

Cisplatin-induced sudden cardiac death with hemodynamic collapse: a severe adverse drug reaction

Case report

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Abstract

Rationale: Cisplatin is responsible for a significant percentage of adverse drug reactions (ADRs) in oncology setting. A great proportion of cisplatin-induced severe adverse events are difficult to foresee, and giving premedication does not always prevent the occurrence of such events.

Patient concerns: A 53-year-old woman with progressive T4 N0 M0 stage IV pleural mesothelioma experienced cardiac arrest with hemodynamic collapse after cisplatin and pemetrexed chemotherapy administration.

Diagnoses: Progressive pleural T4 N0 M0 stage IV mesothelioma of the right lung, primary arterial hypertension, and cardiac arrest with hemodynamic collapse.

Interventions: The cisplatin and pemetrexed chemotherapy was administered intravenously for progressive pleural T4 N0 M0 stage IV mesothelioma of the right lung. During infusion of cisplatin the patient developed cardiac arrest, and cardiopulmonary resuscitation was initiated.

Outcomes: The patient was treated in intensive care unit and recovered successfully. Further chemotherapy with cisplatin and pemetrexed was withheld due to this severe adverse reaction to cisplatin.

Lessons: Cisplatin therapy should be thoroughly monitored including electrolyte, especially magnesium levels. Absence of previous ADRs to cisplatin and premedication should not give false sense of security.

Abbreviations: AA = asystole algorithm, ADR = adverse drug reaction, ECG = electrocardiogram, HR = hypersensitivity reactions, ICU = intensive care unit, RT = resuscitation team.

Keywords: adverse reactions, cisplatin, drug interactions, platinum agents

1. Introduction

A case of cisplatin-induced sudden cardiac death with hemodynamic collapse after 7 courses of cisplatin-based chemotherapy is presented in this case report. Cisplatin is responsible for a sizeable amount of adverse drug reactions (ADRs), in oncology and most of those ADRs are not

preventable.^[1,2] Several probable mechanisms are proposed to explain the cisplatin-induced sudden cardiac death with hemodynamic collapse: an anaphylactic reaction, cardiotoxic event (atrial fibrillation, ventricular arrhythmias),^[3] electrolyte disorder (hypomagnesemia).^[4] The severe ADR could be a result of drug interaction. Hypersensitivity reactions to cisplatin have an overall incidence of 5% to 20%.^[5] Life-threatening cisplatin-induced hypersensitivity reactions are rare conditions that are difficult to foresee. Previous symptoms and repeated exposure to cisplatin are probably the most reliable predictors of such event. In addition, premedication with glucocorticosteroids may not be sufficient to prevent life-threatening anaphylactic reactions to cisplatin.^[6]

Cisplatin is also known to have proarrhythmic effects and is most often associated with supraventricular arrhythmias; however, ventricular arrhythmias have also been reported.^[3,7] In addition, cisplatin is associated with electrolyte imbalances, including hypomagnesemia, hypokalemia, hypophosphatemia, hypocalcemia, and hyponatremia.^[4] We present a case of cisplatin-induced sudden cardiac death with hemodynamic collapse that could have been prevented if more thorough electrolyte screening had been performed and drug-prescribing had been restricted to only absolutely necessary drugs.

1.1. Ethics approval and consent to participate

Approval to analyze the case file was given by the patient. Written consent to publish was obtained from the patient.

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Table 1**Medical history timeline.**

2010	Primary arterial hypertension
2015	Progressive pleural mesothelioma of the right lung T4 N0 M0 stage IV
2015	Cisplatin and pemetrexed chemotherapy
2016	Progression of pleural mesothelioma
2016	Cisplatin and pemetrexed chemotherapy second cycle first course
2016	Cisplatin and pemetrexed chemotherapy second cycle second course: severe hypersensitivity reaction to cisplatin
2016	Withdrawal of chemotherapy and best supportive care

2. Case presentation

A 53-year-old Caucasian woman working in the service sector arrived to the oncology outpatient department for the second course (of second cycle) of cisplatin and pemetrexed chemotherapy. She complained of malaise and fatigue. The patient was diagnosed with primary arterial hypertension several years ago. In 2015, progressive pleural T4 N0 M0 stage IV mesothelioma of the right lung was diagnosed, and the patient was administered cisplatin and pemetrexed chemotherapy (chronological medical history is provided in Table 1). The patient completed the sixth course of chemotherapy in the beginning of November 2015. Later, the disease progression was diagnosed, and the cisplatin-based chemotherapy regimen was reintroduced in November 2016. The patient started premedication at home by consuming 8 tablets of dexamethasone (0.5 mg). Complete blood count and metabolic panel revealed no significant abnormalities; thus, the premedication with intravenous folic acid (1000 µg/d), cyanocobalamin (1000 µg), and mannitol (1000 mL, 10%) along with antiemetic treatment (ondansetron 8 mg) was continued in the department. After the premedication was completed, the patient was given the intravenous infusion of cisplatin. During the infusion, the patient became unresponsive and developed cardiopulmonary arrest. Cardiopulmonary resuscitation was initiated after the asystole algorithm (AA) in accordance with the advanced cardiac life support guidelines, and the resuscitation team (RT) was called. On arrival, the RT continued resuscitation after the AA, and adrenalin was administered. The airway was secured by intubation. Restoration of cardiac sinus rhythm and the return of spontaneous circulation were achieved on the 12th minute of cardiopulmonary resuscitation. In the intensive care unit (ICU), the differential diagnostics was performed to identify the cause of cardiac arrest. Acute coronary syndrome after ECG,

troponin T level measurement, and cardiac examination; neurological disease after computed tomography of the head and neurological examination; pulmonary embolism after computed tomography of the chest; and electrolyte imbalance (potassium and sodium levels were within the reference range) were excluded. However, magnesium levels were not evaluated. Previous ECGs revealed no abnormalities.

After exclusion of all other possible explanations, the case was identified to be a drug-related severe ADR, likely caused by cisplatin, possibly predisposed by multiple drug interactions. The comprehensive list of medications used by the patient are presented in Table 2. Later, a decision, in the light of such events, patient's opinion, and the recommendations of treating physicians, was made to withhold further chemotherapy with cisplatin and pemetrexed. The provision of the best supportive care was set as the main goal.

3. Discussion

The frequency of hypersensitivity reactions to cisplatin is estimated to be 1% to 5% if this drug is used as a single agent.^[5] Some authors estimate the overall incidence of cisplatin hypersensitivity reactions to be 5% to 20%. It has been suggested that multiple and repeated infusions of platinum agents are likely the most predictive factor for hypersensitivity reactions.^[8] In our case, the patient had 7 previous cisplatin infusions. Hypersensitivity reactions to platinum compounds are likely to be type 1, mediated via IgE and its action upon tissue mast cells and basophils in peripheral blood, prompting the release of histamines, leukotrienes, and prostaglandins, and are associated with repeated exposure.^[9] These reactions are often accompanied by rash (urticaria), flushing, and pruritis.^[10] Hypersensitivity to platinum agents could also result from the type IV hypersensitivity reaction via activation by antigen binding to the already sensitized T cells.^[11]

Cisplatin may exhibit toxicity toward the cardiovascular system. The cardiac toxicity of cisplatin includes electrocardiographic changes, arrhythmias, myocarditis, cardiomyopathy, and congestive heart failure. This can be explained by a direct toxic action on cardiac myocytes or by the production of reactive oxygen species and oxidative stress resulting in the prothrombotic condition.^[12] Sudden cardiac death has been reported with the use of cisplatin and 5-fluorouracil^[13] and cisplatin, gemcitabine, and bevacizumab.^[14] In our case, however, sudden

Table 2**Medication history.**

Drugs used by the patient	Method of administration	Dose per day	Date of administration	Indication
Cisplatin (Cisplatin Teva) 0.5 mg/mL 100 mL	Intravenous	150 mg	II cycle (after 6 previous cycles of cisplatin and pemetrexed)	Pleural mesothelioma
Dexamethasone	Oral	4 mg	2016	Premedication for increasing tolerance of cisplatin
Aprepitant	Oral	125 mg	2016	Prophylaxis for emesis
Ondansetron	Oral	8 mg	2016	Prophylaxis for emesis
Mannitol	Intravenous	1000 mL 10 proc.	2016	Prevention of cisplatin toxicity
Fentanyl patch	Local	75 µg/h	Long-term use	Pain management
Tramadol	Oral	100 mg	Long-term use	Pain management
Metoprolol succinate (Betaloc ZOK)	oral	47.5 mg	Long-term use	Arterial hypertension
Alprazolam	oral	0.5 mg	Long-term use	Anxiety disorder
Tianeptine	oral	12.5 mg	Long-term use	Depression and pain management
Angiocell plus (liquid shark cartilage extract)	oral	7.5 mL	2016	—

cardiac death is unlikely to have occurred as a result of supraventricular or ventricular arrhythmia or as a result of ischemic or thromboembolic events, because these conditions were excluded by appropriate investigations. Hypomagnesemia has been linked to platinum, especially cisplatin, chemotherapy,^[4] and could contribute to cisplatin-induced sudden cardiac death in our case, and cannot be ruled out as magnesium levels were not evaluated in the patient.

The sudden cardiac arrest suffered by the patient could also have been precipitated by other factor—multiple drug interactions. The concomitant use of tramadol with fentanyl and alprazolam may result in profound sedation, respiratory depression, coma, and/or death.^[15] An interaction between aprepitant, a moderate CYP3A4 inhibitor, and fentanyl, a CYP3A4 substrate, increases the risk of fentanyl toxicity.^[15] However, dexamethasone as a CYP3A4 inducer could alleviate this interaction.^[15] Fentanyl is proserotonergic and has been associated with serotonin syndrome when coadministered with serotonergic drugs.^[15] It should also be mentioned that ondansetron has been implicated as an agent inducing anaphylactoid-type reactions.^[16] In addition, a case of ondansetron-induced asystole with return of spontaneous circulation after advanced cardiac life support has also been reported,^[17] and ondansetron along with other setrons have been described as drugs prolonging the QT interval.^[15]

The patient's perspective is provided below as part of our case report in accordance with the 2013 CARE guidelines.^[18]

Experience of the event. "I have a vague recollection of what had happened. I remember that in the morning on which I had to go to oncology outpatient clinic I felt very sick, though I did not vomit. I barely remember the course of that day. Basically, I woke up in the pulmonology department. I do not understand what exactly happened, I feel as if I would have had an episode of lost consciousness. Currently, the expressions on the faces of my relatives appear rather vexing, as they seem really worried. I have never experienced such an event in my life. The doctors say that I will no longer receive chemo due to this event".

4. Conclusions

Administration of premedication should not give a false sense of safety. We presented a suspected severe ADR with cardiac arrest and hemodynamic collapse most likely caused by cisplatin after repeated exposure to it. Until the life-threatening reaction, no signs of hypersensitivity to cisplatin or other ominous signs were identified. This could result due to anaphylactic reaction, direct cardiotoxicity, or electrolyte imbalance (especially hypomagnesemia) caused by cisplatin. The use of additional drugs and their major interactions could contribute. In addition, drug

interactions and undiagnosed electrolyte disorders may serve as inconspicuous factors predisposing to severe adverse effects. Thus, cisplatin therapy should be thoroughly monitored.

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