Trastuzumab Emtansine (T-DM1): Hitching a Ride on a Therapeutic Antibody

By Howard A. Burris III, MD

Overview: **The treatment of cancers with chemotherapy is frequently limited by side effects. The effectiveness may be improved by the use of monoclonal antibodies to deliver cytotoxic agents to cancer cells while limiting exposure to normal tissues. The use of antibody-drug conjugates (ADCs) is one such strategy: a drug connected by a linker to an antibody specific for a tumor antigen is the basic makeup of an ADC. Overexpression and amplification of HER2 is associated with clinically aggressive breast cancers, and the use of trastuzumab to target HER2 has been highly effective. That said, most patients with HER2-positive metastatic breast cancer will eventually have disease progression during targeted therapy. Trastuzumab emtansine (T–DM1) is a novel ADC that combines the humanized antibody trastuzumab and the potent antimicrotubule agent T-DM1 (derivative of maytansine) using a unique and highly stable linker. The potential of maytansine was found in the 1970s with clinical responses noted against breast cancer; however, substantial toxicity prohibited further development. DM1 possesses in vitro cytotoxicity 10 to 200 times greater than that of taxanes and vinca alkaloids. A phase I trial of T-DM1 for patients with heavily pretreated HER2-positive breast cancer determined a recommended dose of 3.6 mg per kilogram delivered every 3 weeks. Responses were seen in multiple patients. T-DM1 was then studied in phase II trials of patients with HER2-positive metastatic breast cancer. In a studies of 112 and 110 patients in whom disease had progressed during HER2-directed therapy, T-DM1 was associated with objective response rates of 26% and 34%, respectively. The agent was well tolerated in both trials, with most toxicities being grade 1 and 2, and no bleeding episodes or cardiac events occurring. Additional phase II and III trials are now evaluating T-DM1 in the first-line setting. In one such trial, T-DM1 was compared with standard dosing of trastuzumab every 3 weeks plus docetaxel every 3 weeks. Objective response rates were comparable and grade 3 or4 adverse events were substantially reduced in the T-DM1 arm. The anticipated selective activity and reduction in side effects were thus noted. Randomized multicenter phase III trials are ongoing, including the EMILIA trial, an open-label trial of T-DM1 compared with the U.S. Food & Drug Administration-approved regimen of capecitabine plus lapatinib. The results of studies completed to date suggest T-DM1 is active in patients who have cancer resistant to trastuzumab-based combinations.**

THE TREATMENT of many cancers is often based on the use of standard chemotherapy agents and regimens. The effectiveness of this approach is frequently limited by substantial systemic toxicities associated with these agents. The therapeutic index can be markedly improved with the use of monoclonal antibodies to deliver potent cytotoxic agents to cancer cells, thus minimizing the exposure of the agents to normal tissues. The use of antibody-drug conjugates (ADCs) is one such strategy; a cytotoxic drug connected by a chemical linker to a monoclonal antibody specific for a tumor antigen is the basic makeup of an ADC. More stable linkers and different cytotoxic agents have enabled a new generation of ADCs to enter the clinic. First and foremost, the design of an ADC centers on the selection of an antigen that is tumor-specific and accessible to antibody binding at the tumor cell.

Overexpression and amplification of HER2 is associated with clinically aggressive breast cancers that have historically had an overall poor prognosis and therapeutic resistance to traditional drugs. The use of trastuzumab to target the extracellular domain of HER2 has been highly effective in the treatment of this type of breast cancer. Multiple mechanisms for the efficacy of trastuzumab have been proposed, including inhibition of the PI3K signal transduction pathway, antibody-dependent cell-mediated cytotoxicity (ADCC), and induction of apoptosis. When combined with chemotherapy, trastuzumab improves the time to disease progression and overall survival for patients with HER2-positive metastatic breast cancer. Furthermore, mature data from four large phase III trials in which trastuzumab was evaluated in the adjuvant setting, have demonstrated marked improvements in both disease-free and overall survival. That said, most patients with HER2-positive metastatic breast cancer will eventually have disease progression

express HER2 and demonstrate sensitivity to antimicrotubule agents.

T-DM1 is a novel ADC that combines the humanized antibody trastuzumab and the potent antimicrotubule agent DM1 (derivative of maytansine) using a unique and highly stable linker.[1] T-DM1, with its ability to bind HER2 with the same affinity as trastuzumab, maintains the activity of trastuzumab in addition to providing intracellular delivery of the antimicrotubule agent DM1. It is hypothesized that when T-DM1 binds to HER2 receptors, a portion of them undergo receptor internalization, followed by lysosomal degradation. Activated DM1 is then released from lysosome into the cellular cytoplasm after antibody degradation, inhibiting microtubule assembly and causing cell death. Potent cytotoxic agents are needed to maximize the role of drug conjugates. In addition, the drug must be inactive and nontoxic in the conjugated form to avoid systemic toxicities. Few agents are able to fulfill these characteristics, including the inhibitors of tubulin polymerization (the maytansinoids and the auristatins).

The potential of maytansine as an anticancer agent was originally discovered in the 1970s with clinical responses noted against breast cancer. However, substantial and random toxicities of neuropathy and myelosuppression were prohibitive of further clinical development. Recently, an attempt at improving the therapeutic index through conjugation with trastuzumab was undertaken, leading to the

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Table 1. Summary of Clinical Efficacy Data from Trastuzumab Emtasine (T-DM1) Clinical Trials

Trial and Reference	Treatment Regimens	Number of Patients	ORR, Number of Patients (%)
TDM3569g[2]	T-DM1 0.3 tp 4.8 mg/kg q3w for previously treated HER2$^+$ MBC after previous chemotherapy and disease progression on trastuzumab	24	6/24 (25.0)
TDM4258g[3]	T-DM1 3.6 mg/kg q3w for HER2-positive MBC after previous chemotherapy and disease progression on HER2-targeted therapy	112	29 (26)
TDM4374g[4]	T-DM1 3.6 mg/kg q3w for HER2-positive MBC after previous exposure to an anthracycline, a taxane, capecitabine and 2 HER2-directed therapies in the metastatic setting	110	38 (34.5)
TDM4373g[5]	T-DM1 3.6 mg/kg q3w + pertuzumab 840 mg loading dose then 420 mg q3w, for HER2$^+$ MBC first-line treatment or after previous chemotherapy and HER2-directed therapy	67	First line: 9/22 (41), Relapsed: 19/45 (42)
TDM4450g[6]	T-DM1 3.6 mg/kg q3w		
	Or	67	32 (47.8)
	Trastuzumab 8 mg/kg loading dose then 6 mg/kg q3w + docetaxel 75 mg/m^2 or 100 mg/m^2 q3w	70	29 (41.4)

Abbreviations: MBC, metastatic breast cancer; MTD, maximum tolerated dose; NR, not reported; ORR, objective response rate; q3w, every 3 weeks.

development of DM1 (derivative of maytansine 1). DM1 possesses in vitro cytotoxicity that is 10 to 200 times greater than that of other tubulin inhibitors, such as taxanes and vinca alkaloids. A suitable linker is critical to this process, and it must have a higher degree of stability in the circulation and allow efficient release of the potent cytotoxic agent once inside the tumor cell. The cytotoxic drug DM1 is conjugated to lysine residues of trastuzumab using a unique hetero-bifunctional reagent, N-succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC), in a two-step process. Trastuzumab is initially reacted with SMCC to form trastuzuamb-MCC. Next, T-MCC is then conjugated to DM1 to make T-DM1. The thioether linker was developed to provide a bond between trastuzumab and DM1 that is more stable than hydrazone or disulfide linkers. The therapeutic index of DM1 is thus enhanced by minimizing systemic exposure to free DM1 and improving exposure to T-DM1. Before development in the clinic, the conjugate was extensively studied in preclinical models. The effectiveness of T-DM1 was established in three murine models of HER2-expressing human breast carcinoma. In contrast, little activity was seen in the normal human cells or breast cancer cells not overexpressing HER2, demonstrating the specificity of the ADC.[1]

T-DM1 was the first HER2-targeted ADC with this unique SMCC linker to be studied in patients. A phase I trial in patients with HER2-positive breast cancer that had progressed during prior trastuzumab-based therapy determined a maximum tolerated dose of 3.6 mg per kilogram, delivered every 3 weeks.[2] The dose-limiting toxicity was grade 4 thrombocytopenia that was rapidly reversible and not associated with clinically meaningful bleeding events. No cardiac events or left ventricular ejection fraction declines were noted. In addition, no alopecia greater than grade 1 was noted, further evidence for the lack of systemic toxicity.

Six of the 24 patients had an objective partial response. All patients had previously been treated with trastuzumab, with a median exposure of approximately 2 years, as well as microtubulin inhibiting agents. Of the six responses, four occurred in the nine patients treated at the maximum tolerated dose. The trial pharmacokinetics demonstrated peak free (unconjugated) DM1 plasma concentrations immediately after dosing which were low on all time points, suggesting that any systemic toxicity was unrelated to circulating unconjugated DM1. Weekly dosing was also explored and was both active and well tolerated, but it showed no particular advantage from either a dose intensity or density standpoint.

After these results, T-DM1 was studied in phase II trials of patients with HER2-positive metastatic breast cancer at the recommended dose of 3.6 mg per kilogram every 3 weeks. In a study of 112 patients who had disease progression during HER2-directed therapy, T-DM1 was associated with

KEY POINTS

- The therapeutic index for treating patients can be improved by the use of monoclonal antibodies to deliver potent cytotoxic agents to cancer cells while minimizing exposure of the agents to normal tissues.
- The use of antibody-drug conjugates (ADCs) is one such strategy; a cytotoxic drug connected by a chemical linker to a monoclonal antibody specific for a tumor antigen is the basic makeup of an ADC.
- Trastuzumab emtansine (T–DM1) is a novel ADC that combines the humanized antibody trastuzumab and the potent antimicrotubule agent T-DM1 (derivative of maytansine) with use of a unique and highly stable linker.
- In phase II studies of patients in whom metastatic breast cancer previously progressed during multiple HER2-directed therapies, T-DM1 was associated with response rates of 26% to 34% and was reasonably well tolerated.
- The results of phase II studies suggest T-DM1 can improve outcomes for patients with cancers that are resistant to trastuzumab-based combinations, and

agent was well tolerated, with most toxicities being grade 1 and 2, and no bleeding episodes or cardiac events.

A second trial was conducted in 110 patients with HER2-positive metastatic breast cancer who had received prior treatment with an anthracycline, a taxane, capecitabine, trastuzumab, and lapatinib (and had had disease progression during treatment with the most recent regimen).[4] T-DM1 demonstrated an objective response rate of 34.5% and a median progression-free survival of 6.9 months, based on independent reviews. The agent was again well tolerated in this heavily pretreated population, and no cardiac toxicity signals were noted. During these phase II trials, central review for HER2-positivity was required. Response rates were higher amongpatients with centrally verified HER2-positive tumors, whereas few responses were noted among patients with tumors that tested negatively on central review, confirming the relationship with drug activity.

Additional trials are now being done to evaluat T-DM1 asfirst-line treatment. One such trial involved 137 patients who received either T-DM1 or standard dosing of trastuzumab every 3 weeks plus docetaxel 75 or 100 mg/m^2 every 3 weeks.[5] Objective response rates were comparable, at 48% and 41%, respectively. Of note, grade 3 or 4 adverse events were substantially reduced in the T-DM1 arm (37% compared with 75%). The selective activity and proposed reduction in side effects were demonstrated in this randomized phase II trial.

Two randomized multicenter phase III trials are ongoing to evaluate the role of T-DM1 in earlier lines of therapy. MARIANNE is designed to compare the efficacy and safety of single-agent T-DM1, alone or in combination with pertuzumab, with the standard trastuzumab plus a taxane (paclitaxel or docetaxel). The exposure to pertuzumab is blinded, and the standard arm is open-label.[6]

Another study, EMILIA, is an open-label trial in which T-DM1 is being compared with the U.S. Food and Drug Administration (FDA)-approved regimen of capecitabine plus lapatinib in patients previously treated with both a taxane and trastuzumab. Interestingly, in another trial, T-DM1 is being compared with physician's choice of treatment in patients who had disease progression after multiple prior regimens. Trastuzumab alone or with chemotherapy is allowed in the physician's-choice arm.

Conclusion

The discovery of *HER2* gene amplification and the subsequent development of trastuzumab has markedly improved the prognosis for patients with HER2-positive breast cancer. Unfortunately, not all patients have a response to trastuzumab, and disease will progress in most patients with metastatic HER2-positive disease. T-DM1 meets the criteria for a successful ADC by combining the targeted effect of trastuzumab with the cytotoxic potency of DM1 using a stable linker and minimizing systemic toxicity. In addition, other tumor histologies, such as gastrointestinal cancers that are HER2-positive may be sensitive to this agent. The results of phase II studies suggest T-DM1 can improve outcomes for patients with cancers that are resistant to trastuzumab-based combinations. An aggressive portfolio of phase II and III clinical trials will help determine the role of T-DM1 in earlier lines of therapy or with combinations of other targeted agents.

Author's Disclosures of Potential Conflicts of Interest

Author	Employment or Leadership Positions	Consultant or Advisory Role	Stock Ownership	Honoraria	Research Funding	Expert Testimony	Other Remuneration
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*No relevant relationships to disclose.

REFERENCES

1. Burris HA. Trastuzumab emtansine: A novel antibody-drug conjugate for HER2-positive breast cancer. *Expert Opin Bio Ther.* 2011;11:807-819.

2. Krop IE, Beeram M, Modi S, et al. Phase I study of trastuzumab-DM1, a HER2 antibody-drug conjugate, given every 3 weeks to patients with HER2-positive metastatic breast cancer. *J Clin Oncol.* 2010;28:2698-2704.

3. Burris HA 3rd, Rugo HS, Vukelja SJ, et al. Phase II study of the antibody drug conjugate trastuzumab-DM1 for the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer after prior HER2-directed therapy. *J Clin Oncol.* 2011;29:398-405.

4. Krop I, Lorusso P, Miller KD, et al. A phase II study of trastuzumab-DM1 (T-DM1), a novel HER2 antibody-drug conjugate, in patients with HER2-positive metastatic breast cancer who were previously treated with an anthracycline, a taxane, capecitabine, lapatinib, and trastuzumab. Paper presented at: the European Society for Medical Oncology. October 10, 2010, Milan, Italy, abstract 277O.

5. Perez EA, Dirix L, Kocsis J, et al. Efficacy and safety of trastuzumab-DM1 versus trastuzumab plus docetaxel in HER2-positive metastatic breast cancer patients with no prior chemotherapy for metastatic disease: Preliminary results of a randomized, multicenter open-label phase 2 (TDM4450g). *Ann Oncol.* 2010; 21 Suppl 8:LBA3.

6. A study of trastuzumab-MCC-DM1 (T-DM1) in combination with pertuzumab administered to patients with HER2-positive locally advanced or metastatic breast cancer who have previously received trastuzumab. http://www.clinicaltrials.gov/ct2/show/NCT00875979?term=t-dm1+4373&rank=1. Accessed August 3, 2010.