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Exploration of the Mechanism of Action of Cisplatin and Paclitaxel in the Treatment of Triple-Negative Breast Cancer

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Abstract. Triple-negative breast cancer (TNBC) is a particularly aggressive type of breast cancer characterized by the absence of estrogen receptor, progesterone receptor, and HER2 expression. Due to these receptor characteristics, traditional endocrine therapy and HER2-targeted treatment are ineffective, and the treatment options are limited. This article discusses the mechanism of action of two key chemotherapy drugs used to treat triple-negative breast cancer: cisplatin and paclitaxel (PTX). Cisplatin is a platinum-based compound with a planar square geometric structure that can form water-soluble complexes in the body. These complexes can generate intramolecular and intermolecular cross-linkages with DNA, thereby interfering with DNA replication and ultimately leading to cell apoptosis. Paclitaxel is a naturally extracted plant compound with a complex four-ring taxane structure. It functions by binding to the M ring of β-tubulin, thereby enhancing the interaction between tubulin dimers and stabilizing microtubules. Stable microtubules prevent cells from progressing to the next stage, causing them to stop at the G2/M phase, and subsequently triggering cell apoptosis. A deeper understanding of these mechanisms can help optimize the treatment plan for triple-negative breast cancer, given its tendency for early metastasis and poor prognosis. This may potentially serve as a new adjuvant treatment option.

Keywords: triple-negative breast cancer, cisplatin, paclitaxel

1. Introduction

1.1. Symptoms

Breast cancer may present as a palpable, usually hard and painless lump in the breast or armpit area. However, some lumps may cause pain. It can also lead to changes in the size or shape of the breast, such as asymmetry or a significantly enlarged breast on one side, as well as changes in the skin, such as redness, depression, or a pitted texture resembling an orange peel. These indicate tissue changes. Changes in the nipple may also occur, including nipple retraction, abnormal discharge (especially bloody or clear), or irritation. Breast or nipple pain is relatively rare, but it may occur when the tumor invades the surrounding tissues. Triple-negative breast cancer (TNBC) is a specific type of breast cancer. TNBC patients lack expression of estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2 (HER2). TNBC is a highly aggressive type of breast

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cancer. Notably, the characteristics of TNBC are rapid growth and high risk of metastasis, especially to the lungs and brain [1]. Unlike other subtypes of breast cancer, TNBC lacks targets for hormones and HER2, making endocrine therapy and HER2-targeted therapy ineffective.

1.2. Impact and number of mortalities

Breast cancer is one of the most common cancers in the world. Around 2.3 million new cases and over 680,000 fatalities are related to the disease annually, according to the World Health Organization (WHO) [2]. Due to a variety of factors, including early identification, treatment effectiveness, and access to healthcare, the incidence and mortality rates of breast cancer vary greatly between areas. African American populations, young women, and those with the BRCA1 gene mutation are more likely to be affected by TNBC. It accounts for between 10 and 20 percent of all incidences of breast cancer worldwide.

1.3. Significance in China and other countries

According to GLOBOCAN, in 2022, the global number of new breast cancer cases and deaths was 2.297 million and 666,000, respectively, which includes Chinese cases about 15.6% and 11.3% respectively [3].

1.4. Drugs used to treat the disease and their origins

1.4.1. Cisplatin

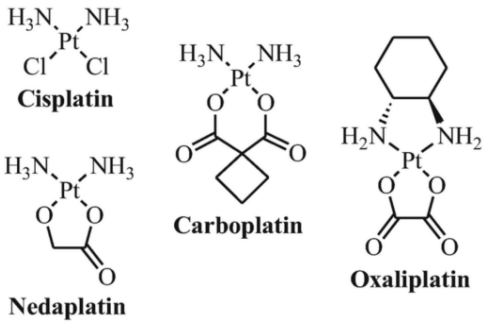

Figure 1. The structure of cisplatin and other platinum-based complexes

Cisplatin was discovered in the 1960s by Barnett Rosenberg during an experiment on bacterial cell division [4].(Cisplatin had been chemically synthesized as early as 1845 by Michel Peyrone. Today, cisplatin is industrially produced from platinum salt through controlled synthesis, serving as a cornerstone chemotherapy drug. The structure of cisplatin is shown in Figure 1.

1.4.2. Paclitaxel (PTX)

Paclitaxel is an anticancer compound of plant origin, initially discovered between 1962 and 1971 from the bark of the slow-growing Pacific yew tree, scientifically known as Taxus brevifolia. However, a tiny amount of paclitaxel is produced because the yew tree will die when the drug is removed from its bark. The primary method for obtaining paclitaxel is semi-synthesis, which involves extracting 10-decanoyl-bacillus III from renewable Taxus branches and combining it with synthetic side chains.

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2. Description of chemical structures of drugs

2.1. Cisplatin

The system name of Cisplatin is cis-diamminedichloroplatinum(II). The molecular formula of cisplatin is $Pt(NH_3)_2Cl_2$. The chemical structure of cisplatin is a highly symmetrical and simple planar tetracoordinate structure, with the central metal being Pt(II), an electronic configuration of $5d^8$, and a hybridization mode of dsp^2. This forms an almost ideal square coordination geometry (The bond angles for N-Pt-N and Cl-Pt-Cl are close to 90 degrees). Crystallographic data show that the Pt—N bond length is about 2.02 Å, and the Pt—Cl bond length is about 2.30 Å. The molecule is approximately symmetric in D_2h, has no chiral centers, and exists only as geometric isomers.

2.2. Paclitaxel (PTX)

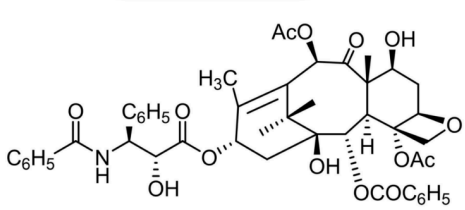

Figure 2. The chemical structure of paclitaxel

The molecular formula of paclitaxel is $C_{47}H_{51}NO_{14}$. The structure of paclitaxel is shown in Figure 2. Its structure is centered around a fused 6/8/6-tricyclic taxane core, which is connected to a distinctive oxetane (D-ring), creating a rare 6/8/6/4 tetracyclic system. Within the taxane skeleton, there are 11 stereogenic centers at positions C-1, 2, 3, 5, 7, 8, 9, 10, and 13, as well as on the side chain at C-2' and C-3'. The absolute configuration of these chiral centers has been determined using X-ray crystallographic analysis to be (2aR, 4S, 4aS, 6R, 9S, 11S, 12S, 12aR, 12bS). The molecule contains a variety of functional groups; acetoxy groups are present at positions C-2 and C-7, the C-10 position may contain either an acetoxy or a hydroxyl group, and a ketone group is found at C-9. At C-13, an ester linkage connects to an N-phenylacetyl-3-phenylisostearoyl side chain, which incorporates an extra stereocenter (2'R, 3'S). This side chain is essential in forming a key hydrogen bonding interaction with the β-tubulin subunit residues Thr276 and Arg282, mediated by the hydroxyl group at C-2' and the amide at C-3'.

3. Discussion of drug pharmacology

3.1. Cisplatin

Cisplatin exhibits cytotoxic effects that vary with cell type and drug concentration, primarily through disruption of transcription and DNA replication processes. Furthermore, it can also eliminate tumors by triggering cell apoptosis. This process is achieved by activating multiple signaling pathways, including the calcium signaling pathway, the death receptor signaling pathway, and the mitochondrial pathway. After cisplatin is introduced into the body, one of the chloride ions is gradually substituted by a water molecule, resulting in the formation of $[PtCl(H_2O)(NH_3)_2]^+$. In this newly formed complex, the water molecule can readily dissociate, enabling the platinum ion to bind with a specific site on a DNA base. Subsequently, the second chloride ion is released, allowing

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platinum to form intrastrand or interstrand cross-links at two locations (as shown in Figure 3), as illustrated in the lower pathway of the figure below [5].These crosslinks cause the DNA replication process in cancer cells to malfunction, ultimately resulting in programmed cell death. Since cancer cells usually do not exhibit cytotoxic reactions and apoptosis, cisplatin may also cause a series of adverse reactions, including bone marrow suppression, nephrotoxicity, and/or neurotoxicity [6].

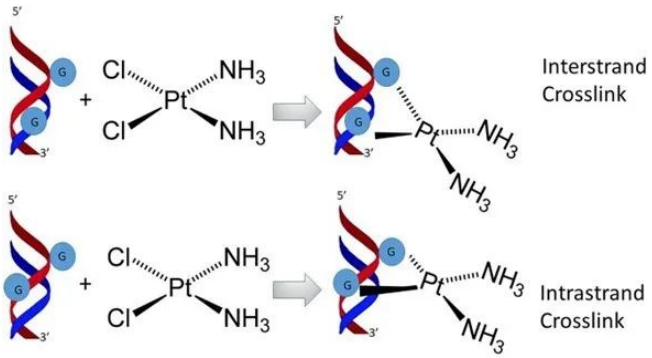

Figure 3. Interstrand crosslink and intrastrand crosslink of DNA and cisplatin

3.2. PTX

Paclitaxel exerts its anticancer effect by specifically binding to tubulin. Microtubules, key cytoskeletal components, consist of α- and β-tubulin heterodimers that maintain a dynamic equilibrium of polymerization and depolymerization—critical for spindle fiber formation and chromosome segregation during cell division. Paclitaxel disrupts this balance by promoting tubulin polymerization and stabilizing microtubules. It binds to a unique site in the M-loop region of β-tubulin, a domain vital for inter-dimer interactions in microtubule assembly. This binding induces a conformational change in β-tubulin, strengthening lateral interactions between adjacent dimers and "locking" microtubules in a polymerized state to prevent disassembly. Through hydrogen bonds with residues such as Asn256 and His229, and hydrophobic interactions with surrounding side chains, paclitaxel enhances the stability of the complex. This blocks microtubule depolymerization, which is essential for mitosis, arresting cells in the G2/M phase and triggering apoptotic death. Its precise targeting of microtubule dynamics makes paclitaxel a potent cancer therapy [7].

4. Conclusion

This study comprehensively explored the molecular structures and anti-cancer mechanisms of cisplatin and paclitaxel, two key chemotherapeutic drugs for triple-negative breast cancer (TNBC). Cisplatin is a planar square compound centered on a platinum (II) ion, whose efficacy depends on its binding to DNA in the body, forming intra- and inter-strand cross-links, thereby interfering with the DNA replication process of cancer cells and inducing apoptosis. However, due to its lack of specificity, it is often accompanied by adverse reactions such as nephrotoxicity. Paclitaxel, on the other hand, is a naturally occurring four-ring taxane with a 6/8/6/4 ring system. It enhances microtubule stability by binding to the M ring of β-tubulin, leading to programmed cell death after cell cycle arrest at the G2/M phase [8].

The mechanism, as mentioned above, reveals that although cisplatin and paclitaxel have different targets in combating TNBC, they are complementary in their approach. This provides an important treatment option for this breast cancer subtype that lacks effective therapeutic means (as endocrine therapy and HER2-targeted therapy are ineffective for it) [9].However, the toxic side effects and

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drug resistance caused by cisplatin still limit its clinical application. Therefore, future research should focus on optimizing its chemical structure to enhance targeting or developing paclitaxel derivatives with greater safety advantages. Overall, the in-depth analysis of the mechanisms of action of these two drugs lays a theoretical foundation for creating more efficient and safer TNBC treatment strategies and improving the long-term prognosis of patients.

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