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Transforming HER2+ Breast Cancer with T-DXd Insights from SABCS 2024

EDITORIAL

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Revolutionizing HER2-Positive Breast Cancer Treatment: Insights from the 47th San Antonio Breast Cancer Symposium on Trastuzumab Deruxtecan

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Abstract

This editorial discusses the groundbreaking advancements in the treatment of HER2-positive breast cancer presented at the 47th San Antonio Breast Cancer Symposium, focusing on trastuzumab deruxtecan (T-DXd). T-DXd, an innovative antibody-drug conjugate, has shown significant improvements in progression-free survival (PFS) and overall survival (OS) compared to traditional chemotherapy, particularly in patients with HER2-positive metastatic breast cancer. Key studies, including DESTINY-Breast03 and DESTINY-Breast04, demonstrate T-DXd's efficacy and safety across diverse populations, including those with HER2-low tumors and brain metastases. The editorial also highlights the importance of real-world applications, ongoing research into biomarkers, and the potential of combination therapies, such as T-DXd with pyrotinib. The findings suggest that T-DXd not only extends survival but also enhances health-related quality of life for patients, promising a transformative shift in treatment paradigms for HER2-positive breast cancer.

Keywords: HER2-positive breast cancer- trastuzumab deruxtecan- progression-free survival- overall survival

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Dear the Editor,

The recent 47th San Antonio Breast Cancer Symposium (SABCS), held from December 10 to 13, 2024, showcased groundbreaking developments in the treatment of HER2-positive breast cancer, with a particular emphasis on trastuzumab deruxtecan (T-DXd). This cutting-edge antibody-drug conjugate (ADC) has positioned itself as a transformative option in managing this aggressive cancer, showing significant improvements in both progression-free survival (PFS) and overall survival (OS) when compared to conventional chemotherapy treatments.

T-DXd targets the HER2 protein, which is overexpressed in many breast cancers, and is composed of a humanized immunoglobulin G1 monoclonal antibody linked to a potent cytotoxic agent. This unique formulation allows T-DXd to deliver targeted therapy directly to cancer cells while minimizing damage to surrounding healthy tissue. Its efficacy has been particularly notable in patients with HER2-positive metastatic breast cancer (MBC), leading to its approval for use in individuals who have previously undergone treatment with other HER2-targeted therapies [1].

The DESTINY-Breast03 study established T-DXd as the preferred second-line treatment for HER2-positive MBC, showing a 36% reduction in death risk compared to trastuzumab emtansine (T-DM1). Patients treated with T-DXd had a median PFS of 28.8 months, significantly longer than the 6.8 months for T-DM1. This improvement is both statistically significant and clinically relevant, indicating a meaningful extension of time without disease progression. Updated analyses indicated a median OS of 52.6 months for T-DXd versus 42.7 months for T-DM1, suggesting T-DXd's potential to prolong life and enhance quality of life [2]. Additionally, the DESTINY-Breast04 study reported promising results for T-DXd in patients with HER2-low tumors, with a median PFS of 9.9 months compared to 5.1 months for chemotherapy, and a median OS of 22.9 months versus 16.8 months. These findings are particularly relevant for patients with limited treatment options, highlighting T-DXd's ability to address unmet medical needs [3]. A recent study on Asian patients further supports T-DXd's efficacy, showing significant improvements in PFS and OS compared to T-DM1. In the subgroup analysis from DESTINY-Breast03, the median PFS for T-DXd was 25.1 months, while T-DM1 had a

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PFS of 5.4 months (hazard ratio 0.30). The median OS for T-DM1 was 37.7 months, with T-DXd's median OS still not reached [4]. These results reinforce T-DXd's favorable benefit-risk profile, demonstrating its effectiveness across diverse populations, especially in Asian patients.

The safety profile of T-DXd has also been a point of interest. While the treatment is generally well-tolerated, some patients may experience side effects such as nausea, fatigue, and changes in blood counts. Notably, the long-term effects of T-DXd are still under investigation, and ongoing studies will be essential to fully understand its impact on diverse patient populations, including those with specific genetic mutations.

At SABCS, the innovative TROPHY study was presented, exploring the combination of T-DXd with pyrotinib as a first-line treatment for advanced HER2-positive breast cancer. Preliminary results indicated that this combination therapy was well-tolerated, with no severe adverse events reported and all evaluable patients achieving partial remission. This combination could represent a significant advancement in the treatment paradigm, providing new hope for patients battling this aggressive cancer type.

Real-world applications of T-DXd were a primary focus at the symposium. The HER2 REAL study analyzed discrepancies between global treatment guidelines and actual practices for HER2-positive advanced breast cancer, revealing significant deviations in Brazil due to drug availability challenges [5]. In China, the limited use of T-DXd stemmed from the absence of medical insurance coverage, but its planned inclusion in the 2025 insurance catalog is anticipated to improve patient access [6, 7]. The DE-REAL study across 12 Italian hospitals confirmed T-DXd's consistent efficacy and safety, with a median PFS of 16 months. Notably, the treatment demonstrated significant intracranial activity, achieving a 12-month PFS rate of 61.6% in patients with brain metastases and a 62.7% objective response rate in those without [8]. Beyond survival, T-DXd improved health-related quality of life (HRQoL) and neurological function, which are essential for clinical management regardless of brain metastases. Insights from the phase 3b/4 DESTINY-Breast12 trial further elucidate T-DXd's evolving role in the treatment of MBC [9].

The positive impact of T-DXd on patients' quality of life is significant. Analyses from prior DESTINY-Breast studies showed improved HRQoL for T-DXd patients compared to those on control therapies. The recent DESTINY-Breast12 study supported these findings, indicating that T-DXd preserves HRQoL and neurological function in patients, irrespective of brain metastases. These results are promising, suggesting that T-DXd may not only extend survival but also enhance the quality of life during treatment [9].

Another important aspect of the discussions at SABCS was the exploration of biomarkers in relation to T-DXd therapy. Researchers in the DESTINY-Breast03 study sought to determine whether baseline genomic variations could predict treatment efficacy. While no specific genomic variations were identified as predictors of treatment outcomes, the study highlighted that T-DXd maintained its effectiveness across various genomic backgrounds. This finding suggests that T-DXd could be a broadly effective treatment option for HER2-positive patients, regardless of their genetic profiles [2]. Further research into emerging mutations and their potential impact on treatment resistance will be crucial for refining patient selection for T-DXd therapy.

Despite the promising advancements with T-DXd, it is essential to consider potential limitations. Treatments following T-DXd have shown shorter time to treatment failure (TTF), indicating that regimens including trastuzumab may be more effective post-T-DXd treatment compared to HER2 tyrosine kinase inhibitors. Understanding these dynamics is crucial for clinicians and patients when considering treatment options.

Looking ahead, the future of T-DXd in treating HER2-positive breast cancer appears bright. Ongoing studies, including DESTINY-Breast09, are exploring its efficacy as a first-line treatment in comparison to traditional combinations. As researchers continue to unveil data on T-DXd's effectiveness and safety, there is hope that this innovative therapy will become a cornerstone in managing HER2-positive breast cancer, ultimately improving outcomes for patients and enhancing their quality of life.

In conclusion, the advancements presented at the 47th SABCS highlight the transformative potential of T-DXd in the treatment of HER2-positive and HER2-low breast cancer. The compelling data from the DESTINY-Breast studies underscore T-DXd's superiority in terms of PFS and OS compared to existing therapies. However, it is crucial for healthcare professionals and patients to consider both the benefits and potential drawbacks of T-DXd. The integration of T-DXd into clinical practice, particularly with its recent inclusion in medical insurance coverage in China, promises to enhance accessibility and significantly improve patient outcomes. Moreover, the exploration of biomarkers and ongoing studies, such as the TROPHY trial, suggest a future where T-DXd can be further optimized through combination therapies and tailored treatment strategies. The overall improvements in health-related quality of life reported in various studies emphasize that T-DXd not only extends survival but also enhances the well-being of patients. As research continues to evolve, T-DXd stands poised to redefine treatment paradigms for patients with HER2-positive breast cancer, offering hope for better management of this challenging disease.

Author Contribution Statement

H.N., M.K.-M., and A.N. were responsible for the concept and design of the study. Data acquisition and analysis were performed by S.S., A.A., and H.Ne. The manuscript was drafted by A.N. and H.N. Critical review and supervision were provided by M.K.-M. and H.Ne. All authors reviewed and approved the final manuscript.

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