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The side effects of platinum-based chemotherapy drugs: a review for chemists

Rabbab Oun, ^a Yvonne E. Moussa ^b and Nial J. Wheate *^b

The platinum-based drugs cisplatin, carboplatin and oxaliplatin are regularly prescribed in the treatment of cancer and while they are effective, their use is limited by their severe, dose-limiting side effects (also referred to as adverse effects/events). In total, a cancer patient can experience any combination of around 40 specific side effects. The dose-limiting side effect for cisplatin is nephrotoxicity, for carboplatin it is myelosuppression, and for oxaliplatin it is neurotoxicity. Other common side effects include anaphylaxis, cytopenias (including leukopenia and neutropenia, thrombocytopenia, and anaemia), hepatotoxicity, ototoxicity, cardiotoxicity, nausea and vomiting, diarrhea, mucositis, stomatitis, pain, alopecia, anorexia, cachexia, and asthenia. The side effects may require patients to be prescribed dose reductions in their platinum drugs of between 25 and 100%. Furthermore, patients require extensive monitoring of their biochemistries, kidney and liver function, and depending on the drug, hearing tests. Finally, patients are commonly co-prescribed additional non-chemotherapy based drugs to treat the side effects which can include antiemetics, antibiotics and myeloid growth factors, mannitol, propafenone, saline hyperhydration, magnesium supplements, monoclonal antibody cytokine blockers, and antioxidants.

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Introduction

There are three platinum-based drugs that are used throughout the world for the treatment of cancer: cisplatin, carboplatin, and oxaliplatin (Fig. 1).¹ There are also four platinum-based drugs that have regulatory approval in individual nations: heptaplatin (Korea), lobaplatin (China), miriplatin (Japan), and nedaplatin (Japan).

All platinum drugs are administered *via* bolus intravenous injection (relatively large volume but administered over just a few minutes) or slow intravenous infusion, and while these drugs are thought to stay largely intact within the blood

stream, they are known to bind to serum proteins, especially human serum albumin.²

Platinum drugs are taken into cells *via* a range of mechanisms, most notably copper transporters, and specifically high affinity copper transporter 1.^{3,4} Upon entering a cell, the low salt concentration results in the aquation of the drug and the loss of its labile groups (chlorides or carboxylate-based ligands). Once aquated, the drug is highly reactive and can bind to a number of intracellular biomolecules.⁵

As a soft nucleophile, platinum-based drugs readily bind peptides and proteins that contain sulfur residues of cysteine or methionine, especially the antioxidant peptide glutathione; but the important target of platinum drugs is nuclear DNA.⁵

Predominantly, the drugs bind at the N7 position of guanine, but also adenosine residues, which causes an unwinding and bending of the DNA.⁵ Ultimately, this prevents DNA transcription and replication, which initiates apoptosis (programmed cell death).⁶

Resistance is a major limitation of platinum-based drug treatment because cancers can be inherently resistant to platinum drugs or can develop resistance over time. Acquired resistance to the drugs can occur through three main mechanisms: increased drug degradation and deactivation before it reaches nuclear DNA, decreased uptake of the drugs into cancer cells, and improved DNA repair by the cell of the damage caused by the platinum.⁶

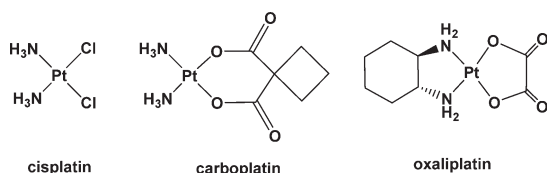


Fig. 1 The three platinum-based chemotherapy drugs with global approval.

^aUniversity of Strathclyde, Glasgow, G4 0NT, UK

^bSydney Pharmacy School, The University of Sydney, NSW, 2006, Australia.

E-mail: nial.wheate@sydney.edu.au

The mechanism of platinum-drug toxicity

All cytotoxic chemotherapy drugs, including platinum-based drugs, display a range of severe side effects due to their poor selectivity for cancerous tissue over normal tissue. What little selectivity they have is due to the high nutrient requirements of cancer cells. So while these drugs are taken up by fast growing cancer cells, they are also taken up into other tissues that are fast growing.

Fast growing tissues that can be affected by chemotherapy drugs include the mucous membranes of the mouth, throat, stomach and intestines, which leads to gastrointestinal toxicities. It includes bone marrow which can result in reduced white and red blood cell production. Hair follicles also comprise fast growing cells, which means that chemotherapy drugs can result in the loss of hair (alopecia), which includes eyebrows, facial and body hair, as well as hair follicles in the ear, which can result in ototoxicity (ear damage). Finally, chemotherapy drugs are commonly known to also display nephrotoxicity (kidney damage), and hepatotoxicity (liver damage). The kidney damage arises because excretion of the drugs occurs in urine and the liver toxicity arises because the body tries to metabolise and detoxify the drugs in the liver, giving the platinum the opportunity to be taken up by cells in both organs.

The side effects experienced by patients treated with a platinum-based chemotherapy drug are similar, although the specific dose-limiting toxicity (DLT) is different for each drug. Dose-limiting toxicity is defined as the side effect of a drug, or other type of treatment, that is serious enough to prevent an increase in the drug dose or that level of treatment. For cisplatin the DLT is nephrotoxicity, for carboplatin it is myelosuppression, and for oxaliplatin it is neurotoxicity.

There is a direct link between the toxicity of a platinum drug and its level of reactivity. The reactivity of a platinum drug (how fast it binds to biomolecules in the body) is determined mostly by how labile its leaving groups are. The more labile the group(s), the more reactive the complex and the more toxic side effects it produces at equidoses to other platinum drugs.

The development of carboplatin was based directly on this structure–activity relationship. Replacement of the chloride ligands of cisplatin with the bis-carboxylate ligand of carboplatin results in a significantly reduced rate of aquation, and hence, a reduced level of toxicity when compared with cisplatin.

An important aspect of reducing the side effects of platinum drugs is to ensure that minimum aquation occurs during drug preparation and administration. Cisplatin is always formulated in a 0.9% saline (NaCl) solution so as to slow the removal of the chloride ligands. Dissolution of carboplatin or oxaliplatin in saline would convert carboplatin to cisplatin, and transform oxaliplatin into $[\text{PtCl}_2(\text{R,R-dach})]$ which is both more reactive and less soluble than the parent drug. Therefore

carboplatin and oxaliplatin are always formulated in 5% glucose solutions.⁷

Assessing the severity of platinum-based drug side effects

The severity of all side effects that can be experienced by a patient are measured on a grading scale of 1–5. There is no standard scale used consistently throughout the world, but the Common Terminology Criteria for Adverse Events scale developed and maintained by the National Cancer Institute (NCI) of the USA is used widely.

Version 4 of the guidelines defines Grade 1 as mild and is for asymptomatic or mild symptoms where intervention is not indicated. Moderate (Grade 2) is defined as when minimal, local or non-invasive intervention is needed; or the side effects limit age-appropriate instrumental activities of daily life (ADL). Severe (Grade 3) includes medically significant side effects that are not immediately life-threatening but require acute or prolonged hospitalisation; are disabling; or limit self-care ADL. Grade 4 is a life-threatening side effect that requires urgent medical intervention, while Grade 5 is defined as death due to the side effect.

Drug dosing and monitoring

For platinum drugs, the prescribed dose is dependent on the cancer type, the chemotherapy protocol to be used, the patient's overall health, whether the chemotherapy is being used in conjunction with other treatments (*i.e.* radiotherapy), and the intended outcome of the treatment (*e.g.* palliative, consolidation, or salvage therapy). Platinum-based treatment protocols differ from country to country, and in some nations, from region to region. In Australia, the EviQ guidelines are the national standard in chemotherapy whereas the National Institute of Health and Clinical Excellence guidelines, and the Scottish Intercollegiate Guidelines Network guidelines are used in England and Scotland, respectively.

Patients treated with a platinum drug are not generally treated with a fixed dose. Rather the dose for cisplatin and oxaliplatin is adjusted taking into account the patient's body surface area (BSA) which is calculated as the patient's weight in kilograms divided by the square of their height in metres. Understanding drug doses is important as many of the side effects of platinum drugs are dose related. Doses of cisplatin and oxaliplatin for patients are always stated in units of milligrams per square metre (mg m^{-2}). Drug doses for cisplatin are typically in the range of 10–100 mg m^{-2} , and for oxaliplatin the typical doses are 85–130 mg m^{-2} , based on EviQ guidelines.

In contrast to cisplatin and oxaliplatin, the dose of carboplatin for a patient is not calculated based on BSA, but is instead calculated using the Calvert formula:

$$\text{Total dose (mg)} = \text{target AUC} \times (\text{GFR} + 25)$$

where the area under the curve (AUC) is the drug dose in $\text{mg min}^{-1} \text{ mL}^{-1}$ and GFR is the glomerular filtration rate in mL min^{-1} (a measure of flow through the kidneys). In some cases, creatinine clearance (CrCl) is substituted for GFR but it is considered to be a less accurate method for calculating the appropriate dose.⁸ Drug doses for carboplatin are generally in the range of 2–8 AUC, based on EviQ guidelines.

Where the side effects from the platinum drugs are sufficiently detrimental to the patient, then the patient may be given a dose reduction (also referred to as a dose modification). The criteria for a dose reduction are different for each platinum drug, but are all based on the severity of the side effects (Grade 1–4) and their frequency. As such, to adequately assess the severity of the side effects being experienced by the patient it is common practice to conduct baseline tests on patients before they begin treatment. Such tests can include whole blood cell (WBC) counts, hearing, liver function test (LFT), and CrCl.

Creatinine is a small organic molecule that is produced by muscles and excreted from the body through the kidneys (Fig. 2); a high concentration of creatinine indicates poor kidney function. For some patients, if their CrCl is too low, they can be contraindicated for treatment with cisplatin and oxaliplatin and a different chemotherapy protocol may be needed.⁸

Uric acid is a breakdown product of purines (one of the two types of DNA bases) and is excreted through the kidneys (see Fig. 2). Similar to creatinine, the buildup of uric acid in blood serum is another method to assess kidney function. High concentrations of uric acid can cause crystallisation of the chemical leading to the condition known as gout.⁹

For men, CrCl is calculated using the formula:

$$\text{CrCl}(\text{mL min}^{-1}) = \frac{(140 - \text{age}) \times (\text{weight in kg})}{0.815 \times \text{Se}_{\text{cr}}(\text{micro mol L}^{-1})}$$

where Se_{cr} is the serum concentration of creatinine and weight is either the patient's actual weight or their ideal weight, whichever is lower. The same formula is also used for women, but the calculated CrCl is then multiplied by 0.85.

Dose reductions are usually recommended at levels of 10, 25, 50 or 100% of the recommended starting dose. Where a 100% dose reduction is recommended (*i.e.* the patient should not be administered the drug at all), then a replacement drug is not generally recommended. Other recommendations for

dealing with chemotherapy drug side effects, other than dose reductions, include treatment delays or management with protective agents.

Specific side effects of platinum drugs

For the three platinum drugs there are more than 40 specific side effects that can be experienced by a patient, and these can be broadly grouped into seven categories: nephrotoxicity, ototoxicity, neurotoxicity, cardiotoxicity, hematological toxicity, hepatotoxicity, and gastrointestinal toxicity. The following sections provide details on each of these broad categories, including the known or proposed mechanisms behind the side effects and any appropriate medicines or treatments to reduce their severity.

Nephrotoxicity

Nephrotoxicity is damage to the kidneys and is a broad term that covers more than 12 specific side effects related to its key functions of filtration, reabsorption, and excretion (Table 1). While all three platinum drugs can cause nephrotoxicity,¹⁰ it is most commonly associated with cisplatin treatment, a side effect that has been known about the drug since its first animal trials.¹¹ Nephrotoxicity is the main reason for patients

Table 1 The common types of nephrotoxic side effects associated with platinum-based treatment. Based on the table in Miller *et al.*, 2010¹³

Nephrotoxic side effect	Definition
Acute kidney injury	Sudden onset of kidney damage or failure resulting in a build-up of waste products in blood serum and difficulty in maintaining correct fluid balance
Hypomagnesemia	Low levels of serum magnesium
Fanconi-like syndrome	Excess levels of potassium, uric acid, phosphates, bicarbonate, glucose, and select amino acids in urine
Distal renal tubular acidosis	A defect in the kidneys that causes acid to build up in blood serum
Hypocalcemia	Lower than average levels of serum calcium
Renal salt wasting	Also known as cerebral salt wasting, is extracellular volume depletion due to a renal sodium transport abnormality with or without high urinary sodium concentration, presence of hyponatremia or cerebral disease with normal adrenal and thyroid function
Renal concentrating defect	Decreased ability of the kidneys to concentrate solutes for excretion in urine
Hyperuricemia	Excess serum levels of uric acid
Transient proteinuria	Temporary increase in the level of proteins excreted in the urine ($>150 \text{ mg day}^{-1}$)
Erythropoietin deficiency	Low levels of erythropoietin, a hormone produced by the kidneys that promotes red blood cell formation
Thrombotic microangiopathy	Damage of the capillaries in the vital organs, especially the kidneys
Chronic renal failure	The gradual loss of kidney function over time

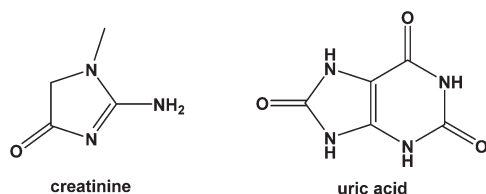


Fig. 2 The chemical structures of creatinine and uric acid. Their concentrations in blood serum are used as markers to determine the level of kidney function in a patient.

to discontinue treatment, especially when cisplatin is combined with radiotherapy.¹² Treatment with any of the three platinum drugs requires monitoring before, during, and after treatment and includes measurement of CrCl as well as other biochemistries.

The two most common nephrotoxic side effects of cisplatin are acute kidney injury (also known as acute renal failure) and hypomagnesemia, which is reported to affect up to 90% of cisplatin treated patients.¹⁴ The hypomagnesaemia stems from the damaged kidney's inability to reabsorb magnesium.¹⁵

How platinum cause nephrotoxicity is not fully understood, but is believed to be due to both direct and indirect damage to the kidneys. The main mechanism is attributed to acute tubular necrosis of proximal tubular cells.¹⁶ There is some evidence that cisplatin binding to mitochondria may play a role, but the role of drug binding to nuclear DNA in kidney cells is not known.¹⁵

Nephrotoxicity is dose related with risk increasing with the number of chemotherapy cycles and the size of the dose. The risk of kidney damage due to cisplatin is lessened when the drug is given as a slow infusion rather than a bolus injection.¹⁴ Depending on the patient, their nephrotoxicity may or may not be reversible.

There are a number of additional risk factors that increase a patient's chance of experiencing nephrotoxicity. These include prescription of cisplatin instead of carboplatin and oxaliplatin, pre-existing renal dysfunction, hypertension (high blood pressure), and the previous removal of a kidney. Specific patient characteristics will also increase their risk, and include: female gender, older age, and history of smoking.¹³ Co-treatment with other drugs is also known to cause kidney

damage, such as non-steroidal anti-inflammatory drugs, the aminoglycoside-based gentamicin, the cephalosporin-based cefalotin antibiotics,¹⁵ and the chemotherapy drugs ifosfamide and methotrexate (Fig. 3). There is debate in the literature as to whether diabetes increases or has no effect on a patient's risk of experiencing nephrotoxicity.^{13,14}

There are a number of established treatments for reducing nephrotoxicity due to cisplatin. The most used is hyperhydration which can involve the administration of normal saline at a rate of 100 mL per hour for up to 12 hours before treatment and for up to three days after cisplatin administration.¹⁵ Additional treatments include antiemetics to prevent fluid loss due to vomiting, and magnesium and other supplements. There is disagreement as to whether diuretics provide any benefit,^{13,15} and the side effects do not appear to be reversed when patients are administered a calcium channel blocker or an angiotensin converting enzyme inhibitor.¹⁵ Recently, drugs designed to combat the formation of reactive oxygen species (ROS) by cisplatin, like tetrahydrocurcumin, have been investigated as potential nephrotoxicity reducing agents.¹⁷

Ototoxicity

Ototoxicity is damage to the inner ear which results in impairment of a patient's hearing and balance. For platinum-based drugs the predominant ototoxicity is permanent hearing loss in both ears, although other side effects can include otalgia (ear pain), tinnitus (noises or ringing in the ears), and vestibular alterations (affects balance). Hearing loss is assessed either by audiometric testing if a hearing baseline has been established

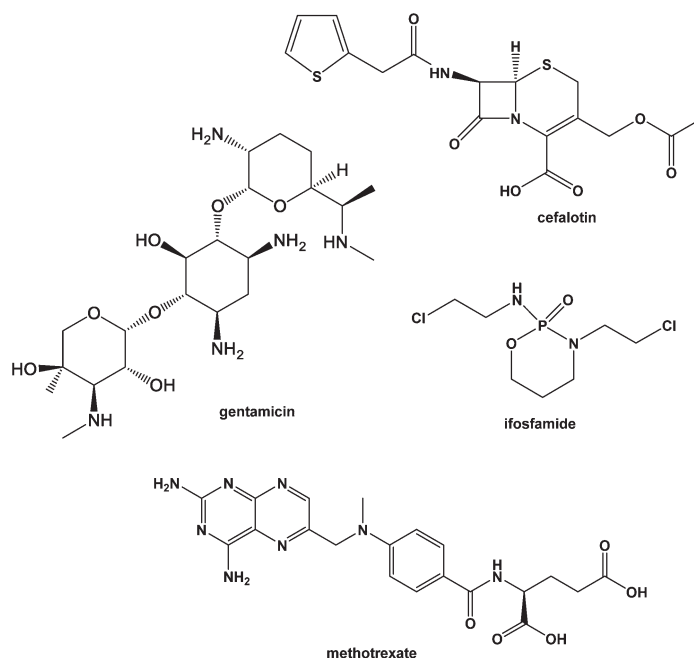


Fig. 3 The chemical structures of some of the drugs known to increase the risk of nephrotoxic side effects for patients undergoing treatment with a platinum drug.

before the patient commences chemotherapy, or alternatively, through the patient's self-assessment of their hearing.

For cisplatin, hearing loss generally occurs at higher frequencies (>4 kHz) and is proportional to the dose/cumulative dose of the drug. The rate of hearing loss is highly variable and is between 4 and 90%, depending on the drug dose and the age of the patient.¹⁸ Hearing loss is common at the higher frequencies when the cisplatin dose is greater than 60 mg m^{-2} .¹⁹

While hearing loss is generally considered non-reversible, tinnitus is commonly reversible upon the completion of treatment.⁸ When treated with cisplatin, hearing loss has been found to be more common in children than adults. Concurrent treatment with cisplatin and radiotherapy on the head or base of the head has also been found to increase the incidence of hearing loss.²⁰

Several studies have examined the role of functional polymorphism in key genes and related ototoxicity. A correlation between genetic variants and hearing loss has been found for cisplatin-detoxifying enzymes (such as glutathione-S-transferase),^{21,22} nucleotide excision repair proteins,²³ and megalin which is a low density lipoprotein.²⁴

Ototoxicity due to platinum treatment is thought to be due to damage in the inner ear *via* several mechanisms. Cisplatin is known to accumulate in cochlear tissue where it can generate ROS, particularly *via* nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and downregulate important antioxidant enzymes such as glutathione reductase and peroxidase, catalase and superoxide dismutase. It is also thought that cisplatin induced ototoxicity is due to the drug activating big conductance potassium channels which leads to follicle apoptosis.²⁰

There is no effective method to manage or reduce the ototoxicity of platinum-based drugs. Given that the side effects are thought to involve the production of ROS, there have been several studies into the utility of antioxidants, such as *N*-acetyl cysteine, sodium thiosulphate and amifostine to reduce the damage to the ear (Fig. 4), but none of these have gained broad clinical use.

In the absence of effective drugs to prevent or treat hearing loss, patients may alternatively be given a hearing aid, cochlear implant, or other assistive device (such as text messaging or audio streamers), and other special accommodations.¹⁸

Neurotoxicity

Neurotoxicity is damage to the nervous system principally as peripheral sensory neuropathy (PSN; pain, weakness or numb-

ness in the hands or feet). While neurotoxicity is a known side effect of cisplatin,²⁵ it is more usually associated with oxaliplatin treatment. Between 60 and 95% of oxaliplatin treated patients experience some level of neurotoxicity,^{26,27} with around 20% of cases due to grade 3 or 4 toxicity.²⁸ The incidence of the side effect increases with cumulative dose. Chronic PSN commonly occurs when patients are treated with a cumulative dose exceeding 500 mg m^{-2} for cisplatin or 750 mg m^{-2} for oxaliplatin.²⁷

The side effects are reversible and can be acute or chronic with an onset of a few days, and with chronic symptoms reported to persist for time periods of up to four years.²⁹ Symptoms tend to be worse in patients' hands, feet and the perioral and pharyngolaryngeal areas (pharynx/larynx and the tissues around the mouth), and manifests as paresthesia which includes numbness, or tingling, prickling, tickling, or burning sensations.²⁹ It also includes muscle weakness and dysesthesia which exhibits as pain due to stimulation that does not ordinarily cause pain or another abnormal sense of touch.²⁸ Exposure to cold is known to increase neurotoxic side effects.

Oxaliplatin induced acute PSN is thought to be due to the oxalate ligand of the drug, rather than the drug's active component; aquated Pt(II)-1R,2R -diamminocyclohexane. The oxalate ligand has a direct effect on voltage-gated Na^+ and K^+ channels and an indirect effect on these channels through its chelation of Ca^{2+} and Mg^{2+} .^{26,29,30} The chronic effects of oxaliplatin arise from the cumulative administration of the drug and result from accumulation in dorsal root ganglia, where uptake is controlled by the organic cation transporter 2 protein.^{30,31} For these chronic cases, the neurotoxicity is thought to be derived from oxaliplatin inhibiting rRNA synthesis.²⁹

There are few effective treatments to prevent or modulate the level of neurotoxicity experienced by the patient. There are inconsistent reports as to whether infusions of calcium or magnesium reduce the side effect and whether these infusions reduce the effectiveness of oxaliplatin.^{29,31} The use of antioxidants, like acetylcysteine, vitamin E, diethyldithiocarbamate, amifostine, oxycarbazepine, and glutathione, to prevent cisplatin or oxaliplatin induced ROS have been shown not to work.²⁸

Cardiotoxicity

Cardiotoxicity is defined as toxicity that affects the heart and includes either direct damage to the heart muscle or indirect damage, through electrophysiological changes, that affect the heart's sinus rhythm.

Cardiotoxicity is not listed as a common side effect of the platinum-based drugs; however, over the past ten years there has been a rise in the number of clinical cases reporting a wide range of cardiotoxic events occurring during, or shortly after, cisplatin infusion.³² These include silent and symptomatic arrhythmias (abnormal heart rhythm), cardiac ischemia (inadequate blood supply to the heart), diastolic disturbances

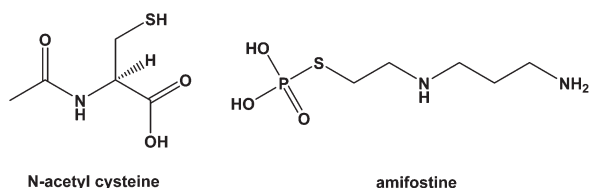


Fig. 4 Two antioxidants that have been examined as potential drugs to reduce the ototoxicity of platinum drugs.

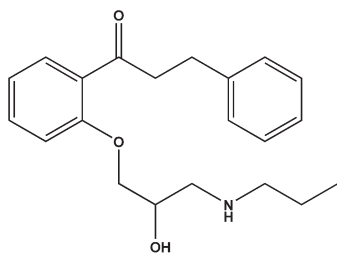


Fig. 5 The chemical structure of propafenone, a drug used in the treatment of arrhythmias.

(the ventricles do not properly relax before the next contraction), myocardial infarction (heart attack), angina, pericarditis (inflammation of the pericardium which is the sac-like tissue that surrounds the heart), thromboembolic events (obstruction of a vessel in the heart or veins), and chronic heart failure.^{32–34}

Compared with cisplatin, there are few clinical reports of cardiotoxicity induced by oxaliplatin or carboplatin. Unlike other chemotherapeutic drugs, the platinum-based drugs are not routinely administered with cardiac monitoring and this may have resulted in under reporting of cardiotoxicity induced by these drugs, both short and long term, especially where the symptoms are silent.³²

Tachycardia, which is a type of arrhythmia in which the heart rate exceeds the normal resting range of 60–100 beats per minute (bpm), is the most commonly reported cardiotoxic side effect of cisplatin (20–100 mg m⁻²), and can occur either minutes, hours, or days after treatment.^{32,34,35} It is important to note that silent tachycardiac events are identified only after patients complain of chest pain and difficulty.^{35,36} In most cases the patients' heart rates were found to be in the range of 160–230 bpm and blood electrolyte analysis revealed that patients were suffering from hypomagnesaemia (magnesium serum levels below 1.7 mg dL⁻¹).^{35–37} In all cases, return to sinus rhythm was achieved within 48 hours after treatment with propafenone or magnesium sulfate (Fig. 5).^{35–37}

On the other hand, cisplatin has also been reported to induce bradycardia (heart rate below 60 bpm).^{38,39} For these cases, patients' serum electrolyte levels are generally within the normal range and sinus rhythm returns without any medical intervention.^{38,39}

The mechanism of action of cisplatin's cardiotoxicity is unknown, yet it has been hypothesised to either occur as a secondary toxic effect to nephrotoxicity (as explained above due to poor magnesium reabsorption) or that it may affect the SA node.³² There is some evidence the cardiotoxicity of cisplatin is linked to direct ROS attack of the heart.³³

Hematological toxicities

Hematological side effects caused by platinum drugs include those that affect bone marrow function and blood cell production and include leukopenia (reduced levels of white blood cells), neutropenia (which is a subclass of leukopenia and is

defined as a low level of neutrophils), thrombocytopenia (a low level of platelets, which are responsible for blood clotting), and anaemia (a low level of red blood cells).^{40,41} Myelosuppression is a term used to describe the condition when bone marrow production of all blood cells is affected and results in low levels of white and red blood cells, and platelets.

All three platinum drugs are known to cause some form of hematological toxicity, and myelosuppression is the dose-limiting toxicity of carboplatin. Risk factors for hematological toxicities include kidney function, age, and race, and the severity of the side effects are directly linked to the drug doses.

These side effects can leave patients feeling dizzy, tired and lethargic, and when they experience leukopenia or neutropenia, can leave them susceptible to infections and increase the length of their hospital stay.⁴² As such, any patient treated with a platinum drug is closely monitored which includes measuring their WBC count and platelet levels, and their absolute neutrophil count (ANC).

Of particular concern for patients is the development of febrile neutropenia (development of a fever with a temperature greater than 38 °C) because 5–7% of patients who develop this side effect die during their hospital stay.⁴³ Treatment with a platinum drug generally gives patients an intermediate (10–20%) or high (>20%) chance of developing febrile neutropenia, depending on the other chemotherapy drugs that are co-prescribed.⁴²

Treatments for patients can include blood transfusions, administration of broad spectrum antibiotics, and in some cases, administration of myeloid growth factors,⁴² which include granulocyte colony stimulating factors.⁴³ These biologically-based drugs reduce the incidence of neutropenia by promoting the production and survival of mature neutrophils and neutrophil granulocyte progenitor cells.

Hepatotoxicity

While there are different types of liver damage that can be caused by chemotherapy drugs, cisplatin and oxaliplatin are known for their ability to damage liver sinusoids; the blood vessels that serve to bring oxygen to the liver.⁴⁴ Such damage leads to sinusoidal dilatation and obstruction which results in reduced liver function with visible signs in the patient of abdominal pain and swelling.⁴⁵ Damage to the sinusoids can also result in nodular hyperplasia which is the development of benign tumours in the liver.⁴⁶ The rate of hepatotoxicity varies with each platinum drug, but for oxaliplatin it is between 10 and 50%.⁴⁴

The hepatotoxicity of the drugs arises from their creation of ROS in the mitochondria of the epithelial cells lining the sinusoids.^{46,47} These ROS lead to an increase in cytokines that then sensitize healthy liver cells to apoptosis and other cellular damage. Several studies have also shown a link between CYP450 levels, especially CYP2E1 and CYP4A11, and the level of hepatotoxicity. The mechanism of action appears to be

direct attack of the drugs on these enzymes that leads to the generation of ROS.⁴⁸

There are no established treatments for platinum induced hepatotoxicity beyond monitoring for signs of damage (liver function test) and limiting the patient's treatment duration.⁴⁶ There is limited evidence that the administration of antioxidants can reduce damage; however, since the ROS generated by the platinum drugs leads to increased cytokine levels, then the co-administration of drugs that stop cytokines, such as infliximab which blocks the action of tumour necrosis factor- α , may be useful in limiting liver damage.⁴⁹

Gastrointestinal toxicity

Gastrointestinal toxicities due to platinum drugs principally include emetic effects such as chemotherapy induced nausea and vomiting (CINV)⁵⁰ and dyspepsia (reflux). While diarrhea⁵¹ and abdominal pain/abdominal cramps are rare for patients treated with cisplatin they are more common with experimental platinum drugs, like triplatin.⁵² Some patients have inadequate food intake which can lead to cachexia (weight loss) and some patients treated with a platinum can develop anorexia (a psychological condition where the patient fears gaining weight).^{53,54}

Cisplatin is considered a high risk emetic drug with more than 90% of patients expected to experience nausea and vomiting. In contrast, carboplatin and oxaliplatin are both rated as moderate risk drugs with nausea and vomiting rates between 30 and 90%.⁵⁵ If patients are also co-administered radiotherapy with their platinum drug, this can increase the incidence of CINV. While treatment with antiemetic drugs is largely successful, 10–30% of patients still experience break-through nausea and vomiting.^{53,56}

Most CINV in patients is due to the release of 5-hydroxytryptamine (5-HT, Fig. 6) when the platinum drugs attack the cells of the gastrointestinal tract. When released, 5-HT binds to serotonin receptors, especially 5-HT₃ receptors, which are found in the central and peripheral nervous system, which leads to CINV. Antiemetic drugs that are 5-HT₃ receptor antagonists block the binding of 5-HT, and through this, stop the cascade of effects that lead to nausea and vomiting.

The mechanisms behind the development of cachexia when patients are treated with cisplatin are unclear; however, it has been proposed that a reduction in the secretion of the appetite-stimulating hormone, ghrelin, may play an important role.⁵³

Treatment of CINV due to a platinum drug is based on a combination of antiemetic medicines (Fig. 6). For cisplatin, the latest clinical guidelines recommend a combination of four different drugs, a 5-HT₃ antagonist drug, such as ondansetron, a neurokinin 1 (NK₁) antagonist drug, such as aprepitant, as well as dexamethasone and olanzapine. For carboplatin a combination of 5-HT₃- and NK₁-based drugs, and dexamethasone is recommended, and for oxaliplatin, treatment with just dexamethasone is considered sufficient.⁵⁵ At the

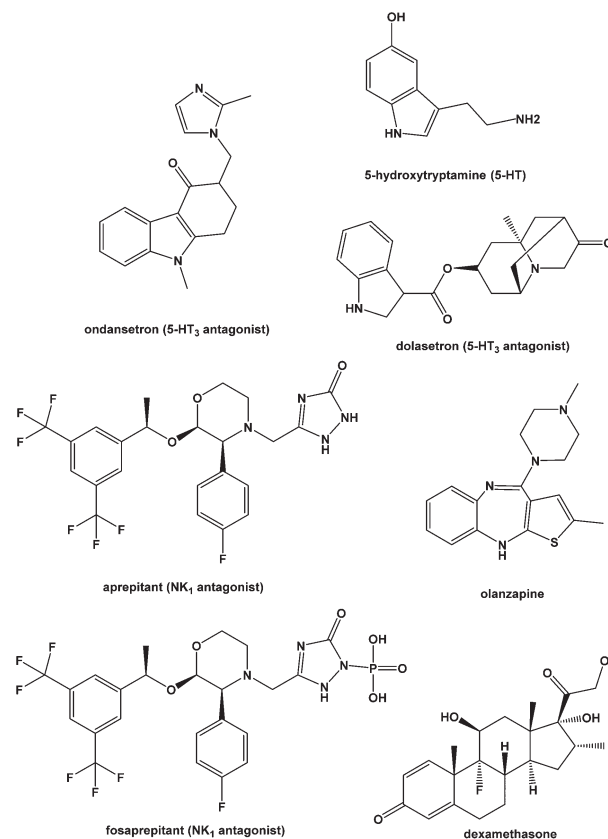


Fig. 6 The chemical structures of 5-hydroxytryptamine (5-HT) and examples of antiemetic drugs used to treat the CINV effects of platinum drugs.

moment, there is insufficient evidence for the efficacy of medicinal cannabis and cannabinoids in the treatment of CINV.⁵⁵

Dexamethasone is a corticosteroid that is also used for cerebral oedema and prevention of neonatal respiratory distress syndrome. Olanzapine is an antipsychotic drug which is also used to treat schizophrenia and bipolar disorder and is used because it can block neurotransmitter receptors, including dopamine receptors 1–4.⁵⁶

It is important to note that the antiemetic drugs prescribed to patients receiving platinum drugs can also have their own side effects. For example, dopamine 2 receptor antagonist drugs are known to induce restlessness and muscle spasms which may then require treatment with benzodiazepines.⁵⁷

Conclusions

The three platinum drugs used extensively throughout the world, while effective, remain severely limited by the number, and the severity, of their side effects which can result in dose reductions and poor quality of life for patients. In our opinion, if platinum drugs are to continue to have a future role in chemotherapy then better management of their side effects is needed, more so than the development of new platinum-based drugs.

This would include better strategies for the administration and delivery of the drugs so they are less likely to affect healthy tissue. Previously investigated delivery strategies have included the use of nanoparticles, polymers and macrocycles^{58–60} as delivery vehicles or active targeting of the drugs through the use of antibodies, aptamers, and important nutrients, like folic acid.^{61–63} Additionally, given that the root cause for the many side effects of all three drugs is the production of ROS, then novel methods to reduce ROS, or lessen the effects of ROS, could also potentially have an enormous impact on the side effects of platinum drugs.

Finally, there has been limited research into examining the factors that make specific patients susceptible to the side effects of platinum. In this review we have highlighted a few instances where genetic testing has demonstrated a link between over/under-expression of particular genes and the severity of side effects. What is needed now is a much better understanding of the mechanisms underlying platinum toxicity and the role that genetics plays in the experience of side effects.

Abbreviations

ADL	Activities of daily life
ANC	Absolute neutrophil count
AUC	Area under the curve
bpm	Beats per minute
BSA	Body surface area
CINV	Chemotherapy induced nausea and vomiting
CrCl	Creatinine clearance
DLT	Dose-limiting toxicity
GFR	Glomerular filtration rate
5-HT	5-Hydroxytryptamine
Hgb	Hemoglobin
LFT	Liver function test
NCI	National Cancer Institute of the USA
NADPH	Nicotinamide adenine dinucleotide phosphate
NK ₁	Neurokinin 1
PSN	Peripheral sensory neuropathy
ROS	Reactive oxygen species
WBC	Whole blood cell

Conflicts of interest

There are no conflicts to declare.

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