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Preventive strategies of cancer therapeutics-related cardiotoxicity in childhood cancer survivors: a protocol of systematic review

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ABSTRACT

Introduction Five-year survival in childhood cancer has been improved markedly in the past decades. Childhood cancer survivors are at high risk of cardiovascular diseases due to anticancer therapy-induced cardiotoxicity. The comprehensive evidence for the prevention of anticancer therapy-induced cardiovascular disease is, however, sparse. The systematic review described in the protocol aims to summarise the effect of current prevention for anticancer therapy-induced cardiotoxicity among childhood cancer survivors.

Methods and analysis This protocol is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols checklist. We will search PubMed (via Medline), Embase and the Cochrane Library and include the studies investigating the effect of prevention against anticancer therapy-induced cardiotoxicity of childhood cancer. To assess the risk of bias, we will use the Cochrane Collaboration's risk of bias tool for randomised control trials and the Newcastle-Ottawa Scale for cohort studies and case–control studies. Furthermore, we will conduct meta-analyses if there is no substantial clinical heterogeneity between included studies. The Grading of Recommendations, Assessment, Development and Evaluation will be used to evaluate the quality of evidence.

Ethics and dissemination Ethical approval is not needed for systematic review of published data. The findings will be published in a peer-reviewed journal and disseminated at scientific conferences.

PROSPERO registration number CRD42022333877.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The systematic review reported in this protocol will systematically assess the evidence regarding preventive strategies for anticancer therapy-induced cardiotoxicity among childhood cancer survivors.
⇒ The review will be conducted in accordance with Cochrane Handbook for Systematic Reviews of Interventions and the process is to large extent transparent by registering the protocol in PROSPERO.
⇒ Our study results will provide reference to the further research about preventive strategies of cardiotoxicity in cancer survivors.
⇒ The study selection, data extraction and risk of bias assessment will be performed independently by two reviewers.
⇒ Our findings may be affected by the potential publication bias because of the restriction to English language.

INTRODUCTION

Due to the advance of cancer therapeutics and healthcare system, the survival of childhood cancer has been improved substantially.[1] Five-year survival rate among children with cancer has reached 80% in high-income countries, although it is only about 30% in low-income and middle-income countries. The health equity of long-term survival in childhood cancer survivors has attracted increasing attention. The Global Initiative for Childhood Cancer launched by the WHO aims to improve this figure to 60% averagely in the world by 2030.[2]

Childhood cancer survivors are at high risk of cardiovascular diseases (CVDs) due to cardiotoxicity of anticancer therapies.[3 4] The risk of CVDs has been found in a previous study to be 2–10 folds higher in survivors of childhood cancer than that in general population, partly due to high oxidative metabolism and low antioxidant defence level of cardiomyocytes.[5] In addition, the cardiovascular system of children and adolescents is vulnerable due to its developmental nature.[4 6] A recent study found that mitochondria from young mice and humans exhibited high level of sensitivity and less resistance to the same toxic stimuli compared with that from corresponding adult species.[7] The common CVDs in childhood cancer survivors are hypertension, left ventricular dysfunction, arrhythmias and myocardial ischaemia.[4] Furthermore, CVD has been one of the leading causes of death in childhood cancer, which the risk of cardiac death in childhood cancer survivors

Table 1 Common cardiovascular diseases induced by anticancer therapies[4 8 16 17]

Category	Cardiovascular diseases
Myocardial dysfunction	Cardiomyopathy, myocarditis, ventricular dysfunction, heart failure
Coronary artery diseases	Myocardial ischaemia, coronary vasospasm, atherosclerosis, angina, myocardial infarction
Arrhythmia	QT prolongation, tachycardia, bradycardia, atrial flutter, atrial fibrillation, ventricular fibrillation, atrioventricular block, cardiac arrest
Valvular diseases	Aortic stenosis, aortic regurgitation, mitral valve stenosis, mitral valve regurgitation, tricuspid valve stenosis, tricuspid valve regurgitation
Others	Hypertension, thromboembolic diseases, pericardial complications

is 8–10 times higher than that in age-matched cancer-free persons,[4] emphasising the importance of prevention of CVDs among childhood cancer survivors.

Several protocols have been suggested to be taken for preventing anticancer therapy-induced CVDs. The reduction of cumulative anthracycline dose (eg, limited to 450–500 mg/m^2), anthracycline analogues (eg, liposomal doxorubicin and liposomal daunorubicin), continuous anthracycline infusion (eg, over 48 hours instead of bolus infusion) and dexrazoxane have been found to be cardioprotective.[4 8 9] However, some above approaches have not been routinely applied in clinical practice to date due to the limited evidence of their long-term effect.[10 11] Given the above concern, nutritional supplements, angiotensin-converting enzyme inhibitors and β-blockers have also been proposed for the prevention of CVDs among children with cancer.[4 12] However, to date, no systematic reviews have comprehensively evaluated the evidence of prevention against anticancer therapy-induced CVDs among childhood cancer survivors. Therefore, the study described in this protocol aims to systematically review the effect of current preventive interventions against anticancer therapy-induced cardiotoxicity among childhood cancer survivors.

METHODS

This protocol is designed in accordance with Cochrane Handbook for Systematic Reviews of Interventions and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol.[13 14]

Patient and public involvement

No patient involved.

Inclusion and exclusion criteria

We will include the studies, if (1) study participants are children with any types of cancer (diagnosed before the age of 18 years[15] and received anticancer therapeutics including chemotherapy, radiotherapy, molecular targeted therapy and immunotherapy, (2) interventions of interest for preventing anticancer therapy-induced CVDs are at least one of the following strategies: anticancer drug analogues, new approaches of drug infusion,

Table 2 Subclinical indicators of anticancer therapy-induced cardiotoxicity[8 22]

Category	Indicators	Abbreviation
Echocardiography	left ventricular ejection fraction	LVEF
	left ventricular fractional shortening	LVFS
	left ventricular end-systolic diameter	LVESD
	left ventricular end-diastolic diameter	LVEDD
Serum cardiac markers	creatine kinase	CK
	creatine kinase-MB	CK-MB
	lactate dehydrogenase	LDH
	aspartate transaminase	AST
	brain natriuretic peptide	BNP
	N-terminal pro-brain natriuretic peptide	NT-proBNP
	cardiac troponin	cTn
Oxidative stress markers	malondialdehyde	MDA
	superoxide dismutase	SOD
	glutathione	GSH
	glutathione peroxidase	GPx
	catalase	CAT

Table 3 Search strategy in PubMed (via Medline) database

Number	Search term
#1	"Neoplasms"[MeSH] OR Neoplasm*[Title/Abstract] OR Neoplastic*[Title/Abstract] OR Tumor*[Title/Abstract] OR Tumour*[Title/Abstract] OR Cancer*[Title/Abstract] OR Oncolog*[Title/Abstract] OR Malignan*[Title/Abstract] OR Leukemi*[Title/Abstract] OR Leucocythaemia*[Title/Abstract] OR Leucocythemia*[Title/Abstract] OR Lymphoma*[Title/Abstract] OR Sarcoma*[Title/Abstract] OR "Central Nervous System Neoplasm*"[Title/Abstract]
#2	"Child"[MeSH] OR "Adolescent"[MeSH] OR "Pediatrics"[MeSH] OR Child*[Title/Abstract] OR Kid[Title/Abstract] OR Kids[Title/Abstract] OR Adolesce*[Title/Abstract] OR Teen*[Title/Abstract] OR Young[Title/Abstract] OR Youth[Title/Abstract] OR Juvenil*[Title/Abstract] OR Pediatric*[Title/Abstract] OR Paediatric*[Title/Abstract] OR Pediatry[Title/Abstract] OR Pubert*[Title/Abstract] OR Prepubert*[Title/Abstract] OR Under ag*[Title/Abstract] OR Underag*[Title/Abstract]
#3	"Antineoplastic Protocols"[MeSH] OR "Antineoplastic Combined Chemotherapy Protocols"[MeSH] OR "Chemotherapy, Adjuvant"[MeSH] OR Chemotherap*[Title/Abstract] OR "Antineoplastic Protocol*"[Title/Abstract] OR "Antineoplastic Drug Combination*"[Title/Abstract] OR "Antineoplastic Agent*"[Title/Abstract] OR "Anticancer Drug Combination*"[Title/Abstract] OR "Cancer Treatment Protocol*"[Title/Abstract] OR "Adjuvant Drug Therap*"[Title/Abstract] OR Anthracycline*[Title/Abstract] OR Daunorubicin[Title/Abstract] OR Doxorubicin[Title/Abstract] OR Adriamycin[Title/Abstract] OR Cyclophosphamide[Title/Abstract] OR Cisplatin[Title/Abstract] OR Vincristine[Title/Abstract] OR Methotrexate[Title/Abstract]
#4	"Radiotherapy"[MeSH] OR "Chemoradiotherapy"[MeSH] OR Radiotherap*[Title/Abstract] OR "Cancer Radiotherap*"[Title/Abstract] OR "Tumor Radiotherap*"[Title/Abstract] OR "Tumour Radiotherap*"[Title/Abstract] OR "Cancer Radiation"[Title/Abstract] OR "Tumor Radiation"[Title/Abstract] OR "Tumour Radiation"[Title/Abstract] OR "Cancer Irradiation"[Title/Abstract] OR "Tumor Irradiation"[Title/Abstract] OR "Tumour Irradiation"[Title/Abstract] OR Chemoradiotherap*[Title/Abstract] OR Radiochemotherap*[Title/Abstract] OR Chemoradiation[Title/Abstract]
#5	"Immunotherapy"[MeSH] OR Immunotherap*[Title/Abstract] OR "Cancer Immunotherap*"[Title/Abstract] OR "Tumor Immunotherap*"[Title/Abstract] OR "Tumour Immunotherap*"[Title/Abstract]
#6	"Molecular Targeted Therapy"[MeSH] OR "Molecular Targeted Therap*"[Title/Abstract] OR "Molecular Target Therap*"[Title/Abstract] OR "Targeted Cancer Therap*"[Title/Abstract] OR "Targeted Molecular Therap*"[Title/Abstract] OR Immunoconjugate[Title/Abstract] OR "Antibody Drug Conjugate*"[Title/Abstract]
#7	#3 OR #4 OR #5 OR #6
#8	"Cardiotoxicity"[MeSH] OR "Heart Diseases"[MeSH:NoExp] OR Cardiotoxicit*[Title/Abstract] OR "Cardiac Toxic*"[Title/Abstract] OR "Cardio Toxic*"[Title/Abstract] OR "Heart Toxic*"[Title/Abstract] OR Cardiotoxi*[Title/Abstract] OR "Cardiovascular Toxicit*"[Title/Abstract] OR "Heart Disease*"[Title/Abstract] OR "Heart Dysfunction*"[Title/Abstract] OR "Heart Disorder*"[Title/Abstract] OR "Cardiac Disease*"[Title/Abstract] OR "Cardiac Dysfunction*"[Title/Abstract] OR "Cardiac Disorder*"[Title/Abstract] OR Cardiopath*[Title/Abstract] OR Cardiomyopath*[Title/Abstract] OR Myocardiopath*[Title/Abstract] OR "Myocardial Dysfunction*"[Title/Abstract] OR Myocarditis[Title/Abstract] OR "Ventricular Dysfunction*"[Title/Abstract] OR "Heart Failure"[Title/Abstract] OR "Cardiac Death"[Title/Abstract] OR "Myocardial Ischaemia"[Title/Abstract] OR "Coronary Artery Disease*"[Title/Abstract] OR "Coronary Vasospasm"[Title/Abstract] OR Angina[Title/Abstract] OR Atherosclerosis[Title/Abstract] OR "Myocardial Infarction"[Title/Abstract] OR "Valvular Disease*"[Title/Abstract] OR "Aortic Stenosis"[Title/Abstract] OR "Aortic Regurgitation"[Title/Abstract] OR "Mitral Valve Stenosis"[Title/Abstract] OR "Mitral Valve Regurgitation"[Title/Abstract] OR "Tricuspid Valve Stenosis "[Title/Abstract] OR "Tricuspid Valve Regurgitation"[Title/Abstract] OR Arrhythmia[Title/Abstract] OR "QT Prolongation"[Title/Abstract] OR "QT Interval Prolongation"[Title/Abstract] OR "Atrial Fibrillation"[Title/Abstract] OR "Atrial Flutter"[Title/Abstract] OR "Ventricular Fibrillation"[Title/Abstract] OR "Sick Sinus Syndrome"[Title/Abstract] OR "Premature Heartbeats"[Title/Abstract] OR Tachycardia[Title/Abstract] OR Bradyarrhythmia[Title/Abstract] OR Bradycardia[Title/Abstract] OR "Cardiac Arrest"[Title/Abstract] OR "Heart Block"[Title/Abstract] OR Hypertension[Title/Abstract] OR "Hypertensive Heart Disease*"[Title/Abstract] OR "Thromboembolic Disease*"[Title/Abstract] OR "Venous Thromboembolism"[Title/Abstract] OR "Arterial Thromboembolism"[Title/Abstract] OR Hyperlipidaemia[Title/Abstract] OR Stroke[Title/Abstract] OR Pericarditis[Title/Abstract] OR Myopericarditis[Title/Abstract] OR Endocarditis[Title/Abstract] OR "Pleural Effusion"[Title/Abstract] OR Bleeding[Title/Abstract] OR "Cardiovascular Complication*"[Title/Abstract]
#9	#1 AND #2 AND #7 AND #8

nutrition supplements and cardiovascular medications, (3) outcomes of interest should include at least one of the following indicators: any CVDs (primary outcomes, listed in table 1) or abnormal left ventricular function or structure evaluated by echocardiography, serum cardiac markers or oxidative stress markers (secondary outcomes, presented in table 2), (4) study type is randomised controlled trial, clinical trial, cohort study or case–control study.

We will exclude the studies, if they (1) are published only as conference abstracts, and (2) are animal studies.

Search strategy and study selection

We will do literature search in PubMed (via Medline), Embase and the Cochrane Library from the inception to July 2022. In addition, a manual search will be also conducted by screening references of included studies and of the reviews in this area. According to the descriptions of the definition of cardiotoxicity in the related clinical practice guidelines, we will consider the manifestation of cardiotoxicity as any adverse event affecting cardiovascular system during or after cancer treatment.[8 16–18] The search strategy set in Pubmed (via Medline) is presented in table 3 and similar strategies will be performed in Embase and the Cochrane Library.

Two reviewers (X-YZ and K-LY) will screen independently the titles and abstracts of records retrieved from the databases by using Endnote and Rayyan software and review the full text of the potentially eligible

studies. In case of disagreements in any phase of selection process, a discussion with two other reviewers (QW and DW) will be taken place to reach a consensus.

Data extraction

Two reviewers (X-YZ and K-LY) will extract independently data of the included studies using a prespecified data extraction sheet. The following information will be extracted: first author, year of publication, study design, sample size, age at diagnosis, gender, cancer diagnosis, intervention characteristics, the length of follow-up and outcomes of interest.

Risk of bias assessment

Two reviewers (X-YZ and K-LY) will independently assess the risk of bias for the included studies. For randomised controlled trials, we will use the risk of bias tool recommended by the Cochrane Collaboration.[19] It contains six domains, including selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. The items can be assessed as low, unclear or high risk of bias. For cohort studies and case–control studies, we will use the Newcastle-Ottawa Scale, containing eight items with a total scale of 9.[20] Higher score suggests the lower risk of bias. Any disagreements are resolved by consulting two other reviewers (QW and X-NL).

Data synthesis and analyses

We will report characteristics of included studies (eg, study design, sample size, interventions, length of follow-up, outcomes of interest, etc) and results of risk of bias assessment in descriptive narrative form and in a table format as appropriate. We will calculate relative risk with 95% CI for dichotomous data and mean differences with 95% CI for continuous data. We will synthesise the results of included studies using Review Manager (RevMan V.5.3.0) if there is no significant clinical heterogeneity and present the results of the analyses by using forest plots; otherwise, we will not pool the data. We will choose the fixed effect model to synthesise the data in case of no or moderate statistical heterogeneity and the random effect model in case of high heterogeneity. χ^2 test will be used to evaluate statistical heterogeneity of results between included studies (I^2<25%, no heterogeneity; I^2:25%–50%, moderate heterogeneity; and I^2>50%, high heterogeneity).

We plan to synthesise the results of included studies separately by age at diagnosis, sex, types of cancer and types of cancer treatment, if the relevant data are available. The tests of interaction term will be performed for statistical differences of effect estimates in different subgroups.

If there are more than 10 studies included in a meta-analysis, we will assess publication bias using funnel plots.

Quality of evidence

Two reviewers (X-YZ and K-LY) will independently evaluate the quality of evidence produced in this systematic review by using the Grading of Recommendations, Assessment, Development and Evaluation.[21] If there is a divergence, it will be resolved by discussion between a third and fourth reviewers (QW and X-NL). The quality of evidence will be graded as high, moderate, low or very low.

The review is under study selection and is anticipated to be completed in December 2022.

DISCUSSION

This review will systematically summarise current evidence of prevention against anticancer therapeutics-related cardiotoxicity in childhood cancer survivors. The cardiovascular system may be affected substantially by anticancer treatments due to the low antioxidant defence level of cardiomyocytes in children or adolescents. Therefore, cardiotoxicity is a more prominent and severe issue in patients with paediatric cancer among childhood cancer survivors than among adult cancer survivors.[4 6] Given the markedly improve survival in childhood cancer survivors, anticancer-induced cardiotoxicity may play an important role in childhood cancer survivors' survivorship. An evidence map of cardioprotective strategies for childhood cancer survivors will be reported on the completion of this systematic review. According to our findings, future research recommendations will be suggested and an evidence-based preventive strategy for cardiotoxicity may be conducted.

Amendments

If necessary to amend the protocol, we will record the date, description and rationale for each amendment. And the differences between the published protocol and final article will be reported and explained in detail in the section Discussion.

Contributors QW, DW and X-NL conceived the idea and designed the study protocol. X-YZ and K-LY developed the search strategy and drafted the manuscript. All authors read and approved the final version.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Ethical approval is not required to undertake this review.

Provenance and peer review Not commissioned; externally peer reviewed.

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