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# Metal-based organic complexes with anticancer activity

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## Abstract

The discovery of the mechanism of action and the main structure-activity dependencies of platinum complexes create opportunities for rational synthesis of new metal-based organic complexes as potential antitumor drugs with reduced resistance and toxicity and / or a wider spectrum of antitumor activity. In the field of targeted synthesis of antitumor complexes has been working hard for 40 years. Initial research focused on obtaining complexes with a structure similar to cisplatin, and later on the search for new "non-classical" antitumor complexes. Selection of a suitable ligand system, ensuring effective accumulation in the antitumor tissue, replacement of platinum with other metals of the platinum groupg – ruthenium and palladium or metals with similar properties, such as gold, changing the degree of oxidation of the metal ion with for the purpose of kinetic and thermodynamic control over the binding of the metal complex to DNA bases.

## Keywords

Metal-based organic complexes, antitumor drugs, platinum complexes

## Introduction

In recent decades, about 3,000 platinum derivatives have been synthesized and tested against cancer cells; but only 30 compounds have reached clinical trials and most have already been rejected. Currently used in clinical practice: worldwide Cisplatin and its structural analogue of II generation Carboplatin, analogue of III generation Oxaliplatin in France, Nedaplatin in Japan, Lobaplatin in China and Heptaplatin in the North Korea. Some platinum complexes are still under clinical examination, including for oral administration. To date, no analogue of Cisplatin has been developed that is completely superior to it both in terms of therapeutic effect and spectrum of action. [1,2]

The problems with anticancer therapy are resistance and toxicity. The strategies for the development of platinum anticancer agents and bypassing of resistance to Cisplatin derivatives and their toxicity are: combination therapy, Pt(IV) prodrugs, the targeted nanocarriers

The trend for the improvement of the anticancer effect is a synergistic combination of different drug molecular mechanisms. In various treatment regimens are applied platinum agents with radiation or in combination with the following drugs:

1. anticancer agents: Fluorouracil, Gemcitabine, Fludarabine, Pemetrexed, Ifosfamide, Irinotecan, Topotecan, Etoposide, Amrubicin, Doxorubicin, Epirubicin, Vinorelbine, Docetaxel, Paclitaxel, and Nab-Paclitaxel
2. modulators of resistant mechanisms
3. signaling protein inhibitors: Erlotinib; Bortezomib; and Everolimus
4. immunotherapeutic drugs: Atezolizumab, Avelumab, Bevacizumab, Cemiplimab, Cetuximab, Durvalumab, Erlotinib, Imatinib, Necitumumab, Nimotuzumab, Nivolumab, Onartuzumab, Panitumumab, Pembrolizumab, Rilotumumab, Trastuzumab, Tremelimumab, and Sintilimab. [3,4]

The advantages of the reported drug regimens and the rationality of combination therapy at the molecular level are:

1. achieving the maximum possible removal of tumor cells in different phases within the permissible toxicity
2. affecting the cells located in different phases of the cell cycle
3. realization of prevention or delay of the development of resistant cell branches
4. slowing the process of adaptation of tumor cells and delay of cell mutations, due to using more drugs, that have different molecular targets
5. reduction of dose of combined components with one and the same dose-limiting effects
6. schemes with components with different toxicity to normal tissues, allowing the application of optimal doses of each drug in the absence of superimposition of toxic effects on an organ or cell system. [5,6,7] For overcoming the drug resistance and reduction of toxicity of Cisplatin derivatives is the application of nanocarriers (polymers and liposomes), which provide improved targeted delivery, increased intracellular penetration, selective accumulation in tumor tissue, and enhanced therapeutic efficacy. An important approach for overcoming the drug resistance and for reduction of toxicity is the combibation therapy of liposomally encapsulated Cisplatin and Oxaliplatin with other anticancer agents, which provide improved targeted delivery, improved intracellular penetration, selective accumulation in tumor tissue, and enhanced therapeutic efficacy. [8,9]

One of the strategies to reduce the overall toxicity and resistance is the use of "prodrugs" that can be activated locally by internal stimuli - physiological changes in the environment (pH, redox potential); by enzyme-catalyzed chemical transformation or by external stimuli such as light.

Platinum complexes are among the most widely used anticancer chemotherapeutics. 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. The electronic configuration determines the use of Pt(II) and Pt(IV) compounds as antitumor agents. Upon oxidation, irradiation with light or electron bombardment of Pt(II) complexes, intermediates are formed, in which the platinum is in the unstable oxidation state (+III) and is stabilized by complexation with suitable ligands. Compared to Pt(II) and Pt(IV), Pt(III) compounds exhibit in vivo intermediate behavior, in terms of kinetic inertness and thermodynamic stability. Mixed-valence Pt(III)-Pt(II) complexes with a polymer structure have high anticancer activity, but the inability for obtaining a precise chain length, makes difficulty for creation of a drug. Pt(III) monomer complexes [9, 10] and stable octahedral Pt(III) hematoporphyrin compounds are promising in Cisplatin-resistant tumor cell lines [11,12,13].

Some cytostatic towards advanced small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), breast, pancreatic, liver, kidney, and prostate cancer [14,15,16,17], refractory non-Hodgkin's lymphoma, sarcoma, neuroblastoma, malignant brain multiform glioblastoma, peritoneal and pleural mesothelioma, metastatic melanoma, leukemia [19]

In combination cancer treatment regimens, greater effectiveness is a result of synergism of the different molecular mechanisms of drugs. In the therapy of first-line advanced NSCLC, the advantage of schemes is due to the inhibition of DNA-synthetic pathways, involved in the reduction of platinum-DNA adducts. Cisplatin is the most commonly used platinum-containing component in various treatment schedules, due to its synergistic effects with the following drugs: Capecitabine, Docetaxel, Epirubicin, Etoposide, Everolimus, Fluorouracil, Gemcitabine, Irinotecan, Nab-Paclitaxel, Paclitaxel, Vinorelbine, immunotherapeutic drugs: Atezolizumab, Cemiplimab, Cetuximab, Durvalumab, Necitumumab, Rilotumumab, Trastuzumab, and with radiation therapy.

Prospects for the creation of new platinum complexes are various ligands – amines, alkylamines, purines, pyrimidines, hydantoines, 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. A suitable ligand systems have been selected, for obtaining effective accumulation in target tissues, reduced side effects, low nephrotoxicity. Strategies for optimization of effectivity of antitumor agents include [15,20].

Compared to Cisplatin, the side effects of Carboplatin: neuropathy, nephro-, oto- and gastrointestinal toxicity are less pronounced and more easily overcome, due to the slower hydrolysis of leaving bidentate dicarboxylate ligands, compared to labile chloride ligands of Cisplatin. A limiting side effect of compound is myelosuppression, clinically manifested as severe thrombocytopenia, neutropenia and leukopenia, which requires monitoring of blood parameters or dose reduction [14,21]. Although the low nephrotoxicity of Carboplatin is an advantage, especially in patients with kidney disease, it is not an alternative to Cisplatin in resistant tumors, due to the presence of cross-resistance.

Oxaliplatin has less pronounced side effects, such as neutropenia, than Cisplatin, and the dose-limiting factors are significant neurotoxicity and tubular necrosis. Neurotoxicity is: 1) initial transient peripheral sensory neuropathy, manifesting as paresthesias and dysesthesia in limbs and muscle contractions of the jaw; 2) long-term neuropathy, manifested by profound sensory loss, sensory ataxia, and functional impairment resulting from the ability to alter the potential of the outer surface membrane. Nedaplatin gives better results than Cisplatin in preclinical studies, and official indications in Japan are for the treatment of head, neck, esophagus [22], non-small cell lung [23], cervical, testicular, and prostate cancer.

Despite in vitro efficacy, in clinical trials in ovarian cancer with recurrence after first-line treatment with Cisplatin, the lower activity than Cisplatin has been reported. The approval of Lobaplatin is based mainly on reduced side effects: no nephro-, neuro-, and ototoxicity. The main side effects are thrombocytopenia, leucopenia, neutropenia, granulocytopenia, and anemia.

The toxicity is problem with chemotherapy with Cisplatin derivatives. 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 a gastrointestinal tract. Myelosuppression leads to a risk of infection. Despite its significant therapeutic efficacy, the clinical application of Cisplatin in effective high-dose courses, is limited by the manifestation of severe dose-limiting side effects, as a result of an interaction with other biomolecules in the body, and the development of resistance, due to inefficient accumulation in tumor tissue.

Anticancer chemotherapy with Cisplatin analogs is based on inhibition of the growth of the tumor cells, with DNA being the main target molecule, and is associated with growth inhibition of the tumor cells, due to suppression of DNA synthesis and repair as a result from modification of the three-dimensional structure of DNA, induced by metal adducts. The antitumor effect of Pt-containing drugs has been best studied for Cisplatin, which acts as a bifunctional alkylating agent on DNA. 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. 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) [21,24]. Due to slower hydrolysis and the stability of carboxylate (Carboplatin) and oxalate (Oxaliplatin) ligands, these drugs bind to DNA more slowly.

Combination therapy is an important trend in the development of platinum anticancer agents and for bypassing of resistance to Cisplatin derivatives [24]. The need for the development of different cytostatics is a result from the data on the kinetics of tumor growth and from the comparative analysis of clinical outcomes in mono- and combination treatment. Today, the monotarget strategy is being replaced by a polytarget one, which achieves greater clinical efficacy in tumors. The administration of multiple anticancer regimens is a major strategy in oncology, and is important to exploit synergy between the drugs and for a better outcome, than monotherapy.

## Conclusion

In the last few years, interest in platinum drugs has increased. Successful treatment depends to a large extent on complex therapy and early diagnosis, which determines the great importance of knowledge of risk groups, clinical symptoms and targeted use of diagnostic methods with biomarkers, biopsy and diagnostic imaging for early detection of the malignant process. Today, the monotarget strategy is being replaced by a polytarget therapy strategy, which achieves greater clinical efficacy in tumors with defined biomarkers. Key developments include elucidation of the mechanisms of tumor resistance to these drugs, the introduction of new platinum-based agents (oxaliplatin, satraplatin, and picoplatin), and clinical combination studies using platinum drugs with resistance modulators or new drug-targeted drugs. Improved delivery of platinum drugs to tumors has been studied in early clinical trials using liposomal or copolymer-based products, as well as through the use of localized intraperitoneal administration of cisplatin or carboplatin in patients with ovarian cancer.

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