Primary prevention of cardiotoxicity in paediatric cancer patients receiving anthracyclines: systematic review and meta-analysis of efficacy and safety profiles

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Abstract

Aims: This review aims to evaluate prospective controlled trials of primary prevention of anthracycline cardiotoxicity in paediatric cancer patients. **Methods and Results:** Prospective controlled trials in which any cardioprotective agent was compared to no additional therapy or placebo in paediatric cancer patients receiving anthracyclines (PROSPERO: CRD42022367791). Outcomes were assessed using random and fixed-effects meta-analysis models as well as a synthesis without meta-analysis approach. A total of 24 reports of 19 trials were included in our review, 11 trials administered dexrazoxane, two trials administered the angiotensin converting enzyme inhibitor enalapril, one trial administered the beta-blocker carvedilol, one omega-3 fatty acids, one coenzyme Q10, one amifostine, one silymarin and one black seed oil. A total of 1333 paediatric patients receiving anthracyclines were included in meta-analysis of the cardio-protective effect of dexrazoxane in reducing the risk of developing significant systolic dysfunction. A risk ratio of 0.44 (95% CI: 0.33 to 0.61; I2 = 0%) was found, showing that the administration of dexrazoxane was highly effective. Overall, enalapril, carvedilol and dexrazoxane resulted in less left ventricular dysfunction and fewer cardiac biomarker abnormalities compared to placebo. Omega-3 fatty acids, silymarin and black seed oil each demonstrated benefit through less reduction of systolic function and fewer cardiac biomarker abnormalities. **Conclusion:** Enalapril and dexrazoxane are highly effective in preventing the anthracycline-induced cardiotoxicity in paediatric cancer patients with a highly acceptable safety profile. More randomised-controlled trials are required to reach a conclusion on the efficacy of omega-3 fatty acids, co-enzyme Q10 and amifostine.

Title Page

Primary prevention of cardiotoxicity in paediatric cancer patients receiving anthracyclines: systematic review and meta-analysis of efficacy and safety profiles

Running title: Cardioprotection in anthracycline chemotherapy

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Abbreviations key

Abbreviation	Full term
ACE-I	Angiotensin-converting enzyme inhibitor
CAD	Cumulative anthracycline dose
CK-MB	Creatine kinase MB isoenzyme
CI	Confidence intervals
cTnI	Cardiac Troponin I
HR	Hazard ratio
LVEF	Left ventricular ejection fraction
LVESWS	Left ventricular end-systolic wall stress
LVFS	Left ventricular fractional shortening
MCI	Maximal cardiac index
proBNP	Pro-brain natriuretic peptide
RR	Risk ratios
SD	Standard deviations
SMD	Standardised mean differences

Abstract

Aims: This review aims to evaluate prospective controlled trials of primary prevention of anthracycline

cardiotoxicity in paediatric cancer patients.

Methods and Results: Prospective controlled trials in which any cardioprotective agent was compared to no additional therapy or placebo in paediatric cancer patients receiving anthracyclines (PROSPERO: CRD42022367791). Outcomes were assessed using random and fixed-effects meta-analysis models as well as a synthesis without meta-analysis approach. A total of 24 reports of 19 trials were included in our review, 11 trials administered dexrazoxane, two trials administered the angiotensin converting enzyme inhibitor enalapril, one trial administered the beta-blocker carvedilol, one omega-3 fatty acids, one coenzyme Q10, one amifostine, one silymarin and one black seed oil. A total of 1333 paediatric patients receiving anthracyclines were included in meta-analysis of the cardio-protective effect of dexrazoxane in reducing the risk of developing significant systolic dysfunction. A risk ratio of 0.44 (95% CI: 0.33 to 0.61; I2 = 0%) was found, showing that the administration of dexrazoxane was highly effective. Overall, enalapril, carvedilol and dexrazoxane resulted in less left ventricular dysfunction and fewer cardiac biomarker abnormalities compared to placebo. Omega-3 fatty acids, silymarin and black seed oil each demonstrated benefit through less reduction of systolic function and fewer cardiac biomarker abnormalities.

Conclusion: Enalapril and dexrazoxane are highly effective in preventing the anthracycline-induced cardiotoxicity in paediatric cancer patients with a highly acceptable safety profile. More randomised-controlled trials are required to reach a conclusion on the efficacy of omega-3 fatty acids, co-enzyme Q10 and amifostine.

Introduction

Anthracyclines form the backbone of many chemotherapy regimens, treating more than half of all paediatric cancers [1]. Although survival rate has been steadily increasing across the years, anthracyclines are well-associated with risk of cardiotoxicity, ranging from asymptomatic cardiac dysfunction to congestive heart failure[2-4]. Paediatric cancer survivors are five to ten times more likely to develop congestive cardiac failure compared to the general population [5,6].

Existing guidelines recommend initiation of pharmacotherapy including angiotensin-converting enzyme inhibitors (ACE-I) and dexrazoxane for primary prevention of anthracycline-related cardiac dysfunction in high-risk adult cancer patients receiving anthracyclines[7]. However, there are no clear recommendations for initiation of primary prevention therapy within the paediatric cancer population. Only several controlled trials have been performed evaluating the role of pharmacotherapy in primary prevention of anthracycline-related cardiac dysfunction in paediatric cancer patients. It remains unclear if such therapies in the adult cancer population can be extrapolated to the paediatric cancer population.

To date, reviews have only examined the use of dexrazoxane in paediatric patients [8]. No systematic reviews have been performed to date comparing other interventions in primary prevention of anthracycline-related cardiotoxicity in paediatric cancer patients. As such, this systematic review and meta-analysis aims to evaluate the efficacy of pharmacotherapy in primary prevention of anthracycline-related cardiac dysfunction and myocardial injury.

Methods

This systematic review with meta-analysis was reported in accordance with the PRISMA statement for systematic reviews. The protocol was registered on PROSPERO (registration: CRD42022367791).

Selection of studies

We searched Medline, Embase, Cochrane Central Register of Controlled Trials, from database inception until 29 September 2022. Our search combined an exhaustive list of concepts, language, and keywords for controlled clinical trials, cardiotoxicity and pharmacotherapeutic agents. We also searched reference lists of relevant systematic reviews and clinical guidelines.

Two authors (ARYBL and JL) independently selected eligible studies first based on the titles and abstracts, followed by full text articles, with conflicts resolved by a third author (CHS). We included randomised and non-randomised controlled studies with paediatric participants, defined as participants younger than 18 years

of age, with a diagnosis of any solid or haematological cancer for which they were receiving antineoplastic therapy containing anthracyclines, and involved at least one arm of the study administering pharmacotherapy for the prevention of long-term cardiac dysfunction.

Data extraction

Data of each included study was extracted by two authors (ARYBL and JL) independently and checked for quality at the end of the extraction phase. Outcomes of interest related to measures of systolic dysfunction, diastolic dysfunction, symptoms of cardiac dysfunction and major adverse cardiac events with details.

Quality assessment

Quality control was performed by two researchers using the Cochrane Risk of Bias 2.0 tool [9] which assesses five domains: bias arising from (1) the randomisation process, (2) deviations from intended interventions, (3) missing outcome data, (4) outcome measurement and (5) bias in reporting results. Data related to the risk of bias was acquired during data extraction.

Data analysis

The extracted data were quantitatively pooled and analysed in R statistical software version 4.1.0 (The R Foundation for Statistical Computing, Vienna, Austria) using the meta and metafor packages. For continuous outcomes, in studies without standard deviations (SDs), confidence intervals (CIs) were converted to SDs. In studies without relevant baseline data, the simple analysis of the final values method was used. Studies were pooled for meta-analysis using standardised mean differences (SMD) and the common-effects model. For dichotomous outcomes, we used the DerSimonian and Laird random effects model to estimate the pooled risk ratios (RR) and their corresponding 95% confidence intervals for the primary outcomes of interests. A RR of less than 1 indicates that the intervention group had a lower risk of a negative outcome than the comparator group.

Between-study heterogeneity was represented by I2 and $\tau 2$ statistics. I2 of <30% indicated low heterogeneity between studies, 30% to 60% showed moderate heterogeneity, and >60% indicated substantial heterogeneity. Two-sided P values of <0.05 were considered to indicate nominal statistical significance. Unless specified otherwise, we considered a two-sided P value of <0.05 statistically significant.

Results

A total of 6,561 reports were found in our search in PubMed, EMBASE, CENTRAL and Scopus. The results of our search is presented in Figure 1. A total of 24 reports of 19 trials were included in our review. Only prospective randomised and non-randomised controlled trials were included. Eleven trials administered dexrazoxane[10-25], two trials administered the angiotensin converting enzyme inhibitor enalapril [26,27], one trial administered the beta-blocker carvedilol [24], one omega 3 fatty acids [28], one coenzyme Q10[29], one amifostine [30], one silymarin[31] and one black seed oil [32]. Key trial characteristics of included trials are detailed in Table 1.

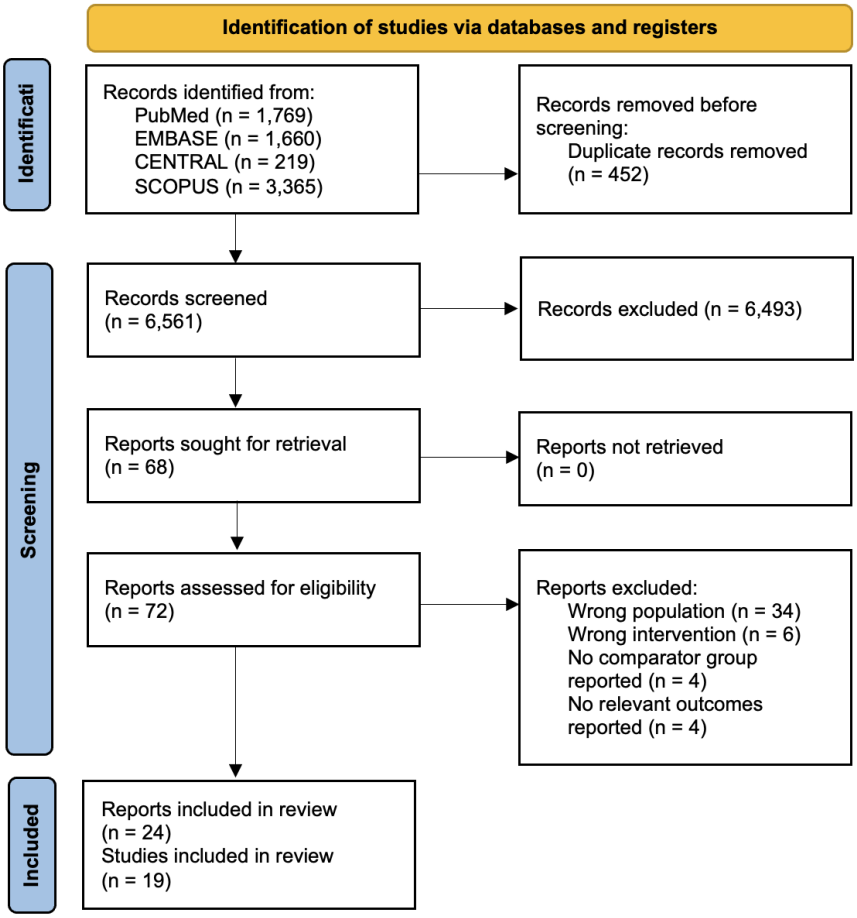

Fig. 1 PRISMA flowchart

Most trials recruited paediatric patients receiving anthracyclines for the treatment of haematological malignancies, with one recruiting sarcoma patients [13] and one recruiting osteosarcoma patients [30]. There was great homogeneity in the anthracycline paediatric patients received, with almost all trials administering doxorubicin or daunorubicin which are considered isotoxic. One trial by the Children's Oncology Group used doxorubicin or mitoxantrone [15-17,25]. Baseline demographic and cardiac parameters were similar in the intervention and comparator arms of all included studies.

Dexrazoxane

Sixteen reports of 11 trials administered dexrazoxane to paediatric patients receiving anthracyclines [10-25]. A total of 1333 paediatric patients receiving anthracyclines were included in meta-analysis of the cardioprotective effect of dexrazoxane in reducing the risk of developing significant systolic dysfunction. Overall, a risk ratio of 0.44 (95% CI: 0.33 to 0.61) was found, showing that the administration of dexrazoxane was highly effective with a pooled estimated risk reduction of 56%. Minimal heterogeneity (I2 = 0%) was found.

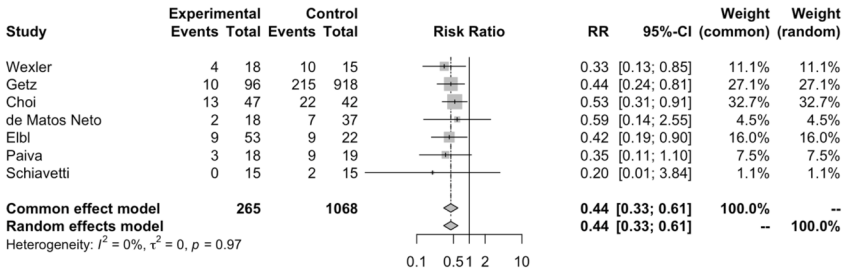

Fig. 2 Risk of significant cardiotoxicity measured by systolic function following anthracycline chemotherapy in paediatric cancer patients receiving dexrazoxane versus no dexrazoxane. An RR <1 favours dexrazoxane.

Wexler assessed for decline in systolic function using left ventricular ejection fraction (LVEF), Lipshultz using left ventricular fractional shortening (LVFS) and left ventricular thickness-to-diameter ratio and De Berranger using LVFS and mean wall stress.

Wexler found the LVEF decline per 100mg/m^2 cumulative anthracycline dose (CAD) was lower in the dexrazoxane group (-1.0% versus -2.7%, p = 0.02). Mean LVEF, comparable at baseline, was significantly higher after the full CAD 410 mg/m2 of doxorubicin in the dexrazoxane group (53.9% ± 2.2% versus 44.0% ± 2.8%, p = 0.03). Dexrazoxane significantly reduced the risk of developing dose-limiting cardiotoxicity (p < 0.01) as well.

Lipshultz, evaluating the protective effect of dexrazoxane over the longest period of follow-up of five years, similarly proved the long-term benefit of dexrazoxane with LVFS change of -0.41 (95% CI: -0.88, 0.06) versus -0.85 (95% CI: -1.31, -0.33) and end-systolic dimension Z-score of 0.15 (95% CI: -0.20, 0.51) versus 0.57 (95% CI: 0.21, 0.93).

De Berranger, on the contrary, found no differences in LVFS and mean wall stress between dexrazoxane versus placebo over the median study period of 28.5 months.

For cardiac enzymes, only Lipshultz assessed cardiac Troponin I (cTnI) over the study period of five years, at a mean total of 15 samples per patient, finding dexrazoxane administered patients with a reduced risk of developing any elevation in cTnI (21% versus 50%, p < 0.001), extreme elevations in cTnI (10% versus 32%, p < 0.001) or multiple elevations in cTnI (12% versus 37%, p < 0.001).

Studies by the Children's Oncology Group were the only ones to measure and report the risk of all-cause and cardiovascular mortality. In randomized trials, dexrazoxane was not associated with relapse (hazard ratio [HR], 0.84; 95% CI, 0.63-1.13), second cancers (HR, 1.19; 95% CI, 0.62-2.30), all-cause mortality (HR, 1.07; 95% CI, 0.78-1.47), or cardiovascular mortality (HR, 1.45; 95% CI, 0.41-5.16).

However, the risk of serious cardiovascular outcomes (cardiomyopathy, ischemic heart disease, and stroke) were less common in the dexrazoxane group (5.6%) versus without dexrazoxane (17.6%; P = 0.02). Similarly, Choi found the dexrazoxane group experienced significantly fewer cardiac events compared to the comparator group (27.7% vs 52.4%) and less severe congestive heart failure (6.4% vs 14.3%). Thirteen major adverse cardiac events including one cardiac death and two incidences of congestive cardiac failure occurred in the dexrazoxane group compared to 22 events including two cardiac deaths and four incidences of congestive cardiac failure in the comparator group. The 5-year cardiac event-free survival rate was also significantly higher in the dexrazoxane group (69.2% vs 45.8%; P=0.04).

Overall, the studies did not highlight any detrimental effect of dexrazoxane on chemotherapy response rates, relapse rates or risk of secondary cancers.

Angiotensin-converting enzyme inhibitors

Two studies were evaluated comparing enalapril versus placebo in patients receiving anthracyclines [26,27]. Gupta determined systolic function using LVEF measured by echocardiography. LVEF at baseline was comparable but a repeat measurement after six months demonstrated a protective effect of enalapril versus placebo (62.25 ± 5.49 versus 56.15 ± 4.79, $p < 0.001$). A decrease in LVEF of at least 20% was considered a clinically-significant decline which was noted in 3/44 (6.8%) of patients receiving placebo compared to zero in those receiving enalapril.

Silber determined systolic function using maximal cardiac index (MCI) on exercise testing or increase in left ventricular end-systolic wall stress (LVESWS), with similar rate of change in MCI per year (0.30 versus 0.18 L/min/m2, $p = 0.55$, in enalapril versus placebo groups. However, a significant protective effect was noted in LVESWS, highest in the first year (-8.59 versus +1.85 g/cm2, $p = 0.033$, in enalapril versus placebo groups) and an overall 9% decrease in the enalapril group over five years. Using a definition of two consecutive significant declines in cardiac performance below baseline levels, Silber found this developed in 1/69 (1.4%) receiving enalapril versus 6/66 (9.1%) receiving placebo.

Only Gupta measured and reported cardiac biomarkers including cardiac cTnI, creatine kinase MB isoenzyme (CK-MB) and pro-brain natriuretic peptide (proBNP). An overall protective effect favouring enalapril was demonstrated for cTnI ($p = 0.035$) and proBNP ($p < 0.001$) but not CK-MB ($p = 0.079$). Furthermore, a proBNP cutoff of 100 pg/mL was used to determine the risk of developing subclinical cardiac dysfunction, demonstrating a significantly-lowered risk ($p < 0.001$) in the intervention group (4/44 patients, 9.1%) compared to the control group (15/40 patients, 37.5%).

Carvedilol

One randomised-controlled trial by El-Shitany included 50 paediatric ALL patients receiving anthracyclines with or without carvedilol[24]. The degree of left ventricular systolic dysfunction as assessed by a significant decrease in LVFS (5.466 versus -6.5; $p < 0.05$) and global peak-systolic strain (1.86 versus -3.55; $p < 0.05$) was lower in those receiving carvedilol. Additionally, the comparator group had a significantly elevated level of troponin I ($p = 0.0008$) and lactate dehydrogenase ($p = 0.0001$).

Omega-3 fatty acids

Only one study utilised omega-3 fatty acids as an intervention[28]. A total of 60 patients with ALL receiving anthracyclines were randomised to receive 1000mg of omega-3 fatty acids daily or placebo for six months. Cardiac biomarkers included cTnI, CK-MB and N-terminal proBNP. Patients in the intervention group had significantly lower elevations in all cardiac biomarkers over the study period. A significant protective benefit was demonstrated only in the intervention group for left ventricular peak mitral annulus systolic velocity and 2D-global longitudinal strain, while mean differences were similar in other parameters. There were no safety concerns associated with receiving omega-3 fatty acids.

Co-enzyme Q10

One study assessed the protective effect of co-enzyme Q10[29]. Systolic function was assessed using LVFS and interventricular septum wall thickening. Co-enzyme Q10 demonstrated a protective effect on LVFS at the end of follow-up (35.82 ± 5.02 versus 33.43 ± 3.46; $p < 0.05$) and interventricular septum wall thickening with only the control patients experiencing a significant mean decline (46.10 ± 10.1 versus 27.00 ± 18.54; $p < 0.01$).

Amifostine

One study assessed the protective effect of amifostine in 28 patients with osteosarcoma receiving cisplatin and doxorubicin[30]. No patients receiving amifostine developed subclinical cardiac failure compared to 2/13 (15.4%) in the control group, a difference that was non-significant ($p = 0.21$). Of interest, response rate to chemotherapy, defined as necrosis percentage of at least 60% after tumorectomy, was observably higher in the intervention group (14/15 patients, 93.3%) compared to the control (7/12 patients, 58.3%) but statistically

insignificant (p = 0.06). Vomiting was the only recorded adverse event higher in the intervention than control group. Notably, this study featured a small sample size that limited evidence.

Silymarin

One randomised-controlled trial evaluated the protective effect of silymarin [31]. Silymarin 420 mg/day was administered for one week after each doxorubicin dose starting from the day of doxorubicin infusion. After doxorubicin therapy, there was a significantly higher reduction of systolic function measured by LVEF, LVFS and s wave in the comparator group compared to those receiving silymarin. There was no significant reduction in diastolic function measured by E/A or e/a ratio in both groups. Silymarin also resulted in a significantly lower elevation in serum troponin levels.

Black seed oil

One randomised-controlled trial evaluated the protective effect of black seed oil [32]. Black seed oil of 80 mg/kg/dose divided into 3 doses starting at the same moment of beginning of doxorubicin infusion therapy and continued for 1 week after each doxorubicin dose. Black seed oil resulted in a significant protective effect on systolic function measured by LVEF, LVFS and s wave. However, neither groups experienced a significant reduction in diastolic function measured by E/A or e/a ratio.

Risk of bias

Supplementary figure 2 reports the methodological quality of retained studies using the Cochrane Risk of Bias 2.0 to assess the risk of bias in randomised controlled trials. The study by Gallegos-Castorena was found to be at high risk of bias due to a lack of clarity in the reported outcomes and risk of selection as well as lack of blinding. The study by Iarussi were judged to be at high risk of bias due to a lack of mention of blinding and information regarding the method of obtaining data. Supplementary figure 3 reports the methodological quality of retained studies using the Cochrane ROBINS-I instrument to assess the risk of bias in randomised controlled trials. No studies were judged to be at a high risk of bias.

Discussion

In this first meta-analysis examining pharmacotherapy in the primary prevention of anthracycline cardiotoxicity in paediatric cancer patients, we demonstrate that the use of ACE-I enalapril, beta-blocker carvedilol and dexrazoxane resulted in less left ventricular dysfunction and fewer cardiac biomarker abnormalities compared to placebo. Omega 3 fatty acids demonstrated benefit through less reduction of left ventricular strain and fewer cardiac biomarker abnormalities. Other therapies such as amifostine and coenzyme Q10, although through smaller studies, also demonstrated possible cardioprotective benefits. Follow-up durations across studies were as long as 18.6 years.

Dexrazoxane was the most well-studied drug amongst all therapies for primary prevention of anthracycline-related cardiac dysfunction in paediatric cancer patients. Dexrazoxane, an iron chelator licensed by the United States Food and Drug Administration for the prevention of anthracycline-induced cardiotoxicity, also demonstrated significant benefit across trials. Importantly, studies included in our systematic review, with the largest following up 205 patients for a median of 6.2 years [11], corroborates with and supports evidence from other large studies that dexrazoxane does not have a significant safety concern regarding the risk of secondary malignancies[33,34].

Enalapril also demonstrated consistent cardioprotective effects across the included trials. These findings of enalapril in primary prevention are consistent with trials showing similar benefit in adult cancer patients receiving cardiotoxic cancer therapies [35]. Antagonists of the renin-angiotensin-aldosterone system have also been established to rarely cause severe adverse events in those without cardiovascular dysfunction [36], thus enalapril may be a safe and efficacious cardioprotective agent in paediatric cancer patients. While some benefit was observed in randomised-controlled trials evaluating omega-3 fatty acids and co-enzyme Q10, these were limited to single studies of each drug and future studies will be required to better elucidate their efficacy.

Cardinale [37] established in a large cohort that the median length of time between the last cycle of anthracycline and the development of significant cardiotoxicity was 3.5 months (interquartile range: 3-6 months) with a peak toxicity at six months. As such, the protective benefit demonstrated in trials evaluating the efficacy of enalapril and dexrazoxane beyond six months is likely to persist and may be extrapolated beyond the end of follow-up in patients.

There are currently no guidelines for primary prevention of anthracycline-related cardiac dysfunction in paediatric cancer patients. The European Society of Cardiology guidelines recommend dexrazoxane, ACE-I, angiotensin receptor blockers and beta-blockers for primary prevention in high-risk adult cancer patients receiving anthracyclines[7]. Existing guidelines for paediatric cancer patients suggest varying strategies for early detection and monitoring for cardiac dysfunction, but there are no clear recommendations for pharmacotherapy in primary prevention [38-40]. As such, further randomised controlled trials evaluating ACE-I, angiotensin receptor blockers, beta-blockers and dexrazoxane within the paediatric population are needed. Further studies may also explore the efficacy of other pharmacotherapeutic agents shown to have potential in cardioprotection such as angiotensin receptor-neprilysin inhibitors[41-43].

Many further challenges remain beyond establishing if pharmacotherapy is effective for primary prevention within the paediatric cancer population. Firstly, there is a clear need to identify high-risk patients within the paediatric cancer population who would best benefit from primary prevention. Although guidelines have suggested risk stratification methods, these are mainly within the adult cancer population and not within the paediatric cancer population[44]. Certain risk stratification models for the paediatric population have been proposed, but are not accurate enough to be adopted for routine clinical use [6,40,45]. Secondly, there is no clear evidence presently regarding timing of initiation of primary prevention therapy. There is often a long latency period between the asymptomatic subclinical cardiac dysfunction and clinically evident congestive heart failure [46]. Given that there is also no clear guidance regarding cessation of primary prevention therapy, further research is required to better understand when to initiate primary prevention therapy and for how long. Overall, the prevention of cardiotoxicity is of critical concern given the long-term risks it can have on morbidity, mortality and quality of life[47-49].

The study faced several limitations. Firstly, the limited number of randomised-controlled trials conducted in the paediatric population and the small sample size in many randomised-controlled trials to date affects the certainty of evidence. Secondly, while studies evaluated echocardiographic parameters and cardiac biomarkers, few studies have investigated clinical outcomes such as incidence of heart failure or cardiac mortality. Thirdly, the lack of baseline characteristics and individual patient available for meta-analysis may have resulted in heterogeneity across studies not being adequately accounted for in our analysis. Details of outcome measurement, such as instrument, calculations and assumptions made in determining parameters of cardiovascular function were also not explicitly reported in numerous studies.

Conclusion

Our systematic review demonstrated that enalapril and dexrazoxane are highly effective in preventing the development of systolic cardiac dysfunction and elevations in cardiac enzymes following anthracycline chemotherapy in paediatric cancer patients. These benefits were observed to be significant up to as long as five years following administration of anthracycline chemotherapy. Their safety profile in paediatric cancer patients were also highly acceptable. More randomised-controlled trials are required to reach a conclusion on the efficacy of omega-3 fatty acids, co-enzyme Q10 and amifostine.

Conflict of Interest: The authors did not receive support from any organization for the submitted work.

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no others meeting the criteria have been omitted.

Ethics statement: not applicable.

Data availability statement: The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

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Figure Legends

Figure 1: PRISMA flowchart

Figure 2: Risk of significant cardiotoxicity measured by systolic function following anthracycline chemotherapy in paediatric cancer patients receiving dexrazoxane versus no dexrazoxane. An RR <1 favours dexrazoxane.

Tables

TABLE 1 Characteristics of included studies

Study	Cardioprotective regimen	Anthracycline type and regimen*	N, patients	Patient age+	Types of cancer	Outcomes and follow-up++	Follow-up duration+
Lipshultz [10-12]	Dexrazoxane 300 mg/m2 prior to each doxorubicin dose	Doxorubicin CAD 300 in both groups	I: 68 C: 66	I: 7.6 (4.9) C: 7.9 (5.4)	ALL	LVFS, left ventricular thickness-to-diameter ratio, cardiac enzymes	11.8 years

Study	Cardioprotective regimen	Anthracycline type and regimen*	N, patients	Patient age+	Types of cancer	Outcomes and follow-up++	Follow-up duration+
Children's Oncology Group [15-17,25]	Dexrazoxane	Daunorubicin (50 mg/m2/dose) or Mitox-antrone (12 mg/m2/dose), Doxorubicin equivalent of 48mg/m2/dose	I: 96 C: 918	0-1y: 236 2-10y: 370 11+y: 486	AML	LVEF, LVSD	Median: 18.4 years
	Dexrazoxane	Separate cohorts involving doxoru-bicin at CAD 100-360 mg/m2 and 450-600 mg/m2	I+C: 1308	Not reported	Haematological cancers	All-cause mortality, cardiovas-cular mortality, heart transplan-tation rate, major adverse cardiac events and heart failure	
De Berranger [14]	Dexrazoxane at 1g for 50mg of doxoru-bicin isotoxic equivalent dose	Cumulative doxoru-bicin equivalent doses were 310 and 450mg/m2 for EORTC 58951 and LAME01	16	8.5 (2.4-16.1)	ALL, AML	LVFS, mean wall stress	Median: 28.5 months
Wexler [13]	Dexrazoxane was given at 20 times the dose of doxorubicin	Doxorubicin	I: 18 C: 23	I: 15.5 (9-24) C: 18.5 (4-24)	Sarcoma	LVEF, cardiac enzymes	Median: 39 months
Choi [18]	Dexrazoxane in ratio 10:1 to doxorubicin	I: Doxorubicin 280.8±83.4 mg/m2 C: Doxorubicin 266.1±75.0 mg/m2	I: 47 C: 42	I: median 24 months C: median 30 months	Solid tumours	Major adverse cardiac events, congestive cardiac failure	Median: 54 months

Study	Cardioprotective regimen	Anthracycline type and regimen*	N, patients	Patient age+	Types of cancer	Outcomes and follow-up++	Follow-up duration+
De Matos Neto [19]	Dexrazoxane	I: Doxorubicin 405 mg/m2 C: Doxorubicin 345 mg/m2	I: 18 C: 37	I: 15.1 C: 15.4	Osteosarcoma	LVFS	Duration not reported
Elbl [20]	Dexrazoxane	I: CAD 234±58 mg/m2 C: CAD 203±86 mg/m2	I: 53 C: 22	Median 6.5 (Range: 2-17)	Haematological cancers	LVFS	1 month
Paiva [21]	Dexrazoxane in ratio 10:1	I: Doxorubicin 396.5 ± 55 mg/m2 C: Doxorubicin 348.4 ± 18 mg/m2	I: 18 C: 19	I: 16.8 (5) C: 19.7 (4)	Osteosarcoma	LVD, ESWS during low dobutamine stress echocardiography	12.5 months
Schiavetti [22]	Dexrazoxane	I: Doxo-danu 340 mg/m2 or doxorubicin 280 mg/m2 C: Doxo-danu 309 mg/m2 or doxorubicin 270 mg/m2	I: 15 C: 15	Not reported	Various cancers	LVEF, LVFS	6 months
Bu'Lock [23]	Dexrazoxane	Doxorubicin or daunorubicin I: CAD 550-1650 mg/m2 C: CAD 600-1150 mg/m2	I: 5 C: 5	Not reported	Various cancers	LVFS, ventricular diameters during diastole and systole	1 year
Gupta, 2017 [26]	Enalapril 0.1 mg/kg/day for 6 months	Doxorubicin and/or daunorubicin CAD >=200mg/m2	I: 44 C: 40	I: 8.85 (3.15) C: 8.77 (2.86)	ALL, HL, NHL	LVEF, cardiac biomarkers	6 months

Study	Cardioprotective regimen	Anthracycline type and regimen*	N, patients	Patient age+	Types of cancer	Outcomes and follow-up++	Follow-up duration+
Silber [27]	Enalapril Dosing not reported	I: CAD 305 C: CAD 300 Specific anthracycline not reported	I: 69 C: 66	I: 17 (8.3-31.5) C: 18.9 (8.1-30.6)	Not reported	LVEF, LVESWS	3 years
El-Shitany [24]	Carvedilol Dosing not reported	Doxorubicin 4 rounds of 30 mg/m2	I: 25 C: 25	Not reported	ALL	LVFS, GPSS, cardiac enzymes	1 week after each anthracycline dose
El Amrousy [28]	Omega-3 fatty acids 1000 mg/day for 6 months	Not reported	I: 30 C: 30	I: 9 (2) C: 8.5 (1.9)	ALL	LVFS, LVS, E/A ratio, 2D-GLS, MASV, cardiac enzymes	6 months
Iarussi [29]	CoQ 100 mg twice daily	Doxorubicin or daunorubicin I: 240 ± 20.0 C: 252.0 ± 20.1	I: 10 C: 10	I: 5.6 (3-12) C: 5.1 (1-15)	ALL, NHL	LVFS, interventricular septum thickness	Duration not reported
Gallegos-Castorena [30]	Amifostine 740 mg/m2/dose prior to treatment	Doxorubicin 75 mg/m2/dose every 4 weeks	I: 15 C: 13	11.5 (7-15)	Osteosarcoma	Risk of cardiac toxicity	Duration not reported
Hagag 2019 [31]	Silymarin 420 mg/day for one week after each doxorubicin dose	Doxorubicin 25mg/m2/dose weekly for a total of 6 doses	I: 40 C: 40	Not reported	ALL	LVEF, LVFS, E/A, e/a, cardiac enzymes	1 week after each anthracycline dose

Study	Cardioprotective regimen	Anthracycline type and regimen*	N, patients	Patient age+	Types of cancer	Outcomes and follow-up++	Follow-up duration+
Hagag 2020 [32]	Black seed oil 80 mg/kg/dose divided into 3 doses starting at the same moment of beginning of doxorubicin infusion therapy and continued for 1 week after each dose	I: Doxorubicin 134.6 ± 35.8 mg/m2 C: Doxorubicin 117.8 ± 31.6 mg/m2	I: 20 C: 20	I: 8.60 (4.66) C: 7.40 (3.46)	ALL	ECG changes, LVEF, LVFS, E/A, e/a	1 week after each anthracycline dose

Abbreviations: Cumulative anthracycline dose, CAD; Intervention group, I; Comparator group, C; Left ventricular ejection fraction, LVEF; Left ventricular fractional shortening, LVFS; Left ventricular end-systolic wall stress, LVESWS; Left ventricular peak mitral annulus systolic velocity, LVS; Acute lymphocytic leukemia, ALL; Acute myelocytic leukemia, AML; mitral flow early phase filling velocity / peak atrial phase filling velocity, E/A; mitral annulus early phase filling velocity / peak atrial phase filling velocity, e/a; Electrocardiogram, ECG; Hodgkin lymphoma, HL; Mitral annular systolic velocity, MASV; Non-Hodgkin lymphoma, NHL.

*Where available, values for cumulative anthracycline dose reported unless otherwise specified. Where relevant, the doxorubicin isotoxic equivalent is reported by multiplying the total anthracycline dose by 4 for mitoxantrone. All other trials reported doxorubicin and daunorubicin which are isotoxic [50].

+Values represent mean (standard deviation), unless otherwise specified.

++Outcomes of interest included measures of systolic and diastolic function as defined in the methods, elevations in cardiac enzymes and risk of adverse events, measured over a long-term period of at least six months.