“COMPARATIVE EVALUATION OF TARGETED THERAPIES IN HER2-POSITIVE BREAST CANCER.”

By

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Declaration

It is hereby declared that

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Approval

The thesis/project titled "Comparative Evaluation of Targeted Therapies in HER2-Positive Breast Cancer" was submitted by [Lamia Kabir, ID-22146055] of Spring, 2025 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons).

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Ethics Statement

This study did not include any harm to humans or animals.

Abstract

Approximately 15% to 20% of breast cancer is HER2-positive, and such breast cancer is characterized by rapid development of cancer as well as poor prognosis in case they are not treated. Treatment of this type has been much better with the development of the HER2-targeted therapies. Tyrosine kinase inhibitor, dual HER2 and antibody-drug conjugate significantly enhanced the therapy efficacy following trastuzumab, the initial monoclonal antibody directed at HER2, and established a new standard of care. This review evaluates the therapy choices that are best available through a comparison of their mechanisms, clinical efficacy, and safety profiles. PubMed, Google Scholar, and ScienceDirect were used to search relevant research published between 2001 and 2024. Newer drugs, especially antibody-drug conjugates like trastuzumab deruxtecan are more promising, especially in patients who are more advanced and have received previous therapy. Trastuzumab is the most significant treatment option, and such drugs have different safety profiles, such as Hematologic and pulmonary toxicity in ADCs, gastrointestinal toxicity in TKIs, and cardiotoxicity that allow achieving the best outcome.

Keywords: Breast cancer; HER2-targeted therapy; Trastuzumab; Tyrosine kinase inhibitors (TKIs); Dual HER2 blockade.

Dedication

I would like to dedicate this to my parents and my husband. They inspire me to do it properly and never forget to appreciate me.

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List of Acronyms

ADCs	Antibody-drug conjugates
T-DM1	Trastuzumab emtansine
T-DXd	Trastuzumab deruxtecan
HER2	Human epidermal growth factor receptor 2

Chapter 1

Introduction

1.1 Background

Breast cancer is the most commonly diagnosed cancer across all women in the entire world and represents a significant health challenge in society. According to the World Health Organization, breast cancer accounts for a major proportion of cancer types and mortality rate globally, with millions of new cancer cases that are diagnosed every year. In 2020, worldwide, approximately 19.3 million new cancer cases were reported, as well as almost 10.0 million cancer-related deaths (9.9 million without including nonmelanoma skin cancer). The most frequently diagnosed cancer in the world is female breast cancer, and an estimated 2.3 million new cancer cases occur each year, followed by lung, colorectal, prostate, and stomach cancers (Sung et al., 2020). The disease is heterogeneous; it contains a great number of biological subtypes with different kinds of molecular characteristics, treatment responses, and prognosis. Based on the presence or absence of molecular indications for receptors like estrogen or progesterone, and human epidermal growth factor 2 (ERBB2), Breast cancer is classified into 3 main subclasses. Previously, it was known as HER2. The major subclasses are: 1. Hormone receptor positive or ERBB2-negative, 2. ERBB2-positive, and 3, triple-negative (Waks & Winer, 2019).

1.2 HER2-Positive Breast Cancer Therapy

The percentage of breast cancers that are overexpressed or amplified with HER2 is around 15-20%. HER2-positive cancer can be identified by the overexpression of HER2 protein, estimated by immunohistochemistry status (IHC3) or a ratio of at least 2.0 between HER2/CEP17, which indicates that the HER2 gene is suppressed, and this aspect can be detected by fluorescence in situ hybridization (FISH) (Loibl & Gianni, 2017). HER2 is activated by the development of homodimers or heterodimers with other EGFR proteins. Due to dimerization, tyrosine residues occur in EGFR intracellular areas because of autophosphorylated and/or transphosphorylated, which causes the phospholipase Cγ (PLCγ)/protein kinase C (PKC), phosphoinositide 3-kinase/Akt, and Ras/Raf/mitogen-activated protein kinase pathways. The most effective stimulant of downstream pathways is the HER2-HER3 heterodimer; in particular, PI3K/Akt is a significant regulator of cellular development and survival. HER2 dimerization causes the dislocation and immediate degradation of cell cycle inhibitor p27Kip1 protein, which results in further progression of the cell cycle (Claret & Vu, 2012).

One of the significant developments in the treatment of HER2-positive breast cancer was the introduction of HER2-targeted therapy. The effectiveness and safety of trastuzumab, a recombinant monoclonal antibody that targets HER2, in patients with HER2 overexpression and metastatic breast cancer (Slamon et al., 2001). Combination therapy with the two antibodies showed significant activity and an acceptable safety profile in HER2-positive breast cancer patients. Pertuzumab, which is known as an anti-HER2 humanized monoclonal antibody, blocks receptor dimerization and has a mechanism of action complementary to trastuzumab (Baselga et al., 2012). Additionally, Lapatinib, a human epidermal growth factor receptor type 2 and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, is effective in combination with capecitabine in women with HER2-targeted metastatic breast

cancer that has progressed despite treatment using trastuzumab (Geyer et al., 2006). Antibody-drug conjugates (ADCs) have turned out to be a highly effective therapeutic method over the last few years. A combination of cytotoxic power of chemotherapy medications with the specificity of monoclonal antibodies allows the targeted delivery to cancer cells that express HER2. Two significant milestones in this class are trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd), shows positive therapeutic outcomes in advanced disease cases (Verma et al., 2012; Modi et al., 2020).

1.3 Aim of the project

Even though various HER2-targeted medications are available, identifying the most effective form of action remains difficult because of differences in resistance patterns, safety profiles, clinical efficacy, and mechanisms of action. In patients with treatment-resistant disease, newer agents such as T-DM1 and T-DXd have shown increased efficacy, even though trastuzumab remains the standard of care. Ado-tratuzumab emtansine (T-DM1) was the first ADC authorized in 2013 for the treatment of HER2-positive breast cancer (common solid tumor) (Lambert & Morris, 2017). Comparative analysis of different kinds of HER2-targeted therapies is important to identify the most effective and safe treatment methods according to the current evidence. This awareness of the relative benefits and disadvantages of each medication can allow physicians and pharmacists to optimize treatment plans and enhance patient outcomes.

Comparison of the drug safety and effect profile of five different HER2-targeted medicines: trastuzumab, lapatinib, pertuzumab, trastuzumab deruxtecan, and trastuzumab emtansine, in the management of HER2-positive breast cancer, is the purpose of this narrative review. The objective of this review is to analyze the molecular mechanisms of action of specific HER2-targeted drugs and to compare and contrast their clinical efficacy using data from

published research. To give an adequate understanding of their clinical application, each therapeutic agent's safety and tolerability profiles are also evaluated. This review also aims to identify the most effective HER2-targeted medication based on the available data.

1.4 Significance of the project

This review illustrates an extensive summary of existing and recent HER2-targeted drugs, which is essential in clinical practice and education in pharmacy. This review shows how tailored treatment can enhance patient outcomes in cases of HER2-positive breast cancer and promote informed decision-making using pharmacotherapy by summarizing the existing evidence that is readily available in the literature.

Chapter 2

Methodology

This study was carried out as a narrative review with a particular focus on HER2-positive breast cancer and the comparative effectiveness of specific HER2-targeted treatments. Because it allows a comprehensive and descriptive synthesis of the body of literature, a narrative review approach was selected in order to compare drug mechanisms, clinical efficacy, and safety profiles without the statistical limitations of a systematic review. The information in the review comes from the pre-reviewed studies, journals, published articles, websites, and news. These study articles are from Nature Cell, MDPI, Frontiers, PubMed, PMC, ResearchGate, Google Scholar, and others. All the information is carefully recorded. Most of the review is focused on HER2-positive breast cancer, HER2-targeted therapy, Trastuzumab, Lapatinib, Pertuzumab, Trastuzumab emtansine, Trastuzumab deruxtecan, Antibody–drug conjugates, Tyrosine kinase inhibitors. In this review, peer-reviewed journals that discussed the mechanisms of action, clinical efficacy, or safety profiles of particular medicines and emphasized HER2-positive breast cancer were included. Eligible studies were

all clinical trials, review articles, and observational studies that have free or easy access to full-text versions published in English. Only those studies whose clinical relevance and methodological quality were appropriate were considered for inclusion. The research studies that did not directly deal with HER2-positive breast cancer or those that only dealt with non-pharmacological interventions were eliminated. Duplicate publications, case reports having fewer clinical applications, and articles that were only available as paid access and did not have full-text versions were also excluded from this review. The obtained information was synthesized in order to enable comparison between the five selected HER2-targeted drugs. According to the narrative nature of the review, no statistical meta-analysis was carried out.

Chapter 3

Overview of HER2-Positive Breast Cancer Medicines

3.1 Molecular background of HER2-positive breast cancer

The ErbB2 gene, also called human epidermal growth factor receptor 2 (HER2/neu), which is a member of the EGFR family of tyrosine kinase receptors, is amplified in HER2-positive breast cancer and makes important contributions to the regulation of signaling pathways in normal and malignant breast epithelial cells. The persistent stimulation of this receptor leads to activation of intracellular signaling pathways that determine cell proliferation, survival, angiogenesis, and metastasis. The amplification of HER2 is a valuable predictive and prognostic factor in breast cancer (Rojhannezhad et al., 2023). HER2 activation triggers two downstream signaling cascades, Mitogen-Activated Protein Kinase (MAPK) and phosphatidylinositol-3-kinase (PI3K)/AKT. These pathways have a huge influence on tumor aggressiveness, apoptotic resistance, and failure of treatment (Claret & Vu, 2012). Before the development of targeted therapy, HER2-positive breast cancer used to be historically related

to higher recurrence rates and worse survival due to such molecular characteristics.

3.2 HER2 targeted therapy medicine

3.2.1 Trastuzumab

Trastuzumab, which is known as a humanized monoclonal antibody, binds to HER2 receptors and inhibits activation and dimerization of the receptor. This suppresses downstream signaling pathways that stimulate cell growth, proliferation, and survival, preventing the growth of tumour cells. Moreover, it also induces antibody-dependent cellular cytotoxicity (ADCC) (Hudis, 2007). In addition to that, trastuzumab suppresses HER2 signaling through receptor internalization and degradation. When used in combination with chemotherapy, trastuzumab is of great benefit both overall and disease-free survival in patients with HER2-positive breast cancer, according to various clinical trials. Trastuzumab and paclitaxel, together with doxorubicin and cyclophosphamide, are effective in improving the outcomes of women with surgically removed HER2-positive breast cancer. In female breast cancer with HER2, treatment with trastuzumab after adjuvant chemotherapy changes the survival without any disease after a year or longer. Trastuzumab and conventional chemotherapy with the aim of reducing relapse and improving long-term survival rates in early and metastatic breast disease according to the initial landmark trials (Romond et al., 2005; Piccart-Gebhart et al., 2005). Long-term follow-up studies showed that the benefits of trastuzumab remain over time and would firmly earn its place as the foundation of HER2-targeted therapy (Slamon et al., 2001). Despite these benefits, there are some patients who develop resistance even with the above therapeutic benefits, which emphasizes the need for additional therapeutic strategies. Trastuzumab does not induce adverse effects, but cardiotoxicity is still a major risk, especially when combined with anthracyclines. Some of the side effects reported include

asymptomatic decreases in left ventricular ejection fraction, infusion-related reactions, and exhaustion (Swain et al., 2013). Therefore, cardiac monitoring is recommended during treatment.

3.2.2 Pertuzumab

Pertuzumab prevents the HER2 ligand from generating heterodimers or homodimers; more precisely, it prevents the strong HER2–HER3 interaction in the presence of heregulin (HRG), and it activates the PI3k/Akt signaling pathway. Its primary mode of action is the induction of ADCC, just like trastuzumab (Capelan et al., 2013). Pertuzumab gives an effect as a dual HER2 blocker when used with trastuzumab. Clinical studies have shown that, compared to trastuzumab therapeutic effect when given alone, dual HER2 blockade with trastuzumab and pertuzumab considerably increases progression-free survival and overall survival. According to the CLEOPATRA study, Pertuzumab patients receiving trastuzumab and chemotherapy had longer survival outcomes (Swain et al., 2015). Pertuzumab-containing regimens have been associated with higher pathological complete response rates in the neoadjuvant disease setting that implies improved tumor eradication prior to the surgical procedure (Schneeweiss et al., 2013). In general, pertuzumab is well tolerated. Most common adverse effects are Alopecia, neutropenia, diarrhea, nausea, exhaustion, rash, and mucosal inflammation. Similar to trastuzumab, there is a similar incidence of cardiotoxicity, which calls for cardiac monitoring throughout treatment (Gianni et al., 2012).

3.2.3 Lapatinib

Lapatinib is an orally administered drug. It is known as a small-molecule tyrosine kinase inhibitor that targets the cytoplasmic domain of the receptors, HER2 and EGFR. Therefore, it reduces phosphorylation of target receptors, Raf, ERK, AKT, and PLCγ proteins, which

inhibit the activation of major downstream signaling pathways, including MAPK, PI3K-AKT, and PLCγ. As a result, lapatinib limits tumor growth and improves cancer cell control by blocking cell migration and proliferation in breast cancer cell lines that express different amounts of EGFR and HER2 (Segovia-Mendoza et al., 2015). Lapatinib has been clinically useful in metastatic or progressive breast cancer patients who have first undergone trastuzumab therapy, particularly those who have become resistant to the drug. In comparison to chemotherapy, studies show that lapatinib increases progression-free survival when used in conjunction with endocrine therapy or chemotherapy (Blackwell et al., 2010). However, lapatinib's overall effectiveness is typically inferior to ADCs and monoclonal antibodies, that restricts its use to subsequent methods of therapy (Johnston et al., 2009).

The most common toxicities of lapatinib include rash, fatigue, diarrhea, nausea, and gastroesophageal reflux disease. Cardiac toxicity is rare with Lapatinib. These toxicities may result in some patients getting dose reductions or discontinuation of treatment (Moy & Goss, 2007).

3.2.4 Trastuzumab Emtansine (T-DM1)

Binding of T-DM1 to HER2 triggers HER2–T-DM1 complex internalization by receptor-mediated endocytosis. The non-reducible linker is a stable one that enables DM1 to stay in the circulatory and within the tumor microenvironment, only to be released upon lysosomal degradation of the antibody functional group. The DM1-containing released metabolites suppress the microtubule formation and cause cancer cells to be killed. Interestingly, conjugation of DM1 to trastuzumab does not impact on its HER2 binding ability or reduce its inherent anti-tumor activity. Therefore, T-DM1 can enjoy the inhibition of signaling through trastuzumab and the cytotoxic DM1 metabolites as its methods of accomplishing its therapeutic effects (Barok et al., 2014). T-DM1 has shown a significant

clinical response in patients with HER2-positive breast cancer who had previously received trastuzumab and chemotherapy. T-DM1 was much better than standard treatment with lapatinib plus capecitabine in terms of progression-free survival and overall survival, with less adverse effects. Clinical trials in patients with locally advanced or metastatic disease showed an improvement in progression-free survival rate (6.4 to 9.6 months) and overall survival (25.1 to 30.9 months). Such result indicates that T-DM1 has better efficacy and a better safety profile than traditional chemotherapy treatment regimens in this patient population (García-Alonso et al., 2020; Verma et al., 2012). Many treatment guidelines now recommend T-DM1 as the second-line treatment of choice as a result of these findings. T-DM1 has fewer systemic toxicities in comparison to traditional chemotherapy and tends to have a more positive safety profile than its clinical activity in general. Fatigue, nausea, thrombocytopenia, headache, and constipation are the most frequently reported events of all grades. The most common grade 3 to 4 adverse events are laboratory abnormalities, specifically thrombocytopenia and increased levels of aspartate aminotransferase that are generally manageable and do not generally have serious clinical manifestations. In general, these results argue in favor of the tolerability of T-DM1 in patients with HER2-positive breast cancer (Dieras et al., 2014).

3.2.5 Trastuzumab Deruxtecan (T-DXd)

The next-generation antibody-drug conjugate of HER2 is trastuzumab deruxtecan (DS-8201a). It is strongly attached to HER2 and transfers a cytotoxic molecule that induces DNA damage and destroys cancer cells. Since the released drug can diffuse to the nearby cancer cells, DS-8201a can also kill the surrounding HER2-negative tumor cells, and as such, it can be used on tumours that have low or heterogeneous expression of HER2. Its activity is more active in resistant and heterogeneous tumors compared to T-DM1. Besides, DS-8201a can bypass multiple resistance mechanisms to previous HER2-targeted therapy. It is

structured in such a manner that trastuzumab is bound with a topoisomerase I inhibitor through an activating cleavable linker that allows the release of the drug to be successful in the tumor tissue (Andrikopoulou et al., 2021). According to clinical trials, patients with HER2-low or HER2-positive status may benefit from new therapeutic options when using trastuzumab deruxtecan (DS-8201) alone (Li et al., 2023). Patients with HER2-positive metastatic breast cancer who have received extensive pretreatment exhibit long-lasting antitumor activity from trastuzumab deruxtecan. According to a study, trastuzumab deruxtecan was approved more quickly for the treatment of patients with HER2-positive metastatic breast cancer who had previously undergone two or more anti-HER2 antibody-based regimens in the context of metastatic disease. Trastuzumab deruxtecan treatment was superior to trastuzumab emtansine in terms of progression-free survival (Cortés et al., 2022). Neutropenia, anemia, nausea, vomiting, and alopecia were the most common grade 3 adverse events (AEs), and half of the patients had grade 3 AEs. Thrombocytopenia, leukopenia, fatigue, anemia, nausea, and neutropenia are adverse effects that are frequent. No high rates of cardiotoxicity linked to T-DXd were observed. Interstitial lung disease is the most prominent side effect linked to T-DXd, and if it is not identified early, it could be quite serious (Ciruelos et al., 2024).

Overall, research indicates that the better is the HER2-targeted therapy, the better the outcomes of treatment become. Even more modern drugs, especially antibody drug conjugates, have demonstrated better effectiveness in advanced disease exposes where trastuzumab remains vital in initial therapy.

Chapter 4

Comparative Discussion

4.1 Comparative Analysis of HER2-Targeted Therapies

The treatment landscape of HER2-positive breast cancer has dramatically enhanced over the years as the evolution of certain types of treatments referred to as targeted therapies that directly inhibit the activity of the HER2 signaling has evolved. The treatments are specifically effective in preventing tumor growth, proliferation, and survival by blocking the HER2-mediated signaling pathways that mediate these processes. Therefore, targeted therapies have significantly improved the quality of life of patients with HER2-positive breast cancer.

This study reviewed five medications of the different generations of HER2-targeted medications: trastuzumab, pertuzumab, lapatinib, ado-trastuzumab emtansine (T-DM1), and trastuzumab deruxtecan (T-DXd). Each drug has different mechanism of action, molecular structure, clinical use and safety profile. The combination of all these medicines demonstrates the way in which the HER2-directed treatment strategies have been changing throughout the years, aiming at increasing the therapeutic benefits and minimizing the systemic toxicity.

The first monoclonal antibody to target HER2 was trastuzumab, which marked the beginning of customized treatment of breast cancer. Trastuzumab has significantly improved the overall survival and disease-free survival in both early-stage and metastatic cancer in combination with chemotherapy (Romond et al., 2005; Piccart-Gebhart et al., 2005). Fluorescence in situ hybridization (FISH) is used to assess ErbB2 gene amplification in breast cancer patients prior to trastuzumab therapy. Unfortunately, resistance is fairly significant even with the strict patient selection criteria. In patients with elevated levels of ErbB2 overexpression, the response rate to trastuzumab alone is still approximately 35%, which is less than satisfactory.

Trastuzumab treatment also has the drawback that 40% of patients experience other negative side effects, and 2 to 5 percent experience severe side effects like heart failure (Lan et al., 2005).

To overcome this limitation, Pertuzumab, a complementary monoclonal antibody, was introduced. When pertuzumab binds to a particular HER2 receptor epitope, it blocks the receptor from dimerizing with other EGFR family members. Pertuzumab was first utilized with trastuzumab and docetaxel compared to trastuzumab, placebo, and docetaxel, significantly improving overall survival among patients with metastatic breast cancer that was HER2-positive. Trastuzumab and pertuzumab also inhibit signaling pathways by dual HER2 blockade. This combination has been compared with trastuzumab alone in clinical trials and has been found to increase overall survival and progression-free survival, particularly in metastatic disease patients, dramatically. Since pertuzumab treatment did not increase cardiac toxicity (including asymptomatic and symptomatic left ventricular dysfunction) when compared to placebo, long-term cardiac safety was preserved. Nonetheless, the most challenging part of treating the disease in the long term remains, and a significant number of patients who have been treated with pertuzumab develop resistance (Swain et al., 2015).

Lapatinib is a small-molecule tyrosine kinase inhibitor that specifically binds to ligand-binding domains of EGFR and HER2, thus being an alternative mechanism of therapy. Its oral administration is convenient and effective to those patients who cannot be administered intravenously. Lapatinib is particularly useful in cases when resistance to monoclonal antibodies occurs. However, its application is often limited by gastrointestinal and hepatic toxicities, and the clinical efficacy of it is generally lower than that of antibody-based therapies (Blackwell et al., 2010). Lapatinib is therefore mostly saved for subsequent treatment modalities.

4.2 Summary of HER2-targeted therapies

The main HER2-targeted treatments were assessed according to their efficacy, safety profile, mechanism of action, and therapeutic benefits in order to enable systematic comparison. A summary of these characteristics is presented in the table given below:

Comparison of Major HER2-Targeted Therapies:

Name of Drug	Drug Class	Mechanism of Action	Clinical Efficacy	Advantages	Common Adverse Effect
Trastuzumab	Humanized monoclonal antibody	Blocks the signaling through HER2 binding and causes immune-mediated cytotoxicity.	Improves survival at both the early and advanced stages of disease.	For the treatment of solid tumors, trastuzumab (Herceptin) is the first oncogene-targeted therapeutic agent that is clinically available.	Cardiotoxicity, nasopharyngitis, fatigue, infusion reactions, insomnia

Pertuzumab	Humanized monoclonal antibody	Pertuzumab activates the PI3k/Akt signaling pathway and stops the HER2 ligand from forming heterodimers or homodimers.	When combined with trastuzumab, it increases survival.	The anti-HER2 dual blockade of pertuzumab and trastuzumab is probably going to be a significant step forward for HER2-positive patients and a new turning point in the development of personalized medicine.	Diarrhea, rash, fatigue, Cardiotoxicity,

Lapatinib	Tyrosine kinase inhibitor	Inhibits the activity of EGFR kinase and intracellular HER2.	Relatively useful with metastatic disease.	It can easily be taken orally and has the capacity to overcome resistance and the blood-brain barrier.	Diarrhea, rash, nausea, gastroesophageal reflux disease, hepatotoxicity
Trastuzumab emtansine (T-DM1)	Antibody-drug conjugate (ADCs)	Delivers DM1 to cells that are HER2-positive. DM1-containing released metabolites kill cancer cells by suppressing microtubule formation.	Cells that are positive enhance OS and PFS after trastuzumab failure.	The most important advantages of T-DM1 are targeted chemotherapy and dual mechanism of action.	Thrombocytopenia, fatigue, nausea, thrombocytopenia, headache, constipation

Trastuzumab deruxtecan (T-DXd)	Antibody-drug conjugate (ADCs)	Secretes an inhibitor of the topoisomerase I in the tumor cells and the surrounding cells. A cytotoxic molecule that damages the DNA and kills the cancer cells, and is closely associated with HER2.	The topoisomerase I inhibitor is released by tumor cells and neighboring cells.	Strong bystander effect	Fatigue, interstitial lung disease, thrombocytopenia, leukopenia, anemia, nausea, and neutropenia

Table: Collected from Capelan et al. (2013), Waks and Winer (2019), García-Alonso et al. (2020), Andrikopoulou et al. (2021), Jackson et al. (2022)

4.3 Antibody–Drug Conjugates Comparison

The toxic effect of chemotherapy drugs, along with the specificity of monoclonal antibodies introduce antibody-drug conjugates as a promising breakthrough in HER2-targeted therapy.

This technique reduces the penetration of healthy tissues and it is possible to deliver drugs to tumor cells selectively.

T-DM1 was the first to be approved as a combination of antibodies and drug against breast cancer of the HER2-positive type. It is composed of the microtubule inhibitor DM1 coupled with trastuzumab. Clinical trials revealed that in individuals who had undergone trastuzumab therapy before, T-DM1 produced a significant effect as it was found to significantly increase the overall survival and progression-free survival compared to conventional chemotherapy (Verma et al., 2012). Moreover, T-DM1 had a favorable benefit-to-risk profile that contained reduced systemic adverse effects.

An example of next generation of antibody-drug conjugates is trastuzumab deruxtecan.Due to its cleavable linker and greater ratio of drug to antibody, it can release its cytotoxic cargo in the target and surrounding cells. With this bystander effect, T-DXd has the ability to eliminate tumor cells with low or variable HER2 expression. Clinical research has shown that T-DXd has substantially greater response rates and longer survival outcomes than T-DM1 (Modi et al., 2020; Cortés et al., 2022). These results show that it has superior antitumor activity in patients who are resistant and have received a lot of prior treatment.

4.4 Safety and Tolerability Considerations

In case of long-term treatment success, determining safety and tolerability are critical factors. The drugs possess individual side effects that must be monitored closely despite the generally improved tolerance of HER2-targeted therapies compared to traditional chemotherapy.

Trastuzumab and pertuzumab might cause cardiotoxicity that can result in heart failure and reduced left ventricular ejection fraction. Therefore, periodic heart examination should be suggested in the course of treatment (Swain et al., 2013). There are also common side effects

of lapatinib such as hepatotoxicity, skin rashes and diarrhea, which complicate the adherence plan to treatment.

T-DM1 has a safe profile; the most common side effects are fatigue and thrombocytopenia. The supportive care and dose adjustment are normally sufficient to manage these side effects.T-DXd, on the other hand, is associated with the development of interstitial lung disease that is fatal when left unchecked. Consequently, in the case of this agent, regular follow-up and prompt intervention are of great importance (Modi et al., 2020).

4.5 Overall comparison of effectiveness

The first-generation monoclonal antibodies are improved by next-generation antibody-drug conjugates, which are observable to have a discernible improvement in therapeutic efficacy. Although dual blockade (pertuzumab) is more effective, trastuzumab remains the standard approach in the initial treatment of HER2-positive breast cancer. In certain patients, lapatinib offers a slight advantage, but its results are not as good as those of antibody-based treatments.

Among the five drugs evaluated, trastuzumab deruxtecan has been the most effective in terms of the longest progression-free survival and the highest response rates. This has enhanced its performance especially because it is capable of attacking heterogeneous tumor and defeating resistance mechanisms. According to available data, T-DXd seems to be the best HER2-targeted treatment for advanced HER2-positive breast cancer.

The comparative review considers the importance of the individual treatment scheme in the treatment of HER2-positive breast cancer. Even though newer treatments are more effective, patient characteristics, comorbidities, previous treatments, toxicity profiles, and resource availability should all be taken into account when choosing a course of treatment. Pharmacists can contribute to the greatest therapeutic outcomes by managing drug interactions, tracking side effects, assisting with drug choice, and promoting compliance. For

oncologists, pharmacists, nurses, and other medical professionals to provide safe and efficient patient care, multidisciplinary collaboration is crucial.

Chapter 5

Conclusion and Future Perspective

5.1 Conclusion

HER2-positive breast cancer is a biologically aggressive form of breast cancer, which, when untreated, may aggressively develop and result in adverse clinical outcomes. Developments in molecular biology have produced HER2-targeted treatments, which have revolutionized the treatment of this illness and greatly increased survival rates.

In this narrative review, five of the most significant HER2-targeted therapies were compared in terms of their mechanisms of action, clinical efficacy, and safety profiles, including trastuzumab, pertuzumab, lapatinib, trastuzumab emtansine (T-DM1), and trastuzumab deruxtecan (T-DXd). Treatment is still dominated by trastuzumab, making HER2-targeted therapy the standard. Trastuzumab In combination with dual HER2 blockade with pertuzumab, enhances therapeutic performance, especially in advanced disease. Although its efficacy is relatively low, lapatinib offers an alternate intracellular strategy and is most helpful in those who have monoclonal antibody therapy resistance.

The findings of antibody-drug conjugates are one of the major advances in the treatment of breast cancer that is HER2-positive. T-DM1 has a higher tolerance rate and enhanced survival rates in patients who have received trastuzumab previously than traditional chemotherapy. Trastuzumab deruxtecan has been shown to be the most effective in terms of clinical performance of the treatment discussed, even in individuals who have already undergone a significant amount of pretreatment, showing better response and longer periods of free

survival of disease. These findings mean that with improvement in treatment modalities, there are stronger HER2-targeted drugs being used.

However, toxicities associated with treatment are a matter of concern. The gastrointestinal toxicity of tyrosine kinase inhibitors, cardiotoxicity of monoclonal antibodies, and the possibility of interstitial lung disease with trastuzumab deruxtecan are examples of the importance of careful patient selection and monitoring. Based on available data, trastuzumab deruxtecan appears to be the most efficient treatment option; still, to maximize benefits and minimize risks, customized treatment options are essential.

5.2 Future perspective

Future research of HER2-positive breast cancer could be aimed at the identification of predictive biomarkers that could guide individualized therapy and enhancing the sequence of treatment. To enhance long-term outcomes, we will rely on the capability to understand the molecular processes driving resistance to treatment. Studies on the development of the next-generation antibody drug-conjugates with improved safety profiles and tumor specificity are in progress, though it appears optimistic.

Immunotherapy and HER2-targeted medicines in combination therapies can also present new chances that can be used to enhance clinical outcomes. Practical research needs to be long-term in future to determine the safety and effectiveness of newer treatment in a diverse patient population. In patients with the HER2-positive breast cancer, there is an expected increase in survival and quality of life due to the progressive advances in the precision medicine and targeted drug development.

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