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Abstract

Recent estimate revealed that in the year 2012, about 227,000 American women suffered from metastatic breast cancer (mBC). The U.S. Food and Drug Administration (FDA) have approved ado-trastuzumab emtansine (T-DM1) on 22 February 2013 for the treatment of human epidermal growth factor receptor (HER2)-positive mBC who has previously been treated with trastuzumab and a taxane. T-DM1 received the European Commission approval on November 2013 based on results from the pivotal Phase III EMILIA trial and Switzerland is the first country which has the marketing permission for T-DM1 in Europe. In September 2013, it received marketing approval in Japan based on results from a Japanese Phase II trial and the EMILIA Phase III trial and also approved by Health Canada. T-DM1 is an antibody-drug conjugate (ADC). ADC consists of monoclonal antibody trastuzumab, which covalently linked with DM1 (cytotoxic, microtubule inhibitor) by mitotic checkpoint complex (MCC) linker. The ADC delivers the toxin specifically to tumor cells. DM1 binds to tubulin, and it disrupts microtubule network in the cell. Cell cycle arrest and apoptotic cell death were occurred. In clinical trials, patients (991) were randomly assigned in a 1:1 ratio to kadcyla or lapatinib plus capecitabine. The recommended dose is 3.6 mg/kg every 3 weeks (21-day cycle).

Key words: Ado-trastuzumab emtansine, antibody-drug conjugate, DM1, human epidermal growth factor receptor 2 positive metastatic breast cancer, kadcyla, linker mitotic checkpoint complex, overall survival, progression-free survival, TD1

INTRODUCTION

Breast cancer (BC) is main cancer seen in women of various developed and developing countries across the globe. BC is the most important reason of cancer deaths in females between 20 and 59 years. About 39,620 women were died due to BC in 2013 and approximately 2,240 men were identified with BC, and out of this, 410 men were died in 2013. Metastatic BC (mBC) is the proliferation of cancer cells from the actual site where cancer was first occurred in the body. It is connected with expanded severity and is chiefly incurable. The median survival for a woman with this form of BC is about 2 years. In the United States, according to a survey report of 2012, BC was the most common cancer, about 227,000 American women suffered from mBC. Ductal carcinoma and lobular carcinoma are two most common types of BC. About 1 of every 10 women BC has lobular carcinoma. Each year about 70,000 persons in Europe were diagnosed with advanced BC, of whom approximately one in five will have Human epidermal growth factor receptor (HER2)-positive disease. In Canada, BC is the preponderance ordinary cancer diagnosed in women. A rating of 26% of all cancer cases, BC is the second leading reason of death in women. Approximately, 65 women are diagnosed with BC every day and every week, and it declares the lives of 100 Canadian women every week. BC may be affected by various factors [Table 1 and Figure 1].

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Non-Hispanic white women have higher incidence rates of BC compared to African American women. Figure 2 explains BC incidence and death rates by race and ethnicity during 2004-2008 and 2003-2007.

BC incidence and death rates by race and ethnicity during the most recent period (2006-2010) is presented in Figure 3.

The epidermal growth factor receptor is a prototype compound of the category I superfamily of receptor tyrosine kinases (RTKs), which consists HER1, HER2, HER3, and HER4. All compounds have a ligand-binding region, a single membrane-spanning region and a cytoplasmic intracellular tyrosine-kinase-containing domain. HER2 is a transmembrane RTK that is part of a complex signal transduction network involved in cell differentiation, proliferation, and survival. HER2 is expressed in normal epithelial tissues at relatively low levels in healthy adults, but it is overexpressed in approximately 20% of tumors from patients with positive mBC. In this mBC, the cancer cells make much of a protein known as HER2/neu. In U.S, it has been found that the maximum numbers of mBC patients are HER2-positive because cancer cells display abnormally high numbers of HER2 proteins on their surface.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Description</th>
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<tbody>
<tr>
<td>Age</td>
<td>Age is a crucial factor for breast cancer. It has been found that aged women have a maximum tendency of breast cancer than younger.[6,7] 79% of novel cases and 88% of breast cancer deaths occurred in women 50 years of age and older. The middle age at the moment of breast cancer diagnosis was 61 years for the period of 2006-2010[8]</td>
</tr>
<tr>
<td>Sex</td>
<td>In various countries, it has been found that the number of breast cancer patients is much more in women than men. In 1999-2009, women have more usual normalized occurrence rates approx 60.5/100,000 of breast cancer than men 1.4/100,000. Males have 45 times lesser the average normalized occurrence rates than females[7,9]</td>
</tr>
<tr>
<td>BRCA&lt;sub&gt;1&lt;/sub&gt; and BRCA&lt;sub&gt;2&lt;/sub&gt;</td>
<td>BRCA&lt;sub&gt;1&lt;/sub&gt; and BRCA&lt;sub&gt;2&lt;/sub&gt; are autosomal dominant genes which play a very important role to cause breast cancer.[7,10] It is expected that 5-10% of breast cancer cases effect from BRCA1 and BRCA2, including inherited mutations. It is estimated that about 15%-20% of breast cancers occurs due to BRCA1 or BRCA2 gene mutations, 44% and 78% of women with BRCA1 mutations and between 31% and 56% of women with BRCA2 mutations will increase breast cancer[11-14]</td>
</tr>
<tr>
<td>Dietary factors</td>
<td>Alcohol- Excess drinking cause MBC.[15] It has been proved that alcohol utilization enhances the danger of breast cancer in women (about 7%-12% for each 10 g of alcohol drink/day). The enhanced danger of breast cancer is dose-dependent, and alcohol increases this risk by rising androgen and estrogen intensity. Alcohol consumption has a good relationship with raised danger for ER+than ER- breast cancers[16-21]</td>
</tr>
<tr>
<td></td>
<td>Fat intake- low fat intake decreases the risk of mBC[22] Specific dietary fatty acids- higher level of monosaturated fatty acids (oleic acid) in the erythrocyte membranes of postmenopausal women caused mBC Calcium- cancer prevention study II Nutrition cohort concluded 20% lower risk of breast cancer with 1250 mg of calcium intake Vitamin D- reduces the risk of breast cancer</td>
</tr>
<tr>
<td>Obesity and lack of exercise</td>
<td>It has been found that obesity increased risk of developing breast cancer. Obesity associated raised the possibility of relapses in breast cancer patients behind menopause. It is proposed that the danger of breast cancer is about 2 times superior in obese women compared to women who are normal weight. It has been found by a large meta-analysis that in the middle of women ages 40-49, the threat of increasing breast cancer was about 26% lower in obese women than in lean women. Those women do not engage constantly a number of physical actions and exercise increases breast cancer hazard approximately 30% or more. There is proof that lack of exercise increased the tendency of breast cancer[7,23,24]</td>
</tr>
<tr>
<td>Hormones</td>
<td>Increased levels of progesterone have the tendency to decrease the risk of breast cancer, but increased levels of estrogen hormone increased risk of breast cancer.[25,26] Many epidemiological learning incompatibly demonstrated amalgamation flanked by serum insulin or C-peptide and the risk of breast cancer. Elevated serum insulin intensity and Insulin-like growth factor-I are associated with a raised possibility of relapses in breast cancer.[7]</td>
</tr>
<tr>
<td>Tobacco</td>
<td>According to American Cancer Society researchers, It is estimated that those women who never smoked had a 12% lower danger of breast cancer than other women[27]</td>
</tr>
</tbody>
</table>
The association between HER2 overexpression and tumor pathogenesis in BC, together with the accessibility of the extracellular domain of the receptor, has made HER2 a suitable target for antibody therapy.\cite{29,31-33} Previously three drugs, namely, trastuzumab (in 1998), lapatinib (in 2007), and pertuzumab (in 2012) have been approved by Food and Drug Administration (FDA) to treat HER2-positive BC.\cite{34} Trastuzumab [Figure 4a] a humanized anti-HER2 monoclonal antibody and lapatinib [Figure 4b] is a twin RTK inhibitor that reduces both HER1 and HER2.\cite{35,36} Pertuzumab (humanized monoclonal antibody) binds to the extracellular domain of HER2.\cite{37}
ADO-TRASTUZUMAB EMTANSINE (T-DM1) AN FDA APPROVED DRUG

TDM1 is a new (fourth) approved drug, and it is used for the treatment of HER2-positive mBC in patients who have been treated previously with trastuzumab and a taxane, and who have already been treated for mBC or developed tumor recurrence within 6 months of adjuvant therapy. It is marketed in many countries such as Europe, Canada, US, Switzerland, and Japan. T-DM1 has been approved by U.S. FDA in February 2013.[38-40] T-DM1 received European Commission approval on November 2013 based on results from the pivotal Phase III EMILIA trial and Switzerland is the first country which has the marketing permission for T-DM1 in Europe.[5] In September 2013, it received marketing approval in Japan based on results from a Japanese Phase II trial and the EMILIA Phase III trial and also approved by the Health Canada.[41]

T-DM1 is also known as TDM1, and the trade name is kadcyla. TDM1 is an antibody-drug conjugate (ADC) and a highly complex prodrug. ADC is composed of an antibody trastuzumab (humanized anti-HER2 IgG1), a stable, non-reducible linker mitotic checkpoint complex (MCC) (N-Succinimidyl-(maleimidomethyl) cyclohexane) and tubulin polymerization inhibitors (DM1). The source of ADC can be outlined reverse over a century to the Paul Ehrlich (German physician and scientist), who suggested the theory of selectively distributing a cytotoxic medicine to a tumor through a targeting agent (ADC). DM1 is obtained from the extremely effective antitumor agent maytansine.

Trastuzumab is a recombinant monoclonal antibody produced by mammalian (Chinese hamster ovary) cells. The small molecular components (DM1 and MCC) are produced by chemical synthesis. Trastuzumab [Figure 5] alone stops the growth of cells by binding to the HER2/neu receptor. TDM1 contains an average of 3.5 DM1 molecules per antibody.[42-44] Features and properties of this are shown in Table 2.
PHARMACODYNAMIC AND MECHANISM OF ACTION

TDM1 is an ADC. ADC consist of monoclonal antibody trastuzumab which covalently linked with DM1 (cytotoxin, microtubule inhibitor) by the MCC linker (Stable, non-reducible). On binding to HER2, The HER2–T-DM1 complex is endocytosed by receptor-mediated process and ultimately fused with a lysosome where it undergoes proteolytic degradation with the release of the active DM1, the trastuzumab component and exerts its antitumor effects [Figure 6]. The primary active metabolite, lysine–SMCC–DM1, does not readily cross the plasma membrane and therefore does not cause any effect in neighboring cells but it mitotically disrupts the microtubule network of HER2-overexpressing cell by binding to tubulin which ultimately leads to cell cycle arrest at G2-M phase and causes apoptotic cell death. Figure 7 shows the apoptosis of the cells, as well as the presence of cells with aberrant mitotic figures and a giant multinucleated structure, indicates the mitotic catastrophe of HER2-overexpressing cell after prolonged xenografting with T-DM. 

PHARMACOKINETICS

The pharmacokinetics of T-DM1 were evaluated in the phase 1 study along with the pharmacokinetic analysis of T-DM1 conjugate (ADC) which is done using pooled data from trials of patients having BC. The data obtained is then analyzed in a linear two-compartment model along with first-order elimination from the central compartment which

| Table 2: Some important properties of ado-trastuzumab emtansine |
|----------------------------------|---------------------------------------------------------------|
| **Synonyms** | T-DM1, trastuzumab-DNM1, trastuzumab-MCC-DNM1 antibody-drug conjugate |
| **Category** | Anticancer (metastatic breast cancer) |
| **Manufacturer** | Genentech |
| **Original source** | Maytenus serrata (plant) |
| **Mechanism of action** | Tubulin depolarization |
| **Drug release mechanism** | Peptidase and linker degradation |
| **Free drug potency (EC50)** | 10–11–10–12 M |
| **Ab-drug linker** | Peptide-thioether through cysteine residues on mAb |
| **Drug-mAb ratio** | Less homogeneous3.5 |
| **Route of administration** | Intravenous infusion |
| **Dose** | 3.6 mg/kg every 3 weeks |
| **Pharmacokinetics** | Bound to plasma protein, metabolized by CYP3A4/5, clearance level 0.68 L/day, t1/2 4 days |
| **Adverse reaction** | Hepatotoxicity, left ventricular dysfunction, embryo-fetal toxicity, pulmonary toxicity, thrombocytopenia, peripheral neuropathy |
| **Shelf life** | 3 Years |
| **ATC code** | L01XC14 |
| **Chemical formula** | C_{648}H_{994}N_{172}O_{2012}S_{44} (C_{47}H_{62}ClN_{4}O_{13}S)_{n} |
| **Molecular weight** | 148.5 kDa |

T-DM1: Ado-trastuzumab emtansine, MCC: Mitotic checkpoint complex

Figure 6: Schematic diagram of antibody-drug conjugate
in turn depicts the ADC concentration-time profile. The pharmacokinetics of T-DM1 are as follows.

**Absorption**

Trastuzumab emtansine is only administered through intravenous route. There have been no other studies reported with other routes. The maximum plasma concentration ($C_{max}$) of Trastuzumab emtansine is 74.3 ± 20.1 mcg/kg and the systemic exposure (AUC) is 295.2 ± 65.4 mcg•d/mL when the patients received doses of 3.6 mg/kg every 3 weeks. The terminal half-life ($T_{1/2}$) of Trastuzumab emtansine is found to be 3.5 ± 0.8 days, and the volume of distribution ($V_d$) is 60 ± 13.6 mL/kg.[51] The maximum plasma concentration ($C_{max}$) of Trastuzumab emtansine is 54.8 ± 12.6 mcg/kg, $T_{1/2}$ is 3.4 ± 1.1 days, AUC is 198.5 ± 54.5 mcg d/mL, and the $V_d$ is 55.4 ± 13 mL/kg when the patients received doses of 2.4 mg/kg weekly.[52]

**Distribution**

In the distribution study, the maximum concentration ($C_{max}$) of ADC and MC1 were found at the end of the infusion. In the phase-I study, the mean standard deviation of ADC and DM1 followed by T-DM1 administration was found to be 83.4 µg/mL and 4.61 ng/mL, respectively.

In the in-vitro, analysis the plasma protein binding of DM1 was found to be 93%, and it was also found that DM1 was a substrate of p-glycoprotein. Based on the population pharmacokinetics study, the central volume of distribution of ADC was found to be 3.13 L.[38-40,44]

**Metabolism**

In the in-vitro study, it was observed that MD1 and a small molecule component of Kadcyla were metabolized by CYP3A4/5. It was also observed that MD1 is not inhibited or induced by major CYP450 enzymes. Catabolites of T-DM1 such as the MCC- DM1, Lys-MCC-DM1, and DM1 was found to a very low level in the human plasma.[38-40,44]

**Elimination**

Based on the pharmacokinetic study, followed by the intravenous infusion of Kadcyla, it is observed that the clearance level of ADC was 0.68 L/day and an elimination half-life ($t_{1/2}$) of approximately 4 days. It was also observed that no accumulation was seen even after a repetitive intravenous infusion of KADCYLA for 3 weeks.

Based on the pharmacokinetics study of patients having a renal impairment which include moderate ($CL_{cr}$ 30-59 mL/min) and mild ($CL_{cr}$ 60-89 mL/min) renal impairment, depicts that the ADC is not affected renal impairment as compared to the normal renal function ($CL_{cr}$ ≥ 90 mL/min).[38-40,44]

**CLINICAL TRIALS**

Patients (991) were randomly assigned in a 1:1 ratio to kadcyla or lapatinib plus capecitabine. Patients in the trial [Figure 8] must have received therapy with a taxane and trastuzumab before enrollment.[44] A randomized, multicenter, openable trial compared kadcyla 3.6 mg/kg intravenously on day 1 of a 21-day cycle ($n$ = 495) and lapatinib at 1250 mg/day orally once per day of a 21-day cycle plus capecitabine at 1000 mg/m² orally twice daily on days 1-14 of a 21-day cycle ($n$ = 496) in patients with previously treated mBC.[47] At the time of the primary analysis, median time on study drug was 5.7 months (range: 0-28.4) for kadcyla, 4.9 months (range: 0-30.8) for lapatinib, and 4.8 months (range: 0-30.4) for capecitabine. The
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progression-free survival (PFS) of kadcyla or lapatinib plus capecitabine was 9.6 months and 30.9 months. The overall survival (OS) of kadcyla or lapatinib plus capecitabine were 6.4 months and 25.1 months.\textsuperscript{[53-55]}

On July 25, 2013, genentech/roche announced that a Phase 3 trial comparing Kadcyla to the physician’s choice of treatment in patients with HER2-positive BC who have already been treated with an HER2-targeted therapy, met its coprimary endpoint of progression-free survival. The other endpoint is OS [Figures 9 and 10], but these data are not yet mature.\textsuperscript{[56]}

**DRUG-DRUG INTERACTIONS**

Microtubule inhibitor DM1 (also known as cytotoxic component) of ADC is metabolized mainly by an enzyme CYP3A4. However, CYP3A5 enzyme is less responsible for the metabolism of DM1. It should be also kept in mind that continuous use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) with kadcyla should be avoided because it causes a potential rise in DM1 exposure and toxicity. To solve this problem, kadcyla treatment is being delayed until the stronger CYP3A4 inhibitors have cleared from circulation.\textsuperscript{[39,40,44]}

**ADVERSE REACTION**

**Hepatotoxicity**

In clinical trials of kadcyla, severe hepatotoxicity, including drug-induced liver injury and hepatic encephalopathy was reported. Nodular regenerative hyperplasia of the liver has been also identified from liver biopsies. In trial condition, the concentration of serum transaminase is increased. Before the treatment, serum transaminases and bilirubin should be controlled.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure8.png}
\caption{Trials profile of ado-trastuzumab emtansine (Kadcyla)}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure9.png}
\caption{Kaplan-Meier curve of IRC-assessed progression-free survival for study 1\textsuperscript{[44]}}
\end{figure}
Left ventricular dysfunction
In study 1, the percentage of adverse reaction of the left ventricular dysfunction of kadcyla treated group is 1.8%, and lapatinib plus capecitabine-treated group is 3.3%.

Embryo-fetal toxicity
When T-DM1 is administered with monoclonal antibody in case of pregnancy, it causes various adverse reactions such as oligohydramnios, fetal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Based on the mechanism of action, the microtubule inhibitor DM1 (cytotoxin) in ADC sometimes cause embryo-fetal toxicity.

Pulmonary toxicity
In clinical trials with kadcyla, it has been found various pulmonary toxicity such as pneumonitis, interstitial lung disease, acute respiratory distress syndrome, or fetal outcome.

Hypersensitivity reactions, infusion-related reactions
In clinical trials of kadcyla, various infusion-related reactions are found. These are:
- Tachycardia
- Bronchospasm
- Wheezing
- Hypotension
- Dyspnea
- Pyrexia
- Chills
- Flushing.

Hypersensitivity reactions such as allergic/anaphylactic-like reaction have been observed in clinical trials of single-agent kadcyla.

Thrombocytopenia
In study 1, the percentage of adverse reaction of thrombocytopenia of kadcyla-treated group is 31.2%, and lapatinib plus capecitabine-treated group is 3.3%. Before the treatment, platelet counts should be monitored.

Neurotoxicity
Peripheral neuropathy was reported in clinical trials of kadcyla. In study 1, the percentage of the adverse reaction of peripheral neuropathy of kadcyla-treated group is 21.2%, and lapatinib plus capecitabine-treated group is 13.5%.

Others
The other most common adverse reactions are:
- Nausea
- Fatigue
- Pain in the muscles or joints
- Increased liver enzymes
- Headache and
- Constipation.[44]

Miscellaneous information

Ingredients
The active ingredient of kadcyla includes trastuzumab emtansine. Inactive ingredients include succinic acid, sodium hydroxide, sucrose, and polysorbate 20.
**Dosage and administration**

The recommended dose is 3.6 mg/kg in every 3 weeks (21 days cycle). The dose should be maintained till it reaches maximum therapeutic level. It should also be kept in mind that kadcyla should not be administered at a dose greater than 3.6 mg/kg. It is administered through intravenous infusion and should not be submitted with trastuzumab.[45,57]

**Cost**

According to the opinion of Genentech, the cost of kadcyla is about $9,800 for a month and $94,000 for a typical course of treatment. This is about twice the price of Herceptin.[39]

**Storage and supplied**

T-DM1 should not be frozen or shake. It is stored in vials in a refrigerator at 2°C-8°C (36°F-46°F). It is supplied in a single-use vial (100 mg vial) or single-use vial (160 mg vial).[39,44]

**Treatment of special populations with special care**

**Pregnancy**

Kadcyla should not be administered to a pregnant woman because it causes a potential hazard to the fetus. TDM1 is an ADC. ADC consists of two components such as trastuzumab and DM1. They cause fetal harm or death when administered to a pregnant woman. It should be reported to the Genentech adverse event line at 1-888-835-2555 if kadcyla is administered during pregnancy.

**Nursing mothers**

IgG is secreted in human milk, but it has not a clear idea about kadcyla whether it also secreted or not. It has been reported that trastuzumab is secreted in small amounts in breast milk and causes various adverse reactions to nursing mothers as well as the neonate. To prevent adverse reaction, it should be kept in mind that the mother should not be treated with kadcyla or should be discontinued from the treatment.

**Females of reproductive potential**

Females should be advised to use contraceptives while receiving kadcyla as it may cause an adverse reaction to embryo-fetal.

**Renal and hepatic impairment**

No dose adjustment was recommended for patients with severe renal and hepatic impairment.[39,40,44]

**Brands for mBC**

The following list [Table 3] describes an update on information about the various products use for the treatment of mBC.[58]

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Licensee</th>
<th>Approve indications</th>
</tr>
</thead>
</table>
| Avastin      | Genentech (US) and Roche (ex-US) | Metastatic colorectal cancer  
Advanced non-small cell lung cancer  
Renal cancer  
Metastatic HER2+ breast cancer  
Glioblastoma  
Ovarian cancer |
| Herceptin    | Genentech (US) and Roche (ex-US) | Metastatic HER2+breast cancer  
Metastatic HER2+stomach cancer |
| Lucentis     | Genentech (US) and Novartis (ex-US) | Wet AMD  
Macular edema or swelling following retinal vein occlusion  
Diabetic macular edema |
| Actemra      | Roche and Chugai | Moderate to severe RA, including patients who have had an inadequate response to one or more DMARDS |
| Kadcyla      | Genentech (US) and Roche (ex-US) | Second line metastatic HER2+breast cancer  
First line in patients with metastatic HER2+breast cancer with disease recurrence within 6 months of adjuvant treatment |

HER2: Human epidermal growth factor receptor, mBC: Metastatic breast cancer, RA: Rheumatoid arthritis, AMD: Age-related macular degeneration

**CONCLUSION**

Nowadays, BC is the most common cancer in the United States and other parts of the globe. Hence, the treatment of BC is essential for a healthy lifestyle. T-DM1 (T-DM1, kadcyla) is a new drug which got the approval on 22 February 2013 from US-FDA for marketing. The trials conducted so far have proven to be worth in treating HER2+ metastatic disease. The trials are going on to address its role in front-line metastatic and nonmetastatic diseases. T-DM1 is a single-agent (3.6 mg/kg), and it is predictable, well characterized,
and unaffected by circulating levels of HER2 extracellular domain or residual trastuzumab but being a highly therapeutic molecule, acquired resistance to T-DM1 has been observed. This article highlights about description about kadcyla for the treatment of patients with HER2-positive mBC.

REFERENCES


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