Dean&Francis
ISSN 2959-409X

Platinum Drug Resistance in the Treatment of Lung Cancer Patients

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Abstract:

As a typical example of highly prevalent cancers worldwide, lung cancer poses a serious threat to human health. Therefore, this disease has various kinds of treatments. Among them, the treatment with platinum-based drugs has been greatly restricted due to the drug resistance. This problem poses a threat to the modern cancer medical system. In recent years, researchers have made great efforts to solve this difficult problem. Research on platinum-based drug resistance has achieved certain results. In clinical practice, some lung cancer patients have received effective treatment. This article analyzes the research on drug resistance, why lung cancer cells can produce drug resistance during the treatment process. The research was conducted from the aspects of the mechanism of action of platinum-based medicines, the expression of genes in lung cancer patients, the dysregulation of microRNAs, and epigenetics. Through various experimental studies, methods for improving the responsiveness of lung cancer cells to related medications have been obtained. For example, combined drug therapy, inhibition of gene expression, assisted treatment with nanotechnology, and combined with other therapies such as immunotherapy. The research can enhance the cure rate of lung cancer patients and provide a new approach for the effective treatment of lung cancer. However, at present, this problem still requires more innovative approaches to make lung cancer cells respond to related medications, so as to provide more options for cancer patients. In the future, in clinical research, modern technological methods can be combined with drugs to enhance the effect of platinum-based medications on lung cancer patients.

Keywords: Lung cancer, Platinum drugs, Drug resistance.

1. Introduction

Lung cancer is one of the most common malignant tumors in most countries, there are about 11% to 13% of all new cancer cases and is also a significant cause of cancer-related deaths worldwide. Among them, platinum-based drugs, which are the typical representatives of chemotherapy drugs in treatment at present and as one of the important and useful treatment methods for lung cancer. After the effective treatment with platinum-based drugs, the lifespan of lung cancer patients worldwide can be effectively extended. At the same time, the possibility of curing lung cancer patients will also increase. The platinum-based medications oxaliplatin, carboplatin, and cisplatin are frequently used as some chemotherapy drug for treating cancer. Platinum medications' adverse effects, including drug resistance, high systemic toxicity, and lack of selectivity, severely restrict their clinical use [1]. Some patients respond well to platinum-based drugs in the early treatment stage. However, after some time passed, some patients develop drug resistance and significantly reduce the effectiveness of the drug, which greatly limits the drug in treating lung cancer patients in clinical practice. Platinum-based drugs have a very complicated resistance mechanism that includes reprogramming tumor metabolism, apoptosis escape, and nuclear DNA damage repair. Through metabolic variability, tumor cells can alternate between glycolysis and mitochondrial oxidative phosphorylation (OXPHOS), and they can become resistant to chemotherapy medications [2]. Additionally, it has been demonstrated that medications like cisplatin, carboplatin, oxaliplatin, and others can react with other compounds that have an aromatic ring with a free electron group in the structure of the nitrogen atom. As a result, these structures might affect DNA nucleobases in a competitive way [3]. How to deal with drug resistance to platinum-based drugs has always been a challenge faced by clinical practice. In the face of this challenge, the first step is to investigate the reasons why lung cancer patients develop resistance to platinum-based drugs, and then further explore how to reduce the resistance of lung cancer cells to platinum-based drugs.

The main content of this article is divided into two parts. The first part is about the causes of drug resistance, and the second part is about how to deal with platinum-based drug resistance in clinical research. Through further analysis of the characteristics of platinum-based drugs, in clinical research, the method of enhance the effectiveness of related drugs and reduce it resistance, by adjusting the drug dosage, combining it with other chemotherapy drugs or targeted drugs for combination therapy, inhibiting the expression of related genes, and using nanotechnology. In addition, other methods such as immunotherapy can also be used in combination with platinum-based drugs to target lung cancer cells. This research can not only improve the targeting of tumors but also help eliminate drug resistance, making the effect of platinum-based drugs in the treatment of lung cancer more significant, and promoting the research on new platinum-based drugs in clinical research.

2. The Mechanism of Action of Platinum-based Drugs

There are many platinum-based drugs used for treating cancer. Among them, cisplatin, which drug first came into people's view in 1965 and was approved by the US Food and Drug Administration in 1978. In clinical practice, it is usually chosen as the primary platinum-based anti-cancer medication [4]. Cisplatin, as a commonly used chemotherapy drug, usually enters cells through passive diffusion and is subsequently activated. In the cytoplasm, various forms of cisplatin can react with various cell membranes and cytoplasmic components, as well as nuclear DNA and RNA. To form the positively charged monohydrate and dihydrate forms of cisplatin, it is necessary to replace the chloride ion complex with water molecules. In clinical studies, the mechanism of cisplatin resistance is multifactorial. Firstly, it is related to the activation of anti-apoptotic signals. This way, it is possible to resist cisplatin-induced cell death in this treatment. Secondly, the active efflux of the drug from the cytoplasm is also an influence factor, which method can reduce the drug concentration within the cells. Moreover, the epigenetic regulation of microRNAs(miRNA) can influence the expression of related drug resistance genes. In addition to these, the disruption of growth regulatory pathways by obtaining growth factor independence, the inhibition of the immune system, and the low expression of antigens that can activate T lymphocytes all are related to the drug's resistance mechanism [4]. Therefore, to explore the reasons why lung cancer patients develop resistance to platinum-based drugs, in-depth research can be conducted from aspects such as the expression of related genes in patients themselves, the expression of miRNA, epigenetic mechanisms, and the tumor microenvironment. At the same time, these aspects can also be utilized to improve the sensitivity of people with cancer to related drugs.

3. The Mechanisms of Drug Resistance in Lung Cancer Patients

Platinum-based drugs are among the effective chemother-

ISSN 2959-409X

apeutic agents widely used in the treatment of lung cancer. However, some patients do not respond to platinum-based drugs, and those who initially benefit from the treatment will eventually develop resistance to these drugs. Drug resistance refers to the tolerance of pathogens to the effects of drugs, resulting in a decline in drug efficacy. Therefore, it is crucial to explore the reasons for drug resistance and enhance drug sensitivity according to the conditions of different patients.

On the one hand, the gene expression of lung cancer patients themselves can lead to resistance to platinum-based drugs. For example, the nucleus factor of activated T cells and cytoplasmic 1(NFAT2) gene, when they overexpress, will lead to the deterioration of various cancers during their disease progression and their resistance to therapeutic drugs. In a carboplatin-resistant lung cancer cell line, the overexpression of NFAT2 will have a negative impact on the prognosis of lung cancer patients, indicating its role in regulating drug response [5]. The researchers have cloned tongue cancer resistance-related protein 1 (TCRP1), a newly discovered gene, has been shown in studies to have significantly higher expression levels in lung cancer samples than in the normal control group, confirming that TCRP1 can improve the situation where related drugs gradually lose their effectiveness against lung cancer cells [6]. Therefore, inhibiting the expression of the NFAT2 and TCRP1 genes can restore the efficacy of platinum-based drugs.

On the other hand, the dysregulation of miRNAs may lead to the sensitivity of non - small cell lung cancer (NSCLC) to platinum-based drugs. miRNAs are small, non-coding molecules that participate in the regulation of gene expression and biological processes, such as cell proliferation, apoptosis, and the cellular response to chemotherapy drugs. Compared with the corresponding non-malignant tissues, the expression of miRNAs in lung cancer is often dysregulated [7]. Recently, in clinical trials, researchers have found that a connection between the expression level of miR-572 and NSCLC. By detecting the expression level of miR-572 in 46 NSCLC and paracancerous samples. And through functional tests, which experiment can conducted to evaluate the regulatory effect of miR-572 on the proliferation and migration abilities of lung cancer cells. The final step is to conduct the luciferase assay method to test the downstream genes of miR-572, and their roles in the development of NSCLC were investigated through rescue experiments. It was discovered that the expression of miR-572 was too high in NSCLC samples. A high miR-572 level will lead to a poor prognosis in NSCLC patients, as high-level expression will increase the probability of lymphatic metastasis and distant metastasis in lung cancer patients [8]. The above content demonstrates that miRNA dysregulation is associated with platinum-based drug resistance in lung cancer patients.

Apart from the above two points, epigenetics also affects the resistance to platinum-based drugs. In clinical practice, the genes that control the absorption, excretion (ADME), distribution and metabolism of drugs are all related to various epigenetic factors. What is even more worth mentioning are the processes that play a crucial role in the treatment of cancer, such as cell multiplication, DNA repair, apoptosis, and signal transduction. These processes also have a profound impact on the development of drug resistance in platinum-based therapies. Therefore, epigenetic mechanisms such as histone modification, DNA methylation, microRNAs and long non-coding RNAs can influence the resistance to platinum-based drugs during chemotherapy [9]. Take ncRNAs as an example, they can regulate the expression of certain transport proteins, thereby altering the present situation of platinum-based drugs gradually lose their effectiveness. The overexpression of this drug efflux transporter in cancer cells enhances the efflux of chemotherapeutic drugs from the inside of the cells. Therefore, by overexpressing these drug efflux transporters, drugs are unable to act on cancer cells, enabling the cancer cells to “evade” the treatment, which leads to a decline in the effectiveness of chemotherapy. At the same time, some drug transporters, are involved in the uptake or excretion process of platinum-based drugs [10]. Therefore, the regulatory effect of ncRNA on these drug transporters is a crucial step in the development of drug resistance.

4. Methods to Enhance the Sensitivity of Lung Cancer Patients to Platinum-based Drugs

4.1 Combination Therapy for Enhancing the Sensitivity one Platinum-based Drugs

Combination therapy for enhancing the sensitivity one Platinum-based Drugs based on the nature of drug resistance, combination therapy is a very promising approach in terms of reducing drug resistance. For patients resistant to platinum-based drugs, non-platinum-based chemotherapy drug combination regimens can be used. By combining drugs with different mechanisms of action, cross-resistance can be reduced, and the effective treatment time can be prolonged. Creating new platinum(IV)-based prodrugs is one of the methods.Through this approach, combined therapy can be achieved. The essential characteristic of this prodrug is that it possesses a functional active ligands. This method can achieve two purposes. Firstly, it enables

the candidate drugs to act on multiple targets. Secondly, it enhances the kinetic inertness of platinum complexes, allowing the active drugs to accumulate more fully at the target site. In this study, a platinum(IV)-based prodrug platin-c was synthesized. The ligand at the end of this compound is the active component of the traditional herbal ingredient curcumin. This complex exhibited a better chemotherapy effect than the individual components in the A2780/CP70 platinum-resistant cell line. Furthermore, the amine-terminal biodegradable polymer was functionalized with triphenylphosphine ion (TPP) cations, successfully constructing a drug delivery platform targeting mitochondria. This experiment successfully achieved the functional combination of the two components through the use of a high-performance liquid chromatography method based on the optical properties of curcumin and a complementary technique based on platinum-inductively coupled plasma mass spectrometry, and quantitatively detected the loading amount of platinum-curcumin in the nanoparticles. This study advances the understanding of the cisplatin prodrug approach to combine chemotherapeutic and inflammatory effects in accessing combinatory pathways [11]. This study further deepens our understanding of this strategy of combining cisplatin prodrugs with chemotherapy and anti-inflammatory effects, thereby exploring more diverse and effective ways of drug combination.

4.2 Inhibit the Expression of Related Genes

NFAT2 plays a crucial role in promoting cell proliferation and overcoming DNA damage and cell cycle arrest induced by carboplatin. By using cyclosporine A to inhibit its nuclear translation and knockdown NFAT2 or inhibit its nuclear translocation, it is possible to restore the sensitivity of drug-resistant cell lines to carboplatin by inducing DNA damage, blocking the cell cycle process, and activating apoptosis death. Therefore, clinical research has proposed that NFAT2 is a possible therapeutic target that can be used to overcome carboplatin resistance in lung cancer [5]. Furthermore, research has demonstrated that TCRP1 helped human lung and ovarian cancer cells become resistant to DDP and L-OHP. The cells become resensitive to the platinum-based drugs when TCRP1 was knocked down. In the meantime, the study found that initial resistance to DDP and L-OHP in lung cancer cells was positively correlated with TCRP1 expression [6]. The above experiments demonstrate, the expression of genes such as NFAT2 and TCRP1 can improve the situation where platinum-based drugs gradually lose their effectiveness against lung cancer cells. Therefore, in clinical research, it is feasible to make the treatment with related drugs more effective by inhibiting the expression of these related genes.

4.3 Enhancing Sensitivity to Platinum-based Drugs through Nanotechnology

Research has demonstrated that biocompatible nanoparticles composed of amphiphilic triblock copolymers (polyethyleneimine-polybutyl ether-polyethylene glycol (PEI-PCL-PEG)) prepared by microfluidic assembly, carrying siRNAs targeting ERCC1 and XPF, achieve effective gene silencing and make lung cancer cells more sensitive to cisplatin. This study proves that PEI-PCL-PEG micelles carrying ERCC1 and XPF siRNAs can effectively reduce the expression of ERCC1/XPF proteins. Secondly, it indicates that nanoparticles carrying siRNAs enhance the sensitivity of platinum-based drugs in an in vitro p53 wild-type non-small cell lung cancer model. At the same time, the research results show that targeting ERCC1/XPF through nanoparticles mediated is serviceable and it is expected to become a new treatment method targeting the ERCC1/XPF [12]. Meanwhile, scientists are also exploring new alternative methods for delivering drugs to cancerous areas. Nanotechnology holds great promise in this regard. By creating new nano-drugs, the dosage of the drugs can be reduced to the absolute minimum level, thereby limiting the toxic effects of the drugs. On one hand, it allows for so-called targeted therapy, avoiding healthy cells. On the other hand, it can introduce other treatment options, such as direct radiotherapy to the cancerous area. Moreover, it will also provide the possibility of diagnosis [3]. All in all, nanotechnology holds great promise in enhancing the efficacy of raleted drugs and provide better chances for lung cancer patients to receive more effective treatment using platinum-based drugs.

4.4 Combined with Other Treatment Methods

In clinical studies, the prognosis of lung cancer patients is still not satisfactory, and there is an urgent need to develop more effective treatment methods. In recent decades, a series of studies have demonstrated the importance of the immune system in the control of malignant diseases, and immunotherapy has gradually attracted the attention of researchers. Through the passive or active anti-tumor responses of the immune system to malignant tumors, it is an extremely attractive treatment strategy. Thanks to the researchers' in-depth understanding of the human immune system, immunotherapy has achieved a breakthrough, and its application in lung cancer treatment has been expanded as a result [13]. Immunotherapy is one of the fundamental approaches for treating cancer. The types of immunotherapy include therapeutic vaccines, immunomodulators, autologous cellular therapies, and monoclonal

ISSN 2959-409X

antibodies (mAbs) targeting checkpoint inhibition signals related to activated T cells or cancer cells. However, since each treatment method has its own unique advantages and disadvantages, it is more advisable to combine multiple therapies or treatment strategies with immunotherapy [14]. Combining platinum-based drug treatment with immunotherapy can offer new hope for breaking through the barrier of platinum drug resistance, while enhancing the cytotoxicity against lung cancer cells. Significantly enhance the treatment effect of lung cancer.

5. Conclusion

Compared with other types of cancer, the number of lung cancer patients is larger and it is one of the cancers that are particularly prevalent worldwide. If patients are diagnosed early and receive curative treatment, they are more likely to survive. This article elaborates on the mechanism of action of platinum-based drugs, the reason why platinum-based drugs gradually lose their effectiveness against lung cancer cells, and the methods to improve the efficacy of the drug while enhancing the responsiveness of lung cancer cells. A certain summary has been made on how to make platinum-drugs more effective in treating lung cancer cells during the treatment process. Nowadays, many studies have proved that compared with healthy individuals, the expression of miRNA in lung cancer patients is abnormal, and the expressions of genes such as NFAT2 and TCRP1 are all related to the resistance to platinum drugs. Therefore, by influencing the expression of related genes, using combination therapy, and employing nanotechnology and other techniques, the targeting of tumors can be improved while eliminating drug resistance, making the cure of lung cancer with platinum drugs more effective. Furthermore, this article only discusses platinum-based drugs gradually lose their effectiveness against lung cancer cells, so the discussion on the resistance to platinum-based drugs is not comprehensive. Platinum drugs, as one of the commonly used chemotherapy drugs, can also explore the mechanism of platinum drug resistance in other cancers or further explore new platinum drugs during the process of breaking through the resistance of lung cancer to platinum drugs. All in all, it is hoped that this problem can be combined with modern technological means to achieve more effective and safer treatment methods.

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