

Successful Treatment of Cisplatin Overdose with Plasma Exchange

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We report a 48-year-old man with laryngeal cancer who received a massive cisplatin toxic overdose without intravenous prehydration through an error in prescription. He received 400 mg/m² of cisplatin over a 4-day period. On day 4, he exhibited a broad range of cisplatin toxicities and emergency plasma exchange was started. From day 5 through 19, he underwent 9 cycles of plasma exchange and his plasma cisplatin concentration decreased from 2,470 ng/ml to 216 ng/ml. He completely recovered without any sequelae. No previous reports exist in the English literature of survival without complication after the administration of such a high cisplatin dosage without prehydration.

Key Words: Cisplatin overdose, plasma exchange

INTRODUCTION

Since its introduction in the 1960s, cisplatin has become one of the most widely used and effective antineoplastic agents. This heavy metal causes interstrand cross linking of DNA, thereby preventing tumor cell replication.¹ Preclinical data suggests that cisplatin has a steep dose-response relationship for ovarian cancer and other tumors.²

However, because of the dose limiting neurologic and renal toxicity of cisplatin, the maximum dose usually administered is 100 to 120 mg/m² per one cycle of chemotherapy.³ Even in high dose chemotherapy, maximally tolerated cisplatin dosage is no more than 200 mg/m². The most com-

mon side-effects of cisplatin include nephrotoxicity, neurotoxicity, ototoxicity, gastrointestinal disturbances and bone marrow suppression.⁴ To prevent dose-limiting cisplatin-induced side effects like renal toxicity and emesis, intravenous hydration with hypertonic saline and repetitive dosing of parenteral antiemetics are mandatory.²

We report a 48-year-old man who suffered an accidental toxic cisplatin overdose of 400 mg/m², which in the English literature is the highest dose in the absence of intravenous prehydration ever survived by a patient. Yet this patient was completely recovered after plasma exchange without any sequelae).

CASE REPORT

A 48-year-old man was diagnosed with stage IV laryngeal carcinoma (T3N2MX). CT examination of the neck revealed a right vocal cord tumor with para-laryngeal fat infiltration extending further than the infra-glottic level inferiorly and the cricoid cartilage anteriorly. Metastatic lymph node involvements in region II, III and IV were noted. Histopathology revealed well-differentiated squamous carcinoma. He refused the initially recommended surgery and accepted only chemotherapy and radiotherapy as treatment modalities. The patient entered into a treatment protocol consisting of cisplatin, 100 mg/m² I.V. on Day 1 and 5-Fluorouracil 750 mg/m² I.V. from Day 1 to 5. This treatment was ruined by an overdose of cisplatin when the chemotherapy orders were misprescribed. Rather than receiving 100 mg/m² for the first day, the patient received 100 mg/m² for 4

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days without undergoing any prehydration procedure for cisplatin.

From the fourth day of treatment, the patient developed hearing difficulty, paresthesia on lower extremities, sudden aggressive behavioral patterns with visual hallucinations and abdominal pain. At this time the mistake was discovered and a laboratory test revealed BUN, 69.7 mg/dL; creatinine 4.3 mg/dL; AST, 2,090 IU/L; ALT, 1,180 IU/L; total bilirubin, 2.61 mg/dL; amylase, 2,874 U/L; LDH 4,590 U/L. Ototoxicity, ocular toxicity, neurotoxicity, non-oliguric renal failure, hepatic failure, cholestasis and acute pancreatitis developed initially and emergency plasma exchange was started.

Platinum concentrations were measured by

flameless Zeeman atomic absorption spectrophotometry by Spectra AA 300 (Varian, Victoria, Australia) using samples obtained from pre- and post-exchange plasma and urine (Fig. 1). Plasma samples were obtained from centrifugation of blood and free-form cisplatins were obtained by filtering the anticoagulated plasma by centrifree filter (Amicon, Massachusetts, U.S.A.). From day 5 through 19, the patient underwent plasma exchange nine times and his plasma cisplatin concentration decreased from 2,470 ng/ml to 216 ng/ml.

Seven days after the last cisplatin administration, the WBC count decreased to 1700/uL (ANC, 816/uL) and then recovered after use of concomitant GM-CSF. As fever was developed

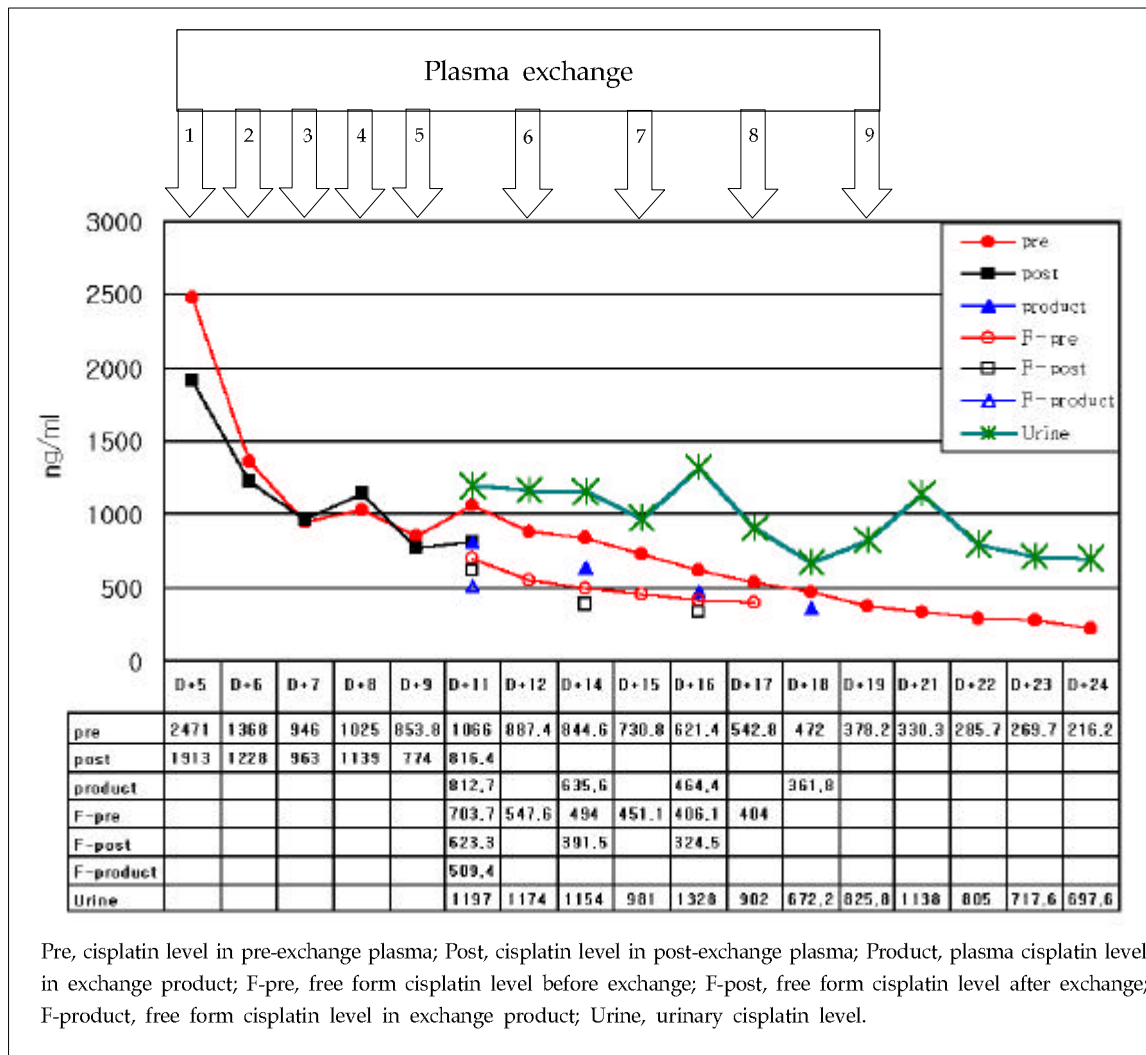


Fig. 1. Time course for plasma cisplatin level.

from D+7 to D+27, broad-spectrum antibiotics (vancomycin, imipenem, itraconazole) were administered. The patient was kept on fasting status for severe mucositis and to reduce the risk of intestinal perforation.

After undergoing 9 cycles of vigorous plasma exchange followed by 18 of hemodialysis, the creatinine level fell to 1.7 mg/dL and the creatinine clearance stabilized at 29.8 mL/minute. For one month after the toxic overdose, the patient experienced unstable mood changes and complained of the impairment of taste and the weakness of lower extremities which had recovered slowly. He also recovered completely from ototoxicity and ocular toxicity. The total bilirubin level was raised to 17 mg/dL and subsequently decreased to less than 2 mg/dL with steroid tapering (Fig. 2).

One month later, the palpable lymph nodes on his neck had all disappeared and his general

condition was good without any complications arising from the cisplatin overdose.

DISCUSSION

To our knowledge, this is the first reported case of a patient receiving a cisplatin dose of 400 mg/m² who completely recovered without any sequelae. Accidental cisplatin overdose could occur

due to three different types of dosing errors; (1) mistaking dosing orders when they are written as the total dosage divided over a period of several days, (2) erroneous administration of cisplatin instead of carboplatin, and (3) writing the wrong cisplatin dose.^{5,6} Most overdoses range between 200 and 500 mg/m². Patients with less than 300 mg/m² of cisplatin infusion usually recover, whereas an overdose exceeding 400 mg/m² usually results in death (Table 1).

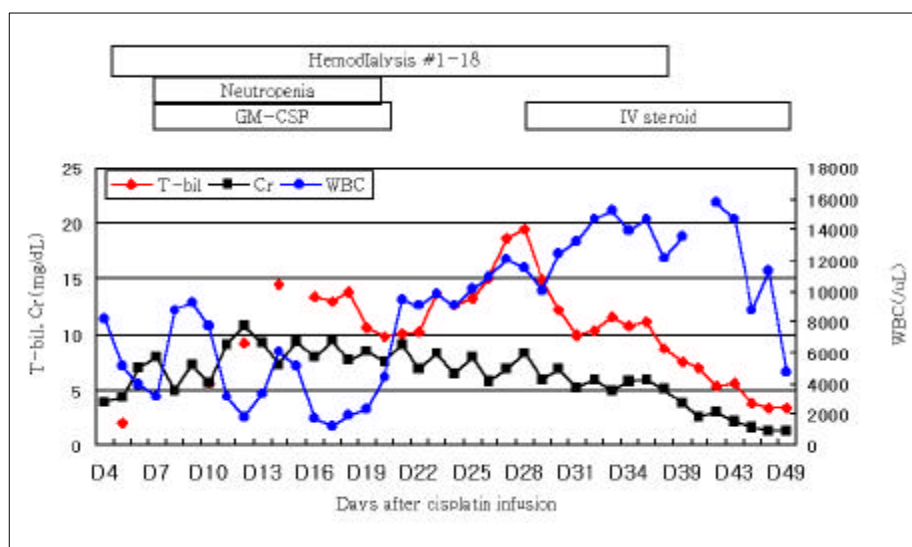


Fig. 2. Serum levels of total bilirubin, creatinine and WBC during treatment course.

Table 1. Cisplatin Dosage, Treatment and Outcomes of Published Cases on Cisplatin Overdose

Authors	Dose of Cisplatin	Treatment modaliti	Outcome
Schiller ³ et al. (1989)	480 mg/m ²	PE, HD	Alive, irreversible hearing loss
Chu ⁴ et al. (1993)	280 mg/m ²	PE, HD	Alive, irreversible renal failure treated with kidney transplantation
Lagrange ² et (1994)	205 mg/m ²	HD	Alive
Jung ¹³ et al. (1995)	300 mg/m ²	PE	Alive
Kamad ⁷ et al. (1997)	400 mg/m ²	N-ACS	Dead due sepsis

PE, Plasma exchange; HD, Hemodialysis; N-ACS: N-acetylcysteine.

Toxicities of cisplatin include severe emesis, nephrotoxicity, neurotoxicity, hearing loss, visual impairment, cholestasis, gastrointestinal disturbances and bone marrow suppression.² The most serious complication is cisplatin nephrotoxicity which may result in irreversible renal failure.⁷⁻¹⁰ As the toxicity of cisplatin is dose-dependent, early removal of the drug is critical in overdose management.¹¹ *In vivo*, cisplatin is heavily bound to plasma protein, which cannot be removed by hemodialysis as free form cisplatin.⁴ As the transit time of cisplatin from plasma to intra-cellular binding is short, early and vigorous plasma exchange is the mainstay of treatment modality. The immediate commencement of plasma exchange in this patient is certainly/likely the reason for the complete recovery without any complication.

Although the appropriate frequency of plasma exchange to remove plasma and intracellular cisplatin to non-toxic levels is debatable, at least 10 cycles over a period of 10 to 14 days after cisplatin administration is suggested to manage the deleterious toxicity. Although the effectiveness of plasma exchange in the treatment of cisplatin overdose is controversial, our impression from this clinical experience is that enhancing the clearance of platinum was beneficial to the patient. After five initial cycles of plasma exchange treatment, the plasma platinum concentration decreased significantly, and there was a concomitant recovery of mental deterioration and improvement in visual hallucination.

Unlike plasma exchange, hemodialysis exerted only a modest effect on the clearing of unfiltered platinum which is the protein bound form of platinum. With each hemodialysis cycle, plasma platinum decreased substantially but returned to predialysis levels over the following 2-day period. This rebound phenomena is explained by protein bound platinum serving as an exchangeable pool of platinum and thereby causing the continued cellular response. Although hemodialysis clears free-form platinum effectively, the cytotoxicity of cisplatin is mainly caused by the protein-bound platinum which is removed more effectively by plasmapheresis.⁴

In cisplatin overdose nephropathy, pathologic damage, such as acute tubular necrosis, dilatation of convoluted tubules and thickened tubular

basement membranes, persists even after the renal function becomes normalized.⁵ We can suggest renal impairment findings in this patient with creatinine level normalized to 1.7 mg/dL, but with an abnormal creatinine clearance of 29.8 mL/min. The nephrotoxicity is almost always associated with cisplatin and results in significant morbidity and complications which often limits its tolerable dosage. This complication can be prevented by intensive parenteral hydration, mannitol diuresis, and administration of the drug in hypertonic saline.³

Our patient also exhibited a cholestatic feature which was resolved with steroid administration. In 2 previously reported cases of hyperbilirubinemia after cisplatin-based chemotherapy, one patient died of respiratory distress and an autopsy revealed chronic cholangiolitis with intrahepatic bile stasis. The other patient recovered following steroid treatment. The exact cause of indirect hyperbilirubinemia remains obscure.¹²

In conclusion, the complications resulting from an accidental cisplatin overdose of 400 mg/m² were successfully treated with vigorous plasma exchange supported by GM-CSF and broad spectrum antibiotics. To prevent the recurrence of such a deadly error, the utilization only of personnel with wide experience in the use of high dose cisplatin, double check systems and careful monitoring are all mandatory for treatment with any cytotoxic agent.

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