The Mechanism of Supramolecular Platinum Drugs Acting on Tumor or Tissue

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Abstract. In recent years, the morbidity and mortality of malignant tumors are increasing, and the incidence trend is younger. With the continuous development and application of chemotherapy drugs, chemotherapy has become one of the important means to treat tumors. Platinum drugs are the most commonly used non-specific anti-tumor drugs in the clinical treatment. Cisplatin (CCP) used in this study is a new platinum complex with supramolecular structure synthesized in China, aiming to investigate the effect of CCP on gastrointestinal tumors. The inhibitory effects of carboplatin and cisplatin on hepatocellular carcinoma, gastric cancer, colon cancer and embryonic lung fibroblast pancreatic cancer were determined by cell culture (IC50). The results showed that CCP and carboplatin (CBP) had significant inhibitory effects on liver cancer, stomach cancer, colon cancer and embryonic lung fibroblast pancreatic cancer, and the inhibitory effects were concentration-dependent. The IC50 value of CCP for liver cancer, stomach cancer, colon cancer and embryonic lung fibroblast pancreatic cancer was significantly lower than that of CBP (P<0.05), which was about 1/3~1/2 of the IC50 value of carboplatin. Meanwhile, the IC50 value of CBP and CCP for embryonic lung fibroblast pancreatic cancer was both more than 240ml/L. It indicates that the supramolecular platinum drugs CCP have a significant inhibitory effect on gastrointestinal tumors, which is stronger than the clinical effect of CBP.

Keywords: Supramolecular Drugs, Platinum Drugs, Gastrointestinal Tumors, Cissy Platinum

1. Introduction
Platinum-based drugs are a class of non-specific cell cycle anti-tumor drugs. Currently, cisplatin, carboplatin and oxaliplatin are widely used in clinical treatment [1]. These drugs can exert anticancer effects by affecting the structure and function of tumor cell DNA [2]. After entering the cell, platinum
drugs first dissociate and lose negative ions of acid radical, and then combine two molecules of water to form positively charged platinum hydrate [3]. This positively charged hydrated platinum binds to DNA, RNA and proteins in the cell. DNA of purine bases on the N7 loci is critical in platinum antitumor drug targets, thus forming the chain stated, chain between crosslinking and crosslinking between DNA - protein molecules, which is given priority to with matching crosslinking within the chain, all crosslinking local reverse or unwinding in the strand of DNA, and DNA damage, eventually lead to tumor cell cycle arrest or apoptosis [4-5].

Currently, among all anti-tumor drugs in clinical practice, platinum drugs have become first-line chemotherapy drugs and are widely used in the treatment of various solid tumors [6]. However, due to the serious side effects and frequent drug resistance of platinum drugs, the further development of platinum drugs is limited [7-8]. In order to overcome these shortcomings of platinum, we adopted a new method for the chemotherapy of platinum [9]. Modern nanotechnology has been widely used in various clinical treatments and diagnostics, which provides the possibility of targeted delivery of specific anti-tumor drugs to the tumor site. By using this method, the toxic and side effects of drugs can be reduced and the efficacy can be improved [10].

In this paper, the inhibition of CBP and CCP on liver cancer, stomach cancer, colon cancer and lung cancer was studied. The results showed that CCP and CBP had significant inhibitory effects on liver cancer, stomach cancer, colon cancer and lung fibroblast, but CCP had significantly lower IC50 values on liver cancer, stomach cancer, colon cancer and lung fibroblast pancreatic cancer than CBP (P<0.05), and the IC50 values of both CBP and CCP increased to 240ml/L.

2. Method

2.1 Platinum Anti-tumor Drugs
Platinum antitumor drugs, as first-line chemotherapy drugs, have been widely used in the treatment of various solid tumors. Cisplatin (CDDP) was the first platinum drug to be approved for the market and has been used as a standard chemotherapy regimen for more than 30 years. Due to the low concentration of chloride ions in the cell, when cisplatin enters the cell, it can quickly hydrate to form highly reactive molecules: [Pt(NH3)2Cl(OH2)]+. However, severe adverse reactions to cisplatin, including nephrotoxicity, neurotoxicity, ototoxicity, and bone marrow suppression, as well as the intrinsic and acquired resistance of various tumor cells to cisplatin, have severely limited the use of cisplatin. As a result, a series of improved platinum-based anticancer drugs have been marketed that reduce the toxic side effects and partially overcome tumor resistance.

2.2 Mechanism of Cell Resistance to Platinum Drugs
Cells to cisplatin resistance is the study of platinum drugs is facing a big problem, because once the body resistance, means that the curative effect of drug is reduced, the need to increase the dosage or change the drug, it will bring a series of negative impacts, so the cells to cisplatin resistance can help us to better study the mechanism of inhibiting cell resistance method. Studies have shown that the mechanisms of cell resistance are mainly as follows: proteins or biological small molecules inactivate cisplatin and Pt/DNA bonds are repaired by the intracellular repair system.

Proteins or biological small molecules inactivate cisplatin: most proteins in the cell contain sulfur elements, and platinum complexes have a high affinity for sulfur. Sulfur can easily be used as a coordination atom to form a new complex with platinum to inactivate cisplatin, which leads to the generation of drug resistance. Pt/DNA binding was repaired by intracellular repair system: Pt/DNA binding formed by cisplatin and DNA binding was recognized by cells and led to automatic cell apoptosis. However, intracellular repair proteins could inhibit cell apoptosis. Therefore, for some cancer cells with repair function, the massive expression of repair proteins would increase the drug resistance of cells.

3. Experiment
3.1 Experimental Materials
The materials used in the experiment are shown in Table 1.

Table 1. Materials Used in the Experiment

| Name                      | Culture                                      |
|---------------------------|----------------------------------------------|
| Cissy platinum (CCP)      | 20.0mg/ml                                    |
| Carboplatin (CBP)         | 5% of the glucose solution is dissolved       |
| RPM1640 culture           | 37℃, 50ml/LCO2                               |

3.2 Experimental Methods
(1) The cells in the logarithmic growth stage were digested with 0.25% trypsin and blow-beaten into single cells, and the cell density was adjusted to include 1×10^6/ml cells;
(2) 100 l cell suspension was added to each well in the 96-well culture plate, and then cultured for 4h;
(3) CCP and CBP solutions were diluted separately, and blank control Wells were set at each concentration and 3 multiple Wells were set at each concentration. After the drug was added, the cells were put back into the CO2 incubator for 64h
(4) The supernatant was carefully absorbed, and 200 l tetrazolam (MTT) solution with concentration of 5g/l was added into each well, and then placed in a CO2 incubator for further culture. The supernatant was absorbed after 4h and washed twice with PBS solution.
(5) After that, 200 l dimethyl sulfoxide was added and placed on a shaker to oscillate for 10min. Finally, the absorbance value was measured with an enzyme marker. The detection wavelength was 570nm and the reference wavelength was 450nm.

The experiment was repeated three times for each cell line.

3.3 Data Processing
All data were analyzed using SPSS18.0 statistical software. Measurement data were expressed as mean ± standard deviation (x±s) and t test was used. The rate of count data was expressed using the chi-square test. P<0.05 indicated a statistically significant difference.

4. Discussion
Since platinum was approved for clinical use, it has been widely used for chemotherapy of various solid tumors. However, due to the premature hydration of cisplatin in the blood circulation and its combination with human serum protein (HSA) and other biomolecules, a large number of toxic and side effects can be produced. Another serious disadvantage is the development of drug resistance. The main reasons of platinum resistance are as follows: first, the absorption of the drug is reduced; Second: increased detoxification of drugs by intracellular mercaptan compounds such as glutathione (GSH) metallothionein (MT). In order to reduce the hydration induced by HSA binding and reduce the detoxification of GSH in cells, a ligand with a three-dimensional structure was first combined with platinum to improve its steric hindrance. Then, in order to improve drug absorption, the spatially structured drug is further loaded onto the nanoparticles, thereby avoiding the reduction in traditional nano-drug absorption. Cisplatin studied in this paper is a supramolecular compound. Supramolecular substance means that a variety of molecules are tightly bound through non-covalent bonds, such as hydrogen bonds, to form a molecular polymer with new properties and functions such as recognition, selection, energy transfer and information transfer. Supramolecular materials mainly of subject and object drug molecule under certain conditions by non covalent bonds between the molecules to form a kind of stable supramolecular materials, its function mainly is to change drug membrane transport, make drugs that can be applied effectively to targets, increase its affinity with specific targets, thus improve the bioavailability of drugs and reduce the side effects. Cisplatin takes carboplatin as the main molecule and citric acid as the guest molecule, and forms a kind of cage-like polymer through
intramolecular hydrogen bond. This supramolecular compound can effectively prevent and protect carboplatin from binding to water, reduce its hydrolysis rate, increase its stability and reduce its toxic and side effects. In this paper, the inhibition effects of supramolecular platinum drugs CCP and CBP on liver cancer, stomach cancer, colon cancer and embryonic lung fibroblast pancreatic cancer were observed through cell culture experiments. The experimental results are shown in Figure 1 and Figure 2.

![Figure 1](image1.png)

**Figure 1.** Inhibition of CCP and CBP by Supramolecular Platinum Drugs

![Figure 2](image2.png)

**Figure 2.** T and P Values of the Supramolecular Platinum Drugs CCP and CBP on the Inhibition of Liver Cancer, Stomach Cancer, Colon Cancer and Embryonic Lung Fibroblast Pancreatic Cancer

According to the results in figure 1 and figure 2, the supramolecular platinum drug cisplatin has an inhibitory effect on liver cancer, stomach cancer, colon cancer and embryonic lung fibroblast pancreatic cancer, and the inhibitory effect is concentration-dependent, indicating that supramolecular compounds have an obvious anti-digestive system tumor effect. In addition, the IC50 value of cisplatin on liver cancer, stomach cancer, colon cancer and embryonic lung fibroblast pancreatic cancer was significantly lower than that of carboplatin (P<0.05), which was about 1/3~1/2 of the IC50 value of carboplatin. Meanwhile, the IC50 value of both cisplatin and carboplatin on embryonic lung fibroblast pancreatic cancer was more than 240ml/L, indicating that supramolecular platinum drugs had stronger anti-tumor effect than carboplatin. In conclusion, supramolecular platinum drugs have a significant inhibitory effect on gastrointestinal tumors, and their inhibitory effect is stronger than that of carboplatin.

Digestive system tumors are the most common type of tumors in China. In terms of chemical drug therapy, there are many kinds, among which platinum drugs are the commonly used anti-tumor drugs in the clinical treatment of digestive system tumors. In the aspect of drug treatment of colon cancer, generally, irinotekang or oxaliplatin combined with aldehydrotetrahydrofolic acid and 5-fluorouracil are used for chemotherapy, in addition, anti-epidermal growth factor receptor antibody is used for treatment, and its clinical effect is significantly improved. In the treatment of gastric cancer, aldehyde-tetrahydrofolic acid and 5-fluorouracil combined with oxaliplatin is the most common chemotherapy regimen. Platinum-based drugs combined with gemcitabine hydrochloride are still used in the clinical treatment of pancreatic cancer. However, there is a lack of effective drugs for liver...
cancer and esophageal cancer. Therefore, the clinical treatment of digestive system tumor needs to be further studied, need to find a treatment of digestive system tumor really effective drugs or programmes.

5. Conclusion
Supramolecular materials mainly of subject and object drug molecule under certain conditions by non covalent bonds between the molecules to form a kind of stable supramolecular materials, its function mainly is to change drug membrane transport, make drugs that can be applied effectively to targets, increase its affinity with specific targets, thus improve the bioavailability of drugs and reduce the side effects. Cisplatin takes carboplatin as the main molecule and citric acid as the guest molecule, and forms a kind of cage-like polymer through intramolecular hydrogen bond. This supramolecular compound can effectively prevent and protect carboplatin from binding to water, reduce its hydrolysis rate, increase its stability and reduce its toxic and side effects. Through cell culture experiments, the supramolecular platinum drug cisplatin was found to have an inhibitory effect on liver cancer, stomach cancer, colon cancer and embryonic lung fibroblast pancreatic cancer in a concentration-dependent manner, indicating that supramolecular compounds have an obvious anti-digestive system tumor effect. In addition, the IC50 value of cisplatin on liver cancer, stomach cancer, colon cancer and embryonic lung fibroblast pancreatic cancer was significantly lower than that of carboplatin (P<0.05), which was about 1/3–1/2 of the IC50 value of carboplatin. Meanwhile, the IC50 value of both cisplatin and carboplatin on embryonic lung fibroblast pancreatic cancer was more than 240ml/L, indicating that supramolecular platinum drugs had stronger anti-tumor effect than carboplatin. In conclusion, supramolecular platinum drugs have a significant inhibitory effect on gastrointestinal tumors, and their inhibitory effect is stronger than that of carboplatin.

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