

ORIGINAL ARTICLE

Efficacy and tolerability of trastuzumab emtansine in advanced human epidermal growth factor receptor 2–positive breast cancer

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ABSTRACT

Introduction: The management of human epidermal growth factor receptor 2 (HER2)–positive breast cancer has changed dramatically with the introduction and widespread use of HER2-targeted therapies. There is, however, relatively limited real-world information about the effectiveness and safety of trastuzumab emtansine (T-DM1) in Hong Kong Chinese patients. We assessed the efficacy and toxicity profiles among local patients with HER2-positive advanced breast cancer who had received T-DM1 therapy in the second-line setting and beyond.

Methods: This retrospective study involved five local centres that provide service for over 80% of the breast cancer population in Hong Kong. The study period was from December 2013 to December 2015. Patients were included if they had recurrent or metastatic histologically confirmed HER2+ breast cancer who had progressed after at least one line of anti-HER2 therapy including trastuzumab. Patients were excluded if they received T-DM1 as first-line treatment for recurrent or metastatic HER2+ breast cancer. Patient charts including biochemical and haematological profiles were reviewed for background information, T-DM1 response, and toxicity data. Adverse events were documented during chemotherapy and 28 days after the last dose of medication.

Results: Among 37 patients being included in this study, 28 (75.7%) had two or more lines of anti-HER2 agents and 26 (70.3%) had received two or more lines of palliative chemotherapy. Response assessment revealed that three (8.1%) patients had a complete response, eight (21.6%) a partial response, 11 (29.7%) a stable disease, and 12 (32.4%) a progressive disease; three patients could not be assessed. The median duration of response was 17.3 (95% confidence interval, 8.4–24.8) months. The clinical benefit rate (complete response + partial response + stable disease, ≥ 12 weeks) was 37.8% (95% confidence interval, 22.2%–53.5%). The median progression-free survival was 6.0 (95% confidence interval, 3.3–9.8) months and the median overall survival had

not been reached by the data cut-off date. Grade 3 or 4 toxicities included thrombocytopenia (13.5%), raised alanine transaminase (8.1%), anaemia (5.4%), and hypokalaemia (2.7%). No patient died as a result of toxicities.

Conclusions: In patients with HER2-positive advanced breast cancer who have been heavily pretreated with anti-HER2 agents and cytotoxic chemotherapy, T-DM1 is well tolerated and provided a meaningful progression-free survival of 6 months and an overall survival that has not been reached. Further studies to identify appropriate patient subgroups are warranted.

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New knowledge added by this study

- This study confirms that the efficacy and toxicity profiles of trastuzumab emtansine (T-DM1) among Chinese patients are similar to the published data that have been based mainly on western populations.

Implications for clinical practice or policy

- T-DM1 is effective in HER2-positive advanced breast cancer in the second-line setting and beyond. It has tolerable toxicity. Further research is warranted to enable identification of the appropriate patient population to enhance cost-effectiveness.

Introduction

Breast cancer is the most common female cancer in Hong Kong. The human epidermal growth factor receptor *HER2/neu* gene is amplified and overexpressed in 15% to 25% of breast cancers.¹ The management of human epidermal growth factor receptor 2 (HER2)-positive (HER2+) breast cancer has changed dramatically with the introduction and widespread use of HER2-targeted therapies. The landmark study reported by Slamon et al² over a decade ago established the combination of trastuzumab with chemotherapy as the standard of care for patients with HER2+ metastatic breast cancer. The later CLEOPATRA trial showed that the combination of pertuzumab with trastuzumab and chemotherapy (specifically, docetaxel) could further improve survival when compared with the standard arm of trastuzumab plus chemotherapy in the first-line setting.³

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that incorporates the HER2-targeted antitumour properties of trastuzumab with the cytotoxic activity of the microtubule inhibitor DM1 (which is a derivative of maytansine). The high potency of the cytotoxic DM1 moiety has been suggested as a key factor in the enhanced activity of this compound.^{4,5} In the second-line setting, the pivotal EMILIA study compared T-DM1 with lapatinib plus capecitabine among patients with HER2+ breast cancer who had previously been treated with trastuzumab and a taxane; T-DM1 showed remarkable activity with an acceptable toxicity profile.⁶ There is, however, relatively limited real-world information about the effectiveness and safety of T-DM1 in Hong Kong Chinese patients.

In this multicentre retrospective study, we assessed the efficacy and toxicity profiles among local patients with HER2+ advanced breast cancer who had received T-DM1 therapy in the second-line setting and beyond.

Methods

This was a retrospective study that involved five local centres that care for over 80% of the local breast cancer population, and included the Pamela Youde Nethersole Eastern Hospital, Prince of Wales Hospital, Queen Mary Hospital, Queen Elizabeth Hospital, and Tuen Mun Hospital between December 2013 and December 2015, the period when the relevant treatment was first started. The institutional ethics committee of each participating centre approved the study.

Inclusion criteria included patients who had recurrent or metastatic histologically confirmed HER2+ breast cancer who either had progressed during trastuzumab with chemotherapy in the first-line treatment setting, or had developed progressive

T-DM1在晚期HER2陽性乳腺癌中的療效和耐受性

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引言：HER2陽性乳腺癌的治療隨着HER2靶向治療的引入和廣泛應用發生了巨大變化。然而，T-DM1在香港華籍病人的有效性和安全性方面的相關信息有限。本文評估二線TDM1治療在晚期HER2陽性乳腺癌患者的療效和安全性。

方法：這項回顧研究涉及2013年12月至2015年12月期間，負責提供護理服務給香港八成以上乳癌病人的5間中心。有以下疾病的患者會被列入研究範圍：有復發或轉移的HER2+乳腺癌，並曾接受至少一線的抗HER2+藥物，包括曲妥珠單。接受T-DM1作為復發或轉移性HER2+乳腺癌一線治療的患者則不被列入研究範圍。我們回顧患者的病歷紀錄，包括生物化學和血液學數據，T-DM1反應和毒性數據，並記錄化療期間和最後一次藥物治療後28天的不良事件。

結果：共37名晚期HER2陽性乳腺癌患者中，28人（75.7%）曾經接受二線或以上的HER2靶向治療，26人（70.3%）曾經接受二線或以上的緩解性化療。評估結果顯示，3人（8.1%）有完全緩解，8人（21.6%）部分緩解，11人（29.7%）情況穩定，12人（32.4%）有腫瘤進展；3人無法評估。治療效果持續時間的中位數為17.3個月（95%置信區間：8.4至24.8個月），臨床獲益率（完全緩解+部分緩解+情況穩定≥12週）為37.8%（95%置信區間：22.2%至53.5%）。中位無惡化生存期為6.0個月（95%置信區間：3.3至9.8個月），中位總生存期截至研究完結均未達到。3級或4不良事變包括血小板下降（13.5%）、丙氨酸轉氨酶上升（8.1%）、貧血（5.4%）和低鉀（2.7%）。沒有患者因副作用死亡。

結論：在曾經接受多種HER2靶向治療和化療的HER2陽性晚期乳腺癌患者中，T-DM1耐受性良好，並提供了6個月有意義的無惡化生存期和尚未達到的總生存期。進一步研究有助確定合適的患者，以便更有效應用T-DM1。

disease after at least one line of anti-HER2 agent including trastuzumab. Patients who had received endocrine therapy for recurrent or metastatic disease were included. Exclusion criteria included patients who received T-DM1 as first-line treatment for recurrent or metastatic HER2+ breast cancer.

Patient charts were reviewed for background information, T-DM1 response, and toxicity data by medical staff who were not blinded to the study objectives. Biochemical and haematological profiles were extracted from patient charts. Tumour response assessments were recorded according to the Response Evaluation Criteria in Solid Tumors Committee.⁷ Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0). Adverse events were also documented during chemotherapy and 28 days after the last dose of study medication.

TABLE 1. Patient characteristics and prior treatments (n=37)

Characteristic	Median (range) or No. (%) of patients/sites/cycles
Age (years)	52 (29-70)
ECOG PS at cycle 1	
0	4 (10.8)
1	29 (78.4)
2	4 (10.8)
Time since last anti-HER2 therapy	32 (14-274)
No. of disease site(s)	
1	4 (10.8)
2	12 (32.4)
3	12 (32.4)
≥4	9 (24.3)
Disease site(s)	
Lymph nodes	27 (73.0)
Lungs	20 (54.1)
Bones	19 (51.4)
Liver	12 (32.4)
Soft tissue/skin	11 (29.7)
Brain	9 (24.3)
Breast	7 (18.9)
Others	3 (8.1)
Prior adjuvant treatment	
Neo/Adjuvant trastuzumab	13 (35.1)
Neo/Adjuvant chemotherapy	
Anthracycline-containing only	6 (16.2)
Taxane-containing only	7 (18.9)
Anthracycline- and taxane-containing	8 (21.6)
Neo/Adjuvant endocrine therapy	
Tamoxifen	7 (18.9)
Aromatase inhibitors	1 (2.7)
Adjuvant radiation therapy	19 (51.4)
Prior treatment for recurrent/metastatic disease	
No. of prior lines of anti-HER2 therapy	
1	9* (24.3)
2	11 (29.7)
≥3	17 (45.9)
Prior anti-HER2 agents	
Trastuzumab	37 (100)
Lapatinib	22 (59.5)
Pertuzumab	5 (13.5)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; HER2 = human epidermal growth factor receptor 2

* As first-line anti-HER2 treatment, 6 patients received trastuzumab, 3 patients received trastuzumab and pertuzumab

† Others included fluorouracil, cyclophosphamide, carboplatin, pemetrexed, etoposide, and nab-paclitaxel

TABLE 1. (cont'd)

Characteristic	Median (range) or No. (%) of patients/sites/cycles
Prior treatment for recurrent/metastatic disease (cont'd)	
No. of prior lines of chemotherapy	
1	11 (29.7)
2	12 (32.4)
3	2 (5.4)
≥4	12 (32.4)
Prior cytotoxic chemotherapy	
Taxanes	33 (89.2)
Capecitabine	23 (62.2)
Vinorelbine	17 (45.9)
Gemcitabine	12 (32.4)
Anthracyclines	6 (16.2)
Eribulin	3 (8.1)
Others†	14 (37.8)
No. of prior lines of endocrine therapy	
1	13 (35.1)
2	4 (10.8)
≥3	2 (5.4)
Prior endocrine therapy	
Tamoxifen	8 (21.6)
Aromatase inhibitors	15 (40.5)
Ovarian ablation—medical/surgical/radical	7 (18.9)

Statistical analysis

Outcomes in terms of tumour response, progression-free survival (PFS), and overall survival (OS) were determined. The PFS was assessed from day 1 of treatment cycle 1 to the date when objective disease progression was observed, and OS was calculated from day 1 of treatment cycle 1 to the date of death. Death was regarded as a progression event in those subjects who died before disease progression. Subjects without documented objective progression at the time of the final analysis were censored at the date of their last tumour assessment; data cut-off was on 31 August 2016. Survival curves were constructed using the Kaplan-Meier method.

Results

Patient characteristics

Patient characteristics are shown in Table 1. Of a total of 37 patients, 33 (89.2%) had an Eastern Cooperative Oncology Group performance status of 0 or 1.

Of the 37 patients, tumour biology studies at initial disease presentation showed that 15 (40.5%)

patients were oestrogen receptor (ER)-positive, 10 (27.0%) were progesterone receptor (PR)-positive, and 31 (83.8%) had HER2+ breast cancer. Overall, 21 patients had tumour re-biopsy at the time of developing metastatic disease, 10 (47.6%) patients were ER-positive, nine (42.9%) PR-positive, and 21 (100%) had HER2+ (which included six patients who were found to have HER2+ tumours only when anti-HER2 therapy was considered for metastatic disease).

At the time of initiating T-DM1 therapy, 21 patients had three or more disease sites involved; the most common sites included lymph nodes (n=27, 73.0%), lungs (n=20, 54.1%), and bones (n=19, 51.4%).

Prior treatments

Prior treatments that patients received are listed in Table 1. With regard to adjuvant treatments, 13 (35.1%) patients had prior adjuvant trastuzumab, 21 (56.8%) had adjuvant chemotherapy, eight (21.6%) had adjuvant endocrine therapy, and 19 (51.4%) had adjuvant radiotherapy.

With regard to treatment for recurrent/metastatic disease, nine (24.3%) patients had one line of prior trastuzumab with chemotherapy including three who had trastuzumab in combination with pertuzumab and chemotherapy; 11 (29.7%) had two lines while 17 (45.9%) had three or more lines of anti-HER2 therapy. Overall, 22 (59.5%) patients had received prior lapatinib, and five (13.5%) had received pertuzumab beyond the first-line setting.

A total of 26 (70.3%) patients had received two or more lines of palliative chemotherapy, with the majority having received taxanes (n=33, 89.2%), capecitabine (n=23, 62.2%) and vinorelbine (n=17, 45.9%). Nineteen patients had received one or more lines of palliative endocrine therapy, these included eight (21.6%) with tamoxifen, 15 (40.5%) with aromatase inhibitors, and seven (18.9%) with ovarian ablation.

Trastuzumab emtansine dose and dose interruptions

The median number of days from last anti-HER2 therapy to the first dose of T-DM1 was 32 days (range, 14-274 days).

The median number of cycles was six (range, 1-43). The follow-up data were frozen on 31 August 2016. The median follow-up period was 15.6 months (95% confidence interval [CI], 8.1-20.4 months). Overall, 33 patients were started on the standard dose of 3.6 mg/kg, given once every 3 weeks; 13 patients had dose delay, 10 patients had dose reduction for subsequent cycles, and six patients had both dose delay and dose reductions for subsequent cycles. A total of 326 cycles were administered; 44 (13.5%) cycles were

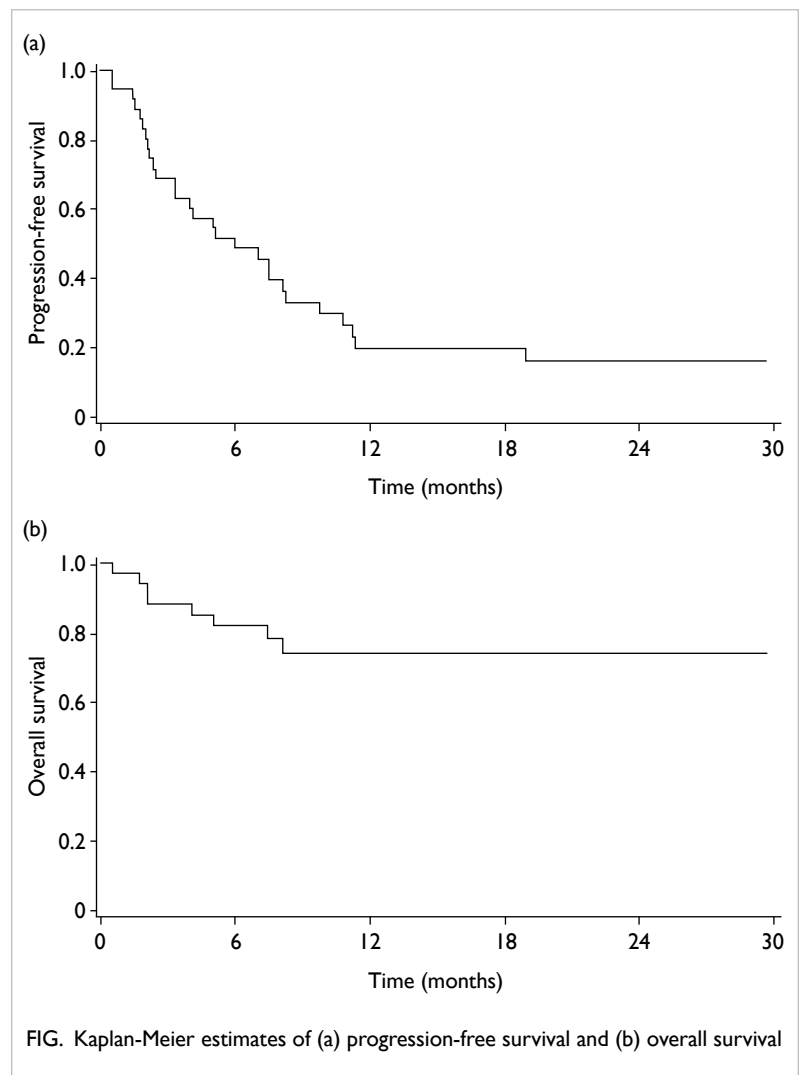


FIG. Kaplan-Meier estimates of (a) progression-free survival and (b) overall survival

delayed, 11 (3.4%) cycles had further dose reductions in the subsequent cycles, and 51 (15.6%) cycles had both dose delay and dose reductions.

At the time of data cut-off, 28 had discontinued T-DM1 treatment: 20 (71.4%) due to progressive disease, four (14.3%) were lost to follow-up, one (3.6%) due to patient withdrawal, and three (10.7%) due to unspecified causes. No patient discontinued treatment due to intolerable toxicities.

Response and survival

Among the 37 patients, there were three (8.1%) complete response (CR), eight (21.6%) partial response (PR), 11 (29.7%) stable disease (SD), and 12 (32.4%) progressive disease; three patients could not be assessed (ie they did not have response assessment documented during their treatment). The median duration of response was 17.3 months (interquartile range, 9.4-24.5; 95% confidence interval, 8.4-24.8 months). The clinical benefit rate, defined as CR,

TABLE 2. Haematological and non-haematological toxicities according to the National Cancer Institute Common Toxicity Criteria version 3.0 (n=37)

	Grade					
	0	1	2	3	4	5
Thrombocytopenia	20	8	4	3	2	0
Raised alanine transaminase	19	14	1	3	0	0
Anaemia	28	6	1	2	0	0
Hypokalaemia	29	7	0	1	0	0
Hypoalbuminaemia (n=33)	30	0	3	0	0	0
Raised alkaline phosphatase	28	7	2	0	0	0
Hyponatraemia	33	2	2	0	0	0
Neutropenia	32	4	1	0	0	0
Hyperbilirubinaemia	34	2	1	0	0	0
Left ventricular ejection fraction	35	1	1	0	0	0
Leukopenia	32	5	0	0	0	0
Fatigue	32	5	0	0	0	0
Creatinine	33	4	0	0	0	0
Diarrhoea	33	4	0	0	0	0
Stomatitis	35	2	0	0	0	0
Nausea	35	2	0	0	0	0
Anorexia	36	1	0	0	0	0
High plasma urea (n=33)	32	1	0	0	0	0
Rash	36	1	0	0	0	0
Septic episode	36	1	0	0	0	0
Raised aspartate transaminase	36	1	0	0	0	0
Heartburn	36	1	0	0	0	0
Malaise	36	1	0	0	0	0
Sensory neuropathy	36	1	0	0	0	0
Myalgia	36	1	0	0	0	0
Peripheral numbness	36	1	0	0	0	0

PR, or SD of 12 weeks or longer, was 37.8% (95% CI, 22.2%-53.5%).

Overall, based on the Kaplan-Meier method, the median PFS was 6.0 (95% CI, 3.3-9.8) months; the 6-month and 12-month PFSs were 51.6% and 23.1%, respectively (Fig a). The median duration of follow-up for PFS was 5.0 (interquartile range, 2.2-10.3) months. The median OS was not reached; the 6-month and 12-month OSs were 82.1% and 74.4%; respectively (Fig b).

Toxicity

Haematological and non-haematological toxicities are listed in Table 2. Grade 3 or 4 toxicities that occurred in one or more patients included thrombocytopenia (n=5, 13.5%), raised alanine transaminase (n=3, 8.1%), anaemia (n=2, 5.4%),

and hypokalaemia (n=1, 2.7%). Apart from these, other toxicities that occurred in more than 10% of patients included raised alkaline phosphatase, hyponatraemia, neutropenia, leukopenia, fatigue, raised serum creatinine, and diarrhoea. There was no cardiac toxicity and no patients died as a result of toxicities.

Discussion

During the past decade, the treatment of HER2+ breast cancer has rapidly evolved, and patients with HER2+ metastatic breast cancer have experienced a remarkable improvement in clinical outcomes in terms of OS.⁸

The efficacy of T-DM1 was well demonstrated in the pivotal EMILIA study that compared T-DM1 with lapatinib plus capecitabine among HER2+ breast cancer patients in the second-line setting. The studied patients had previously been treated with trastuzumab and a taxane. For the T-DM1-treated patients, the objective response rate was 44%, the median PFS was 9.6 months, and the median OS was 30.9 months.⁶

In the current multicentre retrospective study among the Chinese patients with breast cancer, over 70% were heavily pretreated with anti-HER2 agents as well as cytotoxic chemotherapy. The efficacy results are consistent with previous findings from the TH3RESA study.⁹ The latter involved over 600 HER2+ patients with advanced breast cancer who had received two or more anti-HER2-containing regimens, including trastuzumab and lapatinib, and previous taxane therapy. At a median follow-up of 6.5 months, the TH3RESA study reported that among the T-DM1-treated patients, the objective response rate was 31%, the median duration of response was 9.7 months, the median PFS was 6.2 months, and the median OS was not reached.⁹ Similarly, the safety profile in the current study was consistent with the reported clinical trials, where grade 3 or worse thrombocytopenia was the most commonly reported adverse event (13.5%), followed by raised alanine transaminase (8.1%), anaemia (5.4%), and hypokalaemia (2.7%). Notably there was no grade 3 or worse neutropenia, no febrile neutropenia, and no cardiac toxicity noted in the current study.

In heavily pretreated patient populations, two studies, namely the TH3RESA study⁹ and the EGF104900 study¹⁰ (which assessed combination of trastuzumab and lapatinib in the absence of chemotherapy), have shown that even after a median of four prior regimens, the use of anti-HER2 therapy can lead to meaningful clinical benefits. In the TH3RESA study, the PFS benefit with T-DM1 was observed in subgroups including hormone receptor-positive tumours and non-visceral disease, as well as asymptomatic or treated brain metastases. An exploratory analysis conducted in the present study

revealed that the median PFSs for patients with hormone receptor–positive disease and hormone receptor–negative disease were 7.5 and 6.0 months, respectively. Owing to small patient numbers, the finding was not significant ($P=0.78$) but nonetheless lends support to the published data.

Among the 37 patients in the current study, five had prior pertuzumab therapy in addition to trastuzumab (including one who also had lapatinib). One of these patients achieved PR and had a total of eight cycles of T-DM1 treatment. The efficacy of T-DM1 among patients previously treated with trastuzumab and pertuzumab has recently been reported in a retrospective study.¹¹ Although the response rate was relatively low at 18%, 30% of the patients had received prolonged T-DM1 therapy, defined as treatment duration of 6 months or longer.

It has to be noted that despite the efficacy shown in the second-line and beyond setting among HER2+ patients with advanced breast cancer, the MARIANNE study, which tested three different anti-HER2 regimens in the first-line setting, did not show T-DM1 to be superior to standard treatment.¹² In that study, previously untreated patients with HER2+ metastatic breast cancer were randomised to one of the three arms: control (trastuzumab plus taxane), T-DM1 alone, or T-DM1 plus pertuzumab. Although the results revealed that grade 3 or higher adverse events were lower in the T-DM1 arm, efficacy data on PFS were similar in all three arms, at 13.7 months, 14.1 months, and 15.2 months, respectively. In another exploratory analysis in the present study, the PFS of those patients who had undergone only one line of prior anti-HER2 therapy was compared with those who had two or more lines of anti-HER2 therapy revealed corresponding figures of 8.2 and 5.1 months, respectively ($P=0.34$).

In addition, cost-effective analysis has been conducted in a number of countries with regard to the use of T-DM1. For patients with HER2+ metastatic breast cancer, the Canadian analysis demonstrated that utilising T-DM1 could lead to substantial savings for the public health care system when the costs of treatment-related adverse events incurred by other anti-cancer agents were taken into account.¹³ Nonetheless, analyses based in the United Kingdom and the United States have not supported such findings.^{14–16}

The identification of an appropriate patient population for the utilisation of T-DM1 may enable better resource allocation. Yet to date, no biomarkers have been identified that can predict better outcome among patients with HER2+ advanced breast cancer treated with T-DM1. Based on the biomarker analyses from EMILIA and TH3RESA studies, T-DM1 was similarly effective in the presence of PI3K wild-type or mutated tumours, and the benefit with T-DM1 was seen irrespective of HER2 mRNA,

HER3 mRNA, or PTEN protein level.^{17,18}

The current study is limited by its retrospective design, possible information bias during data retrieval/extraction/coding, as well as the small number of patients (especially for subgroup analysis) and inadequate follow-up period for OS. Although the results could not be compared directly with reported prospective trials, patients were representative, and treatment and outcomes reflect routine clinical practice. The T-DM1 therapy provided a meaningful PFS with a favourable toxicity profile among heavily pretreated patients with HER2+ advanced breast cancer. Research is needed to identify biomarkers that will predict sensitivity and resistance to individual anti-HER2 agents, and thereby enable identification of those patients most likely to respond to T-DM1 and appropriate treatment to optimise patient benefit, reduce excessive toxicities, and minimise costs.

Conclusions

The T-DM1 therapy has a tolerable toxicity profile among local patients with recurrent or metastatic HER2+ breast cancer. For patients who responded to T-DM1 therapy, there was a durable response. In our study, T-DM1 is associated with a PFS of 6 months and an OS that has not been reached. Further biomarker study is needed to enable appropriate patient selection for this treatment.

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Declaration

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