The Efficacy and Safety of Trastuzumab in the Metastatic Breast Cancer

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ABSTRACT

The aim of this study was to explore the efficacy and safety of Trastuzumab-Deruxtecan (T-DXd) in metastatic breast cancer (mBC). This retrospective observational study was conducted between January 2021 and 2023. Patients' clinical and pathological characteristics and previous medicinal treatments were reviewed. The efficacy of T-DXd and its influencing factors, as well as the adverse reactions of T-DXd were also observed. The median age of the patients was 43 years, and the median number of treatment lines was 4. In the overall population, the objective response rate (ORR) was 72.7%, the disease control rate (DCR) was 90.9%, and the median progression-free survival (mPFS) was six months. Among them, two patients temporarily discontinued treatment after two cycles of T-DXd due to financial reasons, but their disease remained stable for 5 and 8 months, respectively. Efficacy was better in patients with HER-2 amplification, who had not previously used antibody drug conjugates (ADC) drugs, were sensitive to anti-HER-2 treatment, and had ≤3 lines of therapy. Common adverse reactions during T-DXd treatment included gastrointestinal reactions such as nausea, vomiting, diarrhoea, and constipation, as well as haematological toxicities, decreased appetite, hair loss, and fatigue. Some patients experienced gastritis, abnormal liver function, and weight gain, but none of the patients developed interstitial pneumonia. T-DXd can achieve significant and durable survival benefits with controllable safety in patients with HER2-positive or HER2 low-expressing mBC.

Key Words: *Metastatic breast cancer, Trastuzumab-Deruxtecan, Efficacy, Safety.*

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INTRODUCTION

Breast cancer has become the most common cancer among women worldwide that seriously threatens women's health. Among newly diagnosed cases of breast cancer each year, approximately 3 to 10% of women already have distant metastasis. Metastatic breast cancer (mBC) lacks standardised recommendations for later-line therapy, and patients with mBC have specific considerations and challenges when making treatment decisions. The treatment for mBC patients needs to balance survival with quality of life, aiming to prolong survival while ensuring the quality of life.

With the improvement of medical technology, the overall survival (OS) of breast cancer has been continuously improving. However, the prognosis for patients with mBC is not optimistic, with a 5-year OS rate of only 25.9% and a median OS of 2 to 3 years.[1] The treatment strategies for mBC differ according to its molecular subtypes, and targeted therapy has greatly improved the prognosis for these patients.

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Antibody-drug conjugates (ADC) are a novel type of targeted therapy that combines the advantages of strong antibody selectivity and high drug potency. T-DXd is a new-generation ADC drug composed of an anti-HER2 monoclonal antibody and a Topoisomerase I inhibitor linked by a tetrapeptide-based cleavable linker. Based on the impressive data from the Phase II DESTINY-Breast01 study, T-DXd was granted accelerated approval by the FDA in 2019 for the treatment of HER2-positive mBC in patients who have previously received at least two anti-HER2 therapies in the metastatic setting.[2] In the confirmatory phase III study DB02, T-DXd significantly prolonged PFS and OS compared to the investigator's choice of therapy (TPC), 17.8 *vs.* 6.9 months and 39.2 *vs.* 26.5 months, respectively.[3] In the DB03 study, compared to T-DM1, T-DXd had a significant improvement on PFS (28.8 vs. 6.8 months) in second-line treatment.[4] Results from the DB04 study showed that T-DXd provided clinically and statistically significant improvements in PFS and OS for patients with HER2-low-expressing breast cancer. T-DXd treatment delayed also the deterioration of quality of life, demonstrating advantages over (TPC) in terms of the quality of life.[5]

Real-world studies can evaluate the efficacy and characteristics of specific medicine outside of clinical trials. Although T-DXd is currently available in the domestic market, its use is limited in China due to its short time on the market and high cost. Therefore, it is necessary to further evaluate the efficacy

and safety of T-DXd in real-world patients. This study aimed to assess the efficacy and safety of T-DXd in mBC, providing a better understanding of its clinical application, characteristics, and laying a foundation for guiding clinical treatment.

METHODOLOGY

Patients treated with T-DXd were collected in Xi'an International Medical Center Hospital from January 2021 to 2023. The clinicopathologic features of these patients were reviewed from medical records. Inclusion criteria were female breast cancer patients with clear diagnosis and pathological confirmation; in Stage IV, with clear clinical and pathological features including age, HR immunohistochemical (IHC) status, HER-2 IHC status, Ki-67 value, number of metastatic sites, prior use of CDK4/6 inhibitors, prior use of ADCs, presence of brain metastasis, whether it was primary resistance to anti-HER2 treatment or not, number of prior treatment lines, and those who received T-DXd treatment. Exclusion criteria were early breast cancer, patients who did not receive T-DXd treatment, and those with unclear pathological characteristics.

A total of 11 patients were included in this study, with a median age of 43 years and a median of 4 treatment lines. All 11 patients had infiltrating ductal carcinoma as the pathological type, and had received anthracycline and taxane medicines during neoadjuvant and/or adjuvant stages. All the patients had metastases in ≥3 sites, including visceral metastases. Among the patients, five had low expression of HER-2, two had previously used CDK4/6 inhibitors (18.2%), and six had previously used ADCs (54.5%; 4 with RC-48 and 2 with T-DM1). Nine (81.8%) patients had brain metastases, seven (63.6%) patients had primary resistance to anti-HER-2 therapy, and six (54.5%) patients had more than three treatment lines. Objective response rate (ORR) was 72.7%, disease control rate (DCR) was 90.9%, and median progression-free survival (mPFS) was 6 months. Among them, the 8th and 9th patients stopped treatment with T-DXd after two cycles due to economic reasons but their conditions remained stable for 5 months and 8 months, respectively. The 10th and 11th patients consistently used T-DXd and their conditions were still improving, with PFS of 8 months and 10 months, respectively (Table I and II).

RESULTS

During the treatment process with T-DXd, bone marrow suppression was common, manifested by decreased neutrophils, anaemia, and reduced platelets, mostly at grades 1 to 2. Gastrointestinal reactions are also common, including nausea, vomiting, constipation, and diarrhoea, all at grades 1 to 2, with no grade 3 to 4 adverse reactions. Decreased appetite, hair loss, and fatigue have a relatively high incidence (36.4%, 36.4%, and 27.3%) and are also grades 1 to 2. Two cases had elevated transaminases, and two cases had weight gain, while no cases had interstitial lung disease.

All patients had a number of metastasis ≥3 sites, and all had visceral metastasis, with a median of 4 treatment lines. Among them, 45.5% of patients had low expression of HER-2, 54.5% had previous use of ADC, 63.6% had primary resistance to anti-HER-2 therapy, and 54.5% had more than 3 treatment lines. The ORR was 72.7%, DCR was 90.9%, and mPFS was 6 months. Among them, two patients temporarily discontinued treatment after two cycles of T-DXd due to financial reasons but their conditions remained stable for 5 months and 8 months, respectively. Another two patients who regularly used T-DXd, experienced sustained relief of symptoms, with PFS exceeding 8 months. This study is consistent with previous studies, as the benefits of T-DXd were observed regardless of previous medical history, systemic treatments, treatment lines, CDK4/6i, and the use of ADC drugs. However, patients with HER-2 amplification, no previous use of ADC drugs, sensitivity to anti-HER-2 therapy, and ≤3 treatment lines had better short-term efficacy compared to patients with low expression of HER-2, previous use of ADC drugs, resistance to anti-HER-2 therapy, and >3 treatment lines.

Table I: Clinical and pathological characteristics and prognosis of patients.

No. of patients	Age (years)	HR IHC	HER-2 IHC	Ki-67	Number of metastatic sites	Previous use of CDK4/6i	Previous use of ADC	Brain metastases	Presence of primary resistance to anti-HER2 treatment	Treatment lines	Recent treatment efficacy	PFS (m)
1	50	-	IHC 2+(FISH-)	30%	≥3	No	RC-48	No	Yes	5	PD	2
2	43	-	IHC 1+	10%	≥3	No	No	Yes	Yes	3	PR	3
3	53	-	IHC 2+(FISH+)	20%	≥3	No	No	Yes	Yes	10	PR	4
4	42	+	IHC 1+	30%	≥3	No	RC-48	Yes	No	3	PR	5
5	42	+	IHC 3+	25%	≥3	No	T-DM1	Yes	Yes	3	PR	6
6	45	-	IHC 3+	10%	≥3	No	No	Yes	Yes	2	SD	9
7	59	+	IHC 2+(FISH-)	50%	≥3	Yes	No	No	No	7	PR	8
8*	31	+	IHC 3+	70%	≥3	No	T-DM1	Yes	No	8	SD	5
9*	61	-	IHC 3+	40%	≥3	No	RC-48	Yes	Yes	4	PR	8
10**	30	+	IHC 1+	8%	≥3	Yes	No	Yes	No	4	PR	8
11**	41	-	IHC 3+	70%	≥3	No	RC-48	Yes	Yes	2	PR	10

*Note: ** indicates sustained remission of the disease during T-DXd treatment; * indicates that T-DXd treatment was temporarily discontinued after a short course, with a longer period of disease stability. According to literature reports in The Oncologist, primary resistance refers to disease progression within 3 months after first-line treatment with T-DXd or at the first imaging evaluation at 8 to 12 weeks; or the diagnosis of a new recurrence event within 12 months after adjuvant treatment with T-DXd.*

Table II: Clinical efficacy of T-DXd treatment in advanced breast cancer patients.

Pathological characteristics	n	CR (n)	PR (n)	SD (n)	PD (n)	ORR (n, %)	DCR (n, %)	mPFS (m)
Total patients	11	0	8	2	1	8 (72.7%)	10 (90.9%)	6
HR IHC								
Positive	5	0	4	1	0	4 (80.0%)	5 (100%)	7
Negative	6	0	4	1	1	4 (66.7%)	5 (83.3%)	6
HER-2 IHC								
Low expression	5	0	4	0	1	4 (80.0%)	4 (80.0%)	5
Her-2 amplification	6	0	4	2	0	4 (66.7%)	6 (100%)	7
Ki-67 value								
<30%	5	0	4	1	0	4 (80.0%)	5 (100%)	6
≥30%	6	0	4	1	1	4 (66.7%)	5 (83.3%)	6
Previous use of CDK4/6i								
Yes	2	0	2	0	0	2 (100%)	2 (100%)	8
No	9	0	6	2	1	6 (66.7%)	8 (88.9%)	6
Previous use of ADC								
Yes	6	0	4	1	1	4 (66.7%)	5 (83.3%)	6
No	5	0	4	1	0	4 (80.0%)	5 (100%)	6
Brain metastases								
Yes	9	0	7	2	0	7 (77.8%)	9 (100%)	7
No	2	0	1	0	1	1 (50.0%)	1 (50.0%)	5
Presence of primary resistance to anti-HER2 treatment								
Yes	7	0	5	1	1	5 (71.4%)	6 (85.7%)	7
No	4	0	3	1	0	3 (75.0%)	4 (100%)	6
Treatment lines								
≤3	5	0	4	1	0	4 (80.0%)	5 (100%)	7
>3	6	0	4	1	1	4 (66.7%)	5 (83.3%)	5

DISCUSSION

Breast cancer is the second most common cause of brain metastases. In patients with HER2+ mBC with active or stable brain metastases, T-DXd treatment has shown promising anti-tumour activity, indicating its effectiveness and durable clinical activity against brain metastases.[4,6,7] Furthermore, patients maintained a stable quality of life during T-DXd treatment, with preserved neurocognitive, physical, emotional, and social functioning. The DEBBRAH trial demonstrated preliminary anti-tumour activity of T-DXd in HER2-low expressing, previously treated patients with asymptomatic untreated or locally treated progressive brain metastases.[8] In this study, 9 (81.8%) cases were identified among patients with brain metastases, with an ORR of 77.8%, DCR of 100%, and median PFS of 7 months. Among patients with brain metastases and low expression of HER2 (cases 2, 4, and 10), all the cases experienced symptomatic relief, indicating that T-DXd demonstrates good efficacy regardless of the presence of brain metastases.

Clinical studies have shown that T-DXd has a good safety profile with manageable adverse reactions.[9] In this study, common adverse reactions of T-DXd included gastrointestinal reactions, myelosuppression, decreased appetite, alopecia, and fatigue. Some patients experienced gastritis, abnormal liver function, and weight gain, mostly grade 1 or 2 adverse reactions. Only a few patients experienced grade 3-4 myelosuppression, while all other adverse reactions were grade 1 or 2. There was no interstitial pneumonia.

This study demonstrates that T-DXd has an effect in a broader range of HER2 expression levels or heterogeneous tumours, providing favourable short-term efficacy and PFS for ABC patients, with a good safety profile. Although T-DXd is recommended for use in multiple guidelines, its clinical application in China is relatively new, and there are still many questions that need further research, such as the optimal timing of T-DXd administration and the selection of therapeutic agents after T-DXd resistance develops. However, this study is exploratory in nature and is based on a small sample size, necessitating further research with a larger sample size.

CONCLUSION

T-DXd can achieve significant and durable survival benefits with controllable safety in patients with HER2-positive or HER2 low-expressing mBC.

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ETHICAL APPROVAL:
This study was exempted by the Ethics Committee of Xi'an International Medical Center Hospital, China.

PATIENTS' CONSENT:
This clinical study is a retrospective study, only collecting patients' clinical data without interfering with patients' treatment plans, which will not bring physiological risks to patients. The authors did not reveal patients' personal privacy.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
XW: Contributed to the design of the study, collected the data, and drafted the manuscript.

YX: Contributed to the conception and design of the study and revised the manuscript critically.
Both authors approved the final version of the manuscript to be published.

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