

Review Article

Whether HER2-positive non-breast cancers are candidates for treatment with Ado-trastuzumab emtansine?

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ABSTRACT

The National Comprehensive Cancer Network (NCCN) has recommended Ado-trastuzumab emtansine (T-DM1) as a preferred agent for patients with human epidermal growth factor receptor-2 (HER2)-positive metastatic breast cancer and prior trastuzumab therapy. Overexpression of HER2 was reported in other cancer types such as bladder, gastric and urogenital carcinomas similar to what is discovered in breast cancer. Some preclinical studies demonstrated the potential anti-tumor effects of T-DM1 in HER2-positive non-breast cancers. There is a paucity of data over the clinical evaluation of T-DM1 in human studies of non-breast cancer patients. We review some preclinical and ongoing clinical studies that assessed the efficacy of T-DM1 administration in the treatment of non-breast HER2 positive malignancies. Performing large and well-designed trials in this area is matter of interest and highly recommended.

Keywords: Ado-trastuzumab emtansine; cancer; human epidermal growth factor receptor 2; recombinant humanized monoclonal antibody

INTRODUCTION

Overexpression of human epidermal growth factor receptor 2 (HER2) is reported approximately in 15–20% primary human breast cancers.^[1] HER2 and other member of HER superfamily, consist of tyrosine kinase receptors which have roles in the proliferation's regulation and epithelial cells' survival.^[2] HER2 is a proto-oncogene encoded by ErbB2 located on chromosome 17. It is one of the members of HER family and has four plasma membrane-bound receptors of tyrosine kinases that transmit extracellular signals to initiate cellular signaling pathways via mitogen-activated protein kinase, phosphoinositide 3-kinase, phospholipase C,

protein kinase C, and signal transducer and activator of transcription. Recently, there are some reports that HER2 is expressed in many tissues, including the breast, gastrointestinal tract, kidney, and heart. It has been suggested that possession of HER2 lead to cell proliferation and also apoptosis suppression. This irregularity induces excessive/uncontrolled cell growth and tumorigenesis.^[3-5]

In the past, patients who suffer HER2-positive breast cancer had poor outcome;^[6] however, after introducing trastuzumab, a recombinant humanized monoclonal antibody that binds to the extracellular subdomain of HER2, the destinies have changed.^[7] It is worth noting that not all the patients take advantages of trastuzumab administration, approximately

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15% of patients relapse after treatment, indicating trastuzumab resistance eventually emerges in the patients. Several resistance mechanisms have been noted to be responsible including changes in receptor-antibody interaction, induction of the downstream pathways due to increasing in signaling from either other members of the HER family or other receptors, and finally constitutive activation of downstream elements.^[8,9]

Resistance to trastuzumab as a HER2 receptor antagonist, causing concerns, and in recent years, great efforts were applied in developing therapeutic agents to either potentiate the effect of trastuzumab or target cells which have become resistant to trastuzumab.

Ado-trastuzumab emtansine (T-DM1), is an antibody-drug conjugate, in which trastuzumab linked to the fungal cytotoxic agent, mertansine. This agent was approved for the HER-positive metastatic breast cancer. Antibody-drug conjugate such as T-DM1 are composed of antigen-specific antibodies binds to cytotoxic agents in order to selectively transfer drugs to tumor cells and minimize systemic toxicity.^[10,11]

T-DM1 consists of the monoclonal antibody trastuzumab linked to a potent microtubule inhibitor (emtansine), leading to a targeted delivery of chemotherapy agent to cells that overexpress HER2.^[12]

A derivative of maytansine, emtansine (also known as DM1), is a cytotoxic agent that its mechanism of action is, microtubule inhibition similar to vinca alkaloids. Off note, emtansine are more potent than vincristine and vinblastine *in vitro* and failed to show therapeutic effect at tolerable doses.^[13]

T-DM1 binds to the HER2 receptors, and makes the HER2 receptor and drug-antibody conjugate internalized via endocytosis. Inner of cells, emtansine separates from the attached antibody by lysosomal degradation. Hence, emtansine binds to its target, tubulin, and causes cell cycle arrest and apoptosis. The role of trastuzumab is targeted delivery of emtansine and inhibition of HER2 signaling pathways.^[14,15]

T-DM1 has primarily been evaluated as a single agent in patients with metastatic HER2-positive breast cancer. There are several Phase II studies on which T-DM1 was administered every 3 weeks as a single agent.^[16-18]

Afterwards, the Phase III clinical trial, trastuzumab emtansine for HER2-positive advanced breast cancer (EMILIA), was released. This study was the only competed Phase III clinical study, in which T-DM1 administration was randomly compared to lapatinib plus capecitabine in patients with

HER2-positive, unresectable, locally advanced, or metastatic breast cancer who were previously treated with trastuzumab and a taxane. The results were in favor of the positive effects of T-DM1 administration in overall survival and median duration of response.^[19]

According to the package labeling, appropriate candidates for T-DM1 include patients who have received prior therapy for metastatic disease or those who have developed recurrent disease during or within 6 months of completing adjuvant therapy.^[20]

The National Comprehensive Cancer Network has recommended T-DM1 as a preferred agent for patients with HER2-positive metastatic breast cancer and prior trastuzumab therapy.^[21]

According to promising and hopeful results of T-DM1 administration in patients with HER2-positive metastatic breast cancer, this agent attracts attention in using in other HER2-positive non-breast cancers. New investigation unleashed the presence of HER2 receptors in other malignant organs such as bladder, gastric, and urogenital carcinomas.

In this article, we reviewed the available published data from preclinical and clinical trials over the use of T-DM1 in HER2-positive non-breast cancers. This review focuses on encouraging researchers and clinicians to perform future investigation in this era.

ADO-TRASTUZUMAB EMTANSINE IN HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2-POSITIVE GASTRIC CANCER

One of the most frequent and fatal human malignancies all over the world is gastric cancer.^[22] Since it is asymptomatic in preliminary phase, many patients suffered from gastric cancer are diagnosed when cancer develop beyond curative strategy. By recent development in molecular biology of HER2 and analyses in genomics and proteomics finding, it has now been discovered that HER2 is implicated in other severe forms of cancer, especially gastric cancer.^[23] The frequency of HER2-positive overexpression in gastric cancer estimated around 20% and is associated with poor clinical outcome.^[23] Hence, inhibiting the HER family signal transduction is likely contribute to improved survival of patients surfed from gastric cancer.

One of the milestone studies over the use of anti-HER2 antibody in the treatment of gastric cancer is trastuzumab for gastric cancer (ToGA) study.^[24] ToGA was an open-label, international, Phase III, randomized controlled trial undertaken in 122 centers worldwide. In this study, patients with gastric or gastro-esophageal

junction cancer who have overexpression of HER2 protein were included. Participants were randomly assigned to receive a standard chemotherapy regimen or chemotherapy in combination with intravenous trastuzumab. The ToGA trial is a landmark in the treatment of gastric cancer, since following the successful completion of the study, trastuzumab, in combination with chemotherapy, approved for this indication. Results showed that median overall survival was 13.8 months (95% confidence interval [95% CI] 12–16) in those received trastuzumab plus chemotherapy compared to 11.1 months^[10-13] in those received chemotherapy alone (hazard ratio 0.74; 95% CI 0.60–0.91; $P = 0.0046$). Prolonged overall survival in trastuzumab administrated group, led to the guidelines recommendation that HER2 testing should be routinely performed in patients with metastatic or recurrent gastric cancer.^[25] Due to promising results by trastuzumab combination therapy in HER2-positive gastric cancer, consequently T-DM1 became the corn stone of consideration.

In gastric cancer, T-DM1 has been evaluated in several preclinical, *in vitro* and *in vivo*, HER2 positive cell culture.^[26,27] For the first time in 2011, Barok *et al.*^[26] studied the effects of T-DM1 on HER2-positive human gastric cancer cells and xenograft tumors. *In vitro* study, four HER2-positive gastric cancer cell lines including (N-87, OE-19, SNU-216, and MKN-7) were applied. Results showed that except in SNU-216 cells, T-DM1 has superior inhibitory activity against cancer cells in comparison to trastuzumab. *In vivo* study, using same cell lines in xenograft tumors, similar positive antitumor effects was found by T-DM1. In this study, T-DM1 has a promising antitumor effect in HER2-positive gastric cancer cell lines by direct effects including apoptotic cell death and improper mitosis as well as antibody-mediated cellular cytotoxicity, even in tumors which had developed resistance to trastuzumab.

In another preclinical study, T-DM1 as a single agent showed statistically significant antitumor activity in three HER2-rich expression tumor models evaluated (NCI-N87, SCH and 4-15T). In addition, the combination of T-DM1 and pertuzumab, a HER2 dimerization inhibitor, in xenografted gastric tumors induced significant tumor regression. The possible mechanisms involved in tumor regression of combination treatment are enhancement of antibody-dependent and increase in cellular cytotoxicity by AKT, v-akt murine thymoma viral oncogene homolog 1, and signal inhibition.^[27]

Nowadays, in a clinical trial which is underway, the efficacy and safety of T-DM1 compared with standard taxane therapy in patients with HER2-positive

advanced gastric cancer was examined.^[28] In this multicenter, randomized, adaptive Phase II/III study, patients will be randomized to one of the three arms, 3.6 mg/kg T-DM1 every 3 weeks, 2.4 mg/kg T-DM1 every week, or taxane therapy (docetaxel or paclitaxel per investigator choice), for at least four cycles (12 weeks). Patients will receive study protocol treatment until disease progression, unacceptable toxicity, or withdrawal. Considered endpoints of the study are overall survival, progression free survival, duration of response, and time to gastric cancer symptom progression, as well as safety.

Using T-DM1 in HER2-positive gastric cancer is in infancy, lots of well-designed randomized control trials must be handled to clarify the real indication, proper doses, and duration of treatment by this agent.

ADO-TRASTUZUMAB EMTANSINE IN HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2-POSITIVE BLADDER CANCER

Urothelial bladder carcinoma is a major global health concern responsible for 165,000 deaths annually. Over the two past decades, there has been no statistically significant improvement in 5-year patients' survival rates for locally advanced and metastatic condition.^[29] In recent study, several mutations in the extracellular and tyrosine kinases domains of HER2, was reported in urothelial bladder cancers. HER2 amplifications were detected in 9% of bladder cancer specimens.^[30] It has been suggested that having HER2 expression correlated with inferior recurrence-free survival.^[31,32]

Furthermore, identifying of HER2 mutations and the role of this pathway in bladder carcinogenesis is desirable. More heavily reason back to the use of anti-HER2 agents, (e.g., trastuzumab, lapatinib, ado-trastuzumab emtansine, and pertuzumab) in the bladder carcinoma's treatment.

In a Phase II study done by Hussain *et al.*,^[31] the safety and efficacy (response rates, time to disease progression, survival) of trastuzumab, carboplatin, gemcitabine, and paclitaxel in advanced urothelial carcinoma with HER2 over-expression were evaluated. These patients achieved a remarkable response rate of 70% (31 out of 44 patients; 5 complete responses, and 26 partial responses), and a median time to progression and overall survival of 9.3 and 14.1 months, respectively. The primary end point of the study was cardiac toxicity that was higher than projected.

Today, it is believed that novel strategies targeting HER2 lead to outcomes of HER2 positive bladder

cancer's improvement. An encouraging preliminary study was designed by the aim of evaluating the effect of T-DM1 compared to trastuzumab in different cell lines and xenograft models of HER2 over expressing in bladder cancer. In this study, RT4V6 cell line was used as a highest HER2 expressing bladder cancer cell line. In comparison to trastuzumab, T-DM1 showed higher growth inhibition. T-DM1 made apoptosis of RT4V6 cells after G2/M arrest on cell cycle analysis. The most interesting finding was that HER2 expression was higher in cell lines with acquired cisplatin resistance's cell line. Moreover, in an orthotopic bladder cancer xenograft model, tumor growth of cisplatin resistant cells, RT112, was significantly inhibited by T-DM. These inhibitory effects are suggested to be via the induction of apoptosis compared to treatment with control IgG or trastuzumab.^[33]

Taken together, although there is a paucity of data around the administration of HER2-positive bladder cancer, but when we want to looking for emerging strategy, in bladder cancer treatment, targeting this pathway must be considered. However, T-DM1 showed promising antitumor effects in preclinical models of HER2 over expressing bladder cancer, but running several well-designed clinical trial is warranted to prove the potential positive effects of T-DM in affected patients.

ADO-TRASTUZUMAB EMTANSINE IN HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2-POSITIVE UTERINE AND OVARIAN CARCINOSARCOMAS

Carcinosarcoma, also characterized as malignant mixed Müllerian tumors, are one of the rarest and challenging tumors among all gynecological malignancies. These tumors compromise in any genital tract anatomical organs of the female body such as endometrium, ovary, cervix, vulva, vagina or fallopian tube. But among that, endometrium is the most common affected site.

On the other hands, uterine sarcoma accounts for 3–5% of all corpus uteri malignancies with an incidence in the United States of 1–4/100,000 women. On the other hands, ovarian carcinosarcoma has a worse prognosis than uterine carcinosarcoma, with a median survival rate of 8–32 months and recurrence rates of 50–100%.^[34,35]

This high rate of tumor recurrence, resistance to therapy, and the poor median survival of patients suffered from carcinosarcoma propose a need to identify more effective treatment modalities. By identifying carcinomatous component-induced tumor

growth, it is suggested that therapeutic interventions targeting cellular pathways that drive epithelial cell proliferation may potentially be beneficial against these kind of tumor. It has been reported that HER2/neu is overexpressed and amplification in uterine carcinosarcoma ranged from 17% to 43%.^[34]

Having HER2, raising the possibility that anti-HER2 therapies may be an effective modalities in the treatment of carcinosarcoma.

For the first time, English *et al.*^[36] evaluated the T-DM1 against HER2-positive uterine serous carcinoma *in vitro* followed by developing a supportive carcinosarcoma *in vivo* model.

In this study, fifteen primary uterine serous carcinoma cell lines were assessed for HER2 protein expression by the aim of immunohistochemistry and flow-cytometry. They found that near 33% of uterine serous carcinoma were positive for HER2 gene amplification and protein overexpression. *In vitro*, T-DM1, and trastuzumab cytostatic and apoptotic activities were evaluated by flow-cytometry-based proliferation assays and showed that T-DM1 was notably more effective than trastuzumab in inhibiting cell proliferation and inducing apoptosis in HER2 overexpression's cell line. Moreover, in mice model, T-DM1 treatment led to highly reduction in tumor size and longer survival comparing to trastuzumab and control group. Furthermore, T-DM1 showed effective antitumor activity in both xenograft and cell lines models. It may represent a novel treatment option for HER2-positive uterine serous carcinoma patients with disease refractory to trastuzumab and traditional chemotherapy.

The positive effects of T-DM1 against primary HER2 positive and HER2 negative carcinosarcoma cell lines were documented in another report. Nicoletti *et al.* in 2015,^[37] in a similar experimental study noted that T-DM1 was dramatically more effective than trastuzumab in inhibiting cell proliferation and in inducing G2/M phase cell cycle arrest in the HER2 expressing cell lines *in vitro* and *in vivo*.

According to new and promising finding from these two study, we can conclude that T-DM1 at least may represent a novel treatment option for the subset of HER2 positive carcinosarcoma patients with disease refractory to chemotherapy. Although these results must be reconfirm in several well-designed clinical studies.

CONCLUSION

Antibody-mediated therapy for the treatment of various human malignancies has proved efficacy in the past 30 years, and it is now one of the most successful

strategies for targeted treatment of patients suffering from hematological malignancies and solid tumors.^[38]

Not so far days, when trastuzumab, as a recombinant humanized monoclonal antibody, has been introduced to HER2 positive breast cancer treatment, hope opens door for these group of poor prognosis cancers. But today's concerns were raised along to trastuzumab resistance that was induced by malignant cells. Furthermore, resistance to HER2-directed therapies remains a challenge.^[8] Evidence suggests that combinations of HER2-directed agents by other cytotoxic ones may show additive or synergistic effects and lead to improving outcome.^[39]

By developing the antibody–drug conjugates technique, the opportunity came up to take advantage of selectively delivery of potent cytotoxic drugs by monoclonal antibodies to antigen-expressing tumor cells.

Base on the success results from experimental studies, recently, Food and Drug Administration was approved brentuximab vedotin (Adcetris®) and T-DM1 (Kadcyla®), for clinical applications of cancer treatment. Other new agents are rapidly expanding.^[39]

The clinical studies demonstrated that T-DM1 is associated with improved efficacy and safety compared with traditional chemotherapy. Several clinical trials showed the beneficiary effects of T-DM1 in the HER2-positive metastatic setting and in patients with prior exposure to trastuzumab and lapatinib.^[40]

The use of T-DM1 in other malignancies with HER2 overexpression and gene-amplification except than breast cancer is of key interest. New technical development has demonstrated that HER2 overexpression is seen in some other malignancies such as gastric cancer, bladder cancer, uterine and ovarian carcinomas. It has suggested that up to 20%, 9%, 30% of gastric, bladder, and uterine carcinomas, respectively, overexpress HER2 and is associated with significantly worse outcomes.^[23,31,34] In comparison to HER2 positive breast cancer by near 30% overexpression,^[5] these quantities are large enough to be considering in treatment modalities.

By developing the new concern around trastuzumab resistance and on the other hand, documented efficacy of T-DM1 as better therapeutic option, T-DM1 is now in the spotlight.

This review has discussed just some of the limited data showing the preclinical benefits of T-DM1 for treating HER2-positive non-breast cancer. All *in vitro* and *in vivo* study confirmed that T-DM1 administration led to prolonging overall survival and progression-free survival. Hence, by considering

these promising results, it is time to assessed clinical responses by designing Phase I/II clinical trials. If future clinical results can demonstrate the similar results as preclinical data, then new era in the treatment of any HER2-positive non-breast cancer and survival prolongation will be created.

In March 2011, based on the results of the ToGA trial,^[24] trastuzumab was intensively approved in gastric cancer. The introduction of trastuzumab made new term in gastric cancer entitled “HER2-positive gastric cancer,” similar to HER2-positive breast cancer. This discovery gives us a clue that HER2-positive non-breast cancers are developing and identifying. Finding new agents for treatment of them are important future issues.

As an example, new advancing in the knowledge of urothelial carcinoma pathophysiology and underlying molecular mechanisms showed the most relevant molecular pathways that might demonstrate therapeutic potential.^[34] The most important relevant overactive signaling networks are fibroblast growth factor receptor, PI3K/AKT/mTOR, and HER2. Any development in identifying the signaling networks on each cancer types leads to use of another possible effective treatment modality in the future. Furthermore, if clinical trials reach to same prominent results as we reviewed. In the near future, we will see the routine use of trastuzumab conjugated agents such as T-DM1 in chemotherapy regime of other HER2-positive non-breast malignancies.

We strongly recommend managing well-designed control trials to clarified future additional data, over the more precise number and roles of HER2 receptors as a therapeutic target in HER2-positive non-breast malignancies. We need to know many details about the best administrated regime in HER2-positive non-breast malignancies. While we are in the beginning of way and it is soon for any important decision.

AUTHORS' CONTRIBUTION

Azadeh Moghaddas was responsible for literature review, data collection, and preparing and editing the manuscript draft. Ali Borhani helped in data gathering.

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Conflicts of interest

A part of this study was presented in 18th International Conference on Non Communicable Diseases (ICNCD 2016) which was held in Amsterdam, The Netherlands.

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