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Next-Generation HER2-Targeted ADCs: Comparative Mechanisms and Efficacy of T-DXd versus T-DM1 in Breast Cancer

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Abstract:

Breast cancer is widely regarded as the most prevalent cancer across populations worldwide, among which HER2-positive breast cancer represents a key subtype. A comparative analysis of two prominent HER2-directed antibody–drug conjugates (ADCs), namely trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd), is presented in this study. Both take trastuzumab as the targeting basis, but they differ significantly in payload type, linker design and drug release mode. T-DM1 mainly acts on tumor cells with high HER2 expression and can effectively internalize the drug. Its released products have poor membrane permeability with relatively limited bystander effects. In contrast, T-DXd has a higher drug-to-antibody ratio. The free toxins released by it can diffuse across cell membranes, generate effects on surrounding tumor cells and produce a bystander effect. Therefore, it also shows certain strengths in overcoming tumor heterogeneity and partial drug resistance. Existing clinical studies have shown that in advanced HER2-positive breast cancer, T-DXd presents superior disease control, survival benefits and remission effects compared with T-DM1. In HER2-low expression breast cancer, T-DXd also exhibits broader application potential, while the efficacy of T-DM1 is relatively limited. In general, next-generation ADCs have significantly improved the efficacy of HER2-targeting therapy through structural optimization. Further improvements are still needed in reducing toxicity, delaying drug resistance and promoting individualized treatment in the future.

Keywords: HER2-positive breast cancer; Antibody–drug conjugates (ADCs); Trastuzumab emtansine (T-DM1); Trastuzumab deruxtecan (T-DXd).

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1. Introduction

Breast cancer (BC) is a highly heterogeneous tumor with significant differences in molecular characteristics, clinical courses and treatment responses. As the most common cancer and a major cause of death among women worldwide, its pathological mechanism has attracted widespread attention [1]. In BC, human epidermal growth factor receptor 2 (HER2) is a key molecule driving tumor progression. Approximately 15%–20% of cases have HER2 gene amplification, leading to overexpression of receptors on the cell membrane surface. As a member of the receptor tyrosine kinase (RTK that mediates transmembrane signal transduction) family, high-density HER2 continuously activates both the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) and mitogen-activated protein kinase (MAPK) signaling pathways through homodimerization or heterodimerization, thereby promoting cell proliferation and inhibiting apoptosis, respectively [2].

Owing to its abundant expression on the tumor cell surface, HER2 has been recognized as a principal target in the evolution of antibody–drug conjugate (ADC) development. ADCs recognize tumor-associated antigens such as HER2 through antibody specificity, and accurately deliver cytotoxic drugs to tumor cells to achieve targeted killing. This strategy can not only exert effects on both HER2 high-expression and low-expression tumor cells, but also can improve anti-tumor efficacy, and reduce damage to normal tissues. With higher specificity and lower systemic side effects than conventional chemotherapy, using ADCs has become a vital treatment for HER2-positive BC.

Trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd) are two representative ADCs for HER2-positive BC. Among them, T-DM1 is an early clinically applied HER2-targeting ADC, which links the cytotoxic payload DM1 with trastuzumab as the base. It plays an important role in the treatment of HER2-positive BC. As a new-generation HER2-targeting ADC, T-DXd also uses trastuzumab as the targeted backbone, and performs optimizations in linker design, payload type and drug delivery efficiency. As a result, it also shows stronger anti-tumor activity and broader application prospects. In recent years, research on these two agents has mainly focused on their structural characteristics, mechanisms of action, drug resistance issues and clinical efficacy. Meanwhile, the therapeutic strengths of T-DXd in HER2-positive and HER2-low expression BC have attracted extensive attention.

In this context, this paper aims to summarize the pathogenesis of BC, and systematically compares the differences between the first-generation HER2 ADC (T-DM1) and the new-generation ADC (T-DXd) in molecular structure, killing mechanism and clinical application status. This paper has certain theoretical significance and practical value for improving the understanding of HER2-positive BC treatment, facilitating the rational selection of targeted therapeutic agents and providing references for subsequent research on ADCs.

2. Pathogenesis of HER2-Positive BC

The occurrence of HER2-positive BC usually originates from structural abnormalities at the genomic level. These abnormalities directly affect the expression level of cell membrane surface receptors. Studies have shown that about 15%–20% of BC cases have somatic amplification of the ERBB2 gene (encoding the HER2 receptor) [3]. The increase in gene copy number is gradually amplified through transcription and translation, resulting in a significant elevation of HER2 receptor protein on the cell membrane. Consequently, the receptor density may even reach hundreds of times of the normal level. A large number of HER2 receptors gather on the cell membrane, providing an important physical basis for tumor signal transduction.

When HER2 proteins are highly enriched on the cell membrane, spontaneous dimerization (including HER2 homodimerization and heterodimerization with HER3) between receptors occurs more frequently. After dimerization, the tyrosine kinase activity of the receptor's intracellular domain is activated, thus initiating a continuous cascade of downstream signaling pathways. Studies have found that this process can persistently activate the PI3K/AKT axis. The activated AKT can inhibit a variety of pro-apoptotic proteins, including BAD (a pro-apoptotic regulator) and Caspase-9 (an apoptosis-executing cysteine protease), enabling tumor cells to evade immune clearance or programmed cell death even in adverse environments [4].

At the same time, HER2 dimerization can also activate the MAPK signaling cascade. This pathway continuously transmits proliferation signals to the nucleus through the RAS-RAF-MEK-ERK axis and strengthens the instructions for cell growth and division. Long-term activation of molecular signals eventually transforms into abnormal proliferation at the cellular level, thereby promoting the continuous progression of tumors in the host.

The synergistic effect of the PI3K/AKT and MAPK pathways significantly upregulates the expression of Cyclin D1. Cyclin D1 subsequently binds to CDK4/6 to form a complex, which promotes the phosphorylation and functional inactivation of retinoblastoma protein (Rb). It is generally accepted that when Rb protein loses its inhibitory effect, E2F (which drives transcription of S-phase-related genes) transcription factors are released, forcing cells

to pass the G1/S checkpoint, and ultimately leading to continuous DNA replication and unrestricted cell division.

3. Molecular Mechanisms of Drug Therapy

In the structural composition of ADCs, the antibody part is mainly responsible for tumor targeted recognition and drug delivery. Studies have shown that in clinical application, ADCs represented by T-DM1 are typical successful cases of humanized antibodies. Kadcyla (T-DM1) is one of the representative drugs in ADC design. It is composed of humanized anti-HER2 monoclonal antibody conjugated with DM1, The antibody portion can specifically recognize and bind to HER2 receptors on the surface of tumor cells, so as to realize precise localization and selective delivery of drugs in HER2-positive BC cells [5].

In comparison, as another important ADC, T-DXd also adopts trastuzumab as the targeting structure in antibody design. Relevant literature indicates that this antibody has high affinity for HER2 receptors, so it can effectively realize targeted localization of HER2-positive tumor cells. While conjugating cytotoxic drugs, this design retains the inherent biological activity of trastuzumab, enabling it to inhibit the HER2 signaling pathway and further enhance anti-tumor effects [6].

In the mechanism underlying ADC action, the payload is a key factor determining the intensity of cytotoxicity. Studies have shown that during the action of T-DM1, the drug enters cells through receptor-mediated endocytosis and releases DM1 in lysosomes, which enters the cytoplasm and exerts potent cytotoxicity. As a microtubule inhibitor, DM1 mainly inhibits tubulin polymerization and destroys cytoskeleton structure, thereby blocking cell mitosis, inducing cell cycle arrest and ultimately inducing tumor cell apoptosis [7].

The lethal efficiency of early toxin molecules has been demonstrated. For example, in a mouse L-cell experimental model, researchers used erythrocyte carriers to deliver a quantified fragment A of diphtheria toxin into originally drug-resistant cells. The results showed that even a single toxin molecule entering the cell could damage the cell cloning ability and eventually lead to cell death. This study highlighted the extremely high cytotoxicity of toxin payloads.

In addition, DM1 molecules carry charges and highly hydrophilic, so they cannot freely penetrate the cell membrane. They can only kill cells that take up the drug and has no diffuse killing effect on adjacent cells.

In contrast, in the design of T-DXd, a novel topoisomerase I inhibitor (DXd) is selected as the payload. The literature indicates that different from microtubule inhibitors commonly used in conventional ADCs, DXd kills tumor cells by inhibiting topoisomerase I and inducing DNA damage. By changing the cytotoxic mechanism, the drug shifts from “destroying microtubule structure” to “inducing DNA damage”, which effectively avoids cross-resistance among drugs caused by prior taxane chemotherapy. Meanwhile, DXd has extremely high cytotoxicity and can induce apoptosis of tumor cells even with relatively low HER2 receptor density [6].

In summary, differences in payload, mechanism of action and drug efficacy will ultimately be reflected in drug resistance outcomes. Accordingly, the following section discusses relevant drug resistance mechanisms. Within the established therapeutic framework for HER2-positive BC, studies have shown that patients usually receive taxane-based drugs in early or first-line treatment, such as pertuzumab combined with trastuzumab plus docetaxel or paclitaxel [8]. Taxanes block cell division by inhibiting tubulin depolymerization, but after long-term use, tumor cells often develop drug resistance by altering microtubule structure or upregulating drug efflux pumps (e.g., P-gp, which mediates drug efflux). Since DM1 carried by T-DM1 is also a microtubule inhibitor, patients resistant to prior taxane chemotherapy are prone to cross-resistance to T-DM1, which shares a similar mechanism. In contrast, DXd induces DNA double-strand breaks and further promotes cell apoptosis by inhibiting topoisomerase I. Even when tumor cells have evolved defensive mechanisms against microtubule inhibitors, the distinct differences in their modes of action determine that the drug-resistant phenotypes developed against microtubule inhibitors cannot significantly reduce the therapeutic sensitivity to payloads of topoisomerase I inhibitors.

The linker is an important structure connecting antibodies and cytotoxic payloads. Its stability and cleavability directly affect the way of drug release. Studies have shown that T-DM1 adopts a non-cleavable thioether linker (MCC) in structural design [9]. After binding to HER2 receptors, T-DM1 enters cells through receptor-mediated endocytosis and finally reaches lysosomes environment. Since the linker cannot be enzymatically cleaved, the release of DM1 depends on the complete degradation of antibodies in lysosomes, and the final active product is the lysine-MCC-DM1 complex. The complex is charged and highly hydrophilic, so it cannot penetrate the cell membrane and diffuse into the extracellular environment [10].

In contrast, T-DXd adopts a cleavable tetrapeptide linker (GGFG). Literature shows that this linker can be specifically cleaved by cathepsins highly expressed in tumor cells to achieve efficient and accurate payload release. Therefore, compared with T-DM1, which relies on com-

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plete antibody degradation, T-DXd has higher payload release efficiency [9].

At the same time, the tetrapeptide linker of T-DXd has certain hydrophilic adjustment capacity in structural design. Relevant literature emphasizes that through optimized linker-payload design, T-DXd achieves a DAR of 8, maintaining low hydrophobicity, less aggregation, favorable pharmacokinetics and high activity. In other words, it alleviates molecular aggregation under high drug-loading conditions. By reducing the overall hydrophobicity of the system, T-DXd realizes a high drug-to-antibody ratio (DAR≈8) and solves the aggregation problem caused by high drug loading to some extent. Meanwhile, the linker optimizes the physicochemical properties of the whole molecule to some extent, ensuring favorable stability and solubility in blood. The increase of DAR directly improves clinical efficacy [11]. It is thus clear that the structural characteristics of linkers largely affect payload release efficiency. The following part further illustrates its diffusion ability in tumor tissues based on the charge state and membrane permeability of released toxins, extending the anti-tumor effect of ADCs from single target cell killing to adjacent cells.

Studies have pointed out that the anti-tumor effect of ADCs is not limited to directly killing target-positive tumor cells, but may also exert killing effects on adjacent cells that do not express the target. This phenomenon is known as the bystander killing effect.

In the mechanism of T-DM1, the released lysine-MCC-DM1 complex is charged and highly hydrophilic, unable to penetrate the cell membrane and diffuse to surrounding cells, so T-DM1 has no bystander effect and only kills cells with high HER2 expression and successful drug internalization. In addition, T-DM1 relies on complete antibody degradation in lysosomes to release toxins, and the released toxin remains bound to amino acid residues, making diffusion out of the cell difficult. T-DM1 is highly antigen-dependent, and internalization and toxin release can only occur after binding to HER2 on cancer cells [12]. Therefore, its efficacy mainly depends on the uptake capacity of HER2-positive cells. In HER2-low expression BC, HER2 expression presents intratumoral heterogeneity, that is, some cells have high HER2 expression, while others have extremely low or even no expression. Hence, T-DM1 only kills recognized cells and has limited killing effect on surrounding HER2-negative cancer cells, affecting the overall therapeutic effect [13].

In contrast, studies have proved that T-DXd has a prominent bystander killing ability. Under the action of intracellular cathepsins, the tetrapeptide linker of T-DXd is cleaved to release free DXd toxin. The DXd molecule is electrically neutral and highly membrane-permeable, so it can diffuse out of target cells and enter adjacent cells to exert toxicity. Even in tumor tissues with low HER2 expression, T-DXd can deliver high-concentration toxins to the tumor area, overcoming the heterogeneity of tumor cells [9].

Studies indicate that there is a synergistic relationship between the high DAR of T-DXd and its bystander killing effect. As mentioned above, a higher DAR creates a higher toxin concentration gradient inside the target cell, and membrane-permeable DXd diffuses to adjacent cells along the gradient to expand the killing range. Meanwhile, after the linker is cleaved by proteases in lysosomes, free and original toxin molecules are released. This release mode avoids redundant amino acid residues on toxins and maintains their hydrophobicity and transmembrane diffusion capacity [14].

4. Clinical Applications

Studies have shown that in clinical research on HER2-positive metastatic BC, the efficacy of T-DXd and T-DM1 has been directly compared. Researchers systematically evaluated the efficacy of the two ADCs in patients with previously treated HER2-positive metastatic BC. The results show that T-DXd is superior to T-DM1 in several key efficacy indicators.

Specifically, with respect to progression-free survival (PFS), the median PFS of patients in the T-DXd group was about 29.0 months, significantly longer than 7.2 months in the T-DM1 group, with a hazard ratio (HR) of about 0.30, indicating that T-DXd can significantly delay disease progression. In terms of overall survival (OS), the T-DXd group was 52.6 months, while the T-DM1 group was 42.7 months, with an approximately 27% reduction in mortality risk. In addition, in terms of objective response rate (ORR), the ORR of the T-DXd group was about 79%, significantly higher than 35% of the T-DM1 group, showing stronger anti-tumor activity [15].

In conclusion, compared with T-DM1, T-DXd can significantly prolong progression-free survival and overall survival and increase tumor remission rate in the treatment of HER2-positive metastatic BC. It shows obvious strengths in clinical efficacy and has gradually become an important option for the treatment of this disease.

In the field of HER2-low subtype BC, T-DXd and T-DM1 present completely different therapeutic potential. Conventionally, both T-DM1 and T-DXd are mainly used for patients with high HER2 expression (HER2-positive). However, HER2-low tumors usually have obvious tumor heterogeneity, with great differences in HER2 expression levels in different cells of tumor tissues, so the efficacy of T-DM1 in this population is relatively limited. In contrast,

with its bystander effect and higher drug loading, T-DXd can still exert significant anti-tumor effects in tumor tissues with low HER2 expression, thereby significantly prolonging patients' survival time.

For patients with advanced HER2-low BC who received previous treatment, relevant clinical studies have shown that T-DXd has better efficacy than conventional treatment regimens. In terms of objective response rate, the T-DXd group was 52.3% (195/373), much higher than 16.3% in the conventional chemotherapy group. Meanwhile, previous studies also suggested that the remission level of T-DM1 in HER2-low population was not superior than chemotherapy. In terms of survival outcomes, the median PFS of the T-DXd group was 9.9 months, and 10.1 months in the HR-positive subgroup; the median OS was 23.4 months, while that of the conventional chemotherapy group was 16.8 months. The above results indicate that T-DXd can bring significant survival benefits to patients with HER2-low BC [16]. The DESTINY-Breast03 trial confirmed the generational survival improvement of T-DXd over T-DM1 in the second-line treatment of advanced HER2-positive BC: median PFS was significantly prolonged (28.8 months vs 6.8 months, HR=0.33), and ORR increased to 79.7%. Clinical studies have also shown that T-DXd has significant strengths in overall survival and other key indicators, and presents promising application prospects in HER2-low BC. Therefore, the new-generation ADC T-DXd has significantly improved the effect of HER2-targeting therapy through the optimization of structural design and mechanism of action, and provided an important direction for the development of therapies targeting HER2-positive and HER2-low BC [17].

Therefore, T-DXd demonstrates superior therapeutic effects than T-DM1 in populations with different HER2 expression levels, marking the transformation of therapy with ADCs from conventional high-expression dependence to wider population coverage.

5. Conclusion

By systematically sorting out the pathogenesis of HER2-positive BC and comparing the structural design, mechanism of action and clinical efficacy of two generations of ADCs, T-DM1 and T-DXd, this paper finds that T-DXd has achieved key structural optimization, with the DAR increased from 3.5 to 8.0. Different from the non-cleavable design of T-DM1, T-DXd adopts a cleavable peptide linker, and the released payload produces a bystander effect, which effectively overcomes the limitations of T-DM1 in killing heterogeneous tumors and low-expression cells, and shows greater potential in overcoming drug resistance. Even so, ADCs still have certain limitations in clinical application. First, insufficient linker stability and premature payload release will compromise drug delivery efficiency and may induce off-target toxicity. Meanwhile, although T-DXd has stronger efficacy, its related toxicity and potential drug resistance restrict its further application to a certain extent.

In this context, current studies explore optimization paths from the two aspects of pharmaceutical design and clinical strategy. On the one hand, improving linker stability, optimizing payload physicochemical properties and developing new-generation or dual-epitope ADCs to enhance effective intratumoral delivery and reduce non-specific toxicity; on the other hand, carrying out combined therapy (e.g., combined signaling pathway inhibitors or immunotherapy) and sequential medication strategies targeting drug resistance mechanisms to enhance therapeutic sensitivity and prolong clinical benefits. Most existing studies focus on mechanism exploration and early clinical stages, lacking systematic verification of their safety and effectiveness through randomized controlled trials on a large scale. Further efforts should be put to integrate precise stratification and prospective clinical studies in the future to optimize drug efficacy, balance toxic risks, and promote the high-efficiency and individualized development of therapy of ADCs.

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