low, this study would suggest that if patients are going to be given statins during anthracycline chemotherapy treatment, they should be given a high dose (40-80 mg/day) rather than lower doses, which did not show as much cardiac benefit.\textsuperscript{11}

\textbf{CONCLUSION}

Overall, the quality of evidence supporting the use of statin therapy concurrently with anthracycline is low. This area of research is very young and the studies that have been done are either retrospective observational studies or very small, short duration randomized controlled
trials. However, the data from these studies are significant and warrant further investigation with larger, longer duration, randomized controlled trials.

Heart failure is a disease with a significant mortality rate and is a major problem for adult cancer survivors who have received anthracycline chemotherapy. Statins are generally well tolerated medications with few significant side effects. Also, there is evidence that statins are beneficial with less than one year of therapy. In summary, the current evidence suggests that the benefits of using statins concurrently and for six months after anthracycline chemotherapy outweigh the risks unless otherwise contraindicated.
References


anthracycline chemotherapy. *Journal of the American College of Cardiology, 60*(23), 2384-2390.


## Table I: Quality Assessment of Reviewed Articles

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a The study had a very small sample size, with only 40 participants total.
b The study did not adjust for patients in the statin group also taking other potentially cardioprotective medications.
c This study had a HR of 0.3.
d The study had poor exclusion criteria and they did not match the demographics of the control group to that of the therapy group.
e The study had a very small sample size, with only 51 participants total.
f This study showed a dose-response with patients receiving high-dose (40-80mg) statins having an improvement in LVEF rather than lessened decline, as seen in patients receiving low-dose (10-20mg) statins.