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Systemic toxicities of trastuzumab-emtansine predict tumor response in HER2+ metastatic breast cancer

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Abstract

The mechanism by which trastuzumab-emtansine (T-DM1) causes systemic toxicities apart from trastuzumab alone is currently unknown. We hypothesized that the systemic toxicities from T-DM1 may have been caused by the free and active maytansine released from the lysed HER2+ tumor cells, and if so, they may correlate with the response to treatment and eventually disease-free survival or patient outcome. In a retrospective, observational study, we evaluated 73 patients from three centers in the United States and Canada with advanced HER2+ breast cancer that received at least one dose of T-DM1. Toxicity grades were summed to create a corresponding toxicity sum score (TSS), and its association with clinical outcomes was analyzed. A higher TSS was significantly associated with longer progression-free survival with an HR = 0.66 [95% confidence interval [CI]: 0.47-0.92], P = .014, for each 1-point increase in the TSS score. Adjusted for baseline platelet count, aspartate transaminase and alanine transaminase, higher TSS remains significantly associated with longer progression-free survival with adjusted HR = 0.67 [95% CI: 0.47-0.93], P = .020. The analysis suggests that the systemic toxicities of T-DM1 were significantly correlated with its clinical efficacy. This is the first report to correlate the systemic toxicities of T-DM1 with clinical outcome. Further, this suggests that systemic toxicities of antibody-drug conjugates (ADCs) may serve as a predictive biomarker, particularly if noncleavable linkers are used. If confirmed in larger prospective studies, the present finding is significant because most ADCs do not have a biomarker predictive of clinical outcome other than the presence or absence of the antibody target.

Abbreviations: ADC, antibody-drug conjugate; AKT, a serine/threonine-specific protein kinase; ALT, alanine transaminase; AST, aspartate transaminase; CR, complete response; CT, computed tomography; HER2, receptor tyrosine-protein kinase erbB-2; MR, mixed response; PD, progressive disease; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; PR, partial response; RECST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; T-DM1, trastuzumab-emtansine; TSS, toxicity sum score.

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KEYWORDS
antibody-drug conjugate, clinical outcomes, correlative study, systemic toxicities, trastuzumab-emtansine

1 | INTRODUCTION

Breast cancer is the most common female cancer, with about 1.6 million new cases diagnosed annually. Further, it is also the leading cause of cancer-related deaths in women worldwide. In the United States, breast cancer accounts for 30% of all new cancer diagnoses and 15% of cancer-specific mortality in women. Approximately 268 600 new breast cancer cases and 41 760 related deaths have been reported in 2019.[1] About 20% of all breast cancers overexpress the HER2 receptor, which is known to correlate with shortened survival.[2-4] The monoclonal antibody trastuzumab has demonstrated major benefits for metastatic disease for two decades now, stimulating efforts to greatly expand the role of this drug in HER2-positive disease.[5] The effectiveness of anticancer drugs may be improved by the use of monoclonal antibodies to deliver cytotoxic agents to cancer cells while limiting exposure to normal tissues. The use of antibody-drug conjugates (ADCs) is one such strategy; a drug connected by a linker to an antibody specific for a tumor antigen is the basic makeup of an ADC. Maytansine is a plant alkaloid with antimicrotubule activity, though early trials of maytansine and its derivatives failed due to toxicity and lack of efficacy.[6-10] However, when linked to trastuzumab, maytansine derivatives were delivered directly into the target cell while limiting systemic toxicity.[11] This became clinically important in breast cancer when the use of trastuzumab-emtansine (T-DM1) demonstrated a survival benefit in metastatic HER2+ breast cancer.[12] T-DM1 became the standard of care in patients with HER2+ metastatic breast cancer in whom the disease progressed after initial anti-HER2 therapy.[13] Preclinical research to identify the most efficacious and tolerable mechanism to link the antibody and the payload demonstrated that compared to a disulfide link, a nonreducible thioether linkage generated a greater antitumor effect without a bystander effect or systemic toxicities.[14] However, side effects such as thrombocytopenia and transaminitis, unique to T-DM1 as compared to trastuzumab, are observed and indicate the need for further studies on the mechanism of systemic toxicities from this ADC. Our study aimed to investigate whether the systemic toxicities of T-DM1 predict tumor response in HER2+ metastatic breast cancer. We hypothesized that the systemic toxicities of T-DM1 may be due to the free emtansine released from lysed tumor cells, and therefore may correlate with the efficacy of the drug.

What's new?

Linkage of trastuzumab to emtansine (T-DM1), a tumor-antigen specific antibody, is associated with improved survival in patients with metastatic HER2+ breast cancer. Relative to trastuzumab alone, however, trastuzumab-emtansine (T-DM1) has unique side effects, including throbocytopenia and transaminitis. In this investigation of systemic toxicities, tumor response, and patient outcome, higher toxicity sum score for T-DM1 was significantly associated with improved tumor response and increased progression-free survival in metastatic HER2+ breast cancer patients. The findings suggest that emtansine freed from lysed HER2+ breast cancer cells potentially influences T-DM1 toxicity and that systemic toxicities of antibody-drug conjugates function as predictive biomarkers.

2 | METHODS

2.1 | Study design and patients

This multicenter retrospective study was approved by the institutional review board of the University of Mississippi Cancer Center and Research Institute, Jackson, Mississippi; Cross Cancer Institute, Edmonton, Alberta, Canada; and Georgia Cancer Center, Augusta University, Augusta, Georgia.

Informed consent was not applicable due to the retrospective nature of the study.

The eligible patients were women with metastatic or locally advanced/inoperable HER2+ breast cancer who received at least one dose of T-DM1 since its approval in 2013. The patients' characteristics are shown in Table 1. Most patients were Caucasian (71%), had hormone receptor-positive disease (61%) and had recurrent/metastatic disease (66%) as opposed to de novo metastatic disease. Of the 82 patients identified, 9 were excluded due to a concurrent diagnosis of idiopathic thrombocytopenic purpura (n = 1) and due to lack of follow-up imaging after starting T-DM1 (n = 8). Thus, 73 patients were included in the analysis.

2.2 | Assessments

Platelet count, aspartate transaminase (AST) and alanine transaminase (ALT) levels at baseline and at each subsequent cycle were recorded and graded as defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0 hematologic and hepatobiliary toxicity scales.[15] These grades were summed to create a corresponding toxicity sum score (TSS) ranging from 0 to 12. Treatment response was assessed using computed tomography (CT) or positron emission tomography/CT according to the Response Evaluation Criteria in Solid Tumors (RECIST), with the addition of a

mixed response (MR) category. The cumulative frequency of complete response (CR), partial response (PR), stable disease (SD), MR and progressive disease (PD) was recorded at each interval scan.

2.3 | Statistical analysis

Modified RECIST imaging response of disease at ≤ 8 cycles of T-DM1 as an ordinal scale from most to least favorable category (CR, PR, SD, MR, PD) were cross-tabulated with the ordinal TSS from 0 to highest observed score of 5 at ≤ 8 cycles. The null hypothesis of no association between the ordinal TSS and ordinal imaging response was tested using the two-sided Jonckheere-Terpstra α = 0.05 level test for the two-way ordinal trend.[16-18]

Meanwhile, the null hypothesis of no association between progression-free survival (PFS) and TSS was evaluated using the Cox proportional hazards model. The association between PFS and TSS is expressed as the hazard ratio per one-point increase in the TSS. Martingale and Schoenfeld residuals were used to test the proportional hazards assumption.[19,20] Given that the Cox model regression coefficient (β_{TSS}) was significantly different from 0, the optimal TSS cutoff score was determined as the cutoff maximizing the log-rank statistic.[21] This optimal TSS stratification was depicted using the Kaplan-Meier estimates of PFS with Hall-Wellner 95% simultaneous confidence intervals (CIs).

The association between TSS and PFS was further evaluated by multivariate Cox regression models adjusting individually for ethnic group, baseline platelet count, baseline ALT and baseline AST as well as these in combination. Missingness in baseline platelet count for four patients and ALT and AST in five patients was addressed with both a complete-case analysis and multiple imputation. The SAS PROC MI regression method was utilized which imputes a subject's missing data through random value draws from multivariable models predictive of the missing factors conditional on the individual subject's known data except the outcome data.[22] The complete-case analysis was also performed for comparison to the analysis with multiple-imputation (Supplemental Tables 1-3). Linear regression models with verification of the assumptions were used to evaluate the association between TSS and ethnic group, baseline platelet count, baseline ALT and baseline AST.

TABLE 1 Patient cohort[a]

	n (%)
Ethnic group	
Caucasian	58 (71)
African American	19 (23)
Asian	1
Not recorded	4
Nature of disease	
Recurrent	54 (66)
De novo metastatic	24 (29)
Not recorded	4
Histology	
Invasive ductal carcinoma	74 (90)
Poorly differentiated carcinoma	3
Other	1
Not recorded	4
Hormone receptor status	
ER/PR positive	50 (61)
ER/PR negative	27 (33)
Not recorded	5
Baseline laboratories (n = 73 evaluable patients)[a]	
Platelet count (SD), thousands	278k (±81k)
Platelet count range	134k-509k
ALT (SD) IU/L	30.3 (±19.9)
AST (SD) IU/L	40.5 (±54.2)

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; ER, estrogen receptor; PR, progesterone receptor.

[a]Total of 82 patients identified. Nine exclusions: one due to concurrent ITP. Eight due to lack of follow-up imaging for various reasons. A total of 73 evaluable patients had follow-up scans. Up to five patients were missing baseline lab values. These were multiply imputed and complete case data and analyses compared to those with imputation are outlined in Supplemental Tables 1 to 3.

2.4 | Sensitivity analyses

Robustness of the observed association between TSS and PFS to unknown and/or unmeasured confounders was assessed with calculating the e-value.[23,24] Robustness of the observed association between TSS and PFS was further evaluated with adding simulated "null association" patients. TSS and PFS values were independently drawn from the observed distributions in the cohort generating patients under the null hypothesis assumption of no association.[25] The "null association hypothesis" patients were produced randomly by random number generator. They are added to the actual cohort until the observed association no longer meets the α = 0.05 threshold for statistical significance. The association was also evaluated under the assumptions of expanding the cohort up to 2-fold with additional simulated patients generated under the assumption of the null hypothesis holding to assess numerical stability of the results.

3 | RESULTS

The baseline characteristics of the cohort including ethnic group, recurrent vs metastatic disease, histology, hormone receptor status and baseline laboratories are summarized in Table 1. Table 2 provides the relationship between TSS and disease progression by follow-up imaging after 8 cycles of therapy at the second interval scan. The maximum TSS was 5 and this was identified in only two patients by the eighth cycle (Table 2). In total, 5, 18, 21, 5 and 24 patients achieved CR, PR, SD, MR and PD, respectively, at the second interval scan. The proportion of patients with TSS ≤ 1 was higher among the patients who developed disease progression (MR or PD) than in those

TABLE 2 RECIST disease imaging response by toxicity sum score (≤ 8 cycles)*

Toxicity sum score	CR	PR	SD	MR	PD	Total
0	1	2	2	1	5	11
1	0	4	6	0	10	20
2	3	5	7	4	6	25
3	1	3	5	0	1	10
4	0	3	1	0	1	5
5	0	1	0	0	1	2
Total	5	18	21	5	24	73

Abbreviations: modified Response Evaluation Criteria in Solid Tumors (RECIST): CR, complete response; MR, mixed response; PD, progressive disease; PR, partial response; SD, stable disease.
*P = .028; Jonckheere-Terpstra test for ordinal trend.

without progression (CR, PR or SD) (55% vs 34%). The null hypothesis of no association between TSS and ordinal disease response category was rejected in the Jonckheere-Terpstra two-sided test (Z = −2.194, P = .028). Higher TSS was significantly associated with better ordinal imaging response. Conversely, lower TSS was significantly associated with an increased likelihood of a higher ordinal category consistent with disease progression on imaging (Figure 1). The relative risk (RR) of disease progression with TSS ≥ 2 vs TSS ≤ 1 was 0.70 (95% CI: 0.46-1.06, χ^2 = 3.18, df = 1; odds ratio = 0.42, 95% CI: 0.16-1.10, P = .075).

A higher TSS was significantly associated with longer PFS in the Cox proportional hazards regression analysis, with an HR of 0.66 (95% CI: 0.47-0.92) for each 1-point increase in the TSS score (β = −0.418, SE[β] = 0.169, χ^2 = 6.08, df = 1, P = .014). Given that the Cox model regression coefficient (β_{TSS}) was significantly different from 0, the optimal TSS cutoff score of TSS ≤ 1 vs ≥ 2 (P = .015) was determined as the cutoff maximizing the log-rank statistic.[21] The association between PFS and TSS was also significant for a cutoff score of TSS ≤ 2 vs ≥ 3 (P = .035). Consistent findings were obtained with all possible binary cutoff scores with estimated hazard ratios of 0.49 for TSS ≤ 0 vs TSS > 0, 0.39 for TSS ≤ 1 vs TSS > 1, 0.28 for TSS ≤ 2 vs TSS > 2 and 0.49 for TSS ≤ 3 vs TSS > 3, except for TSS ≤ 4 vs > 4 (hazard ratio = 0.87), possibly because of the small sample size (n = 2 for TSS = 5).

The Kaplan-Meier PFS estimates with 95% Hall-Wellner simultaneous CIs are displayed for the total sum score cutoff of ≤ 1 vs ≥ 2, which is the optimal cutoff determined in the log-rank analysis. The null hypothesis of homogeneity of strata was rejected for PFS stratified by a TSS of ≤ 1 vs ≥ 2 in the log-rank test (χ^2 = 6.35, df = 1, P = .012) (Figure 2). Kaplan-Meier estimates of PFS stratified by the cutoff of TSS ≤ 2 vs ≥ 3 are also shown with the log-rank test (χ^2 = 5.11, df = 1, P = .024) in Figure 3, indicating TSS ≥ 3 is associated with significantly longer PFS than TSS ≤ 2.

3.1 | Multivariable analyses

In Cox proportional hazards regression analysis, patient ethnic group was not significantly associated with PFS (P = .91), Adjusting for ethnic group did not modify the observed significant association between higher TSS and longer PFS (adjusted HR = 0.65 [95% CI: 0.46-0.90] for each 1-point increase in the TSS score (β = −0.428, SE [β] = 0.171, χ^2 = 6.22, df = 1, P = .013) compared to the unadjusted HR = 0.66 (95% CI: 0.47-0.92), P = .014. Likewise, the observed significant association between higher TSS and longer PFS was not appreciably different after adjusting for baseline platelet count (adjusted HR = 0.64 (95% CI: 0.45-0.90), P = .013, baseline ALT (adjusted HR = 0.66 (95% CI: 0.48-0.91), P = .013, or baseline AST (adjusted HR = 0.69 (95% CI: 0.50-0.94), P = .021. The lack of significant influence of baseline lab values on the observed significant relationship between higher TSS and longer PFS were not appreciably different with imputation of missing baseline lab values vs the complete case analysis (Supplemental Table 3). The analysis with missing baseline laboratory data imputed is numerically more conservative but not significantly different from the complete case analysis.[25]

The observed significant association between higher TSS and longer PFS was also not appreciably different after simultaneously adjusting for baseline platelet count, ALT and AST (adjusted HR = 0.67 [95% CI: 0.47-0.93]), P = .020. Baseline platelet count (HR = 1.00 [95% CI: 0.61-1.38], P = .873) per SD (81 000 platelets) and baseline ALT (1.17 [95% CI: 0.82-1.54]) per SD (19.9 IU/L), P = .308 were not associated with PFS. However, higher baseline AST was associated with shorter PFS (HR = 1.91 [95% CI: 1.24-3.43]) per SD (54.2 IU/L), P = .005. As noted above, higher TSS is significantly associated with longer PFS adjusted for baseline AST (adjusted HR = 0.69 [95% CI: 0.50-0.94], P = .021) with higher baseline AST significantly associated with shorter PFS (adjusted HR = 1.91 [95% CI: 1.18-3.08]) per SD (54.2 IU/L), P = .003, adjusted for TSS.

Baseline laboratories explain essentially none of the variance in TSS nor do baseline laboratories have any apparent linear or higher order association between TSS with baseline platelet count (R^2 = 0.013, P = .345), baseline ALT (R^2 = 0.0008, P = .815) and baseline AST (R^2 = 0.0044, P = .575). There was also no significant explanation of variance in TSS or significant association between ethnic group and TSS (R^2 = 0.0033, P = .632) or TSS and recurrent vs metastatic disease (R^2 = 0.0053, P = .540) as factors in regression analysis.

3.2 | Sensitivity analyses

To evaluate the possibility that the observed significant associations may be explained by unknown or unmeasured confounders, the e-value was calculated as recently recommended for observational studies.[23,24] The e-value point estimate = 2.03 on the risk ratio scale. To fully explain away the observed association between higher TSS and longer PFS, unmeasured confounders would need to be associated with both TSS and PFS with a RR of approximately 2.0, generally considered at least moderate evidence that the observed association may be robust to unmeasured and unknown confounding. As an additional sensitivity analysis, simulated patients with only random association between TSS and PFS have been sequentially added to the cohort generated with randomly chosen random number generator seeds.

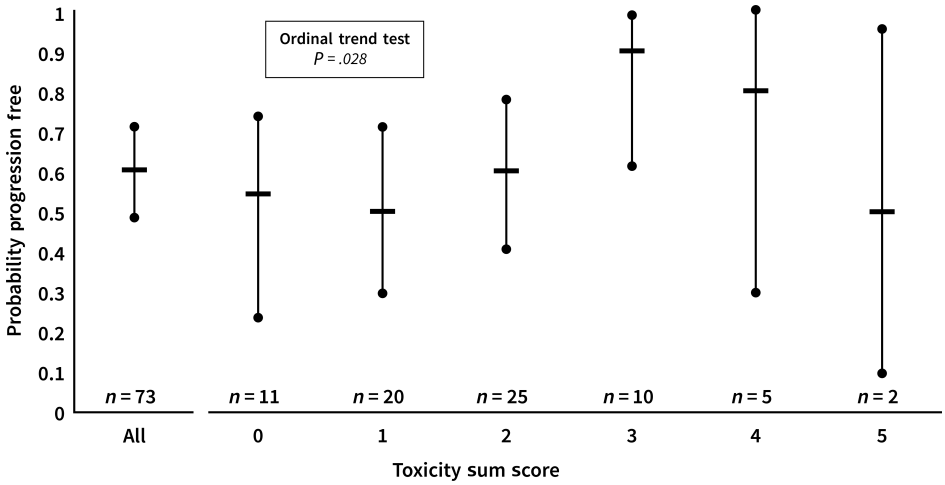

FIGURE 1 Probability of progression-free survival according to the toxicity sum score

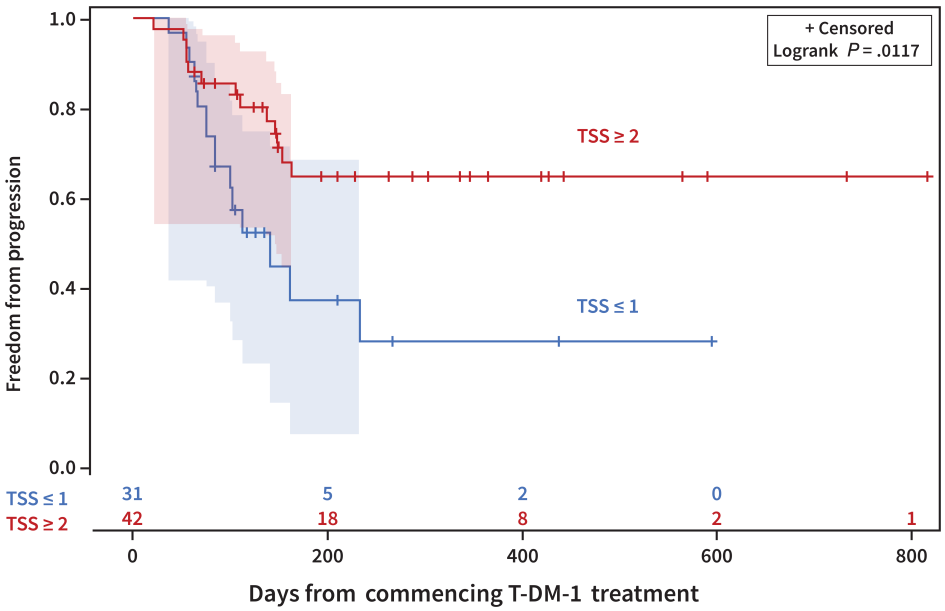

FIGURE 2 Kaplan-Meier estimate of disease progression-free survival according to the toxicity sum score of ≥2 vs ≤1

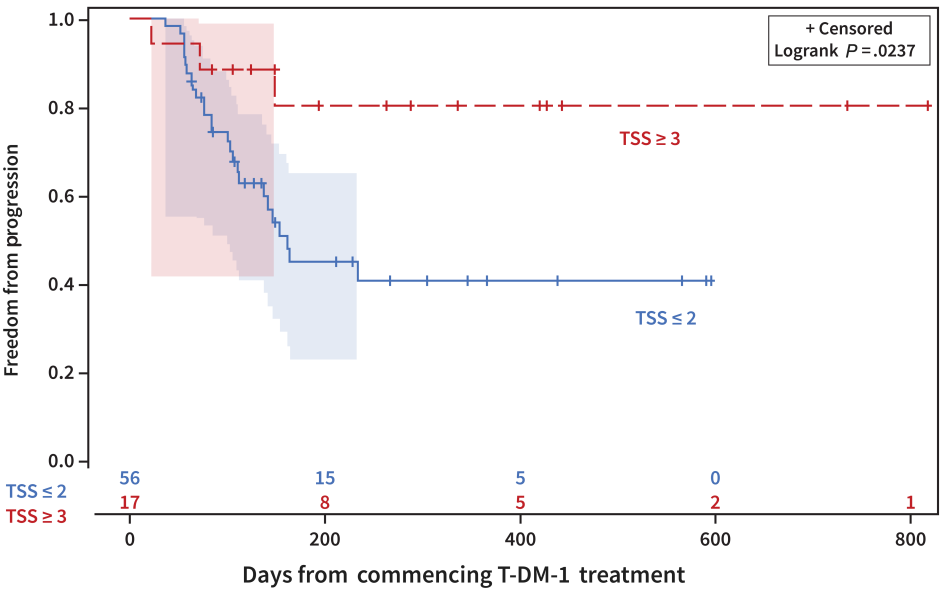

FIGURE 3 Kaplan-Meier estimate of disease progression-free survival according to the toxicity sum score of ≥3 vs ≤2

The observed association between TSS and PFS at the two-sided $\alpha = 0.05$ level is robust with up to 12 counterfactual "null association" patients added to the 73 observed patients. The combined 73 observed patients and 12 null association patients yielded an average HR = 0.75 (95% CI: 0.56-0.99), $P < .05$. With adding 37 null association patients (half the observed sample size), the observed association between higher TSS and prolonged PFS averaged HR = 0.85 (95% CI: 0.66-1.07), no longer statistically significant.

4 | DISCUSSION

Thrombocytopenia and transaminitis are unique to T-DM1 compared to trastuzumab alone. These systemic toxicities appear attributable to emtansine. One hypothesis is that this observation is due to systemic release of active emtansine from the lysed HER2+ tumor cells. Our study created a summation of the systemic toxicities and demonstrates greater toxicity does indeed correlate with improved response and survival.

The mechanisms of action of ADC for T-DM1 include all of the effects of trastuzumab plus the effects of the conjugated maytansine derivative. T-DM1 binds with HER2, and the HER2/T-DM1 complex undergoes internalization, followed by lysosomal degradation. This process results in the intracellular release of DM1-containing catabolites that bind to tubulin and prevent microtubule polymerization and suppress microtubule dynamic instability. T-DM1 also has been shown to retain the mechanisms of action of trastuzumab, including disruption of the HER3/phosphoinositide 3-kinase (PI3K)/AKT signaling pathway and Fcγ receptor-mediated engagement of immune effector cells, which lead to antibody-dependent cellular cytotoxicity.[26]

Preclinical data suggested that when using a noncleavable thioether link, the amount of maytansinoid released from the T-DM1 in circulation was negligible. The trastuzumab antibody component of this ADC is metabolized into lysine-MCC-DM1, and this does not cross the membrane of neighboring cells and thus cannot be responsible for a bystander effect.[27] A retrospective pharmacokinetic compilation did not demonstrate a significant correlation between the exposure of T-DM1 and its efficacy and these specific adverse effects.[28] However, despite the noncleavable linker used in T-DM1 and the earlier safety data, frequent systemic toxicities have been observed. In an integrated analysis of 884 patients, the most commonly reported grade ≥3 adverse events were laboratory abnormalities (thrombocytopenia, 11.9%; elevated AST, 4.3%). All-grade thrombocytopenia was reported in 32.2% of patients, and all grade increases in serum AST and ALT occurred in 23.5% and 15.7% of patients, respectively. Though relatively well tolerated, adverse events lead to drug discontinuation in 7.0% of patients.[29]

Recent large-scale clinical trials involving T-DM1 alone demonstrated a high rate of systemic toxicities. A recent multicenter real-life study that investigated the long-term systemic toxicities of T-DM1 found that systemic toxicities such as thrombocytopenia and transaminitis persisted throughout the course of T-DM1 treatment.[30] Thrombocytopenia has been reported in both phase I and phase II clinical trials of T-DM1. In the EMILIA trial, grade ≥3 thrombocytopenia occurred in 12.9% of the T-DM1 group and in only 0.2% of the lapatinib/capecitabine group (overall incidence, 28% and 2.5%, respectively).[31]

The mechanism of T-DM1-induced thrombocytopenia remains unclear because platelets do not overexpress HER2. However, recent data indicate that thrombocytopenia may be mediated in part by DM1-induced impairment of megakaryocytic differentiation, with a less-pronounced effect on mature megakaryocytes, independent of HER2 binding.[31] We hypothesized that the systemic toxicities of T-DM1 are in part due to the active emtansine released from the lysed HER2+ tumor cells. Thus, in this context, its systemic toxicities should correlate with the tumor response and disease-free survival. Given that there are widely accepted and standardized ordinal scales to express the severity of toxicity, we created a TSS. Toxicity grade scores were summed over the adverse effect categories and hypothesized to reflect systemic release of emtansine, as should be pathophysiologically consistent. Using this methodology, we found that a higher TSS was significantly associated with improved or SD burden on imaging and longer PFS. These findings support a significant association between the degree of systemic toxicities (eg, thrombocytopenia and transaminitis) and the efficacy of T-DM1.

Our study was initiated before two adjuvant trials of T-DM1 were published. The CATHERINE trial explored the utility of T-DM1 for the adjuvant treatment of patients with locally advanced HER2+ breast cancer treated with neoadjuvant anti-HER2 therapy and with residual disease. The T-DM1 group showed a significantly higher invasive disease-free survival than did the trastuzumab group.[32] In contrast, the recently published ATEMPT trial failed to demonstrate the superiority of T-DM1 for disease-free survival or safety over paclitaxel plus trastuzumab in the adjuvant setting for patients with Stage I HER2-positive breast cancer.[33] Both the CATHERINE and ATEMPT trials were conducted in the adjuvant setting when minimal or no residual tumor cells remain.[32,33] However, systemic toxicities such as thrombocytopenia and transaminitis were still observed, suggesting that there may be other causes of systemic toxicities of T-DM1 aside from free emtansine released by lysed tumor cells. Some systemic toxicities of this ADC may be due to link cleavage in circulation despite the use of noncleavable linker. They may also be due to the T-DM1 internalized in a HER2-independent, FcγRIIa-dependent manner by megakaryocytes.[31] However, systemic toxicities such as high-grade (grade ≥3) thrombocytopenia were more frequent in the metastatic setting in the EMILIA trial than that in the adjuvant setting in the CATHERINE trial (12.9% vs 5.7%).[13,32] This further supports our hypothesis that free emtansine released from the lysed tumor cells contributes to the systemic toxicities of T-DM1 and that its systemic toxicities may be used as a predictive biomarker for treatment response, particularly if noncleavable linkers are used.

In addition to our main finding that higher TSS was significantly associated with improved tumor response and longer PFS, maximum TSS at up to 8 cycles of T-DM1 therapy was not significantly associated with pretreatment baseline levels of the platelet count, ALT or

AST. In contrast to the findings of Modi et al, PFS was not associated with pretreatment baseline platelet count in our cohort which may reflect our considerably smaller sample size being unable to detect this recently reported association.[34] PFS was also not significantly associated with pretreatment ALT in our cohort. However, higher pretreatment AST was significantly associated with shorter PFS. This suggests elevated AST at baseline may be a marker of underlying disease severity. Multivariable adjustment for these pretreatment laboratory levels did not appreciably alter the observed significant association between higher TSS and longer PFS. Finally, our cohort lacks sufficient representation of Asians to examine this subgroup found to be prognostically significant by Modi et al. Albeit our sample size has limited power to address this question, we did not observe an association between Caucasian vs African ethnic group and PFS.

The main limitations of our study are small sample size and retrospective data collection. Additional limitations of our study are novel TSS, eight patients lost to follow-up for various reasons, one patient developing ITP and five missing baseline laboratory data. Strengths include multicenter involvement, moderate robustness of the primary findings (association of higher TSS to both better follow-up imaging results and PFS) to e-value and sensitivity analyses, and robustness of the primary finding to multivariable complete-case or multiple imputation analyses incorporating baseline data. If our findings were to be duplicated and confirmed in a larger metastatic clinical cohort, such as that in the EMILIA trial, it could be applied to other ADCs in clinical use and development. Further, it would help clinicians to identify patients who may benefit from ADCs and avoid premature discontinuation of effective chemotherapy when systemic toxicities are encountered.

In summary, this multicenter retrospective correlative study found a significant association between higher TSS and more favorable imaging response and PFS in women with metastatic or locally advanced/inoperable HER2+ breast cancer who develop progression after treatment with T-DM1. Our data suggest for the first time that the systemic toxicities from T-DM1 may be partly due to the lysed HER2+ breast cancer cells that release the free emtansine, particularly if noncleavable linkers are used. The TSS from T-DM1 may serve as a novel predictor of therapeutic response. If independently confirmed, a similar toxicity score may be developed as a valuable predictive biomarker for the clinical application of other ADCs and the management of their associated toxicities.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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