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ORIGINAL RESEARCH

Investigation of Thrombocytopenia Associated with Trastuzumab Emtansine Treatment in Breast Cancer: A Retrospective Study in a Chinese Population

Kun Zhang, Shijie Wu, Yunxiang Zhou, Huihui Chen, Chi Pan

Department of Breast Surgery, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, People's Republic of China

Correspondence: Chi Pan, Email panchi@zju.edu.cn

Purpose: Thrombocytopenia is a common adverse event associated with trastuzumab emtansine (T-DM1) treatment in patients with HER2-positive metastatic breast cancer. This study aims to evaluate the incidence, clinical characteristics, and risk factors of T-DM1-associated thrombocytopenia.

Patients and Methods: This retrospective study included patients with breast cancer who received T-DM1. Thrombocytopenia was defined as a platelet count of less than 100×10^9/L. Potential risk factors for thrombocytopenia were analyzed.

Results: The study cohort consisted of 47 patients with a median age of 55 years, including one male patient. Thrombocytopenia was observed in 74.5% of patients during T-DM1 treatment. A total of 63.3% of patients with Ki-67 expression levels ≥30% experienced thrombocytopenia, which was significantly lower than the 94.1% incidence in patients with Ki-67 expression <30% (P=0.034). Patients with completed or ongoing T-DM1 treatment had a thrombocytopenia incidence of 90.5%, compared to 64% in those who discontinued treatment (P=0.036). Although not reaching statistical significance, concurrent radiotherapy was associated with a higher incidence of thrombocytopenia (87.5%). After appropriate interventions, 70% of patients showed restored platelets, while 17.1% required dose reductions.

Conclusion: Thrombocytopenia is a prevalent adverse event during T-DM1 treatment in real-world practice. An increased incidence with concurrent radiotherapy was observed. While the incidence of thrombocytopenia appears to rise with prolonged exposure in completed or ongoing T-DM1, it may have a minor impact on the overall duration of therapy. Future studies should examine these findings to guide prophylactic strategies and interventions for high-risk patients.

Keywords: trastuzumab emtansine, T-DM1, breast cancer, thrombocytopenia, incidence

Introduction

In recent years, antibody-drug conjugates (ADCs) have emerged as a prominent option for cancer therapy. Trastuzumab emtansine (T-DM1) represents a notable ADC carrying the cytotoxic agent DM1, which is linked to trastuzumab via a stable thioether bond.[1] Relative to other treatment combinations, such as trastuzumab plus docetaxel[2] or lapatinib plus capecitabine,[3] T-DM1 has demonstrated promising efficacy and better tolerability, exhibiting fewer adverse events (AEs). Nonetheless, the development of thrombocytopenia following T-DM1 administration remains a significant clinical concern, prompting ongoing research into its mechanistic foundations.[4]

In pivotal Phase III trials, including EMILIA,[3] TH3RESA,[5] and KATHERINE,[6] which investigated the treatment of HER2-positive metastatic breast cancer, T-DM1 has shown a favorable safety profile. Among the AEs, thrombocytopenia emerged as one of the most frequently observed. A meta-analysis of studies on T-DM1 reported a thrombocytopenia incidence of 38.3%, with grade ≥3 thrombocytopenia occurring in approximately 10.7% of patients.[7] Although the majority of thrombocytopenia cases are mild and manageable with appropriate interventions, severe instances may

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necessitate dose reductions or even discontinuation of T-DM1, potentially reducing the likelihood of achieving optimal therapeutic outcomes. The pathophysiology of T-DM1-induced thrombocytopenia is not fully elucidated, with prior studies mainly examining mechanisms such as binding to Fcγ receptors or phagocytosis by megakaryocytes. This interaction disrupts the differentiation and maturation of megakaryocytes, predominantly affecting platelet production without necessarily impacting the function of existing platelets.[8] Consequently, while thrombocytopenia is common during T-DM1 therapy, it does not frequently result in life-threatening bleeding. Remarkably, there are notable disparities in the susceptibility to T-DM1-induced thrombocytopenia across different populations. Data indicate that Asian patients experience a higher incidence of grade ≥3 thrombocytopenia compared to non-Asian patients (44.4% vs 10.6%), though the rates of bleeding remain similar (37.4% vs 36.4%), with very low occurrences of grade ≥3 bleeding (1.0% vs 2.2%).[9] The underlying causes of the increased susceptibility among Asian populations to T-DM1-induced thrombocytopenia are not well understood and merit further exploration.

Currently, the comprehension of thrombocytopenia induced by T-DM1 is largely derived from previous clinical trials that focused on its frequency and severity. Nonetheless, there is a considerable gap in our knowledge regarding the incidence and risk factors for T-DM1-associated thrombocytopenia within the diverse and intricate real-world context. Retrospective studies that have investigated the incidence of thrombocytopenia present inconsistent results and provide limited information concerning the timing of its onset and the incidence under various combination treatment regimens.[10–12] Moreover, there is a critical need to conduct studies based on the Chinese population to elucidate factors associated with thrombocytopenia and improve the management of T-DM1-induced thrombocytopenia. Consequently, this study aims to explore the incidence, clinical features, and risk factors associated with thrombocytopenia in patients with breast cancer undergoing T-DM1 treatment, thereby providing essential insights for informed clinical decision-making.

Methods

Study Design and Patients

In this retrospective cohort study, we reviewed medical records of patients diagnosed with breast cancer at the Department of Breast Center at The Second Affiliated Hospital, Zhejiang University School of Medicine, between July 2021 and August 2023. Eligible participants met the following inclusion criteria: (1) aged between 18 and 65 years; (2) histologically confirmed diagnosis of breast cancer; and (3) receipt of treatment with T-DM1. T-DM1 used in any setting was eligible for this real-world study.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Institutional Review Board of The Second Affiliated Hospital, Zhejiang University School of Medicine, approved the study protocol (approval No. 2024–0893). Given the retrospective nature of this research, the requirement for informed consent was waived by the ethics committee. All patient data were handled with strict confidentiality in compliance with relevant privacy regulations.

Data Collection and Assessment

Data collection included demographic characteristics, medical history, laboratory results, clinicopathological features, therapeutic details, and AEs. Detailed monitoring of platelet count was performed throughout the treatment period, with specific documentation of interventions employed for managing thrombocytopenia. The Ki-67 value was from the biopsy for patients who underwent neoadjuvant therapy or with unresectable disease; otherwise in the adjuvant setting, the Ki-67 value was obtained from the surgical specimen. Breast cancers were staged using the AJCC 8th Edition classification system. Early stage breast cancer included stage 0/I/IIA/IIB, while advanced stage encompassed stage III/IV.

The main outcome was the incidence of thrombocytopenia in patients receiving T-DM1, defined as a platelet count of less than 100×10^9/L, in accordance with the Consensus on the Clinical Diagnosis, Treatment, and Prevention of Cancer Treatment-Induced Thrombocytopenia in China. A thorough evaluation was conducted to identify the clinical characteristics of thrombocytopenia during T-DM1 treatment. This included analysis of the timing of thrombocytopenia onset,

identification of potential risk factors such as demographic variables, disease characteristics, and treatment-related factors, as well as a review of treatment specifics, including any interventions and adjustments in T-DM1 dosage. Treatment completion for T-DM1 was defined as achieving 13 cycles for patients with early-stage breast cancer, while patients with advanced-stage disease continued treatment until disease progression. AEs were classified and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical Analysis

Categorical variables were summarized as frequencies and percentages, and comparisons between groups were conducted using either the chi-square test or Fisher's exact test, as appropriate. The normality of continuous data was evaluated using the Shapiro–Wilk test. Continuous variables with a normal distribution were presented as mean ± standard deviation (SD), while those not normally distributed were expressed as median with range. A two-sided P-value of less than 0.05 was considered statistically significant. All statistical analyses were conducted using R software (version 4.3.0).

Results

Baseline Characteristics of Patients

The study included a cohort of 47 patients with breast cancer who were treated with T-DM1, among whom was a male patient (2.1%). The median age of participants was 55 years (range, 31–69 years). A total of 18 patients (38.3%) were diagnosed with advanced-stage breast cancer. Estrogen receptor (ER) positivity was observed in 55.3% of patients, while progesterone receptor (PR) positivity was noted in 42.6%. A significant majority (n=44, 93.6%) had undergone chemotherapy preceding T-DM1 treatment, whereas a smaller subset (n=7, 14.9%) had received prior radiotherapy. Among the patients with previous chemotherapy, the time interval between TDM1 initiation and the last chemotherapy distributed as follows: <1 month in two, 1–6 months in 28, 6–12 months in one, >12 months in 11, and unknown in two patients. Among all patients, 19 received T-DM1 as first-, second-, third-, fourth-, or fifth-line treatment for metastatic breast cancer, one received T-DM1 in the adjuvant setting, two received T-DM1 in the neoadjuvant setting, and 25 received T-DM1 as adjuvant therapy because pathological complete response was not achieved after neoadjuvant therapy. Additionally, concurrent radiotherapy during T-DM1 treatment was administered in eight cases (17%). Comprehensive demographic and disease-specific information is detailed in Table 1.

Table 1 Baseline Characteristics of Patients

Characteristics	All (n=47)
Age (year), median (range)	55 (31, 69)
Female, n (%)	46 (97.9)
BMI (kg/m²), median (range)	22.9 (17.6, 29.0)
With underlying disease, n (%)	7 (14.9)
ER-positive, n (%)	26 (55.3)
PR-positive, n (%)	20 (42.6)
Ki67, n (%)	
<30%	17 (36.2)
≥30%	30 (63.8)
Disease stage, n (%)	
Early	29 (61.7)
Advanced	18 (38.3)
Lymph node metastasis, n (%)	
Yes	40 (85.1)
No	6 (12.8)
Missing data	1 (2.1)

(*Continued*)

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Table 1 (Continued).

Characteristics	All (n=47)
Chemotherapy prior to T-DM1 treatment, n (%)	
Yes	44 (93.6)
No	1 (2.1)
Missing data	2 (4.3)
Radiotherapy prior to T-DM1 treatment, n (%)	
Yes	7 (14.9)
No	40 (85.1)
Concurrent radiotherapy during T-DM1 treatment, n (%)	
Yes	8 (17.0)
No	39 (83.0)
Thrombocytopenia prior to breast cancer diagnosis, n (%)	4 (8.5)
Transient reductions in red blood cells, platelets, or neutrophils before chemotherapy, n (%)	
Yes	26 (55.3)
No	20 (42.6)
Missing data	1 (2.1)
Decreased red blood cell before chemotherapy, n (%)	
Yes	22 (46.8)
No	24 (51.1)
Missing data	1 (2.1)
Decreased white blood cell before chemotherapy, n (%)	
Yes	9 (19.1)
No	37 (78.7)
Missing data	1 (2.1)
Decreased neutrophils before chemotherapy, n (%)	
Yes	5 (10.6)
No	41 (87.2)
Missing data	1 (2.1)
Decreased platelets before chemotherapy, n (%)	
Yes	4 (8.5)
No	42 (89.4)
Missing data	1 (2.1)
Prior chemotherapy-induced thrombocytopenia, n (%)	
Yes	8 (18.2)
No	36 (81.8)
Prior chemotherapy-induced thrombocytopenia recovered to normal, n (%)	8 (100.0)
Thrombocytopenia during prior radiotherapy, n (%)	
Yes	1 (14.3)
No	6 (85.7)

Abbreviations: BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor.

Regarding pre-treatment hematological abnormalities, a minority of patients (n=4, 8.5%) exhibited thrombocytopenia before their breast cancer diagnosis. More than half of the cohort (n=26, 55.3%) experienced transient reductions in red blood cells, platelets, or neutrophils prior to initiating chemotherapy, with red blood cell reduction being most prevalent, followed by neutrophils and platelets (Table 1). All eight patients who developed chemotherapy-induced thrombocytopenia experienced a return to normal platelet levels before commencing T-DM1 therapy. One patient experienced thrombocytopenia during radiotherapy prior to T-DM1 treatment; this patient's platelet count normalized following appropriate intervention. Within one month preceding T-DM1 treatment, all patients (n=47, 100%) demonstrated normal platelet counts.

Table 2 Incidence and Timing of Thrombocytopenia During T-DM1 Treatment

Variable	Evaluable Patients	Incidence of Thrombocytopenia, n (%)
Thrombocytopenia during T-DM1 treatment	47	35 (74.5)
Cycle number of T-DM1 treatment at first occurrence of thrombocytopenia	35	35 (100)
1	-	15 (42.9)
2	-	2 (5.7)
3	-	4 (11.4)
4	-	1 (2.9)
5	-	1 (2.9)
8	-	1 (2.9)
9	-	1 (2.9)
Missing data	-	10 (28.6)
Thrombocytopenia during T-DM1 treatment with concurrent radiotherapy	8	7 (87.5)

Incidence of Thrombocytopenia During T-DM1 Treatment

During treatment with T-DM1, thrombocytopenia of any grade was observed in 74.5% of patients (n=35). Among these cases, the onset of thrombocytopenia predominantly occurred during the first cycle of T-DM1 therapy, accounting for 42.9% (n=15) of occurrences. The incidence rates of thrombocytopenia varied across subsequent treatment cycles, from cycles 2 to 9, as detailed in Table 2. Notably, among the subset of patients receiving concurrent radiotherapy, a significant proportion (87.5%) developed thrombocytopenia.

Risk Factors for Thrombocytopenia Associated with T-DM1 Treatment

A comparative analysis was conducted between 35 patients who developed thrombocytopenia during T-DM1 treatment and 12 patients who maintained normal platelet levels, as detailed in Table 3 and Figure 1. Various factors, including demographic characteristics, disease features, abnormal laboratory results, pathological characteristics, history of

Table 3 Risk Factors for Thrombocytopenia During T-DM1 Treatment

Factors	Patients with Thrombocytopenia During T-DM1 Treatment (n=35)	Patients Without Thrombocytopenia During T-DM1 Treatment (n=12)	P Value
Age (year), n (%)			0.559
<55	18 (51.4)	5 (41.7)	
≥55	17 (48.6)	7 (58.3)	
BMI (kg/m²), n (%)			0.21
<22.9	16 (45.7)	8 (66.7)	
≥22.9	19 (54.3)	4 (33.3)	
With underlying disease, n (%)			>0.999
No	30 (85.7)	10 (83.3)	
Yes	5 (14.3)	2 (16.7)	
Transient reductions in red blood cells, platelets, or neutrophils before chemotherapy, n (%)			0.227
Yes	21 (61.8)	5 (41.7)	
No	13 (38.2)	7 (58.3)	
Decreased red blood cell before chemotherapy, n (%)			0.066
Yes	19 (55.9)	3 (25.0)	
No	15 (44.1)	9 (75.0)	

(*Continued*)

Table 3 (Continued).

Factors	Patients with Thrombocytopenia During T-DM1 Treatment (n=35)	Patients Without Thrombocytopenia During T-DM1 Treatment (n=12)	P Value
Decreased white blood cell before chemotherapy, n (%)			>0.999
Yes	7 (20.6)	2 (16.7)	
No	27 (79.4)	10 (83.3)	
Decreased neutrophils before chemotherapy, n (%)			0.594
Yes	3 (8.8)	2 (16.7)	
No	31 (91.2)	10 (83.3)	
Decreased platelets before chemotherapy, n (%)			>0.999
Yes	3 (8.8)	1 (8.3)	
No	31 (91.2)	11 (91.7)	
Thrombocytopenia prior to breast cancer diagnosis, n (%)			0.560
Yes	4 (11.4)	0	
No	31 (88.6)	12 (100.0)	
Disease stage n (%)			0.493
Early	23 (65.7)	6 (50.0)	
Advanced	12 (34.3)	6 (50.0)	
Lymph node metastasis, n (%)			0.644
Yes	30 (88.2)	10 (83.3)	
No	4 (11.8)	2 (16.7)	
ER-positive, n (%)			0.270
Yes	21 (60.0)	5 (41.7)	
No	14 (40.0)	7 (58.3)	
PR-positive, n (%)			0.454
Yes	16 (45.7)	4 (33.3)	
No	19 (54.3)	8 (66.7)	
Ki67, n (%)			0.034
<30%	16 (45.7)	1 (8.3)	
≥30%	19 (54.3)	11 (91.7)	
Chemotherapy prior to T-DM1 treatment, n (%)			>0.999
Yes	34 (97.1)	10 (100.0)	
No	1 (2.9)	0	
Prior chemotherapy-induced thrombocytopenia, n (%)			0.355
Yes	5 (14.7)	3 (30.0)	
No	29 (85.3)	7 (70.0)	
Radiotherapy prior to T-DM1 treatment, n (%)			0.166
Yes	7 (20.0)	0	
No	28 (80.0)	12 (100.0)	
Thrombocytopenia during prior radiotherapy, n (%)			NA
Yes	1 (14.3)	0	
No	6 (85.7)	0	
Concurrent radiotherapy during T-DM1 treatment, n (%)			0.659
Yes	7 (20.0)	1 (8.3)	
No	28 (80.0)	11 (91.7)	
Thrombocytopenia during T-DM1 treatment with concurrent radiotherapy, n (%)			0.125
Yes	7 (100.0)	0	
No	0	1 (100.0)	

(*Continued*)

Table 3 (Continued).

Factors	Patients with Thrombocytopenia During T-DM1 Treatment (n=35)	Patients Without Thrombocytopenia During T-DM1 Treatment (n=12)	P Value
Completion of T-DM1 treatment			0.036
Complete or ongoing	19 (54.3)	2 (18.2)	
Discontinuation	16 (45.7)	9 (81.8)	
Last cycle of T-DM1 for patients with ongoing treatment or discontinuation			>0.999
≤7 cycle	15 (57.7)	6 (54.5)	
>7 cycle	11 (42.3)	5 (45.5)	

Abbreviations: BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor; NA, not applicable.

thrombocytopenia, and treatment-related information, were examined. Factors of interest, such as previously diagnosed thrombocytopenia before breast cancer diagnosis, prior to the initiation of chemotherapy, or during previous chemotherapy, did not demonstrate a statistically significant impact on thrombocytopenia occurrence during T-DM1 treatment (Table 3, all P>0.05). Statistically significant risk factors identified included Ki-67 expression and the completion status of T-DM1 therapy. Specifically, 19 out of 30 patients with Ki-67≥30% (63.3%) experienced thrombocytopenia, compared to a significantly higher proportion in those with Ki-67<30% (16 out of 17, 94.1%; P=0.034). Regarding patients with completed or ongoing T-DM1 treatment, a substantial number of 19 patients out of 21 (90.5%) developed thrombocytopenia, compared to 16 out of 25 patients (64%) who discontinued T-DM1 therapy (P=0.036).

Among the 29 early-stage breast cancer cases, thrombocytopenia was observed in 23 patients (79.3%), compared to 12 out of 18 advanced-stage cases (66.7%), indicating no statistically significant difference (P>0.05). Furthermore, patients receiving concurrent radiotherapy during T-DM1 treatment exhibited a higher incidence of thrombocytopenia (7 out of 8 cases, 87.5%) compared to those not receiving concurrent radiotherapy (28 out of 39 cases, 71.8%), although this difference was not statistically significant (P=0.659).

Thrombocytopenia Outcome and Impact on T-DM1 Treatment

Among the 35 patients who developed thrombocytopenia during T-DM1 treatment, 30 underwent pharmacological intervention. Of these, 21 patients (70%) experienced a restoration of platelet counts to normal levels post-intervention, while 8 patients (26.7%) did not achieve normalization of platelet counts. The outcome for one patient remained undetermined.

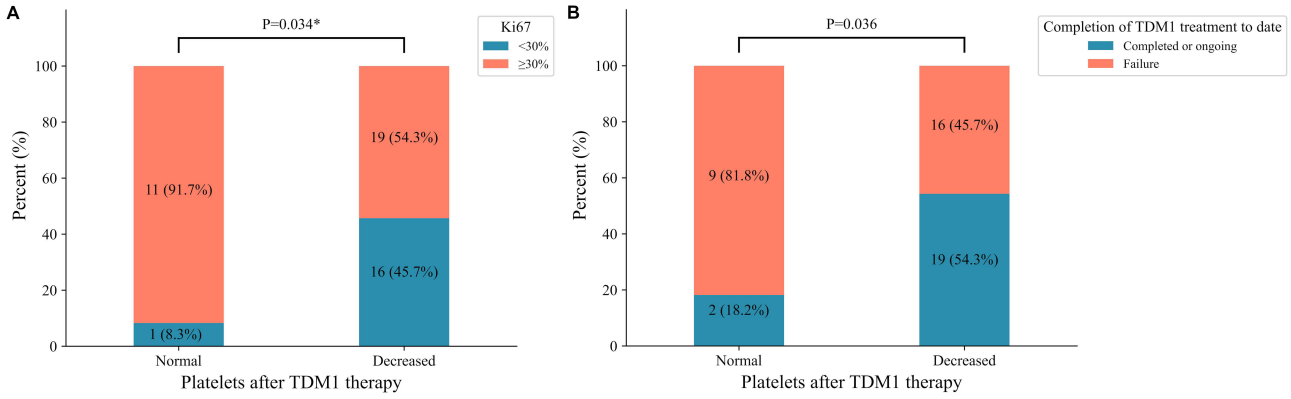

Figure 1 Associations between thrombocytopenia during T-DM1 treatment and (**A**) Ki-67 expression, and (**B**) completion of T-DM1 treatment.

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In 17.1% (6 out of 35) of the thrombocytopenia cases, there was a necessity for dose reduction of T-DM1. Regarding treatment completion, 9 patients (19.1%) successfully completed the full course of T-DM1 therapy, 12 patients (25.5%) were undergoing treatment, and 25 patients (53.2%) did not complete the planned treatment regimen. Additionally, treatment completion status was unknown for one patient (2.1%). The mean duration of T-DM1 treatment among patients with ongoing therapy was 9.3 cycles for early-stage breast cancer and 10.3 cycles for advanced-stage breast cancer. Notably, four patients were nearing completion of the treatment regimen, with two patients in the early-stage group completing 13 cycles and two in the advanced-stage group completing 14 cycles. For patients who discontinued T-DM1 treatment, the mean treatment duration was 6.9 cycles for early-stage and 6.8 cycles for advanced-stage patients.

Six patients received secondary prophylaxis, comprising four early-stage and two late-stage breast cancer cases. All patients undergoing secondary prophylaxis had experienced thrombocytopenia during T-DM1 therapy, with a recovery rate of 66.7% (4 out of 6 patients). The remaining two patients, one with early-stage and one with advanced-stage breast cancer, had platelet counts of 70 and 82 $\times$ 10^9/L, respectively. Of these six patients, two completed the full T-DM1 treatment course, both with early-stage breast cancer.

Safety

In this study, other AEs associated with T-DM1 were infrequent. These included two cases of hematochezia (4.3%) and one case each of pharyngalgia and gingival bleeding (2.1%).

Discussion

In this study, thrombocytopenia was observed in up to 74.5% of breast cancer patients undergoing T-DM1 therapy, with the majority of cases occurring during the first treatment cycle. A comparative analysis between patients who developed thrombocytopenia and those who maintained normal platelet counts identified significant risk factors, including Ki-67 expression levels and the completion status of T-DM1 therapy. The impact of thrombocytopenia on T-DM1 treatment was notable, as 17.1% of patients required dose reduction due to decreased platelet counts. However, the majority of patients who received interventions for thrombocytopenia experienced normalization of platelet levels. These findings underscore the high incidence of thrombocytopenia during T-DM1 treatment and highlight the importance of identifying potential risk factors. Clinicians should maintain vigilant monitoring of platelet levels throughout the treatment course, allowing for timely intervention to minimize treatment disruptions and safeguard patient safety. Furthermore, the study investigated secondary prophylaxis in certain patients, demonstrating that a significant proportion could achieve platelet count restoration. This suggests that secondary prophylaxis may offer a viable approach to managing thrombocytopenia in clinical practice.

As demonstrated in our study, there was a notably high incidence of thrombocytopenia during T-DM1 treatment, with a rate reaching 74.5%. This is in stark contrast to the findings reported in previous randomized controlled trials. For example, the EMILIA trial reported an incidence of 28%,[3] the TH3RESA trial reported 20.6%,[5] and the KATHERINE trial reported 28.5%.[6] Additionally, a meta-analysis of multiple clinical trials indicated a thrombocytopenia incidence of 38.3% during T-DM1 treatment.[7] A recent real-world study of T-DM1 in China reported a thrombocytopenia rate of 58.3%.[13] The higher thrombocytopenia rates observed in our study compared with these clinical trials may be attributed to differences in patient populations and treatment durations. In real-world clinical practice, the risk of thrombocytopenia during T-DM1 administration might have been underestimated. This underestimation could partly stem from the limitations inherent to clinical trials, such as restrictions on concurrent therapies that may increase thrombocytopenia risk. In our study, although not statistically significant, 87.5% of patients receiving concurrent radiotherapy developed thrombocytopenia. This suggests that concurrent radiotherapy might enhance the risk of thrombocytopenia, emphasizing the need to consider patient tolerability when making treatment decisions. Furthermore, several retrospective clinical studies support our observations. For instance, one retrospective analysis documented thrombocytopenia in 45.9% of 37 patients,[11] while another reported a 57% incidence among 119 breast cancer cases.[14] These findings, which show higher thrombocytopenia rates compared with previous clinical trials, may also be influenced by information biases that tend to underestimate thrombocytopenia occurrence since these studies did not specifically focus on this AE. Moreover, the observation that most cases of thrombocytopenia occurred during the first treatment cycle of T-DM1 highlights the

importance of close monitoring and timely preventive measures during the initial cycle of treatment. Therefore, the current findings underscore the necessity for clinicians to remain vigilant regarding thrombocytopenia occurrence during T-DM1 treatment, emphasizing the importance of timely preventive measures and monitoring. These results highlight the need for enhanced awareness and monitoring of thrombocytopenia during T-DM1 therapy in clinical practice to ensure patient safety and optimize treatment outcomes.

Previous clinical trials, along with some retrospective investigations and real-world studies, have primarily focused on the incidence of thrombocytopenia. However, a comprehensive analysis of various risk factors, such as disease staging, combination therapies, and prior occurrences of thrombocytopenia, remains limited. A prior study explored the impact of obesity on treatment safety but found no significant association with thrombocytopenia incidence.[14] Our current study aims to partially address these knowledge gaps by evaluating these factors in the context of T-DM1 treatment. In our study, we observed no significant difference in thrombocytopenia incidence between early-stage and advanced-stage breast cancer. This aligns with findings from the KATHERINE trial, where 28.5% of early-stage patients experienced decreased platelet counts,[6] and the EMILIA study, which reported a 28.0% thrombocytopenia incidence in advanced-stage patients.[3] These results suggest that disease stage may not be a critical risk factor for thrombocytopenia in T-DM1 therapy. Conversely, a significantly higher incidence of thrombocytopenia was observed in patients with Ki-67 levels below 30%. Ki-67, a marker of cellular proliferation, is used to assess the proliferative activity of tumor cells and is closely associated with patient prognosis.[15] To our knowledge, no studies have elucidated the intrinsic connection or mechanisms between Ki-67 expression and thrombocytopenia. Considering the mechanisms by which T-DM1 induces thrombocytopenia, it is hypothesized that in tumor cells with low Ki-67 expression, the efficiency of T-DM1 binding may be related to the proliferative activity of the tumor cells. As a result, T-DM1 might be more readily internalized by megakaryocytes, potentially increasing the risk of thrombocytopenia. However, this hypothesis currently lacks empirical evidence. It is crucial to acknowledge that due to the small sample size of the current study, we cannot definitively establish a causal relationship between Ki-67 expression and thrombocytopenia occurrence. The limited sample size may introduce biases, and therefore, further studies are necessary to confirm these findings. Additionally, our study identified a significant association between treatment completion and thrombocytopenia incidence. Patients who completed or were undergoing treatment were more likely to develop thrombocytopenia, potentially due to the higher cumulative exposure to T-DM1 across multiple treatment cycles. Notably, nearly half of the thrombocytopenia cases occurred during the second treatment cycle and beyond, indicating a cumulative risk with an increasing number of cycles. This suggests that patients with higher treatment completion rates may experience thrombocytopenia more frequently. However, these findings also imply that thrombocytopenia may not substantially impede T-DM1 treatment.

Our study observed an increased incidence of thrombocytopenia in patients receiving concurrent radiotherapy during T-DM1 treatment. Although this finding did not achieve statistical significance due to the limited sample size, it warrants careful consideration. The potential impact of radiotherapy on T-DM1-induced thrombocytopenia has not been thoroughly investigated in previous studies, nor has it been sufficiently addressed in clinical practice. Radiotherapy, a common modality in breast cancer treatment, inherently carries the risk of inducing thrombocytopenia. The effects of radiotherapy can vary depending on factors such as dosage, anatomical site, and combination with other therapies. Reported rates of radiotherapy-induced thrombocytopenia range from 5% to 30%.[16] However, our findings suggest a significantly elevated incidence of thrombocytopenia when T-DM1 is combined with concurrent radiotherapy. A recent meta-analysis evaluated the safety profile of T-DM1 in combination with radiotherapy but did not specifically address hematological toxicity.[17] Additionally, other clinical trials often consider radiotherapy as an optional component,[18–20] resulting in limited detailed reporting of platelet counts in patients undergoing concurrent radiotherapy. This underscores the importance of enhanced hematological monitoring in clinical practice for patients receiving T-DM1 alongside radiotherapy. Prompt intervention is essential upon detection of thrombocytopenia to mitigate adverse effects and ensure the successful completion of treatment. Further clinical studies and accumulated clinical experience are necessary for the effective management of T-DM1-induced thrombocytopenia in patients receiving concurrent radiotherapy. Healthcare providers should be well-informed about the potential occurrence of thrombocytopenia to address it promptly, ultimately improving patient outcomes and quality of life. This issue warrants further investigation and inclusion in clinical guidelines to optimize patient care.

The majority of patients experiencing thrombocytopenia during treatment with T-DM1 can achieve normalization of platelet counts through pharmacological interventions, with only a small proportion (17.1%) requiring dose reduction. This suggests that T-DM1-induced thrombocytopenia is generally manageable and does not significantly impede the treatment regimen in most cases. Previous studies have indicated that while thrombocytopenia is a common AE associated with T-DM1, it is typically reversible, and only a few patients require treatment discontinuation. For instance, in the KATHERINE trial, thrombocytopenia was a notable AE; however, only 4.2% discontinued T-DM1 due to thrombocytopenia.[6] The current findings are consistent with previous data, collectively indicating that T-DM1-induced thrombocytopenia is generally amenable to effective management through pharmacological intervention, with only a minority of patients necessitating treatment discontinuation or dose reduction. Notably, in patients requiring further control of thrombocytopenia, secondary prophylaxis proved effective in this study. Most of these patients experienced restoration of platelet counts to normal levels following the implementation of secondary prophylaxis during T-DM1 administration. This underscores the critical importance of timely adoption of prophylactic and intervention measures for thrombocytopenia during T-DM1 therapy.

This study included four patients with a previous history of thrombocytopenia prior to diagnosis of breast cancer, which may bias the results. For patients with a history of thrombocytopenic events before treatment decision, physicians may hesitate to use T-DM1 in such cases due to concerns about thrombocytopenia. It remains worth exploring whether T-DM1 may lead to worsened thrombocytopenia, and whether it impacts treatment outcomes. Therefore, these patients were also included and analyzed in this real-world study. The results suggested that it might not significantly impact T-DM1-induced thrombocytopenia. Still, the sample size was small, and it's difficult to draw confirmatory conclusion. But the results raised a point worth exploring in future studies and trials of T-DM1, as it would provide valuable guidance for clinical decision-making.

Despite these encouraging findings, our study has several limitations. Firstly, the retrospective nature of this study means that the analyses were based on pre-existing data, limiting our ability to control and adjust for potential confounding variables. Secondly, the sample size was relatively small due to the single-center nature of the study. HER2-positive breast cancer represents only a small proportion (about 15%–20%) of all breast cancers,[21] and not all patients are eligible or suitable to receive T-DM1. The study period started in 2021, when T-DM1 began to be used routinely (ie, outside clinical trials) at the study center. Although we aimed to conduct a comprehensive analysis of these patients, the limited sample size may have affected the statistical power of the study. Additionally, this was a single-arm investigation with no control group. Therefore, future studies should address these limitations to better assess T-DM1-induced thrombocytopenia in breast cancer patients.

Conclusion

Thrombocytopenia remains a prevalent AE in the complex clinical management of breast cancer with T-DM1, but its impact on the duration of T-DM1 therapy may be relatively minor. Although this study observed no instances of severe bleeding, and platelets recovered in the majority of cases, the results will require validation. Nevertheless, this study provides insights into the clinical characteristics of T-DM1-induced thrombocytopenia and preliminarily identifies factors associated with its occurrence. The results of this study may be considered in the design of future studies and trials of T-DM1 to provide additional evidence for the monitoring and management of thrombocytopenia in breast cancer patients undergoing T-DM1 therapy. The results suggest that for patients at high risk of thrombocytopenia, tailored prophylactic strategies, rigorous monitoring, and prompt interventions may be considered.

Data Sharing Statement

The data underlying this article are available in the article; further requests can be directed to the corresponding author.

Disclosure

All authors report no conflicts of interest in this work.

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