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Review article

Cardiotoxicity in platinum-based chemotherapy: Mechanisms, manifestations, and management

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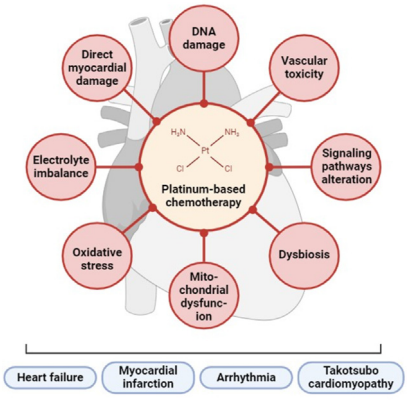
HIGHLIGHTS

- Platinum-based chemotherapies cause direct myocardial/DNA damage, oxidative stress, and alterations in signaling pathways.
- Clinical manifestations range from asymptomatic changes to severe conditions, including Takotsubo cardiomyopathy.
- Advancements in diagnostic tools of echocardiography, cardiac magnetic resonance (CMR), and cardiac biomarkers have improved disease detection.
- Management of cardiotoxicity includes the use of cardioprotective agents and alternative chemotherapy regimens.

GRAPHICAL ABSTRACT



Systemic toxicities of platinum-based chemotherapy: a visual summary of adverse effects.

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ABSTRACT

Platinum-based chemotherapy, a cornerstone in the treatment of various malignancies, is often limited by its potential cardiotoxic effects. Understanding these effects is crucial for optimizing patient outcomes and guiding treatment decisions. This review explores the mechanisms, clinical manifestations, detection, management, and future directions in the research of cardiotoxicity associated with platinum-based chemotherapy. The mechanisms discussed here include oxidative stress, reactive oxygen species production, DNA damage, and alterations in signaling pathways. Clinical manifestations range from mild symptoms to severe complications, including Takotsubo cardiomyopathy, as highlighted by recent case studies. The role of diagnostic tools such as echocardiography, cardiac magnetic resonance imaging, and cardiac biomarkers in early detection is emphasized, underscoring the importance of regular cardiac monitoring. Management strategies focus on cardioprotective agents, alternative chemotherapy regimens, and emerging therapeutic approaches, including the potential of nano liposomal and cubosomal formulations. The review also delves into the future of personalized medicine in predicting and managing cardiotoxicity, advocating for ongoing research to mitigate these adverse effects. This

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comprehensive overview aims to enhance the understanding of cardiotoxicity in platinum-based chemotherapy, informing clinical practices and promoting patient-centric care.

Introduction

Platinum-based chemotherapy is a fundamental part of modern cancer treatment, offering effective options for various malignancies. These chemotherapy agents, including cisplatin, carboplatin, and oxaliplatin, have been integral in managing ovarian, lung, bladder, and testicular cancers, among others.[1] Their widespread use has been attributed to their ability to induce DNA damage in cancer cells, thereby inhibiting tumor growth and proliferation. One of the primary mechanisms by which platinum compounds exert their antineoplastic effect is through the formation of platinum-DNA adducts. These adducts disrupt DNA replication and transcription, leading to cell death. Due to this mechanism, platinum-based drugs are often used in combination with other chemotherapeutic agents, enhancing the overall efficacy of cancer treatment.[2] For example, in ovarian cancer, platinum agents combined with taxanes have become the standard of care for both adjuvant treatment in early stages and first-line therapy for advanced disease.[3] The effectiveness of platinum-based chemotherapy, however, is not universal across all patient populations. The response to these drugs can vary significantly due to genetic variations influencing drug metabolism and DNA repair pathways. Studies have shown that polymorphisms in genes related to DNA repair mechanisms can predict the response to platinum therapy, particularly in breast and lung cancers.[4,5] These findings highlight the move toward personalized medicine in oncology, where treatments can be tailored based on individual genetic profiles.

Despite their efficacy, platinum-based chemotherapeutics have notable drawbacks. One of the most concerning side effects of these drugs is their potential for cardiotoxicity, which manifests in various forms, ranging from mild symptoms to severe cardiovascular events. The cardiotoxic effects of platinum compounds are multifactorial and may include direct myocardial damage, vascular effects, and electrolyte imbalances. This toxicity can be acute, occurring shortly after drug administration, or delayed, presenting long after the completion of therapy. The precise mechanisms underlying platinum-induced cardiotoxicity are intricate and involve oxidative stress, inflammation, endothelial dysfunction, and direct myocardial injury.[6] The clinical implications of cardiotoxicity are significant, as they can restrict the dosage and duration of chemotherapy, impacting cancer treatment outcomes. Additionally, the long-term cardiac effects pose a substantial burden on survivors of cancer, necessitating ongoing cardiac monitoring and, in some cases, lifelong management of cardiac complications. As such, understanding and managing cardiotoxicity are paramount in the context of platinum-based chemotherapy, requiring a multidisciplinary approach that includes oncologists, cardiologists, and primary care providers. In this review, we aimed to explore the mechanisms, clinical manifestations, detection, management, and future directions in the research of cardiotoxicity associated with platinum-based chemotherapy. This comprehensive overview aims to enhance the understanding of cardiotoxicity in platinum-based chemotherapy, informing clinical practices and advocating for patient-centric care.

Mechanisms of cardiotoxicity

Platinum-based chemotherapies can cause significant cardiovascular harm, which in many cases is more impactful than the underlying disease itself.[7] One of the primary mechanisms of cardiotoxicity is direct

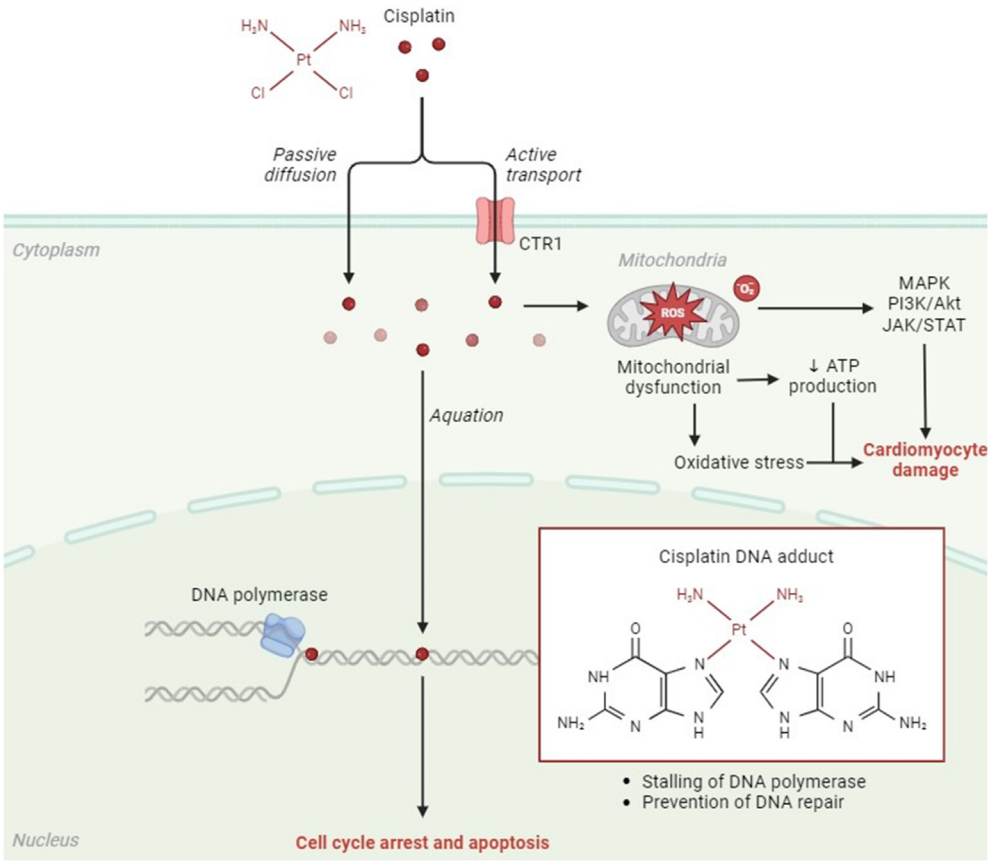

Figure 1. Mechanisms of cisplatin-induced cytotoxicity in cardiomyocytes. This diagram illustrates the multifaceted cytotoxic mechanisms of cisplatin in cardiomyocytes. Cisplatin can enter the cell through passive diffusion or active transport via the copper transporter CTR1. Upon entry, it undergoes aquation, leading to the formation of cisplatin-DNA adducts that stall DNA polymerase and prevent DNA repair, triggering cell cycle arrest and apoptosis. Concurrently, cisplatin also impairs mitochondrial function, leading to increased ROS production, a decrease in ATP production, and oxidative stress, culminating in cardiomyocyte damage through various signaling pathways including MAPK, PI3K/Akt, and the JAK/STAT. This diagram is modified from Huang, E. (2023) BioRender. Akt: Protein kinase B; ATP: Adenosine triphosphate; CTR1: Copper transporter 1; JAK: Janus kinase; MAPK: Mitogen-activated protein kinase; PI3K: Phosphoinositide 3-kinase; ROS: Reactive oxygen species; STAT: Signal transducer and activator of transcription.

myocardial damage. Chemotherapy agents can directly harm myocardial cells, leading to both acute and chronic manifestations. This damage may be due to the interaction of platinum compounds with cellular components, triggering apoptosis and necrosis of cardiomyocytes [Figure 1].[8] Platinum compounds form DNA adducts, causing substantial DNA damage. This damage, if unrepaired, can result in apoptosis of cardiac cells. The extent of DNA damage correlates with the severity of cardiotoxicity.[9] This damage can manifest as reductions in left ventricular ejection fraction (LVEF), heart failure, or even acute coronary syndromes. Another key aspect of cardiotoxicity in platinum-based chemotherapy is vascular toxicity. These compounds can induce vascular toxicity, leading to endothelial dysfunction and arterial hypertension. This contributes to the overall burden of cardiotoxicity by exacerbating the risk of thromboembolic events and ischemia. The early vascular toxicity occurring at the time of chemotherapy or immediately thereafter is particularly noteworthy. Molecular mechanisms associated with this vascular toxicity include changes in protein kinase C (PKC) isoforms, transient receptor potential channel (TRPC)1 expression, and nuclear factor "kappa-light--chain-enhancer" of activated B-cells (NF-κB), which lead to endothelial hyperpermeability and leakage of albumin.[10,11] Additionally, electrolyte imbalances, particularly hypomagnesemia, are another concern with platinum-based chemotherapies such as cisplatin. These imbalances can lead to arrhythmias and other cardiac complications, further complicating the treatment landscape for patients undergoing these therapies.[12]

Oxidative stress also plays a crucial role in the pathological process of platinum-induced cardiotoxicity [Figure 1]. Reactive oxygen species (ROS) generation is a key factor, leading to cell apoptosis and overt cardiotoxicity. For instance, Cheng et al.[13] explored the cardiotoxic effects of carboplatin *in vivo* and *in vitro*. Their findings indicate that carboplatin can induce cardiotoxicity through a mitochondrial pathway associated with ROS production.[13] Increased ROS production during chemotherapy can result in substantial myocardial damage. This involves the activation of stress-related signaling pathways and subsequent cell death. ROS-mediated damage is not only confined to direct oxidative injury but also includes secondary damage through the activation of various cell signaling cascades, including mitogen-activated protein kinases (MAPKs) and phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathways.[14] Apelin-13, a bioactive peptide, has been shown to mitigate cisplatin-induced cardiotoxicity by reducing ROS and superoxide anion generation, inhibiting DNA damage, and suppressing poly adenosine diphosphate (ADP)-ribose polymerase (PARP) cleavage and caspase activation in both *in vitro* (using H9c2 rat myocardial cells) and *in vivo* (i.e., C57 mice) animal models.[15]

Chemotherapy agents such as cisplatin have also been associated with mitochondrial dysfunction in various tissues, including the heart. Mitochondrial impairment can lead to decreased energy production and increased oxidative stress, contributing to cardiomyocyte damage.[16] An experimental study investigated the cardiotoxic effects of chronic oxaliplatin treatment, a platinum-based alkylating chemotherapeutic agent, on heart metabolism in mice. This study reported that oxaliplatin-induced significant alterations in the heart's metabolic profile, leading to cardiotoxicity and heart damage characterized by focal myocardial necrosis and infiltration by neutrophils. Significant changes in gene expression related to energy metabolic pathways were also observed, affecting fatty acid oxidation, amino acid metabolism, glycolysis, the electron transport chain, and nicotinamide adenine dinucleotide (NAD) synthesis pathway. Additionally, a shift in heart metabolism from fatty acids to glycolysis with increased lactate production, alongside strong overexpression of genes in NAD synthesis pathways, notably *Nmrk2*, were observed.[17]

Chemotherapy-induced cardiotoxicity is also influenced by its alterations in various signaling pathways. Keys among these are the MAPK and Akt pathways, involved in cell survival and apoptosis. Aberrant activation or inhibition of these pathways can contribute to cardiotoxicity.[15] Additionally, other pathways, such as the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway, have been implicated in the response to cardiac stress and damage.[18] Dysbiosis was also shown to be involved in the pathogenesis of platinum-induced cardiotoxicity. A study evaluated the impact of cisplatin on cardiac function and gut microbiota in C57Bl6 mice, and the potential protective role of *Lactobacillus* supplementation. The results showed that a 3-week treatment with 6 mg/kg cisplatin significantly reduced body weight by approximately 33% and decreased LVEF by approximately 15%, indicating a loss of cardiac function. Additionally, cisplatin treatment resulted in a dramatic alteration of the gut microbiota, characterized by a 27% decrease in *Firmicutes* and an increase in pathological bacteria. Supplementation with *Lactobacillus* significantly countered the negative effects of cisplatin, leading to an increase in body weight and restoration of cardiac function. This improvement was associated with reduced expression of inflammation-related genes.[19]

Clinical manifestations

Cardiotoxicity associated with platinum-based chemotherapy presents a wide range of clinical manifestations, from mild symptoms to severe complications.[20–22] One of the most severe manifestations of chemotherapy-induced cardiotoxicity is heart failure, ranging from asymptomatic left ventricular dysfunction to symptomatic congestive heart failure [Table 1]. This condition can significantly impact the patient's quality of life and overall survival.[20–22] A case of a 53-year-old woman diagnosed with cervical cancer reported cardiotoxicity as a side effect of cisplatin treatment. After receiving cisplatin ($37\ mg{\cdot}m^{-2}{\cdot}week^{-1}$) for 3 weeks, her LVEF dropped from 70% to 48%. Initial diagnostic tests revealed a first-degree atrioventricular block and ST-segment depression, but no elevation in cardiac markers or N-terminal pro-B-type natriuretic peptide (NT-pro BNP). A thorough examination ruled out cancer progression or other causes, leading to the conclusion that the cardiotoxicity was likely induced by cisplatin. Upon discontinuing cisplatin and initiating cardioprotective therapies (i.e., coenzyme Q10 and trimetazidine), the patient's LVEF improved to 50% after 17 days and further to 53% after 90 days, as measured by M-mode echocardiography.[23]

Myocardial ischemia, including angina pectoris and myocardial infarction, is also a significant risk, particularly in patients with pre-existing cardiovascular risk factors. Additionally, tachyarrhythmias, including atrial fibrillation and ventricular tachycardia, as well as bradyarrhythmias are not uncommon and can lead to severe complications.[24–26] Chen et al.[27] presented a case of a 76-year-old male with adenocarcinoma of the esophagogastric junction and a 40-day history of non-ST-elevation myocardial infarction who developed a new third-degree atrioventricular block after receiving oxaliplatin. Upon recognizing the cardiotoxicity, oxaliplatin was discontinued, and the

Table 1
Cancer therapy-related cardiac dysfunction (CTRCD) classification.[21,22]

Severity level	Criteria
Asymptomatic CTRCD	
Mild	LVEF ≥50% and a new relative decline in GLS > 15% from baseline and/or new rise in cardiac biomarkers
Moderate	New LVEF reduction by ≥ 10 percentage points to an LVEF of 40%–49% or new LVEF reduction by <10% to an LVEF of 40%–49% and either new relative decrease in GLS by >15% from baseline or new rise in cardiac biomarkers
Severe	New LVEF <40%
Symptomatic CTRCD	
Mild	Mild HF symptoms, no intensification of therapy required
Moderate	Need for outpatient intensification of diuretic and HF therapy
Severe	HF hospitalization
Very severe	HF requiring inotropic or mechanical circulatory support or consideration of transplantation

GLS: Global longitudinal strain; HF: Heart failure; LVEF: Left ventricular ejection fraction.

patient was treated with the implantation of a permanent pacemaker and administration of diltiazem hydrochloride to manage and prevent further cardiac complications. The patient's third-degree atrioventricular block resolved after the withdrawal of oxaliplatin, with no recurrence observed in subsequent chemotherapies. This case highlights the critical need for vigilant cardiovascular monitoring in patients with cancer receiving chemotherapy, especially those with a history of acute coronary syndrome.[27]

Morrow et al.[28] presented a case where a patient experienced two ST-elevation myocardial infarctions during (day 9 after the first cycle) and post-chemotherapy (10 months after completion) for testicular germ cell tumor (i.e., bleomycin, etoposide, and cisplatin [BEP]), with deteriorating lipid profiles and evidence of accelerated atherosclerosis despite statin therapy. Similarly, a retrospective observational study also explored the long-term cardiovascular implications of cisplatin-based chemotherapy in testicular cancer survivors 30 years post-treatment. It found that survivors, compared to matched controls, had a higher use of anti-hypertensive and lipid-lowering medications, and exhibited worse diastolic function, though there were no significant differences in systolic function, arrhythmias, or valvular heart disease. The findings suggest that the long-term cardiovascular impacts of cisplatin-based chemotherapy might be limited to metabolic dysfunction and impaired diastolic function.[29] Recently, a study also examined the long-term cardiac effects of platinum-based chemotherapy in germ-cell cancer survivors through cardiac magnetic resonance (CMR) imaging. It was observed that survivors showed reduced left and right ventricular ejection fractions and deformation, indicating decreased heart function. Additionally, myocardial fibrosis was observed in 20% of the survivors, suggesting heart tissue damage. The study concludes that chemotherapy with cumulative cisplatin doses $\geq$200 mg/m^2 can lead to significant cardiac function and tissue changes in asymptomatic long-term germ cell cancer survivors.[30] These studies underscore the importance of long-term monitoring of cardiovascular risk factors and cardiac function in cancer survivors treated with platinum-based chemotherapy.

A notable case study also reported a patient developing Takotsubo cardiomyopathy after receiving the FOLFOX regimen (a combination of 5-fluorouracil and platinum-based chemotherapy) for colorectal adenocarcinoma. The patient presented with cardiogenic shock but recovered with the aid of a percutaneous left ventricular assist device, highlighting the reversible nature of some forms of chemotherapy-induced cardiotoxicity.[31] Another study reported the experience of a 64-year-old female diagnosed with stage IV gastric adenocarcinoma who had no previous cardiovascular disease. She was undergoing palliative treatment with a regimen that included fluorouracil, leucovorin, oxaliplatin, and docetaxel, which she managed well for five cycles. However, upon the sixth cycle, while only receiving oxaliplatin (and not docetaxel or 5-fluorouracil), she exhibited hemodynamically unstable cardiovascular conditions. Despite these challenges, her hospitalization was complication-free, and she was discharged after 10 days, maintaining normal systolic function without any myocardial structural alterations. The diagnostic tests (i.e., electrocardiogram, echocardiogram, cardiac catheterization, and magnetic resonance imaging) indicated an oxaliplatin-associated Takotsubo syndrome.[32] In general, the incidence and severity of cardiotoxic effects can vary depending on several factors, including the type of chemotherapeutic agent, patient age, underlying cardiovascular status, and genetic background. For example, studies have shown that the incidence of Takotsubo cardiomyopathy and other severe cardiac events can be influenced by factors such as the specific chemotherapy regimen and the patient's baseline cardiac function.[33]

Detection and diagnosis

Key tools in detecting and diagnosing chemotherapy-induced cardiotoxicity are advanced multimodality imaging, including echocardiography, and cardiac biomarkers, both playing specific roles in identifying cardiac dysfunction.[34,35] Traditional echocardiography, measuring LVEF, is widely used for initial cardiac assessment in chemotherapy-treated patients. It helps evaluate the overall impact of chemotherapy on the heart but has limitations in sensitivity, especially in the early stages of cardiac dysfunction. Newer echocardiographic techniques, like three-dimensional echocardiography and strain imaging, show promise in improving the diagnosis efficiency. These techniques enable more accurate and early detection of subclinical changes in cardiac function, critical in managing cardiotoxicity.[36] CMR shows promise in identifying subtle morphological and functional changes in the myocardium induced by chemotherapy or radiotherapy in patients with breast cancer. It can detect subclinical cardiotoxicity and predict left ventricular performance deterioration, suggesting an essential role in reducing mortality rates from heart failure in these patients.[37] Additionally, applying myocardial strain imaging, notably global longitudinal strain (GLS) assessed by speckle-tracking echocardiography (STE), is highlighted as a valuable parameter for detecting early myocardial changes and predicting subsequent adverse cardiac events, typically preceding a reduction in LVEF.[38] These techniques, therefore, not only provide cardiotoxicity detection at an early stage but also aid timely management and intervention to prevent further cardiac deterioration among patients undergoing chemotherapy.

Cardiac troponins (cTns) are the most studied biomarkers in the context of chemotherapy-related cardiac injury.[35] They show high diagnostic efficacy in detecting early subclinical phases of cardiotoxicity, even before clinical symptoms or echocardiographic changes become apparent. An increase in troponin levels correlates with the severity of the disease and can guide clinical decision-making.[39–42] Natriuretic peptides, such as BNP and NT-pro-BNP, have been evaluated as potential biomarkers for cardiotoxicity. While some studies have shown promising results, definitive evidence of their diagnostic and prognostic role in the context of chemotherapy-induced cardiotoxicity is still lacking. These biomarkers, however, can be useful in monitoring cardiac function and detecting early signs of heart failure.[40,43]

Early detection of cardiotoxicity, especially in its subclinical stage, is vital for preventing irreversible cardiac damage. By identifying cardiotoxicity before a significant decline in cardiac function, clinicians can tailor cancer therapy to minimize cardiac risk while still effectively treating the cancer. Ongoing monitoring using echocardiography and cardiac biomarkers is recommended for patients undergoing chemotherapy. This approach allows for the detection of changes in cardiac function over time and provides an opportunity for early intervention. Regular assessments can help in adapting cancer therapy to mitigate cardiac risks without compromising the efficacy of cancer treatment.

Management of platinum-induced cardiotoxicity

The management of cardiotoxicity due to chemotherapy involves a multifaceted approach, including the use of cardioprotective agents and alternative chemotherapy regimens. The management of cardiotoxicity requires an integrated and multidisciplinary approach, combining the expertise of oncologists, cardiologists, and other healthcare providers. This collaboration is essential to balance the efficacy of cancer treatment with the minimization of cardiac risks.[44] Regular cardiac monitoring using echocardiography and biomarkers is crucial for early detection and management of cardiotoxicity. Early stratification of high-risk patients is important for tailoring therapeutic strategies and preventing adverse events.[45]

While there is no single, unified international guideline specifically for chemotherapy-induced cardiotoxicity, various national and international cardio-oncology and cardiac imaging organizations have made recommendations. These recommendations often include increased cardiac surveillance during or after treatment, measurement of cardiac biomarkers, and, in some cases, initiation of cardioprotective drug therapy in asymptomatic individuals. However, these approaches also raise concerns about medicalization and increased healthcare costs when the value of providing such care is unknown. The need for further

research to assess the long-term benefits, harms, and value of expanded cardiac surveillance and prophylactic cardioprotective therapy in asymptomatic patients with limited exposure to anthracyclines is emphasized.[46] This highlights the complexity and evolving nature of managing chemotherapy-induced cardiotoxicity. While current practices are informed by a combination of small trials, case reports, and guidelines developed for the general population, there is a pressing need for more extensive, randomized trials specific to cardiac care in patients with cancer. These should focus on optimizing treatment and monitoring strategies to prevent late-onset left ventricular dysfunction and congestive heart failure, leveraging both traditional and novel diagnostic methods.[47]

Various pharmacological interventions have been explored to protect the heart from the cardiotoxic effects of chemotherapy.[48] These include beta-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, statins, ADP receptor inhibitors, nitrates, and antioxidants.[48–50] A study demonstrated that apelin-13, a bioactive peptide, effectively attenuates cisplatin-induced cardiotoxicity. It reduces ROS and superoxide anion generation, inhibits DNA damage, and suppresses PARP cleavage and caspase activation. These results suggest apelin-13 as a potential strategy for countering cardiotoxicity induced by platinum-based chemotherapy.[15] Next, a systematic review and network meta-analysis of randomized controlled trials evaluated the preventive or therapeutic effects of cardioprotective agents on heart failure caused by chemotherapy-induced cardiotoxicity. The study found that aldosterone antagonists, ACE inhibitors, statins, and beta-blockers significantly improved left ventricular systolic function, indicating their cardioprotective effect.[51] Another study explored the cardioprotective effects of pravastatin against carboplatin-induced cardiotoxicity. The findings showed that pre-treatment with pravastatin attenuated apoptosis and decreased caspase-3, -9, and cytochrome C activity in cardiomyocytes, suggesting its potential as a cytoprotective agent before carboplatin chemotherapy.[13] Additionally, a study investigated the protective effects of acetyl-L-carnitine, DL-α-lipoic acid, and silymarin against myocardial injury caused by cisplatin, a chemotherapy drug known for its cardiotoxicity. The findings showed that cisplatin significantly increased markers of heart damage, oxidative stress, and DNA damage. Conversely, pre-treatment and post-treatment with acetyl-L-carnitine, DL-α-lipoic acid, and silymarin significantly mitigated these adverse effects, indicating their potential as protective agents against cisplatin-induced cardiotoxicity.[52–54] Taurine, another amino acid, was also shown to be protective against cisplatin-induced cardiotoxicity in mice. In this study, cisplatin exposure elevated serum creatine kinase and troponin T levels, disrupted the normal arrangement of cardiac muscle fibers, and increased oxidative stress, as well as inflammatory and apoptotic markers. Specifically, cisplatin-induced the upregulation of NF-κB, proinflammatory cytokines, adhesion molecules, chemokines, and markers of endoplasmic reticulum (ER) stress and apoptosis, including C/EBP homologous protein (CHOP), glucose-regulated protein 78 (GRP78), eukaryotic initiation factor 2 alpha (eIF2α), calpain-1, caspase-12, caspase-3, and cleavage of PARP, while inhibiting the antiapoptotic protein B-cell lymphoma 2 (Bcl-2). Remarkably, taurine administration significantly reduced the production of ROS, decreased the expression of NF-κB and proinflammatory markers, and countered the ER stress and apoptosis triggered by cisplatin. These effects suggest that taurine protects against cisplatin-induced cardiac damage by modulating inflammatory responses and ER stress.[55]

A study explored the potential benefit of apocynin, a naturally occurring methoxy-substituted catechol experimentally used as a NAD phosphate (NADPH)-oxidase inhibitor, in alleviating platinum-induced cardiotoxicity. The study found that apocynin pretreatment effectively countered adverse effects by preventing cisplatin-induced reductions in heart rate and blood pressure, reducing oxidative stress and inflammation, preserving mitochondrial membrane potential crucial for cellular energy production and viability, and mitigating overexpression of nuclear factor erythroid 2-related factor 2 (Nrf2), heme oxygenase-1 (HO-1), and NF-κB, key markers of oxidative stress and inflammation. Additionally, apocynin reduced caspase-3 activity, cell apoptosis, decreased nuclear DNA fragmentation, and preserved cardiomyocyte cross-sectional area, indicators of reduced cell death and cardiac muscle damage.[56] Furthermore, studies have investigated the antioxidant properties of other compounds in this context, such as curcumin,[57] ginger,[58,59] N-Acetylcysteine,[60] icariin,[61] cyanidin,[62] and resveratrol.[63]

The selection of a cardioprotective agent often depends on the specific chemotherapeutic agent and the patient's cardiac risk profile.[64] Sometimes, modifying the chemotherapy regimen, such as reducing the dose or altering the infusion schedule, can help mitigate cardiotoxicity. This approach requires balancing cancer treatment efficacy with the risk of cardiac damage.[65] Clinical trials have provided insights on innovative therapeutic strategies and interventions for addressing chemotherapy-induced cardiotoxicity. These include novel biomarkers for early detection and the development of targeted therapies with lower cardiotoxicity.[66] Trials have also emphasized the importance of prevention and early intervention in managing cardiotoxicity, including baseline cardiovascular examination, controlling cardiovascular risk factors, and adopting lifestyle changes to reduce cardiac risks.[67] Table 2 provides an overview of the cardiotoxicity associated with various platinum-based chemotherapeutic drugs and proposed interventions to mitigate further injury.

Future directions and research

The ongoing research and development in oncology increasingly focus on reducing chemotherapy's cardiotoxic effects. Novel therapeutic strategies, drug formulations, and personalized medicine approaches are at the forefront. Recent advances include the development of nano liposomal and cubosomal formulations. These nanocarriers are designed to enhance the delivery of chemotherapeutic agents specifically to tumor cells while minimizing exposure to healthy cells, including cardiac cells. This targeted approach could significantly reduce the incidence and severity of cardiotoxicity associated with chemotherapy.[68] Understanding molecular mechanisms contributing to cardiotoxicity is essential for developing effective cardioprotective strategies. This includes researching cellular pathways affected by anticancer drugs and identifying potential therapeutic targets to prevent or mitigate cardiac damage.[69] Personalized medicine explores using genomic variants and biomarkers to predict an individual's risk of developing chemotherapy-induced cardiotoxicity. Identifying genetically predisposed patients allows for tailoring chemotherapy regimens, minimizing cardiac risks while maintaining treatment efficacy.[70] Integrating advanced imaging techniques and biomarkers for early detection and ongoing monitoring of cardiotoxicity is another area of focus. Early identification of subclinical cardiac dysfunction allows for timely intervention and potential reversal of cardiac damage before symptomatic heart failure occurs.[71]

Another promising approach to mitigate platinum-induced cardiotoxicity involves utilizing human-induced pluripotent stem cell (iPSC)-derived cardiomyocytes for *in vitro* screening. Studies have shown that iPSC-derived cardiomyocytes offer a predictive and mechanistically interpretable evaluation of cardiotoxicity, applicable in high-throughput formats for early drug development screening.[72–74] This method has successfully identified specific physiological parameters of cardiomyocyte beating as good predictors of cardiotoxicity, highlighting its potential utility in identifying of cardioprotective agents. Moreover, zebrafish models have emerged as versatile tools for assessing chemotherapy-induced cardiotoxicity.[75–78] The discovery of the protective effects of visnagin against doxorubicin-induced cardiomyopathy in zebrafish, which acts through modulation of mitochondrial malate dehydrogenase, is an example of the model's efficacy in screening and identifying potential cardioprotective compounds.[75] Finally, *in silico* modeling presents a promising frontier in studying platinum-induced cardiotoxicity, offering an efficient, ethical, and cost-effective alternative to traditional *in vivo* and *in vitro* methods. One notable study

Table 2
Cardiotoxic effects of platinum-based chemotherapeutic agents.

Chemotherapy	Cardiotoxic effect	Mechanism of cardiotoxicity	Incidence	Risk factors	Monitoring and management
Cisplatin	Myocardial ischemia, arrhythmias, hypertension, thromboembolic events	Endothelial damage, oxidative stress, electrolyte imbalances (especially hypomagnesemia and hypokalemia)	Relatively low but significant, varies with dose and combination with other agents	High cumulative dose, pre-existing cardiovascular disease, combination with other cardiotoxic agents	Electrolyte monitoring and correction, blood pressure control, ECG monitoring, consideration of dose reduction or alternative therapies in high-risk patients
Carboplatin	Generally considered less cardiotoxic than cisplatin, but may cause hypertension, low risk of myocardial ischemia and arrhythmias	Less clear, possibly related to less severe electrolyte imbalances and oxidative stress compared to cisplatin	Lower than cisplatin, the incidence is not well-quantified	Pre-existing cardiovascular disease, high doses or prolonged therapy	Blood pressure control, monitoring for signs of heart failure or arrhythmias, electrolyte monitoring
Oxaliplatin	Rare reports of acute coronary syndrome, hypertension, arrhythmias	Hypersensitivity reactions, possibly oxidative stress	Very rare for acute coronary syndromes, hypertension, and arrhythmias incidence not well quantified	Pre-existing cardiovascular disease, hypersensitivity to platinum compounds	Monitoring for hypersensitivity reactions, blood pressure control, ECG monitoring, and immediate management of acute coronary syndromes if they occur

ECG: Electrocardiogram.

demonstrated the higher accuracy of human *in silico* drug trials over animal models in predicting clinical pro-arrhythmic cardiotoxicity based on ion channel information.[79] This study underscored the potential of computational models to integrate and interpret complex electrophysiological data, providing insights into drug-induced cardiac abnormalities at a cellular level.[80] Considering these findings, we advocate further exploration of computational modeling (*in silico*), iPSC cardiomyocyte (*in vitro*), and zebrafish-based (*in vivo*) screening platforms. These platforms offer a robust basis for identifying small molecules with cardioprotective effects against cisplatin and other platinum-based drugs' induced cardiotoxicity, significantly advancing our understanding and development of strategies to mitigate chemotherapy-associated cardiotoxicity.

Conclusion

The extensive research on cardiotoxicity related to platinum-based chemotherapy underscores the critical need for vigilant and proactive management in clinical practice. This review has emphasized key aspects ranging from the mechanisms and clinical manifestations of cardiotoxicity to the emerging strategies for its detection, management, and treatment. Cardiotoxicity remains a significant challenge in oncology, as platinum-based chemotherapies can lead to a spectrum of adverse cardiac effects. The pathophysiological mechanisms are multifaceted, involving direct myocardial damage, oxidative stress, DNA damage, and alterations in signaling pathways. Clinical manifestations vary from asymptomatic changes to severe conditions like heart failure and Takotsubo cardiomyopathy, necessitating early detection and regular monitoring for effective management. Advancements in diagnostic tools, particularly echocardiography and cardiac biomarkers, have improved early detection. However, there remains a significant need for personalized approaches to predict individual patient risk and tailor treatment accordingly. The exploration of nano liposomal and cubosomal formulations offers a promising direction for reducing cardiotoxicity without compromising the efficacy of cancer therapy. In conclusion, while progress has been made in understanding and managing cardiotoxicity associated with platinum-based chemotherapy, ongoing research is crucial in this area. Clinicians must remain vigilant in monitoring and managing cardiac health in patients undergoing these treatments. The ultimate goal is to achieve a balance where effective cancer treatment can be administered without compromising cardiac health, thereby enhancing the overall prognosis and quality of life for cancer patients.

Authors contribution

Betty Rachma: conceptualization, writing – original draft, and writing – review & editing; Merlyna Savitri: conceptualization, supervision, writing – original draft, and writing – review & editing; Henry Sutanto: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, validation, visualization, writing – original draft, and writing – review & editing. All the authors critically revised and approved the final version of the manuscript.

Ethics statement

None.

Declaration of Generative AI and AI-assisted technologies in the writing process

In the preparation of this work, the authors used ChatGPT version 3.5 to enhance readability and language. Following the use of this tool/service, the author reviewed and edited the content as necessary, taking full responsibility for the content of the publication.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability statement

The datasets used in the current study are available from the corresponding author on reasonable request.

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