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ROLE OF DEXRAZOXANE IN THE PREVENTION OF CHEMOTHERAPY RELATED CARDIOTOXICITY: A SYSTEMATIC META-ANALYSIS REVIEW

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ABSTRACT

Background: Cardiotoxicity is a well-recognized complication of chemotherapy with Anthracycline and its prevention remains an important challenge in cancer survivorship. Several successful preventative strategies have been identified in animal trials. This study sought to assemble the clinical evidence that prophylactic interventions with Dexrazoxane could prevent cardiotoxicity in patients undergoing Anthracycline chemotherapy. (Kalam, 2013). ***Methods:*** This is a meta-analysis of the evidence from randomized trials where Dexrazoxane was used as the prophylactic intervention and compared with a control arm in patients with a normal ejection fraction and no past history of heart failure. The primary outcome was development of heart failure (HF), a drop in ejection fraction (EF) or any other investigation that identifies cardiotoxicity. A random-effects model was used to combine odd's ratio (OR) and 95% confidence intervals (CI). ***Findings:*** Data were collated from 5 published articles (n = 914 pediatric and adult patients) comprising 5 randomized controlled trials. The most studied chemotherapeutic agent was Doxorubicin. The average odds of cardiotoxicity in presence of Dexrazoxane was found to be 0.251 (95% CI, 0.171-0.370 with P=0.000). ***Interpretation:*** Prophylactic therapy with Dexrazoxane was found to be effective in preventing cardiotoxicity caused by Anthracycline chemotherapy for cancer.

INTRODUCTION

Meta-analyses constitute fundamental tools of the Evidence-Based Medicine (EBM) aiming at synthesizing outcome data from individual trials in order to produce pooled effect estimates for various outcomes of interest. Combining summary data from several studies increases the sample size, improves the statistical power of the findings as well as the precision of the obtained effect estimates. For all these reasons, meta-analyses are thought of providing the best evidence to support clinical practice guidelines.

Meta-analysis is a statistical technique that combines the results of multiple scientific studies to identify overall trends and draw more precise conclusions. By integrating data from several studies, meta-analyses enhance the statistical power and provide a more comprehensive understanding of the research question.

Cardiac toxicity associated with cancer treatment is a growing source of significant morbidity and mortality, and may vary from subclinical myocardial dysfunction to irreversible heart failure (HF) or even death. Cumulative doses and concomitant use of adjuvant therapies, thorax radiation therapy combined with other risk factors, such as preexisting cardiovascular disease, age, obesity, smoking, hypertension, diabetes and physical inactivity,

may increase cardiovascular vulnerability. (Van der Woude, 2007).

Cancer outcomes continue to improve due to earlier detection and newer targeted therapies, And with Anthracycline chemotherapy playing a major role in the modern era of cancer treatment. Anthracycline chemotherapy maintains a prominent role in treating many forms of cancer. But cardiotoxic side effects limit their dosing and improved cancer outcomes expose the cancer survivor to increased cardiovascular morbidity and mortality. (McGowan *et al.*, 2017).

At present, the most prevalent screening method is based on the periodic measurement of left ventricular ejection fraction (LVEF) before, during, and after chemotherapy with conventional 2-D transthoracic echocardiography. When LVEF decreases, there has already been considerable myocardial damage.

Therefore, there is a need to investigate biomarkers that enable the early identification of cardiac deterioration. Early interval changes in individual biomarkers, such as ultrasensitive troponin I (TnI, cardiomyocyte injury), N-terminal proB-type natriuretic peptide (NT-proBNP, neurohormonal activation), and myeloperoxidase (MPO, oxidative stress) has been shown to be of incremental utility in identifying patients at risk for adverse outcomes with doxorubicin and Traztuzumab. (Noyes, 1959).

The molecular mechanism responsible for Anthracycline-induced cardiotoxicity remains poorly understood, although experimental and clinical studies have shown that oxidative stress plays the main role. Hence, antioxidant agents, especially Dexrazoxane have proved to have a beneficial effect in protecting against Anthracycline-induced cardiotoxicity. (McGowan *et al.*, 2017).

METHODOLOGY

Aim- To perform A Systematic meta-analysis review on role of Dexrazoxane in the prevention of chemotherapy related cardiotoxicity.

Search Strategy- The literature search was conducted using the PubMed and Cochrane databases. The search terms "Dexrazoxane treatment or prevention of cardiotoxicity with Anthracycline chemotherapy", "Dexrazoxane" and "Dexrazoxane and Anthracycline" were used. Papers were limited to human studies written in English. Reference lists of relevant individual publications and review articles were also searched for additional studies. The timeline was set between 1998-2018 and an additional filter of Randomized Trials was used in Cochrane.

Inclusion and Exclusion Criteria- We included studies of patients with cancer who were given prophylactic treatment with Dexrazoxane to prevent cardiotoxicity in relation to Anthracycline chemotherapy. We included 5 randomized controlled– data extracted from these 5 studies also included estimated odd's ratio (OR) and 95% confidence intervals (CIs). We excluded patients with known ischemic heart disease, previous chemotherapy-related heart failure or cardiac dysfunction, EF < 50% or multiple organ failure. The studies with primary end-point of cardiotoxicity were included. This review incorporated interventional RCT providing baseline and follow-up data.

Outcomes- The primary outcome of interest was any changes in Troponin levels, EF, development of heart failure (HF), or any other investigation that determines cardiotoxity.

Data Extraction- I conducted an independent review of literature. I extracted the following population study data: age, sex, number, study design, primary oncological condition, primary treatment, prophylactic treatment, cardiac risk factors and primary outcome.

Statistical Analysis- Pooled OR and CI ranges were used to construct a Forrest plot that showed the overall effect of intervention against control in all the studies grouped together.

RESULTS

Study Selection- The selection process is illustrated in Fig. 1. There were 28 studies that were considered to be potentially eligible based on full text review. 16 were excluded on the basis of an inappropriate study design or significant co-founding, inability to match the inclusion criteria or absence of the required data. From the remaining 12 articles- 7 were excluded due to lack of sufficient information or inappropriate design for this study. The excluded articles had unrelated outcome measurements for this study.

DZR (Dexrazoxane) treatment significantly reduces cardiac toxicity and the frequency of cardiac events associated with anthracycline based chemotherapy followed by a 1-year trastuzumab treatment. discontinuing trastuzumab in patients, we suggest that prevention of cardiac toxicity might facilitate the completion of 12-month trastuzumab treatments, which has a significant Prognostic benefit. The incorporation of this approach may enable patients to undergo chemotherapy while minimizing cardiac-related mortality and morbidity.

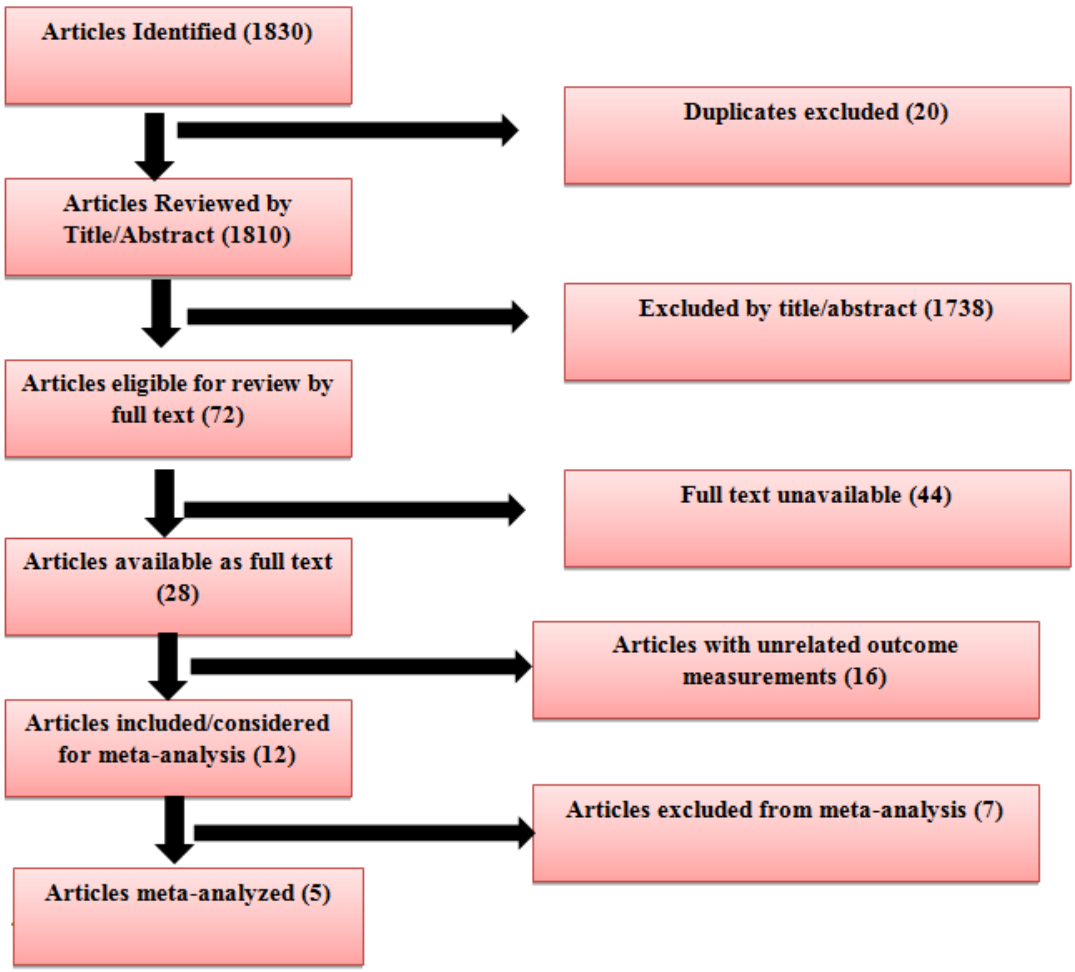

Fig. 1: Selection Process for incorporation of studies into this meta-analysis *Patient.*

The 5 RCTs yielded a total n of 914, out of which 295 were children and 619 were adults. Most subjects were female since 3 out of 5 studies were on breast cancer.

Table 1.

Author	n	Age	Control	Treatment	Cancer type	Chemo agent	Study type	Outcome measure	Cut off
(Swain, 2003)	349	55±10	181	168	Breast cancer	Doxorubicin	RCT	HF/EF	Drop >20 %
(Lipshultz *et al.*, 2004)	206	14±10 years	101	105	Acute Lympho-blastic Leukemia	Doxorubicin	RCT	Troponin T	>0.0 25ng /ml
(Marty *et al.*, 2006)	95	50± 20 years	46	49	Breast cancer	Doxorubicin	RCT	HF/EF	Drop >10%
(Hyoung *et al.*, 2010)	89	3-127 months	42	47	Solid tumor	Doxorubicin	RCT	LVD Diameter	Increase
(Kim *et al.*, 2017)	175	50±30 years	131	44	Breast Cancer	Traztuzumab	RCT	HF/EF	Drop >10%

***Effect of Therapy on Outcome (Forest Plot)* –**
The effect of therapy on outcomes is depicted in Fig. 2. The combined effect from the 5 trials improved the primary outcome when compared to controls (OR: 0.251 [95% CI 0.171–0.370], p< 0.00001).

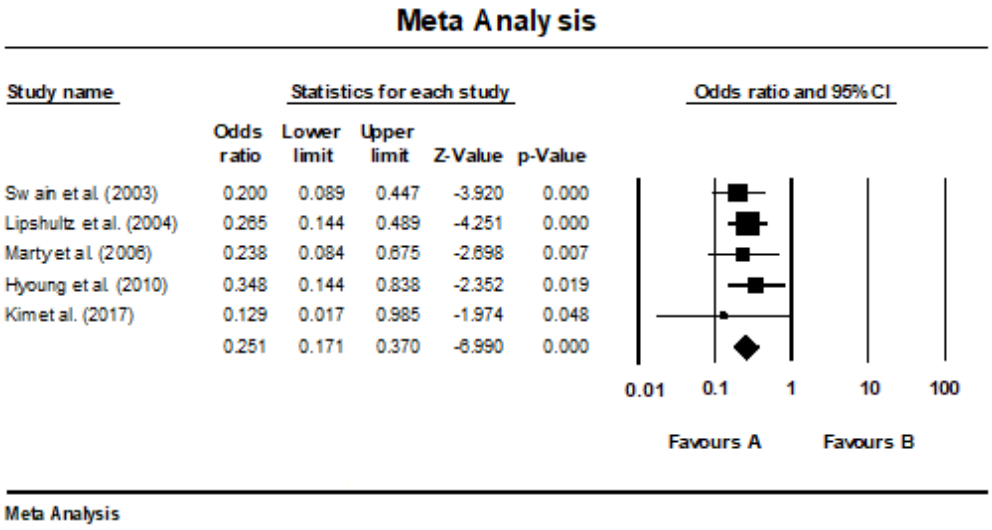

Fig. 2.

DISCUSSION

Mechanism of Cardiotoxicity- Chemotherapeutic cardiotoxicity can be characterized as either type 1 or type 2 cardiotoxicity based on the effect of the agent on cardiomyocyte. Type I cardiotoxicity is caused by cardiomyocyte death, either through necrosis or apoptosis, and as a result is not reversible. Type II cardiotoxicity is caused by cardiomyocyte dysfunction rather than cell death and therefore may be reversible. The long-term cardiotoxicity caused by the Anthracycline includes cardiomyocyte death and therefore represents a type I toxicity. (Volkova, 2012) The toxicity that Doxorubicin exhibits in cardiomyocytes is related to free radical formation caused by Doxorubicin metabolism. Specifically, the reduction of Doxorubicin by NADH dehydrogenase in mitochondrial respiratory complex I, forms a Semiquinone radical that can react with molecular oxygen to form the superoxide radical. Subsequently, redox cycling results in the production of hydrogen peroxide and the hydroxyl radical. In addition, formation of Doxorubicin-iron complexes may catalyze a Fenton reaction (Fe2+-catalyzed conversion of hydrogen peroxide to hydroxyl radical), resulting in the generation of reactive oxygen species. It is likely that cardiomyocytes are much more sensitive to the oxidant stress caused by doxorubicin because of their high reliance on oxidative substrate metabolism and therefore the high fraction of cardiomyocyte volume made up by mitochondria compared to glycolytic tumor cells. In fact, oxidant damage by doxorubicin in tumor cells is only seen at very high doxorubicin concentrations. (Csapo and Lazar, 2014).

Effect of Dexrazoxane

Dexrazoxane acts by chelation of iron redox-active molecules, thus preventing the formation of Anthracycline-iron complex and subsequent development of reactive oxygen species. Although there is some controversy regarding this drug that it may reduce the antitumor efficacy of chemotherapeutics, the meta-analysis on the use of Dexrazoxane during doxorubicin treatment was associated with a low risk of symptomatic heart failure, and no significant difference in oncological response. (Csapo and Lazar, 2014).

Lipshultz S. E. *et al* found 35 percent of the patients had higher troponin T levels (55 of 158). Patients treated with doxorubicin alone were more likely to have higher troponin T levels than those treated with doxorubicin and dexrazoxane (50 percent vs. 21 percent, P<0.001) and extraordinarily high troponin T levels (32 percent vs. 10 percent, P<0.001). The follow-up was on average 2.7 years. At 2.5 years, there were 83 percent of survivors without an incident. When they were doing the study (P=0.87 by the log-rank test) in both groups.

Swain S. M et al found 32 out of 630 patients had a CHF diagnosis. At a cumulative dose of 550 mg/m2, analysis revealed that an expected 26 percent of individuals will develop CHF linked to doxorubicin. Age seemed to be a significant risk. After a cumulative dose of 400 mg/m2, doxorubicin-related CHF risk factor, with patients above the age of 65 who exhibit a higher incidence of CHF compared to patients that are younger (65 years old). Additionally, the left ventricular ejection decreased by 30% in 50% of individuals who developed CHF linked to doxorubicin. These results further suggest that in individuals who receive doxorubicin, LVEF is not a reliable predictor of CHF.

Marty M. *et al.* Patients treated with dexrazoxane had considerably fewer cardiac events (39% versus 13%, P < 0.001) and a reduced incidence of congestive heart failure (11% versus 1%, P < 0.05) compared to those receiving anthracycline alone. Dexrazoxane treatment had no effect on the cancer response rate. Between groups, there were no discernible differences in the frequency of adverse events or the number of dose adjustments or interruptions.

Dexrazoxane dramatically decreased the incidence and severity of anthracycline-induced cardiotoxicity in individuals who were more likely to develop cardiac dysfunction as a result of prior anthracycline therapy, without impairing the chemotherapeutic regimen's ability to treat the cancer.

Kim I. et al. A cardiac episode was experienced by 12% of patients. Time had a significant main influence on the ejection % and a significant group dexrazoxane (DZR) time interaction, according to a repeated-measures analysis of variance. Compared to the group receiving only adjuvant chemotherapy, the group treated with adjuvant chemotherapy and DZR had considerably reduced frequency of cardiac events. DZR treatment was linked to noticeably fewer cardiac events in multivariate analysis. Additionally, DZR administration was a reliable independent predictor of cardiac event-free duration (CFD). Only one patient (2.3%) in the adjuvant chemotherapy with DZR group received an early termination of trastuzumab due to cardiac toxicity, whereas 10 patients (7.6%) in the adjuvant chemotherapy alone group experienced a trastuzumab stop event.

Study Limitations

This meta-analysis was obtained from a literature with homogeneous study design (RCT's) but heterogeneous outcomes (Table 1). All studies involved prevention of cardiotoxicity with use of Dexrazoxane but by different methods (3 used EF, 1 used Troponin T and another used Left Ventricular Diastolic Diameter). One of the studies used Traztuzumab and the other four used Doxorubicin as the choice of Anthracycline chemotherapy. There was incomplete information regarding baseline characteristics in some of these studies. Second, some trials had a very small number of patients with short follow up periods. Third, most of the trials were single centered with only females being recruited (3/5 studies). Some trials lacked rigorously defined clinical end points. Finally, the studies involved a variety of oncological conditions with different dose schedules and age groups.

CONCLUSION

Cardioprotective agents, used pre-chemotherapy, can prevent clinical heart failure and chemotherapy-related cardiotoxicity. Dexrazoxane prevents or reduces cardiac injury, as reflected by elevations in troponin T, on event-free survival. Dexrazoxane prevents or reduces cardiac injury, as reflected by elevations in troponin T, Longer follow-up will be necessary to determine the influence of dexrazoxane on echocardiographic findings at four years and on event-free survival. Five-year cardiac event free survival rates were 69.2% in the dexrazoxane group and early and late anthracycline cardiotoxicity in childhood solid tumors. DZR treatment significantly reduces cardiac toxicity and the frequency of cardiac events associated with anthracycline based chemotherapy followed by a 1-year trastuzumab treatment. Discontinuing trastuzumab in patients, we suggest that prevention of cardiac toxicity might facilitate the completion of 12-month trastuzumab treatments, which has a significant prognostic benefit.

The incorporation of this approach may enable patients to undergo chemotherapy while minimizing cardiac-related mortality and morbidity.

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Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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