Nursing Perspectives on Trastuzumab Emtansine for the Treatment of Metastatic Breast Cancer

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Increased understanding of the molecular composition of breast cancer tumors has led to the development of targeted anticancer agents. Novel therapies directed against human epidermal growth factor receptor 2 (HER2) in breast cancer have been developed. One such agent, trastuzumab emtansine (T-DM1), is an antibody drug conjugate that has been shown to be effective in the treatment of women with HER2-positive breast cancer. Phase I and II studies have determined a maximum tolerated dose, and several phase Ib/II, II, and III studies have shown improved tolerability and efficacy compared with the combination of trastuzumab and chemotherapy. The most concerning grade 3 or higher adverse events associated with T-DM1 include thrombocytopenia and transaminitis. To ensure that these adverse events do not delay or interrupt treatment, oncology nurses need to familiarize themselves with these risks and their management. This article reviews the clinical development of T-DM1 and its usage, with a focus on the nurse’s role in preventing and managing adverse events associated with T-DM1 therapy.

Breast cancer is the most common cancer among women in the United States, with an estimated 234,580 new cases diagnosed and 40,030 breast cancer-related deaths occurring in 2013 (Siegel, Naishadham, & Jemal, 2013). Breast cancer comprises multiple distinct subtypes, including estrogen receptor (ER) and progesterone receptor (PR) positive; human epidermal growth factor receptor 2 (HER2) positive; or ER, PR, and HER2 negative (i.e., triple negative). Treatment is individualized based on the biologic-driven mechanism: hormonal (ER and/or PR positive) responding best to antihormonal therapy, HER2 positive responding best to combination therapy that includes anti-HER2 therapy, and triple negative responding best to chemotherapy. HER2 is overexpressed in 25%~30% of breast cancer cases (Carey et al., 2006). Women with breast cancers that overexpress HER2 have a worse prognosis with significantly lower disease-free and overall survival (Carey et al., 2006; Ravdin & Chamness, 1995). To date, the treatment for patients who have breast cancer with overexpressed HER2 involves the use of anti-HER therapy: trastuzumab, lapatinib, and pertuzumab. Trastuzumab was approved in 2006 by the U.S. Food and Drug Administration (FDA) as the first targeted anti-HER2 agent. Trastuzumab showed improvement in overall survival in metastatic breast cancer in about one-third of patients with HER2-positive breast cancer (Vogel et al., 2002). However, primary or acquired trastuzumab resistance usually occurs and leads to tumor progression in the majority of the patients within a year of treatment initiation (Esteva et al., 2002). The second FDA-approved (in 2007) targeted anti-HER2 agent, lapatinib, in combination with capecitabine, has been associated with improvement in progression-free survival in the metastatic setting and appears to lengthen overall survival in patients with metastatic HER2-positive breast cancer resistant to trastuzumab (Cameron et al., 2008). When combined with letrozole, lapatinib provides an improvement in progression-free survival for women with hormone receptor-positive, HER2-positive metastatic breast cancer (Johnston et al., 2009). The data also suggest that the combination of lapatinib and trastuzumab in patients with heavily pretreated HER2-positive metastatic breast cancer improves median overall survival by 4.5 months (Blackwell, Burstein, et al., 2012). Pertuzumab, approved by the FDA in 2012, targets the HER2 receptor, in combination...
with trastuzumab and docetaxel, for women with metastatic HER2-positive breast cancer (Baselga et al., 2012). Additional investigations in the targeted therapy area, aimed to overcome the resistance drawback of trastuzumab, led to the development of trastuzumab emtansine (T-DM1). T-DM1 is a novel antibody drug conjugate (ADC) that has activity against overexpressing HER2 in patients with breast cancer. This article describes clinical development of T-DM1 and its usage, with a focus on nursing considerations.

**Clinical Development**

T-DM1 is an HER2-targeted ADC composed of the microtubule polymerization inhibitor DM1 (derivative of maytansine) and trastuzumab (Lewis Phillips et al., 2008). ADCs are agents that consist of a cytotoxic agent and an antibody targeting an antigen expressed on tumor cells and are designed to selectively deliver chemotherapy to the tumor cell only, therefore sparing the normal tissues (Chari, 2008).

Initially maytansine, as a free drug (not linked to trastuzumab), was found to have high anti-tumor potency but was associated with intolerable side effects such as peripheral neuropathy and nausea (Issell & Crooke, 1978). Research was then shifted toward the development of a trastuzumab-maytansinoid conjugate that culminated in the development of T-DM1 (Lewis Phillips et al., 2008). The highly potent cytotoxic derivative of maytansine, DM1, causes apoptosis through inhibition of microtubule assembly, leading to cell cycle arrest at the G2/M phase (Cassady, Chan, Floss, & Leistner, 2004; Lewis Phillips et al., 2008; Remillard, Rebhun, Howie, & Kupchan, 1975). DM1 is linked to trastuzumab via 4-(3-mercaptopeto-2,5-dioxo-1-pyrrolidinylmethyl)-cylohexanecarboxylic acid (MCC), a unique nonreducible thioether linker known as N-maleimidomethyl cyclohexane-1-carboxylate (Lewis Phillips et al., 2008). The MCC linker minimizes systemic exposure and molecular dissociation of the T-DM1, therefore reducing the T-DM1 toxicity and improving its efficacy (Lewis Phillips et al., 2008).

Preclinical assessment of T-DM1 identified in vitro anti-tumor potency in HER2-positive cell lines, trastuzumab-resistant cell lines, and lapatinib-resistant cell lines (Lewis Phillips et al., 2008). T-DM1 led to complete tumor regression in the HER2-positive trastuzumab responsive mouse model, and tumor reduction in trastuzumab- and lapatinib-resistant tumor xenograft models (Junttila, Li, Parsons, Phillips, & Sliwkowski, 2011; Lewis Phillips et al., 2008). In addition, T-DM1 was found to potentiate the anti-tumor effects of doxorubicin, paclitaxel, GDC-0941 plus rapamycin, docetaxel in vitro, and docetaxel with in vivo models (Junttila et al., 2008, 2011; Parsons, Fields, Gunter, & Phillips, 2010; Sampath et al., 2010).

The encouraging results of the preclinical studies led to several phase I trials examining the dosing of T-DM1 (Aogi et al., 2011; Beeram et al., 2012; Krop, Beeram, et al., 2010; Krop, Modi, et al., 2010; Krop, Wolf, et al., 2010). A dose of 3.6 mg/kg via IV every three weeks was selected for subsequent phase II clinical trials. Although these studies were not intended to evaluate efficacy, the overall response rate was more than 40%.

To date, several phase II and I/II trials with T-DM1, either as a single agent or in combination with other agents, have reported encouraging activity in HER2-positive breast cancer (Burriss et al., 2011; Dírcas et al., 2010; Hurvitz et al., 2011; Krop et al., 2012). The overall response rate of these trials was 26%–64%, as reported by trial principal investigator review (as opposed to an independent review). Of the patients receiving T-DM1 after previously failing several lines of therapy, 46%–73% had a clinical benefit rate.

Phase III data of T-DM1 compared with capecitabine plus lapatinib were reported by Blackwell, Miles, et al. (2012). In the trial, 978 patients who failed first-line treatment with trastuzumab were randomized to receive T-DM1 versus capecitabine and lapatinib until progressive disease or unmanageable toxicity. A significant improvement was noted in progression-free survival in patients receiving T-DM1 (median = 9.6 versus 6.4 months, HR = 0.65, 95% confidence interval [CI] [0.55, 0.77], p < 0.0001). The median overall survival for patients receiving T-DM1 had not been reached versus 23.3 months (HR = 0.62, 95% CI [0.48, 0.81], p = 0.0005).

Other randomized phase III studies are studying T-DM1 alone or in combination with pertuzumab versus trastuzumab and taxane, as well as T-DM1 versus physician choice in the metastatic, adjuvant, or neoadjuvant setting (see Table 1).

### Adverse Events

The National Cancer Institute’s Common Terminology Criteria for Adverse Events was used to grade the adverse events of the treatment. The most notable adverse events of T-DM1 appear to be related to elevation of the liver enzymes aspartate aminotransferase and alanine aminotransferase and thrombocytopenia.

<table>
<thead>
<tr>
<th>Trial Identifier</th>
<th>Trial Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01276041</td>
<td>Paclitaxel, trastuzumab, and pertuzumab in the treatment of metastatic HER2-positive breast cancer</td>
</tr>
<tr>
<td>NCT01730833</td>
<td>Pertuzumab, trastuzumab, and paclitaxel albumin-stabilized nanoparticle formulation in treating patients with HER2-positive metastatic breast cancer</td>
</tr>
<tr>
<td>NCT01835236</td>
<td>Trastuzumab and pertuzumab followed by T-DM1 in MBC</td>
</tr>
<tr>
<td>NCT01120184</td>
<td>A study of trastuzumab emtansine (T-DM1) plus pertuzumab/pertuzumab placebo versus trastuzumab [herceptin] plus a taxane in patients with metastatic breast cancer (MARIANNE)</td>
</tr>
<tr>
<td>NCT01419197</td>
<td>A study of trastuzumab emtansine in comparison with treatment of physician’s choice in patients with HER2-positive breast cancer who have received at least two prior regimens of HER2-directed therapy (TH3RESA)</td>
</tr>
<tr>
<td>NCT01702571</td>
<td>A study of trastuzumab emtansine in patients with HER2-positive breast cancer who have received prior anti-HER2 and chemotherapy-based treatment</td>
</tr>
<tr>
<td>NCT01196052</td>
<td>A study of trastuzumab emtansine (T-DM1) sequentially with anthracycline-based chemotherapy as adjuvant or neoadjuvant therapy for patients with early stage HER2-positive breast cancer</td>
</tr>
</tbody>
</table>

*Note. Based on information from ClinicalTrials.gov, 2012.*
(Blackwell, Miles, et al., 2012; Burris et al., 2011; Genentech, 2013; Krop et al., 2012). These effects are mostly grade 1 and 2, and appear to be transient and manageable. In addition, relative to the standard-of-care treatment, T-DM1 was found to have fewer grade 3 or 4 adverse events (Blackwell, Miles, et al., 2012; Burris et al., 2011; Genentech, 2013; Krop et al., 2012). A complete list of adverse events is detailed in Table 2.

Although generally reversible, thrombocytopenia was one of the most frequently reported grade 3 or 4 adverse events across the phase I and II studies of T-DM1. Thrombocytopenia occurred as early as day 1, reached a nadir by day 8, and recovered by day 18. Patients receiving multiple cycles experienced a slow downward drift in the platelet count. Thrombocytopenia was seldom associated with severe hemorrhage or platelet transfusions. Patients with thrombocytopenia reportedly needed reductions in the T-DM1 dose; however, no patients discontinued treatment because of thrombocytopenia or its sequelae (Blackwell, Miles, et al., 2012).

Elevations in hepatic enzymes were seen in all grades with T-DM1. In clinical trials using T-DM1 as a single agent, transaminisits occurred in about 50% of the patients (Blackwell, Miles, et al., 2012; Burris et al., 2011; Genentech, 2013; Krop et al., 2012). Grade 3 or higher transaminisits was seen in fewer than 10% of patients receiving T-DM1. One patient with underlying nonalcoholic fatty liver disease died of hepatic dysfunction, although whether the death was related to the administration of T-DM1 is unclear (Krop et al., 2012).

Fatigue occurred in about 65% of patients receiving T-DM1 in all grades across all studies. Grade 3 or higher occurred in less than 10%, with one grade 3 fatigue leading to discontinuation of treatment (Blackwell, Miles, et al., 2012).

Cardiotoxicity is an infrequent but potentially serious adverse event of trastuzumab; however, no reports of grade 3 or 4 left ventricular ejection fraction (LVEF) declines or symptomatic heart failure with T-DM1 have occurred. In phase II trials, T-DM1 had minimal effect on the QT interval and did not increase the risk of cardiotoxicity. Relative to trastuzumab, the absolute decreases in LVEF of 10%–20% were observed in 8% of patients in the T-DM1 arm versus 16% of patients in the trastuzumab plus docetaxel arm (Perez et al., 2010).

### Nursing Implications

Oncology nurses should be intimately aware of the indication, administration, and adverse events associated with T-DM1 treatment. For T-DM1, the common adverse events are thrombocytopenia, transaminitis, and fatigue. Early identification of these side effects can lead to prompt supportive care measures that may ensure patient safety.

#### Indication

Currently, T-DM1 as a single agent is approved via IV in the treatment of patients with HER2-positive metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination, for metastatic disease. The agent also is indicated for patients who developed disease recurrence during or within six months of completing adjuvant therapy with trastuzumab and a taxane (Genentech, 2013).

#### Administration

The dose for T-DM1 is 3.6 mg/kg, using the actual body weight, every three weeks. The drug comes in a single-use vial that requires aseptic technique for reconstitution. Only sterile water should be used to reconstitute the vial of T-DM1 (Genentech, 2013). The vial should then be gently mixed until the solution is completely dissolved. The reconstituted T-DM1 solution should be added to an infusion bag containing sodium chloride injection only and mixed gently. The infusion should be administered immediately after preparation, using a 0.22 micron in-line nonprotein adsorptive polymersulfone membrane filter. If administration of the drug must be delayed, the prepared drug should be stored at 2°C–8°C (36°F–46°F) until time of use, but no longer than four hours. At no point in the process should the solution be shaken or frozen. No other drugs should be added to the mixture (Genentech, 2013).

### Side-Effect Management

**Thrombocytopenia:** Thrombocytopenia can be a significant problem for patients with breast cancer because of the numerous clinical complications it can initiate. Bleeding is a common complication of thrombocytopenia and has the potential to become an oncologic emergency. Nurses should screen patients for signs of bleeding with each visit, such as ecchymosis, petechiae, epistaxis, hemoptysis, hematemesis, melena, hematuria, vaginal bleeding, and bleeding around wounds and vascular access lines. In addition, understanding when platelet count nadir occurs and the types of patients at risk for thrombocytopenia are essential to providing proper monitoring, counseling, and future targeted prophylaxis measures (Damron et al., 2009). Grade 3 or 4 thrombocytopenia occurs in as many as 12% of the patients receiving T-DM1, with platelet count nadir typically occurring around day 8 of each treatment cycle, with recovery before the next cycle. However, the effect of T-DM1 is cumulative, leading

### Table 2. Most Common Adverse Events With Trastuzumab Emtansine

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Any Grade (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>95.9</td>
<td>40.8</td>
</tr>
<tr>
<td>Specific events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>10.4</td>
<td>2.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Elevated alanine aminotransferase</td>
<td>16.9</td>
<td>2.9</td>
</tr>
<tr>
<td>Elevated aspartate aminotransfera</td>
<td>22.4</td>
<td>4.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>35.1</td>
<td>2.4</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>8.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>6.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>39.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5.9</td>
<td>2</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia</td>
<td>1.2</td>
<td>–</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>28</td>
<td>12.9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*Note. Based on information from Blackwell, Miles, et al., 2012; Burris et al., 2011; Genentech, 2013; Krop et al., 2012.*
Implications for Practice

- Trastuzumab emtansine (T-DM1) is an antibody drug conjugate that has been shown to be effective in the treatment of women with human epidermal growth factor receptor 2-positive breast cancer.
- Oncology nurses must have a working knowledge of the potential side effects of T-DM1 to ensure that treatment outcomes are optimized.
- Oncology nurses are vital in predicting potential adverse events that may occur during treatment with T-DM1.

to a slower recovery with subsequent cycles. This can lead to T-DM1 discontinuation, dose reduction, or platelet transfusions (Blackwell, Miles, et al., 2012).

Transaminitis: Although the vast majority of transaminase elevations were generally mild, a fatal hepatotoxicity event occurred in association with T-DM1 therapy (Blackwell, Miles, et al., 2012). Although grade 3 or higher transaminitis occurs in less than 10% of patients receiving T-DM1, monitoring of liver function tests (LFTs) during the course of treatment should be stringent. Nurses should ensure that patients have LFTs drawn at baseline and with each cycle of T-DM1 thereafter. Patients with mild hepatic impairment may receive a reduced T-DM1 dose, and therapy should be avoided in cases of severe hepatic impairment (Blackwell, Miles, et al., 2012).

Fatigue: Fatigue is a common adverse event of T-DM1, with all-grade fatigue occurring in more than 65% of patients, but grade 3 or higher occurring in less than 10% of patients receiving T-DM1. Therefore, nurses should screen the patients for fatigue prior to each cycle of therapy. In addition, nurses should assess other contributing factors, such as anemia, psychological distress, or pain. If present, the oncology nurse should educate the patient on strategies for managing fatigue, such as exercising, prioritizing chores, and pacing themselves throughout the day (Mitchell, Beck, Hood, Moore, & Tanner, 2006). Anticipatory guidance about patterns of fatigue and recommendations for self-management should be provided to the patients and families. In addition, educational interventions such as coping skills, training, and coaching should be offered to promote positive coping in patients with fatigue (Mitchell et al., 2006). The prescribing clinician should be informed of any grade 3 or higher fatigue because this may require withholding treatment or lessening the dose of T-DM1 (Blackwell, Miles, et al., 2012).

Conclusion

With the FDA approval of T-DM1 in 2013 as therapy for women with HER2-positive metastatic breast cancer, oncology nurses should become aware of its adverse events. These include, but are not limited to, thrombocytopenia, transaminitis, and fatigue. In addition, T-DM1 is being explored in a variety of different settings of breast cancer treatment, with encouraging preliminary activity in HER2-positive metastatic breast cancer. This agent is potentially expanding in use; therefore, oncology nurses must familiarize themselves with T-DM1. Oncology nurses are integral in evaluating and managing the side effects associated with this treatment.

References

Blackwell, K.L., Miles, M., Gianni, L., Krop, I.E., Welslau, M., Baselga, J., . . . Verma, S. (2012). Primary results from EMILIA, a phase III study of trastuzumab emtansine (T-DM1) versus capecitabine (X) and lapatinib (L) in HER2-positively locally advanced or metastatic breast cancer (MBC) previously treated with trastuzumab (T) and a taxane [Abstract LBA1]. Journal of Clinical Oncology. Retrieved from http://meeting.asco.org/cgi/content/short/30/18_suppl/LBA1?rss=1


