



Adverse Cardiac Manifestations of Cisplatin - A Review

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ABSTRACT

The purpose of the review is to consolidate the reported risk of cardiotoxicity in patients treated with cisplatin based chemotherapy. Cisplatin can induce direct myocardial toxicity leading to atrial fibrillation whereas the potential of myocardial toxicity is amplified when the drug is administered in combination with other cardiotoxic agents. Chemotherapy with cisplatin can alter endothelial cell integrity and induce spasm, whereas antiangiogenic activity of cisplatin has also been reported. Elevated levels of endothelia and inflammatory marker proteins are measured in the plasma of the patient years later after the therapy. Delayed toxicity associated with cisplatin comprises of hypertension, elevated cholesterol levels, increased BMI and cardiovascular events. This review summarizes the adverse cardiac manifestations of cisplatin reported in previous studies and shows that the remarkable therapeutic benefit of cisplatin may be temporized with substantial risk of cardiovascular morbidity posing a greater threat than the relapse of cancer itself.

Keywords: Cisplatin, Cardiac toxicity, Ischemia, Delayed toxicity.

INTRODUCTION

Cisplatin, *cis-diamminedichloroplatinum* is an effective and widely used chemotherapeutic agent in clinical oncological practice. The therapeutic benefit of Cisplatin as a standard component of combination chemotherapy is employed in a variety of malignant conditions specially the solid tumors such as ovarian, testicular, head, neck and small cell lung cancer for the last four decades¹. Acquired resistance following initial use in ovarian and small cell lung carcinoma has been documented, whereas tumors like colorectal carcinoma and non small cell lung carcinoma show intrinsic resistance against Cisplatin, hence limiting its clinical use to a narrow range of tumor types². The cytotoxicity occurs from DNA cross-links and bifunctional and monofunctional DNA adducts, in addition to the generation of superoxide radicals which induce direct cytotoxicity. The anti tumor activity of Cisplatin is widely associated with gastrointestinal toxicity, myelotoxicity, ototoxicity and neurotoxicity³, whereas the chief dose limiting toxicity of Cisplatin is nephrotoxicity due to inflammation, oxidative stress injury and apoptosis, experienced by 20% of patients receiving chemotherapy⁴. There are several case reports of adverse cardiac effects of cisplatin due to hydro electrolytic imbalances (depleted Mg levels) owing to nephrotoxicity⁵. The possible association between Cisplatin administration and development of cardiac manifestations is less frequently reported and associated. Over the past few decades, there have been occasional reports of Cisplatin associated cardiotoxicity manifested as both delayed effects and acute reactions. Successful treatment advances are made with Cisplatin therapy in the last few decades (5 years

survival exceeds 90%) which implicates that the focus be directed to the improvements in the quality of life of the patients minimizing the drug induced late cardiovascular toxicity⁶.

Incidence of cisplatin induced cardiovascular adverse effects

Cardio toxic potential of Cisplatin chemotherapy may be reported during treatment or subsequently in patients who experience ischemic syndrome, palpitations, distress and chest pain and rare lethal Myocardial Infarction (MI)⁷. Acute MI and diastolic heart failure is reported in cisplatin therapy⁸. The risk of MI as a delayed toxicity is reported 5.7% in a median observation time of 19 years (13-19 years) by Hauges et al., who conducted a study on 990 cured survivors of cancer treated with Cisplatin⁹. Czaykowski et al., reported 12.9% of vascular events in patients subjected to Cisplatin based chemotherapy in a retrospective study of 271 patients treated with Cisplatin, 77% of these adverse events occurred during the first two cycles of chemotherapy whereas three events were lethal¹⁰. Shah et al., reported thromboembolic events in 30% of patients treated with Cisplatin¹¹. The risk of thrombosis is higher in patients with metastatic disease or comorbid conditions like immobility, atrial fibrillation, dehydration or heart failure¹². Stefenelli et al., reported 38% patients developed Angina pectoris during Cisplatin based chemotherapy¹³. Hashimi et al., reported two episodes of supraventricular tachycardia during a 5 day continuous infusion of Cisplatin in the absence of any risk factors¹⁴. Cisplatin toxicity on cardiac electrical activity is reported by Fassio et al., in a case study of paroxysmal supraventricular tachycardia¹⁵. Sinus bradycardia is



reported with recurrent incident during chemotherapy with Cisplatin^{16, 17}. The incidence of atrial fibrillation is 12-32% in patients subjected to intrapleural or intrapericardial administration of Cisplatin¹⁸⁻²⁰. Greater incidence of atrial fibrillation is reported with Cisplatin chemotherapy especially during intrapericardial administration, inducing direct toxicity to the pericardium thus indicating the need of intensive monitoring²¹. Cardiotoxicity of Cisplatin in children may occur during the treatment or may appear after months or years of treatment. Mild myocardiocyte injury in children has greater adverse complications than adults because of the risk of subsequent cardiac growth defect unable to match the somatic growth²². Chemotherapy with Cisplatin can alter endothelial cell integrity and induce spasm²³, whereas antiangiogenic activity of Cisplatin has also been reported²⁴. Ischemia and hypertension are commonly reported cardiovascular adverse effects of Cisplatin, whereas increased risk of CHF in elderly is reported who are subjected to concurrent radiation therapy or have previously been treated with anthracyclines²⁵. Development of heart failure is reported in patients receiving Cisplatin with cyclophosphamide, whereas the risk is intensified in elderly or prior mediastinal irradiation²⁶. Acute cardiotoxic syndrome during Cisplatin infusion is marked by palpitations, chest pain or occasional elevation of cardiac biomarkers indicating Myocardial Infarction²⁷. Vascular damage and platelet aggregation with enhanced thromboxane formation leading to adverse cardiac implications is reported in patients subjected to Cisplatin therapy²⁸.

Delayed cardiovascular toxicity by cisplatin

A unique aspect of Cisplatin induced cardiovascular effects is that, they can be manifested later in a patient's life. The exacerbation of late cardiovascular toxicity may

be associated to the fact that Cisplatin can be measured in the blood even after 20 years of treatment²⁹. Elevated levels of endothelia and inflammatory marker proteins are measured in the plasma of patients years later after the therapy which can lead to severe endothelia dysfunction and over atheloscclerosis³⁰. Reports of delayed toxicity associated with Cisplatin manifested as hypertension, elevated cholesterol levels, increased BMI and cardiovascular events are summarized in Table 1³⁰⁻³⁸.

Feldman et.al., reported in a recent study, that although Cisplatin based chemotherapy has turned germ cell tumor into the most curable cancer in young adult men, however, the excellent therapeutic edge of this drug is temporized with the increasing evidence of late cardiovascular toxicity, which is apparent as coronary artery disease in these patients usually after ten years of follow up time³⁹. A study conducted to identify the late toxicity of Cisplatin in a median follow up time of 58 months identified cardiovascular risk factors in one third of patients with high cholesterol levels with and without obesity, and 15% with arterial hypertension, whereas 20% had depleted magnesium or phosphate levels³⁷. Efstathiou et al., stated that the cure rate of testicular cancer with Cisplatin is 95% with a 25 year risk of cardiovascular toxicity in 16% patients due to direct endothelial damage of Cisplatin or indirectly induced hormonal and metabolic changes⁴⁰. Delayed cardiovascular toxicity such as acute myocardial Infarction and cerebrovascular events is reported by Choudhary et al⁴¹. A study specifically designed to assess the development of cardiovascular risk factors in cured patients of testicular cancer treated with Cisplatin reported elevated LDL and cholesterol levels, depleted HDL levels and increased BMI in 28% patients at 4-6 years⁴².

Table 1: Delayed Cardiac Toxicity of Cisplatin

S.#	References	Followup time	Patients Count	Hypertension	Hypercholesteremia	Increased BMI
30	Meinardi et.al 2000	9-16 year	85	39%	79%	21%
31	Haugnes et.al 2010	20 years	990	22%	15%	17%
32	Dollet.al 1986	Day 7 - 18 Months	4	None	None	None
33	Strumberg et.al 2002	13years	32	25%	82%	48%
34	Huddart et.al 2003	10.2 years	992	212%	1.60%	None
35	Sagstuen et.al 2005	4-22 years	1980	50%	N/A	15%
36	Samuels et.al 1987	1-10 years	65	None	None	None
37	Bookmeyer et.al 1996	58 months	90	15%	30	N/A
38	Roth et.al 1988	8.5 years	229	31%	15%	None



Acute cardiovascular toxicity by cisplatin

Acute adverse effects with Cisplatin chemotherapy are chest pain, distress, palpitations or elevated cardiac enzymes indicative of myocardial infarction⁴³. Nuver et al., reported significant decrease in blood pressure of the patients subjected to chemotherapy and significant increase in the intima-media thickness of the carotid artery and plasma von Willebrand factor levels as compared to the pretreatment values. The study reported two events of MI with elevation in cardiac enzymes and abnormal ECG, and 5 cases of venous thromboembolic events in 65 evaluable patients⁴⁴. The central finding of an investigational study for acute cardiovascular toxicity of Cisplatin is reported by Dieckmann et al., as 'increase of vWF' (factor released by endothelial cells due to vascular damage) during chemotherapy and subsequent normalization of this value within several months, thus leading to platelet adhesion and initiation of coagulation process⁴⁵. Cisplatin can induce direct myocardial toxicity leading to atrial fibrillation whereas the potential of myocardiotoxicity is amplified when the drug is administered in combination with other cardiotoxic agents^{46, 47}. Ozcan et al., reported an unusual case of complete atrioventricular block, hypotension and renal failure during Cisplatin infusion in a 50 years old male patient with no previous cardiac disease or disorder⁴⁸. Fakuda et al., presented two cases of vasospastic angina and suspected myocardial damage during chemotherapy associated with preexisting CAD (atherosclerosis)⁴⁹. Dieckmann et al., reported twenty five cases of CVE (0.30% estimated incidence), twenty cases of MI (0.24% estimated incidence), three with cerebral ischemic infarction, and two with peripheral arterial thromboembolism, after an extensive nationwide survey concluding a definite risk of early cardiovascular event with Cisplatin based chemotherapy. The median age of 42 years in patients of MI treated with Cisplatin is in contrast with the median age of 71 years for MI risk in general population⁵⁰. Tassinari et al., reported three cases of cardiac arrhythmia associated with electrolyte imbalance, following Cisplatin chemotherapy, identifying the cases as perplexing and not dose related⁵¹. Acute anterior Myocardial Infarction in a 27 years old patient in the second cycle of Cisplatin chemotherapy having no previous cardiovascular disease or risk factor is reported by Ozben et al.⁵².

Platelets and thrombosis

Platelets have an identified role in the development and genesis of pulmonary embolism (low platelet count during pulmonary embolism). The patients of deep vein thrombosis have a fall in platelet count during thrombosis⁵³. Cisplatin is frequently associated with thrombocytopenia, impairment of platelet function and platelet apoptosis (through ERK signaling pathway)⁵⁴. Papet et al., reported two cases of cerebral sinus venous thrombosis in patients treated with Cisplatin based chemotherapeutic regimen, identifying the risk of thromboembolism with the disease (germ cell carcinoma)

and the therapy (Cisplatin)⁵⁵. Similarly high risk of thromboembolism is reported during chemotherapy with Cisplatin, specifically in patients of germ cell carcinoma receiving high doses of corticosteroids^{56, 57}. Cerebral dural sinus thrombosis is reported by Karam et al., in two patients treated with Cisplatin⁵⁸. Nuver et al., recognized the Cisplatin induced arterial and venous thromboembolism as an increasing area of concern due to associated morbidity and mortality, stating that these events can interfere with a curative therapy and may also predict delayed vascular toxicity⁵⁹. The risk of thrombosis is increased by damage imparted to the vessel wall or changes in the clotting cascade by the cytotoxic agent⁶⁰. A case of endo aortic thrombosis is reported by Dieckmann et al., which was resolved by anticoagulant therapy⁶¹. An *in vitro* study demonstrated that Cisplatin increases human platelet reactivity (onset of platelet aggregation wave and thromboxane production), in turn inducing thrombotic complication⁶².

Effects on blood pressure, cholesterol and lipid levels

Although a subsequent drop in blood pressure is observed in patients during chemotherapy with Cisplatin⁶³, there has been occasional report of cases when patient experiences hypertension after receiving Cisplatin based chemotherapy⁶⁴⁻⁶⁷. Hypertension develops in 20-50% patients as a delayed adverse effect in patients subjected to Cisplatin based chemotherapy⁶⁸. The mechanism of delayed hypertension is not well defined however is attributed to the direct endothelial activation and damage by Cisplatin⁶⁹. Hypotension as a manifestation of cardiotoxicity after Cisplatin and 5-FU chemotherapy is reported by Jakubowski et al. In these cases hypotension is associated with chest pain, dyspnea and tachycardia and abnormal EKG changes associated with electrolyte imbalance⁷⁰. Elevated levels of cholesterol, LDL and triglycerides are measured in patients who are treated with Cisplatin. Raghavan et al., reported increased levels of serum cholesterol and LDL cholesterol in 41% patients who had no prior history of cardiac diseases or hypercholesterolemia. The study reported absolute increase in serum cholesterol in 14 of 17 unselected patients with biopsy proven germ cell cancer receiving Cisplatin based chemotherapy⁷¹. Although hypercholesterolemia, hypertriglyceridemia and dyslipidemia are frequently reported as delayed adverse effects of Cisplatin based chemotherapy (Table 1), data from many other studies do not confirm the hypothesis⁷². Koc et al., reported that Cisplatin based chemotherapy does not impart negative effects on the lipid profile of patients in a 5 years follow up study⁷³. Ellis et al., studied the lipid profiles of 47 patients with metastatic testicular cancers treated with Cisplatin and compared the readings with 59 patients diagnosed with germ cell tumors in a control group, not treated with Cisplatin and reported no significant difference in total plasma cholesterol levels ($p>0.4$) in the two groups⁷⁴.

Underlying mechanism of cardiac toxicity and diagnosis



Dolci et al., described the chemotherapy induced cardiac toxicity into two types, acute or sub acute cardiotoxicity which can occur at anytime from the initiation of chemotherapy up to two weeks after completion of treatment. The clinical findings are abnormalities detected in ventricular repolarization and QT interval, supraventricular and ventricular arrhythmias, acute heart failures, myocarditis, pericarditis or coronary syndrome. The frequent chronic, cumulative dose dependent cardiotoxicity can be subdivided into early (within 1 year) or late (after 1 year) toxic reactions. The most typical type of such toxicity is asymptomatic systolic or diastolic left ventricular dysfunction leading to severe congestive cardiomyopathy and death⁷⁵. The underlying mechanism of CAD in patients treated with cytotoxic agents is due to coexistent coronary atherosclerosis, coronary embolization or compression by the tumor, tumor associated hypercoagulopathy, vasculitis, thrombotic endocarditis (nonbacterial) or drug induced direct endothelial damage⁷⁶⁻⁷⁸. Cardiotoxicity by Cisplatin is due to increased oxidative stress and apoptosis⁷⁹. Ma et al., reported depressed cardiomyocyte contraction and mitochondrial abnormalities, enhanced endoplasmic reticulum stress and associated apoptosis as manifestations of Cisplatin induced cardiac injury⁸⁰. Yen et al., reported that prothrombinase activity of Cisplatin is dependent on the presence of platelets and rate of thrombin formation is accelerated by factor Xa generated by tissue factor VIIa complex whereas the vascular and thrombotic toxicity of Cisplatin is associated with platelet activation and aggregation and monocyte procoagulant activity⁸¹. Cisplatin induces cytotoxicity by binding to DNA (gDNA) and non DNA (GSH, MT) targets and induces necrosis and apoptosis in the heterogenous cell population of tumor mass⁸²⁻⁸⁴.

CONCLUSION

Cardiotoxicity is becoming an increasing area of concern for cancer chemotherapy and chemoprevention. Assessment of cardiac risk factors by the oncologist and cardiologist should be a primary goal. This can be achieved by definition of personalized cytotoxic therapy⁸⁵. There is a "need to train a generation of cardio-oncologist or onco-cardiologist"⁸⁶ for the successful estimates and management of cardiotoxicity in cancer patients.

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