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Impact of Trastuzumab Emtansine with Dose Escalation on Thrombocytopenia in Chinese Patients with HER2-Positive Breast Cancer: A Multicenter Retrospective Study

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Abstract

Background: Trastuzumab emtansine (T-DM1) is associated with a high incidence of grade ≥3 thrombocytopenia (40.4%) in patients with HER2-positive breast cancer. This study investigated if a dose-escalation strategy could reduce this incidence in Chinese patients.

Methods: This multicenter, retrospective study enrolled 46 HER2-positive BC patients with ≥1 prior systemic therapy. Patients received T-DM1 escalated in a stepwise manner (2.4→3.0→3.6 mg/kg) over subsequent cycles. The primary outcome was the incidence of thrombocytopenia.

Results: The incidence of any-grade and grade ≥3 thrombocytopenia was 58.7% and 30.4%, respectively. The regimen was well-tolerated; only 8.7% of patients discontinued T-DM1, with no discontinuations attributed to thrombocytopenia.

Conclusion: Stepwise dose escalation of T-DM1 appears to be a feasible and well-tolerated approach that may meaningfully reduce the occurrence of severe thrombocytopenia. These findings strongly support prospective validation of this approach to optimize T-DM1 therapy.

Introduction

- Trastuzumab Emtansine (T-DM1), an antibody-drug conjugate of trastuzumab and emtansine, is an established adjuvant or second-line therapy for HER2-positive breast cancer (BC), widely used in China for both early-stage and advanced HER2-positive BC.
- This study was designed to investigate the impact of T-DM1 with dose escalation on thrombocytopenia incidence.

Methods and Materials

This multicenter, retrospective study enrolled HER2-positive BC patients treated with T-DM1 between May 2024 and March 2025, all of whom had received at least one prior systemic therapy.

Patients were stratified into two cohorts: (1) early-stage disease with residual disease (non-pCR) post-neoadjuvant therapy; (2) advanced-stage disease with progression following prior systemic treatments.

T-DM1 dose was escalated in a stepwise manner: 2.4 mg/kg administered in Cycle 1, followed by 3.0 mg/kg in Cycle 2, and 3.6 mg/kg in Cycle 3. Non-pCR patients received up to 14 cycles of T-DM1, while those with advanced-stage continued treatment until disease progression or unacceptable toxicity.

The primary outcome was thrombocytopenia incidence. Data on treatment patterns, adverse events, and clinical efficacy were also collected and analyzed.

Results

Patient Characteristics

A total of 46 patients were included (37 non-pCR; 9 advanced). The mean age was 52.8±8.9 years. All 37 non-pCR BC patients received neoadjuvant chemotherapy: 78.4% platinum-based, 13.5% anthracycline-based, and 8.1% other regimens. For advanced breast cancer, Seven and two patients received T-DM1 as second and later-line therapy, respectively.

Table 1. Baseline Demographics, Treatment Exposure.

Variables	Total (N=46)
Age, years, Mean ± SD	52.81±8.92
Treatment setting, n (%)	
Advanced	9 (19.6)
Non-pCR (non-pathologic complete response)	37 (80.4)
Prior systemic therapy, n (%)	46 (100.0)
T-DM1 Treatment Pattern	
Initial dose, mg, Mean ± SD	139.05±21.20
Maximum dose, mg, Mean ± SD	171.33±38.38
Maximum dose level, n (%)	
2.4 mg/kg	18 (39.1)
3.0 mg/kg	8 (17.4)
3.6 mg/kg	20 (43.5)
Treatment exposure duration, days, median (range)	75.00 (7.00, 377.00)
Treatment discontinuation rate, n (%)	4 (8.7)
Reason for discontinuation, n (%)	
Permanent discontinuation due to physician's advice	1 (2.2)
Permanent discontinuation due to disease progression	3 (6.5)

Table 2. Thrombocytopenia Events.

Grade	Total (N=46)
Grade 1, n (%)	8 (17.4)
Grade 2, n (%)	5 (10.9)
Grade 3, n (%)	13 (28.3)
Grade 4, n (%)	1 (2.2)
None, n (%)	19 (41.3)

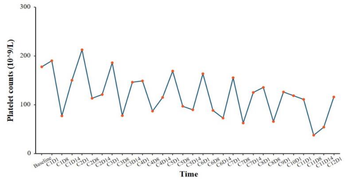


Figure 1. Platelet Count Dynamics During T-DM1 Therapy.

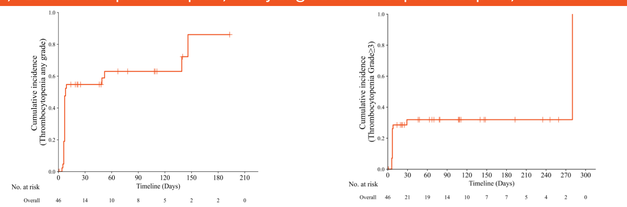


Figure 2. Kaplan-Meier Estimates of Cumulative Incidence of Thrombocytopenia in the Overall Cohort.

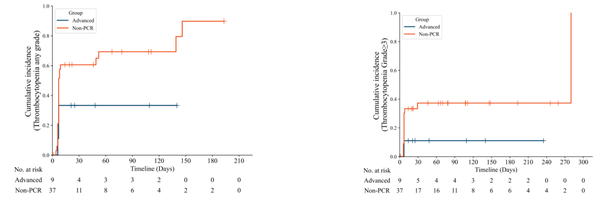


Figure 3. Kaplan-Meier Estimates of Cumulative Incidence of Thrombocytopenia by Patient Cohort.

T-DM1 Treatment

The initial dose of all the patients was 2.4 mg/kg. Maximum dose levels were 2.4 mg/kg in 39.1%, 3.0 mg/kg in 17.4%, and 3.6 mg/kg in 43.5% of patients, respectively. The median treatment duration was 75 days (range 7–377). The platelet counts during the course of T-DM1 treatment dropped from the baseline to a nadir approximately on Day 8 of each cycle, with recovery noted prior to the next administration (Figure 1).

Thrombocytopenia

The overall incidence of any-grade and grade ≥3 thrombocytopenia was 58.7% and 30.4%, respectively, with a median time to onset was 8 days for any-grade events and 280 days for grade ≥3 events (Figure 2) (Table 2).

When stratified by cohort, the cumulative incidence of any-grade thrombocytopenia was 64.9% in the non-pCR cohort versus 33.3% in the advanced cohort; for grade ≥3 events, the rates were 35.1% versus 11.1%, respectively (Figure 3).

Clinical Outcomes

With a median follow-up of 77 days, the survival data for the non-pCR cohort remain immature, and the median survival has yet to be reached. In the advanced cohort, one patient (11.1%) achieved a partial response (PR) and four patients (44.4%) experienced progressive disease (PD) (Figure 4).

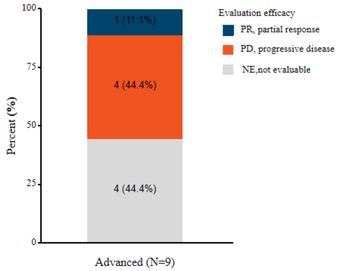


Figure 4. Distribution of best overall response to T-DM1 therapy in the Advanced cohort (N=9).

Discussion

- The 30.4% incidence of grade ≥3 thrombocytopenia observed in our study is consistent with findings reported in other Asian cohorts [1,2], supporting a greater risk in this population but appears favourable in comparison with historical data from standard-doses, suggesting potential benefit from dose escalation strategy.
- The pattern of platelet counts that fell to a nadir around Day 8 before spontaneously recovering has previously been associated with T-DM1-induced thrombocytopenia in the Phase I study when observed at a later stage. This transient, reversible profile of thrombocytopenia does not cause persistent cumulative toxicity， which is also clinically predictable and manageable. This study provides important evidence for the safety of dose escalation strategies.[3,4].
- While the higher incidence of thrombocytopenia in the non-PCR cohort was not statistically significant, it could be reflective of a population with greater underlying risk factors, such as more extensive prior therapy or radiotherapy, as shown by other real-world analyses[5].
- This dose-escalation approach may be a feasible clinical strategy to improve the therapeutic window of T-DM1 in this high-risk population. It may allow more patients to complete their planned treatment and maximise dose intensity[6,7].

Limitations: (1) multicenter, single-arm, retrospective study; (2) limited sample size; (3) limited follow-up.

Conclusions

- T-DM1 dose escalation was well tolerated and effective with a relatively low incidence of grade ≥3 thrombocytopenia.
- Further prospective studies are warranted to confirm the benefit of initial low-dose T-DM1.

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