



Iberoamerican Journal of Medicine

ISSN: 2695-5075

ISSN-L: 2695-5075

iberoamericanjm@gmail.com

Hospital San Pedro

España

Cavdar, Eyyup; Karaboyun, Kubilay; Iriagac, Yakup; Avci, Okan; Seber, Erdoğan Selcuk
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with metastatic HER-2 positive breast cancer: a single center study
Iberoamerican Journal of Medicine, vol. 4, núm. 4, 2022, pp. 191-198
Hospital San Pedro
España

DOI: <https://doi.org/10.53986/ibjm.2022.0033>

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JOURNAL OF
MEDICINE**

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Journal homepage: www.iberoamjmed.com

Original article

Efficacy and safety of trastuzumab emtansine treatment in patients with metastatic HER-2 positive breast cancer: a single center study

Eyyup Cavdar ^{a,*}, Kubilay Karaboyun ^a, Yakup Iriagac ^a, Okan Avci ^a, Erdoğan Selcuk Seber ^a

^a Department of Medical Oncology, Tekirdağ Namık Kemal University, Tekirdağ, Turkey

ARTICLE INFO

Article history:

Received 23 July 2022

Received in revised form 15

August 2022

Accepted 23 August 2022

Keywords:

Metastatic breast cancer

Trastuzumab emtansine

Survival

Adverse events

ABSTRACT

Introduction: Trastuzumab emtansine (T-DM1) is one of the effective treatment options in human epidermal growth factor receptor 2 (HER2) positive breast cancer patients. In this study, we aimed to find the effect of T-DM1 on survival, its tolerability and prognostic factors of T-DM1 treatment.

Material and methods: The study was designed as a single-center, retrospective study that included patients treated in the oncology department of a university hospital in Turkey. HER2-positive patients with metastatic breast cancer who had a progression response to trastuzumab and taxane treatment and received T-DM1 treatment for at least 2 months between 2016-2022 were included in the study. Adverse events were defined according to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE). Kaplan-Meier methodology and Cox proportional hazard modelling were used for survival analyses.

Results: The median progression-free survival (mPFS) for T-DM1 was 10.4 months and the median overall survival (mOS) was 22 months. In the created univariate cox regression model, liver metastasis, ECOG performance status, and pre-treatment serum CA 15-3 were found to be factors associated with PFS. Liver metastasis (HR=2.54, p=0.019), ECOG performance status (HR=4.66, p=0.002), and serum CA 15-3 (HR= 2.55, p=0.041) maintained their statistical significance for PFS in the established multivariate analysis. In the regression analysis for OS, only ECOG performance status (HR= 2.61, p=0.023) was found to be prognostic. While toxicity occurred in 46 (82.1%) of the patients, grade 3-4 toxicity developed in 10 (17.9%) patients. The most common side effects were anemia, thrombocytopenia, fatigue and nausea.

Conclusions: T-DM1 is a safe and tolerable agent that prolongs survival. Liver metastasis, ECOG performance status, and pre-treatment serum CA 15-3 levels are independent prognostic factors for patients using T-DM1.

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* Corresponding author.

E-mail address: eyyupcavdar@hotmail.com

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<https://doi.org/10.53986/ibjm.2022.0033>

Eficacia y seguridad del tratamiento con trastuzumab emtansina en pacientes con cáncer de mama metastásico HER-2 positivo: estudio de un solo centro

INFO. ARTÍCULO

Historia del artículo:

Recibido 23 Julio 2022

Recibido en forma revisada 15

Agosto 2022

Aceptado 23 Agosto 2022

Palabras clave:

Cáncer de mama metastático

Trastuzumab emtansina

Supervivencia

Eventos adversos

RESUMEN

Introducción: Trastuzumab emtansina (T-DM1) es una de las opciones de tratamiento eficaces en pacientes con cáncer de mama positivo para el receptor 2 del factor de crecimiento epidérmico humano (HER2). En este estudio, nuestro objetivo fue encontrar el efecto de T-DM1 en la supervivencia, su tolerabilidad y los factores pronósticos del tratamiento con T-DM1.

Material y métodos: El estudio se diseñó como un estudio retrospectivo unicéntrico que incluyó pacientes tratados en el departamento de oncología de un hospital universitario en Turquía. Se incluyeron en el estudio pacientes HER2 positivas con cáncer de mama metastático que tuvieron una respuesta progresiva al tratamiento con trastuzumab y taxanos y recibieron tratamiento con T-DM1 durante al menos 2 meses entre 2016 y 2022. Los eventos adversos se definieron de acuerdo con los Criterios de Terminología Común para Eventos Adversos v5.0 (CTCAE). Se utilizaron la metodología de Kaplan-Meier y el modelo de riesgos proporcionales de Cox para los análisis de supervivencia.

Resultados: La mediana de supervivencia libre de progresión (mPFS) para T-DM1 fue de 10,4 meses y la mediana de supervivencia general (mOS) fue de 22 meses. En el modelo de regresión de cox univariable creado, se encontró que la metástasis hepática, el estado funcional ECOG y el CA 15-3 sérico previo al tratamiento son factores asociados con la SLP. La metástasis hepática (HR = 2,54, p = 0,019), el estado funcional ECOG (HR = 4,66, p = 0,002) y el suero CA 15-3 (HR = 2,55, p = 0,041) mantuvieron su significación estadística para la SLP en el estudio multivariable establecido. análisis. En el análisis de regresión para OS, solo se encontró que el estado funcional ECOG (HR= 2.61, p=0.023) era pronóstico. Si bien se produjo toxicidad en 46 (82,1 %) de los pacientes, se desarrolló toxicidad de grado 3-4 en 10 (17,9 %) pacientes. Los efectos secundarios más comunes fueron anemia, trombocitopenia, fatiga y náuseas.

Conclusiones: T-DM1 es un agente seguro y tolerable que prolonga la supervivencia. La metástasis hepática, el estado funcional ECOG y los niveles séricos de CA 15-3 previos al tratamiento son factores pronósticos independientes para los pacientes que usan T-DM1.

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HOW TO CITE THIS ARTICLE: Cavdar E, Karaboyun K, Iriagac Y, Avci O, Seber ES. Efficacy and safety of trastuzumab emtansine treatment in patients with metastatic HER-2 positive breast cancer: a single center study. Iberoam J Med. 2022;4(4):191-198. doi: 10.53986/ibjm.2022.0033.

1. INTRODUCTION

Breast cancer is the most common cancer in women and is one of the leading causes of cancer-related deaths [1]. Breast cancer, which has a heterogeneous structure, has been molecularly subtypes according to its hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status. Treatment approaches and survival times also vary according to the subtypes [2, 3]. One of the subtypes, HER2-positive breast cancers, is an aggressive subtype that constitutes 15-20% of breast malignancies and has a high risk of recurrence [4]. In addition to conventional chemotherapies, HER2-targeted therapies significantly improved treatment outcomes of HER2-positive breast cancer patients [5].

HER2 is a transmembrane glycoprotein with tyrosine kinase activity. Its overexpression is associated with poor prognosis, but the presence of trastuzumab, the target treatment for HER2, has improved the prognosis [6]. However, since it is inadequate in metastatic patients, new treatment options were needed. The TH3RESA study conducted in 2017 reported the efficacy of trastuzumab emtansine (T-DM1), a new treatment option in metastatic breast cancer patients [7]. T-DM1 is an antibody-drug conjugate formed by the addition of cytotoxic drug emtansine to the monoclonal antibody trastuzumab [8]. Thanks to this new molecular complex, the effect of trastuzumab on tumor cells has been increased without harming healthy cells [9]. However, very different adverse events, which are thought to be related to DM1 but may also be caused by the structure of trastuzumab, can be observed

[10].

In this study, we aimed to investigate the prognostic factors affecting the response time and the effect on survival as well as drug toxicity related to T-DM1 in patients received T-DM1 treatment in our center.

Table 1: Demographics, tumor, and clinical characteristics of patients

Clinic-pathological characteristics	N (%)
Age	
<65	44 (78.6)
≥65	12 (21.4)
Menopausal status	
Pre/Peri	25 (44.6)
Post	31 (55.4)
BMI	
≤25	25 (44.6)
>25	31 (55.4)
ECOG performance status	
0	22 (39.3)
1	26 (46.4)
2	8 (14.3)
PgR status	
Negative	31 (55.4)
Positive	25 (44.6)
ER status	
Negative	23 (41.1)
Positive	33 (58.9)
Her2 status	
2+	10 (17.9)
3+	46 (82.1)
Ki-67	
<18	14 (25)
≥18	42 (75)
Metastasis on initial diagnosis	
No	33 (58.9)
Yes	23 (41.1)
CNS metastasis	
No	43 (76.8)
Yes	13 (23.2)
Liver metastasis	
No	32 (57.1)
Yes	24 (42.9)
Bone metastasis	
No	17 (30.4)
Yes	39 (69.6)
T-DM1 line	
1	5 (8.9)
2	41 (73.2)
≥3	10 (17.9)

BMI: Body Mass Index; ECOG: Eastern Cooperative Oncology Group; ER: Estrogenic receptor; PgR: Progesterone receptor; CNS: Central nervous system; T-DM1: Trastuzumab emtansine; Her2: Human epidermal growth factor receptor 2.

2. MATERIAL AND METHODS

2.1. STUDY POPULATION

This study has been designed as a single center and retrospective study. The institutional ethics committee approved this study (approval no: 2022.121.06.11). The study included outpatient metastatic breast cancer patients who received treatment between 2016 and 2022. The study included patients with: 1) HER2 positive breast cancer with pathological diagnosis; 2) 18 years of age or older; 3) patients who completed at least 2 months of T-DM1 therapy; 4) metastasis was confirmed in organs using computed tomography, magnetic resonance imaging scans, or other imaging methods; 5) concomitant or no previous history of malignancy; 6) no active infectious disease, no immunosuppressive drug use. All patients received at least one line of cytotoxic chemotherapy (taxane) and trastuzumab for metastatic disease and progressed on or after the last treatment.

The HER2-positive disease was considered as those with positive results by immunohistochemistry (IHC) 3+ or IHC 2+ expression and those with positive results by fluorescent in-situ hybridization (FISH). According to the guide of the American Society of Clinical Oncology/College of American Pathologists, those with estrogen receptor (ER) and progesterone receptor (PgR) above 1% were evaluated as positive [11].

2.2. TREATMENT

Patients were treated with T-DM1 at a standard dose of 3.6 mg per kg of body weight intravenously every 21 days. Computed tomography (CT) and positron emission tomography (PET-CT) was used at 3-4 cycle intervals to evaluate the treatment response. Treatment responses were determined according to RECIST (Response Evaluation Criteria In Solid Tumors) 1.1. According to the information obtained from the patient archive files, adverse events were defined according to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE).

2.3. STATISTICAL ANALYSIS

Progression-free survival (PFS) was defined as the time from the beginning of the T-DM1 treatment to the time of any documented clinical progression, relapse, or death from any cause. Overall survival (OS) was defined as the time from the diagnosis to death for any reason. All statistical analyses were performed using SPSS version 26.0 (IBM Corp, Armonk, NY). Survival analysis was performed using the Kaplan-Meier method and the Log-Rank test was used

for group comparison. Univariate vs multivariate analyses of factors affecting survival were created with the Cox Proportional-Hazards Model. Statistical significance defined as a P value<0.05.

(95% CI, 17.1-25.9). Median PFS (mPFS) for T-DM1 was 10.4 months (95% CI, 8.6-16.4) and the median OS was (mOS) 22 months (95% CI, 14.9-29.2) (Figure 1). In the created univariate cox regression model, liver metastasis

Table 2: Univariate and multivariate analysis for progression-free survival (PFS)

Variable	Category	Univariate analysis		Multivariate analysis	
		HR (95% CI)	p value	HR (95% CI)	p value
Age	<65/≥65	0.63(0.26-1.50)	0.294		
Menopausal status	Pre-Peri/Post	1.14(0.60-2.15)	0.696		
BMI	≤25/>25	1.51(0.79-2.89)	0.217		
Metastasis of initial diagnosis	Yes/No	0.90(0.47-1.72)	0.752		
CNS metastasis	Yes/No	1.13(0.53-2.41)	0.744		
Liver metastasis	Yes/No	2.12(1.12-3.99)	0.021		
Bone metastasis	Yes/No	0.92(0.46-1.85)	0.812	2.54(1.17-5.51)	0.019
ER status	Positive/Negative	0.65(0.34-1.25)	0.199		
PgR status	Positive/Negative	0.62(0.33-1.18)	0.147		
Her2 status	+3/+2	0.92(0.40-2.10)	0.846		
ECOG	1-2/0	3.05(1.47-6.33)	0.003	4.66(1.80-12.04)	0.002
Line of T-DM1	≥3/1-2	1.25(0.57-2.74)	0.579		
Treatment related toxicity	Yes/No	0.99(0.38-2.56)	0.978		
Thrombocytopenia	Yes/No	0.78(0.36-1.69)	0.529		
NLR	≥2.87/<2.87	1.07(0.54-2.11)	0.851		
PLR	≥193.3/<193.3	1.69(0.86-3.31)	0.129		
SII	≥659.1/<659.1	0.94(0.48-1.82)	0.848		
CA 15-3	<28.5/≥28.5	2.40(1.06-5.43)	0.035	2.55(1.09-6.25)	0.041
CA 125	<35/≥35	0.89(0.39-2.10)	0.804		

Significant values are indicated in bold.

BMI: Body Mass Index; ECOG: Eastern Cooperative Oncology Group; ER: Estrogenic receptor; PgR: Progesterone receptor; CNS: Central nervous system; T-DM1: Trastuzumab emtansine; Her2: Human epidermal growth factor receptor 2; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet to lymphocyte ratio; SII: Systemic immune inflammatory index; CA 15-3: Cancer antigen 15-3; CA 125: Cancer antigen 125.

3. RESULTS

56 patients were included in the study. All of them consisted of female patients and the median age was 56 (range 33-88). While there was progression after T-DM1 treatment in 39 patients (69.6%), 30 patients (53.6%) were dead at study completion. The number of HR negative (ER and PgR negative) patients was 23 (41.1%). 13 patients (23.2%) had brain metastases, 24 patients (42.9%) had liver metastases, and 39 patients (69.6%) had bone metastases (Table 1).

The best responses of patients to T-DM1 treatment were detected as complete response (CR) in 5 patients (8.9%), partial response (PR) in 30 patients (53.6%), stable response (SR) in 10 patients (19.6%), and progression (PD) in 11 patients (19.6%). Objective response rate (CR; complete plus partial response) was 62.5%. Median best response time was 4.1 months (95% CI 4–7.1).

3.1. SURVIVAL TIMES

The median follow-up period in our study was 21.5 months

(HR=2.12, 95% CI: 1.12-3.99, p=0.021), ECOG performance status (HR=3.05, 95% CI: 1.47-6.33, p=0.003), and serum CA 15-3 (HR= 2.40, 95% CI: 1.06-5.43, p=0.035) were found to be factors associated with RFS. Liver metastasis (HR=2.54, 95% CI: 1.17-5.51, p=0.019), ECOG performance status (HR=4.66, 95% CI: 1.80-12.04, p=0.002), and serum CA 15-3 (HR= 2.55, 95% CI: 1.09-6.25, p=0.041) remained statistically significant for PFS in the established multivariate analysis (Table 2). The corresponding mPFS values according to liver metastasis, ECOG performance status, and CA 15-3 were 14.5 (95% CI 11.7–17.3) versus 7.7 months (95% CI 2.7–12.7) (log rank p =0.017), 21.1 (95% CI 14.4–34.4) versus 9 months (95% CI 5.6–12.4) (log rank p =0.002), and 15.9 (95% CI 14–17.8) versus 8.9 months (95% CI 6.2–11.6) (log rank p =0.029), respectively, with statistically significant difference (Figure 2).

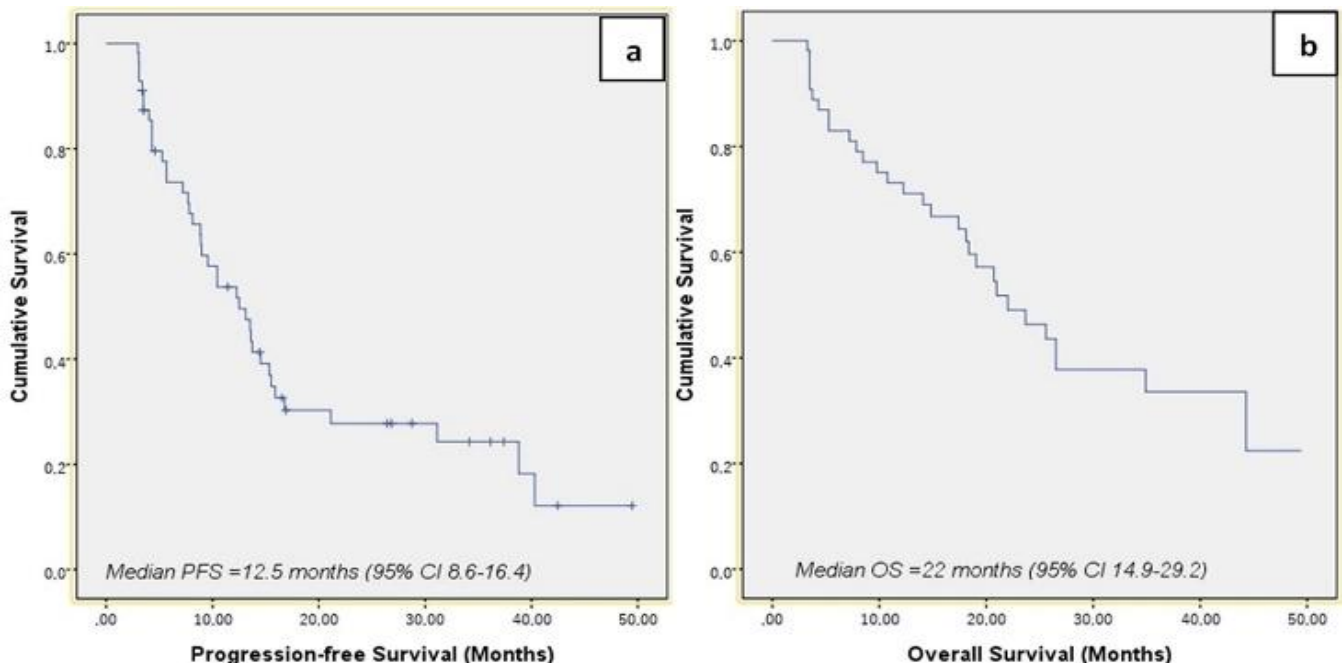


Figure 1: Kaplan–Meier survival curves for the study population. a: Progression-free survival; b: Overall survival.

In the univariate cox regression analysis for OS, only ECOG performance status (HR=2.61, 95% CI: 1.14-5.96, $p=0.023$) was found to be prognostic (Table 3). The mOS of patients with poor performance status was 18.4 months (95% CI 11.8–24.9), while mOS was 44.3 months (95% CI 16.7–71.9) in patients with good performance status.

3.2. TOXICITY AND SIDE EFFECTS

In the adverse event assessment according to CTCAE v5.0, T-DM1 was found to be well tolerated in most patients. There was no patient who died due to toxicity or whose

Table 3: Univariate analysis for overall survival (OS)

Variable	Category	Univariate analysis	
		Univariate analysis	p value
Age	<65/≥65	1.09(0.44-2.67)	0.859
Menopausal status	Pre-Peri/Post	1.11(0.54-2.29)	0.779
BMI	≤25/>25	1.07(0.51-2.25)	0.869
Metastasis on initial diagnosis	Yes/No	0.58(0.58-1.20)	0.145
CNS metastasis	Yes/No	1.95(0.88-4.34)	0.101
Liver metastasis	Yes/No	1.68(0.82-3.46)	0.156
Bone metastasis	Yes/No	1.36(0.58-3.17)	0.484
ER status	Positive/Negative	0.59(0.28-1.21)	0.151
PgR status	Positive/Negative	0.52(0.25-1.09)	0.081
Her2 status	+3/+2	1.14(0.39-3.32)	0.810
ECOG	1-2/0	2.61(1.14-5.96)	0.023
Line of T-DM1	≥3/1-2	1.14(0.46-2.82)	0.774
Treatment related toxicity	Yes/No	1.01(0.38-3.18)	0.859
Thrombocytopenia	Yes/No	1.23(0.54-2.78)	0.622
NLR	≥2.87/<2.87	1.13(0.52-2.47)	0.758
PLR	≥193.3/<193.3	1.75(0.79-3.85)	0.165
SII	≥659.1/<659.1	1.15(0.53-2.50)	0.725
CA 15-3	<28.5/≥28.5	2.36(0.87-6.39)	0.090
CA 125	<35/≥35	1.45(0.57-3.68)	0.435

Significant values are indicated in bold.

BMI: Body Mass Index; ECOG: Eastern Cooperative Oncology Group; ER: Estrogenic receptor; PgR: Progesterone receptor; CNS: Central nervous system; T-DM1: Trastuzumab emtansine; Her2: Human epidermal growth factor receptor 2; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet to lymphocyte ratio; SII: Systemic immune inflammatory index; CA 15-3: Cancer antigen 15-3; CA 125: Cancer antigen 125.

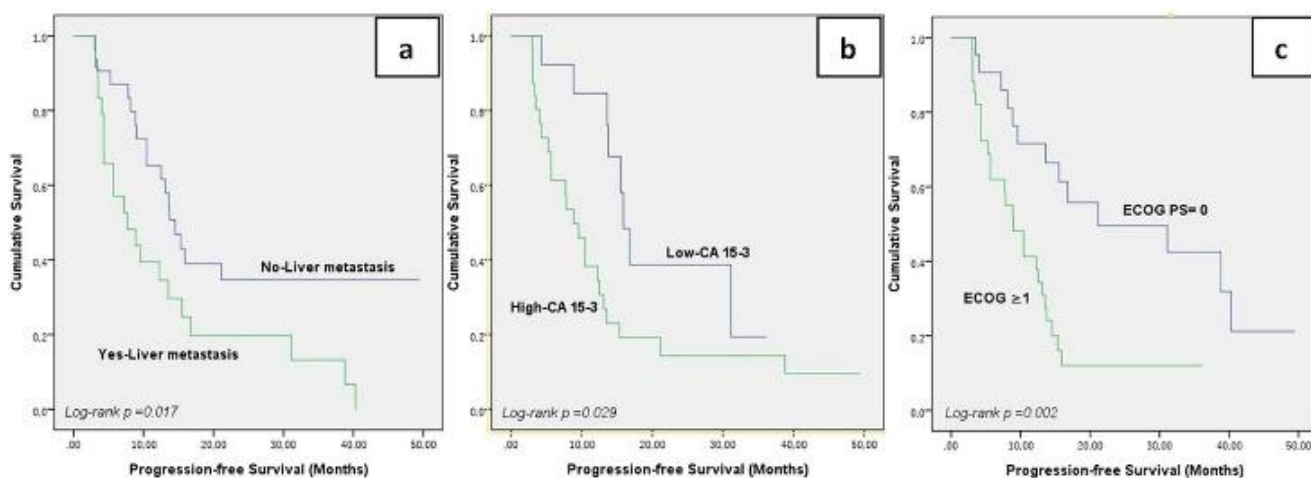


Figure 2: Kaplan Meier survival curves for progression-free survival according to liver metastasis (a), pre-treatment serum CA 15-3 levels (b), and ECOG PS (c).

CA 15-3: Cancer antigen 15-3; ECOG PS: Eastern Cooperative Oncology Group performance status.

treatment was terminated due to toxicity. While toxicity occurred in 46 (82.1%) of the patients, grade 3-4 toxicity developed in 10 (17.9%) patients. Grade 3-4 toxicities that developed were fatigue (7.1%), anemia (3.6%), nausea (3.6%), headache (1.8%), thrombocytopenia (3.6%), and diarrhea (1.8%) (Table 4).

4. DISCUSSION

In this study, we aimed to investigate the survival effect of T-DM1 in patients who received trastuzumab and taxane treatment, the prognostic factors affecting response time of T-DM1 treatment, and T-DM1-related adverse events as a single-center experience with real-life data. In our study, we found that T-DM1 was safe and a tolerable medication in the majority of patients. Our survival analyses found that ECOG performance status, liver metastasis and pre-treatment

serum CA 15-3 level were prognostic for T-DM1-related PFS. We found that only the ECOG performance status was prognostic for OS.

In the EMILIA study, which included 991 patients receiving trastuzumab and taxane, mPFS was reported as 9.6 months in advanced breast cancer patients [12]. In a multicenter study including 441 patients, mPFS was reported as 9 months while PFS was reported as 10 months in another study conducted in Italy [13, 14]. In our study, mPFS was found to be 10.4 months, similar to previous studies.

The relationship between performance status and survival time in breast cancer is known [15, 16]. As expected, this important connection was also demonstrated in studies that included patients using only T-DM1 [17-49]. In this study, ECOG performance status was found to be prognostic, and mPFS was detected as 9 months in patients with poor performance status and 21.1 months in patients with good performance status. Despite its low sensitivity, CA 15-3

Table 4: Trastuzumab emtansine (T-DM1) related toxicity

Toxicity type	Grade 3-4 n (%)	Grade 1-2 n (%)	Any grade (Total) n (%)
Fatigue	4 (7.1)	31 (55.4)	35 (62.5)
Myalgia	-	26 (44.8)	26 (44.8)
Nausea	2 (3.6)	23 (41.1)	25 (44.6)
Headache	1 (1.8)	15 (26.8)	16 (28.6)
Anemia	2 (3.6)	13 (23.2)	15 (26.8)
Thrombocytopenia	2 (3.6)	11 (19.6)	13 (23.2)
Vomiting	-	11 (19.6)	11 (19.6)
Diarrhea	1 (1.8)	6 (8.9)	7 (12.5)
Epistaxis	-	7 (12.5)	7 (12.5)
Neuropathy	-	5 (8.9)	5 (8.9)
Hepatotoxicity	-	5 (8.9)	5 (8.9)
Pulmonary Toxicity	-	1 (1.8)	1 (1.8)
TOTAL	10 (17.9)	36 (64.3)	46 (82.1)

levels are one of the most frequently used tumor markers in patient follow-up in daily oncology practice. The American Society of Clinical Oncology (ASCO) has reported CA 15-3 as a useful marker in making treatment decisions [20]. However, there is no consensus in previous studies that included breast cancer patients for its prognostic feature [21-23]. Ozyukseller et al. investigated the prognostic feature of CA 15-3 levels in patients using only T-DM1 and found the change in CA 15-3 levels during treatment as prognostic [17]. In our study, on the other hand, the relationship between pretreatment serum CA 15-3 levels and survival was investigated, and a longer survival time was found in patients with high pretreatment serum levels. CA 15-3 level was found to be an independent prognostic factor for patients using T-DM1.

The liver is one of the most common visceral organs to which advanced breast cancer metastasizes, and the presence of liver metastases has been reported as a poor prognosis in studies including all breast cancer subtypes [24-27]. In previous studies that included patients using T-DM1, the prognostic feature of the presence of visceral metastases was investigated, but liver metastasis was not investigated as a subgroup. In the studies of Ozyukseller et al., Fabi et al., and Noda-Narita et al., visceral metastasis was not found to be prognostic, similar to our study [14, 17, 28]. However, liver metastasis status was also analyzed in our study and this was found to be prognostic for T-DM1 response time. To the best of our knowledge, this is the first study to detect the presence of liver metastases as prognostic for patients using T-DM1.

In our study, it was observed that T-DM1 was well tolerated and although 82.1% of the patients had adverse events, no treatment was changed due to toxicity in any of the patients. The rate of those who experienced grade 3-5 adverse events was 17.9%. This rate was 40% in the TH3RESA study, 25.7% in the KATHERINA study, and 37.5% in the KAMILIA study [7, 29, 30]. These differences in the incidence of adverse events between studies may be related to many factors, such as the median age of the patients included, performance status, treatment lines, and sites of metastasis [10, 31]. The most common serious adverse events were fatigue, nausea, thrombocytopenia, and anemia, consistent with previous studies [10, 32]. Further multicenter studies with large patient populations are needed for more generally accepted information on adverse events. Our study has some limitations. The first of these is that the study has a single-centered and retrospective design. Second, even if the patient selection criteria were carefully chosen, various circumstances can influence laboratory markers. However, the strengths of the study are that it

includes real-life data and extensive prognostic factor analysis for T-DM1.

5. CONCLUSIONS

T-DM1 is an important treatment agent that has shown its survival effect in patients with advanced HER2 positive breast cancer. In this study, we found that ECOG performance status, liver metastasis status, and pretreatment serum CA 15-3 levels were prognostic factors associated with the response time of T-DM1 treatment. In addition, our results showed that T-DM1 is a safe and tolerable treatment agent.

6. CONFLICT OF INTERESTS

The authors have no conflict of interest to declare. The authors declared that this study has received no financial support.

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