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Ado-trastuzumab emtansine for HER2 Positive Breast Cancer

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Introduction to Breast Cancer

Breast cancer is the leading cause of cancer related death in women between the ages of 20 and 59 in the United States.¹ In women of all ages, breast cancer is the most frequently diagnosed cancer and second only to lung cancer with regard to cancer related deaths.² Women have a 12.3 percent lifetime risk of being diagnosed with breast cancer,³ and in 2012, there were 232,340 new cases and 39,620 deaths due to breast cancer.² The five year survival rate for localized breast cancer is 98 percent; however, as nearby lymph nodes and distant lymph nodes with organs become involved, the survival rate drops to 84 percent and 24 percent respectively.² The incidence of breast cancer varies across racial groups with Caucasians having the highest incidence. This is thought to be due to lifestyle, reproductive factors and increased access to screening.1 Despite this fact, African Americans have the highest rate of mortality, which could be attributed to more advanced stages at diagnosis and possibly more aggressive biologic features.¹ Breast cancer is staged based on three factors: the size of the primary tumor, presence/extent of lymph node involvement, and presence/ extent of metastases. The larger the tumor, the more lymph node involvement and a greater extent of metastases all lead to a more advanced stage of cancer.1 However, there are several other factors affecting the final prognosis.

Poor prognostic factors include the patient being less than 35 years old at the time of diagnosis (because there is an increased likelihood of the breast cancer being more aggressive) and alcohol use, especially in patients who are postmenopausal or obese. Factors which may lead to a better prognosis include the patient following a low fat diet, exercising at least moderately on a regular basis, and maintaining a healthy weight. Every woman diagnosed with breast cancer is tested to see if she has hormone (estrogen and progestin) receptor positive cancer. While this is not a strong prognostic factor, it does predict response to hormone therapy.1 Likewise, it is important to test for human epidermal growth factor receptor 2 (HER2) gene status; this gene encodes a transmembrane tyrosine growth factor receptor, and is expressed at low levels in the epithelial cells of normal breast tissue. The HER2 receptor is expressed on the cell surface and when activated signals the cell to grow and divide more rapidly. In 20 to 30 percent of breast cancers, this gene is overexpressed and is generally associated with a poorer prognosis. Presence of the HER2 gene indicates the cancer has the potential to respond to trastuzumab therapy.¹ Since HER2 is a poor prognostic factor for a cancer with the potential to be highly fatal if not identified early, it is important to find an effective treatment. While trastuzumab, a recombinant humanized monoclonal antibody that binds to HER2 and inhibits signaling, may improve outcomes in these patients, there are still many patients who fail this therapy. Historically there have been no consistently effective regimens for these patients who have failed trastuzumab therapy.

Traditional Treatments

Though not consistently effective, traditional regimens for HER2 positive breast cancer that does not respond to trastuzumab include combination lapatinib and capecitabine, combination trastuzumab and capecitabine, and combination trastuzumab and lapatinib.⁴ Bartsch et al. performed a study regarding combination trastuzumab and capecitabine in patients who had already been treated with several chemotherapy regimens and had failed.5 This study found the median time to progression was eight months and the median overall survival was 24 months. Overall, the combination was welltolerated with the most common toxicities being diarrhea and hand-foot syndrome, with seven out of 40 patients in the study requiring a dose reduction of 25 percent. A study conducted by Geyer et al. utilizing lapatinib and capecitabine in combination found the median time to progression was 8.4 months and overall response rate was 22 percent. The most common adverse effects were diarrhea, hand-foot syndrome, nausea, vomiting, fatigue and rash. However, 22 of the women were forced to drop out because they developed intolerable side effects.⁶ The combination of lapatinib and trastuzumab showed a median progression free survival of 12 weeks with a median overall survival of 51.6 weeks. Similarly to the other combinations, the most common adverse effects with this combination were diarrhea, rash, nausea, fatigue, vomiting and dyspnea. In addition, one patient died of cardiac failure that was attributed to the treatment, while all other deaths were considered to be independent of treatment.7 While these therapies are beneficial in many patients, there are still many patients for whom the treatments have failed. The limitations of these regimens, such as combination therapy and the side effects associated with each agent, create a need for a better treatment option, preferably monotherapy. According to the National Comprehensive Cancer Network (NCCN) breast cancer guidelines, ado-trastuzumab emtansine (T-DM1 or Kadcyla®) has become first-line treatment for HER2 positive breast cancer that does not adequately respond to trastuzumab treatment.4

Mechanism of Action and Resistance for Trastuzumab and Lapatinib

Trastuzumab is a monoclonal antibody that binds to the extracellular domain of the HER2, potentially causing internalization and receptor down-regulation.^{8,9} The antibody is able to decrease the phosphatidylinositol 3-kinase-phosphatase and tensin homolog (PI3K-PTEN) signaling pathway, thus inhibiting AKT (protein kinase B, PKB) activation and therefore cell proliferation.^{10,11} Immune mechanisms induced include antibody-dependent cellular cytotoxicity (ADCC) and HER2 major histocompatability complex class I (MHCI) presentation to cytotoxic T cells. Additionally, the cell cycle is stopped in the G_1 phase by trastuzumab, the first gap of interphase marked by cell growth and protein synthesis in preparation for deoxyribonucleic acid (DNA) synthesis.^{12,13} Overall, this results in reduced proliferation and death of HER2 positive tumor cells. Unfortunately, the body has been able to create multiple mechanisms of resistance to render HER2 positive cancer unresponsive to trastuzumab. Some methods of resistance include reduced ADCC, concealment of the trastuzumab epitope on the receptor, expression of a constitutively active, smaller version of the receptor, p95HER2, and most notably, changes in the PI3K-PTEN-AKT pathway.^{11,14,15,16}

Lapatinib is another therapy used for treatment of HER2 positive cancer that, although it has a different mechanism of action from trastuzumab, it is affected through the same resistance mechanisms. This suggests patients refractory to trastuzumab likely also become refractory to lapatinib.^{17,18} As a tyrosine kinase inhibitor, lapatinib is able to inhibit both epidermal growth factor receptor (EGFR) and HER2 by binding to the kinase and preventing it from phosphorylating second messengers, such as AKT, that are responsible for cellular proliferation.¹⁹

Resistance to capecitabine currently does not seem to be a problem; however, since it is used in combination with either of the above two medications, resistance to these decreases the efficacy of therapy with capecitabine.²⁰ Resistance to these therapies, in addition to burden of combination therapy, side effect profiles, and tolerability issues prompted the development of T-DM1.

Novel Mechanism of Action of Ado-trastuzumab em-

T-DM1 is an antibody-drug conjugate (ADC) that has been developed as an alternative to traditional HER2 therapies in an attempt to lessen systemic chemotherapy toxicities by transporting cytotoxic molecules specifically into tumor cells.²¹ This specific ADC is a human epidermal growth factor receptor inhibitor, trastuzumab, linked to DM1 (derivative of maytansine 1 or N-methyl-N-[3-mercapto-1- oxopropyl]-Lalanine ester of maytanisol), which inhibits microtubule polymerization and induces depolymerization by binding tubulin, the building blocks of microtubules.^{21,22} Microtubules play a vital role in cellular structural support and mitosis, where they form the apparatus responsible for alignment and separation of the chromosomes. By inhibiting not only the production, but also inducing the disassembly of microtubules, the integrity of the cell is compromised and it cannot divide, eventually leading to apoptosis. Maytansine is a highly potent plant-derived antibiotic that displays antimitotic activity, but produces systemic toxicities too great to be given as traditional chemotherapy.²³ The ability to use ADCs prompted development of maytansine derivatives, such as DM1, to be delivered directly into cancer cells.²⁴ While previous attempts at maytansine conjugates were linked using disulfide bonds that were not readily cleaved by intracellular lysosomes and endosomes, trastuzumab is connected to DM1 by a thioester linkage that has incorporated a cyclohexane

carboxylate spacer.²¹ Following HER2 receptor binding to the antibody trastuzumab and internalization into the cell, proteolytic degradation separates T-DM1 at the thioester linkage. Upon cleavage of the thioester, a zwitterionic active metabolite, lysine-Nɛ-4-(N-maleimidomethyl) cyclohexane-1-carboxylate (MCC)-DM1 is released.^{21,25} The charged nature of this molecule greatly reduces its ability to cross cell membranes, therefore keeping it in the HER2 positive cells, and reducing systemic toxicities.

T-DM1 activity has been tested in tissues that overexpress HER2 and are refractory to other targeted HER2 therapies such as trastuzumab and lapatinib, where it has been shown to have direct cytotoxicity.²¹ The ability of T-DM1 to precipitate ADCC and mediate immune response, as well as binding affinity to the HER2 receptor, is similar to trastuzumab.26 Additionally, the ADC works by other mechanisms differentiating T-DM1 from the unconjugated trastuzumab.27 DM1 is able to be delivered by trastuzumab into cells with HER2 overexpression, thereby inhibiting microtubule polymerization that would eventually lead to apoptosis.²¹ Because T-DM1 is able to directly target specific tumor cells, it is able to be much more potent than other chemotherapies, concurrently minimizing systemic cell death.^{21,22,26} Another feature of the ADC is increased clearance by a number of mechanisms, including deconjugation, proteolytic degradation, and CYP450 metabolism causing its half-life to be considerably shorter than unconjugated trastuzumab (~four days versus three to four weeks).^{27,28} Lastly, the DM1 portion of the ADC is active, even in cells with constitutively active PI3K signaling, which is believed to be a cause of trastuzumab resistance.26

Indications

According to the NCCN guidelines, first-line therapy for metastatic or recurrent breast cancer that is HER2 positive includes pertuzumab and trastuzumab plus either docetaxel or paclitaxel.⁴ This therapy fails for some patients, and a change in therapy is required. T-DM1 is indicated for patients with metastatic breast cancer that is HER2 positive and has been exposed to trastuzumab and a taxane. If the patient has recurrent breast cancer within six months of completing chemotherapy, T-DM1 as monotherapy is the preferred regimen. Although T-DM1 has no contraindications at this time, it should not be used in pregnant females.²⁸ Additionally, nursing mothers should discontinue either T-DM1 or nursing based on importance of treatment for the mother.

Efficacy

Krop et al. performed a study of T-DM1 as monotherapy in a phase I, dose escalation trial where patients received 0.3 mg/kg initially and were titrated up to 4.8 mg/kg.²⁹ The results showed patients had a maximum tolerable dose of 3.6 mg/kg every three weeks based on the side effect of transient, grade 4 thrombocytopenia (platelet count <25,000 /µL) associated with doses of 4.8 mg/kg. Patients who were treated with the maximum dose had a 73 percent chance of having a significant benefit, objective partial tumor response plus stable disease at six months, compared to those patients who received doses of 2.4 mg/kg or less of T-DM1.²⁹ Barginear et al.

performed an analysis of several studies comparing T-DM1 to lapatinib/capecitabine combination and concluded that T-DM1 prolongs progression free survival.³⁰ Patients treated with T-DM1 had 9.6 months of progression free survival compared to 6.4 months in patients that were treated with a combination of lapatinib and capecitabine for a p value of <0.0001. Likewise, the authors concluded the median time to symptom progression was longer with T-DM1 (7.4 months) compared to lapatinib/capecitabine (4.6 months).30 Verma et al. studied 991 patients with HER2 positive and locally advanced or metastatic breast cancer who were randomly assigned to either T-DM1 or lapatinib plus capecitabine. Similar to the previous studies, the investigators also demonstrated that T-DM1 improved progression free survival and median overall survival compared to lapatinib and capecitabine.12 The one year survival rate in patients treated with T-DM1 was 85.4 percent compared to 78.4 percent for the lapatinib/ capecitabine group.³¹ More patients in the lapatinib/ capecitabine group required a dose reduction due to intolerable side effects. T-DM1 has statistically been shown to be more efficacious than lapatinib and capecitabine in combination in patients previously exposed to trastuzumab.

Safety and Quality of Life

The most common side effects associated with T-DM1 are consistent with many chemotherapy regimens, which include fatigue (37 to 65 percent), anemia (25 to 50 percent), and hypokalemia (2 to 24 percent).27 While T-DM1 may cause serious adverse effects (such as thrombocytopenia and elevated serum concentrations of aspartate and alanine aminotransferase), the rate at which these occur is lower in T-DM1 compared to lapatinib treatment.³¹ Elevation of aspartate aminotransferase was reported in 4.3 percent of patients and alanine aminotransferase was elevated in only 2.9 percent of patients. Thrombocytopenia was more common but still only occurred in 12.9 percent of the 495 patients assigned to T-DM1. The most common time for thrombocytopenia to occur was within the first two cycles of T-DM1, and with therapy modification, most were able to continue the therapy with only 10 patients dropping out .³¹ In a study by Hurvitz et al., thrombocytopenia of any grade occurred in most patients on a dose above 1.2 mg/kg; however, this was most often transient. The highest incidence of grade 3 (platelet count 25,000 to 50,000 /µL) or higher thrombocytopenia happened in 11.9 percent of patients who were being treated with T-DM1 and pertuzumab.24

Additionally, Hurvitz et al. assessed the quality of life of patients treated with T-DM1 using the Functional Assessment of Cancer Therapy-Breast (FACT-B) trial outcome index, which assesses physical, functional, emotional, and social/ family well-being, in addition to breast cancer symptoms. The authors determined that those patients treated with T-DM1 had an improved quality of life across all aspects of the index compared with those treated with trastuzumab and docetaxel.²⁴

Pharmacist Role

Pharmacists have an important role in advising physicians on when to use T-DM1 over alternative therapies. The main advantage of T-DM1 over traditional treatments for HER2 positive breast cancer is the increased time to progression and increased overall survival compared to the three alternatives for breast cancer that has already been exposed to anti-HER2 treatment. The use of additional anti-HER2 therapies after T-DM1 showed no benefit over only using T-DM1 in patients previously exposed to trastuzumab therapy. Therefore, decisions for further anti-HER2 treatment after T-DM1 should be based on patient and physician preference.³² The maximum tolerated dose of T-DM1 was determined to be 3.6 mg/kg every three weeks, which is the current NCCN breast cancer guidelines recommendation.^{4,30}

Although T-DM1 is an intravenous therapy and would be administered in an inpatient setting, pharmacists can play a key role in educating both physicians and patients about the common adverse effects and special considerations. Important counseling points would be common adverse effects of T-DM1, most notably nausea, fatigue, musculoskeletal pain, thrombocytopenia and headache. Physicians should be advised that certain adverse effects, such as thrombocytopenia, hepatotoxicity and left ventricular cardiac dysfunction may require a dose reduction, longer duration between doses, or discontinuation of therapy depending on severity and patient tolerability. T-DM1 is pregnancy category D and, if T-DM1 is indicated, use should be delayed until after the child is born. It is important to educate patients on risks to the fetus and the importance of utilizing proper birth control during treatment with T-DM1 and for six months following termination of T-DM1.²⁸

The FDA recently issued a safety warning to all health care professionals that the generic name for Kadcyla^M (adotrastuzumab emtansine) was incorrectly entered in some medication electronic systems and may be confused with the generic for Herceptin^M (trastuzumab). This is a potential risk in any system that uses generic names. It is critical that the pharmacist clarify orders for these products to prevent risk to patients, since the dosing and schedules for these two medicines are different.³³

Conclusion

Breast cancer is the second leading cause of cancer related deaths in women; therefore, it is important to find adequate treatment that is tolerated by patients.² T-DM1 has been shown to be effective in increasing time to progression in patients that have developed targeted HER2 treatment resistance.27 In addition, T-DM1 has a decreased risk of adverse effects compared to other agents utilized in the same line of therapy, as well as having the benefit of being monotherapy.24,27,31 T-DM1 should be considered in eligible patients due to the increased overall survival and the decreased rate of adverse effects such as thrombocytopenia.28 However, cardiotoxicity and hepatotoxicity are possible and may require dosage adjustments or discontinuation based on severity, as well as monitoring of left ventricular ejection fraction and liver function tests (LFTs). T-DM1 has no contraindications but is not recommended during pregnancy or in nursing mothers. After FDA approval of T-DM1 on Feb. 22, 2013, the NCCN included it in the guidelines as preferred treatment for HER2 positive cancer that had been exposed to trastuzumab previously and should be utilized in therapy.4, 34

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