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ADC for the Treatment of Breast Cancer

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Abstract: With environmental factors, personal factors and people's negligence of health issues, breast cancer has become a very serious problem for contemporary women. This has become one of the most common cancer diseases among women nowadays and has a very high mortality rate. In addition to traditional chemotherapy methods, antibody-drug conjugates (ADC) represent a novel therapeutic approach in the medical and pharmaceutical fields, especially in tumor treatment. ADC refers to the precise delivery of drugs to cancer cells using antibodies, which can address the side effects brought about by chemotherapy. Three ADC drugs will be mentioned in this article including Kadcyla, Enhertu and Trodelvy. This article will mainly discuss the mechanisms of three different types of ADC drugs, comparing the clinical manifestations in breast cancer and future development of ADC treatment for the breast cancer.

Keywords: Antibody-Drug Conjugates; Breast Cancer; HER2; Targeted Therapy

1. Introduction

Nowadays, breast cancer is one of the most concerning cancers in society, and it has gradually become the main cause of death among women. The continuous improvement and progress of medical science, the damage caused by traditional chemotherapy methods to body cells is irreversible, leading to serious sequelae. However, with the early detection and treatment of breast cancer, as well as the continuous improvement of ADC drug technology, which has the ability to selectively kill cancer cells, it is constantly developing in the field of cancer. According to the clinical experimental results, the future is promising.

2. Literature Review

2.1 Kadcyla

Kadcyla is a first-generation ADC drug widely used in HER2-positive breast cancer and has been approved and used by the FDA. This drug combines the dual mechanisms of targeted therapy and chemotherapy to enhance the therapeutic efficiency of this drug and reduce damage to normal human tissues. Kadcyla is formed by the stable conjugation of the anti-HER2 monoclonal antibody trastuzumab and the cytotoxic Wurtatin. Clinical studies have shown that in multiple key Phase III clinical trials, the progression-free survival (PFS) and overall survival (OS) of patients with HER2-positive advanced breast cancer have been significantly prolonged. The mechanism of Kadcyla is that the Kadcyla antibody Trastuzumab specifically binds to the HER2 receptor on the surface of HER2-positive breast cancer cells. The complex enters the lysosome through endocytosis and, in the acidic lysosome, after the non-lysable linker is degraded by protease and releases DM1, DM1 is a Maytansine-type microtubule inhibitor. It binds to tubule proteins, preventing microtubule aggregation and ultimately interfering with cell division, causing the cell cycle to be arrested at the G2/M phase and ultimately triggering apoptosis. (cite) (Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer) The research conducted by EMILIA, T-DM1 could prolong the median OS to 30.9 months, compared with 25.1 months in the control group. Side effects such as hair loss and thrombocytopenia were relatively low[1].

2.2 Enhertu

Enhertu is another ADC drug targeting HER2-positive breast cancer, formed by coupling trastuzumab with the novel topoisomerase I inhibitor delutecan. In 2020, the drug received accelerated approval from the US FDA for the treatment of HER2-positive breast cancer. Studies have shown that Enhertu, especially in advanced patients who are resistant to traditional treatments, demonstrates stronger efficacy compared to T-DM1. The mechanism of Enhertu is that Trastuzumab partially targets the HER2 receptor and is endocytosed into HER2-

expressing cells after binding. Enzymes in lysosomes clease the tetrapeptide linker, releasing the potent chemotherapy drug Deruxtecan (DXd). DXd is a topoisomerase I inhibitor, which interferes with the DNA replication process, causes double-stranded DNA breaks, and leads to the death of cancer cells. In addition, Enhertu also has a bystander effect. The released DXd can spread to nearby tumor cells, enhancing the therapeutic scope. For example, according to the DESTINY-Breast03 study, this is a controlled experiment. The laboratory technicians compared the efficacy and safety of Enhertu trastuzumab deruxtecan with the standard ADC drug T-DM1rastuzumab emtansine in the second-line treatment of HER2-positive unresectable or metastatic breast cancer. In terms of the remission rate, Enhertu has shown a significant improvement. This experimental result proved that Enhertu was significantly superior to T-DM1 in the second-line treatment of HER2-positive breast cancer and was the second-generation drug for the treatment of breast cancer[2].

2.3 Trodelvy

The third typical drug is called Trodelvy. The mechanism of this type of ADC drug is Trodelvy is specifically composed of three parts. The first part is the targeted antibody hRS7 IgG1k, the second part is the linker CL2A, and the third part is the cytotoxin. Specifically, the targeted antibody specifically binds to the Trop-2 antigen that is highly expressed in tumor cells. This Trop-2 antigen is usually overexpressed in triple-negative breast cancer. The linker precisely releases toxins into tumor cells through hydrolysis. Cytotoxin SN38, through topoisomerase I, causes irreversible single-strand breakage of DNA and replication of tissue cells. This drug has the advantage of precise targeting. When combined with Trop-2, the complex is endocytosed by tumor cells, and this precise targeting can avoid affecting normal cells. The bystander effect also occurs in this drug. SN-38 can spread to adjacent tumor cells and expand the killing range[3].

3. Analysis

3.1 ADC Indicator

To understand how to treat breast cancer, we first need to know what breast cancer is. Breast cancer is a condition where breast cells, after being subjected to gene mutations or other damages, divide and proliferate out of control, eventually forming lumps or tumors. If not treated in time, these cancer cells can invade the surrounding tissues and even spread to other parts of the body through the blood or lymphatic system. There are five specific types of breast cancer classification, Luminal A, Luminal B, Her2-positive breast cancer, TNBC (Triple Negative Breast Cancer) and HR+. Clinically, there are four indicators to determine the severity of breast cancer, namely TMN staging, Ki-67 index, organizational credits and HER2 and P53 status.

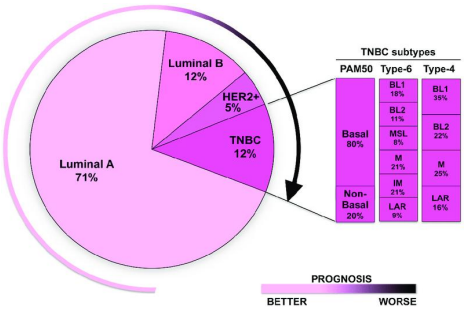

Figure 1. Breast Cancer Type Analysis

Based on the Figure 1, Luminal A accounts for 71%, Luminal B accounts for 12%, HER2 positive accounts for 5%, and Triple-Negative Breast Cancer, TNBC has a relatively small proportion, approximately 12%. Among these four types of breast cancer, TNBC is usually the most serious type of breast cancer. Because TNBC lacks the receptors of estrogen and progesterone, the choice of drugs in clinical treatment is limited and the prognosis is poor. However, the discovery of ADC drugs has brought brand-new hope and treatment directions for the treatment of such patients. Nowadays, in the treatment of TNBC, several new targets such as TROP-2 and LIV-1 have been developed for the construction of ADC drugs. ADC drugs can recognize specific antigens on the tumor surface and precisely transport cytotoxins into the interior of cancer cells to kill cancer cells. The representative drug Trodelvy has been used in clinical practice. This is the first ADC drug of Trop-2 discovered, which is a huge breakthrough in the field of treating TNBC. The survival period of patients has improved after using this medicine.

Back to this graph, the most severe types of breast cancer such as TNBC are classified into basal and non-basal in the graph. The proportion of Basal species is approximately 80%. The so-called Basal-like TNBC refers to the subtype of

breast cancer with the characteristics of Basal epithelial cells. non-Basal refers to triple-negative breast cancer without typical basal cell characteristics, accounting for only 20%.

3.2 Mechanism of ADC Treatment

ADC drugs are based on an important mechanism during treatment. There are five important steps in the Figure 2. The first step is targeted binding. In this step, the monoclonal antibody part of the ADC recognizes and binds to the specific antigen of the tumor cell. The second step is endocytosis into cells. This step mainly involves the ADC antigen entering tumor cells through the endocytosis of receptors, forming early endosomes.

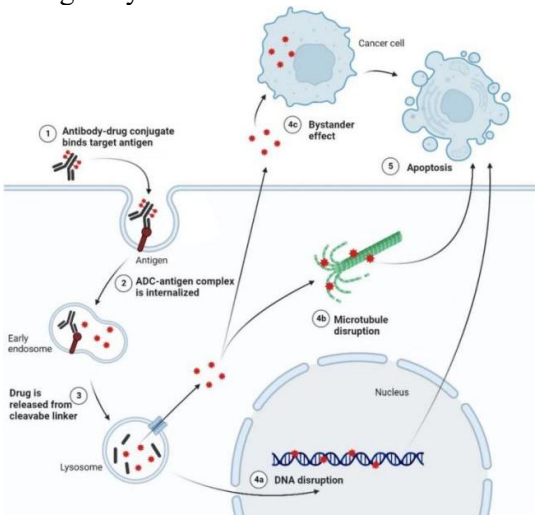

Figure 2. ADC Treatment Process

The third part is that the complex enters the lysosome. Under the acidic conditions and the action of proteases in it, the linker is cleaved and the drug is released. As for Kadcyla, it releases DM1 and acts within the cells. For Enhertu, the release of Deruxtecan can spread to adjacent cells, generating a bystander effect. The effective carriers released in the fourth step exert toxic effects on cells depending on the type. Enhertu's unique bystander effect can enter nearby tumor cells that do not express Her 2, achieving further killing of the heterogeneous tumor microenvironment. The last step is about inducing death. Persistent DNA damage and mitotic interruption can affect the caspase pathway and the death mechanism, ultimately leading to programmed death of tumor cells. This can be regarded as a major mechanism. The mechanisms of different ADC drugs may have some minor changes. The following text will describe the drugs and mechanisms of three different ADC drugs.

3.3 Data Analysis of ADC Clinical Practice

Clinical data is an important basis for evaluating the efficacy of ADC drugs. This section will specifically analyze the specific contents and data analysis of the three clinical trials mentioned above. The first experiment was the EMILIA (Phase III) experiment, as shown in Table 1. The research subjects of this experiment were 496 breast cancer patients who received kadcyla treatment.

By comparing the differences in the survival periods of patients, it was determined that the median OS of patients using T-DM1, such as kadcyla, was 30.9 months, while the median OS of the comparison group using capecitabine and lapatinib was 25.1 months. Moreover, the stratified hazard ratio HR of the T-DM1 group was 0.68, which was less than 1. Data have proved that the T-DM1 drug significantly prolongs the survival period. This experiment also compared the drug resistance mechanism. In the low EGFR expression group, the OS of T-DM1 was 33.9 months, which was better than 24.6 months of CL. The drug effect benefited significantly, but the effect was slightly worse than that of the high EGFR expression group, indicating that high EGFR expression may affect the therapeutic effect of T-DM1. It indicates that a high concentration of EGFR mRNA will reduce the efficacy of targeted drugs. The third comparison point is the expression of HER2 in relation to the efficacy of T-DM1. Through clinical data analysis, it was concluded that with high HER2 expression, the OS of TDM1 reached 34.1 months, while that of its control group was only 24.8 months, indicating a significant therapeutic effect. In the low-expression group of HER2, the efficacy of TDM1 was weakened, and the OS value was only 26.5 months. It indicates that the higher the expression of HER2, the better the therapeutic effect of T-DM1, and the response mechanism of this kadcyla is based on the HER2 target.

Table 1. Univariate Analysis of OS by Biomarker Status in EMILIA

	CL		T-DM1		
	N	Median OS, mo	n	Median OS, mo	Stratified HRa (95% CI)
All patients	496	25.1	495	30.9	0.68 (0.54–0.85)

EGFR mRNA concentration ratio					
≤Median (0.145)	214	24.6	202	33.9	0.59 (0.42–0.83)
>Median (0.145)	210	25.2	206	26.5	0.79 (0.56–1.10)
HER2 mRNA concentration ratio					
≤Median (13.3)	204	23.7	230	26.5	0.80 (0.59–1.09)
>Median (13.3)	235	24.8	197	34.1	0.53 (0.37–0.76)
HER3 mRNA concentration ratio					
≤Median (0.438)	218	23.1	214	NE	0.64 (0.47–0.88)
>Median (0.438)	218	27.1	210	31.9	0.71 (0.51–1.00)
PIK3CA mutation statusb					
Mutated	39	17.3	40	NE	0.26 (0.12–0.57)
Wild type	87	27.8	93	NE	0.68 (0.40–1.15)
PTEN					
None/decreased/slightly decreased	118	23.6	113	NE	0.52 (0.32–0.86)
Equivalent/increased	19	14.8	21	NE	0.43 (0.14–1.32)

Regarding the prospects of ADC drugs, the ADC market is currently expanding rapidly globally. If the bystander effect is maximized, a greater progress will be made in the future efficacy of drugs. For instance, dual-target ADCs and multivalent ADCs will develop rapidly. But challenges in the future do exist, and there are still many areas to be broken through that have not been explored. The toxicity of ADCs is also a very serious problem in the future. The current use of ADC drugs has the problem of off-target, which will lead to high toxicity and significant side effects. In addition to off-target issues, there are also toxic side effects such as diarrhea that need to be improved. The drug resistance mechanism of tumors is also a major challenge. Changes in the pathogen of tumors or the heterogeneity of tumors can lead to a decline in drug efficacy. The last one is the economic issue. The price of drugs is the most realistic problem. High pricing will limit the popularity of drugs. How to reduce production costs is an important challenge in the future.

3.4 Dual-Targeted Therapy

In the important development direction of Dual-Targeted Therapy, the aim is to improve the drug resistance of targeted drugs by simultaneously acting on two tumor-related targets to enhance the selectivity and effectiveness of treatment. Zanidatamab (ZW25) is a novel specific monoclonal antibody that targets two different epitopes of theHER protein.

The mechanism of action of Zanidatamab is divided into nine steps, as shown in Figure 3. The first step is that Zanidatamab is a bispecific antibody that can simultaneously bind to two different epitopes of the HER2 protein. This is the current cutting-edge dual-target therapy, with increased binding strength. In the second step, HER accumulates on the cell membrane, facilitating its endocytosis by the cell. This structure is called the cap structure. The third step is that after Zanidatamab accumulates HER2, it brings multiple antibodies closer together to form a hexmer, thereby initiating cytotoxicity to attack the tumor cell membrane. The fourth part is that HER2 is swallowed into the vesicles in the body. The fifth step is that the endocytosis of HER2 is sent to the enzyme body for degradation, thereby reducing the level of HER2 to weaken the signal transduction of cancer cells. The sixth step is that Zanidatamab blocks dimer generation and inhibits cancer pathways such as PI3K/AKT. The seventh step activates them to release perforin and Granzyme, directly killing tumor cells. Subsequently, C1q binds to the antibody cell membrane, causing necrosis of tumor cells.

The therapeutic prospects of Zanidatamab are expected to make up for the shortcomings of single-target ADC drugs such as Kadcyla in the future. Zanidatamab is mainly focus is on conducting combined therapy research in advanced HER2-positive breast cancer. The EMILIA experiment shows the objective response rate (ORR) : 43.6% vs. lapatinika peitabine (30.8%) for the Kadcyla. By contrast, early Phase I/II trials showed that the ORR of monotherapy was approximately 33% (small sample), and the ORR of combination with paclitaxel could reach over 60%. These data demonstrate that Zanidatamab may be more effective against HER2-low expression or

heterogeneous tumors through dual-target blocking, while Kadcyla depends on the high expression of HER2 and has significant efficacy in the treatment of breast cancer. However, in other types of cancer, the efficacy of the medicine will be affected.

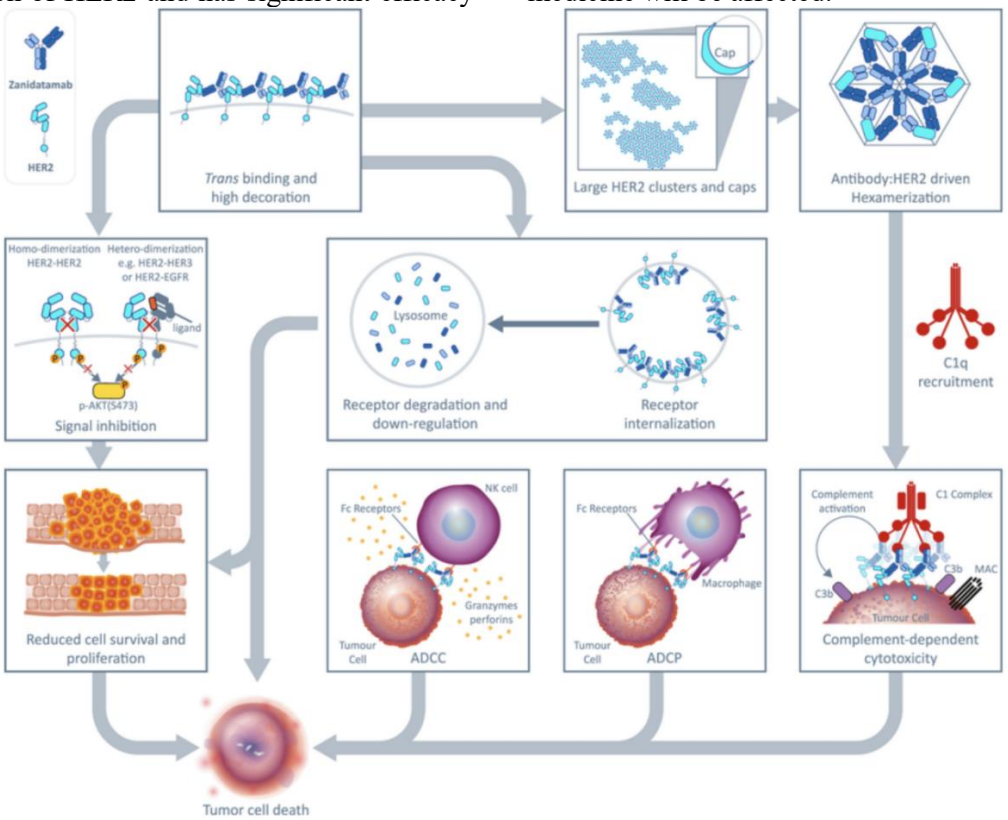

Figure 3. The Mechanism of Action of Zanidatamab

4. Conclusion

In conclusion, although breast cancer is a very serious disease with a relatively high fatality rate, ADC has become an important breakthrough in the precise treatment of breast cancer and shows good prospects in the treatment of different types of patients. Although there are different subtypes of breast cancer, with the efficient cytotoxin delivery mechanism of ADC, it has gradually replaced the traditional chemotherapy treatment method. However, the side effects of ADC drugs still need to be noted, and the issue of safety cannot be ignored. The impact of a series of side effects such as interstitial lung disease and cardiotoxicity on health still needs to be taken seriously. In future research, dual-targeted therapeutic design is a good development direction. It is expected that there will be further progress in the treatment of breast cancer or other cancers, with more economical and effective treatments available.

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