

Pharmacological profile and clinical features of cisplatin

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Abstract: Cisplatin is currently one of the most widely used anticancer drugs in the world. The unlikely events surrounding the discovery of its anticancer activity, subsequent introduction into the clinic, and continuing research into platinum compounds is the subject of this review.

Key words: cisplatin, anticancer drugs, pharmacology, drug interactions

INTRODUCTION

Chemically, cisplatin is cis-Diamminedichloroplatinum [1, 2, 5, 6]. The drug is a heavy metal platinum complex similar to the bifunctional alkylating agents. It covalently binds to DNA and disrupts DNA function [7].

The compound cis-PtCl₂(NH₃)₂ was first described by M. Peyrone in 1845 (known as Peyrone's salt). In the 1960s, Barnett Rosenberg and van Camp et al. at Michigan State University in the USA discovered that electrolysis of a platinum electrode produced cisplatin, which inhibited binary fission in *Escherichia coli* (*E. coli*) bacteria. The bacteria grew to 300 times their normal length, but cell division fails. Rosenberg then conducted a series of experiments to test the effects of various platinum coordination complexes on sarcomas artificially implanted in rats. This study found that cis-diamminedichloroplatinum was the most effective of this group, which started the medicinal career of cisplatin [8].

Approved for clinical use by the United States Food and Drug Administration (FDA) in 1978, cisplatin revolutionized the treatment of certain cancers. Detailed studies on its molecular mechanism of action using a variety of spectroscopic methods, including X-ray, NMR spectroscopy, and other physico-chemical methods, revealed its ability to form irreversible crosslinks with bases in DNA.

The synthesis of cisplatin is a classic in inorganic chemistry. Starting from potassium tetrachloroplatinate, K₂PtCl₄²⁻, the first NH₃ ligand is added to any of the 4 equivalent positions, but the second NH₃ could be added cis or trans to the amine ligand. Because Cl⁻ has a larger trans effect than NH₃, the second amine substitutes trans to a chloride ligand, and therefore cis to the first amine. The trans effect of the halides follows the order I>Br>Cl; therefore, the synthesis is conducted using PtI₄²⁻ to ensure high yield and purity of the cis isomer, followed by conversion of the PtI₂(NH₃)₂ into PtCl₂(NH₃)₂, as first described by Dhara [9, 10].

Mechanism of action. After cisplatin enters the cells, the chloride ligands are replaced by water molecules [11, 12].

This reaction results in the formation of positively charged platinum complexes that react with the nucleophilic sites on DNA. These platinum complexes covalently bind to DNA bases using intra-strand and inter-strand cross-links creating cisplatin-DNA adducts, thus preventing DNA, RNA and protein synthesis [7]. This action is cell cycle phase-nonspecific [12]. Cisplatin also has immunosuppressive, radiosensitizing, and antimicrobial properties [2].

Upon administration, a chloride ligand undergoes slow displacement with water (an aqua ligand) molecules in a process termed aquation. The aqua ligand in the resulting [PtCl(H₂O)(NH₃)₂]⁺ is easily displaced, allowing cisplatin to coordinate a basic site in DNA. Subsequently, the platinum cross-links 2 bases via displacement of the other chloride ligand. Cisplatin crosslinks DNA in several different ways, interfering with cell division by mitosis. The damaged DNA elicits DNA repair mechanisms, which in turn activate apoptosis when repair proves impossible. Most notable among the DNA changes are the 1,2-intrastrand cross-links with purine bases. These include 1,2-intrastrand d(GpG) adducts which form nearly 90% of the adducts, and the less common 1,2-intrastrand d(ApG) adducts. 1,3-intrastrand d(GpXpG) adducts occur but are readily excised by the nucleotide excision repair (NER). Other adducts include inter-strand crosslinks and nonfunctional adducts that have been postulated to contribute to cisplatin's activity. Interaction with cellular proteins, particularly HMG domain proteins, has also been advanced as a mechanism of interfering with mitosis, although this is probably not its primary method of action. trans-PtCl₂(NH₃)₂ [13-15].

The trans-PtCl₂(H₂O)(NH₃)₂ does not exhibit a comparably useful pharmacological effect. Its low activity is generally thought to be due to rapid deactivation of the drug before it can arrive at the DNA. It is toxic, and it is desirable to test batches of cis-platin for the absence of the trans isomer [16]. In a procedure by Woollins et al., which is based on the classic 'Kurnakov test', thiourea reacts with the sample to give derivatives that are easily separated and detected by HPLC [17].

Cisplatin injection should be diluted in 2 L of D51/2S or 0.3%NS, containing 37.5 g of mannitol [18]. The solution is not preservable and should be used within 24 hours. Any unused portion should be discarded. In children, the administration volume of cisplatin should be maintained at >125 mL/m²/hr,

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and contain mannitol 15 g/m² and MgSO₄ 20 mEq/L [19, 20]. Urine output should be maintained at > 90 mL/m²/hr during administration [21, 22].

Pharmacokinetics. Ultrafilterable platinum consists of non-protein-bound intact drug and metabolites, while total platinum consists of all platinum species, both protein-bound or unbound [8, 18, 20]. The primary uses of cisplatin are in the treatment of bladder cancer, brain cancer, cervical cancer, esophageal cancer, gastric cancer, germ cell tumours, gestational trophoblastic neoplasia, head and neck cancer, lung cancer, non-small cell and small cell lung cancer, osteosarcoma and other soft-tissue sarcomas, and lymphoma [21, 22].

Cisplatin is available in the form of sterile, unpreserved; single-dose vials [10 mg/10 mL, 50 mg/50 mL and 100 mg/100 mL] at a concentration of 1 mg/mL [17, 23]. Unopened vials should be stored at room temperature. Cisplatin solutions must not be refrigerated or frozen as a precipitate will form. The solutions should be protected from light [24].

It is important to know that IV needles, syringes or sets that have aluminum components must not be used in the preparation or administration of cisplatin [24, 25]. An interaction between aluminum and platinum will occur resulting in the formation of a black precipitate, accompanied by a loss of potency.

Administer with caution to individuals with pre-existing renal impairment, myelosuppression or hearing impairment [14]. Breastfeeding is not recommended as cisplatin is excreted in human milk [10]. The drug has been found to have a carcinogenic effect in laboratory animals [17]. In patients who have a history of a hypersensitivity reaction to cisplatin [26] or other platinum-containing compounds, use of the drug is contraindicated.

Cisplatin may impair fertility, and cisplatin therapy is associated with at least temporary infertility in the majority of patients [18]. Among males receiving cisplatin for testicular cancer, almost all became azospermic within the first 2 cycles of therapy, but recovery of normal sperm morphology, motility, and sperm count occurred in 40% within 1.5-2 years.

Hydration is required to minimize nephrotoxicity [14]. The manufacturer recommends pre-treatment hydration with 1 or 2 L of fluid infused 8-12 hours prior to a cisplatin dose [17]. Hydration with NS, hypertonic saline infusion, and mannitol, or furosemide-induced diuresis is used to effectively decrease cisplatin-induced nephrotoxicity [8]. Lower doses of cisplatin are given with less intensive hydration. For example, patients receiving doses of 35 mg/m² have been pre-treated with 500 mL NS over 1 hour, with no post-hydration. Patients receiving doses of 25 mg/m² have been pre-treated with vigorous oral hydration [e.g., 600-900 mL] on the morning of treatment, and 8 glasses [e.g., 2,000 mL/day] daily for a few days following treatment. Inadvertent substitution of cisplatin for carboplatin can result in a potentially fatal overdose [14]. Precautions should be taken to avoid overdosing, such as writing the cisplatin dose as a daily dose, not as a total cisplatin dose used in one course of therapy. The manufacturer recommends that an alerting mechanism be instituted to verify any order for cisplatin >100 mg/m² per course every 3-4 weeks. Besides, cisplatin has been shown to be a mild to moderate mutagen in the Ames test [17, 19].

Adverse Effects (AE). A group of adverse events that presented during drug treatment, but may not necessarily have

a causal relationship with the drug, were noticed in the course of cisplatin treatment. In general, a number of immediate and early AE were observed with nephrotoxicity, nausea and vomiting, ototoxicity, etc. [2, 16, 17]. Because clinical trials are conducted under very specific conditions, the AE rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important [19].

Anemia observed with cisplatin use may be caused by a decrease in erythropoietin or erythroid stem cells [2]. Cisplatin has been shown to sensitize red blood cells, sometimes resulting in a direct Coombs' positive hemolytic anemia [17].

Electrolyte disturbances can be serious and mainly include hypomagnesemia, hypocalcaemia and hypokalemia. Hypophosphatemia and hyponatremia have occurred in some patients receiving cisplatin combination regimens [2]. These effects are due to renal tubular damage. Cisplatin greatly increases the urinary excretion of magnesium and calcium; increased excretion of potassium, zinc, copper and amino acids also occurs. Hypomagnesaemia and/or hypocalcaemia may become symptomatic, with muscle irritability or cramps, clonus, tremor, carpedal spasm and/or tetany. Children may be at greater risk for developing hypomagnesaemia in combinations with other emetogenic drugs.

Emetogenic effects are common with cisplatin therapy and may be serotonin-mediated [13].

Incidence and severity. Acute nausea and vomiting may occur within 1-6 (usually 2-3) hours after administration of cisplatin [13]. This early period is the most severe and usually lasts 8 hours, but can last for up to 24 hours. Various levels of nausea, vomiting and anorexia may persist for up to 5-10 days. Delayed nausea and vomiting can occur 24 hours or longer following chemotherapy when complete emetic control had been attained on the day of cisplatin therapy. The incidence and severity of cisplatin-induced nausea and vomiting appear to be increased in females, the young, with high doses, rapid infusion, and decreased in patients with a history of chronic alcohol abuse. Acute nausea and vomiting can be prevented by pre-treatment with a 5-HT₃ antagonist (e.g., granisetron, ondansetron) plus a corticosteroid. This can be continued for the first 24 hours following chemotherapy. Delayed nausea and vomiting should not routinely be treated with 5-HT₃ antagonists [19]; generally, these agents are ineffective more than 24 hours after chemotherapy [21]. Corticosteroids are the cornerstone of the treatment for delayed nausea, although other combinations are widely used [13].

Nephrotoxicity is a major concern when prescribing cisplatin [3]. Renal dysfunction due to cisplatin may manifest as renal insufficiency, hypokalemia and hypomagnesemia. The risk for these adverse effects is related to the dose and interval of cisplatin, and may be minimized by adequate hydration.

Geriatric patients may also be at increased risk. The manufacturer recommends pre-treatment hydration with 1 or 2 L of fluid infused 8-12 hours prior to a cisplatin dose [17]. Others suggest hydration with NS, hypertonic saline infusion, and mannitol, or furosemide-induced diuresis to effectively decrease cisplatin-induced nephrotoxicity [8]. Refer to protocol by which patient is being treated. Numerous hydration regimens exist. Hydration regimens should take into account the following conditions for the patient: adequate renal function, clinically euvolemic prior to administration

of cisplatin, no contraindication to saline loading (e.g., uncompensated cardiac conditions, anasarca), and ability to comply with recommended oral hydration protocol, or expectation that volume status can be maintained (e.g., with fluids via enteral feeding tube or IV) [25]. The volumes and durations are minimum administration standards to accommodate the wide variation in clinical practice in delivery of cisplatin. They should be individualized, based on the clinical situation which may affect the hydration regimen and addition of electrolytes.

In children, for moderate to high-dose cisplatin, administer pre-hydration at 125 mL/m²/h for a minimum of 2 hours to increase urine output to >100 mL/m²/h [> 3 mL/kg/h] [5, 15, 23]. The hydration fluid most commonly used is D51/2NS + 10 mEq/L KCL. In post-hydration, maintain urine output at 65-100 mL/m²/h with oral/IV fluids [2] D51/2NS + 20 mEq/L KCL + 20 mEq MgSO₄ + mannitol. 20 g/L is commonly used for IV post-hydration [7, 17, 18].

Nervous system effects are usually peripheral neuropathies, sensory in nature (e.g., paresthesias of the upper and lower extremities) [2]. They can also include motor difficulties (especially gait); reduced or absent deep-tendon reflexes and leg weakness may also occur. Peripheral neuropathy is cumulative and usually reversible, although recovery is often slow [13]. Geriatric patients may be at greater risk for these cisplatin-induced neuropathies. Muscle cramps have been reported, and usually occurred in patients with symptomatic peripheral neuropathy who received relatively high cumulative doses of cisplatin. Lhermitte's sign, a sensation during neck flexion resembling electric shock, is often present with cisplatin-induced neuropathy. The occurrence of Lhermitte's sign may coincide with the onset of peripheral neuropathies, and can last for 2-8 months. When signs of neuropathy occur, cisplatin should be discontinued.

Otic effects include tinnitus, with or without clinical hearing loss, and occasional deafness [2]. Ototoxicity is cumulative and irreversible, and results from damage to the inner ear [13]. These effects may be more severe in children than in adults [10]. The manufacturer recommends that audiograms be performed prior to initiating therapy and prior to each subsequent dose of the drug [17]. Initially, there is loss of high frequency acuity [4,000 to 8,000 Hz]. When acuity is affected in the range of speech, cisplatin should be discontinued under most circumstances and carboplatin substituted where appropriate. Ototoxicity appears to be dose-related. Higher cumulative doses, higher individual doses, and administration by IV bolus resulted in more severe ototoxicity [24], corresponding with higher plasma levels of ultrafilterable platinum [15]. Ototoxicity may be enhanced in patients with prior or simultaneous cranial irradiation. Vestibular ototoxicity may increase with increasing cumulative dosage and may be more likely to occur in patients with pre-existing vestibular dysfunction.

Sensitivity reactions can include anaphylactoid reactions consisting of facial oedema, flushing, wheezing or respiratory difficulties, tachycardia, and hypotension [17]. These reactions can occur within a few minutes after IV administration of cisplatin. Diaphoresis, nasal stuffiness, rhinorrhea, conjunctivitis, generalized erythema, apprehension, and sensation of chest constriction may also occur. Cisplatin-induced anaphylactoid reactions have usually occurred after multiple cycles of cisplatin [e.g., at least 5 doses], but also can occur after the first dose [2]. There is a case report of a patient

who experienced an anaphylaxis to cisplatin following 9 previous uncomplicated cycles [25]. Occasionally, patients who experienced anaphylactoid reactions have been safely retreated with cisplatin following pre-treatment with corticosteroids and/or antihistamines; however, such prophylaxis is not uniformly effective in preventing recurrence.

Cisplatin and related platinum compounds remain the focus of extensive research. Reliable methods for the synthesis of such compounds have been developed, and it has been established that they exert their anticancer activity through interaction with DNA. The search continues for a platinum drug to improve the clinical performance of cisplatin. Several underwent clinical trials but were abandoned for a variety of reasons. However, preliminary results on novel compounds have been particularly promising.

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