Antibody Coupled Drugs (ADC) in the Treatment of Breast Cancer: From Mechanism to Clinics

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Abstract. Breast cancer is the most common malignant tumor in women. Traditional chemoradiotherapy and targeted therapy suffer from issues such as high toxicity and drug resistance. However, antibody coupled drugs (ADCs) achieve high efficacy and low toxicity in anti-tumor effects by targeting and delivering cytotoxic drugs. This article reviews the progress of ADCs. In the treatment of breast cancer, focusing on the mechanism, efficacy and safety of T-DM1, T-DXd and SG. T-DM1 is suitable for HER2+ breast cancer, with stable efficacy but limited bystander effect; T-DXd significantly improves HER2 low expression and prognosis in patients with brain metastases through high drug loading and cleavable linkers, but caution should be exercised against interstitial lung disease; SG targets Trop-2, providing a new option for triple negative and HR+/HER2- patients, with the main toxicity being hematological and gastrointestinal reactions. Research has shown that ADCs enhance therapeutic efficacy through precise targeting and efficient killing mechanisms. In the future, it is necessary to optimize linker technology, develop novel payloads, and explore bispecific ADCs to further improve efficacy and safety.

Keywords: Antibody conjugated drugs, breast cancer, targeted therapy, drug safety.

1. Introduction

Breast cancer is the most common malignant tumor among women in the world. Its pathogenesis involves multiple effects such as genetic susceptibility, abnormal hormone levels and environmental factors, which lead to the imbalance of cell proliferation and apoptosis, and then form malignant tumors. According to molecular typing, breast cancer can be divided into three subtypes: hormone receptor positive/human epithelial growth factor receptor 2 (HER2) negative (about 70%), HER2+ (15-20%), and triple negative (15%). Each subtype has significant differences in treatment strategies and prognosis. The current clinical treatment methods mainly include surgical resection, radiation therapy, chemotherapy, and targeted therapy. However, traditional chemotherapy drugs, due to their non-specific killing effects, not only inhibit tumor cells but also cause significant damage to normal tissues, leading to frequent adverse reactions such as hematological toxicity, gastrointestinal reactions, and hair loss, and are prone to developing drug resistance. Although targeted drugs such as trastuzumab can specifically target HER2+ cells, there are still primary or secondary resistance issues, and the efficacy of monotherapy is limited, often requiring combination with chemotherapy, further exacerbating the toxicity burden. Although radiotherapy can locally control tumor progression, there is a risk of long-term complications such as tissue fibrosis and radiation pneumonitis. The limitations of the above treatment methods have prompted researchers to explore new treatment strategies that are more targeted, efficient, and low toxic.

In this context, antibody conjugated drugs (ADCs) have emerged, which covalently bind specific monoclonal antibodies (mAbs) with potent cytotoxic drugs through cleavable linkers, forming drugs with both targeting and killing properties. ADCs use antibodies to selectively recognize tumor cell surface antigens, internalize them into cells, and release cytotoxic payloads in lysosomal environments, achieving precise killing of tumor cells [1]. They can also inhibit adjacent tumor cells through the "bystander effect" while minimizing damage to normal tissues. At the beginning of the 21st century, the US Food and Drug Administration approved the first ADC drug for sale - cetuximab ozolomicin, for the treatment of CD33 positive acute myeloid leukemia. Later, Trastuzumab Empire (T-DM1) became the first ADC targeting solid tumors, and T-DXd was approved by the FDA for

human epidermal growth factor receptor (HER) positive breast cancer [2]. At present, many ADCs (such as T- DM1, T-DXd, SG) have been approved for clinical use, covering different subtypes of breast cancer such as HER2+, HER2 low expression and triple negative, providing new treatment options for patients with advanced and refractory breast cancer, and significantly improving the survival prognosis [3]. This article aims to systematically review the research progress and clinical transformation status of antibody coupled drugs in the treatment of breast cancer, compare the clinical research characteristics and safety of three kinds of ADCs, and propose the optimization direction of future ADCs, and propose dual target ADC, which provides the possibility to further improve the targeting efficiency of ADC.

2. The Mechanism of Action of ADCs

ADC is a complex molecule composed of mAbs, cytotoxic drugs (i.e. drug payloads), and linkers. Cytotoxic drugs are formed by binding to mAbs targeting tumor cell antigens through linkers. The core mechanism is to recognize tumor cell surface antigens through antibody partial specificity, and ultimately fuse with lysosomes. Under the acidic environment of lysosomes and the action of specific enzymes (such as proteases), the cleavable linkers in ADC undergo hydrolysis, releasing cytotoxic payloads. Non cleavable linkers rely on complete degradation of lysosomes to release payloads. The released payload exerts anti-tumor effects through different mechanisms: microtubule inhibitors inhibit microtubule polymerization, block cell mitosis, induce G2/M phase arrest and apoptosis; DNA damaging agents cause cell cycle arrest and programmed cell death by inhibiting topoisomerase I or causing DNA double strand breaks.

In addition, some payloads have membrane permeability and can diffuse to adjacent tumor cells (including low antigen expression or negative cells), producing bystander effects and expanding the killing range. This mechanism is particularly suitable for populations with high tumor heterogeneity. Through the "targeting internalization release killing" cascade system, ADCs achieve efficient elimination of tumor cells and significantly reduce systemic toxicity. Its development history reflects the leap from concept to technological breakthrough, especially in the treatment of breast cancer. With the development of linker technology, load optimization, dual specific ADC and other new structures, the application prospect of ADC in the field of precision therapy will be further expanded.

At present, FDA has approved three kinds of ADCs for the treatment of breast cancer, the first is enmetriazumab (T-DM1). T-DM1 targeting HER2 is a combination of trastuzumab and the derivative DM1 of metformin. Next is Dexmedetomidine mAb (T-DXd), which is composed of anti-HER2 mAb and the derivative DXd of itraconazole. And gosatuzumab (SG) targeting human trophoblast cell surface antigen 2 (TROP-2), its unique source and high expression of TROP-2 in various tumors [4]. T-DM1 targeting HER2 first confirmed the clinical efficacy of ADC in HER2+ breast cancer, and then T- DXd further expanded the indications (HER2 low expression patients), providing treatment opportunities for more breast cancer subtypes. At the same time, the drug SG targeting Trop-2 has created a new direction for the treatment of triple negative breast cancer (TNBC), and its excellent efficacy highlights the clinical value of targeting Trop-2. In recent years, new ADCs targeting these two targets are also expanding the therapeutic field of breast cancer.

3. Clinical Characteristics and Safety Comparison of Three Adcs

3.1. T-DM1 (Enmetuximab)

Enmetriazumab is an innovative drug conjugate targeting HER2 antibody, which is suitable for adjuvant treatment of HER2+ breast cancer and treatment of advanced breast cancer [5]. The core principle is that trastuzumab specifically binds to the HER2 receptor on the surface of cancer cells, allowing the chemotherapy drug metformin to enter the interior of cancer cells and achieve targeted therapy Its mechanism of action depends on the high expression of HER2 receptor, which recognizes HER2+ tumor cells with partial specificity through antibodies [6].

After internalization, it releases DM1, inhibits microtubule polymerization, and induces cell apoptosis. The DAR value of T-DM1 is about 3.5, indicating high stability. However, due to the non-cleavable nature of the linker, it does not have a "bystander effect", which limits its effectiveness against HER2 low expression or heterogeneous tumors. In clinical application, T-DM1 is mainly used for second-line treatment of HER2+ advanced breast cancer, especially after the failure of trastuzumab treatment. Key studies such as the EMILIA trial have shown that the combination of T-DM1 and lapatinib can significantly prolong progression free survival (PFS) and overall survival (OS). In terms of cardiac toxicity, T-DM1 is safer than traditional dual target therapy (trastuzumab+pertuzumab), but left ventricular ejection fraction (LVEF) still needs to be monitored [7].

The most common adverse reactions of T-DM1 include fatigue, dry mouth, vomiting, thrombocytopenia, and liver dysfunction, among which the most common is hematological toxicity, such as thrombocytopenia (incidence of 50.0%), neutropenia (26.67%), and anemia (33.33%), with thrombocytopenia being particularly common [8]. A study of 114 patients from multiple centers in China showed that the incidence of fatigue was 67.54%, dry mouth was 55.26%, and vomiting was 49.12%. Most of these reactions were grade 1-2, and patients had good tolerance [9]. It is worth noting that thrombocytopenia is a special toxic reaction of T-DM1 that requires targeted management, with an overall incidence rate of 37.72%. The incidence rate of grade ≥ 3 thrombocytopenia is 12.28%, which is lower than the previous reports of more than 40% in Asian populations in international clinical studies such as EMILIA and KATHERINE studies. It is speculated that this is related to the active adoption of preventive thrombocytopenia treatment and dose adjustment strategies in Chinese clinical practice. The mechanism of its occurrence may be related to the memory mediated entry of T-DM1 into megakaryocytes through Fc γ RIIA receptors, which interferes with platelet production.

In addition, the hepatotoxicity of T-DM1 should also be taken seriously, manifested by elevated levels of alanine aminotransferase (GPT) and aspartate aminotransferase (GOT), with a significantly higher incidence than other anti-HER2 treatment regimens. However, the incidence of severe liver injury events is relatively low, and most cases can be recovered after symptomatic treatment or delayed administration [10]. Compared with other chemotherapy drugs, T-DM1 has a lower incidence of hematological toxicity such as neutropenia and febrile neutropenia, and relatively mild gastrointestinal reactions such as diarrhea and vomiting, demonstrating its advantages as targeted chemotherapy drug Certain demographic characteristics are associated with an increased risk of specific Adverse Drug Reactions (ADRs). For example, Estrogen Receptor/Progesterone Receptor (ER/PR) negative patients are more prone to thrombocytopenia, younger patients (<52 years old) have a higher incidence of dry mouth and nosebleeds, postmenopausal patients have an increased risk of fatigue and peripheral neuropathy, and patients with low BMI (<24 kg/m ^{2}) have a higher incidence of fever. The HP (Pertuzumab Combined with Trastuzumab) regimen can reduce the risk of vomiting and fever to a certain extent [11].

3.2. T-DXd (Trastuzumab)

Tetrostuzumab (T-DXd) is a new type of ADC, which is composed of three parts: Tetrostuzumab, cleavable peptide linker and topoisomerase I inhibitor. It has certain therapeutic activity for unresectable HER2+ and HER2 low expression metastatic breast cancer patients. Its Drug Antibody Ratio (DAR) value is as high as 7.7, which can carry more cytotoxic payloads, and the linker can be cleaved within tumor cells or microenvironments, releasing DXd with high membrane permeability, producing a strong "bystander effect" and significant activity against HER2 low expression tumors.

T-DXd has shown excellent efficacy in multiple clinical trials. In the DESTINY- Beast03 study, T-DXd significantly prolonged PFS (28.8 months vs 6.8 months) compared to T-DM1, with an objective response rate (ORR) of 79.7%. In addition, T- DXd has shown excellent efficacy in patients with brain metastases, with an intracranial remission rate of 73.1% in the TUXEDO-1 study Compared with Amatuximab (T-DM1), T-DXd can significantly prolong patients' OS and PFS, with hazard ratios (HR) of 0.55 and 0.28, respectively, which are statistically significant. In addition, the

ORR of T-DXd reached 61% to 79%, and the median duration of remission (DOR) was not reached, but the lower limit of the 95% confidence interval was 20.3 months, significantly better than the 12.6 months of T-DM1. In patients with brain metastases, the clinical benefit rate (CBR) of T-DXd is as high as 80%, further confirming its therapeutic potential in refractory patients. For patients with breast cancer with low HER2 expression, T-DXd can also significantly prolong OS and PFS compared with traditional chemotherapy, with a median OS of 23.4 to 23.9 months and a median PFS of 9.24 to 9.9 months, suggesting its application prospect in a wider population [12, 13].

In terms of safety, the adverse event characteristics of T-DXd are similar to chemotherapy drugs, mainly manifested as gastrointestinal reactions (such as nausea and vomiting), hematological toxicity (such as anemia and neutropenia), fatigue, and hair loss, most of which are grade 1-2 and clinically controllable. Dequtuzumab, due to its unique topoisomerase I inhibitor loading and high drug antibody ratio (DAR=8), not only has stronger anti-tumor activity, but also brings special risks of concern, including interstitial lung disease (ILD), with an incidence rate of 13%, of which the incidence rate of grade 3 and above events is about 1% [8]. Most ILD events occur within 12 months after treatment, with a median onset time of 5.4 to 5.6 months. The incidence of left ventricular dysfunction is low (4.6%) and rarely leads to symptomatic heart failure Overall, with reasonable supportive treatment and close monitoring, the safety of T-DXd is acceptable.

3.3. SG (Gosatuzumab)

Gosatuzumab (SG) is an ADC targeting Trop-2, consisting of humanized anti- Trop-2 antibodies, cleavable linkers, and topoisomerase I inhibitor SN-38 (an active metabolite of irinotecan). Trop-2 is highly expressed in a variety of epithelial cancers, especially in HR+/HER2- and TNBC, with the expression rate as high as 78%~95%. SG releases SN-38 through Trop-2 mediated internalization, inhibits DNA replication, induces cell apoptosis, and exhibits significant bystander effects. The key phase III study TROPiCS-02 showed that in HR+/HER2 advanced breast cancer treated with multi line therapy (including CDK4/6 inhibitor), SG significantly prolonged PFS (5.5 months vs 4.0 months) and OS (14.4 months vs 11.2 months) compared with doctor selected chemotherapy (TPC), with ORR of 21%.

With the widespread clinical application of gosatuzumab, the understanding and management of adverse drug events (ADEs) related to it are becoming increasingly important. The safety features of SG are mainly hematological toxicity, such as neutropenia (51% ≥ grade 3) and diarrhea (9% ≥ grade 3), but overall, they are controllable. SG provides a new treatment option for endocrine resistant HR+/HER2 breast cancer after chemotherapy, especially for patients with high Trop-2 expression [11].

Based on real-world data mining and analysis using the US FDA Adverse Event Reporting System (FAERS), from the perspective of the system organ classification (SOC) distribution of adverse events, ADEs related to gosatuzumab mainly involve systemic diseases and various reactions at the site of administration (40.56%), blood and lymphatic system diseases (18.83%), various examination abnormalities (13.01%), and gastrointestinal system diseases (12.78%). These data indicate that its toxicity is mainly manifested in systemic symptoms, bone marrow suppression, and gastrointestinal reactions, which are closely related to the cytotoxic mechanism of the topoisomerase I inhibitor SN-38 contained in the drug. Common and frequently reported specific adverse events include disease progression, death, diarrhea, neutropenia, febrile neutropenia, and weight fluctuations. Among them, signals such as neutropenic colitis, cholinergic syndrome, weight fluctuations, and vascular device obstruction show strong drug associations, suggesting that they need to be monitored and intervened as key targets in clinical practice.

4. Discussion

Through the analysis of T-DM1, T-DXd and SG, we can see that they have their own advantages in the treatment of breast cancer. The therapeutic effect of T-DM1 is stable, but its ability to cope

with tumor heterogeneity is limited; T-DXd has achieved stronger and broader anti-tumor effects with high drug loading and cleavable linkers, especially for patients with HER2 low expression and brain metastasis, but the risk of interstitial lung disease should be kept vigilant; SG provides a new choice for TNBC and other refractory types by targeting Trop-2, but its hematology and gastrointestinal toxicity are relatively obvious.

In terms of security optimization, future research can be conducted from multiple levels. One is to continue improving linker technology to enhance its selective cleavage ability in the tumor microenvironment and reduce off target toxicity caused by system exposure; The second is to optimize the humanization degree of antibodies and the drug antibody ratio, balancing the window between efficacy and toxicity; The third is to develop new payloads that reduce the risk of damage to normal tissues while maintaining cytotoxic efficacy. In addition, patient stratification and individualized dosing strategies based on biomarkers will also be key to improving clinical safety.

For example, early assessment and dose adjustment of patients with specific genetic backgrounds or organ dysfunction may help prevent serious adverse events at the source.

Furthermore, the future of ADCs is not limited to single target single loading mode. The emergence of bispecific ADCs provides us with the possibility of simultaneously targeting two different antigens, which is expected to overcome the challenges of tumor escape and heterogeneity. For example, strategies that simultaneously target HER2 and TROP-2 or other tumor associated antigens may achieve deeper remission in a wider patient population. On the other hand, innovation in drug delivery systems, such as utilizing nanocarriers to enhance tumor penetration and adopting conditional response release mechanisms, will further improve the targeting efficiency and therapeutic index of ADCs.

Of course, this study also has certain limitations. The data currently included is mainly from published clinical studies and some real-world analyses, lacking prospective trials comparing the three ADCs head-to-head. Therefore, caution should be exercised when interpreting cross comparisons. In addition, the safety evidence for special populations such as elderly patients and those with organ dysfunction is still insufficient, and long-term toxicity follow-up data also needs to be improved. Future research should focus on building larger real-world databases, promoting biomarker exploration based on multi omics data, and combining artificial intelligence methods to predict toxicity risks, providing more accurate guidance for clinical medication. In conclusion, as an important breakthrough in the treatment of breast cancer, ADCs are constantly promoting the transformation of tumor treatment paradigm [14,15].

5. Conclusion

ADCs have shown important clinical value in the treatment of breast cancer. This article systematically analyzes the three ADCs, T-DM1, T-DXd, and SG, and reveals their respective mechanisms of action, efficacy characteristics, and safety features. Research shows that T-DM1, as the first ADC drug used for HER2 positive breast cancer, has stable clinical efficacy, but its non-cleavable linker limits the exertion of bystander effect; T-DXd, with its high drug antibody ratio and cleavable linker, significantly expands the treatment opportunities for HER2 low expression patients, but attention should be paid to the risk of interstitial lung disease; SG provides new treatment options for TNBC patients by targeting Trop-2 antigen, but its hematological toxicity and gastrointestinal reactions need clinical attention.

The significance of this study lies in providing evidence-based support for clinical treatment decisions by systematically comparing the differential characteristics of three ADCs. The research results confirm that ADCs, through precise targeted delivery systems, improve anti-tumor efficacy while reducing systemic toxicity, providing a new solution to overcome the limitations of traditional chemotherapy and targeted therapy. In depth analysis of safety features, especially the exploration of the mechanisms and management strategies of various drug specific toxic reactions, can provide important references for clinical practice.

The limitation of this study is that it mainly relies on published clinical research data and lacks direct evidence for head-to-head comparisons. Future research should focus on the development of novel linker technologies, optimization of drug antibody ratios, and innovation of loading molecules to further improve the therapeutic index of ADCs. At the same time, it is necessary to strengthen patient stratification research based on biomarkers, explore new drug forms such as bispecific ADCs, and promote the development of ADCs towards more precise, safe, and efficient directions.

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