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Trastuzumab emtansine: the first targeted chemotherapy for treatment of breast cancer

Parvin F Peddi¹ and Sara A Hurvitz^{1,2,*}

¹Department of Medicine, Division of Hematology–Oncology, University of California at Los Angeles, CA, USA

²10945 Le Conte Avenue, PVUB Suite 3360, Los Angeles, CA 90095, USA

Abstract

Trastuzumab emtansine (T-DM1) is a novel antibody–drug conjugate, comprised of a potent cytotoxic drug connected via a stable linker to the anti-HER2 antibody, trastuzumab, thereby primarily targeting chemotherapy delivery to cells overexpressing the HER2 receptor. A Phase II randomized trial of T-DM1 in the front-line metastatic breast cancer setting revealed promising activity and improved safety compared with standard chemotherapy plus trastuzumab. Subsequently, a Phase III trial in patients with trastuzumab-pretreated metastatic breast cancer showed T-DM1 to be associated with prolonged progression-free and overall survival compared with lapatinib plus capecitabine. T-DM1 represents a major shift in the treatment of patients with breast cancer as it replaces traditional nontargeted chemotherapy with a ‘smart’ medication that directs the cytotoxic therapy to cancer cells by using a known biomarker.

Keywords

antibody–drug conjugate; breast cancer; HER2 positive; T-DM1; trastuzumab emtansine

Approximately 20% of breast cancers are characterized by amplification of the *HER2* gene leading to overexpression of HER2, a trans-membrane receptor tyrosine kinase [1]. HER2 is a member of the EGF receptor family, a group of cell surface receptors that also includes HER1 more commonly referred to as EGF receptor, HER3 and HER4. This family of proteins is involved in promoting cell growth through activation of the PI3K/Akt/mTOR and the Ras/Raf/MEK/MAPK pathways [2]. Amplification of HER2 is predictive of aggressive phenotype and poorer outcome unless treated with anti-HER2 therapy [3].

Overview of the market

Trastuzumab, a humanized anti-HER2 monoclonal antibody, has become the established gold standard treatment for HER2-amplified breast cancer since it was first approved by the US FDA in 1998 [4,5]. Subsequently, two other HER2-targeted agents have been approved

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*Author for correspondence: Tel.: +1 310 829 5471 Fax: +1 310 829 6192 shurvitz@mednet.ucla.edu.

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for the treatment of HER2-positive metastatic breast cancer, lapatinib and pertuzumab. Lapatinib, an oral small-molecule tyrosine kinase inhibitor, binds and inhibits both HER1 and HER2. In 2007, it was approved for use in combination with capecitabine in patients whose disease had progressed on or after anthracycline, taxane and trastuzumab therapy based on a Phase III trial that showed an improved time-to-progression and response rate associated with lapatinib–capecitabine compared with capecitabine alone [6]. In 2010, it received FDA approval in combination with letrozole for post-menopausal women with hormone receptor-positive, HER2-overexpressing metastatic breast cancer [7]. The response rate associated with lapatinib as a single agent in trastuzumab-naïve disease is 24%; however, response rates are less than 10% in the trastuzumab-refractory setting [8–11]. In combination with capecitabine or trastuzumab, response rates are 22 and 10%, respectively [6,11]. While lapatinib-based therapy has been shown to be moderately effective in HER2-positive disease, the majority of patients do not respond, and toxicity (diarrhea and rash) can be dose limiting. The third HER2-targeted therapy to receive regulatory approval was pertuzumab. Similar to trastuzumab, pertuzumab is a humanized monoclonal antibody that binds to the extracellular portion of HER2, but binds to a different domain than that of trastuzumab (domain II instead of domain IV) [12,13]. Response rate associated with pertuzumab monotherapy and pertuzumab–trastuzumab combination therapy in previously treated patients is 3 and 24%, respectively [14,15]. In a global randomized Phase III study, pertuzumab was shown to improve progression-free survival (PFS) by 6 months when added to a combination of docetaxel and trastuzumab in patients who had progressed on trastuzumab [16]. In a similar study in the neoadjuvant setting, the addition of pertuzumab to trastuzumab and docetaxel improved pathologic complete response rate by 17%, although event-free and overall survival (OS) from this study have not yet been reported and pertuzumab is not yet approved for use in the neoadjuvant setting [17].

As detailed above, while single agent therapy with the currently available HER2-targeted medications is well tolerated, fewer than 30% of patients will have a tumor response. As a result, these biologically targeted drugs are typically combined with chemotherapy thereby significantly increasing toxicity. Furthermore, *de novo* or acquired resistance to anti-HER2 therapy occurs in the vast majority of patients [18]. Treatment resistance is most commonly due to activation of competing pathways rather than to loss of HER2 expression on the cell surface [19–22]. Therefore, HER2 still represents a unique marker that could be used for targeting cytotoxic therapies when cells become resistant to direct inhibition of the HER2 pathway.

Trastuzumab emtansine

Chemistry

Trastuzumab emtansine (T-DM1) is an antibody–drug conjugate made up of trastuzumab, stably linked to a highly potent chemotherapy (DM1) derived from maytansine (Figure 1). The developmental history of T-DM1 reaches back to the 1970s when the National Cancer Institute sponsored a plant screening program where plant-derived compounds were tested for activity against cancer cell lines. As part of this initiative, maytansine was isolated from an Ethiopian plant, *Maytenus ovatus*, in 1972 by Kupchan and colleagues, and was subsequently shown to have antitumor activities [23]. Similar to vinca alkaloids, it binds tubulin and prevents assembly of microtubules by promoting depolymerization and inhibiting polymerization [24]. While the *in vitro* activity of maytansine was dramatic – it is 100-times more potent than the vinca alkaloids and 24- to 270-times more potent than paclitaxel [24–26] – its clinical development was halted in early trial testing due to dose-limiting toxicities including neuropathy, diarrhea and weakness [25]. The usefulness of maytansine may never have been realized were it not for the engineering of targeted

monoclonal antibodies that could potentially be used to deliver the chemotherapy specifically to cancer cells

The HER2 protein is an ideal target for an antibody–chemotherapy agent conjugate because breast cancers that contain amplification of the *HER2* gene have up to 1–2 million receptors expressed per cell [27]. The greatest challenge in developing a less toxic yet highly effective antibody–drug conjugate proved to be in the linker. The key was to develop a linker that could be broken down inside tumor cells, but stable enough that it would not release the chemotherapy into the systemic circulation. In 2008, Lewis Phillips *et al.* published the results of their work studying various linkers between trastuzumab and DM1 [28]. They demonstrated enhanced potency of trastuzumab–DM1 conjugates compared with trastuzumab in cell lines. Furthermore, after studying both disulfide and thioether linkers, trastuzumab linked to DM1 with a non-reducible thioether linker (SMCC, referred to as MCC in conjugated form) showed superior activity in terms of potency. This molecule, T–MCC–DM1, which contains an average of 3–3.6 DM1 moieties per molecule, is from this point on, referred to as T-DM1.

Pharmacodynamics & preclinical studies

Upon binding to HER2, the trastuzumab component of T-DM1 exerts its antitumor effects [26,29]. The HER2–T-DM1 complex is then endocytosed and ultimately fused with a lysosome where it undergoes proteolytic degradation with release of the active DM1 [30]. The primary active metabolite, lysine–SMCC–DM1, does not readily cross the plasma membrane and therefore should not cause effects in neighboring cells [31]. HER2-overexpressing cell lines, regardless of sensitivity or resistance to trastuzumab, were found to undergo apoptosis and mitotic disruption upon exposure to T-DM1, while normal cell lines were unaffected [28]. T-DM1 also inhibited tumor growth in animal models of HER2-positive breast cancer [28]. A proposed mechanism of resistance to trastuzumab and lapatinib therapy is activation of the PI3K/PTEN pathway via acquired mutations [22,21,32]. Significantly, T-DM1 was found to be highly potent when tested against cell lines resistant to trastuzumab and lapatinib that were harboring PI3K pathway activating mutations [26].

Pharmacokinetics & metabolism

Pharmacokinetic (PK) data from the Phase I trial as well as three Phase II studies of T-DM1 were assessed in aggregate by Girish *et al.* [33]. PKs were found to be nonlinear at doses less than 2.4 mg/kg, after which linearity was established. Volume of distribution approximated that of physiologic blood volume, similar to human IgG antibodies. All PK parameters were consistent at cycle one and in later cycles with no significant accumulation of T-DM1 following the high-dose-every-3 weeks dosing cycle. Peak concentration of free DM1 was <10 ng/ml at all doses confirming very little systemic release of DM1. Body weight, albumin, AST and tumor burden were covariants that influenced T-DM1 PKs, with body weight accounting for most of the variability [34]. No correlation was observed between area under the curve and response at a dose of 3.6 mg/kg [33].

The median half-life of T-DM1 is 4.5 days, and steady state is achieved by cycle two [34]. The route of T-DM1 clearance in mice is primarily through the gastrointestinal and biliary systems, with up to 80% of radioactively labeled metabolites recovered in the feces and 50% in the bile [35]. Normal bilirubin and AST/ALT <2.5-times the upper limit of normal were inclusion criteria for all the clinical studies [36–38]. A study is currently ongoing to evaluate whether normal hepatic function is necessary for the administration of T-DM1 [101]. Renal function, on the other hand, was found to have no impact on T-DM1 clearance [34]. When DM1 is incubated with human liver microsomes and recombinant CYP, DM1 is

demonstrated to be mainly metabolized by CYP3A4, and to a lesser extent by CYP3A5 [39]. Both oxidative and hydrolysis metabolites were detected after the *in vitro* incubation. DM1, however, was found to neither induce nor inhibit CYP isoforms [39]. Therefore, T-DM1 has little potential for drug–drug interactions.

Clinical efficacy

Phase I studies—The first in-human study of T-DM1 was conducted by Krop and colleagues and published in 2010 (Table 1) [36]. T-DM1 was given to 24 patients who had previously received a median of four other chemotherapies, with doses escalated from 0.3 to 4.8 mg/kg given on an every-3-week cycle. At 4.8 mg/kg transient thrombocytopenia was observed and 3.6 mg/kg was identified as the maximum-tolerated dose (MTD). Response rate in these heavily pretreated patients with measurable disease at MTD was 44%. A large majority of patients (73%) treated at the MTD had clinical benefit (objective response or stable disease at 6 months). T-DM1 was well tolerated at the MTD with common adverse events (AEs) including grade 1 or 2 thrombocytopenia, transaminitis, fatigue, nausea and anemia. Importantly, no neuropathy was noted, despite the fact that DM1, like vincristine, acts on microtubulins and that neuropathy is a known AE. Based on this study, 3.6 mg/kg intravenous every 3 weeks was selected as the dose for use in subsequent studies.

A weekly dosing cohort was started after MTD had been determined for the high-dose-every-3 weeks regimen [40]. A third of the 3.6 mg/kg every-3-week dosing (1.2 mg/kg) was chosen for the starting weekly dose. MTD was determined to be 2.4 mg/kg weekly after two out of three patients who received T-DM1 at 2.9 mg/kg experienced grade 3 thrombocytopenia and grade 3 elevated AST. Objective tumor responses were reported in a similar percentage of patients (46.4%) as the high-dose-every-3 weeks dosing. Clinical benefit rate at 6 months was 57%. Similar to the every-3-week schedule, no grade 3 or 4 neuropathy was observed. Overall grade 3 or worse AEs were more frequent with weekly dosing (68%) compared with the every 3-week schedule (50%), although comparison is difficult given low patient numbers [36,40]. Subsequently published trials to date have been with the every-3-week schedule. Larger studies with the weekly schedule are ongoing at this time.

Phase II studies—Based on the safety and promising efficacy of T-DM1 seen in Phase I testing, a proof-of-concept, single-arm Phase II study evaluating T-DM1 was initiated [37]. Study TDM4258g enrolled 112 patients with HER2-overexpressing metastatic breast cancer whose disease had progressed on at least one prior chemotherapy and HER2-directed therapy. By independent review, the objective response rate (ORR) was 26% and median PFS was 4.6 months. HER2 overexpression was centrally confirmed in 66% of patients and of these, 34% had an objective response with a median PFS of 8.2 months. Overall, T-DM1 was well tolerated. Most AEs were grade 1 or 2 and included fatigue (68%), nausea (56%), headache (45%), epistaxis (38%) and pyrexia (38%). The most frequent grade 3 or greater AEs were hypokalemia (8.9%), thrombocytopenia (8%) and fatigue (4.5%).

A confirmatory single-arm Phase II study, TDM4374, was subsequently conducted on a more heavily pretreated patient population [41]. The patients included in this study were required to have previously received an anthracycline, a taxane, capecitabine, trastuzumab and lapatinib. The median number of prior treatment lines was seven. T-DM1 was similarly tolerated as in previous studies with the most common grade 3 or worse AEs being thrombocytopenia (9%), fatigue (4.5%) and cellulitis (3.6%). ORR remained relatively high (34.5%) in this heavily pretreated patient population, and median PFS was 6.9 months. HER2 overexpression was centrally confirmed in 84% of patients, and of these, 41% had an ORR. The median PFS in that subset was 7.3 months.

In TDM4450, the first randomized Phase II trial of T-DM1, 137 patients with HER2-positive metastatic or locally advanced unresectable breast cancer were randomized to T-DM1 or the combination of docetaxel and trastuzumab as first-line therapy [42]. Median PFS was 14.2 months in the T-DM1 arm compared with 9.2 months in the docetaxel/trastuzumab arm. ORR in the T-DM1 arm was 64 versus 58% in the traditional chemotherapy trastuzumab arm. Grade 3 or greater AEs were lower in the T-DM1 group at 46 versus 91%. AEs leading to treatment discontinuation (40.9 vs 7.2%) also occurred less frequently with T-DM1 [43].

Phase III studies—The Phase I and II studies led to the landmark Phase III EMILIA trial discussed above, which was presented at the plenary session of ASCO in 2012 [44] and subsequently published in the *New England Journal of Medicine* [38]. In this trial, 991 patients with advanced HER2-positive breast cancer, whose disease had progressed through treatment with trastuzumab and a taxane, were randomized 1:1 to T-DM1 alone or lapatinib plus capecitabine, an FDA-approved and standard option in this setting. Coprimary end points were PFS and OS, and the trial had a 90% power to detect a hazard ratio (HR) of 0.75 for progression or death from any cause or an 80% power to detect a HR of 0.80 for death from any cause.

Median PFS was significantly prolonged with T-DM1 by approximately 3 months (9.6 vs 6.4 months; HR for progression or death from any cause: 0.65; 95% CI: 0.55–0.77; $p < 0.001$). OS was also significantly improved (30.9 vs 25.1 months; $p < 0.001$), with a HR of 0.68 ($p = 0.0005$) for death from any cause. Estimated 1-year survival rates were 85.2 versus 78.4% in the T-DM1 and lapatinib–capecitabine arms, respectively. Remarkably this improvement in survival was achieved with a concurrent reduction in rates of grade 3 or 4 AEs (41 vs 57%). Rates of cardiac dysfunction, the main adverse effect from trastuzumab, were low in both treatment arms. A total of 1.7% of patients in the T-DM1 group and 1.6% of patients in the lapatinib–capecitabine arm had an ejection fraction that was less than 50% and at least 15 percentage points below baseline. Only one patient developed grade 3 congestive heart failure, which was in the T-DM1 arm. Secondary end points of response rate (44 vs 31%) and median duration of response (12.6 vs 6.5 months) were both improved with T-DM1 compared with lapatinib and capecitabine.

Safety & tolerability

T-DM1 is generally well tolerated and does not seem to have any of the adverse effects expected with DM1, a drug with similar mechanism of action as the vinca alkaloids, namely neuropathy. Cardiac toxicity, a known AE of trastuzumab, has also been low. However, it is unclear whether this is due to a true lower rate with T-DM1 or the fact that all patients in the above studies, except TDM4450, had previously received trastuzumab and, therefore, had passed the ‘trastuzumab stress test.’ Cardiac toxicity rates appeared to be similar between T-DM1 and trastuzumab arms in the TDM4450 study, however, the numbers were too small to be significant [43]. Cardiac event rates related to T-DM1 will be further addressed in the MARIANNE trial an ongoing large first-line study, where it is being directly compared with a trastuzumab-based regimen.

The main grade 3 or 4 AEs from T-DM1 therapy are thrombocytopenia and transaminitis occurring in 12.9 and 4.3% (AST), respectively, in the EMILIA trial. Both adverse effects can be managed in most patients by dose reduction. In the EMILIA trial, a platelet count less than 25,000, AST of over three-times the upper limit of normal or bilirubin of over two-times the upper limit of normal resulted in an automatic dose reduction to 3.0 mg/kg, and subsequently to 2.4 mg/kg if adverse effects occurred on the 3.0 mg/kg dosing. Overall 2%

of all patients discontinued therapy due to thrombocytopenia and less than 1% discontinued it due to transaminitis.

The mechanisms underlying T-DM1-induced platelet and hepatic toxicity are not completely clear. The lowest platelet count typically occurs after the first dose and nadirs by day 8 [45]. T-DM1 has been shown to be taken up by mouse megakaryocytes and to inhibit their differentiation by interfering with microtubule assembly [46]. This is in spite of the fact that megakaryocytes lack HER2 cell surface expression [47]. Therefore, another mechanism of endocytosis appears to be in play for these cells. Regardless, thrombocytopenia has not been associated with significant morbidity or bleeding events. Few grade 3 or 4 bleeding events were observed in T-DM1 studies (one to six patients), mostly consisting of epistaxis. In only two patients did the bleeding occur in association with a low platelet count [37,41]. In addition, the liver toxicity is not typically serious and does not appear to significantly increase risk of fulminant liver failure. In the studies mentioned above, only one patient died of abnormal liver function, which was in the setting of pre-existing nonalcoholic hepatosteatosis and multiple other comorbidities [41].

Regulatory affairs & ongoing trials

T-DM1 is currently being reviewed by the FDA for approval in previously treated patients with metastatic HER2-amplified breast cancer. The ongoing randomized Phase III MARIANNE trial is examining frontline T-DM1 therapy for patients with metastatic or recurrent locally advanced HER2-amplified breast cancer, either with or without pertuzumab, versus trastuzumab and taxane combination therapy [102]. Primary outcome measures in this study are PFS and incidence of AEs. OS and response rate are secondary outcome measures. This study has finished accrual and is currently ongoing, estimated for completion in 2016. Several other studies are examining safety and efficacy of combining T-DM1 with traditional cytotoxic chemotherapies [103–105]. T-DM1 is also being studied in the adjuvant and neoadjuvant setting in one ongoing trial [106], where it is being studied in place of trastuzumab after completion of traditional anthracycline-based chemotherapy.

Conclusion

T-DM1 represents a novel approach for the treatment of HER2-driven breast cancer using HER2 as a biomarker to target toxic chemotherapy directly to the cancer cells. T-DM1 activity relies on continued overexpression of HER2, which has been shown to persist on treatment-resistant cancer cells. T-DM1 is better tolerated and has been shown in two randomized trials to be more effective than standard chemotherapy added to HER2-targeted drugs.

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Future perspective

T-DM1 is likely to usher in a new era of targeted chemotherapy, beginning in breast cancer. FDA approval is currently pending in the pretreated metastatic setting and definitive studies of its use in the first-line and non-metastatic settings are ongoing at this time.

Executive summary

Mechanism of action

- Trastuzumab emtansine (T-DM1) antibody–drug conjugate that uses an anti-HER2 antibody (trastuzumab) to target an antimicrotubule agent to HER2-overexpressing breast cancer cells.

Pharmacokinetics

- Distribution: T-DM1 distributes throughout the blood plasma volume.
- Excretion: gastrointestinal and biliary tracts are the main elimination routes. Adjustments based on liver function were used in the EMILIA trial. T-DM1 has not been used in patients with significant liver dysfunction where it is currently been studied. No adjustment is needed for renal dysfunction.

Clinical efficacy

- T-DM1 has been shown to be effective as a single agent in patients with advanced HER2-positive breast cancers that have progressed through a taxane and trastuzumab. Definitive studies of T-DM1 in the first-line or adjuvant settings, either as a single agent or in combination with other HER2 therapy and chemotherapies, are ongoing.

Adverse effects

- Transaminitis and thrombocytopenia are the most common grade 3 or 4 adverse effects. They usually resolve with dose adjustment.

Dosage & administration

- The starting dose in the EMILIA trial was 3.6 mg/kg intravenously every 3 weeks. The first dose reduction after occurrence of significant adverse events was to 3.0 mg/kg and the second dose reduction was to 2.4 mg/kg. Weekly administration of T-DM1 has been tested in a Phase I study and is currently being studied in larger trials.

Figure 1. Structure of trastuzumab emtansine and mechanisms of action

After T-DM1 binds HER2, the HER2–T-DM1 complex undergoes internalization, followed by lysosomal degradation. This process results in the intracellular release of DM1-containing catabolites that bind to tubulin and prevent microtubule polymerization, as well as suppress microtubule dynamic instability. T-DM1 has also been shown to retain mechanisms of action of trastuzumab, including disruption of the HER3/PI3K/AKT signaling pathway and Fc γ receptor-mediated engagement of immune effector cells that leads to antibody-dependent cellular cytotoxicity.

ADCC: Antibody-dependent cellular cytotoxicity; Lys: Lysine; T-DM1: Trastuzumab emtansine.

Table 1

Summary of clinical trials of trastuzumab emtansine.

Study (year)	Phase	Patient population	Patients (n)	Treatment	Results	Ref.
Krop <i>et al.</i> (2010)	I	Pretreated HER2 + MBC	24	Dose escalation T-DM1 q3wks	ORR: 44% CBR: 73%	[36]
Beeram <i>et al.</i> (2012)	I	Pretreated HER2 + MBC	28	Dose escalation T-DM1 q1wk	ORR: 46% CBR: 57%	[40]
Burris <i>et al.</i> (2011)	II	Pretreated HER2 + MBC	112	3.6 mg/kg iv. q3wks	PFS: 4.6 months ORR: 26%	[37]
Krop <i>et al.</i> (2012)	II	Pretreated HER2 + MBC	110	3.6 mg/kg iv. q3wks	PFS: 7.3 months ORR: 35% CBR: 48%	[41]
Hurvitz <i>et al.</i> (2011/2013)	II	First-line HER2 + MBC	137	T-DM1 3.6 mg/kg iv. q3wks vs docetaxel + trastuzumab	PFS: 14.2 months ORR: 64%	[42,43]
Verma <i>et al.</i> (2012)	III	Pretreated HER2 + MBC	991	T-DM1 3.6 mg/kg iv. q3wks vs capecitabine + lapatinib	OS: 30.9 months PFS: 9.6 months ORR: 44%	[38]

CBR: Clinical benefit rate at 6 months defined as objective response plus stable disease; iv.: Intravenous; MBC: Metastatic breast cancer; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; q1wk: Low dose weekly; q3wks: High dose every 3 weeks; T-DM1: Trastuzumab emtansine.