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Cisplatin Overdose
Toxicities and Management

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Contents

Abstract

Cisplatin is one of the most widely used antineoplastic agents in the treatment of solid tumour and haematological malignancies, including cancers of the testes, ovary, bladder, head and neck, oesophagus, stomach and lung, as well as lymphoma and osteosarcoma. Its non-specific targeting commonly results in adverse effects and toxicities affecting the gastrointestinal, renal, neurological and haematological systems even when administered at standard doses. Since

cisplatin-related toxicities are dose-dependent, these may be more pronounced in the setting of a cisplatin overdose, resulting in significant morbidity and/or mortality. The incidence of cisplatin overdoses is unknown; however, early-phase clinical trials utilizing high-dose cisplatin, and case reports in the overdose setting have characterized the clinical features associated with cisplatin overdoses, highlighting some therapeutic strategies for consideration.

To date, no published guidelines exist for managing a cisplatin overdose. The major toxicities of a cisplatin overdose include nausea and vomiting, renal insufficiency, electrolyte abnormalities, myelosuppression, ototoxicity, peripheral neuropathy, hepatotoxicity and retinopathy. Diarrhoea, pancreatitis, seizures and respiratory failure have also been reported. No specific antidote for cisplatin exists. Key management principles and strategies to lessen toxicities include renoprotection and enhancing drug elimination with aggressive intravenous hydration with or without the use of an osmotic diuretic, and avoidance of nephrotoxic medications. Sodium thiosulfate and plasmapheresis, with or without haemodialysis support, should be strongly considered. Close monitoring of clinical and laboratory parameters, and institution of supportive therapies, including antiemetics and haematopoietic colony stimulating factor support, are warranted. Based on the current literature, experimental therapies such as amifostine, ditiocarb sodium (diethyldithiocarbamate), acetylcysteine, fosfomycin and colestipol are of limited clinical effectiveness and remain investigational.

This review serves to highlight the clinical spectrum of toxicities resulting from a cisplatin overdose, to critically appraise the available literature and to present a suggested algorithmic approach for the initial management of a cisplatin overdose.

Cisplatin is a platinum chemotherapeutic agent widely used in the treatment of solid tumour and haematological malignancies. Intracellularly, it acts primarily by producing DNA inter- and intra-strand crosslinks. Given its non-selective targeting of both healthy and malignant tissues, treatment-related toxicities are common even when used at standard doses. Although the true incidence of cisplatin overdoses is unknown, reported cases in the literature have characterized the serious, life-threatening toxicities associated with a cisplatin overdose. Cisplatin overdoses may result from inadvertent substitution of cisplatin for carboplatin, administration of a single total dose instead of divided daily doses per cycle, as well as prescription and administration errors, including writing the wrong dose.[1,2] To date, no published guidelines exist on the management of a cisplatin overdose. This review serves to highlight the clinical spectrum of toxicities resulting from a cisplatin overdose, to critically appraise the available literature, and to provide a clinical framework and algorithmic approach in the event of an inadvertent cisplatin overdose.

1. Mechanism of Action

First described in 1965 by Rosenberg and colleagues[3] with experiments of platinum electrodes placed in an *Escherichia coli* culture media, the platinum derivative cisplatin, also known as cis-diamminedichloroplatinum (II) or CDDP, exerts its non-cell-cycle specific cytotoxicity by covalently binding to purine DNA bases and forming inter- and intra-strand crosslinks.[4-6] This results in local denaturing of DNA, which is eventually converted into strand breaks via cellular repair mechanisms. Although many of these strand breaks may be repaired by excision repair enzymes, remaining DNA and/or RNA and protein damage result in cellular death via apoptotic or non-apoptotic pathways.[7] The use of cisplatin with other chemotherapy agents may

result in either additive or synergistic cytotoxic effects observed in the clinical setting.

2. Pharmacology

Peak plasma levels of cisplatin are achieved within 1 hour after intravenous administration. Following an intravenous bolus of 50–100 mg/m^2, the removal of cisplatin from the systemic circulation has a triphasic character, with a $t_{½}\alpha$ of 20–30 minutes, $t_{½}\beta$ of 60 minutes, and a $t_{½}\gamma$ of approximately 24 hours, the latter representing the third phase of drug removal from its protein-bound state.[7] With high-dose cisplatin 200 mg/m^2/cycle, the $t_{½}\alpha$ remains approximately 30 minutes.[8] The majority of cisplatin is protein-bound (>90%). It has poor CNS penetration secondary to the blood-brain barrier, and tends to concentrate within the kidneys, liver and intestines.[9] Cisplatin has no known active metabolites and is rapidly converted into inactive metabolites, both intracellularly and in the bloodstream, by its non-enzymatic conjugation to sulfhydryl groups. Covalent drug binding to glutathione, metallothionein and sulfhydryl groups on proteins also occurs.[7]

When standard-dose cisplatin is administered intravenously to a patient with normal renal function, approximately 25% of the dose is eliminated during the first 24 hours,[7] and up to 50% by 5 days.[9] Renal excretion accounts for >90% of its total excretion,[10] with biliary excretion consisting of <10%.[11] With therapeutic use, the elimination half-life is >24 hours,[12,13] but may be as long as 28 days after a cisplatin overdose.[14] Approximately 15% of the drug is excreted unchanged in the urine.[15]

3. Clinical Indications and Dosing

Cisplatin is commonly used in treating cancers of the testes, ovary, bladder, head and neck, oesophagus, stomach and lung, as well as lymphoma and osteosarcoma (table I). Pre-clinical data has established the steep dose-response relationship associated with cisplatin use in ovarian cancer, testicular cancer and other malignancies.[16-18] In adults with normal renal function, the standard dose range is 50–100 mg/m^2 per cycle administered intravenously every 3–4 weeks, often in conjunction with other antineoplastic agents. With routine pre-hydration protocols, neurotoxicity, rather than nephrotoxicity, becomes the key dose-limiting factor. Earlier studies explored the use of high-dose cisplatin (200 mg/m^2 intravenously in divided doses per cycle),[17,19,20] but severe toxicities of myelosuppression and peripheral neuropathy have limited its routine use in clinical practice. Intracavitary or intraperitoneal and intra-arterial routes are rarely used and significant toxicities have been reported with intraperitoneal cisplatin in ovarian cancer.[21] Intra-arterial cisplatin has been utilized in head and neck cancer, whereby it acts primarily as a radio-sensitizer.

Table I. Common tumour site indications for cisplatin use and examples of dosing regimens

Tumour site indication	Examples of dosing regimens
Testicular cancer	20 mg/m^2 IV on days 1–5, every 3 weeks (with etoposide, bleomycin)
Ovarian cancer	50 mg/m^2 IV on day 1, every 3 weeks (with paclitaxel)
Bladder cancer	70 mg/m^2 IV on day 2, every 4 weeks (with gemcitabine)
Head and neck cancer	75–100 mg/m^2 IV on day 1, every 3–4 weeks
Oesophageal cancer	75–100 mg/m^2 IV on day 1, every 3–4 weeks (with fluorouracil)
Gastric cancer	60 mg/m^2 IV on day 1, every 3 weeks (with epirubicin, capecitabine)
Lung cancer	75–100 mg/m^2 IV on day 1, every 3–4 weeks (with vinorelbine) 50 mg/m^2 IV on days 1 and 8, every 4 weeks (with etoposide, radiation therapy)
Hodgkin's or non-Hodgkin's lymphoma	75 mg/m^2 IV on day 1, every 3 weeks (with dexamethasone, gemcitabine)
Osteosarcoma	100 mg/m^2 IV on day 1, every 3 weeks (with doxorubicin)

IV = intravenously.

4. Minimum Lethal and Maximum Tolerated Exposures

A minimum lethal dose for cisplatin has not been established. Although cisplatin overdoses ranging from 180–480 mg/m^2 intravenously have been reported without fatalities, significant toxicities are expected to occur.[2,14,22-31] Patient deaths

have been reported with a total cisplatin dose of 640 mg intravenously over 4 days[32] and 750 mg intravenously over 1 day.[33] Risk factors for morbidity include age and baseline organ function, magnitude of dose administered and cumulative cisplatin dose received.[34] Doses >100 mg/m^2 intravenously as a single bolus or consecutively within a few days are likely to result in at least moderate toxicities, especially without the use of adequate pre-/post-hydration and mannitol. Given that the threshold dose for a cisplatin overdose has not been previously defined, and taking into account both reported cases and earlier studies of high-dose cisplatin use, in this review we will consider a cisplatin administration of >180 mg/m^2 intravenously (administered as either a single dose or divided over a period of up to 5 days) to constitute a cisplatin overdose. However, the clinician also needs to consider other factors, including the age of the patient, pre-existing renal function and severity of toxicities in order to determine whether an overdose situation has occurred, even if the dose administered is <180 mg/m^2 intravenously.

5. System-Specific Toxicities with a Cisplatin Overdose

Table II outlines the major toxicities that are likely to occur with a cisplatin overdose. A general timeline of the onset of expected toxicities is presented in table III.

Table II. Major toxicities with a cisplatin overdose

Toxicity
Nausea and vomiting
Nephrotoxicity
renal insufficiency
electrolyte disturbances
Neurotoxicity
ototoxicity
retinopathy
peripheral neuropathy
Haematological
myelosuppression
Hepatotoxicity
transaminitis

Table III. Timeline of adverse effects and toxicities with a cisplatin overdose

Immediate (hours to days)
Nausea and vomiting
Diarrhoea (rare)
Early (days)
Acute renal insufficiency
Electrolyte abnormalities
Ototoxicity
Retinopathy
Peripheral neuropathy
Hepatotoxicity
Pancreatitis (uncommon)
Respiratory failure (rare)
Seizures (rare)
Early to late (days to weeks)
Myelosuppression
Chronic renal insufficiency
Ototoxicity
Retinopathy
Peripheral neuropathy

5.1 Gastrointestinal

Severe, protracted nausea and vomiting is likely to occur despite routine prophylactic antiemetic use, given the high emetogenicity of cisplatin.[23,25,28,29] This may occur acutely within the first 24 hours, and even as early as within the first hour.[22] Delayed nausea and vomiting, defined as occurring more than 24 hours after cisplatin administration, is also observed with high-dose cisplatin use[35] or in the setting of cisplatin overdose,[23,25,31] and may last up to 2 weeks. Mucositis may occur. Acute pancreatitis,[26,32] metallic or altered taste,[22,26] and diarrhoea within the first hour[22] have also been reported. Combinations of cisplatin with other antineoplastic agents may exacerbate and worsen these gastrointestinal toxicities.

5.2 Renal and Electrolyte Disturbances

Dose-dependent acute and chronic renal failure may develop,[2,23-29,31,36] although the underlying mechanisms have not been fully elucidated.[32,37] Acute oliguric or non-oliguric renal insufficiency may occur within 2–6 days after a cisplatin

overdose.[2,14,22,24-27,29,31] Chronic renal failure may last for more than 2 years at dosages of 20 mg/m^2/day for 5 days administered intravenously every 3 weeks,[38] with prolonged elevations of serum urea and creatinine secondary to proximal and distal tubular necrosis.[19,32,39] Associated metabolic acidosis secondary to renal tubular dysfunction,[22] and electrolyte abnormalities,[40] including hypomagnesaemia,[41-44] hypocalcaemia,[45] hypophosphataemia,[36] hypokalaemia,[36,42] hyponatraemia[46,47] and hyperuricaemia,[19] may be observed even with the use of cisplatin at therapeutic doses, and therefore may be potentiated in an overdose setting. Hyperkalaemia may also be seen in association with renal failure.[23] Concomitant nephrotoxic medications such as diuretics, aminoglycosides, amphotericin B and other antimicrobials may worsen renal toxicities.

5.3 Neurological

Either reversible or irreversible bilateral sensorineural hearing loss may occur, starting 2–7 days after an overdose.[14,23,26,27,29,32,33,36] The underlying pathophysiology likely relates to cisplatin-induced damage to the organ of Corti and stria vascularis.[48,49] In patients receiving cumulative doses of cisplatin >200 mg/m^2, 74–100% will experience a loss of high-frequency sounds, and 13–20% will develop significant hearing loss.[34] Tinnitus[28,29,31] and visual loss, with or without associated permanent loss of colour discrimination,[23,25,26,28,32,33,50] have also been reported in the setting of a cisplatin overdose. If these occur they are likely to develop within the first week of exposure.

Headaches,[22,36] gait imbalance,[51] hallucinations,[23,25,26] delirium,[36] encephalopathy,[52-54] seizures,[23,53-57] dysarthria[14] and sensory peripheral neuropathy with paraesthesias and numbness in a 'stocking-glove' pattern[14,20,25,26,32,36,51,58,59] may all occur with cisplatin use, especially at doses >200 mg/m^2.[14,23,26,36] A reversible, nonconvulsive encephalopathy has also been reported with therapeutic cisplatin use.[60] It is unclear whether these neurological symptoms and signs are primarily reversible or irreversible. One underlying mechanism relates to axonal degradation and damage to the dorsal root ganglion.[61,62] Combination antineoplastic therapy may exacerbate and worsen these neurological toxicities, such as worsening of sensory peripheral neuropathy with taxane or vinca alkaloid use.

5.4 Haematological

Marked myelosuppression with an onset of 5–26 days, especially thrombocytopenia and/or leukopenia, are dose-related and are common with both therapeutic cisplatin use[19,20,63] and in the overdose setting.[2,14,22-33,36] Anaemia may also develop. Persistent myelosuppression is likely to occur in the absence of supportive therapies. Likewise, combination antineoplastic therapy may exacerbate and worsen these haematological toxicities.

5.5 Hepatic

Hepatotoxicity including elevated transaminases,[23,25,26,29,32] hepatic failure consisting of elevated bilirubin[26,32] or elevated prothrombin time and partial thromboplastin time,[23,25] and cholestasis with increased alkaline phosphatase have all been reported.[26,28]

5.6 Cardiovascular

There are no specific cardiovascular toxicities reported in the setting of a cisplatin overdose. Sinus bradycardia[64,65] and tachyarrhythmias, including paroxysmal supraventricular tachycardia[66,67] and atrial fibrillation,[68] have all been reported in the setting of therapeutic cisplatin use, even in patients without a prior history of cardiac dysrhythmias.

5.7 Respiratory

There are no known specific pulmonary toxicities from cisplatin; however, acute respiratory failure and hyperpnoea have been reported.[36]

5.8 Immunological

Anaphylactoid reactions to cisplatin may potentially occur, as with therapeutic use.[69] There

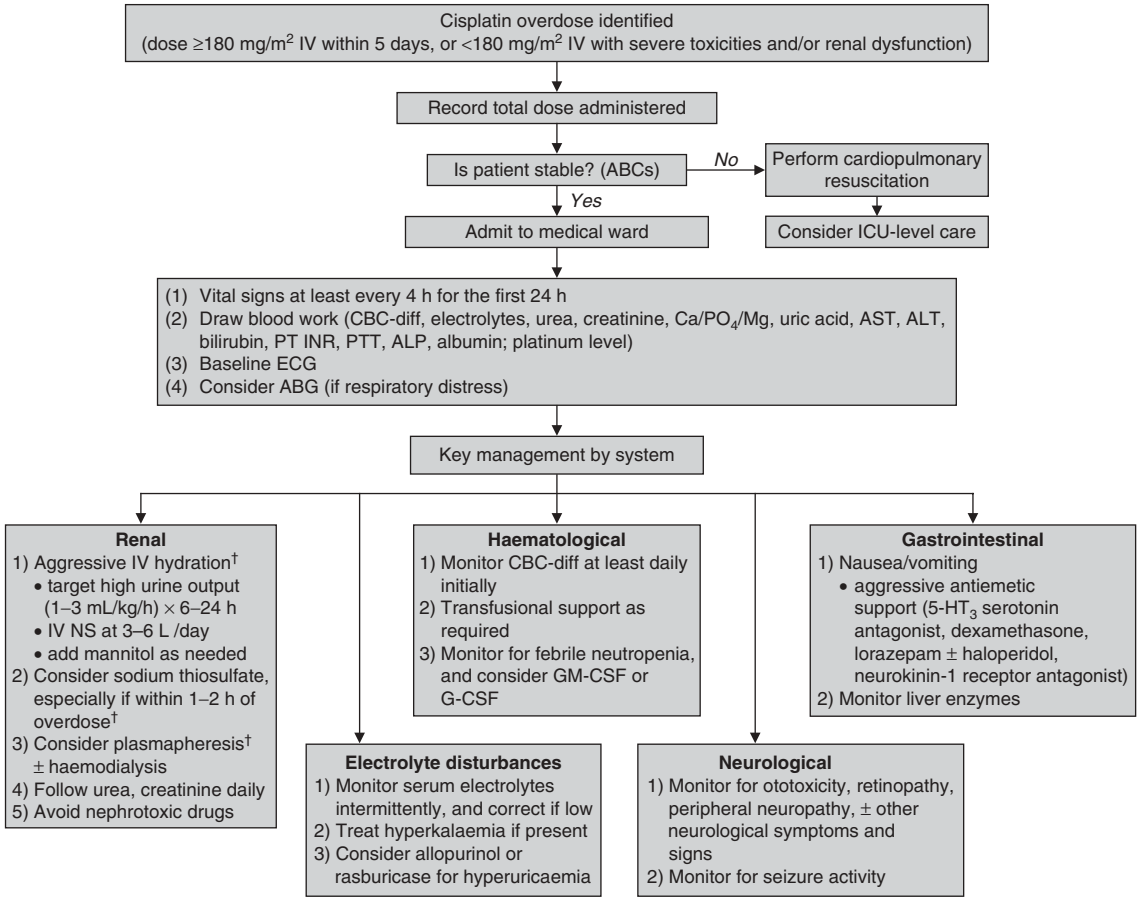

Fig. 1. Suggested approach for the initial management of a patient with cisplatin overdose. **ABCs** = airway, breathing, circulation; **ABG** = arterial blood gas; **ALP** = alkaline phosphatase; **Ca** = calcium; **CBC-diff** = complete blood count with differential; **G-CSF** = granulocyte colony stimulating factor; **GM-CSF** = granulocyte macrophage colony stimulating factor; **ICU** = intensive care unit; **IV** = intravenous; **Mg** = magnesium; **NS** = normal saline; **PO_4** = phosphate; **PT INR** = prothrombin time, international standardized ratio; **PTT** = partial thromboplastin time; † indicates important early therapeutic interventions.

are no specific published data relating to an overdose setting.

6. Management of a Cisplatin Overdose

Key management strategies for a cisplatin overdose involve renal protection and enhancing drug elimination, with aggressive intravenous hydration with or without the use of an osmotic diuretic, and consideration of sodium thiosulfate and plasmapheresis. Close monitoring of the patient, with aggressive institution of supportive therapies for expectant toxicities and avoidance of nephrotoxic medications, is paramount. A suggested algorithmic approach for the initial management of a patient with a cisplatin overdose is presented in figure 1.

6.1 Antidote

No specific antidote is available for cisplatin.

6.2 Close Monitoring of the Overdosed Patient

Once a cisplatin overdose is identified, close monitoring of the patient in an inpatient setting is

paramount, with frequent reassessments and measurement of vital signs at least every 4 hours for the first 24 hours. If signs of cardiovascular and/or respiratory collapse develop, then cardiopulmonary resuscitation measures should be undertaken as per American Heart Association guidelines.[70] Blood work monitoring should consist of at least daily complete blood count (CBC) with differential, electrolytes (sodium, potassium, chloride, bicarbonate), urea and creatinine. Baseline laboratory tests of hepatic function, liver enzymes and secondary electrolytes, including magnesium, calcium, phosphate and uric acid, should be performed and repeated as necessary. Serum platinum levels should be drawn and monitored serially for biochemical improvement. Particular attention should be given to the potential development of specific toxicities, as outlined in table III.

6.3 Nausea and Vomiting

Aggressive antiemetic support is warranted, based on current guidelines.[71-73] In a cisplatin overdose setting, no specific or optimal antiemetic regimens have been compared. Combination agents of a serotonin 5-HT_3 receptor antagonist (e.g. ondansetron 8 mg intravenously every 12 hours), dexamethasone (e.g. 8 mg intravenously every 12 hours) and lorazepam (e.g. 0.5–2 mg intravenously/orally every 4–6 hours) as needed are likely to be more effective as antiemetic control compared with metoclopramide, dexamethasone and lorazepam.[74-77] Antipsychotic agents such as haloperidol, or newer antiemetic agents such as the neurokinin-1 receptor antagonists aprepitant or fosaprepitant may also be additionally considered, although the latter agents are only indicated for use when first administered prior to the commencement of chemotherapy.

6.4 Renoprotection

6.4.1 Hydration

Aggressive intravenous hydration of at least 3–6 litres per day (preferably isotonic saline; dependent on underlying cardiac function) is essential in order to reduce the risk of nephrotoxicity.[37,78,79] The addition of the osmotic diuretic mannitol (e.g. 25–50 g intravenously in 250–500 mL over 60 minutes) should be performed as necessary in order to achieve a high urine output (1–3 mL/kg/h) for 6–24 hours post-exposure, as this may provide additive benefits.[78,80] Aggressive hydration results in an increased urinary excretion of cisplatin.[23,25] The avoidance of nephrotoxins is also critical.

6.4.2 Sodium Thiosulfate

Sodium thiosulfate appears to be an effective agent, although studies in the overdose setting are limited and the majority of the evidence relates to its concurrent use with high-dose intravenous cisplatin (100–225 mg/m^2) in early-phase clinical trials[81-83] or with intracavitary (intraperitoneal) cisplatin.[21,84,85] In two early-phase clinical trials, high-dose intravenous cisplatin was administered concurrently with sodium thiosulfate via two separate intravenous sites at a dose of 3.3 g/m^2 intravenously administered in 500 mL of sterile water over the first hour and 6.6 g/m^2 intravenously administered in 500 mL of sterile water over the second and third hours.[81,83] This protocol enabled the use of high-dose cisplatin 200–225 mg/m^2 before dose-limiting neurotoxicity occurred. Similarly, Markman et al.[85,86] have also reported a low incidence of renal and neurotoxicity in patients receiving up to 200 mg/m^2 of intraperitoneal cisplatin when sodium thiosulfate was administered concurrently as an intravenous bolus of 4 g/m^2 administered in 250 mL of sterile water over 15 minutes, followed by an infusion of 12 g/m^2 in 1 L of sterile water over 6 hours. The mechanism of action of sodium thiosulfate relates to the binding of free platinum, which results in an increase in the total clearance of inactive metabolites,[87] thereby limiting renal tubular cell necrosis. In addition, sodium thiosulfate may also protect against renal magnesium wasting.[88]

A recent paediatric case report highlighted the reversal of acute renal failure at 4 weeks after a cisplatin overdose when sodium thiosulfate was administered shortly after the overdose was identified. The 14-year-old girl with osteosarcoma accidentally received cisplatin 360 mg/m^2

intravenously instead of 120 mg/m^2 intravenously, and was administered sodium thiosulfate 70 hours after overdose, using a loading dose of 4 g/m^2 intravenously followed by a maintenance dose of 2.7 g/m^2 intravenously per day in three doses and continued for a total of 13 days.[27] Based on the limited available evidence, use of sodium thiosulfate should be considered, especially if it can be administered within 1–2 hours after a cisplatin overdose, although the optimal dosing regimen remains uncertain and further studies are warranted to investigate its potential role.

6.4.3 Plasmapheresis

Plasmapheresis, also referred to as plasma exchange, has shown promise in the management of cisplatin overdose. This has been attributed to the removal of cisplatin-bound plasma proteins, although its exact role remains undefined. It should nonetheless be strongly considered, regardless of time elapsed, in order to potentially reduce not only renal toxicities but also other systemic toxicities such as transaminitis.[29] In four separate case reports utilizing plasmapheresis, a fall in blood platinum concentrations was associated with clinical improvement. However, in a fifth reported case in which a 63-year-old male with recurrent lymphoma received a fatal overdose of cisplatin 750 mg instead of 170 mg, plasmapheresis did not appear to be beneficial.[33]

Chu et al.[23] reported a case of a 68-year-old female who received a cisplatin overdose of 280 mg/m^2 without intravenous hydration, in which plasmapheresis on day 12 of exposure for three daily treatments lowered the platinum concentration from >2900 ng/mL to 200 ng/mL. Associated clinical improvement was seen, with a decrease in the patient's nausea and visual symptoms. On day 20, her serum platinum concentration rebounded to 700 ng/mL with worsening symptoms; further plasmapheresis on day 22 lowered the concentration to 290 ng/mL by day 27, again coinciding with symptom improvement. In 1995, Jung et al.[25] reported a case of a 59-year-old male who received a cisplatin overdose of 300 mg/m^2, in which plasmapheresis was started on day 6 after exposure and continued for a total of 4 daily treatments. This was effective in lowering the serum platinum concentration from 2979 ng/mL to 430 ng/mL. Clinical improvement was observed, with a decrease in nausea and an increase in alertness. On day 11, platinum concentrations rebounded to 834 ng/mL, and fell to 279 ng/mL on reinstitution of plasmapheresis. The total amount of platinum removed by the three plasmapheresis trials was 4622 μg.

In a third case report, Choi et al.[26] reported the successful use of plasma exchange in a 48-year-old Korean male who received a cisplatin overdose of 400 mg/m^2 over 4 days without prehydration. The patient underwent nine cycles of plasma exchange from days 5–19, with a reduction of his plasma cisplatin concentration from 2470 ng/mL to 216 ng/mL, with eventual recovery and without any noted sequelae.

Hofmann et al.[29] reported a fourth case of clinical benefit with plasmapheresis in the setting of a cisplatin overdose in which a 46-year-old female with lung adenocarcinoma received a cisplatin overdose of 225 mg/m^2 within 3 days and developed acute renal failure, severe nausea and vomiting, myelosuppression, hearing loss and elevated liver enzymes. Supportive therapy, including 2 consecutive days of plasmapheresis on days 5 and 6 following the cisplatin overdose, resulted in symptom improvement and eventual discharge from hospital on day 18, with only persisting subclinical renal impairment.

6.4.4 Haemodialysis

Haemodialysis, as opposed to plasmapheresis, is ineffective in removing or clearing cisplatin from the body in an overdose setting. This is most likely due to the highly protein-bound nature of the drug.[22,24,33] Nonetheless, haemodialysis is likely to be a beneficial adjunct in the support of acute renal failure.[14] Nephrology and/or intensive care unit (ICU) consultation is therefore advised for consideration of plasmapheresis, with or without haemodialysis support.

6.5 Electrolyte Disturbances

Electrolyte supplementation, including magnesium,[43,44] should be replaced intravenously if

serum levels are low and normalized according to local laboratory reference standards. If hyperkalaemia occurs, medical management (including cation exchange resins, calcium gluconate, sodium bicarbonate, dextrose and insulin) and consideration of haemodialysis are warranted. In the setting of hyperuricaemia, allopurinol administered orally or intravenously at doses of 200–400 mg/m^2/day in one to three divided doses in a hydrated patient should be considered after adjusting for renal function. The dose should be titrated thereafter to achieve a normalization of serum uric acid levels.[89] Rasburicase, a recombinant urate oxidase, at daily doses of 0.1–0.2 mg/kg intravenously may be considered as an alternative to allopurinol or in refractory cases.[90]

6.6 Neurotoxicity

Although no direct supportive measures are available to reverse potential ototoxicity, retinopathy and peripheral neuropathy in the setting of a cisplatin overdose, early institution of renoprotective strategies (as discussed in section 6.4) with the aim of enhancing drug elimination may limit the severity of these neurological toxicities. In the rare event of a seizure,[23] initial stabilization of the patient is of utmost importance, with a focus on the patient's airway, breathing and circulatory status. The standard approach to seizures should then be employed, including the use of an intravenous benzodiazepine (e.g. lorazepam), identification of potentially reversible causes (e.g. hypoxia, electrolyte disturbances or hypoglycaemia) and consideration of intravenous phenytoin to control seizure activity. Subsequent management will depend upon available local resources, including consideration of ICU-level care as deemed necessary.

6.7 Myelosuppression

CBC with differential should be monitored on a daily basis, at least initially, as the onset of myelosuppression, including thrombocytopenia and/or leukopenia, may not be evident until 5–26 days after a cisplatin overdose. Supportive packed red blood cell and platelet transfusions should be strongly considered, especially if the haemoglobin level is <80 g/L or the platelet count is <10–20 000/uL.[91] Erythopoietin may be considered in refractory cases of anaemia if haemoglobin is persistently <10 g/L.[92,93] If febrile neutropenia occurs (temperature >38°C over 1 hour and absolute neutrophil count (ANC) $<0.5\times10^9$/L or predicted nadir $<0.5\times10^9$/L) or an underlying infection is suspected, then emergent septic workup (CBC with differential, blood and urine cultures, chest x-ray, with or without site-specific cultures) and empirical broad-spectrum antibacterials based upon local susceptibility patterns (e.g. pipericillin-tazobactam or meropenem) should be initiated immediately.[94] Haematopoietic colony stimulating factor (CSF) support, such as granulocyte-macrophage CSF (GM-CSF) [250 μg/m^2/day] or granulocyte CSF (G-CSF) [filgrastim 5 μg/kg/day], should be considered in patients with cisplatin overdose as they are at increased risk for severe prolonged neutropenia and/or for developing febrile neutropenia (both dependent on the total amount of cisplatin overdose) and continued until ANC is $>1.5–2.0\times10^9$/L.[95,96] However, currently there is little data available on the use of GM-CSF or G-CSF to treat neutropenia after drug overdoses or idiosyncratic reactions, although these agents have been shown to shorten the duration of severe chemotherapy-induced neutropenia in afebrile patients.[97] A few case reports have highlighted the use of GM-CSF[23,25,26,31] or G-CSF[27,29] following cisplatin overdose.

6.8 Hepatotoxicity

In the setting of cisplatin overdose, supportive therapies remain the mainstay of care in the management of elevated transaminases and liver failure, should they arise.

6.9 Experimental Therapies

6.9.1 Amifostine

There is currently no established role for the use of amifostine, an agent that is activated intracellularly to scavenge free radicals, thereby preventing cisplatin-DNA formation and facilitating DNA repair. It is approved by the US FDA only as a protective agent in the prevention of cisplatin-induced nephrotoxicity.[98] In early clinical

studies, amifostine, administered with cisplatin at therapeutic doses, appeared to be beneficial in reducing the effects of neurotoxicity, nephrotoxicity, ototoxicity and haematological toxicity; however, in a paediatric study conducted in 11 patients with newly diagnosed medulloblastoma, amifostine did not significantly decrease the incidence of nephrotoxicity or ototoxicity.[99] Similarly, a paediatric case report failed to demonstrate clinical benefits when amifostine was administered with high-dose cisplatin.[100] Likewise, Ekborn et al.[101] concluded that amifostine was ineffective in reducing ototoxicity in the setting of high-dose cisplatin for metastatic melanoma.

6.9.2 Ditiocarb Sodium

There is currently no data available on the use of the heavy metal chelating agent ditiocarb sodium (diethyldithiocarbamate) in the setting of a cisplatin overdose, and its use remains investigational. Ditiocarb sodium has primarily been studied in conjunction with therapeutic cisplatin use in attempts to reduce toxicities.[102,103]

6.9.3 Acetylcysteine

A paucity of evidence exists for the use of acetylcysteine in decreasing the incidence of nephrotoxicity or other adverse effects, including in the setting of a cisplatin overdose.[31,32,104] Therefore, its routine use is not recommended.

6.9.4 Fosfomycin

The role of fosfomycin, a phosphonic acid antibacterial produced from *Streptomyces* species, in cisplatin overdose is unknown. In limited animal and human studies involving therapeutic cisplatin use, it appeared to have some effects on reducing cisplatin-induced nephrotoxicity and ototoxicity, either alone or in the setting of aminoglycoside use, possibly by stabilizing the lysosomal membrane of the proximal tubular cells, thereby reducing its damage.[105,106]

6.9.5 Colestipol

In an isolated case report, the use of the oral anion exchange resin and bile acid sequestrant colestipol, in conjunction with supportive measures and the use of albumin and acetylcysteine, resulted in decreased morbidity.[31] Its routine use, however, is not recommended.

7. Conclusions

Medication errors are not an uncommon phenomenon in clinical practice. A recent prospective cohort study at a major US cancer centre found a potential adverse drug event rate of 3% involving chemotherapy use.[107] Given this unacceptably high prevalence, strategies for avoiding chemotherapy overdoses (including cisplatin) or preventing future errors are of utmost importance. These include being cognizant of medication errors through staff education, avoiding medication abbreviations, utilizing computerized prescriber chemotherapy ordering and double checking of chemotherapy orders by pharmacy and nursing staff.[108-111] For cisplatin in particular, one should also recognize the differences in dosing between cisplatin (<200 mg/m^2) and carboplatin (>200 mg/m^2) as it relates to inadvertent substitution of cisplatin for carboplatin.

Despite prevention strategies, medication errors involving chemotherapy will nonetheless continue to occur. Given the widespread use of cisplatin in the treatment of solid tumour and haematological malignancies and the lack of published guidelines in the management of cisplatin overdoses, it is important that a rational, systematic approach be developed. Based on the present review, clinicians and allied health professionals should recognize the common and uncommon systemic toxicities arising from a cisplatin overdose, especially as it relates to the gastrointestinal, renal, neurological and haematological systems. Although there is no specific antidote for cisplatin, important therapeutic strategies include aggressive intravenous hydration with or without the use of an osmotic diuretic, avoidance of nephrotoxic medications, and consideration of sodium thiosulfate and plasmapheresis, with or without haemodialysis support. Close supportive monitoring and treatment are essential, whereas therapeutic options such as amifostine, ditiocarb sodium, acetylcysteine, fosfomycin and colestipol remain purely investigational.

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