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Evaluation of the safety of T-DXd in the Treatment of HER2-positive breast cancer

Nanxi Cheng

School of Life Science and Technology, China Pharmaceutical University, Nanjing, 211198, China

chengnanxi@stu.cpu.edu.cn

Abstract. Breast cancer (BC) is one of the most common diseases in women today, and HER2-positive BC has attracted the attention of researchers. Anti-her2 targeted therapy is an important tool in the treatment of HER2. In recent years, antibody-coupling drugs have entered people's field of vision and triggered a boom, and the research on T-DXd targeted therapy for HER2-positive BC is also gradually advancing and improving. This paper mainly discusses the mechanism of HER2-positive BC, explores the mechanism of action of T-DXd against HER2-positive BC, analyzes the side effects and safety evaluation of T-DXd targeted therapy for adult female patients with HER2-positive BC, and concludes that T-DXd is a relatively safe drug. However, it can be found that the pulmonary interstitial disease after treatment is a serious side effect that should not be ignored. Future studies can focus on discussing the principle of the side effect, ways to reduce the probability of its occurrence and more accurate and safe medication programs.

Keywords: HER2-positive BC, T-DXd, Side effect, safety evaluation.

1. Introduction

BC is one of the most common diseases in the female population, in BC, the amplification of HER2 gene and overexpression of the protein are closely related to the occurrence, development, aggressiveness and prognosis of tumors. About 20-30% of primary invasive BCs have HER2 gene amplification or overexpression. Patients with HER2-positive BC typically have rapid disease progression, short remission periods with chemotherapy, poor response to endocrine therapy, and low disease-free survival and overall survival. In the treatment of HER2 BC, innovative targeted drugs have played an important role in recent decades [1]. Antibo-drug conjugates (ADCs) have been the focus of some researchers, including trastuzumab dercuxtecan (T-DXd).

It consists of an anti-HER2 humanizedmAb (MAAL-9001) combined with a cytotoxic drug named Esatiecan derivative MAAA-1181a (DXd), linked to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable splicer. Its unique design has a high drug-antibody ratio of about 8 that remains stable, thus providing an effective cytotoxic (ADCC) payload that is internalized and selectively cut by an overexpressed lysosomal enzyme in cancer cells.

Studies have shown that T-DXd has a good therapeutic effect on HER2-positive BC patients [2]. In addition, in the DESTINY-Breast03 study, the new progression-free survival (FPS) record for HER2-positive BC has established the status of second-line standard treatment internationally [2,3]. At present,

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several related biosimilars have been introduced into the clinic, providing different treatment schemes for trastuzumab adjuvant therapy [4].

However, in the long-term use of T-DXd, some side effects also appear, such as fatigue, decreased appetite, etc., which is similar to the characteristics of side effects of chemotherapy drugs [2]. In clinical and drug research, not only the effectiveness of drugs needs to be paid attention to, but also the safety of drugs needs to be guaranteed. Therefore, this paper focuses on the generation and analysis of side effects of T-DXd after adjuvant therapy in adult patients with HER2-positive BC, and based on this, discusses the problems that should be paid attention to in future drug development and clinical treatment of T-DXd, and puts forward the aspects that need to be focused on.

2. HER2 positive BC

2.1. Generation mechanism

The HER2 gene encodes a protein called human epidermal growth factor receptor 2 (EGFR). In some BC cells, the HER2 gene replicates multiple times in their DNA, with an increased copy number, which means that the HER2 gene is abnormally amplified, and in turn, excessive HER2 protein is produced during transcription and translation. The HER2 protein belongs to EGFR and its normal function is to regulate the growth and division of cells.

Due to overexpression of the HER2 gene, the concentration of HER2 protein on the surface of BC cells increases significantly, making it easier for HER2 receptors to form heterodimers or homologous dimers with other members of the HER family, such as HER1, HER3, and HER4. The formation of this dimer triggers the autophosphorylation of the receptor, activating multiple downstream signaling pathways.

These signaling pathways play an important role in promoting cell cycle, cell proliferation, invasion and metastasis. At the same time, their continued activation inhibits apoptosis of BC cells and affects the tumor microenvironment (including angiogenesis, immune escape, and stromal cell reprogramming), creating favorable conditions for rapid growth, deterioration, further development, and metastasis of tumor cells.

In general, after a multi-step process, involving gene variation, protein expression dysregulation, signaling abnormalities and other factors work together to promote the emergence and development of HER2-positive BC.

2.2. Treatment means

The treatment of HER2-positive BC includes anti-HER2-targeted therapy, chemotherapy, endocrine therapy (for HR+/ HER2-positive recurrent metastatic BC), surgical therapy, neoadjuvant (pre-operative) and adjuvant (post-operative) therapy, radiation therapy, etc.

Among them, anti-HER2 targeted therapy is an important treatment for HER2-positive BC, which includes large molecular clonal antibodies, small molecular tyrosine kinase inhibitors, and antibody conjugants (such as T-DM1 and T-DXd). With the development of HER2-targeting drugs, the cure rate of early stage patients and the survival rate of late stage patients have been significantly improved [5]. In addition, because T-DXd as ADCs has a high drug-antibody ratio structure and its unique mechanism of action against cancer cells, its outstanding and stable performance in clinical trials has attracted the attention of many researchers, and some people have compared the therapeutic effect of T-DXd with T-DM1, which was put into clinical trials earlier.

Therefore, the development of novel drugs and the implementation of new technologies that can specifically target cancer cells with minimal side effects will be the focus of future research [5].

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3. T-DXd: a HER2-targeting drug

3.1. Structure and mechanism of action

T-DXd is a monoclonal ADC (ATC code :L01XC41). It consists of an anti-HER2 humanizedmAb (MAAL-9001) combined with a cytotoxic drug called the Esatikon derivative MAAA-1181a (DXd), linked to a topoisomerase I inhibitor payload via a tetraceptide-based cleavable adapter. Its unique design has a high drug-antibody ratio of about 8 that remains stable, thus providing an effective cytotoxic (ADCC) payload that is internalized and selectively cut by an overexpressed lysosomal enzyme in cancer cells.

T-DXd specifically binds to HER2 receptors on tumor cells. As shown in Figure 1, it is internalized by lysosomal enzymes and cleaved to intracellular junctions. After that, T-DXd enters tumor cells and plays a role in inducing DNA damage and apoptosis [6].

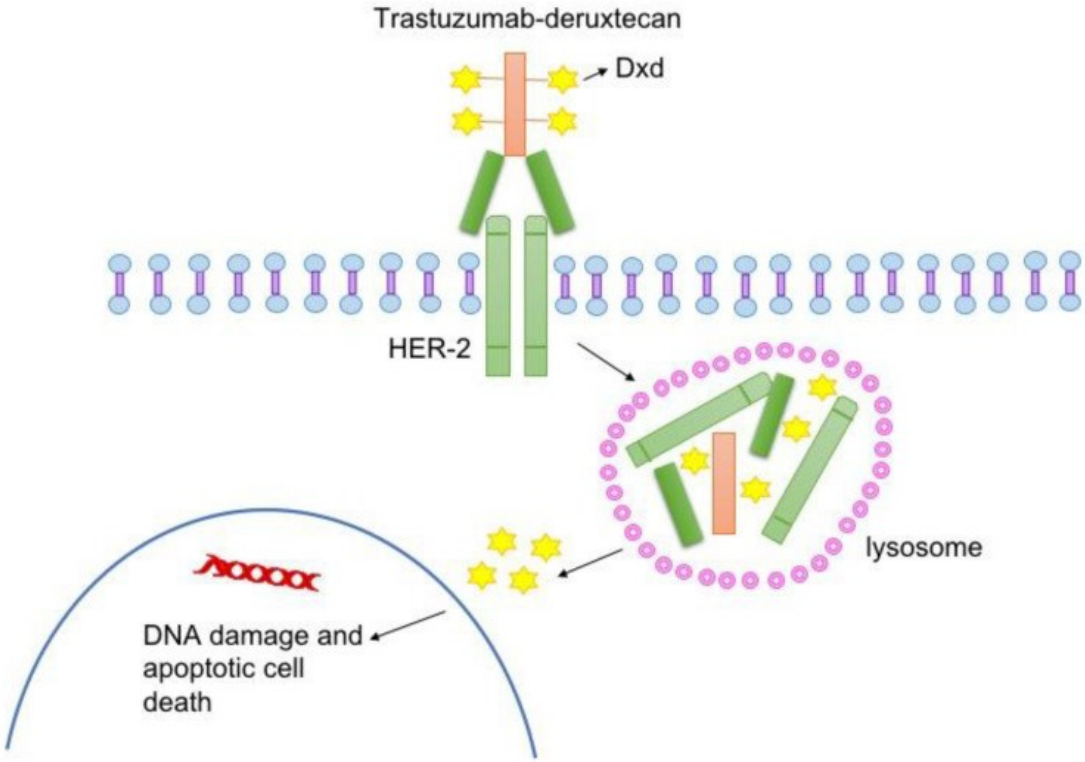

Figure 1. Structure and mechanism of T-DXd [6]

3.2. Development situation

Because of its significant efficacy and superiority in multiple clinical trials, T-DXd has been approved for use by drug regulatory agencies in many countries, and has been included as a recommended treatment in a number of international authoritative guidelines, including the National Cancer Comprehensive Network (NCCN) BC Clinical Practice Guidelines, ESMO Metastatic BC Online Guidelines, etc.

In the DESTINY-Breast03 study, the median progression-free survival (mPFS) of T-DXD-treated patients reached 28.8 months, and the 12-month overall survival (OS) was 94.1% [3]. This demonstrates the groundbreaking efficacy of T-DXd in the second-line treatment of HER2-positive BC.

It is worth mentioning that the specific binding receptor of T-DXd is HER2 receptor, which means that this drug can not only act on HER2-positive BC, but also can act on HER2-positive advanced gastric cancer, HER2 low expression of advanced BC and other indications.

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With the continuous advancement of clinical research, it can be expected that the application scope and influence of T-DXd will continue to expand, and the accessibility of its drugs will also be improved.

4. Side effects and safety evaluation

4.1. Side effects

In the development and testing of any drug, side effects are the core content that needs to be paid attention to.

In the treatment process of T-DXd for HER2-positive BC, not only its comprehensive efficacy needs to be considered, but also the side effects caused by the drug are worth exploring. In Gavin P. Dowling's study, six articles were included as qualitative and quantitative synthesis studies through rigorous screening, and meta-analysis was used for complete data extraction, quality assessment and statistical analysis [7]. Common side effects of any grade can be found including nausea, vomiting, constipation, diarrhea, fatigue, anemia, and central granulocytopenia, while anemia and neutropenia have a relatively high incidence of side effects of grade 3 and above [7].

Special attention should be paid to ILD as a potentially serious side effect [7]. This is a heterogeneous disease with a lack of clinical specificity. In some patients, the imaging changes of ILD can be completely reversed by active immunosuppressive therapy, in some patients, the lesions are irreversible but stable for a long time, and in some patients, the lesions continue to progress and eventually develop into end-stage respiratory failure. Among the six articles included in Gavin P. Dowling's study, about 5.22% of patients in Tamura K 2019 had this symptom [8], 13.59% in Modi S 2019 [9], and 14.81% in Modi S 2020 [10]. 6.67% in Bartsch R 2022 [11], 12.1% in Modi S 2022 [12] and 10.5% in Javier Cortes2022 [3]. These data can not be ignored, but also provide new concerns and ideas for future research direction.

4.2. Safety evaluation

In the articles mentioned above, Tamura K 2019, Modi S 2019, Modi S 2020 and Bartsch R 2022 were single-arm experiments, while Javier Cortes2022 and Modi S 2022 were randomized controlled experiments. Figure 2 shows the single-group rate analysis at any level in all single-arm experiments [7], and it can be seen that the heterogeneity (I2) is large except for the analysis of symptoms of constipation and neutropenia. The small number of studies in Bartsch R 2022 (n=15) may be one of the factors contributing to the high heterogeneity.

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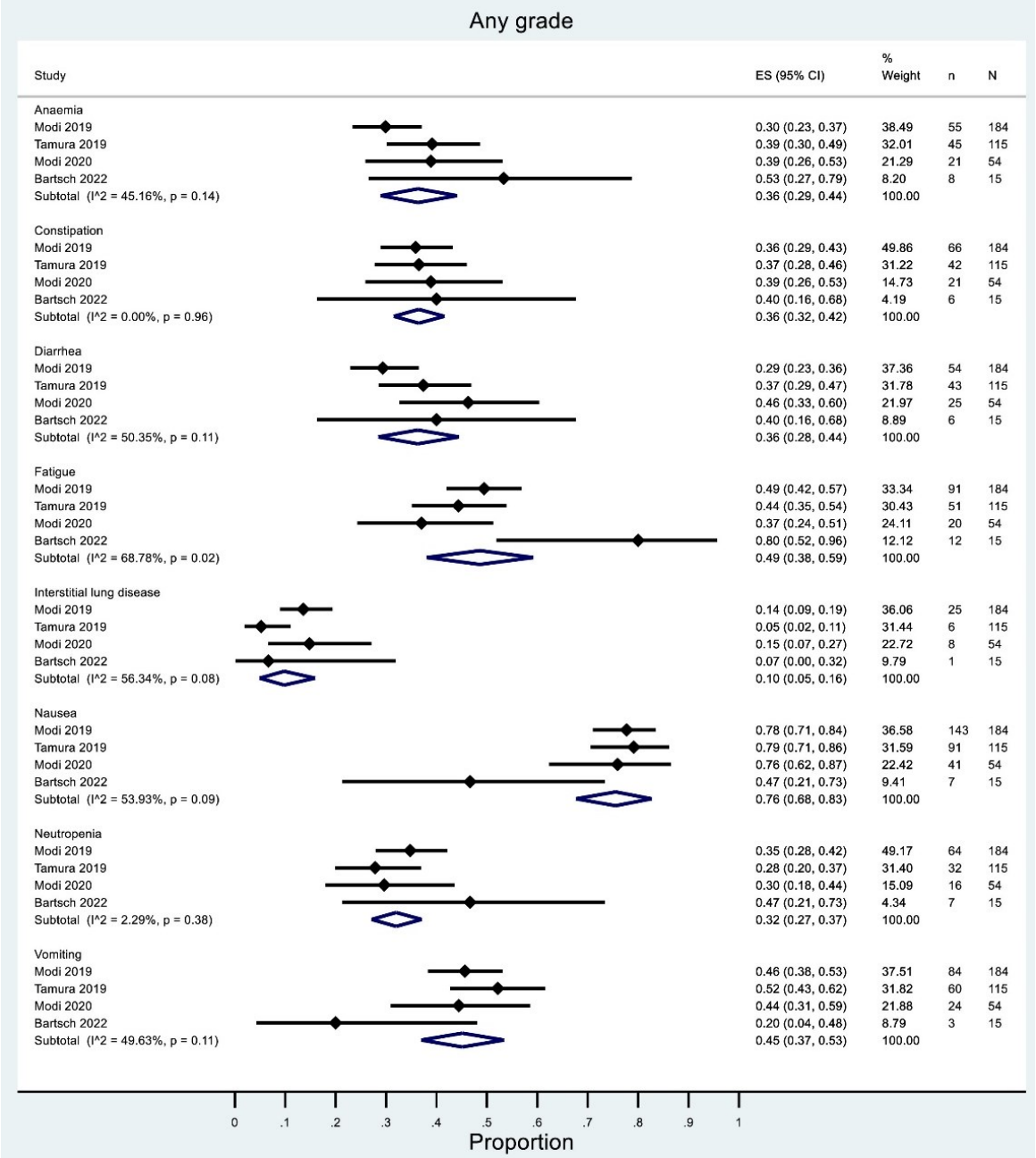

Figure 2. Single-group rate analysis of any level of symptoms in all single-arm experiments [7]

As shown in Figure 3, with a 95% confidence interval, the combined prevalence of nausea was highest (76%), while the combined prevalence of ILD symptoms was lowest (about 10%). The combined prevalence of vomiting and fatigue was higher, neutropenia was lower, and the rest were similar.

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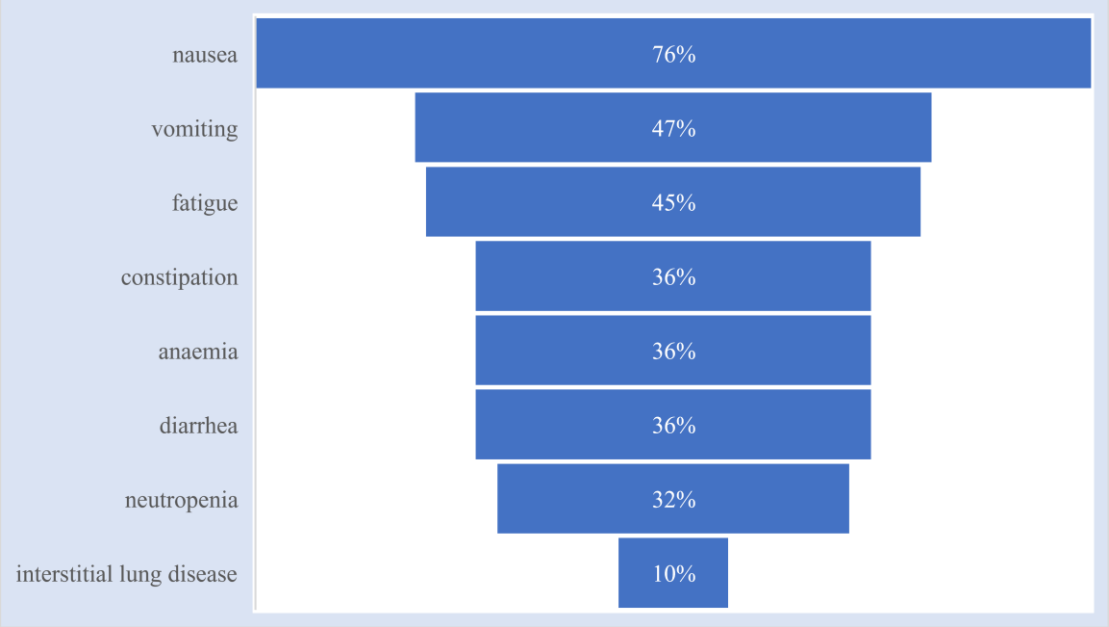

Figure 3. Combined prevalence of any level of symptoms in all one-arm trials (funnel plot)

It should be noted in particular that in the analysis of ILD, the OR value was high, indicating that T-DXd drug treatment was clearly correlated with the generation of ILD [7].

In general, as far as the current data is concerned, although the T-DXd drug will bring different degrees of side effects in treatment, it is still a relatively safe drug on the whole. Due to the different conditions of the included trials, such as some patients who had previously received other treatments, individual and regional differences, more clinical studies, especially randomized controlled trials, are needed in the later stage to evaluate the safety of T-DXd more accurately.

4.3. Pre-scheme for ILD

By comparison, the ILD mortality rate in earlier trials such as Tamura et al. 2019 was more than twice that in the latest trials such as Cortes et al. 2022 [7]. Analysis of T-DXd dosage in each trial, combined with ILD data analysis, showed a strong correlation between symptoms in ILD and T-DXd dosage. The method of reducing drug dosage or intermittent drug use should be considered, and the patient's physical condition and ILD symptoms should be frequently monitored, so as to timely adjust the treatment plan and implement intervention measures as soon as possible [7].

To enhance the safety profile of T-DXd, particularly concerning ILD, future clinical strategies should focus on dose adjustments and intermittent drug administration. Regular monitoring of patients' physical conditions and ILD symptoms is crucial for timely intervention. The observed reduction in ILD mortality rates in recent trials compared to earlier ones highlights the progress in managing this side effect, potentially attributable to improved dosing strategies and better patient management protocols. Continued research, especially through randomized controlled trials, is essential to refine these strategies and further mitigate side effects.

Additionally, exploring biomarkers for early detection of ILD and other severe side effects could significantly enhance patient outcomes. Personalized treatment plans based on individual patient profiles and genetic predispositions may offer a tailored approach, minimizing adverse effects while maximizing therapeutic efficacy. The integration of these strategies into clinical practice will be pivotal in optimizing T-DXd treatment for HER2-positive BC.

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5. Conclusion

This paper mainly discusses the mechanism of HER2-positive BC and existing therapeutic means, explores the mechanism of action and application of T-DXd against HER2-positive BC, and analyzes the side effects and safety evaluation of T-DXd targeted therapy for adult female patients with HER2-positive BC. Through the analysis of this paper, it can be seen that although T-DXd is a relatively safe antibody coupling class of drugs, some of its side effects can not be ignored, especially the pulmonary interstitial disease, which needs more attention. In order to reduce the occurrence of diseases such as pulmonary interstitial disease, close monitoring of patients' physical conditions can be considered, and effective adjustment and intervention can be carried out by reducing drug dosage or intermittent drug use. This provides a new idea for future research, which can focus on the principle and solution of side effects, and try to find the safest and effective drug program. Although the safety of T-DXd is evaluated and a pre-solution is proposed in this paper, the supporting data is small, which makes it impossible to conduct a more macro analysis. The heterogeneity of the study is high, and the pre-solution may be biased. In future studies, this problem should be explored more systematically and comprehensively in an attempt to provide more reliable data support and guidance for clinical trials.

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