Influence of chemical structure and mechanism of hydrolysis on pharmacological activity and toxicological profile of approved platinum drugs

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Abstract
The problems with platinum complexes are resistance and toxicity of anticancer therapy. The aim of current study is the comparison of the influence of chemical structure and mechanism of hydrolysis on pharmacological activity and toxicological profile of approved in platinum drugs: Cisplatin, Carboplatin, Oxaliplatin, Nedaplatin, Lobaplatin, Heptaplatin, Satraplatin. Hydrolysis of Carboplatin and Nedaplatin occurs by double step hydration, to obtain the same active products as with Cisplatin: diaquadiamine-platinum. The similarity in mechanisms of hydrolysis of Oxaliplatin, Lobaplatin Heptaplatin, and Satraplatin is that the first part of the hydrolysis corresponds to the ring-opening and addition of the first water molecule, and in the second step of reaction occur the loss of the ligand and the formation of the di-aquated product by the addition of a second water molecule. Cisplatin, Carboplatin, and Oxaliplatin are nephrotoxic. Cisplatin and Heptaplatin are nephrotoxic. The similar dose-limiting effects of Carboplatin, Oxaliplatin, Nedaplatin, Lobaplatin, and Satraplatin is myelosuppression.

Keywords
Cisplatin, approved derivatives, hydrolysis, pharmacology, toxicology

Introduction
Carcinogenesis is a multi-stage process of transformation of cells into tumors, which includes initiation, promotion, malignant transformation of cells and progression. The breast carcinomas in women and the lung, prostate and colon carcinomas in men, recently have been increased (O’Brien et al. 2021). Platinum complexes are important anticancer agents (Kostova 2006). In the 2009 outpatient database maintained by the USA Centers for Disease Control and Prevention, platinum drugs are listed as being applied with a frequency surpassed only by the anticancer agents: Methotrexate, Medroxyprogesterone, Leuprolide, Raloxefen, and Tamoxifen. Pt IV derivatives has cytotoxic properties after reduction to an active Pt II complex. Pt III hematoporphyrin compounds (Momekov et al. 2010) and Pt III monomer complexes (Momekov et al. 2005; Momekov and Momekova 2006) possess cytotoxic activity.
I. Cisplatin

Cisplatin (cis-dichlorodiamineplatinum II) (Fig. 1) is the first platinum-containing coordination complex, applied for treatment of cancer.

![Figure 1. Chemical structure of Cisplatin.](image)

By the USA Food and Drug Administration Cisplatin has been approved for treatment of testicular and ovarian cancers on December 1978. The compound has been marketed first in Canada and in the USA (Johnstone et al. 2016; Zhou et al. 2020).

The drug causes the DNA damages and formation of the cytotoxic DNA-adducts (Hu et al. 2016). Cisplatin is administered for the treatment of ovarian carcinoma and testicular teratoma (Matysiak and Gustaw-Rothenberg 2009), and for medulloblastoma (Packer et al. 1994). Side effects of compound are: nephrotoxicity, neurotoxicity, transient blindness and seizures (Cattaneo et al. 1988), and encephalopathy syndrome (Bruck et al. 1989). Ototoxicity is manifested with tinnitus (Kaltenbach et al. 2002), and hearing loss (Knight 2008).

Currently applied in clinical practice worldwide are: Cisplatin and it’s structural analog of II generation Carboplatin (1993); derivative of III generation Oxaliplatin (2002) in France, Carboplatin analog – II generation: Nedaplatin in Japan; Oxaliplatin derivatives – III generation: Lobaplatin in China and Heptaplatin in the North Korea; oral derivative Satraplatin (Ndagi et al. 2013). To date, no analog of Cisplatin has been developed, that is completely superior to it, in terms of both therapeutic effect and spectrum of action (Johnstone et al. 2016).

II. Cisplatin derivatives: Carboplatin and Oxaliplatin

1. Carboplatin

In March 1989 Bristol-Myers Squibb has obtained the approval for application of the drug. The compound is the most successful platinum complex of the second generation with clinical administration for the treatment of ovarian, head, neck, lung, breast cancer (Zhou et al. 2020).

The main drawback of Carboplatin is the hematotoxicity (Cheng et al. 2017) as myelosuppressive effects (Schmitt et al. 2010). Ototoxicity is rare with about 1.1% (Amptoulach and Tsavaris 2011).

![Figure 2. Chemical structure of Carboplatin.](image)

The compound is applied for treatment of non-small cell lung cancer, head, neck, ovarian, and breast cancer (Ndagi et al. 2013). Oxaliplatin with Folic acid and 5-Fluorouracil is effective in the therapy of colorectal cancer (Kweekel et al. 2005).

![Figure 3. Chemical structure of Oxaliplatin.](image)

The major reason for the discontinuation of treatment with Oxaliplatin are neurotoxicity (Gamelin et al. 2002), and tubular necrosis (Oun et al. 2018). The dose-limiting neurological dysfunction is manifested with an acute or a chronic forms (Amptoulach and Tsavaris 2011) of sensory peripheral neuropathy.

III. Carboplatin derivatives: Nedaplatin

![Figure 4. Chemical structure of Nedaplatin.](image)

Indications in Japan for Nedaplatin are for the treatment of head, neck, esophagus, non-small cell lung, cervical, testicular, and prostate cancer (Shimada et al. 2013).
Compared with Cisplatin, Nedaplatin has lower nephro-, neuro-, oto-, and gastrointestinal toxicity, and leukopenia. Dose-limiting toxicity is myelosuppression: thrombocytopenia, neutropenia, and anemia (Wu et al. 2021).

IV. Oxaliplatin derivatives – III generation: Heptaplatin and Lobaplatin

1. Heptaplatin

Heptaplatin was approved by the Korean Food and Drug Administration in 1999 for the treatment of gastric cancer (Johnstone et al. 2016). The most important dose-limiting problem associated with Heptaplatin is nephrotoxicity (Ahn et al. 2002).

2. Lobaplatin

Lobaplatin has been introduced in China for the treatment of chronic myelocytic leukemia, hypopharyngeal carcinoma, esophageal squamous cell carcinoma (Du et al. 2017), small-cell lung cancer (Chen et al. 2016), and gastric cancer (Hua et al. 2018).

The side effects of the drug are thrombocytopenia, leukopenia, neutropenia, and granulocytopenia (Wu et al. 2021).

IV. Derivatives of Cisplatin – Pt IV complexes: III generation: Satraplatin

Satraplatin is administered against lung, prostate, and ovarian cancer (Zhou et al. 2020). Dose-limiting is hematotoxicity (Bhargava and Vaishampayan 2009).

Mechanisms of hydrolysis of Cisplatin derivatives

Cisplatin is a complex of platinum (II), coordinated to two chloride and two ammonia groups, where chloride ligands are in cis-geometry. The drug is initially activated intracellularly by hydration with water molecules, whereby labile ligands (chloride atoms in cis-geometry) are sequentially replaced, forming more chemically reactive to DNA mono- and diaqua metabolites (Fig. 8). This process is facilitated by low intracellular concentration of chloride ions (below 100 mmol/l) (Sawant et al. 2015).

Due to their pronounced electrophilic properties, aqua compounds covalently bind to nucleophilic nitrogen-containing purine DNA bases to form DNA adducts: monofunctional in one leaving group or bifunctional in two leaving groups. The presence of two labile ligands appearing as leaving groups in these nucleophilic substitution reactions, determines the possibility of the

Figure 5. Chemical structure of Heptaplatin.

Figure 6. Chemical structure of Lobaplatin.

Figure 7. Chemical structure of Satraplatin.

Figure 8. Hydrolysis mechanism of Cisplatin to cytotoxic mono- and diaqua complexes.
formation of intrachain and, less frequently, interchain crosslinks in the DNA molecule. Cisplatin preferably binds to the N7 atom of the imidazole ring of the purine base guanine (G) of DNA and with N3 and 4-NH₂ of cytosine and N1 and 6-NH₂ adenine (A). Pt-DNA binding is most often performed on one strand of DNA and the internal adducts include GpG (65%), ApG (25%) or the adducts include guanines of opposite strands of DNA G-G cross-linking (5%).

Adducts cause disturbances in the structure of DNA: inhibit cellular processes of replication and transcription, cause prolonged G2 phase of cell cycle and lead to programmed cell death (apoptosis). Adducts are also formed between DNA and some proteins. Bifunctional adducts, which form intra-helix or inter-helix "cross-links", cause basic and local disturbances in the structure of DNA. In intermolecular adducts, such as Cisplatin-DNA proteins, the cross-bonds, responsible for blocking replication, are the main damages, activating apoptosis (Sawant et al. 2015).

In Carboplatin two chloride atoms are replaced by an oxygen bidendate cyclobutane-dicarboxylate group. Slow hydrolysis of the drug occurs by double hydration to the same products as with Cisplatin: diaquadiamine-platinum. The decomposition in water take place through a biphasic mechanism with a ring-opening process and aquation in first part, followed by the loss of the malonato ligand and second aquation (Fig. 9) (Pavelka et al. 2007).

Carboplatin binds to DNA more slowly due to the stability of carboxylate ligand and slower hydrolysis. Aqua-complex species react with DNA, proteins or other macromolecules.

Hydrolysis of Oxaliplatin corresponds to the ring-opening, the addition of water molecules, and the loss of the monodentate oxalato ligand. The rate-limiting process for the neutral hydrolysis is the ring-opening reaction (Fig. 10). Oxaliplatin bind to DNA more slowly due to the stability of oxalate ligands and slower hydrolysis. Aqua-complex species react with DNA and proteins. Oxaliplatin may produce fewer DNA-adducts, but causes higher cyto-toxicity than Cisplatin (Lucas et al. 2009).

Nedaplatin has ten times greater solubility in water than Cisplatin, and is hydrolysed by double hydration to the same active metabolite as with Cisplatin: diaquadiamine-platinum. The hydrolysis reaction processes is illustrated on Fig. 11.

The first step of the mechanism corresponds to the ring opening and first quation, followed by the second part, which is characterized by the loss of ligand and second hydratation. In acid conditions, the second hydrolysis reaction is the rate limiting, and in neutral conditions the rate limiting step is found to be the first hydrolysis process (Alberto et al. 2009).

Nedaplatin binds to guanine in the DNA. In attempts of mismatch repair protein complex for repairing of the DNA by removing of the platinum cross-links, this com-

Figure 9. Hydrolysis mechanism of Carboplatin (Pavelka et al. 2007).

Figure 10. Hydrolysis mechanism of Oxaliplatin (Lucas et al. 2009).
plex forms single strand breaks and induces apoptosis after the repair attempt has failed. In combination with radiation treatment, the radiosensitizing effect of Nedaplatin is due to the formation of lethal double strand breaks (Schimada et al. 2013).

The bio-transformation of Heptaplatin (Fig. 12) results in mono and di-aquated products. Like in mechanism of Oxaliplatin, the first part of the hydrolysis of Heptaplatin corresponds to the ring-opening and addition of the first water molecule. In the second step of reaction occur the loss of the ligand and the formation of the di-aquated product by the addition of a second water molecule. The platination processes is characterized by the binding to the guanine and adenine bases of DNA, forming the DNA-aducts. The binding of Heptaplatin hydrolytic products to guanine occurs more often in comparison with adenine, due to more favorable hydrogen-bonds (Reddy et al. 2017).

In the hydrolysis mechanism of Lobaplatin in aqueous medium under neutral conditions, the ring opening reaction is found to be the rate limiting. The completely hydrolysed complex reacts with the DNA purine bases. The ligand detachment is described as the rate limiting step in acidic conditions and monohydrated complex reacts with DNA. The hydrolysis of Lobaplatin is presented on Fig. 13 (Reddy et al. 2016).

Pt IV-complexes are in an “inactive” form and react mainly with proteins in the bloodstream, and in the cells they accumulate through passive diffusion. Activation of Pt IV complexes is accomplished by reduction to Pt II, with electron transfer occurring in parallel with the release of axial ligands. Reduction of Pt IV to Pt II is a necessary condition for achieving antitumor activity, as six-coordinate octahedral Pt IV compounds are able to minimize unwanted side reactions with biomolecules and are more kinetically inert and less reactive and more resistant to ligand substitution than four-coordinate Pt II. Depending on the nature of the ligands, that determine the specific thermodynamic and kinetic properties, some Pt IV complexes can bind to DNA, causing DNA deformation. Studies on the cytotoxic properties of Pt IV complexes show that, like Pt II compounds, they are
localized in the cell nucleus and the Pt IV-DNA adducts formed are analogous to those formed by Cisplatin. In vitro studies indicate that Pt IV complexes are characterized by higher efficacy, than the respective Pt II complexes. Pt IV complexes bypass inconvenient intravenous administration, due to kinetic inertness, like Satraplatin – the first platinum oral antineoplastic agent. Satraplatin has increased bioavailability due to the two polar acetate groups, which hydrolysis is presented on Fig. 12 (Ritacco et al. 2017). Biochemical studies show, that upon entering the cell, Pt IV is activated by two metabolic pathways:

1) reduction by the bioreducing agents glutathione and Ascorbic acid to a similar complex to Pt II (active metabolite JM 118);

2) antitumor effect of the active Pt IV form JM 383 (Fig. 12). JM 216 can produce Pt-DNA adducts similar to Cisplatin and Oxaliplatin, but in smaller amounts (Ritacco et al. 2017).

The major way of the development of the resistance to Cisplatin and its derivatives is through a mammalian nucleotide excision repair pathway, which repairs damaged DNA. In comparison to other platinum anti-cancer drugs, due to the different adducts on the molecule (cyclohexamine), Satraplatin is not recognized by the DNA repair proteins, the DNA remains damaged, and DNA can not be replicated, resistance is solved. By binding to guanine residues Satraplatin inhibits DNA replication and transcription which leads to apoptosis (Ritacco et al. 2017).
Influence of chemical structure on pharmacological activity and toxicological profile of platinum complexes

The classic structural requirements for the manifestation of antitumor activity, derived on the basis of the structure of Cisplatin are:

1) a flat-square Pt II complex;
2) cis-position of the two “leaving” ligands;
3) amino or imino ligands at the other two coordination sites;
4) the presence of an NH-functional group in the platinum compounds, which is important for the stability of the formed adduct due to additional binding via H-bonds.

Prospects for the creation of new platinum complexes are various ligands – amines and alkylamines, purines and pyrimidines, hydantoins, carbonyl radicals, which produce compounds with selective cytotoxicity or inhibitory effect on resistant tumors. Modifications of leaving groups (labile, hydrolyzable or exchangeable ligands) in the main classes of platinum complexes affect the cytotoxic activity, spectrum of action and the toxicological profile of platinum analogs.

The leaving group is important for the spectrum of platinum cytostatics and in the order: Cl-, oxalato-, cyclobutanedicarboxylato-, reduces cross-resistance in Cisplatin-resistant tumors. In the molecule of Carboplatin, platinum is bound to cyclobutanedicarboxylic acid. In complexes, based on hydroxyxcarboxylic acids (lactic, glycolic), platinum is bidently linked to the oxygen atom of the carboxyl and hydroxyl functional groups. The leaving groups are: cyclobutanedicarboxylic acid in Carboplatin, anion of glycolic acid in Nedaplatin, bidentate-bound lac-tate in Lobaplatin, bidentate oxalate anion in Oxaliplatin. The conversion of carboxylate analogs to active diaqua-complexes: 1) occurs mainly intracellularly, and with the higher stability, than chloride ions, causes of cytotoxicity at higher concentrations, than Cisplatin, and 2) leads in lower nephrotoxic potential, due to reduced direct interaction of cytotoxic metabolites with nucleophilic thiol

![Figure 14. Hydrolysis mechanism of Satraplatin (Ritacco et al. 2017).](image-url)
groups in the kidney. Carboplatin and Nedaplatin are precursors of Cisplatin because their metabolism produces an intermediate derivative dichloro-diamine platinum. The DNA-adducts, formed by Carboplatin are the same, as those, formed by Cisplatin, but 20–40 times higher concentrations of Carboplatin are required and the rate of adducts formation is 10 times slower (Zhou et al. 2020).

The tightly bound carrier ligands (the ammonia molecules in Cisplatin, Carboplatin, Nedaplatin) do not interact with aqueous molecules or nucleophilic nitrogen-containing DNA bases, and their modifications lead to significant changes in the antitumor activity, spectrum of action and profile of toxicological effects. The ammonia groups in Cisplatin are partially or completely replaced by mono- or bidentate nitrogen-containing ligands: aliphatic, alicyclic and aromatic mono- and diamines or heterocyclic compounds: 1,2-diaminocyclohexane (DACH) ligand in Oxaliplatin; seven-membered Pt-1,2-bis-(methylamino) cyclobutane chelated ring (Lobaplatin). An increase in the number of atoms in the heterocycle (4 to 6) contributes to greater efficacy in Cisplatin-resistant tumors. Important characteristic of DACH complexes is activity in Cisplatin-resistant tumors, but a limiting factor is neurotoxicity, associated with DACH-ligand. Oxaliplatin causes higher cytotoxicity than Cisplatin, inhibiting nucleic acid polymerases, and initiating apoptosis. Higher cytotoxicity of Oxaliplatin is due to hydrophobic properties, increasing the accumulation by actively transporting membrane proteins, overexpressed in tumor cells. The problems with chemotherapy are resistance and toxicity. Antitumor drugs have no selectivity for tumor cells, but also can kill normal cells with high proliferative activity: cells of the bone marrow hematopoiesis, and in gastrointestinal tract. Myelosuppression leads to a risk of infection and is characteristic primarily of alkylating cytostatics and antimetabolites. Toxicity can be decreased by combination therapy, polynuclear platinum agents, Pt IV prodrugs, targeted nanocarriers: (polymers, liposomes) (Johnstone et al. 2016).

The dose-limiting effects of approved for chemotherapy platinum complexes are:

1) Cisplatin – nephrotoxicity, ototoxicity (Oun et al. 2018), neuropathy (Krarup-Hansen et al. 2007);
2) Carboplatin – neurotoxicity, myelosuppression (Schmitt et al. 2010);
3) Oxaliplatin – neurotoxicity (Gamelin et al. 2002), hematological and gastrointestinal toxicity (Oun et al. 2018);
4) Nedaplatin – myelosuppression (Wu et al. 2021);
5) Heptaplatin - nephrotoxicity (Ahn et al 2002);
6) Lobaplatin – myelosuppression (Wu et al. 2021);
7) Satraplatin – myelosuppression (Bhargava and Vaishampayan 2009).

Conclusion

The problems with anticancer therapy is toxicity. Cisplatin, Carboplatin, and Oxaliplatin are nephrotoxic. Cisplatin and Heptaplatin are nephrotoxic. The similar dose-limiting effects of Carboplatin, Oxaliplatin, Nedaplatin Lobaplatin Satraplatin is myelosuppression: (Oun et al. 2018). Introduction of different groups in the structure of platinum complexes leads to significant changes in antitumor activity, spectrum of action, and in the toxicological profile of platinum analogues. The new approaches in the development of new platinum antineoplastic complexes are fixed in: increasing of antitumor activity, broadening of the spectrum of action, reduction of the toxicity, creation of citostatics with targeted action. An important approach for overcoming the drug resistance and reduction of toxicity, of Cisplatin derivatives are nanocarriers (polymers and liposomes), which provide improved targeted delivery, increased intracellular penetration, selective accumulation in tumor tissue, and enhanced therapeutic efficacy.

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