

Cisplatin-induced cardiotoxicity with midrange ejection fraction

A case report and review of the literature

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Abstract

Rationale: Cisplatin monotherapy-induced cardiotoxicity is rare, and the prevalence remains unknown. It's extremely important to stop cisplatin when cardiotoxicity is considered.

Patient concerns: A 53-year-old woman developed cervical cancer. She was administered cisplatin (37 mg/m²/wk) for 3 weeks, but the left ventricular ejection fraction (LVEF) declined from 70% to 48%.

Diagnosis: Electrocardiogram showed first-degree atrioventricular block and ST-segment depression by 0.05 mv on leads II, III, and V₃₋₅. Neither cardiac markers nor N-terminal pro-B-type natriuretic peptide (NT-pro BNP) was elevated. After a careful physical examination and laboratory investigation, we confirmed that cervical cancer did not progress and no other cause was evident. So we figured cardiotoxicity might be induced by cisplatin.

Interventions: Cisplatin was stopped and cardioprotective therapies were given to the patient.

Outcomes: After discontinuing cisplatin and adding cardioprotective therapies, the LVEF increased to 50% and 53%, respectively (M-mode echocardiography) after 17 and 90 days, which further confirmed our diagnosis.

Lessons: According to this case and literature review, cisplatin-induced cardiotoxicity should be considered for the patient. When necessary, we should discontinue the suspected drug to confirm diagnosis. Cardioprotective therapies would minimize the drug-induced cardiovascular adverse events and improve patients' outcome.

Abbreviations: ECG = electrocardiogram/electrocardiographic, ESC = European Society of Cardiology, GLS = global longitudinal strain, HF = heart failure, HFmrEF = HF with midrange HF, LVEF = left ventricular ejection fraction, MtDNA = mitochondrial DNA, NT-proBNP = N-terminal Pro-B-type natriuretic peptide, PERK = Protein Kinase RNA (PKR)-like ER Kinase, WHO = World Health Organization.

Keywords: cardiotoxicity, cisplatin, ejection fraction

1. Introduction

Cisplatin is one of the first-generation platinum-based cell-cycle nonspecific antineoplastic agents with a wide range of anticancer activities. The major adverse events of cisplatin include nephrotoxicity, neurotoxicity, ototoxicity, and gastrointestinal toxicities (>50 mg/m²). Cisplatin-induced cardiotoxicity is rare, and the prevalence remains unknown. Jakubowski and Kemeny^[1] showed that cardiotoxicity occurs in 6% of the patients receiving cisplatin

and 5-fluorouracil (5-FU) and in 1.6% of the patients receiving 5-FU alone. In conventional multidrug regimens, investigating the effects of cisplatin on cardiotoxicity is rather challenging.^[2] Here, we report a case that developed cardiotoxicity during the use of cisplatin alone. We also reviewed the literature with respect to clinical characteristics, pathophysiological mechanisms, and treatments of cisplatin-induced cardiotoxicity.

2. Case report

A 53-year-old woman was diagnosed with cervical squamous cell carcinoma stage IIB 1 month ago. After radiotherapy, the patient received cisplatin 37 mg/m² per week. Five days after the third course of treatment, the patient complained of retrosternal burning. Hypotension and abnormal electrocardiogram (ECG) were also observed. Left ventricular ejection fraction (LVEF) declined from 70% to 48% (see Figs. 1 and 2). Electrocardiogram showed first-degree atrioventricular block and ST-segment depression by 0.05 mv on leads II, III, and V₃₋₅. Neither cardiac markers nor N-terminal pro-B-type natriuretic peptide (NT-proBNP) was elevated. We inferred a causative relationship between cisplatin and cardiotoxicity. The clinical characteristics were complied with the diagnostic criteria of cardiotoxicity with midrange ejection fraction listed in the 2016 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic cardiotoxicity.^[3] The comparisons of echocardiographic findings before and after cisplatin were listed in Fig. 1.

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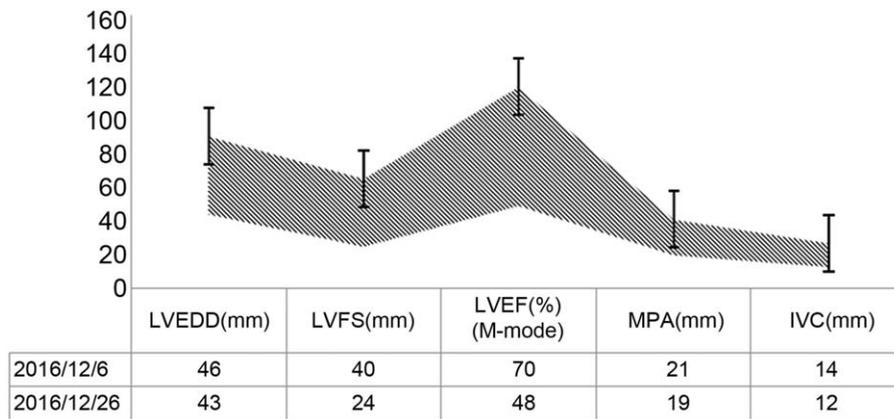


Figure 1. Comparisons of echocardiographic findings before and after DDP use. LVEDD stands for left ventricular end-diastolic ejection fraction; LVFS stands for left ventricular fractional shortening; LVEF stands for left ventricular ejection fraction (M-mode); MPA stands for main pulmonary artery; IVC stands for inferior vena cava.

Therefore, the cisplatin was stopped and LVEF reduced by 22%. Coenzyme Q10 (Ubidecarenone, 10mg tid) and trimetazidine (Vasorel, 20mg tid) were administered to protect cardiomyocytes. After 3 weeks, M-mode echocardiography showed that the left ventricular end-diastolic ejection fraction (LVEDD) was 46mm, LVEF 50%, and E/A [eathy atrial (mitral diastolic filling)] ratio 1.0. Due to cisplatin-induced cardiotoxicity, the fourth course of cisplatin was not started. And the gynecologist suggested continued radiotherapy without cisplatin. The antigen level of squamous cell carcinoma was 1.0ng/mL. She was in stable condition and was advised a repeat check by echocardiography after 3 months; the LVEF was found to be increased to 53% (M-mode echocardiography).

3. Discussion

The patient in this study did not have a history of hypertension, coronary heart diseases, chest distress, and chest pain. Other risk factors such as smoking or drinking were also absent. In addition, we found no direct relationships between cardiotox-

icity and comorbidities and the use of other drugs. We confirmed that the patient’s cardiotoxicity was caused by cisplatin.

According to the criteria of adverse drug reactions recommended by the World Health Organization (WHO),^[4] we identified the “likely/probable” relationship between cisplatin and cardiotoxicity with HF with midrange HF (HFmrEF). The occurrence of HFmrEF is attributable to the accumulation of cisplatin. Based on the criteria of cardiac adverse events (NCI CTC4.0), the patient was graded 2 due to the left ventricular systolic dysfunction with 40% to 50% LVEF.

Although current guidelines of European Society of Cardiology appropriate diagnostic tool to diagnose cardiotoxicity is calculation of ejection fraction using 2D Simpson method, 3-D based or Global longitudinal strain (GLS). In our department of cardiology, physicians always calculate ejection fraction using M-mode echocardiography in our hospital depend on local conditions. Based on M-mode echocardiography before and after the use of cisplatin, we can identify the “likely/probable” relationship.

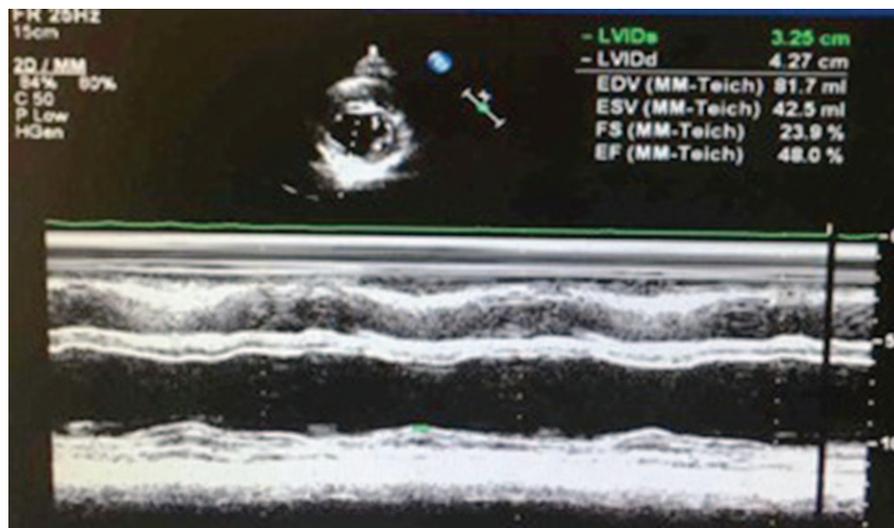


Figure 2. Parasternal short axis view at the mid-left ventricle (papillary muscle) of echocardiogram.

Table 1
Summary of case reports of cisplatin-induced cardiotoxicity.

Reference (year)	Type of HF	Female/ Male	Age	Course of treatment	Site of primary cancer	Complication	Regimen	Cisplatin regimen, mg/m ²	ECHO	Serum enzyme expression	Cardiotoxicity symptoms	Outcome	Mode of administration
Patient in this case	HFmrEF	F	53	3	Cervical carcinoma		Cisplatin	37 mg/m ² /w	LVEF48% (decline22%)	NT-proBNP 22 pg/mL	N	Better	Ubidecarenone 10mg tid, trimetazidinedihydrochloride 20mg tid
Guendouz et al (2011) ^[11]	HFpEF	F	28	2y	Malignant teratoma	Endocardial calcifications	Cisplatin, anthracycline, and vincristine	—	LVEF (normal)	—	Y	HT	—
Martin et al (1989) ^[12]	HF	—	—	—	Epidermoid carcinoma of the soft palate		Cisplatin (100 mg/m ² , day 1) and 5-fluorouracil (1g/m ² /d i.v. days 2–6)	100 mg/m ² , day 1	—	—	N	(Died) fatal left cardiac failure	—
Pratt et al (1983) ^[13]	HF	—	2	—	Disseminated chondrosarcoma and recurrent rhabdomyosarcoma		Cisplatin, doxorubicin, mitoxantrone (128 and 90 mg/m ²)	—	—	—	Y	(Died) 2 weeks after development of congestive cardiotoxicity	—
Cheriparambil et al (2000) ^[14]	HFpEF	M	52	1	Squamous cell carcinoma of the soft palate	Left ventricular thrombus (apex)	Cisplatin (30 mg/m ² /d for 3 days), 5-FU (1000 mg/m ² daily for 4 days)	(30 mg/m ² /d for 3 days)	LVEF 20%, left ventricular thrombus	CK10 32 U/L, CK-MB 8.8 ng/mL	Y	Better	—

5-FU = 5-Fluorouracil, CK = creatine kinase-MB, ECG = electrocardiogram, ECHO = echocardiogram, EF = ejection fraction, HF = heart failure, HFmrEF = HF with mid-range ejection fraction, HFpEF = HF with preserved ejection fraction, HFpEF = HF with reduced ejection fraction, HT = heart transplantation, LVEF = left ventricular ejection fraction, N = no, NT-proBNP = N-terminal Pro-B-type Natriuretic Peptide, Y = yes.

Elevated NT-proBNP was not been found in this case, because sometimes it doesn't occur in early stage of cardiotoxicity.^[3]

Due to the less number of the prevalent studies, the mechanisms of cisplatin-induced cardiotoxicity remain unclear. Jakubowski and Kemeny^[11] reported that cardiotoxicity occurs in 6% of the patients receiving cisplatin and 5-FU. In this case, the following manifestations might contribute to the occurrence of cardiotoxicity after the use of cisplatin. Firstly, the patient with malignant tumor (cervical cancer stage IIB) receiving multiple courses of chemotherapy putatively developed emboli and thrombi and exhibited an imbalanced stress response. Fukuhara et al^[5] demonstrated dose-dependent risks of adverse events with respect to the tumor stage; however, they did not indicate the specific risks for different stages. Secondly, the patient displayed abnormal ECG findings with ST-T segment depression and a PR interval of 0.231 seconds on multiple leads. Subsequently, we observed the newly occurred first-degree atrioventricular block, ST-segment depression by 0.05 mv on leads II, III, and V₃₋₅, and a PR interval of 0.21 seconds. Although ECG abnormalities were not related to cisplatin, the usage might impair the proximal tubules, reduce the reabsorptions of potassium and magnesium, shorten the duration of the action potential, decrease calcium inflow, and finally result in early systolic dysfunction.^[5] Thirdly, the patient received 3 courses cisplatin. Cisplatin activates the transmembrane protein kinase RNA (PKR)-like ER kinase (PERK) signaling pathway, phosphorylates IF2a, activates caspase 3, promotes the formation of apoptosome, and induces apoptosis of the cardiomyocytes.^[6] Furthermore, cisplatin combines with histone-lacking mitochondrial DNA (mtDNA) to form various complexes,^[7,8] disabling the nucleotide excision repair pathways that can remove such complexes. As a result, myocardial mtDNA is impaired, and mitochondria are unable to produce adenosine triphosphate. Cardiomyocytes suffer from dysfunction and subsequently hypoxic necrosis,^[6] resulting in cardiotoxicity.

Few strategies have been proposed to prevent and treat the cisplatin-induced cardiotoxicity effectively. Firstly, we dynamically monitored the echocardiography and ECG of the patient before and during the therapy. Secondly, we stopped the usage of cisplatin at a relatively early stage. Thirdly, we used coenzyme Q10 and trimetazidine to prevent the cardiac function from deterioration, based on potential pathophysiological mechanisms of cisplatin-induced cardiotoxicity.^[9,10] Our experience might provide an example for time management for the use of medications for cardioprotection following cisplatin-induced cardiotoxicity.

Cardiotoxicity has rarely been reported in patients receiving cisplatin. Only 4 cases reported (from January 1, 1980, through April 1, 2017) cisplatin-induced cardiotoxicity or reduced ejection fraction. Table 1 summarizes the clinical characteristics of 5 cases. We reported the first case of cisplatin-induced cardiotoxicity exhibiting a distinct causative relationship between cisplatin use and cardiotoxicity. All the 4 previous cases received a combination therapy containing cisplatin. Two cases finally succumbed to mortality: 1 case was autopsied, and 1 case underwent heart transplantation. The lethal consequences of cisplatin should not be neglected in clinical practice. Cardiotoxicity with midrange ejection fraction and arrhythmias (first-degree atrioventricular block) might be induced by cisplatin in patients without any risk factors for coronary heart disease. The patients receiving cisplatin should be monitored closely for LVEF, cardiac markers, and ECG to identify cardiac dysfunction at an early stage. Once cardiotoxicity occurs, cisplatin should be reduced or discontinued. Consecutively, cardioprotective thera-

pies should be administered to the patient, in particular for those with risk factors for cardiovascular diseases. Currently, neither a dose-dependent nor a temporal relationship between cisplatin and cardiotoxicity is observed. In addition, the 2016 ESC position study on cancer treatments and cardiovascular toxicity does not discuss the cisplatin-induced cardiovascular diseases.^[3] The clinical staff is encouraged to accumulate and exchange relevant experience in order to minimize the drug-induced impairments, prevent disease progression, reduce drug-associated cardiovascular complications, and improve the patient's outcomes.

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Author contributions

Conceptualization: Yang Hu, Bin Sun, Bin Zhao.

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Supervision: Bin Sun, Dan Mei, Zhuang Tian.

Visualization: Bin Zhao.

Writing – original draft: Yang Hu.

Writing – review & editing: Yang Hu, Bin Sun, Bin Zhao, Dan Mei, Qing Gu, Zhuang Tian.

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