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Ado-trastuzumab Emtansine – The Monoclonal Drug Conjugate in Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer

Abstract

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer comprises around 20%–25% of breast cancers. With the discovery of trastuzumab, there was a marked improvement in the survival of patients with HER2-positive breast cancer both in curative and metastatic settings. However, patients with trastuzumab will eventually progress or develop recurrences. Newer anti-HER2 therapies have evolved to improve the outcome of this group of patients. One of them is monoclonal antibody–drug conjugate which is ado-trastuzumab emtansine.

Keywords: *Breast cancer, Human epidermal growth factor receptor 2 positive, trastuzumab emtansine*

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Introduction

Human epidermal growth factor receptor 2 (HER2)-directed therapy is the standard of care in HER2-positive breast cancer.[1] Initially, trastuzumab was the only agent approved in HER2-positive breast cancer patients.[2,3] However, over time, lapatinib, ado-trastuzumab emtansine (T-DM1), pertuzumab, and neratinib have received the Food and Drug Administration approval for this group of patients. Out of these, T-DM1 is a monoclonal antibody–drug conjugate where trastuzumab is covalently linked to mertansine, which is an antimitotic agent. Mertansine is a maytansine derivative which is known as maytansinoid also known as DM1.[4]

Mechanism of Action

Both the components of the drug conjugate are responsible for the action of the drug. Trastuzumab component of the drug binds selectively to the HER2-expressing breast cancer cells and thus tries to minimize systemic exposure of DM1 to reduce systemic toxicity. Binding of trastuzumab leads to antibody-dependent cell death along with downregulation of cellular pathways. Once the drug is attached to the cell surface HER2 receptor, there is receptor-mediated endocytosis of the drug DM1. DM1 gets released by the proteolytic enzymes in the lysosome. DM1 causes inhibition of the assembly of microtubules leading to cell death.[4]

Pharmacokinetics

Both the components of the drug achieve maximum body concentration (C_{max}) at the end of the infusion of the drug. The microtubule component of the drug binds to the plasma proteins with great affinity. DM1 component of the drug gets metabolized by CYP3A4/5 enzymes, and it does not induce or inhibit the cytochrome enzymes. The elimination half-life ($t_{½}$) of the drug is 4 h, and it was found that there is no accumulation of the drug in the body in spite of repeated infusions. Studies have shown that body weight has the maximum influence on the clearance of T-DM1, and thus, body weight-based dosing is appropriate. Dose adjustment based on hepatic and renal impairment is not recommended.

Approval

T-DM1 was initially approved for metastatic breast cancer (MBC). Recently, the drug has obtained approval for adjuvant treatment in early-stage breast cancer.

Dose

The dose of T-DM1 is 3.6 mg/kg intravenously over 3 weeks. In metastatic

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Table 1: The results of ado-trastuzumab emtansine trials

Name of the trial	Setting	Design	PFS (months)	OS (months)
EMILIA	Second-line metastatic/progressed within 6 months of adjuvant trastuzumab	T-DM1 versus lapatinib + capecitabine	9.6 versus 6.4[5] HR - 0.65	29.9 versus 25.9[6] HR - 0.75
TH3RESA	≥2 lines of therapy in metastatic	T-DM1 versus physician choice	6.2 versus 3.3[8] HR - 0.52	22.7 versus 15.8[7] HR - 0.68
MARIANNE	First-line metastatic	T-DM1 versus T-DM1 + P versus T + H	14.1 versus 15.2 versus 13.7[9]	53.7 versus 51.8 versus 50.9[10]

T-DM1 – Ado-trastuzumab emtansine; HR – Hazard ratio; PFS – Progression-free survival; OS – Overall survival

settings, the drug has to be continued till disease progression or unacceptable toxicity. In adjuvant settings, it has to be given for 14 cycles.

Evidence for Using Trastuzumab Emtansine in Breast Cancer

T-DM1 was initially used in patients with HER2-positive MBC who have progressed on trastuzumab and taxane in metastatic setting or those who have progressed within 6 months of completing adjuvant trastuzumab. In the EMILIA trial, patients were randomized to receive either T-DM1 or lapatinib and capecitabine combination. T-DM1 arm had a better progression-free survival (PFS) and overall survival (OS) than the combination arm, as shown in Table 1.[5,6] Even in patients with heavily pretreated HER2 MBC, T-DM1 was found to have better PFS and OS than the comparator arm in the TH3RESA trial, as shown in Table 1.[7,8]

T-DM1 has been tried as first-line therapy in HER2-positive breast cancer patients who are not eligible to receive taxane-based therapy. MARIANNE study is a Phase 3 randomized trial where patients were randomized to receive trastuzumab + taxane, T-DM1 with pertuzumab, and T-DM1 with placebo. It was a noninferiority designed clinical trial with the primary endpoint being PFS. T-DM1 arms were found to have PFS which is noninferior to the trastuzumab and taxane combination. Updated analysis has shown the median OS to be similar among all the arms, as shown in Table 1. T-DM1 was found to be better tolerated among the patients.[9,10]

T-DM1 has been used in early-stage breast cancer post neoadjuvant settings. In the landmark KATHERINE trial, patients who were treated with taxane and trastuzumab irrespective of anthracycline and did not achieve complete pathological response were randomized to receive either T-DM1 or trastuzumab for additional 14 cycles. The primary endpoint was invasive disease-free survival (IDFS). Three-year IDFS was 88.3% in the T-DM1 arm compared to 77% in the trastuzumab arm (hazard ratio – 0.5, $P < 0.001$).[11]

Adverse Effect

The most common Grade 3–4 side effect of the drug is thrombocytopenia and increase in liver enzymes and peripheral neuropathy and anemia. Dose modification has to be done accordingly. The first step is to reduce the dose to 3 mg/kg followed by 2.4 mg/kg. Further dose modification is not advised, and it is recommended to stop the drug permanently.[12] The incidence of left ventricular dysfunction with T-DM1 is found to be 1.8% in patient population.[5] Standard monitoring of left ventricular function every 3 months with echocardiography is recommended when the patient is on T-DM1.

Conclusion

T-DM1 has shown encouraging and promising results both in metastatic and early breast cancer. However, the high cost of the drug has limited the usage of the drug to the common people.

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Conflicts of interest

There are no conflicts of interest.

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