Early thrombocytopenia predicts longer time-to-treatment discontinuation in trastuzumab emtansine treatment

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Abstract. Thrombocytopenia is a characteristic adverse event of trastuzumab emtansine (T-DM1), one of the essential treatment options for human epithelial growth factor receptor 2 (HER2)-positive breast cancer. The present study investigated the predictive value of thrombocytopenia for time-to-treatment discontinuation (TTD) in patients receiving T-DM1 for advanced-stage HER2-positive breast cancer. The present observational study enrolled 138 patients who received T-DM1 at six oncology centers from January 2016 to December 2021. Univariate and multivariate Cox regression analyses were performed to determine the factors affecting TTD. The median age of patients was 50 years (range, 26-83). The median number of T-DM1 cycles was 9 (range, 2-58), the overall response rate was 50.0% and the disease control rate was 69.6%. At a median follow-up time of 19.3 months, the median TTD was 9.5 months [95% confidence interval (CI), 7.3-11.7], and the median overall survival was 28.2 months (95% CI, 19.2-37.2). Thrombocytopenia during treatment was observed in 39% of all patients, and 66.7% of these patients experienced early thrombocytopenia (in the first four treatment cycles). Multivariate analysis revealed that the independent factors for TTD were hormone receptor status [hazard ratio (HR), 1.837; 95% CI, 1.249-2.701; P=0.002], Eastern Cooperative Oncology Group performance status score (HR, 3.269; 95% CI, 1.788-5.976; P<0.001) and thrombocytopenia during treatment (HR, 0.297; 95% CI, 0.198-0.446; P<0.001). Patients with early thrombocytopenia had a significantly longer TTD of 17.3 months (95% CI, 11.8-22.8) compared with 7.6 months (95% CI, 5.8-9.4) for patients without early thrombocytopenia (P<0.001). The results of the present study indicated that patients with early thrombocytopenia had improved survival outcomes compared with those without. Thus, maximum benefit from T-DM1 treatment may be achieved by confirming the predictive role of thrombocytopenia in T-DM1 treatment in prospective studies and large-scale cohorts.

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Introduction

Breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer-related deaths in the United States (1). Human epithelial growth factor receptor 2 (HER2) is overexpressed in ~15% of breast cancer cases in the United States (2), and HER2-positive breast cancer is more common in metastatic settings (3). In breast cancer treatment, the development of targeted therapies has improved the efficacy, reducing damage to normal tissues; however, increased drug resistance against targeted agents has led researchers to develop an antibody-drug conjugate comprising cytotoxic agents and monoclonal drugs (4). Trastuzumab emtansine (T-DM1) is the first antibody-drug conjugate to be approved in a solid tumor and consists of trastuzumab, humanized monoclonal antibodies against HER2 and mertansine, a microtubule inhibitor (4). Based on the results of the EMILIA (5), TH3RESA (6) and MARIANNE (7) trials using various patient groups, T-DM1 has been approved for patients with HER2-positive breast cancer (HPBC) that have previously been treated with trastuzumab and taxane. Although T-DM1 can be used for any line of treatment, it is accepted as one of the standard second-line regimens for the treatment of metastatic HPBC (8,9).

Thrombocytopenia is one of the adverse events observed during T-DM1 treatment and is the most common reason for dose reduction and treatment discontinuation (10-13). Although

previous reports assert the opposite (14), recent studies have reported that a number of systemic toxicities, including thrombocytopenia, may predict T-DM1 efficacy (15,16). As it has been reported that the incidence of thrombocytopenia increases with prolonged T-DM1 treatment duration (17), the predictive value for survival outcome is debatable. Thus, the present study aimed to investigate whether early thrombocytopenia during T-DM1 treatment could predict survival rates.

Materials and methods

Study population and data collection. The present retrospective, multicenter study included patients at six oncology centers (Uludag University, Bursa; Dokuz Eylul University, İzmir; Ataturk City Hospital, Balıkesir; Inonu University, Malatya; Usak University, Usak; Bursa Medicana Hospital, Bursa) in Turkey from January 2016 to December 2021. The inclusion criteria required patients to: i) Have received at least two cycles of T-DM1 due to histopathologically confirmed advanced-stage HPBC; ii) be female; and iii) be ≥18 years old. To provide sufficient periods for the efficacy of the drug, the study excluded patients who did not receive any local treatment (surgery or radiotherapy) for symptomatic brain metastasis. Patients with a history of hematological disease or incomplete laboratory data during T-DM1 treatment were also excluded. T-DM1 was administered intravenously at a dose of 3.6 mg/kg on the first day of the treatment cycle, every 3 weeks. The dose reduction scheme provided by the Food and Drug Administration was followed in cases of toxicity (18). No endocrine therapy was administered concurrently with T-DM1.

After The Clinical Research Ethics Committee of Uludag University Faculty of Medicine (Bursa, Turkey) approved the study, the following variables of the patients were extracted from all electronic records in hospital databases: i) Age; ii) menopausal status; iii) expression of estrogen receptor; iv) expression of progesterone receptor; v) expression of HER2; vi) sites of metastasis; vii) previous treatment regimens; viii) treatment lines for metastatic disease; ix) Eastern Cooperative Oncology Group (ECOG) performance status scores (19); and x) pre- and post-treatment laboratory findings.

Definitions and outcomes. HER2 overexpression was defined as an immunohistochemistry (IHC) staining of 3+ or from a positive identification using *in situ* hybridization (ISH), and hormone receptor status was accepted as positive in patients with ≥1% expression for estrogen and/or progesterone receptor following the American Society of Clinical Oncology/College of American Pathologists guidelines (20,21). Response assessment was conducted according to the Response Evaluation Criteria for Solid Tumors (version 1.1) (22). The overall response rate (ORR) was defined as the proportion of patients that achieved a complete response (CR) or a partial response (PR). The disease control rate (DCR) was expressed as the percentage of patients with CR, PR and stable disease.

Response assessment was performed every 3-4 cycles of T-DM1 and more frequently in cases of clinical deterioration attributed to treatment failure. Time-to-treatment discontinuation (TTD) was defined as the interval from the date of initiating T-DM1 treatment to the date of treatment discontinuation or mortality. T-DM1 treatment was continued beyond radiological disease progression if a clinical benefit persisted according to the evaluation of the physician with local ablative therapies permitted. Overall survival (OS) was defined as the interval from the beginning of T-DM1 until mortality from any cause. Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) (23). Thrombocytopenia attributed to infection or sepsis was not evaluated as an adverse event. Early thrombocytopenia was defined as the occurrence of thrombocytopenia in the first four cycles of T-DM1 treatment.

Statistical analysis. Statistical analyses were performed using SPSS (version 22; IBM Corp.). Continuous variables were expressed as median (minimum-maximum) values, and categorical variables were expressed as frequency and corresponding percentage values. Kaplan-Meier survival estimates were calculated, and comparisons were performed using the log-rank test. The possible factors affecting TTD were examined by Cox regression analysis. The enter model was used for parameters with $P<0.20$ in univariate analysis. $P<0.05$ was considered to indicate a statistically significant difference.

Results

The present study enrolled 138 patients and Table I presents the characteristics of the patients and tumors. The median age was 50 years (range, 26-83 years). Of the 138 patients, 58% were hormone receptor-positive, 83% had a HER2 score of 3+ in the IHC evaluation and 50% were post-menopausal. The majority of the patients (77%) presented with visceral metastasis and 41% had *de novo* metastatic disease. The most common site of metastasis was bone (55%), followed by the lung (50%) and non-regional lymph nodes (45%). The ECOG performance status score was <2 in 90% of the patients. Before T-DM1 administration, all of the patients had received trastuzumab, and 95% had received taxanes. Pertuzumab was administered to only 17% of the patients before T-DM1. The median number of lines of treatment for T-DM1 was 2 (range, 1-8) in metastatic cases.

Tables II and III present the efficacy outcomes and laboratory toxicities of treatment with T-DM1, respectively. The median number of cycles was 9 (range, 2-58), and 33% of the patients received ≥15 cycles of T-DM1. Dose reduction for the subsequent cycle was performed in 12 patients (9%), and half of those were due to thrombocytopenia. At the time of data cut-off, 86% of the patients had experienced TTD events. The ORR and DCR were 50.0 and 69.6%, respectively. The most common all-grade adverse events were increased levels of hepatic enzymes (43 and 38% for AST and ALT, respectively), thrombocytopenia (39%) and anemia (38%). Among grade 3 and 4 toxicities, thrombocytopenia was the most common adverse event (10%). The median number of treatment cycles in which thrombocytopenia first appeared was 3 (range, 1-32) (Fig. 1A), and two-thirds of occurrences of thrombocytopenia (66.7%) were observed in the first four cycles (Fig. 1B).

The median follow-up time was 19.3 months (range, 1-70 months). Based on the Kaplan-Meier analysis, the median TTD was 9.5 months [95% confidence interval (CI), 7.3-11.7] (Fig. 2A), and the median OS was 28.2 months

Table I. Baseline patient and disease characteristics and prior treatments for metastatic disease (n=138).

Characteristic	Median (range)	n	%
Age, years	50.4 (25.5-82.9)		
Histology			
Infiltrating duct carcinoma		130	94.2
Other[a]		8	5.8
Hormone receptor status			
Positive		80	58.0
Negative		58	42.0
HER2 status			
IHC HER2 <3+ and ISH positive		24	17.4
IHC HER2 3+		114	82.6
Menopausal status			
Pre-menopausal		69	50.0
Post-menopausal		69	50.0
Disease presentation			
Recurrent		82	59.4
De novo metastatic		56	40.6
Disease involvement			
Visceral		106	76.8
Non-visceral		32	23.2
Site of metastasis			
Bone		76	55.1
Lung		69	50.0
Lymph node[b]		62	44.9
Liver		45	32.6
Brain		29	21.0
ECOG performance status score			
0		46	33.3
1		78	56.5
2		14	10.2
Prior systemic agent			
Taxanes		131	94.9
Anthracycline		101	73.2
Lapatinib		34	24.6
Pertuzumab		23	16.7
Line of T-DM1 treatment in the metastatic setting	2 (1-8)		
1		11	8.0
2		68	49.3
3		38	27.5
≥4		21	15.2

[a]Other, including invasive lobular and mixed carcinomas. [b]Lymph node, non-regional lymph nodes. IHC, immunohistochemistry; ISH, *in situ* hybridization; ECOG, Eastern Cooperative Oncology Group; T-DM1, trastuzumab emtansine; HER2, human epithelial growth factor receptor 2.

Table II. Efficacy outcomes of treatment with trastuzumab emtansine.

Characteristics	Median (minimum-maximum)	n, n=138	%
Cycles	9 (2-58)		
Dose reduction		12	8.7
TTD event		119	86.2
Mortality		88	63.8
Response			
Complete response		12	8.7
Partial response		57	41.3
Overall response rate		-	50.0
Stable disease		27	19.6
Disease control rate		-	69.6
Progressive disease		42	30.4

TTD, time-to-treatment discontinuation.

Table III. Adverse effects of treatment with trastuzumab emtansine.

Adverse event	Any grade, n (%)	Grade 3 and 4, n (%)
AST increased	59 (42.8)	4 (2.9)
Thrombocytopenia	54 (39.1)	14 (10.2)
Anemia	53 (38.4)	2 (1.5)
ALT increased	52 (37.7)	6 (4.4)
Neutropenia	20 (14.5)	5 (3.6)
Hyperbilirubinemia	14 (10.2)	3 (2.2)
Hypokalemia	13 (9.4)	3 (2.2)

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

(95% CI, 19.2-37.2) (Fig. 2B). Table IV presents univariate and multivariate Cox regression analyses for factors affecting the TTD of T-DM1. The multivariate analyses revealed that hormone receptor status [hazard ratio (HR), 1.837; 95% CI, 1.249-2.701; P=0.002], ECOG performance status score (HR, 3.269; 95% CI, 1.788-5.976; P<0.001) and thrombocytopenia during treatment (HR, 0.297; 95% CI, 0.198-0.446; P<0.001) were independent factors for TTD. Patients who were hormone receptor-positive and patients with high ECOG performance scores had an increased risk of an TTD event. By contrast, patients who developed thrombocytopenia during T-DM1 treatment had a reduced risk of developing a TTD event.

Fig. 3 presents the TTD survival curves according to thrombocytopenia. Patients with thrombocytopenia during treatment had a longer TTD (P<0.001) (Fig. 3A). As a longer duration of T-DM1 treatment was associated with a high incidence of thrombocytopenia, a further analysis was performed to evaluate whether thrombocytopenia was predictive of a

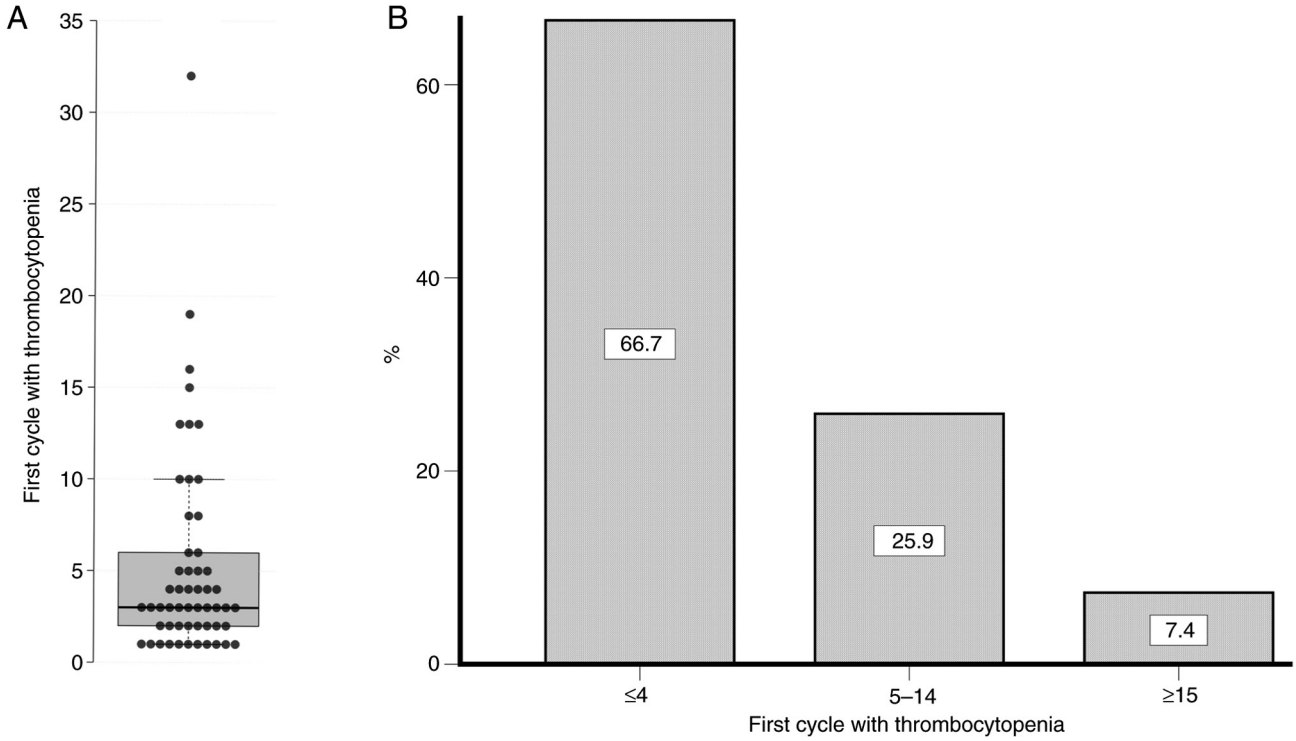

Figure 1. (A) Boxplot scheme of treatment cycles in which thrombocytopenia first occurred in the patients who experienced thrombocytopenia during treatment (n=54). (B) Distribution of treatment cycles in which thrombocytopenia first occurred in the patients with thrombocytopenia.

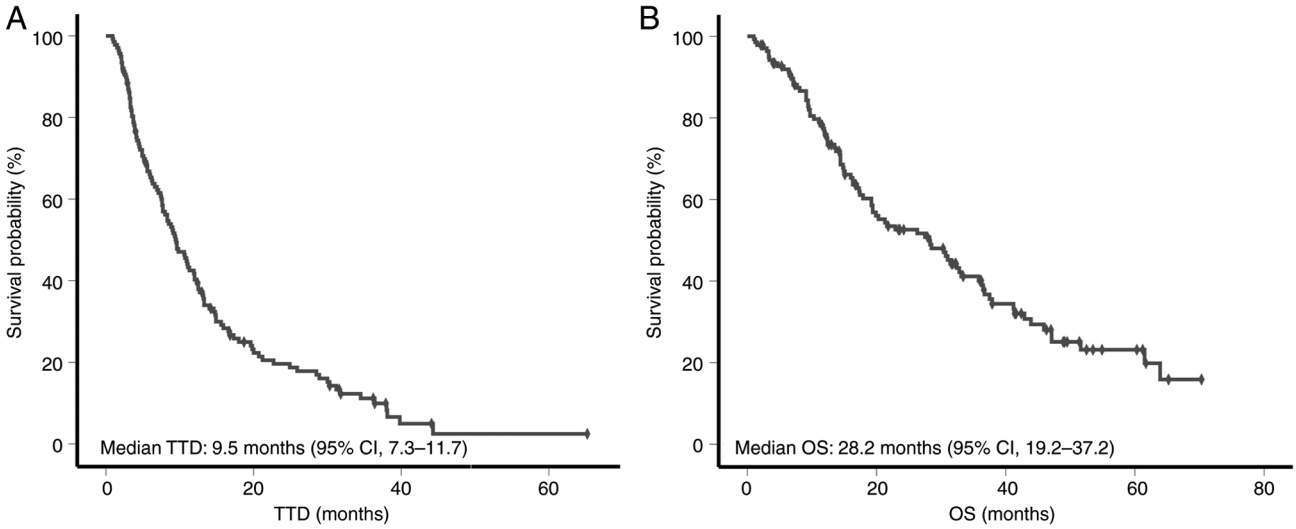

Figure 2. Kaplan-Meier curves of (A) TTD and (B) OS of all patients. TTD, time-to-treatment discontinuation; OS, overall survival; CI, confidence interval.

prolonged survival time. A comparison of the survival rates between patients with and without early thrombocytopenia using a log-rank test revealed that patients with early thrombocytopenia had a significantly longer TTD of 17.3 months (95% CI, 11.8-22.8) compared with 7.6 months (95% CI, 5.8-9.4) for patients without early thrombocytopenia (P<0.001) (Fig. 3B).

Discussion

The present study evaluated the factors affecting survival time during T-DM1 treatment. It was revealed that increased survival time was associated with low ECOG performance scores, negative hormone receptor status and thrombocytopenia. Furthermore, thrombocytopenia that developed in the first four T-DM1 cycles was predictive of a longer TTD in T-DM1 treatment.

Thrombocytopenia has been identified as a characteristic of T-DM1 and as the most common grade ≥3 and dose-limiting adverse event in both clinical trials (10-12) and real-life studies (17,24,25). To the best of our knowledge, only two reports in the literature have studied the predictive value of thrombocytopenia during T-DM1 treatment. Tataroglu *et al* (16) reported that a multivariate Cox regression analysis of 78 patients demonstrated that patients with

Table IV. Univariate and multivariate cox regression analysis of the predictors for time-to-treatment discontinuation.

		Univariate analysis			Multivariate analysis		
Factor	Category	HR	95% CI	P-value	HR	95% CI	P-value
Age	Years	1.000	0.985-1.016	0.996			
Menopausal status	Pre-men. (R) vs. post-men.	0.978	0.681-1.406	0.906			
Hormone receptor status	Negative (R) vs. positive	1.547	1.065-2.247	0.022	1.837	1.249-2.701	0.002[a]
HER2 status	IHC 3+ (R) vs. ISH positive	1.186	0.744-1.892	0.474			
Histotype	IDC (R) vs. other	1.330	0.646-2.735	0.439			
Disease presentation	Recurrent (R) vs. *de novo* metastatic	1.111	0.765-1.611	0.581			
Visceral metastasis	Absent (R) vs. present	1.205	0.782-1.858	0.397			
CNS metastasis	Absent (R) vs. present	1.194	0.771-1.850	0.427			
ECOG performance score	0-1 (R) vs. 2	3.219	1.795-5.774	<0.001	3.269	1.788-5.976	<0.001[a]
Pertuzumab before T-DM1	Absent (R) vs. present	1.153	0.656-2.026	0.620			
Line of T-DM1	<3 (R) vs. ≥3	1.082	0.752-1.557	0.671			
Thrombocytopenia	No (R) vs. yes	0.300	0.202-0.445	<0.001	0.297	0.198-0.446	<0.001[a]
AST increased	No (R) vs. yes	0.963	0.667-1.390	0.841			
ALT increased	No (R) vs. yes	1.149	0.796-1.659	0.458			
Hyperbilirubinemia	No (R) vs. yes	0.736	0.404-1.341	0.316			
Hypokalemia	No (R) vs. yes	0.928	0.520-1.656	0.928			

[a]The Cox regression model is statistically significant (P<0.001). HR, hazard ratio; CI, confidential interval; R, reference category; IHC, immunohistochemistry; ISH, *in situ* hybridization; pre-men, pre-menopausal; post-men, post-menopausal; ECOG, Eastern Cooperative Oncology Group; IDC, invasive ductal carcinoma; T-DM1, trastuzumab emtansine; HER2, human epithelial growth factor receptor 2; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CNS, central nervous system.

thrombocytopenia had longer progression-free survival (PFS) compared with those without thrombocytopenia, consistent with the results of the present study. In the second study, which evaluated 73 patients, Tang *et al* (15) proposed a toxicity score including thrombocytopenia and hepatitis. It was revealed that an increased toxicity score was associated with an improved response and prolonged PFS. However, Yardley *et al* (17) observed that the incidence of thrombocytopenia increased with T-DM1 cycles, and thrombocytopenia was more often observed in patients receiving >18 cycles of T-DM1 compared with in those receiving ≤18 cycles.

Considering that the incidence of thrombocytopenia increases with the duration of T-DM1 treatment, it is a matter of debate whether thrombocytopenia is an inevitable adverse event secondary to long-term use or is a predictive marker for improved survival rates. To investigate this issue, the survival rates of patients with thrombocytopenia in the first four T-DM1 cycles were compared with those without thrombocytopenia in the first four cycles after thrombocytopenia was confirmed as a significant independent factor for survival rate using a multivariate analysis. It was revealed that patients with early thrombocytopenia exhibited improved survival rates compared with those without early thrombocytopenia (17.3 vs. 7.6 months, respectively; P<0.001). Therefore, it was hypothesized that thrombocytopenia may be a predictive marker of TTD in treatment with T-DM1, considering that, in previous studies, the majority of instances of grade ≥3 thrombocytopenia had occurred within the first 42 days (4,26) and that 70% of total dose reductions due to adverse events had occurred within the first 4 months (27).

Experimental studies evaluating the potential mechanisms of thrombocytopenia have demonstrated that, rather than exerting a direct effect on platelets, T-DM1 inhibits the proliferation and differentiation of proplatelet precursors by disrupting microtubules after the uptake of megakaryocytes via micropinocytosis (28,29). Tang *et al* (15) hypothesized that emtansine molecules released from lysed $HER2^+$ tumor cells after the administration of T-DM1 enter the systemic circulation and cause adverse events, such as hepatitis and thrombocytopenia, explaining the association between efficacy and adverse events. The findings of the present study and

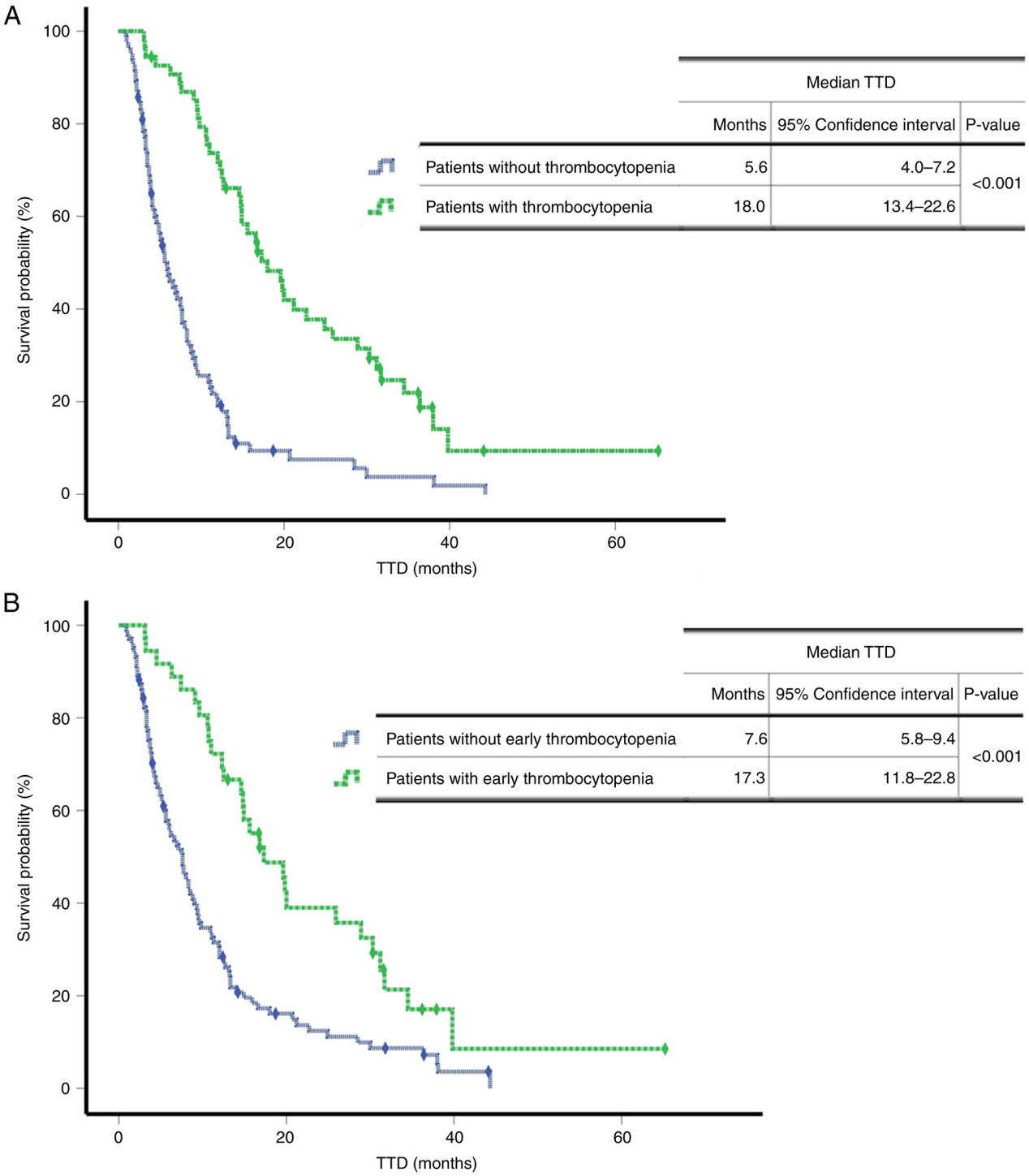

Figure 3. Kaplan-Meier curves of TTD according to (A) thrombocytopenia and (B) early thrombocytopenia (observed in the first four cycles), during trastuzumab emtansine treatment. TTD, time-to-treatment discontinuation.

the high incidence of adverse effects in the first cycles of treatment, that is, during the period when the tumor burden was highest, are in agreement with this hypothesis, but it should be confirmed by further studies.

Treatment beyond radiological progression with targeted anticancer therapies, including tyrosine kinase inhibitors, anti-vascular endothelial growth factor and checkpoint inhibitors, has been studied in various solid organ malignancies, such as lung cancer, renal cell carcinoma and melanoma (30-37). These studies indicate that the continuation of these agents after progression could contribute to increased survival rates, especially in selected patients, and the significance of predictive markers in this regard has been observed. The unique adverse events of numerous targeted agents that occur during treatment have been associated with improved treatment responses and prolonged survival times (38-41). In this context, it is hypothesized that thrombocytopenia may be used to select patients to continue T-DM1 treatment in a post-progression setting after the predictive value is confirmed in large scale studies.

Other factors affecting TTD were the ECOG performance score and hormone receptor status. A low ECOG performance score was associated with improved survival outcomes, consistent with previous reports (16,42,43). It is hypothesized that the significantly shorter TTD of patients with a hormone receptor-positive status in the present study was associated with the preference of clinicians to discontinue T-DM1 and add endocrine therapy after radiological progression in these patients.

The main strength of the present study was the use of TTD instead of PFS as the endpoint. TTD was reported to inform the clinician regarding the continuation of an anticancer agent after objective progression, which is common in oncology practice, particularly for targeted agents, and has a high association with PFS, which is an objective evaluation (44). In addition, the present study included a relatively high number of patients compared with the aforementioned studies on the predictive value of thrombocytopenia. However, the present study also had limitations, including its retrospective design and the lack of toxicity data other than laboratory findings. Furthermore, factors impacting thrombocytopenia could not be analyzed due to a lack of associated data, such as pretreatment platelet counts, which have been identified as a strong predictor for thrombocytopenia during T-DM1 treatment (26). Moreover, tumor burden, one of the aspects affecting response in cancer treatments (45), could not be assessed due to the retrospective and multicenter design of the present study.

In conclusion, the patients that experienced thrombocytopenia in the first four cycles of T-DM1 treatment had a longer TTD compared with those without thrombocytopenia. Thus, future prospective studies and large-scale cohorts should aim to confirm the predictive role of thrombocytopenia for improved survival rates in order to maximize the potential benefit of T-DM1 treatment.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

EC, TE and AS designed the study. The data were collected by AS, BC, BO, SO, AD, BH, IS, AG, MC and HO. GO and AS performed the data analysis. AS, TE, EC, AD and IS conducted the literature review. AS wrote the manuscript. BC, BO, BH, AG, HO and SO contributed significantly to the writing of the manuscript. TE, EC, AD and IS revised the manuscript critically for important intellectual content. AS, BC, BO, SO, AD, AG, HO, BH and MC confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the ethical standards of the institutional research committee and the 1964 Declaration of Helsinki. The Clinical Research Ethics Committee of Uludag University Faculty of Medicine approved the study (Bursa, Turkey; approval no. 2022-18/46), waiving the need for informed consent due to the retrospective nature of the present study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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