Cost-Effectiveness Analysis of Trastuzumab Emtansine as Second-Line Therapy for HER2 Positive Breast Cancer in China

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Research

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Abstract

Objective

To evaluate the cost-effectiveness of trastuzumab emtansine (T-DM1) as the second-line treatment for patients with human epidermal growth factor receptor-2 (HER2) positive breast cancer from the Chinese healthcare perspective. Capecitabine (Cap), capecitabine + lapatinib (Cap+Lap), capecitabine + trastuzumab (Cap+Tra), capecitabine + trastuzumab + pertuzumab (Cap+Tra+Pre) were selected as comparators.

Methods

A three-state Markov simulation model was performed. The state transition probabilities were estimated based on the results of a published network meta-analysis, and utilities were derived from the published literature. The costs populated in the model were acquired from the local charge or previously published studies. Univariate sensitive analysis and probabilistic sensitivity analyses were performed to test the robustness of the results.

Results

Treatment with T-DM1 was estimated to increase the cost by \$109,683.7, \$106,003.7, \$94,212.2, and \$63,214.9, and yield a gain of 0.544 quality-adjusted life years (QALYs), 0.383 QALYs, 0.367 QALYs, 0.087 QALYs in comparison with Cap, Cap+Lap, Cap+Tra, and Cap+Tra+Pre, respectively. Corresponding incremental cost-effectiveness ratios (ICERs) were \$201,624.4, \$276,772.1, \$256,709.0, and \$726,608.0 per QALY. The probabilities of T-DM1 as the dominant option were 0% at the WTP threshold of \$30,829.3/QALY.

Conclusions

T-DM1, as second-line therapy in the treatment of HER2 positive breast cancer, is not a cost-effective option in China. Given the significant clinical efficacy, an appropriate price reduction of T-DM1 is required to benefit more HER2 positive breast cancer patients.

1. Introduction

Breast cancer is the most common malignant tumor and the 5th most common cause of cancer-related death in Chinese women [1]. In 2015, it was estimated 304,000 new cases of breast cancer were diagnosed and nearly 70,000 deaths were due to breast cancer in China [1]. Moreover, the onset age of breast cancer among Chinese women is nearly 10–15 years younger than in western patients [2]. Human epidermal growth factor receptor-2 overexpression has been reported in approximately 20–25% of breast cancers [3, 4]. Breast cancers with HER2 overexpression are associated with poor prognosis and shorter patient survival. Nevertheless, with the development of anti-HER2 targeted therapies, there has been a significant improvement in the survival of patients with HER2 positive breast cancer [5]. As far as we

know, there are five kinds of anti-HER2 targeted agents available for breast cancer treatment in China, including pyrotinib, lapatinib, pertuzumab, trastuzumab, and Trastuzumab emtansine.

Trastuzumab emtansine, an antibody-drug conjugate consisting of the anti-HER2 antibody trastuzumab covalently linked to the highly potent microtubule inhibitory agent DM1, has been approved as second-line therapy for HER2 positive breast cancer by the National Medical Products Administration (NMPA) of China in January 2020. The efficacy and safety of T-DM1 in patients with HER2-positive breast cancer were confirmed in several phase III trials, such as the EMILIA trial, TH3RESA trial, and MARIANNE trial [6–8]. The EMILIA study, as the first randomized, multicenter, phase III study, demonstrated T-DM1 significantly improved progress-free survival (PFS) (median PFS 9.6 months vs 6.4 months; hazard ratio (HR) = 0.65 [95% confidence interval (CI) 0.55–0.77]; $P < 0.001$), and overall survival (OS) (median OS 29.9 months vs 25.9 months; HR = 0.75 [95% CI 0.64–0.88]; $P < 0.001$), when compared with lapatinib plus capecitabine [6, 9]. Results of the TH3RESA study showed that OS was significantly longer with trastuzumab emtansine versus treatment of physician's choice (median 22.7 months vs 15.8 months; HR = 0.68 [95% CI 0.54–0.85]; $p = 0.0007$) [7]. The incidence of grade 3 or above adverse events (AEs) were substantially lower with T-DM1 than with lapatinib plus capecitabine (48% vs. 60%), which indicated that T-DM1 was generally well tolerated [9]. Furthermore, a recent network meta-analysis of seven randomized controlled trials (RCTs) showed that T-DM1 was more effective than all comparators (the combinations of capecitabine, lapatinib, neratinib, trastuzumab, or pertuzumab) [10].

Although therapy with T-DM1 showed certain clinical benefits, the high cost of T-DM1 is also an important factor affecting treatment decisions. The expenditure for breast cancer treatment in China has been constantly increased over the past few years, which brought a huge economic burden on individuals and families [11]. Therefore, we developed an economic model based on the network meta-analysis to evaluate the cost-effectiveness of T-DM1 compared with Cap, Cap + Lap, Cap + Tra, and Cap + Tra + Pre as the second-line treatment for patients with HER2 positive breast cancer from the Chinese healthcare perspective.

2. Methods

2.1 Patient and treatment

The hypothetical cohort matched the inclusion criteria of the network meta-analysis was incorporated into the model [10]. These patients with HER2-positive, unresectable, locally advanced, or metastatic breast cancer had progressed after prior treatment with adjuvant therapy or trastuzumab plus taxane. The treatment strategies evaluated in our study included: 1) T-DM1 group, a dose of 3.6 mg/kg T-DM1 was intravenously infused every 21 days; 2) Cap group, 1,250 mg/m² orally twice daily on days 1–14 of each 21-day treatment cycle; 3) Cap + Lap group, lapatinib 1,250 mg orally once daily plus capecitabine 1,000 mg/m² orally twice daily on days 1–14 of each 21-day treatment cycle; 4) Cap + Tra group, trastuzumab 8 mg/kg loading dose in the first cycle followed by 6 mg/kg maintenance doses every 3 weeks, plus capecitabine 1,250 mg/m² orally twice daily on days 1–14 of each 21-day cycle; 5) Cap + Tra

+ Pre group, pertuzumab 840 mg initial dose in cycle 1 followed by 420 mg maintenance doses every 3 weeks, trastuzumab 8 mg/kg loading dose in the first cycle 1 followed by 6 mg/kg maintenance doses every 3 weeks, capecitabine 1,000 mg/m² orally twice daily on days 1–14 of each 21-day cycle. Treatment was discontinued when the disease progressed or an intolerable level of toxicity was reached.

2.2 Model Structure

A Markov model was constructed by Treeage Pro Suit 2011 (Treeage Software, Inc., MA, USA) to compare the cost-effectiveness of T-DM1 with other 4 treatments over a 10-year time horizon. The model included three mutually exclusive health states: progression-free survival, progressive disease (PD) and death (Fig. 1). The cycle duration was 3 weeks, and the initial health state for all patients was PFS. At the end of each cycle, the patients remained in a PFS state or progressed to the PD state. From the PD state, the patients could either remain at PD or move to death.

Health outcomes were expressed as quality-adjusted life years. The primary result was presented as incremental cost-effectiveness ratio, which was the costs spent to gain one QALY. The willingness-to-pay (WTP) threshold in the analysis was considered as three-times the per capita gross domestic product (\$30829.3) of China in 2019, which was suggested by the World Health Organization (WHO). Both cost and health outcomes were discounted at 3% annually after the first year to allow for current values.

2.3 Transition probabilities

The transition probabilities into each Markov state were measured with the clinical efficacy data derived from a published network meta-analysis and the MILIA trial[6, 9, 10]. OS and PFS values of T-DM1 at multiple time points were read using Engauge Digitizer software version 12.1 (<http://digitizer.sourceforge.net>) from the Kaplan-Meier (KM) curves of MILIA trial. The parametric model of Weibull was fitted to the data extracted from the KM curves by the R statistical software (<http://www.r-project.org>). The Weibull survival models of other four comparators were derived by applying the HRs for each comparator versus T-DM1, with the following formulas: $\lambda_{\text{comparator}} = \lambda_{\text{T-DM1}} \times \text{HR}$ and $\gamma_{\text{comparator}} = \gamma_{\text{T-DM1}}$, where λ was the scale parameter of Weibull distribution, γ was the shape parameter of Weibull distribution [12]. The estimated scale (λ) and shape (γ) parameters of T-DM1, and HRs for comparators versus T-DM1 were described in Table 1.

The time-dependency transition probabilities from PFS to PFS, defined as the ratio of the number of patients at the end of the cycle to the number of patients at the beginning of the cycle, were calculated according to the formulation: $tp(t) = s(t)/s(t-1)$, where t presents the current stage of the Markov model [13, 14]. The transition probabilities from PD to death were calculated based on the difference between the estimated OS and PFS Weibull models.

2.4 Cost and Utility

From the perspective of Chinese healthcare, only direct medical costs were considered in the model. The direct medical costs consisted of anti-cancer agents, management of adverse events (AEs),

hospitalization, and follow-up (Table 1). Average height (155.8 cm) and weight (57.3 kg) of Chinese women were used to calculate the drug doses [15]. There are two package sizes of T-DM1 available in China, 100 mg/vial and 160 mg/vial. According to the dose calculation, each dose required a big vial and a small one. Besides, there is a charity program for T-DM1, that patients would receive T-DM1 for free from cycle 8 to cycle14. Therefore, the costs of T-DM1 were excluded for cycle 8 to cycle14 in the T-DM1 group in the model. The costs of hospitalization included drug administration cost, drug delivery cost, bed fee and nursing fee. Considering that both lapatinib and capecitabine were taken orally, the hospitalization costs were not calculated in the Cap group and Cap + Lap group. Follow-up was associated with radiological examination, laboratory test and echocardiography examination. The radiological examination was performed every 2 cycles, and echocardiography examination was performed at cycle 2, cycle 4, and every 3 cycles thereafter as reported in the EMILIA trial [6].

Grade 3–4 AEs with incidence rates greater than 5% were considered, including diarrhea, Palmar–plantar erythrodysesthesia syndrome (PPES), elevated liver enzymes, neutropenia and thrombocytopenia. The incidence rates of AEs were derived from the relevant RCTs[9, 16, 17]. AEs management costs were obtained from the published literature and were applied once in the first cycle after treatment initiation[18–20]. It was assumed in the model that the cost of post-progression treatment was the same as the average hospitalization expenditure for breast cancer treatment in China [11]. All the costs were converted into 2019 US dollars (CYN 6.8985 = US \$1.00), and adjusted based on the medical care consumer price index (CPI), if necessary.

The health utility values for different health states and disutility values for AEs were obtained from the published literature (Table 1). 0.715 was assigned to the PFS state, and 0.452 to the PD state [21]. Since the disutility of elevated liver enzymes was unavailable, we assumed it was equivalent to the disutility of thrombocytopenia. Like the costs of AEs management, the disutility associated with AEs was only applied to the first cycle.

Table 1
Parameters used in the model

Parameters	Value	Range	Distribution	Reference
Clinical data				
Weibull survival model of PFS for TDM1	Scale = 0.0445; Shape = 1.0374; r2 = 0.9883			[6]
HR _{Cap} VS T-DM1 of PFS	2.62	1.35–5.19	Normal	[10]
HR _{Cap+Lap} VS T-DM1 of PFS	1.54	0.91–2.52	Normal	[10]
HR _{Cap+Tra} VS TDM1 of PFS	1.62	0.85–2.97	Normal	[10]
HR _{Cap+Tra+Pre} VS T-DM1 of PFS	1.34	0.57–3.09	Normal	[10]
Weibull survival model of OS for TDM1	Scale = 0.0055; Shape = 1.2596; r2 = 0.9856			[9]
HR _{Cap} VS T-DM1 of OS	1.47	0.91–2.54	Normal	[10]
HR _{Cap+Lap} VS T-DM1 of OS	1.32	0.93–1.98	Normal	[10]
HR _{Cap+Tra} VS T-DM1 of OS	1.28	0.84–2.27	Normal	[10]
HR _{Cap+Tra+Pre} VS T-DM1 of OS	0.97	0.55–1.96	Normal	[10]
Costs (US\$)				
T-DM1 per cycle	6800.8	5440.6–8160.9	Gamma	Local charge
Lapatinib per 0.25 g tablet	9.7	7.7–11.6	Gamma	Local charge
Capecitabine per 0.5 g tablet	4.0	3.2–4.8	Gamma	Local charge
Trastuzumab per 440 mg	1053.9	843.1–1264.65	Gamma	Local charge
Pertuzumab per 420 mg	718.272	574.618–861.927	Gamma	Local charge
Hospitalization per cycle	40.2	32.1–48.2	Gamma	Calculated
Follow-up cycle 1–4 per cycle	33.6	26.9–40.3	Gamma	Calculated
Follow-up after cycle 4 per cycle	32.5	26.0–39.0	Gamma	Calculated
post-progression per cycle	2383.7	1907.0–2860.4	Gamma	[11]
OS overall survival, PFS progress-free survival, PD progressive disease, HR hazard ratio, T-DM1 trastuzumab emtansine, AEs adverse events, PPES palmar-plantar erythrodysesthesia syndrome.				

Parameters	Value	Range	Distribution	Reference
Costs of AEs management (US\$)				
Diarrhoea	5.6	4.5–6.7	Gamma	[18]
PPES	16.9	13.5–17.7	Gamma	[19]
Elevated liver enzymes	68.3	54.7–82.0	Gamma	[18]
Neutropenia	547.5	438.0–656.9	Gamma	[18]
Thrombocytopenia	193.5	154.8–232.2	Gamma	[20]
Disutilities of AEs				
Diarrhea	-0.103	—	—	[21]
PPES	-0.116	—	—	[21]
Elevated liver enzymes	-0.122	—	—	[22]
Neutropenia	-0.15	—	—	[21]
Thrombocytopenia	-0.122	—	—	[22]
Utilities				
PFS	0.715	0.572–0.858	Beta	[21]
PD	0.443	0.354–0.532	Beta	[21]
Others				
Discount rate	3%	0–8%	—	
OS overall survival, PFS progress-free survival, PD progressive disease, HR hazard ratio, T-DM1 trastuzumab emtansine, AEs adverse events, PPES palmar-plantar erythrodysesthesia syndrome.				

2.5 Sensitivity Analysis

A series of one-way sensitivity analyses were performed to identify the influence of key model parameters on the model. As shown in Table 1, the parameters of costs and utilities were varied at a range of $\pm 20\%$ of their baseline values, HRs were varied over their 95% CIs, and the range of discount rate was from 0–8%. The results of the one-way sensitivity analyses were presented as the tornado diagrams. Probabilistic sensitivity analysis (PSA) was further performed to assess the robustness of the estimated cost-effectiveness ratio using Monte Carlo simulations of 1,000 patients, where samples were taken randomly from the distribution of the included parameters. Gamma, normal, beta distributions were adopted for costs, HRs, and utilities respectively. WTP acceptability curves were generated to illustrate the result of PSA.

3. Result

3.1 Base case analysis

Over a 10-year horizon, the total cost incurred with the T-DM1 arm was \$109,683.7 greater than capecitabine monotherapy, \$106,003.7 greater than Cap + Lap, \$94,212.2 greater than Cap + Tra, and \$63,214.9 greater than Cap + Tra + Pre. Meanwhile, T-DM1 gained an additional 0.544 QALYs compared with capecitabine monotherapy, an additional 0.383 QALYs compared with Cap + Lap, an additional 0.367 QALYs compared with Cap + Tra, and an additional 0.087 QALYs compared with Cap + Tra + Pre, resulting in ICERs of \$201,624.4/QALY, \$276,772.1/QALY, \$256,709.0/QALY, and \$726,608.0/QALY, respectively. It demonstrated that T-DM1 appeared not to be a cost-effective option based on the WTP threshold of \$30,829.3/QALY. Detailed information involved with base-case analysis was displayed in Table 1.

3.2 Sensitivity analysis

The results of univariable sensitivity analyses were shown in Fig. 2. The parameters with the greatest influence on the ICERs were HRs of OS, HRs of PFS, cost of T-DM1, and the utility of PFS state in all comparisons. The impacts of AEs managing costs, hospitalization costs, follow-up costs, and capecitabine costs were almost negligible. Other parameters had a minor influence on the robustness of the model. The ICERs were lower than the WTP threshold of \$30,829.3/QALY in three scenarios, one of which was Cap + Tra dominated, and two of which were Cap + Tra + Pre dominated. Other scenarios did not alter the cost-effectiveness conclusion that ICERs exceeded the WTP threshold.

Cost-effectiveness acceptability curves (Fig. 3) associated with the result of probabilistic sensitivity analysis indicated that the probabilities of T-MD1 as the cost-effectiveness option were 0% at the WTP threshold of \$30,829.3/QALY compared with four comparators. T-MD1 would exhibit a 50% probability of being cost-effective at a WTP value of approximately \$203,360/QALY, \$275,200/QALY, \$259,000/QALY, \$788,000/QALY when compared to Cap, Cap + Lap, Cap + Tra, and Cap + Tra + Pre, respectively.

Table 2
Results of the base-case analysis

Treatment	Cost (US\$)	QALYs	C/E ratio (US\$/QALY)	ΔCosts (T-DM1 - comparators, US\$)	ΔQALYs (T-DM1 - comparators)	ICER (US\$/QALY)
T-DM1	192,701.5	1.732	111,259.5			
Cap	83,017.8	1.188	69,880.3	109,683.7	0.544	201,624.4
Cap + Lap	86,697.8	1.349	64,268.2	106,003.7	0.383	276,772.1
Cap + Tra	98,489.3	1.365	72,153.33	94,212.2	0.367	256,709.0
Cap + Tra + Pre	129,486.6	1.645	78,715.26	63,214.9	0.087	726,608.0
T-DM1 trastuzumab emtansine, Cap capecitabine, Lap lapatinib, Tra trastuzumab, Pre pertuzumab QALY quality-adjusted life year, C/E cost/effectiveness, ICER incremental cost-effectiveness ratio						

4. Discussion

HER2-positive breast cancers tend to develop more rapidly and spread more aggressively than HER2-negative cancers. As the first HER2-targeted antibody-drug conjugate, trastuzumab Emtansine has been proven to be very effective and well tolerated in the second-line or later treatment for HER2-positive breast cancer [23]. A meta-analysis involving 3,720 patients indicated that T-DM1 significantly improved PFS (HR = 0.73, 95% CI: 0.61, 0.86; $P < 0.05$), OS (HR = 0.68, 95% CI: 0.62, 0.74; $P < 0.05$). PFS was significantly prolonged with first-line T-DM1 treatment (HR = 0.86, 95% CI: 0.74, 1.00; $P < 0.05$) or non-first-line treatment (HR = 0.65, 95% CI: 0.53, 0.81; $P < 0.05$) [24]. However, the guideline provided by the National Institute of Health and Healthcare (NICE) did not recommend trastuzumab emtansine, because the probability of trastuzumab emtansine being the most cost-effective was 0% [25]. With the current increase in healthcare expenditure in China, the medical costs of breast cancer remain a significant economic burden particularly on advanced patients [26]. The cost-effectiveness factor needs to be considered before T-DM1 is widely used in clinical treatment.

We conducted an economic analysis to compare the T-DM1 with four alternative regimens as second-line therapy for HER2 positive breast cancer. Head-to-head clinical trials of T-DM1 versus capecitabine, T-DM1 versus Cap + Tra, and T-DM1 versus Cap + Tra + Pre were unavailable. Hence, indirectly evaluated effectiveness was obtained from a published network meta-analysis[10]. According to the base case results of this study, when compared to capecitabine, T-MD1 showed an incremental cost of \$109,683.7 and an incremental benefit of 0.544 QALYs, leading to an ICER of \$201,624.4/QALY. Compared to Cap + Lap, T-DM1 provided an ICER of \$276,772.1/QALY gained. For the comparison with Cap + Tra, T-DM1 had an ICER of \$256,709.0/QALY gained. The ICER of T-DM1 compared to Cap + Tra + Pre was

\$726,608.0/QALY gained. The PSA revealed that T-DM1 was a 100% non-dominated option at the WTP threshold.

Our results were consistent with the previously published reports [22, 27, 28]. The recent study of Wang et al. [27] conducted a lifetime horizon Markov model to evaluate the cost-effectiveness of T-DM1 treatment with metastatic breast cancer in Taiwan. They found that the estimated ICERs of T-DM1 versus Cap + Lap was New Taiwan dollars (NTDs) 5,704,717/QALY gained. T-DM1 was not the cost-effectiveness option based on the WTP threshold of NTD 754,711. And the cost of T-DM1 was the greatest influence on ICER. In Mexico, Diaby et al. [28] evaluated the cost-effectiveness of four different HER2-targeted treatment sequences from three public and one private payer perspectives. Each treatment sequences contained therapy from first-line to third-line. The result of the study indicated that sequences containing T-DM1 were not cost-effective when compared with a sequence including the combination of trastuzumab/docetaxel as first-line without subsequent T-DM1. Four Markov models were performed by Le et al. [22] to compare the cost-effectiveness of T-DM1, Cap + Lap, and capecitabine monotherapy at a WTP threshold of \$150,000. The ICER between T-DM1 and capecitabine was \$183,828/QALY and \$220,385/QALY from the perspectives of the US payer and society respectively.

The present study has some limitations that deserve to be mentioned. First, due to the lack of randomized controlled trials, HR from indirect comparison was used to calculate the transition probabilities. The univariate sensitive analysis indicated that HR was the most important influential factor on ICER, especially for T-DM1 versus Cap + Tra, and T-DM1 versus Cap + Tra + Pre. Second, grade 1/2 AEs and dose reduction due to toxic reactions were not considered in the model. We assumed that the majority of mild AEs were self-limiting, and the costs of AEs management had minimal impact on the ICER base on the univariate sensitive analysis. Dose adjustment (for example, the first dose reduction for T-DM1 was to 3.0 mg/kg, and the second to 2.4 mg/kg) was not applied, which may result in a higher total cost than clinical practice. Third, the utilities of PFS and PD were obtained from published literature based on United Kingdom populations, which may differ in Chinese. Besides, the utilities were assumed to be the same in each therapy, which may be different from the real-world data.

Conclusion

Although T-DM1 as second-line therapy in the treatment of HER2-positive advanced breast cancer showed excellent clinical efficacy, the results of our study suggested that T-DM1, compared with capecitabine monotherapy, capecitabine plus lapatinib, capecitabine plus trastuzumab, capecitabine plus trastuzumab and pertuzumab, was unlikely to be cost-effective from the perspective of the Chinese healthcare system. A significant reduction in the price of T-DM1 may be a potential measure to improve its cost-effectiveness. We expect that the results of this study will be useful for decision-making by patients, doctors and governments. When high-quality head-to-head clinical trials are available, our research will be updated.

Declarations

Funding

This analysis received no funding.

Availability of data and materials

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

Ethics approval and consent to participate

This study was performed by a mathematical model, without any human participants or animals.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no potential conflicts of interest.

Authors' contributions

All authors contributed to the study conception and design. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. All authors read and approved the final manuscript.

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Figures

Figure 1

The simplified three-state Markov model structure. PFS progress-free survival, PD progressive disease.

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The simplified three-state Markov model structure. PFS progress-free survival, PD progressive disease.

Figure 2

Tornado diagrams of one-way sensitivity analyses. a: T-DM1 versus Cap; b: T-DM1 versus Cap+Lap, c: T-DM1 versus Cap+Tra; d: T-DM1 versus Cap+Tra+Pre. OS overall survival, PFS progress-free survival, PD progressive disease, HR hazard ratio, T-DM1 trastuzumab emtansine, AEs adverse events, PPES palmar-plantar erythrodysesthesia syndrome, T-DM1 trastuzumab emtansine, Cap capecitabine, Lap lapatinib, Tra trastuzumab, Pre pertuzumab.

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Figure 3

WTP acceptability curve of probabilistic sensitivity analysis. a: T-DM1 versus Cap; b: T-DM1 versus Cap+Lap, c: T-DM1 versus Cap+Tra; d: T-DM1 versus Cap+Tra+Pre. T-DM1 trastuzumab emtansine, Cap capecitabine, Lap lapatinib, Tra trastuzumab, Pre pertuzumab

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