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Systematic Review and Disproportionality Analysis of Cancer Therapy-Related Cardiovascular Toxicity (CTR-CVT) Induced by Platinum Chemotherapeutic Agents: A Study of FAERS and Case Reports

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ADMINISTRATIVE INFORMATION

Support - No funding is required for this systematic review, and the authors declare no conflicts of interest related to the study.

Review Stage at time of this submission - Piloting of the study selection process.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202520111

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 February 2025 and was last updated on 25 February 2025.

INTRODUCTION

Review question / Objective This systematic review aims to analyze and synthesize existing literature on cancer therapy-related cardiovascular toxicity (CTR-CVT) induced by platinum-based chemotherapeutic agents. The specific objectives are to:
Identify the types and frequencies of CTR-CVT associated with platinum-based agents, including cisplatin, carboplatin, and oxaliplatin.
Assess the quality of case reports and identify significant cardiovascular events.
Conduct a disproportionality analysis using data from the FDA Adverse Event Reporting System (FAERS) to identify potential signals of cardiovascular toxicity.

Rationale Platinum-based chemotherapeutic agents, widely used in cancer treatment, have been associated with cardiovascular toxicity, including coagulation disorders, thromboembolic events, and coronary artery disease. Despite the growing recognition of cancer therapy-related cardiovascular toxicity (CTR-CVT) as a severe complication, it remains under-reported and inadequately studied. This systematic review aims to fill this gap by consolidating data from case reports and post-marketing surveillance.

Condition being studied Cancer therapy treatment-related cardiovascular toxicity (CTR-CVT) refers to adverse cardiovascular events caused by the use of chemotherapeutic agents (especially platinum-based chemotherapeutic agents) during cancer treatment. Platinum-based chemotherapeutic agents (e.g., cisplatin, carboplatin, oxaliplatin) are widely used in the treatment of many types of cancers (including lung, ovarian, and gastric cancers); however, these agents may cause toxic reactions in the cardiovascular system.
Specific manifestations of cardiovascular toxicity include:

Heart failure (Heart failure): including acute or chronic heart failure, which may lead to symptoms such as dyspnoea, weakness and oedema.
Arrhythmia, including atrial fibrillation, premature ventricular contractions, and other heart rhythm abnormalities, which may increase the risk of stroke and other serious cardiovascular events.
Thromboembolic events: such as deep vein thrombosis, pulmonary embolism, and cardiac embolism, which can be fatal.
Coronary artery.

METHODS

Search strategy Using the keywords "platinum chemotherapeutic agents", "cardiotoxicity", "cancer therapy-related cardiovascular toxicity", "cisplatin", "carboplatin", "oxaliplatin","lobaplatin", "nedaplatin". All adverse events related to CTR-CVT were coded using the preferred terms (PTs) in the Medical Dictionary for Regulatory Activities (MedRA, version 23.0). Queries were made using MedDRA SMQ, and the "Narrow" category was selected for retrieval. A total of 12 classes of SMQS and 1268 PTs terms were identified.

Participant or population Patients with cancer.

Intervention Platinum-based chemotherapy (cisplatin, carboplatin, lobaplatin, nedaplatin, and oxaliplatin).

Comparator Not applicable.

Study designs to be included Case report.

Eligibility criteria Case reports documenting CTR-CVT in patients treated with platinum-based chemotherapeutic agents (cisplatin, carboplatin, oxaliplatin).
Studies from PubMed and Web of Science published in English.
Reports that include patient demographics, cancer type, chemotherapy regimen, cardiovascular events, and outcomes.
Exclusion Criteria:
Studies not reporting CTR-CVT or without detailed case information.
Review articles and meta-analyses.
Non-English language reports.

Information sources
PubMed
Web of Science
FDA Adverse Event Reporting System (FAERS).

Main outcome(s) Cancer therapy-related cardiovascular toxicity.

Additional outcome(s) The incidence of cardiovascular disease, treatment response, survival, electrocardiogram, cardiac color Doppler ultrasound and other cardiovascular assessment biomarkers were analyzed.

Data management The literature screening process was divided into three main stages: preliminary screening (title and abstract screening), full-text screening, and data extraction and quality assessment. The screening process will be conducted by at least two independent investigators, assessors 1 and 2, who will receive uniform training to ensure a consistent understanding of the screening criteria. Two reviewers made a double assessment during the literature screening process. In case of disagreement on the inclusion or exclusion of the literature, a third party expert (senior researcher or faculty advisor in the field) would make the final decision.

Quality assessment / Risk of bias analysis A Systematic review will be conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines to screen case reports that meet the criteria. Hadji Murad, etc (2018) is adopted in methodological quality tools for research into the cases quality assessment (doi.: 10.1136/bmjebm-2017-110853), to ensure the reliability of data and scientific.

Strategy of data synthesis Disproportionality analysis was performed using the following four algorithms:
Reporting ratio (ROR) : Assesses the strength of the relationship between a drug and an adverse event.
Proportional reporting ratio (PRR) : identify associations between drugs and CTR-CVT by comparing rates of adverse event reporting for specific drugs.
Bayesian confidence level Propagation Neural Network (BCPNN) : Use Bayesian inference and neural networks to model the relationship between drugs and adverse events.
Multinomial gamma contractions (MGPS) : Provide more conservative estimates of association and reduce false positive rates
These analyses will help to identify potential CTR-CVT signals and determine the relationship between different platinum-based chemotherapy agents and CTR-CVT.
Quantitative data will be pooled and, if appropriate, subjected to meta-analysis. Qualitative data will be

subject to thematic analysis to further interpret the cardiovascular toxicity profile of different platinum drugs and their clinical o.

Subgroup analysis Subgroup analysis: In this study, in order to explore the relationship between platinum-based chemotherapeutic agents and cardiovascular toxicity in depth, in addition to the overall analysis, we will conduct multiple subgroup analyses to identify possible differences between different groups. These subgroup analyses will help to assess more precisely the safety and efficacy of platinum-based chemotherapy agents, especially in specific cancer types, gender, age, and othergroups.

Sensitivity analysis Test of heterogeneity:
For the included literature and reports, heterogeneity between the different studies will be assessed, for example using the I^2 statistic, and the potential impact of heterogeneity on the results will be examined. If heterogeneity is large, subgroup analyses or random effects models will be used to test whether the results are robust.

Publication bias analysis:
Egger regression test and funnel plot were used to check publication bias. If evidence of publication bias is found, we will consider corresponding statistical methods to correct for potential bias to ensure the reliability of the study's conclusions.

Missing data and handling:
Because case reports and FAERS data may have missing data, sensitivity analyses will include the effect of different missing data handling methods on the results. For example, we will compare the results of a complete-case analysis with those after the use of multiple imputation to imputate missing data.

Language restriction English.

Country(ies) involved China.

Other relevant information Scientific significance of the study:
By combining the full volume data of the FAERS database with the detailed information of the case reports, this study will provide a more comprehensive assessment of cardiovascular toxicity caused by platinum-based chemotherapy drugs. This study helps to reveal the potential mechanism of CTR-CVT, evaluate the cardiovascular risk of different platinum drugs in cancer treatment, and provide stronger evidence for clinical medication.
Expected results:
Determine the association and its strength between platinum-based chemotherapy agents and CTR-CVT.
Summarize the types and incidence of CTR-CVT caused by different platinum-based chemotherapy agents.
Provide a safety reference for clinical decision making and facilitate the development of clinical guidelines.

Keywords Platinum-based chemotherapy; CardiotoxicityCancer therapy-related cardiovascular toxicity (CTR-CVT); FAERS database; Disproportionality analysis.

Dissemination plans Publication in academic journals, International academic conference, Lectures to public health agencies and policy makers,clinicians and health care providers, Social media and online platforms.

Contributions of each author
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