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Research Progress on Platinum-Based Antitumor Drugs

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Abstract

Cancer is a prevalent disease characterized by uncontrolled proliferation and differentiation of abnormal cells and the ability to metastasize. The treatment and prevention of cancer have become critical tasks for humanity. Platinum-based drugs are metal complexes containing platinum elements that exhibit antitumor activity and are widely used in clinical therapy. The mechanism of action of platinum (IV) antitumor agents involves inducing DNA damage, arresting the cell cycle, thereby promoting apoptosis of cancer cells and reducing mitochondrial membrane potential. Among them, lipophilicity–hydrophilicity partition-tuned platinum (IV) drugs are mainly used in chemotherapy; DNA-targeted platinum drugs are widely applied in chemotherapy, although they are associated with higher toxicity and drug resistance; mitochondria-targeted platinum drugs are formed by introducing mitochondria-targeting bioactive small molecules into platinum (IV), which not only exert antitumor effects but also show antibacterial activity, repair mitochondrial function, and reduce drug resistance; photodynamic platinum (IV) drugs are characterized by low toxicity, high efficiency, and strong targeting ability. Platinum (IV) complexes remain stable under physiological pH conditions and can maintain biological activity under the action of strong reducing agents. Although photodynamic platinum (IV) drugs exhibit advantages such as low toxicity, high efficacy, and strong targeting, they still face many challenges. The combination of platinum-based antitumor drugs with baicalein can exert multiple biological activities, not only enhancing antitumor efficacy but also offering higher safety and lower toxicity due to the natural origin of baicalein. Combination therapy of platinum-based drugs with other agents is more effective and safer than monotherapy. However, platinum-based drugs are prone to adverse reactions, including nephrotoxicity.

Keywords

platinum-based drugs, antitumor, combination therapy, adverse reactions, nephrotoxicity

1. Introduction

Cancer is a common disease caused by the uncontrolled proliferation and differentiation of abnormal cells, which can metastasize from one site to another through the blood and lymphatic systems. Its etiology is associated with environmental factors, dietary habits, genetic factors, and others. There are many types of cancer, among which common ones include gastric cancer, lung cancer, breast cancer, and colorectal cancer. At present, lung cancer has the highest mortality rate and is more prevalent among smokers around the age of

60, followed by liver cancer. Cancer can be treated by radiotherapy, chemotherapy, surgery, and other approaches; however, the cure rate of advanced-stage cancer remains low. Therefore, the treatment and prevention of cancer have become major global challenges.

Platinum-based drugs are metal complexes containing platinum that possess antitumor activity and are used clinically in radiotherapy and chemotherapy. Common platinum-based anticancer drugs include cisplatin, carboplatin, and oxaliplatin. In the 1960s, American researchers discovered that platinum-based drugs could effectively inhibit the proliferation of cancer cells. In 1979, cisplatin was recommended in the United States for the treatment of testicular cancer. Ten years later, carboplatin became one of the first-line drugs for ovarian cancer, and in combination with paclitaxel, it was established as a standard first-line regimen. In 1996, the application of oxaliplatin in combination with other drugs showed certain efficacy in ovarian cancer and colorectal cancer [1]. Platinum-based drugs exert anticancer effects by interfering with DNA replication, inducing apoptosis, and enhancing immune activity; therefore, they have a wide range of clinical applications. The following sections discuss the research progress of various platinum-based antitumor drugs, studies involving baicalein-containing drugs, mechanisms of action, adverse reactions, and the efficacy of combination therapy.

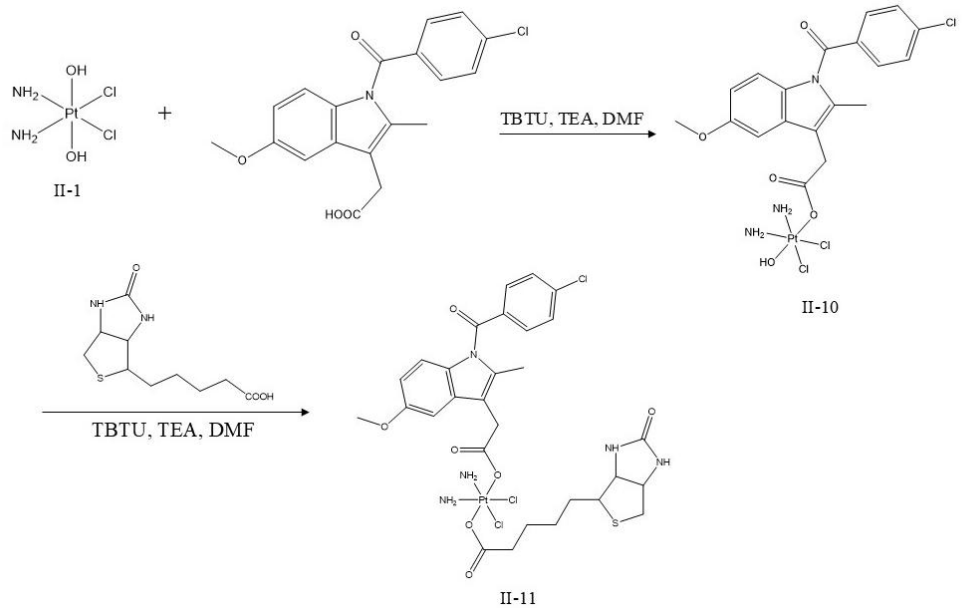
2. Research Progress of Platinum (IV) Antitumor Drugs

2.1 Synthesis of Antitumor Platinum (IV) Complexes Using Indomethacin and Biotin

2.1.1 Synthesis and Characterization of the Complex

The intermediate complex was synthesized using platinum (II) as the starting material, followed by oxidation with NCS and hydrogen peroxide [2].

Figure 1: Synthesis of the target product



Compound II-11 was obtained as a yellow powder with a yield of 53% [2].

2.1.2 Chemical Properties and Biological Activity of the Target Complex

High-performance liquid chromatography (HPLC) was employed to investigate the stability of II-11 in phosphate-buffered saline (PBS) at pH 7.4 and its reduction behavior in the presence of ascorbic acid. The results indicated that II-11 exhibited good stability and could be reduced, although at a relatively slow rate. Therefore, platinum (IV) complexes remain stable under physiological pH conditions and can retain biological activity in the presence of strong reducing agents [2].

2.2 Research on Multifunctional Platinum (IV) Drugs

According to the study by Li Linming et al. [3], five types of platinum (IV) drugs were investigated: lipophilicity–hydrophilicity partition-tuned, DNA-targeted, mitochondria-targeted, enzyme-targeted, and photodynamic platinum drugs. Among these, lipophilicity–hydrophilicity partition-tuned drugs are mainly used in chemotherapy; however, their biological activity is influenced by factors such as lipid solubility, and the influencing mechanisms are not yet fully understood. The introduction of benzoyl groups can enhance their antitumor activity, and these drugs can be administered orally. DNA-targeted platinum drugs are widely used in chemotherapy, but due to the relatively low probability of binding to DNA, they tend to exhibit increased drug resistance and toxicity. The incorporation of naphthalimide and chlorambucil (CLB) into platinum drugs can enhance their antitumor properties. Mitochondria-targeted platinum drugs are developed by introducing mitochondria-targeting bioactive small molecules into platinum (IV). These drugs not only exhibit antitumor effects but also possess antibacterial activity, restore mitochondrial function, and reduce drug resistance. Their primary mechanism involves inducing mitochondrial damage, activating apoptotic proteins, and disrupting mitochondrial function, thereby promoting apoptosis. Currently, some of these drugs have become important targets in tumor chemotherapy [3].

The literature also reports various enzyme-targeted platinum drugs, which can induce cancer cell death through multiple mechanisms, including inhibition of receptor binding, collapse of mitochondrial membrane potential, alteration of protein expression, interaction with other proteins, blockade of enzyme-related pathways, reduction of glucose uptake in tumor cells, cell cycle arrest, enhancement of oxidative stress, and disruption of signaling pathways [3].

Photodynamic platinum drugs represent a novel class of platinum-based agents that utilize unique redox mechanisms to release platinum (II), thereby inducing cellular senescence and activating T cells. Studies have shown that platinum drugs synthesized using boron-dipyrromethene (BODIPY) can kill cancer cells under light irradiation by inducing cell cycle arrest. Ligands formed by azide groups with platinum (IV) can generate reactive oxygen species (ROS) and reactive nitrogen species (RNS) under light irradiation, leading to apoptosis of cancer cells [4].

Studies have demonstrated that photodynamic platinum (IV) drugs exhibit low toxicity, high efficiency, and strong targeting ability. However, they still face many challenges, including issues related to drug resistance, structural optimization of complexes, and the development of nano-scale platinum (IV) drugs. Therefore, this class of drugs has broad development prospects and can provide new strategies for anticancer drug development, making it an important research hotspot [4].

2.3 Research on Platinum (IV) Drugs Containing Wogonin

2.3.1 Introduction

Wogonin is a flavonoid compound that is effective in the treatment of inflammation and infection, and also exhibits antibacterial, antiviral, and antioxidant properties. Therefore, it is widely used in the production of pesticides, pharmaceuticals, biodegradable materials, and food additives, indicating its broad applications and significant potential value. Studies have shown that incorporating wogonin into platinum (IV) drugs can enhance the antitumor activity and overcome drug resistance of platinum-based agents.

2.3.2 Mechanism of Platinum (IV) Antitumor Drugs

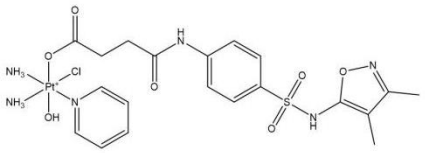
The research group designed two platinum (IV) drugs containing wogonin, namely complex I (Cis-wog) and complex II (DN604-wog). Studies demonstrated that complex I can be reduced in vivo to wogonin and cisplatin, causing DNA damage, inducing cell cycle arrest, and ultimately leading to apoptosis of cancer cells. Complex II shows lower cytotoxicity and improved resistance profiles, and it induces apoptosis by reducing mitochondrial membrane potential [5]. Therefore, the combination of platinum-based drugs with wogonin can exert multiple biological activities, enhancing antitumor properties while maintaining higher safety and lower toxicity due to its natural origin.

2.4 Drug Resistance of Mitochondria-Targeted Platinum (IV) Drugs

The antitumor mechanism of platinum (IV) drugs involves their entry into cancer cells, where they are reduced to platinum (II) by intracellular reducing agents, thereby exerting cytotoxic effects. However, if intracellular reducing substances are deficient, the cytotoxicity of these drugs decreases, leading to drug resistance. Therefore, overcoming drug resistance remains a major challenge in the development of platinum (IV) drugs. Studies have shown that drug resistance can arise from DNA repair proteins, whereas mitochondria lack such DNA repair proteins, thereby avoiding resistance associated with DNA repair mechanisms. Moreover, mitochondria play critical roles in signal transduction, cell differentiation, and apoptosis. Thus, mitochondria-mediated apoptosis can be utilized to design mitochondria-targeted platinum (IV) drugs, which are not only highly effective but also exhibit lower resistance [6].

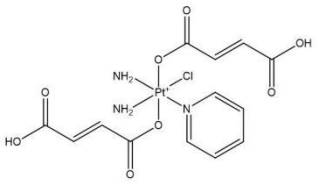
In this study, cisplatin, pyridine (PY), sulfisoxazole (SFX), 4-dimethylaminopyridine (DMAP), and maleic anhydride were used as starting materials to synthesize three compounds through a series of reactions. Figures 2, 3, and 4 present the structures of these compounds [6].

Figure 2



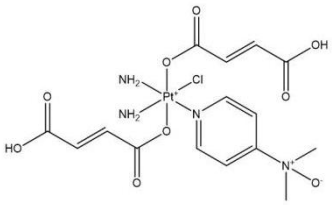
PtPY-SFX

Figure 3



PtPY-COOH

Figure 4



PtDMAP-COOH

The results indicated that these complexes exhibit good stability, time-dependent cytotoxicity, the ability to affect mitochondrial membrane potential, and lower drug resistance [6].

3. Research Progress on Platinum-Induced Nephrotoxicity

3.1 Platinum-Induced Acute Kidney Injury

Acute kidney injury (AKI) is a clinical syndrome characterized by a decline in renal function, disturbances in water–electrolyte balance, and reduced urine output or even anuria. The causes of AKI can be broadly classified into prerenal, renal, and postrenal types. Studies have shown that the use of platinum-based antitumor drugs can lead to severe AKI. Among patients with advanced head and neck squamous cell carcinoma receiving cisplatin-based radiotherapy, the incidence of AKI can be as high as 69%. The primary mechanism involves damage to renal proximal tubular epithelial cells and includes multiple pathways such as transport and reabsorption, oxidative stress, apoptosis, and inflammatory responses. In the transport and reabsorption pathway, platinum drugs enter cells and, after a series of reactions, generate thiols, which bind to cellular macromolecules, causing adverse effects and ultimately leading to cell death. The oxidative stress mechanism involves two pathways: one is the reaction between platinum drugs and intracellular antioxidants, leading to disruption and dysfunction of the antioxidant system; the other is the damage to mitochondria in proximal tubular cells, resulting in excessive production of reactive oxygen species (ROS). Apoptosis

mechanisms include three pathways: intrinsic (mediated by activation of the BCL-2 protein family), extrinsic (mediated by death receptors on the cell membrane), and endoplasmic reticulum stress (characterized by increased CHOP levels, calcium efflux, activation of caspase-12, followed by activation of caspase-3, leading to apoptosis). The inflammatory response mechanism involves platinum drugs inducing the release of injury-related factors, activating corresponding receptors, and triggering the release of cytokines and proteins, which promote adhesion and aggregation of inflammatory cells and ultimately lead to apoptosis [7].

3.2 Mechanisms and Prevention of Nephrotoxicity Induced by Different Platinum Drugs

The mechanism of cisplatin-induced nephrotoxicity involves interference with DNA replication, leading to cellular damage. Unbound cisplatin accumulates in renal tubular cells, resulting in cell injury and death [8]. Cisplatin promotes the release and activation of tumor necrosis factor-α (TNF-α) via pathways such as MAPK and ERK, leading to mitochondrial dysfunction and apoptosis, ultimately causing renal injury [9]. Monitoring creatinine and urea levels can help prevent kidney damage, and agents such as superoxide mimetics and thalidomide may reduce its incidence. Carboplatin induces nephrotoxicity by causing the accumulation of metabolites in the kidney, which can be alleviated by increasing antioxidant substances. Nedaplatin causes renal injury by inducing damage and necrosis of the renal papilla and epithelial cell lesions, leading to continuous apoptosis and proliferation of cells; hydration therapy can be used for treatment. Oxaliplatin primarily induces peripheral neuropathy, and currently, there is no definitive treatment available for this adverse effect [8].

4. Combination Therapy of Platinum-Based Antitumor Drugs with Other Agents

4.1 Combination of Platinum-Based Drugs with Paclitaxel in Cancer Treatment

4.1.1 Introduction

Paclitaxel is a natural anticancer drug that has attracted considerable attention from researchers due to its complex chemical structure, unique mechanism of action, and wide range of applications. At present, paclitaxel remains a key focus in medical research. Given the well-established antitumor efficacy of platinum-based drugs, researchers have designed and synthesized combination regimens of paclitaxel with platinum agents to enhance anticancer activity.

4.1.2 Combination of Albumin-Bound Paclitaxel and Platinum Drugs in the Treatment of Esophageal Cancer

Albumin-bound paclitaxel is water-soluble and can reduce certain adverse reactions. The efficacy of this regimen was evaluated in esophageal cancer patients treated with a combination of PD-1 inhibitors, albumin-bound paclitaxel, and platinum-based drugs.

Patients were divided into a conventional group and a study group. The conventional group received albumin-bound paclitaxel and platinum-based chemotherapy, with intravenous infusion of nedaplatin and albumin-bound paclitaxel administered on day 1 of each cycle for three cycles. The study group received an additional PD-1 inhibitor, sintilimab, on top of the conventional regimen. The results demonstrated that this combination therapy is effective in treating esophageal cancer, with higher safety and improved prognosis [10].

4.1.3 Comparison of Efficacy Between Albumin-Bound Paclitaxel and Paclitaxel Liposomes Combined with Platinum Drugs in Lung Squamous Cell Carcinoma

Lung squamous cell carcinoma (LSCC), a subtype of lung cancer, is closely associated with long-term smoking and predominantly affects elderly male patients. Its clinical manifestations include dyspnea and cough. Studies have shown that albumin-bound paclitaxel combined with platinum drugs is effective in the treatment of LSCC.

Two experimental groups were established: an albumin-bound paclitaxel group and a paclitaxel liposome group. In the albumin-bound paclitaxel group, patients received intravenous infusion of albumin-bound paclitaxel on day 1 of each treatment cycle, followed by platinum-based drugs. In the paclitaxel liposome group, patients received intravenous infusion of paclitaxel liposomes on day 1 of each cycle, followed by

platinum-based drugs. The results indicated that albumin-bound paclitaxel combined with platinum drugs benefits patients with advanced cancer, provides clinicians with an optimal treatment option, and offers higher safety with fewer adverse reactions [11].

4.1.4 Platinum-Based Drugs Combined with Paclitaxel in the Treatment of Ovarian Cancer

Ovarian cancer, one of the three major malignant tumors of the female reproductive system, poses a serious threat to women's health and life [12–13]. Early symptoms are often nonspecific and difficult to detect, including abdominal distension, abdominal pain, indigestion, and urinary abnormalities [14]. In recent years, the standardized incidence rate of ovarian cancer among women in China has continued to rise [15]. Studies have shown that the combination of platinum-based drugs with paclitaxel is effective in the treatment of ovarian cancer.

In the study conducted by Jin Xiaohan [16], patients were divided into a lobaplatin group and a carboplatin group. In the lobaplatin group, patients received intravenous paclitaxel (135–175 mg/m²) combined with lobaplatin (50 mg), with one cycle administered every three weeks. In the carboplatin group, patients received intravenous paclitaxel (135–175 mg/m²) combined with carboplatin, with the dosage calculated based on an AUC of 4–6. Both groups followed a three-week cycle, and adverse reactions were monitored. Follow-up assessments included measurement of serum tumor marker CA125. The results showed that lobaplatin combined with paclitaxel has advantages such as higher molecular weight, better stability, good water solubility, and lower peritoneal irritation. It demonstrated clearer efficacy in initial treatment and can be used in more patients whose dosage is limited due to drug toxicity.

4.2 Research Progress on the Combination of Platinum-Based Drugs with Gemcitabine

Gemcitabine is an antitumor drug used in the treatment of locally advanced or metastatic lung cancer and pancreatic cancer, and it is also applicable in breast cancer. It is a cytidine nucleoside analog that exerts its mechanism by incorporating into newly synthesized DNA within cells. Gemcitabine can also be used in combination with other drugs for antitumor therapy, and its dosage should be administered under the guidance of a qualified physician. Adverse reactions after administration include anemia, diarrhea, rash, headache, and fever.

4.2.1 Gemcitabine Combined with Cisplatin in the Treatment of Breast Cancer

The review by Wang Guiying et al. [17] evaluated the efficacy of gemcitabine combined with cisplatin in the treatment of triple-negative breast cancer. A total of 80 patients were enrolled and divided into a GT group and a GP group. In the GT group, patients received gemcitabine hydrochloride injections on days 1 and 8 of each chemotherapy cycle, and paclitaxel on day 1, with dexamethasone acetate tablets administered prior to paclitaxel infusion. Each chemotherapy cycle lasted three weeks, and patients received 2–6 cycles depending on their condition. In the GP group, patients received gemcitabine hydrochloride in the same manner as the GT group, along with cisplatin sodium chloride injections administered on days 1–3 of each chemotherapy cycle, with the same treatment duration as the GT group. The efficacy of the two regimens was evaluated by tumor diameter, carcinoembryonic antigen (CEA) levels, carbohydrate antigen levels, and pain scores. The results showed that tumor diameter in the GP group was smaller than that in the GT group. Patients in the GP group experienced lower pain scores and higher quality of life during treatment. Although the incidence of thrombocytopenia, decreased hemoglobin, nausea, and vomiting was higher in the GP group, the incidence of constipation, fatigue, and alopecia was lower compared with the GT group. Therefore, gemcitabine combined with cisplatin demonstrated better therapeutic efficacy, milder effects, fewer side effects, and improved patient comfort, making it suitable for clinical promotion. However, challenges remain, including reducing adverse reactions and improving efficacy in genetically mutated breast cancer.

4.2.2 Gemcitabine Combined with Cisplatin in the Treatment of NSCLC

Non-small cell lung cancer (NSCLC) is a malignant tumor originating from neuroendocrine cells and can occur in the lungs, bronchi, pancreas, and intestines. Its etiology may involve genetic and environmental factors and can lead to complications such as diabetes and paraneoplastic syndromes. Clinical manifestations include bleeding, obstruction, localized masses, and pain. Patients presenting with these symptoms should seek timely medical attention and receive treatment such as surgery, chemotherapy, or targeted therapy under professional guidance. Studies have shown that cisplatin, as an antitumor agent, can effectively treat NSCLC when combined with gemcitabine.

In this study, 82 patients with NSCLC were selected and divided into a control group and an observation group. The control group received docetaxel injection combined with cisplatin, while the observation group received gemcitabine hydrochloride combined with cisplatin. Both groups underwent chemotherapy cycles of 21 days, for a total of six cycles. Treatment efficacy was evaluated based on serum tumor markers, biochemical indicators, fatigue, and cancer-related pain. The results showed that disease remission and control rates in the observation group were better than those in the control group. In addition, the Cancer Fatigue Scale (CFS) scores indicated that fatigue levels in the observation group were lower than those in the control group, and the incidence of adverse reactions was also reduced [18]. Therefore, gemcitabine combined with cisplatin is an effective antitumor regimen with mild effects and fewer adverse reactions, making it suitable for clinical application.

5. Adverse Reactions of Platinum-Based Antitumor Drugs

5.1 Adverse Reactions of Platinum Drugs in Patients with Gynecological Tumors

The review by Wang Jing et al. [19] summarized adverse drug reactions (ADRs) associated with different platinum-based antitumor drugs based on reported ADR data. The occurrence of ADRs not only affects treatment outcomes but also increases the burden on both patients and clinicians. Studies have shown that although the overall incidence of ADRs associated with platinum-based antitumor drugs is relatively low, the incidence of newly emerging ADRs is relatively high, with symptoms including systemic allergic reactions, dyspnea, rash, and skin swelling, with an incidence ranging from 38% to 50%. Therefore, researchers suggest that the use of platinum-based drugs may lead to the occurrence of new ADRs. Consequently, further research is still required to improve the safety of platinum drugs and reduce the incidence of adverse reactions.

5.2 Adverse Reactions of Different Platinum Drugs

A total of 486 cancer patients treated with platinum-based antitumor drugs in a hospital were selected, including 312 males and 174 females. The drugs used included cisplatin, oxaliplatin, and nedaplatin, with 172, 176, and 138 cases, respectively. Clinical data, including patient symptoms and treatment regimens, were reviewed to compare adverse reactions, followed by timely intervention and treatment, and documentation of improvement and recovery outcomes. The results showed that the overall incidence of adverse reactions to platinum drugs was 29.01%, with the highest incidence observed for cisplatin, followed by oxaliplatin, and the lowest for nedaplatin. The observed adverse reactions included gastrointestinal toxicity, nephrotoxicity, hematological toxicity, and neurotoxicity. Therefore, the safety of platinum-based drugs still requires improvement. The safety ranking from highest to lowest was nedaplatin, oxaliplatin, and cisplatin. Specifically, cisplatin was more likely to cause hematological toxicity, oxaliplatin was more likely to induce neurotoxicity, and nedaplatin was more likely to cause gastrointestinal and renal toxicity [20].

6. Conclusion and Perspectives

Platinum-based drugs, as a class of antitumor agents, exhibit significant efficacy, rapid onset of action, and a wide variety of types, enabling them to meet the needs of different patients. Among them, platinum (IV) drugs demonstrate good stability, high biological activity, and broad development prospects. Platinum drugs containing wogonin exhibit higher safety and better therapeutic efficacy. In addition, combination therapy of platinum drugs with other agents is more effective and safer than platinum monotherapy. However, adverse reactions of platinum drugs still require further investigation, and their efficacy and structural optimization also need in-depth research. In summary, platinum-based drugs represent an effective option for clinical cancer treatment, but their use should be guided by authoritative therapeutic regimens provided by clinicians to ensure more targeted and efficient treatment. At the same time, efforts should be made to alleviate patient suffering and improve prognosis.

Since the 1970s, platinum-based drugs have played an important role in the field of tumor therapy. With the continuous advancement of research, the types and applications of platinum-based antitumor drugs have been expanding, and their safety and diversity have been gradually improving. Nevertheless, many challenges remain.

First, drug resistance to platinum-based drugs remains a critical issue. This can be addressed by developing novel platinum compounds with new structures or by combining platinum drugs with other agents to reduce resistance. Therefore, further investigation into the mechanisms of action and resistance of platinum drugs is necessary to optimize their structures and improve therapeutic outcomes.

Second, the significant toxicity and frequent adverse reactions of platinum drugs remain major challenges that limit their clinical application. Therefore, more precise evaluation of patients' physical conditions and the development of targeted and safe combination therapy regimens are essential to reduce the incidence and severity of adverse reactions.

In conclusion, with the development of medical technology, personalized therapy, and continuous optimization of drugs, platinum-based agents are expected to be more widely used in tumor treatment, becoming an important tool in combating cancer. At the same time, they will contribute to the advancement of the medical field and provide new insights for anticancer drug research, thereby laying the foundation for future drug innovation.

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Conflicts of Interest

The authors declare no conflict of interest.

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