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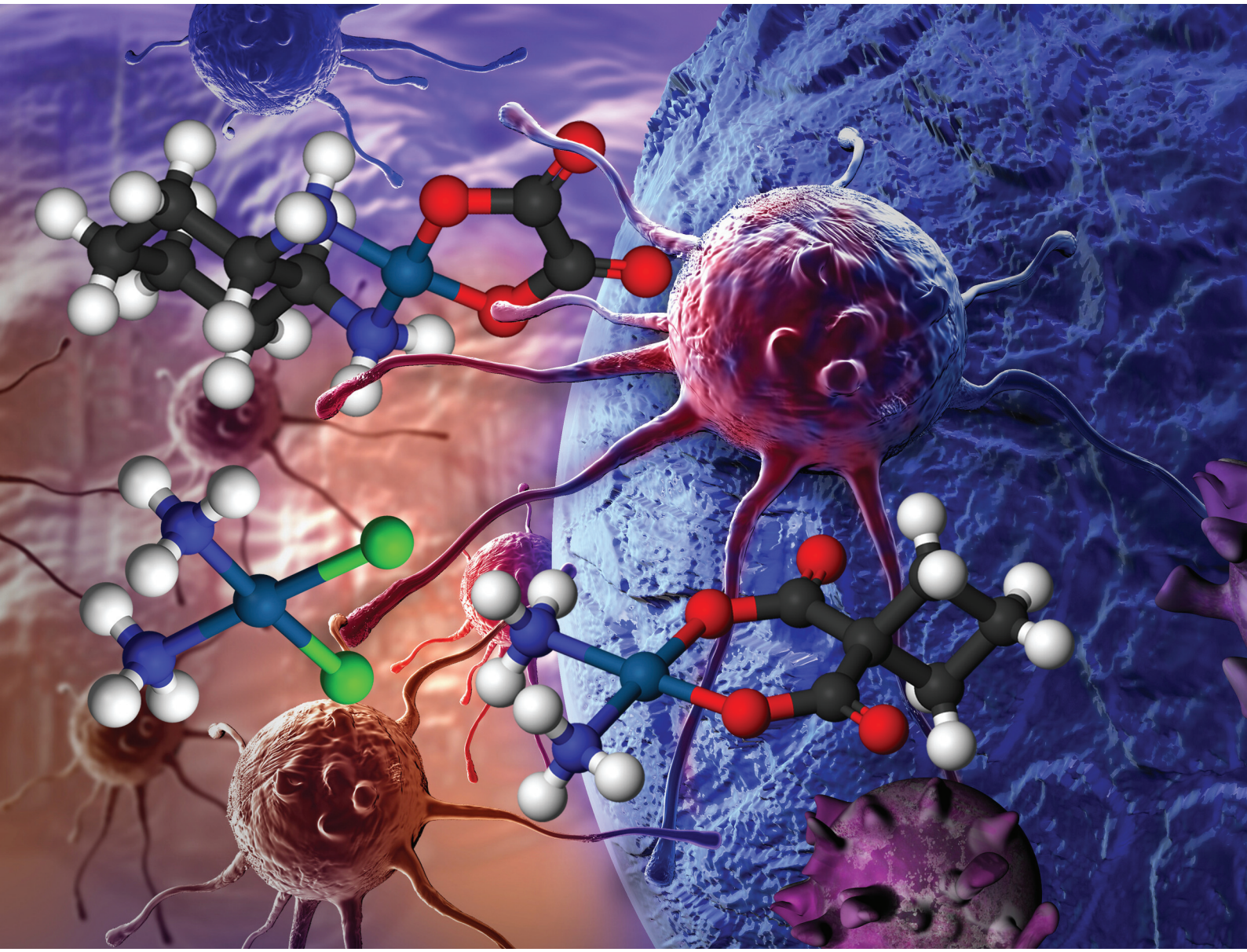

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PERSPECTIVE

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A chemical perspective on the clinical use of platinum-based anticancer drugs

Shoohb Alassadi, [a] Michelle J. Pisani [b] and Nial J. Wheate *[a]

Platinum drugs have been a mainstay of cancer chemotherapy since the introduction of cisplatin in the 1970s. Since then, carboplatin and oxaliplatin have been approved world-wide and nedaplatin, lobaplatin, heptaplatin, dicycloplatin, and miriplatin have been approved in individual countries. The three main platinum drugs are not used in isolation but are combined in chemotherapy protocols from a range of 28 drugs that include: anthracyclines, alkylating agents, vinca alkaloids, antimetabolites, topoisomerase inhibitors, taxanes, and monoclonal antibodies. Interestingly, they are not yet used in combination with tyrosine kinase inhibitors or proteasome inhibitors. How platinum drugs are formulated for administration to patients is important to minimise aquation during storage and administration. Cisplatin is typically formulated in saline-based solutions while carboplatin and oxaliplatin are formulated in dextrose. Pharmacokinetics are an important factor in both the efficacy and safety of platinum drugs. This includes the quantity of protein-bound drug in blood serum, how fast the drugs are cleared by the body, and how fast the drugs are degraded and deactivated. Attempts to control platinum pharmacokinetics and side effects using rescue agents, macrocycles, and nanoparticles, and through the design of platinum(IV)-based drugs have not yet resulted in clinically successful outcomes. As cancer is predominantly a disease of old age, many cancer patients who are administered a platinum drug may have other medical conditions which means they may also be taking many non-cancer medicines. The co-administration of non-cancer medicines to patients can potentially affect the efficacy of platinum drugs and/or change the severity of their side effects through drug–drug interactions.

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Introduction

Platinum-based drugs have been a key component of oncology since the approval in the 1970s of cisplatin.[1] This was followed by carboplatin in the 1980s[2] and oxaliplatin in the 1990s (Fig. 1).[3] These three drugs have broad world-wide approval but there are a number of other drugs which have approval in single nations. These include nedaplatin and heptaplatin which were approved in the 1990s, lobaplatin and miriplatin in the 2000s, and dicycloplatin in the 2010s (see Fig. 1).[4,5]

All platinum agents act as pro-drugs, in that they require the removal of their labile chloride or carboxylate ligands, through their displacement by water, before they can bind their cellular target, DNA. When binding to DNA, platinums predominantly do so through the formation of a coordination bond at the N7 site of guanosine residues. Simultaneous binding at a second, adjacent nucleotide, typically another guanosine base, results in significant bending and unwinding of the DNA which prevents transcription and replication. The cascade effect of this binding is the induction of apoptosis, a form of programmed cell death.[6,7]

Platinum drugs have a wide application across cancer types with a 2018 study demonstrating that 46% of cancer hospital in-patients who receive chemotherapy receive a platinum-based drug, with some patients even being administered two or three drugs at some stage of their treatment journey.[8] A 2019 study found that 25% of chemotherapy protocols included a platinum drug and the drugs are used for 24 specific cancer types including: head and neck, gynaecological, respiratory, upper gastrointestinal, urogenital, colorectal, and breast cancers, and various lymphomas, sarcomas, and multiple myelomas.[9]

When developing and examining platinum-based drugs it can be easy for chemists to consider only the fundamental chemistry of platinums (chemical structure, aquation, and DNA binding) without knowledge and consideration for the chemistry behind how they will be/are used in the clinic. In this review we provide a chemical perspective on the clinical use of platinum drugs with a focus on their use in combination with other chemotherapy agents, their dosage formulation for administration, their pharmacokinetics, and drug–

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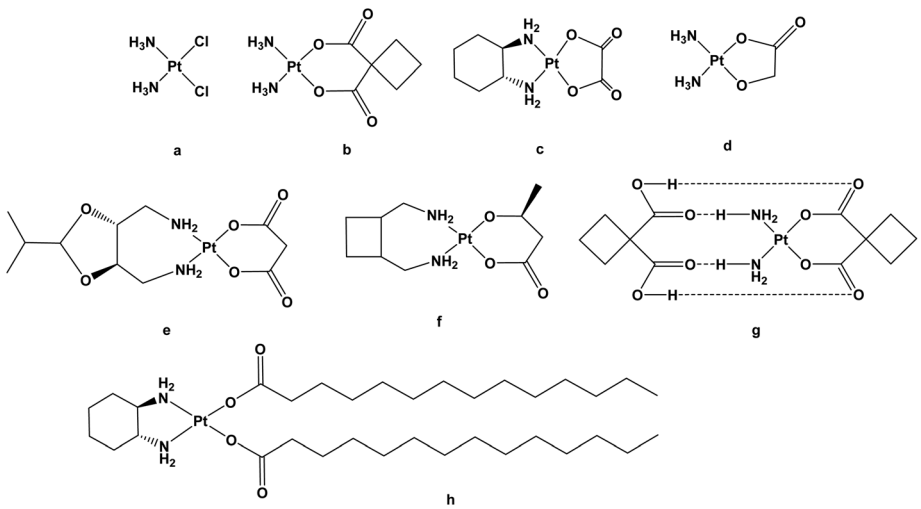

Fig. 1 The main platinum drugs that have broad world-wide approval: (a) cisplatin; (b) carboplatin; and, (c) oxaliplatin; and the drugs that are approved in single nations (d) nedaplatin, Japan; (e) heptaplatin, Korea; (f) lobaplatin, China; (g) dicycloplatin, China; and (h) miriplatin, Japan.

drug interactions. For each section, we also describe the opportunities we see for chemists to improve the clinical delivery of platinum drugs.

Co-administered chemotherapy drugs with platinums

When developing platinums in the laboratory drug efficacy is examined using *in vitro* (cell based) and *in vivo* (animal based) models. Often, chemists will use these models to assess new platinum compounds as single agents, which is not representative of their use in the clinic; there are no chemotherapy protocols that include just a platinum drug.[9] Instead platinums are administered in combination with more than 28 different chemotherapy agents across eight different classes of drugs (Table 1 and Fig. 2).[9]

Table 1 List of chemotherapy agents, organised by drug class, that are commonly co-administered with platinum drugs based on Australian medical oncology EviQ protocols (publicly accessible *via* http://eviq.org.au)

Anthracyclines	**Antimetabolites**	**Monoclonal antibodies**
Doxorubicin	Capecitabine	Atezolizumab
Doxorubicin pegylated liposomal	Fluorouracil	Bevacizumab
Epirubicin	Gemcitabine	Cetuximab
Vinca alkaloids	Methotrexate	Durvalumab
Vinblastine	Pemetrexed	Ipilimumab
Vinorelbine	**Taxanes**	Nivolumab
Topoisomerase inhibitors	Docetaxel	Panitumumab
Irinotecan	Paclitaxel	Pembrolizumab
Alkylating agents	**Other drugs**	Pertuzumab
Cyclophosphamide	Bleomycin	Trastuzumab
Ifosfamide	Dactinomycin	
	Etoposide	

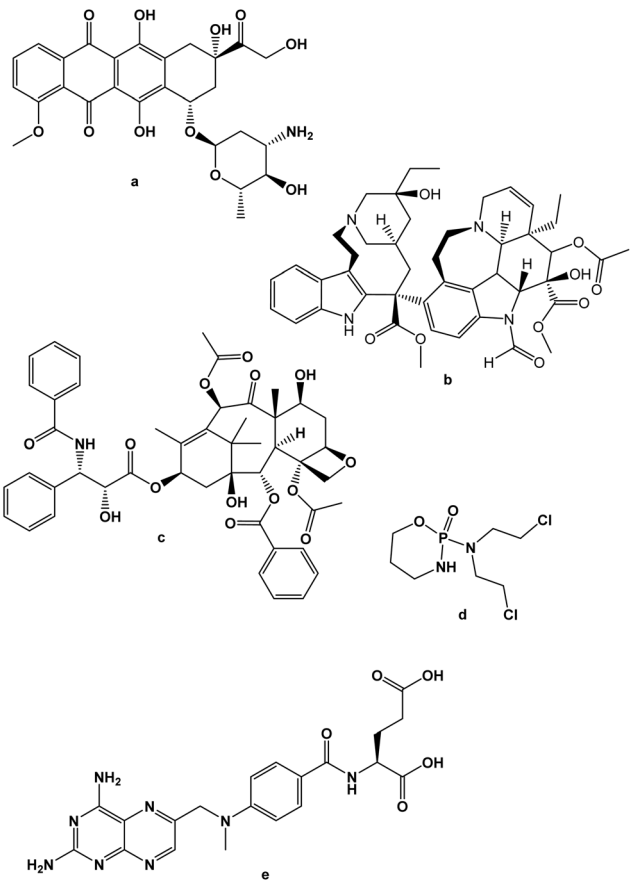

Fig. 2 The chemical structures of representative drugs that are co-administered with platinum drugs showing (a) doxorubicin, (b) vinblastine, (c) paclitaxel, (d) cyclophosphamide, and (e) methotrexate.

These drugs are combined with platinums to utilise their different mechanisms of action, which range from microtubule binding by taxanes (*e.g.* paclitaxel)[10] and vinca alka-

loids (*e.g.* vinblastine);[11] DNA alkylating agents (*e.g.* cyclophosphamide);[12] topoisomerase binding by anthracyclines (*e.g.* doxorubicin),[13] binding of key enzymes needed in the production of chemicals for DNA synthesis (*e.g.* methotrexate against dihydrofolate reductase);[14] to the monoclonal antibody drugs that target key cell receptors and their ligands, such as: programmed cell death ligand 1 (atezolizumab),[15] cytotoxic T-lymphocyte-associated antigen 4 (ipilimumab),[16] human epidermal growth factor 2 (trastuzumab),[17] or vascular endothelial growth factor (bevacizumab).[18]

Despite their age, platinums remain as important in the clinic today as they have in the past. Rather than being replaced by new chemotherapy drugs, they are routinely used in combination with those drugs; for example, the monoclonal antibody drugs which entered the clinic in the past decade. However, the 2000s saw the introduction of two new chemotherapy drug classes; the tyrosine kinase inhibitors (TKIs, *e.g.* gefitinib and imatinib),[19] and the proteasome inhibitors (*e.g.* bortezomib and carfilzomib), but there are no chemotherapy regimens that include a combination of platinums with TKIs or proteasome inhibitors. In fact, at the time of writing, we were unable to find any published clinical trial results that examined platinums with either TKIs or proteasome inhibitors.

When developing new platinum compounds, chemists need to better mimic the clinical application of the drugs when undertaking *in vitro* and *in vivo* experiments. Given screening experiments are completed using specific cancer cell lines or with specific tumour xenografts, chemists should select appropriate co-administered chemotherapy drugs for those cancer types and plan their experiments accordingly. This is important because there may have been instances in the past where researchers have decided not to continue pre-clinical development of a platinum compound, because, when tested in isolation, they obtained negative results or results that showed no significant improvement on cisplatin. If screening experiments include the addition of suitable chemotherapy drugs, these could better predict what may happen in the clinic and potentially show that the compounds work synergistically. Further, if new advances are to be made, new approaches to the design and testing of drug combinations needs to be embraced.

Also, given the lack of clinical trials data regarding synergies of TKIs and proteasome inhibitors with platinums, future laboratory-based studies that examine existing or new platinum drugs with TKIs and proteasome inhibitor drugs could provide the data needed to justify human clinical trials of these combinations.

Dosage formulation of platinums

Cisplatin, carboplatin, and oxaliplatin are all exclusively delivered as intravenous (IV) infusions. As such, it is important to understand how the chemistry of their solutions affects the stability of the drugs and blood upon administration.

Blood cells and blood serum act as an osmotic system. Water molecules can be transported across cell membranes in response to high and low concentrations of dissolved components (salts, peptides and proteins, nutrients, *etc.*) in the blood serum. The body tries to maintain isotonic blood serum, which is defined as the state where the osmotic pressure due to the dissolved components is the same both outside and inside the blood cells, and is achieved at a blood serum concentration of 308 milliOsMolar (mOsM).[20] Solution concentrations above this value are defined as hypertonic and concentrations below this value are referred to as hypotonic solutions. A hypotonic solution can cause human cells to expand and undergo lysis (breaking of the cells) which is irreversible. Conversely, a hypertonic solution will cause the cells to crenate (shrink).

To maintain physiological function it is important for blood serum to remain as close to isotonic as practical, although short duration, and small, fluctuations from 308 mOsM are tolerable. Blood serum osmosis is the basis of sports (*e.g.* Gatorade® and Powerade®) and rehydration (*e.g.* Hydrolyte™) drinks,[21] and the treatment of cholera using oral rehydration salts where antibiotics are not available.[22]

In preparing a platinum intravenous infusion dosage formulation it is necessary to add additional chemicals, called excipients, to the solution so that it mimics the osmotic concentration of human blood serum. The concentration of platinum drugs in IV infusions is not sufficient by themselves to deliver an osmotically safe solution. Not only do the excipients added to the IV infusion with the platinum drugs need to give the solution a close-to isotonic concentration, they must also be compatible with the human body at those concentrations. For example, it would be inappropriate to prepare a 308 mOsM solution of potassium chloride as the patient would likely experience potassium toxicity (called hyperkalaemia).[24] Excipient solutions routinely used to prepare IV infusions are given in Table 2.

Drugs administered *via* IV infusion do not need to be perfectly isotonic. Given the relatively low concentration of drugs needed, it is usually sufficient to dissolve the platinum drugs

Table 2 Common blood serum osmotic solutions with their key excipients that are compatible and incompatible for use in the preparation of small molecule platinum drug intravenous infusions[23]

Name	Description
Common solutions	
Saline	0.9% w/v solution of sodium chloride
Dextrose	5% w/v solution of D-glucose
Glucose in saline	A combination of glucose and saline, where the sodium chloride concentration is not lower than 0.45% w/v
Not used solutions	
Hartmann's	Also known as compound sodium lactate, it is a combination of sodium chloride, sodium lactate, potassium chloride, and calcium chloride
Plasma-lyte148	A combination of sodium chloride, sodium gluconate, sodium acetate, potassium chloride and magnesium chloride
Ringer's	A combination of sodium chloride, potassium chloride, and calcium chloride

in an isotonic solution of suitable excipient(s) to produce a slightly hypertonic solution.

In preparing platinum drug intravenous solutions, it is important to select the correct excipient for each specific drug, as dissolution with the incorrect excipient can increase the quantity of aquated drug and result in toxic concentrations or toxic derivatives being formed. Cisplatin should ideally be dissolved in saline to help slow partial aquation of the drug, whereas the preparation of carboplatin in saline can potentially increase its rate of aquation or result in its transformation to cisplatin. Interestingly, research has shown that saline may actually be a suitable solvent for the formulation of carboplatin. When carboplatin was dissolved and stored in 0.9% saline, the drug was stable for periods up to 7 days at 4 °C, with less than 6% loss.[25] Whether the 6% is significant will depend on what transformation products are formed, and is worthy of further investigation.

The Australian Injectable Drugs Handbook recommends that cisplatin be prepared in saline or glucose in saline solutions to a pH between 3.5 and 4.5. For carboplatin, only dissolution in glucose is recommended to a pH between 4 and 7, and for oxaliplatin, dissolution in glucose to a pH between 3.5 and 7.[23]

An additional important consideration in the formulation of oxaliplatin is that it can not be prepared with the chemotherapy drug fluorouracil, due to potential irreversible interactions between the two drugs (Fig. 3).[23] Where oxaliplatin and fluorouracil do need to be administered together, it is recommended that oxaliplatin is administered first, before the IV line is flushed with glucose after which fluorouracil can be administered. An explanation is not provided as to why but may be due to the active component of oxaliplatin potentially binding at the N3-site of fluorouracil. Interestingly, co-administration of cisplatin or carboplatin with fluorouracil is not contraindicated.[23]

However, a contraindication is given for the administration of cisplatin/carboplatin and mesna, a drug usually prescribed to decrease the risk of bleeding from the bladder (Fig. 3). The available thiol functional group of mesna is capable of displacing both the labile and carrier am(m)ine groups of both cisplatin and carboplatin.

The Japan-only drug miriplatin is an exception when it comes to its injectable formulation for administration. While all other platinum drugs are delivered as an intravenous infusion, miriplatin is delivered *via* intra-arterial infusion. This means the drug is injected in arteries which is a higher risk form of administration. Unlike the other platinum drugs, miriplatin is not prepared in saline or glucose solutions, but is instead formulated as an oily suspension in Lipidol; a solution that comprises four different lysophosphopilids and calcium silicate (Fig. 4). Preparation in Lipidol is due to miriplatin's very poor water solubility (less than 1 mg mL^{-1}). Recently, Lipidol formulation of cisplatin as an injectable emulsion has been examined.[26]

Platinum drugs are administered to patients as infusions (long delivery time, large volume) rather than as bolus injections (short injection time and small volume). The selection of infusion-based formulations is, in part, due to the poor solubility of the platinum drugs (Table 3); the volumes required of these drugs are too large for a typical bolus (≤5 mL) injection from a syringe.[27] As such, if their solubility could be improved then this may open up new clinical avenues for their delivery. Infusions are also currently selected over injections as a way to manage the drugs' pharmacokinetics and side effects; for example, the nephrotoxicity of cisplatin.

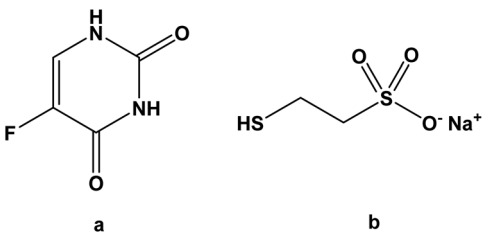

Fig. 3 The chemical structures of contraindicated medicines with platinum drugs showing (a) 5-fluorouracil and (b) mesna.

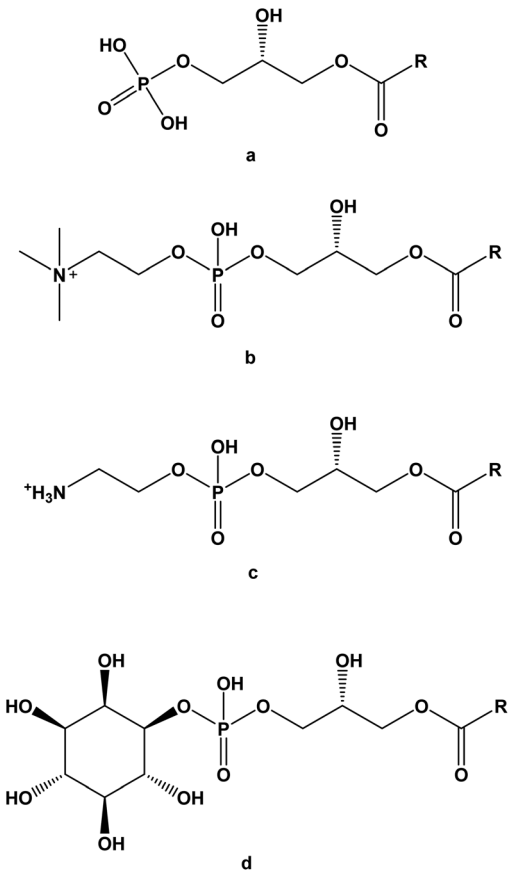

Fig. 4 The chemical structures of the four lysophospholipids used in the formulation of miriplatin, showing (a) lysophosphatidic acid, (b) lysophosphatidylcholine, (c) lysophosphatidylionsitol, and (d) lysophosphatidyethanolamine, where R is a variable fatty acid chain.

Table 3 The solubilities of the three main platinum drugs, and the minimum infusion volumes needed for a typical patient (assumed body surface area of 1.8 m^2) across the range of recommended doses

Drug	Solubility	Administered dose	Minimum viable infusion volume based on solubility
Cisplatin	1 mg mL^{-1} (3.3 mM)	20–100 mg m^{-2}	36–180 mL
Carboplatin	10 mg mL^{-1} (26.9 mM)	800 mg m^{-2}	144 mL
Oxaliplatin	6 mg mL^{-1} (15 mM)	85–130 mg m^{-2}	26–39 mL

Interestingly, while dicycloplatin in clinical trials was administered to patients *via* an intravenous infusion,[28,29] there is a recent case report of the successful treatment of a patient using a hard capsule formulation of dicycloplatin for oral administration.[30] The result is surprising given the high acid concentration in the stomach, which is likely to protonate the carboxylate ligands and facilitate their early release from the drug. It will be important to see if this oral formulation is effective in full human clinical trials. Chemical studies on the stability of dicycloplatin in various gastric fluids is warranted.

A final aspect for consideration in the formulation and administration of platinum drugs is the choice and use of injection equipment. The packaging of all three main platinum drugs comes with a warning against using aluminium-based needles and joints as aluminium is known to cause black precipitates from the solution.[31] While it appears the reaction has never been studied in detail, it would be reasonable to assume that the reaction involves the catalytic reduction of platinum(II) back to metal. There are several methods by which Pt(IV) and Pt (II) can be converted to Pt(0), including catalytic reduction by zinc powder at room temperature.

Overall, there is an opportunity to improve the delivery of carboplatin and oxaliplatin if chemists are able to develop stable formulations that can be prepared in saline rather than glucose. Many cancer types are known to take up and catabolize glucose at rates higher than normal tissue.[32] In theory, the deprivation of glucose to cancers can therefore aid in treatment,[33] and the formulation of carboplatin/oxaliplatin in saline can potentially make treatment more effective. As some advanced cancer targeting systems can also be designed based on targeting glucose receptors,[34] then formulation in this sugar can potentially make that delivery method ineffective (see pharmacokinetics section).

There is also an opportunity for chemists to improve the solubility of platinum drugs so that clinicians can deliver these drugs as injections rather than infusions if they so choose. Typically, the addition of water solubilising functional groups and the creation of a salt form of a drug are ways to increase solubility,[35] but neither is suitable for platinum drugs. Instead, the development of cocrystals of platinum drugs may be an appropriate avenue to explore. Pharmaceutical cocrystals are defined as solids that are neutral crystalline single-phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts.[36] Formulation in the solid state with one or more soluble excipients imparts higher solubility on the drug molecules; this technique could potentially be applied to new and established platinum drugs.

Pharmacokinetics of platinum drugs

The ability of a platinum drug to treat cancer is a function of how much of the administered dose reaches the cancer cells intact and how well it induces apoptosis once it binds to cellular DNA. The amount of drug that reaches cells is directly related its pharmacokinetics (commonly abbreviated as PK) which is defined as drug absorption, distribution, metabolism, and excretion (*i.e.* what the body does to the drug). An important aspect of platinum drug pharmacokinetics is how long they stay in systemic circulation. Fast clearance *via* the kidneys out of the blood stream by the body can result in a lower uptake of drug into cancer cells.

Three important aspects of platinum blood serum concentration are T_{max}, half-life, and area under the curve (AUC). The term T_{max} refers to the amount of time after administration that it takes for a drug to reach its highest concentration (C_{max}) in blood serum. The half-life of a drug is the time taken for the concentration of a drug in blood serum to drop by 50% and AUC, which is also called the plasma concentration time profile, is a measure of total systemic exposure of a drug. It is measured in milligram hours per litre (mg h L^{-1}). Area under the curve is especially important for carboplatin as this is the parameter by which the dose of the drug is controlled for each patient.[9,37] When administering carboplatin, doctors are advised to aim for an AUC of between 1.5 and 8 mg h L^{-1} depending on the cancer type.[9]

These factors are all important as they dictate how long the drug is available to be taken up by cancer cells. Shorter T_{max} and half-life, and lower AUC, values result in reduced drug uptake, and from this, reduced efficacy. Increasing blood circulation times can potentially increase the efficacy of platinum drugs. For example, a slow release of low dose (30 μg) cisplatin from a hydrogel-based formulation was found to reduce tumour size in an ovarian mouse model to the same extent as the intraperitoneal administration of high dose (150 μg) free cisplatin.[38] Likewise, encapsulation of cisplatin with a macrocycle was found to have no effect on the T_{max}/C_{max} of the platinum drug, but did increase the AUC, and from this, overcome resistance in a cisplatin animal model.[39,40]

Another important aspect of platinum pharmacokinetics is whether the drugs reach cancer cells intact. As stated previously, all platinum drugs are prodrugs that require the

removal of their labile ligands (chlorides/carboxylates) before they are able to bind their cellular target, DNA. The carrier am(m)ine ligands, are required to remain coordinated to the platinum atom for the drugs to be effective; removal of the carrier ligands results in platinum–DNA adducts which are not able to induce apoptosis.

Platinum is rapidly bound by soft nucleophiles which are typically sulfur containing residues in human peptides and proteins;[41] this includes the amino acids methionine and cysteine. In particular, the antioxidant peptide, glutathione, which comprises glycine, cysteine, and gamma-glutamic acid residues,[42] is known to rapidly bind to platinum drugs and can be found in high concentrations in some cancers. Platinum drug binding by thiols is significant as it is capable of displacing both the chloride/carboxylate ligands and the am(m)ine carrier ligands. Pharmacokinetically, binding by thiol peptides and proteins can result in insufficient drug reaching cancer cell DNA intact and is one mechanism by which tumours develop resistance to platinum drug treatment.[43]

There are three main ways in which the pharmacokinetics of platinum drugs can be improved. The first is through an increase in blood serum circulation life-times; second, by reducing the degradation/deactivation of the drugs after administration, and third, through better targeting of the drugs to cancer cells.

In the blood stream, platinum drugs can rapidly bind to proteins and peptides, which affects their residence time and deposition in the body. In fact, one day after administration, 65 to 98% of the administered cisplatin dose is blood serum protein bound.[44] Similar figures are also observed for oxaliplatin (up to 98% protein bound) but protein binding by carboplatin is significantly lower at 25–50%.[45] Human serum albumin (HSA) is the most abundant protein in blood serum at a concentration of 35–50 mg mL^{-1} (0.53–0.75 mM) and is a significant contributor to the maintenance of blood serum osmotic balance. In addition to providing osmotic pressure, HSA is also used by the body to transport metal ions (*e.g.* Ca^{2+}, Zn^{2+}, Cu^{2+}) and waste (*e.g.* bilirubin), binding of endogenous molecules like steroids and long chain fatty acids, and as an antioxidant.[44]

Human serum albumin is known to bind to a range of drug molecules and with a number of thiol residues, it readily binds platinum drugs.[46] Originally it was thought that cisplatin bound to HSA at disulphide linkage sites through cysteine residues,[46] but it is now known that platinums, and especially cisplatin, can also bind through methionine (met) and histidine (his) residues. While more than nine platinum binding sites have been discovered on HSA, from X-ray crystallography the two most dominant sites are at the his105 and met329 residues.[47] Binding can be monodentate, through the loss of a chloride ion for cisplatin, or at methionine residues through a bidentate *S*,*N*-chelate.

There continues to be debate with regard to the implications of platinum drug binding to HSA. Some have hypothesised that HSA acts as a reservoir for the slow release of the drugs while others believe that once bound to HSA, the drugs are effectively deactivated.[47] It is known that HSA binding does reduce the urinary excretion of platinum,[48] and based on that, some researchers have developed platinum-derivatives that only interact non-covalently with the protein, thus allowing HSA to act as a longer delivery time vehicle.[49]

Chemistry plays an essential pharmacokinetic role in protecting the drugs from degradation and deactivation, early excretion, and reducing their side effects. Rescue agents have been examined as possible co-administered drugs to reduce the side effects, particularly the nephrotoxicity, of platinums. For a full review on the side effects of platinum drugs, see ref. 37.

The three most investigated rescue agents are sodium thiosulfate (normally used for the treatment of cyanide poisoning),[50] amifostine (normally used to protect tissue against radiation damage),[51] and diethyldithiocarbamate which is normally used to treat nickel and cadmium poisoning (Fig. 5).

The nephrotoxicity of cisplatin is thought to be due to the aquated form of the drug binding to intracellular nucleophiles in renal tubes. This leads to the depletion of cellular thiols and cell death or damage.[52] It has been hypothesised that reducing the rate of platinum drug aquation in the blood stream can result in reduced side effects and that a reduction of the aquation rate can be achieved through "neutralisation" of the drugs by binding the rescue agents.[52] It should be noted, however, that the rescue agents can also have their own side effects, like nausea, vomiting, and hypotension (low blood pressure), which may be additive with the platinum drug side effects.[53]

Each rescue agent contains thiol groups which can bind to cisplatin through the displacement of the chloride ligands,[54]

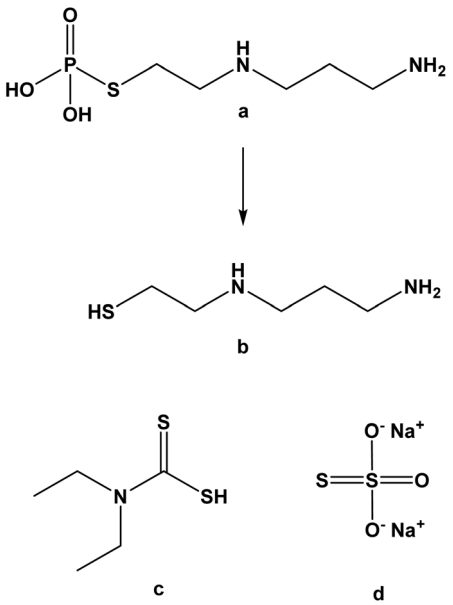

Fig. 5 The chemical structures of the thiol-containing rescue agents that have been clinically examined to reduce the side effects of platinum drugs, showing (a) amifostine, (b) 2-((3-aminopropyl)amino)ethane-1-thiol, the active metabolite of amifostine, (c) diethyldithiocarbamate, and (d) sodium thiosulfate.

although there is evidence that the rescue agents can also displace the am(m)ine carrier ligands of cisplatin and carboplatin as well.[55] Because of the nature of the dicarboxylate ligands in carboplatin and oxaliplatin, rescue agents are typically better at slowing the aquation of cisplatin when compared with those other two drugs.[56]

While both sodium thiosulfate and diethyldithiocarbamate can both reversibly bind platinum drugs in their natural state, amifostine requires hydrolysis by the membrane-bound alkaline phosphatase enzyme before it is able to bind to cisplatin (see Fig. 5).[53]

Despite three decades of rescue agents research, as of 2021 the use of thiol-based rescue agents for platinum drugs is not recommended by any oncology guideline committees, nor are they routinely prescribed in clinical practice.[57]

Other than thiol-containing rescue agents, macrocycle encapsulation of platinum drugs has also been examined as a mechanism to protect drugs from thiol binding and deactivation, although none have been taken into human clinical trials. The naturally occurring cyclodextrins and the synthetic macrocycles: cucurbiturils, calixarenes, and pillararenes are all candidate families.[58] Each macrocycle has a central cavity from which platinum drugs can be stored and released. Formation of a host–guest complex between the drug and the macrocycle is through hydrophobic interactions within the cavity and ion-dipole and/or hydrogen bonding to the macrocycles portal (s).[58]

Encapsulation within a macrocycle therefore provides steric protection to the drug, until such time it is released. For example, oxaliplatin has been shown to form a host–guest complex with cucurbit[7]uril, with the subsequent supramolecular complex demonstrating greater drug stability during storage, and reduced solution reactivity with both guanosine and methionine.[59]

One way to increase the circulation time of platinum drugs in blood serum is through their conjugation onto the surface, or within, nanoparticles. This helps because larger particles are cleared by the kidneys slower than small molecules. The benefit of improved circulation time can be reduced side effects and better uptake by cancer cells. For example, the AUC of a nanoparticle formulation of the active component of cisplatin was 65-fold higher in an animal model when compared with normal cisplatin, which resulted in reduced nephrotoxicity and neurotoxicity.[60]

A second pharmacokinetic benefit of conjugation of platinum drugs to nanoparticles is passive targeting of solid tumours through the enhanced permeability and retention effect (EPR). In contrast to normal, healthy tissue, often cancers have leaky vessels and pores within which nanoparticles can become trapped. Because of this, nanoparticle formulations of a drug can accumulate preferentially on the surface of tumours after which they are taken up by cells *via* endocytosis.[61]

The active components of cisplatin and oxaliplatin have been conjugated to the surface of gold[62,63] and gold-coated iron oxide nanoparticles, the latter of which can also be potentially directed to the site of solid tumours using external magnetic fields.[64] The active components of cisplatin and oxaliplatin have also been attached to, and within, the surface of dendrimers[65] and carbon nanotubes.[66] While these have been shown to be scientifically interesting, these types of platinum drug nanoparticle formulations have not progressed to clinical trials.

In contrast, micelle-, liposome-, and polymer-based nanoparticle formulations of platinums have reached the clinical trials stage, with one formulation (LiPlaCis®) still under development in 2022.[67] Miriplatin is an example of an approved nanoparticle form of a platinum drug. Failed examples include Lipoplatin, Nanoplatin, Aroplatin (a drug similar in structure to miriplatin, but with a shorter fatty acid chain), Stealth Liposomal Cisplatin, and ProLindac (see Fig. 6 for examples). Pharmacokinetically, while these types of formulations are able to increase blood serum circulation times, and target tumours through the EPR, the biggest hurdle to their effectiveness has been the timely release of the platinum drug from the delivery vehicle.

The pharmacokinetics of platinums can potentially be modified by tethering tumour targeting molecules to the drugs. This approach can take advantage of the fact that some proteins/receptors are over-expressed, or only expressed, on the surface of specific cancer cells. This ensures binding and uptake, usually by receptor-mediated endocytosis,[68] into cancer cells while leaving healthy tissue intact. An example is the conjugation of trastuzumab to the active component of cisplatin to target human epidermal growth factor 2-overexpressing cancer cells.[69]

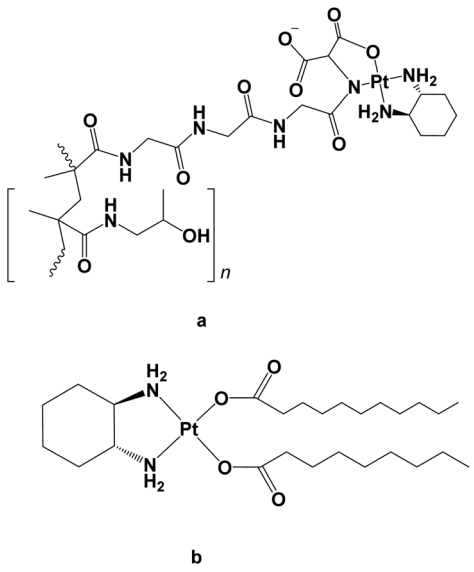

Fig. 6 Examples of nanoparticles formulations of platinum drugs showing (a) ProLindac which is a polymer-bound formulation of the active component of oxaliplatin and (b) Aroplatin which is a liposomal formulation of the active component of oxaliplatin. These types of formulations can be used to tune the pharmacokinetics of platinum drugs.

Another method for addressing the pharmacokinetic short comings of platinum drugs, has been the design and development of platinum(IV) analogues.[70,71] The primary pharmacokinetic benefits of this family of drugs is their inertness within the blood stream, and their bioavailability when administered *via* an oral dosage formulation. Platinum(IV)-based drugs are aquated in the blood stream at very low levels, especially when compared with cisplatin,[72] and remain intact until they are taken up by cells at which point they undergo two election reduction which results in the loss of the axial ligands and the formation of a platinum(II) product (Fig. 7). Reduction is thought to occur *via* ascorbic acid or glutathione.[70] While platinum(IV) drugs still rapidly bind blood serum proteins,[73] the drugs have more mild side effects; more carboplatin-like than cisplatin-like.[74] More recently, platinum(IV) drugs that only interact non-covalently with serum proteins have been developed.[49]

There are a number of platinum(IV) drugs that have been examined in human clinical trials, including satraplatin, LA-12, ormaplatin, and iproplatin (see Fig. 7).[75] Of these, satraplatin was the most successful, having shown efficacy with the steroid prednisolone in Phase III trials for pretreated, metastatic, castrate resistant, prostate cancer.[74] While the oral delivery method provided patients a better quality of life, it was not found to improve overall survival better than current treatments, and so, it was not ultimately approved for use.[74]

The failure of satraplatin has led to the development of further platinum(IV)-based complexes that utilise biologically relevant molecules in the axial positions. These biomolecules can either improve drug targeting and uptake, help to overcome resistance, or provide synergistic co-delivery with other chemotherapy drugs (Fig. 8).

An example of using the axial ligands for active drug delivery is the use of glycosylated platinum(IV) to target cancer cells that overexpress glucose receptors.[76] Platinum(IV) drugs that incorporate axial ligands capable of targeting glutathione-*s*-transferase[71] and glutamate-cysteine ligase[77] have shown an ability to reduce intracellular glutathione levels in cancer cells. Examples of platinum(IV) drugs where other active chemotherapy drugs have been attached as the axial ligands include tamoxifen,[78] gemcitabine and paclitaxel,[71] and chlorambucil.[79] A platinum(IV) drug has even been developed that conjugates two different platinum complexes together.[80] Most recently, a platinum(IV) drug has been developed that incorporates a ligand known to be cytotoxic against cancer stem cells.[81]

One draw-back to the inclusion of biologically relevant molecules into platinum(IV) drugs is the limited platinum drug to additional biological molecule ratio that can be obtained. Given there are two axial positions, then the best ratio is 1 : 2. This means that the other biological molecule must be effective at doses that are only up to double the delivered platinum dose. If higher doses of the biological molecules are needed for them to be effective, then there may be no synergism with the platinum drug. An opportunity is therefore present to develop platinum(IV) drugs in such a way that the

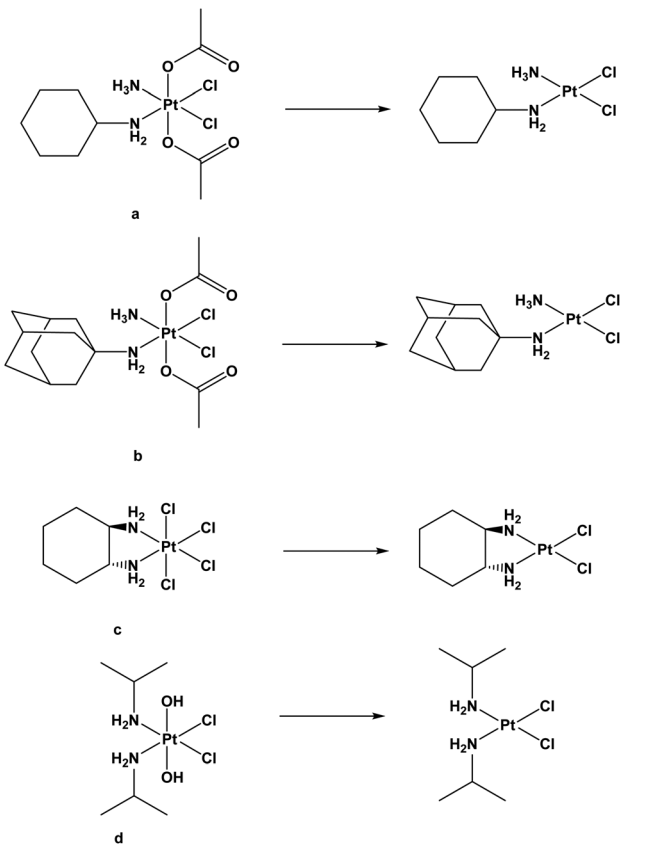

Fig. 7 The chemical structures of the platinum(IV) drugs that have been examined in human clinical trials, showing: (a) satraplatin, (b) LA-12, (c) ormaplatin, (d) iproplatin, and their respective reduction products.

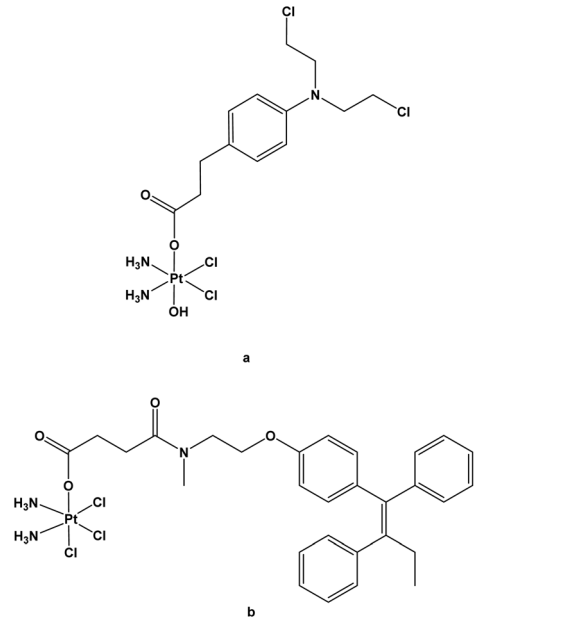

Fig. 8 Examples of platinum(IV)-based drugs that have incorporated other biologically relevant molecules, showing the inclusion of (a) chlorambucil and (b) tamoxifen.

ratio of platinum to other additional biological molecule can be tuned higher.

Platinum drug–drug interactions with non-cancer medicines

The final aspect of clinical platinum drug use focusses on how other medications that patients may be taking can affect the safety and efficacy of their platinum drug. Cancer is predominantly a disease of old age with 60% of cancer patients over the age of 65.[82] At this age it is common for patients to have a number of medical conditions, other than cancer, which are called comorbidities (*e.g.* cardiovascular disease, diabetes, osteoporosis, poor liver or kidney function). With comorbidities comes the need for patients to take a range of other non-cancer medicines. A patient who takes between 5 and 9 different drugs per day is said to have polypharmacy and a patient who takes 10 or more drugs per day is said to have hyper-polypharmacy.[83,84]

This is an issue for chemotherapy, and especially for platinum-based chemotherapy, given that 46% of hospital chemotherapy patients are administered a platinum,[8] and because 35% of elderly (70+ years of age) cancer patients have polypharmacy.[85] Because of this, 30–75% of these patients are likely to experience changes in efficacy and side effects due to drug–drug interactions with their platinum agents.[86,87] A drug–drug interaction is when a patient's response to a drug is modified by the taking of one or more other drugs at the same time.

Drug–drug interactions between platinums and other non-cancer medicines can have four different effects. The non-cancer medicine(s) can increase/decrease the efficacy of the platinum, the non-cancer medicine(s) can increase/decrease the side effects of the platinum, the platinum drug can increase/decrease the efficacy of the non-cancer medicine(s), and the platinum drug can increase/decrease the side effects of the non-cancer medicine(s).

Potentially the biggest problem with drug–drug interactions for platinums is reduced chemotherapy efficacy. In a recent study of more than 2000 ovarian cancer patients treated with carboplatin, it was found there was a direct association between polypharmacy and an increase in mortality within six months of cancer diagnosis.[88] The presumption is that the other medicines reduced the efficacy of carboplatin through drug–drug interactions, leading to more/earlier deaths.

Instead of reducing platinum efficacy, there is some evidence that non-cancer medicines may potentially increase the efficacy of the platinum drugs. For example, lab-based experiments on the co-administration of the antidepressant drugs desipramine and fluoxetine with cisplatin to colon and ovarian cancer cells significantly increased apoptosis when compared with cisplatin alone.[89]

As well as reducing efficacy, non-cancer medicines and other diseases can also increase platinum-associated side-effects. In an observational study that examined the rates of oxaliplatin side effects, it was found that having diabetes resulted in patients experiencing oxaliplatin-induced peripheral neuropathy at a 36% lower cumulative dose of the drug when compared with patients who did not have diabetes.[90] It should be noted that the study did not make it clear what type of diabetes the patients had (Type I or Type 2) or what medicines, if any, the patients were taking for their diabetes.

Drug–drug interactions can be beneficial where they lead to a reduction in the side effects of the platinum drug. For example, in one study researchers examined the effect of the proton pump inhibitor (PPI) drug lansoprazole, used to treat peptic ulcers, on cisplatin-induced nephrotoxicity. The drug primarily works by reducing the amount of acid produced and released by the stomach, but it can also block the action of the human organic cation transporter 2 (hOCT2) protein. As hOCT2 can be used by cisplatin, in part, to enter kidney cells, it was found in cultured cells and rat renal slices that expressed hOCT2, cisplatin accumulation was reduced by 60%.[91] The implication of those results was that co-administration of PPI drugs could potentially be used to reduce the nephrotoxicity of platinum drugs.

A drug–drug interaction between a platinum and another non-cancer medicine can occur in one of four different ways. First the platinum drug can affect the expression of genes that code for the enzymes that are responsible for metabolism in the liver. Second, other drugs can compete with platinums for binding to HSA. Third, other drugs can affect urinary output, and fourth, other drugs can affect the uptake of platinums into various organs and cells.

The primary purpose of the liver is to metabolise nutrients, and drugs, that have been absorbed from the gastrointestinal tract, before the chemicals make their way into systemic circulation in the blood serum; this is called first-past metabolism.[92] Platinum drugs often by-pass first past metabolism as they are injected directly into the blood stream, but for the small number of orally active experimental platinum drugs, such as satraplatin and picoplatin,[93] first-pass metabolism was a factor in their bioavailability and efficacy.

Metabolism in the liver is primarily undertaken by a family of cytochrome P-450 enzymes (CYP450).[94] While there are more than 50 specific CYP450 enzymes they all have common structural features. Most important is the inclusion of a heme-iron group at the centre of the protein, which is the site on the enzymes that is primarily responsible for the oxidative metabolism of molecules.[95]

As platinum drugs target nuclear DNA not just in cancer cells, but also cells in the liver, it is possible that they can affect the gene expression of liver cells, and from this, the type and number of CYP450 enzymes produced. This can then affect the metabolism of any non-cancer medicine(s) that patients are taking. As an example, it was found that both cisplatin and carboplatin are able to change CYP450 mRNA expression in rats, and from this, alter the level of steroid metabolism.[96]

Importantly, it doesn't appear that platinum drugs directly affect the function of CYP450 enzymes. In a study where the

effect of cisplatin, carboplatin, and oxaliplatin on the inhibition of nine different CYP450 enzymes, the researchers found that carboplatin had no effect on any of the enzymes, both cisplatin and oxaliplatin had only a very small effect on the enzyme, CYP2C9, and cisplatin had a minor effect on CYP2B6.[97] These results are not surprising given that binding of the platinum atom to the iron-heme group of the enzymes is unlikely.

The next key drug–drug interaction is the effect that other drugs can have on the serum protein binding of platinum drugs. Because other drugs can also bind HSA, then the presence of other medicines can result in a reduction in the amount of HSA-bound platinum, and from this, change platinum T_{max} and AUC values. For example, the non-steroidal anti-inflammatory drugs meloxicam, ibuprofen, warfarin, and aspirin were found to bind to HSA and subsequently reduce the amount of HSA bound cisplatin by 30–40%.[98]

In some instances, non-cancer medicines can simply affect the pharmacokinetics of platinum drugs without a clear indication as to the cause. For example, antiemetics are medicines that are routinely co-administered with platinums to control their gastrointestinal side effects.[37] In a study that examined the effect of different antiemetics on the AUC of cisplatin it was found that ondansetron reduced the platinum concentration by 19% compared with prochlorperazine.[99] This indicates that the selection of a specific antiemetic can affect the pharmacokinetics, and from that, the efficacy of a platinum drug.

There is a need to better understand the drug–drug interactions of non-cancer medicine(s) with platinum drugs, and chemists can play a key role. Primarily, where a drug–drug interaction is found in the clinic, chemists can collaborate in elucidating the underlying mechanisms of the interaction. This would include examining how different medicines affect platinum binding to serum proteins, not just HSA. Of particular interest is whether there is any binding between platinum drugs and monoclonal antibody-based chemotherapy drugs. It would also include understanding and measuring how platinums affect the metabolism kinetics of non-cancer medicines, including changes to CYP450 levels.

Conclusions

Platinum drugs remain important agents in the treatment of human cancers with chemotherapy. How platinum drugs are used in the clinic can and should drive further research into the development of new platinum drugs and the improved formulation and delivery of existing platinum drugs. Chemists can play a role in the better clinical application of platinums through better *in vitro* and *in vivo* testing of new platinum compounds in combination with the other chemotherapy drugs that are commonly used to treat specific types of cancer. There are also potential opportunities for chemists to develop new dosage formulations of carboplatin and oxaliplatin by improving the solubility of platinum drugs and/or removing the need to prepare IV infusions with glucose. While chemists have already spent considerable time trying to improve the pharmacokinetics of platinum drugs through the development of platinum(IV)-based drugs and through the use of drug delivery vehicles it is essential that we maintain those efforts. Success will result in improved blood circulation times and decreased excretion rates, protection of the drugs from degradation and deactivation, and a reduction in the drugs' side effects, which will significantly improve patient quality of life and drug efficacy. Finally, chemists can play a key role in examining the chemical basis of drug–drug interactions of platinums with any non-cancer medicines that patients may be taking.

Conflicts of interest

There are no conflicts to declare.

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