Cover Letter

Title:

Study of Efficacy and Toxicity of Trastuzumab Deruxtecan in Metastatic HER2-Positive Breast Cancer Patients: Single Center Experience, Madinah, Saudi Arabia.

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Introduction: HER2-positive metastatic breast cancer is an aggressive disease with a high risk of recurrence, progression, and treatment resistance. Trastuzumab deruxtecan (T-DXd) has shown strong activity in clinical trials, but real-world outcomes may differ because some patients are often more heavily pretreated and clinically diverse.

Objectives: This study aimed to evaluate the real-world efficacy and safety of T-DXd in women with HER2-positive metastatic breast cancer and to explore whether outcomes differed according to line of therapy, metastatic pattern, HER2 expression, hormone receptor status, and central nervous system involvement in our locality.

Methods: We conducted a single-center study at King Salman Medical City, Madinah, Saudi Arabia, including all eligible women treated with T-DXd from 2023 with a median follow-up of one year. Patients had histologically confirmed HER2-positive metastatic breast cancer. T-DXd was given at 5.4 mg/kg every 3 weeks. The primary endpoint was disease control rate; secondary endpoints included progression-free survival, overall survival, and treatment-related toxicities.

Introduction

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer represents a biologically aggressive subtype characterized by high rates of recurrence and metastatic spread. The introduction of HER2-targeted therapies, beginning with trastuzumab, has significantly improved survival outcomes; however, metastatic disease remains incurable for most patients, and resistance to sequential HER2-directed therapies inevitably develops. Despite advances with dual HER2 blockade and antibody–drug conjugates, optimizing treatment sequencing and improving outcomes in heavily pretreated populations remain major clinical challenges (Arteaga, Sliwkowski et al. 2011, Swain, Baselga et al. 2015).

Trastuzumab deruxtecan is a novel HER2-directed antibody–drug conjugate composed of an anti-HER2 monoclonal antibody linked to a potent topoisomerase I inhibitor

payload. Its unique design, including a high drug-to-antibody ratio and membrane-permeable payload, enables a “bystander effect,” allowing cytotoxic activity even in tumors with heterogeneous or low HER2 expression. Clinical trials such as DESTINY-Breast01 (Modi, Saura et al. 2020) and DESTINY-Breast03 (Hurvitz, Hegg et al. 2023) have demonstrated remarkable efficacy, with objective response rates of approximately 60–80% and significant improvements in progression-free survival compared with prior standards of care.

Emerging evidence suggests that the efficacy of trastuzumab deruxtecan may vary according to clinical and biological factors, including line of therapy, HER2 expression level, and sites of metastatic disease. Earlier use of T-DXd has been associated with improved outcomes, with higher response rates and longer progression-free survival observed in second-line settings compared with later-line use (André, Hee Park et al. 2023, Hurvitz, Hegg et al. 2023). Additionally, T-DXd has demonstrated activity across a spectrum of HER2 expression, including HER2-low disease, supporting the concept of HER2 as a continuous rather than binary biomarker (Modi, Park et al. 2020, Tarantino, Lee et al. 2025).

Central nervous system (CNS) metastases remain a major unmet need in HER2-positive metastatic breast cancer, historically associated with poor prognosis and limited therapeutic options. Unlike earlier HER2-targeted agents, trastuzumab deruxtecan has shown clinically meaningful intracranial activity in both clinical trials and real-world studies, with intracranial response rates ranging from approximately 40% to 70% and disease control rates exceeding 70% in selected populations. These findings suggest that T-DXd may overcome some of the limitations of prior therapies in the CNS setting, likely due to its potent cytotoxic payload and ability to penetrate disrupted blood–brain barrier environments (Modi, Park et al. 2020).

Despite its efficacy, the safety profile of trastuzumab deruxtecan requires careful consideration. Treatment-related adverse events are common, including hematologic toxicity, gastrointestinal symptoms, and fatigue, but are generally manageable with dose modification and supportive care. However, interstitial lung disease remains a unique and potentially serious toxicity, reported in approximately 10–20% of patients in real-world studies and requiring early recognition and management to prevent severe outcomes (Powell, Modi et al. 2022, Soares, Vilbert et al. 2023, Ma, Li et al. 2026). Additionally, emerging data suggest that toxicity may increase in later lines of therapy due to cumulative treatment exposure, reduced organ reserve, and evolving tumor biology.

Real-world evidence has become increasingly important in complementing clinical trial data, particularly in heterogeneous patient populations often underrepresented in trials. Observational studies have confirmed the effectiveness of trastuzumab deruxtecan in routine clinical practice, while also highlighting variability in toxicity,

treatment sequencing, and outcomes across different subgroups. However, data remain limited regarding the combined impact of clinical factors such as line of therapy, HER2 expression, CNS involvement, and toxicity patterns in our locality. Therefore, the present study aims to evaluate the real-world efficacy and safety of trastuzumab deruxtecan in patients with HER2-positive metastatic breast cancer, with particular emphasis on treatment sequencing, biomarker-defined subgroups, and toxicity outcomes as a single center experience.

Patients and Methods

This is cross sectional prospective and retrospective study was conducted on all Her2 positive female metastatic breast cancer patients were treated at our medical oncology department, King Salman Medical City, Medinah, KSA from 2023 with median follow up duration of one year.

Study Design and Participants

Eligible patients were females age ≥18 years older; with histologically confirmed metastatic breast cancers; who progressed during / within sex months of finishing adjuvant anti Her2 (Tdxd considered as 2nd line) or denovo metastatic disease received previously at least two lines of anti Her2 (Tdxd considered as 3rd line or beyond).

All patients were Eastern Cooperative Oncology Group performance status of 0-1 with left ventricular ejection fraction ≥50% by either echocardiography. Patients must have provided an existing formalin-fixed paraffin-embedded (FFPE) tumor sample for tissue-based IHC staining to centrally determine HER2 expression and other correlatives.

HER2-overexpressing tumors with IHC 3+/2+ with SISH positive (local or central testing) had ≥1 investigator-assessed measurable lesion on the basis of RECIST 1.1. Patients with noninfectious interstitial lung disease (ILD)/pneumonitis requiring steroids were excluded.

Procedures

T-DXd was administered intravenously once every 3 weeks at 5.4 mg/kg of body weight. CT scans were performed before starting therapy and every three cycles until documented disease progression (RECIST 1.1) or development of toxicity. Dose interruptions and/or reduction and supportive therapy were permitted for clinically significant and/or unacceptable toxicity. High-resolution computed tomography and pulmonary function were measured at baseline and at the time of suspected ILD/pneumonitis events. For suspected ILD/pneumonitis, treatment was interrupted pending evaluation, and all events were followed until resolution.

Dosing was interrupted, and supporting therapy was administered as required. On improvement of an adverse event leading to dose interruption, T-DXd therapy could be

resumed at the same dose. If another time of the same adverse event, or a different adverse event, required dose interruption, therapy could be restarted at a reduced dose on improvement (dose level 1: 4.4 mg/kg of body weight once every 3 weeks; dose level 2: 3.2 mg/kg of body weight once every 3 weeks).

End Points

Primary end point:

The primary end point was confirmed disease control rate rate (DCR), defined as the proportion of patients with a confirmed complete, partial response or stable disease by RECIST 1.1; progression-free survival (PFS; time from first dose until date of objective disease progression or death); and overall survival (OS; time from date of first dose until death due to any cause)

Secondary endpoints:

The documented adverse events (including drug-related adverse events, serious adverse events, and adverse events as ILD/pneumonitis, neutropenia, GI upset and left ventricular dysfunction. Adverse events were coded and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).

Ethical approval:

The study Protocol was approved by the local institutional review board and was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice, the Declaration of Helsinki, and local regulations on the conduct of clinical research. All patients provided written informed consent before they started Tdxd.

Statistical analysis:

statistical analysis was carried out using software Excel 2010 and version 21 of SPSS (Statistical System for Social Science). Qualitative data were described in the form of percentages. Quantitative data were described in the form of mean (±) standard deviation (SD). Statistical analysis was performed by comparison between groups using the chi-squared test. &e Kaplan–Meier product-limit estimator was used for calculating the survival measure. Comparison of the survival was performed by the log-rank test; continuous variables were dichotomized at the median cutoff. &e probability of being by chance (P value) was calculated for all parameters (P is significant if ≤ 0.05 at a confidence interval of 95%).

Approval

Study protocol was approved by the King Salman Medical City IRB (H-03-M-11) under no. 25-091. Approval of the managers of the hospital in which the study was conducted. Informed verbal consent was obtained from each participant sharing in the study.

Confidentiality and personal privacy was respected in all levels of the study. Collected data was not used for any other purpose.

Availability of data Data is available upon request.

Conflict of interest The authors declare that they have no conflict of interest to disclose.

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ORCID for corresponding author; Elbaiomy MA: https://orcid.org/0000-0001-8702-7633