Targeted Therapeutic Options in the Treatment of Breast Cancer

By

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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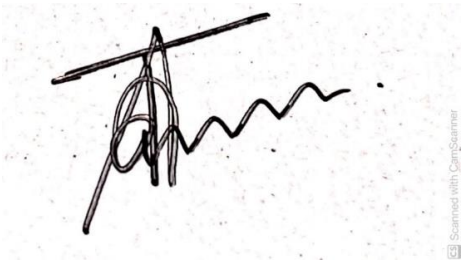

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Approval

The project titled "Targeted Therapeutic Options in the Treatment of Breast Cancer" submitted by Kazi Tasnuva Alam (18146028) of Spring, 2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on 13/4/22.

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Ethics Statement

This project does not involve any clinical trial or human participants and no animals were used or harmed.

Abstract

The recent application of targeted therapies such as biologics, biosimilars, and other targeted biological agents in the treatment of diverse subtypes of breast cancer has been facilitated by the decoding of the human genome and the subdivision of breast cancer on a molecular level. This review focuses on targeted therapeutic approaches used in breast cancer therapy, such as anti-HER2 targeted monoclonal antibodies, CDK4/6 inhibitors, immune checkpoint inhibitors, blockers of the PI3K/AKT/mTOR signaling pathways, PARP inhibitors, Antibody-Drug Conjugates (ADCs), and anti-VEGF agents. Moreover, this paper specifically discusses the role of trastuzumab in the treatment of HER2-positive breast tumors, as well as its approved biosimilars which aim to make breast cancer treatment affordable, while preventing cancer recurrence and improving overall therapeutic efficacy.

Keywords: Breast cancer; Targeted therapy; Biologics; Biosimilars; HER2; Trastuzumab

Dedication

Dedicated to my respected faculty members, family, and friends.

Acknowledgement

I would like to express my earnest gratitude to my supervisor Dr. Eva Rahman Kabir for her constant support and guidance throughout the project. I would also acknowledge Dr.M. Zulfiquer Rahman for his valuable suggestions and kind words of encouragement. My sincere thanks to both of them for taking the time to proofread my paper, help me correct my mistakes, and offer me encouragement.

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List of Acronyms

WHO	World Health Organization
FDA	Food and Drug Administration
HDI	Human Development Index
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hormone Receptor
ER	Estrogen Receptor
PR	Progesterone Receptor
HER2-E	Human Epidermal Growth Factor Receptor 2-Enriched
TNBC	Triple-Negative Breast cancer
ET	Endocrine Therapy
AC	Adjuvant Chemotherapy
PCR	Pathologic Complete Remission
MRI	Magnetic Resonance Imaging
EFGR	Epidermal Growth Factor Receptor
PI3k	Phosphatidylinositol 3-kinase
MAPK	Mitogen-Activated Protein Kinase
CDK	Cyclin-Dependent Kinase
ADC	Antibody-Drug Conjugate
VEGF	Vascular Endothelial Growth Factor

VEGFR	Vascular Endothelial Growth Factor Receptor
PARP	Poly Adenosine Diphosphate-Ribose Polymerase
HRR	Homologous Recombination Repair
DDR	DNA Damage Response and Repair
mTOR	Mammalian Target of Rapamycin
PIP2	Phosphatidylinositol 4,5-Bisphosphate
PDK1	Phosphoinositide-Dependent Protein Kinase 1
PD-1	Programmed Cell Death Protein 1
PDL-1	Programmed Death-Ligand 1
MDR	Multi Drug Resistance
CSF1	Colony Stimulating Factor 1

Chapter 1

Introduction

1.1 Introduction

In women, globally, breast cancer is the most prevalent cause of cancer death (Kondov et al., 2018). It is an incredibly diverse disease with mutations, structural changes, and a variety of anomalies contributing to its heterogeneity. It is the uncontrolled growth and rapid multiplication of breast cells that originate in the lobules or ducts and migrate to other parts of our body. Its early stages are generally characterized by a solid, inflated mass of tissue called a 'lump'. However, there is a change in the appearance of the breasts in later and more advanced phases, as demonstrated by the development of swollen lumps, itching, redness, and pain (Day et al., 2020; Lee et al., 2019). According to the GLOBOCAN predictions of cancer prevalence and mortality provided by the International Agency for Research on Cancer in 2020, female breast cancer accounts for 11.7% percent of all cases with a mortality rate of 6.9 %. In addition, breast cancer incidence rates in countries with high HDI (55.9% per 100,000) and low HDI (29.7% per 100,000) greatly outnumber other malignancies. Moreover, its mortality rate remained the highest among women, and it was the most often reported cause of female cancer deaths (Sung et al., 2021).

Traditional prognostic factors namely histologic subtype, tumor grade, tumor size, axillary lymph node status, and lymph vascular invasion of tumor cells contribute to predicting breast cancer recurrence in individuals. However, previous research suggests that using conventional parameters as therapeutic approaches has limitations and may result in a percentage of patients being treated wrong (Nguyen et al., 2021). Owing to this concern, a new taxonomy in the classification of breast cancer has emerged in the past few years known as the "molecular classification" which includes factors like hormonal receptors (estrogen

and progesterone) present on the surface of the tumor cell, and HER-2 neu receptors contributing to better prognosis of breast cancer (Eliyatkin et al., 2015). Hence, molecular subtyping of breast cancer based on the studies of gene expression profiling and its relationship with diverse phenotypic traits has led to the development of more reliable and precise tools that would not only help to determine patients who will benefit from systemic adjuvant therapy but also will minimize the risk of incorrect prognosis (Nguyen et al., 2021).

1.2 Classification of Breast Cancer

Modern oncological treatment focuses on the correct prognosis of cancer for better patient management and in this new era, high throughput molecular techniques have revolutionized the classification system of breast cancer, revealing the intricacies of genomic mutations and the prevalence of heterogeneity.

1.2.1 Histological Classification

Based on microscopic characteristics entailing morphology, and cytological characteristics of the tumor cells, breast cancer is broadly classified into two groups namely in situ carcinoma and invasive (infiltrating) carcinoma. Furthermore, in situ cancer is sub-categorized into ductal and lobular. Ductal carcinoma has typically been subdivided based on the architectural features of the tumor, yielding five distinct subtypes namely comedo, cribriform, micropapillary, papillary, and solid carcinomas (Malhotra et al., 2010). Today, WHO identifies about 18 different histological subtypes of breast cancer among which invasive carcinoma is the most frequently occurring subtype (40%-80%) and comprises a wide variety of other tumor subclasses such as invasive lobular carcinoma, tubular carcinoma, neuroendocrine, mucinous A, and mucinous B (Stanisławek, 2021).

1.2.2 Molecular Subtypes

Based on the new classification system for breast cancer subtypes, breast cancer is categorized into the following types- Luminal A, Luminal B with HER2 negative, Luminal B with HER2 positive, HER2 enriched, and basal-like triple-negative breast cancer death (Kondov et al., 2018).

1.2.2.1 Luminal A

Luminal A subtype is identified by the expression of estrogen and/or progesterone hormone receptors (ER+/PR+) on the cancer cells and the absence of high levels of HER2 receptors (HER2 negative) along with low levels of the protein Ki-67 (<14%) (Guiu et al., 2012). Individuals with this type of cancer show a low rate of proliferation, good differentiation, and a low risk of relapse thus making it cancer with the best prognosis. However, it shows a poor response to chemotherapy and is sensitive to endocrine therapeutic approaches (Jeibouei et al., 2019; Kondov et al., 2018)

1.2.2.2 Luminal B

Reduced expression of estrogen and progesterone receptors along with the exhibition of positive or negative HER2 receptors, and a high value for Ki-67 protein (>14%) are the characteristic features of the luminal B subtype of breast cancer (Kondov et al., 2018; Z. H. Li et al., 2016). Owing to its aggressive clinical behavior, the prognosis of luminal A subtype is far better than that of luminal B. The luminal B subtype accounts for roughly 40% of all breast malignancies, according to the 2013 St Gallen agreement. As a result, the luminal B subtype's recurrence behavior and clinical outcome should be taken into account. Most luminal B tumors are likely to respond better to neoadjuvant chemotherapy (Z. H. Li et al., 2016).

Luminal B subtype can further be subclassed into 2 groups which are-

1.2.2.2.1 HER2-positve

Around 10% to 20% of cases of all breast cancers are HER2-positive breast cancer, a subset of luminal B, and is defined by ERBB2/HER2 gene amplification and/or overexpression of its associated kinase receptor protein. This results in its increasingly aggressive behavior, which leads to very poor survival outcome of the disease. However, the development of anti-HER2 targeted therapies (lapatinib, pertuzumab, etc.) especially the monoclonal antibody trastuzumab, antibody-drug conjugates such as trastuzumab deruxtecan, and immunotherapy have improved the survival rate in metastatic conditions (Schettini & Prat, 2021). Additionally, this subtype is referred to as a multifaceted disease where the co-expression of HER2 and hormone receptor partly contributes to its heterogeneity in this subgroup (Lee et al., 2019).

1.2.2.2.2 HER2-negative

The Luminal B HER2 negative subtype is the most heterogeneous form of breast cancer which can be identified by a high Ki-67 proliferation index (>20 percent), absence of HER2 receptors on the cell surface, or/and low progesterone (PR<20%), and estrogen receptors of varying intensity and distribution (Rajc et al., 2018). This type of breast cancer is the most prevalent type of all accounting for 60%-70% of cases worldwide. Endocrine therapy remains the cornerstone in the treatment of the HER2-negative subtype of breast cancer. Tamoxifen, letrozole, anastrozole, and fulvestrant are all currently accessible endocrine therapies whereas, for early-stage breast cancer, tamoxifen or AIs are considered standard treatments. Antiestrogen resistance, on the other hand, is a significant barrier to chemotherapy and avoiding cancer relapse. Fortunately, throughout the last decade, several novel targeted drugs, including CDK 4/6 inhibitors, and mTOR/PIK3 inhibitors, have shown improved

effectiveness in combination with antiestrogen therapy, potentially overcoming this resistance (Andrahennadi et al., 2021).

1.2.2.3 HER2-Enriched

With the Human Epidermal Growth Receptor 2 being over-expressed in about 20%–25% of breast cancer cases worldwide, the HER2 enriched (HER2-E) becomes the most characteristic inherent subtype (Godoy-Ortiz et al., 2019; J. Wang & Xu, 2019). This type is identified by the overexpression of growth factor receptor-related genes, low expression of estrogen-related genes, cell cycle-related genes, and basal-related genes. Even though HER2-Enriched is associated with HER2+ breast cancer, 40% of HER2+/HR+ tumors belong to the HER2-Enriched subtype (Schettini et al., 2021). Overexpression of HER2 is linked to increased tumor development, a poorer response to standard chemotherapy, and a lower overall survival rate, resulting in a poor prognosis (Pallerla et al., 2021). Similar to HER2 positive breast cancers, HER2 enriched malignancy gives the best therapeutic outcomes when treated with anti-HER2 based targeted therapies such as trastuzumab, lapatinib, pertuzumab, with or without adjuvant and neoadjuvant chemotherapy (Godoy-Ortiz et al., 2019).

1.2.2.4 Triple-Negative Breast Cancer

The main obstacle in treating patients with triple-negative breast cancer (TNBC) is that they do not exhibit the necessary genes for progesterone receptor (PR), HER2, or estrogen receptor (ER) (Pallerla et al., 2021). Owing to its poor prognosis and high metastatic ability, TNBC patients have a shorter survival time than other breast cancer subtypes, with a 40 percent mortality rate in the first five years after diagnosis. Epidemiological studies suggest that TNBC is most common among premenopausal young women under 40 years old, who constitute 15 to 20 percent of all breast cancer patients (Yin et al., 2020). Nonetheless, the therapeutic options for TNBC comprise standard chemotherapy with taxanes, anthracycline,

antimetabolites, platinum agents, and new microtubule-stabilizing agents (Wahba & El-Hadaad, 2015). Today, several clinical trials are being performed that target specific receptors, and have resulted in the development of novel targeted drugs, such as antibody-drug conjugates, PARP inhibitors, and immune checkpoint inhibitors, which are transforming the therapeutic prospects for TNBC (Yin et al., 2020).

1.3 Rationale

For many years, breast cancer has had the highest occurrence rate among all cancers in women worldwide. Rapid advances in molecular biology, systems biology and genomic studies have substantially broadened our knowledge of this disease in recent decades, leading to the development of targeted therapies such as biologics, biosimilars, cell cycle inhibitors, and inhibitors of various cellular signaling pathways. Traditional treatment approaches have their own set of limitations, and oncologists, as well as the patients, must be aware of the role of novel and promising treatment options in enhancing breast cancer therapy and, ultimately, patient quality of life. This paper seeks to disseminate the current knowledge about the role of novel targeted therapies in realizing and exploring the full potential of these newer treatment approaches in the effective management of breast cancer.

Chapter 2

Methodology

Systematic literature review was followed to conduct this project in accordance with the PRISMA checklist. This 27-item checklist includes all aspects of the manuscript in order to facilitate the preparation of the review paper as well as maintain its quality. The review gives an idea of the uses and prospects of targeted therapies in breast cancer management. All the information was collected from credible sources such as Elsevier, Science direct, nature, The Lancet, Taylor and Francis, and MDPI. The information and evidence gathered were referenced properly to provide a better understanding of the topic.

Chapter 3

Etiology and Pathogenesis

Given inherent, multivariate, life-long exposures to various endogenous and exogenous variables, such as ionizing radiation, endocrine disruptors found in prescription medicines, pesticides and fuels, and tobacco smoke, the etiology of breast cancer may be among the most complex of all malignancies. Furthermore, defects in DNA damage repair (DDR) components, defects of homologous recombination repair (HRR) (Blackwell et al., 2018), as well as inherited proneness owing to autosomal dominant gene mutation, which accounts for 5% to 10% of all breast cancer cases, impact the etiology of breast cancer significantly. Among the genetic anomalies that can contribute to the accumulation of genetic modifications are mutations in the BRCA1 and BRCA2 genes, which actively play role in DNA repair in case of DNA damage. Furthermore, excessive oxidative stress, fetal estrogen exposure, estrogen exposure causing both normal and malignant breast cell proliferation, exogenous hormone exposure, and occupational cancer are all factors to consider. Also, obesity, idleness, alcohol consumption, hormone therapy, high breast density (Nounou et al., 2015), and poor nutrition intake by mothers have all been associated with a higher risk of breast cancer in later stages of life in female children (Blackwell et al., 2018).

These factors can work independently or in combination to initiate tumorigenesis in individuals (Abdulkareem, 2013). Breast cancer can grow and metastasize to other parts of the body after it develops a primary tumor. This is how invasive breast cancer develops as the disease progresses, contributing to the pathogenesis of the disease. Furthermore, pathologic testing, which detects the severity of metastases in the body, aids breast cancer staging. Factors based on tumor progression including the size of the primary tumor, distant

metastasis, status of regional lymph node, and advanced metastases contribute to breast cancer staging in patients (Giuliano et al., 2018).

Metastasis develops when the cancer cells migrate far away from the primary tumor in the fluids to the blood circulation or lymphatic system. The circulating tumor cells (CTC) extravasate into the organs where they form metastatic colonies. Data suggests, 30%–60% of patients with metastatic breast cancer have bone lesions, 4%–10% have lesions in the brain, 15%–32% have lesions in the liver, and 21%–32 % have lesions in the lung (Medeiros & Allan, 2019). These metastatic lesions infiltrate important organs and worsen the patient's health, generating many foci that are difficult to remove surgically and developing resistance to the currently available systemic therapy (Fayad et al., 2013). Metastatic breast cancer has long been associated with lethal outcomes and is usually thought to be incurable. Although overall survival has improved in recent decades, survival rates remain low, with a 5-year survival rate being 27% and a 10-year survival rate being 13% (Westphal et al., 2018). Hence, metastatic breast cancer continues to remain a prime causative factor in patient morbidity, researchers are attempting to develop new treatment agents and biomarkers to combat and prevent breast cancer metastasis (Medeiros & Allan, 2019).

Chapter 4

Diagnosis

4.1 Conventional Methods

Diagnostic imaging and biopsy are essential for confirming the presence of a tumor and making surgical decisions about central tumor care, regional node staging, and treatment sequencing. The severity of the disease is assessed after a diagnosis, which in most situations determines whether or not neoadjuvant therapy is required (Moo et al., 2018). Although the high incidence rate of breast cancer is unavoidable, it is possible to reduce breast cancer mortality by early and correct diagnosis of the disease. Hence, detecting breast cancer early on is critical, as it can considerably increase the odds of successful treatment, resulting in a 20% decrease in overall fatality rates (García-Aranda & Redondo, 2019). Clinical breast examinations, MRI, computerized tomography, mammography, ultrasonography, oncogene identification, digital breast tomosynthesis, and positron emission tomography are some traditional tools for the diagnosis of breast malignancies (He et al., 2020). Nonetheless, these techniques have several drawbacks, such as being costly, not suited for all women, time-consuming, and inflicting radiation harm. To overcome such problems, it is critical to develop high-sensitivity and quick early-stage breast cancer detection techniques. In recent years, researchers have focused their efforts on developing biosensors like optical, piezoelectric, and electrochemical biosensors that can detect breast cancer using several biomarkers. Uses of quick and cost-effective microwave imaging techniques are also explored as potential tools for diagnosis in early-stage breast cancer (L. Wang, 2017). With the development and application of these approaches in the future, they will be able to not only diagnose breast cancer from multiple angles, but also evaluate the effect of treating

breast cancer and assist in obtaining the most accurate result possible, by means of their increased throughput, speed, sensitivity, and specificity (He et al., 2020).

4.2 Biomarkers

Biomarkers are key diagnostic and therapeutic tools in the treatment of breast cancer. In biomedical research, biomarkers that are diagnostic of tumor intrinsic traits at the molecular level have been eagerly pursued as it provides an early and molecular diagnosis of breast cancer (Zubair et al., 2021), assess risk for patients, determine prognosis, guide treatment, and monitor patients with progressive breast cancer due to the insufficient prognostic and predictive ability of histological classification of breast cancer (Michael J. Duffy et al., 2015). Breast cancer molecular biomarkers give diagnostic information and predict treatment response, making them the foundation for better decision-making and clinical outcomes. Human epidermal growth factor receptor 2 (HER2), Estrogen receptor (ER), Progesterone receptor (PR), and protein Ki 67 are examples of biomarkers that eliminate technical difficulties, tumor heterogeneity, and interpretation variability by providing effective diagnostic information (M. J. Duffy et al., 2017; Gamble et al., 2021). Currently, Breast Cancer Index, Endo Predict, MammaPrint, Prosigna, IHC4 Mammostrat, and Oncotype Dx are seven prognostic signature molecular tests available for breast cancer diagnosis (Zubair et al., 2021).

Chapter 5

Treatment Options in Breast Cancer

Chemotherapy, surgery, radiotherapy, and endocrine therapy are the most common treatments available for breast cancer. However, the considerable side effects of existing therapy choices necessitate the development and implementation of innovative therapeutic techniques which have significantly redefined the treatment strategy for breast cancer (Nounou et al., 2015).

5.1 Conventional Modalities

5.1.1 Surgery and Radiation Therapy

The majority of women suffering from early-stage breast cancer are eligible for either mastectomy or lumpectomy (breast-conserving surgery) with radiation (Moo et al., 2018), where radiation therapy will work as an additional treatment after surgery that will help in shrinking the tumor in combination with other systemic therapies (Nounou et al., 2015). The most prevalent radiation therapies are breast irradiation, chest wall radiotherapy, and 'breast boost,' which is a high-dose radiotherapy boost to the tumor bed following surgery (Stanisławek, 2021). Despite radiation being beneficial to many women with breast cancer, adverse health hazards such as cardiac and pulmonary toxicity, lymphedema, and subsequent malignancies are still observable (Brown et al., 2015).

5.1.2 Chemotherapy

Coming towards a systemic therapeutic approach for breast cancer management, neoadjuvant chemotherapy is a potential option, especially in the case of HER2-positive and triple-negative breast cancer in females (Bartsch et al., 2018). It targets all the rapidly proliferating

cells in the body including cancer cells (Pathak et al., 2018). Neoadjuvant chemotherapy increases pathologic complete remission (PCR) and breast conservation rates and as a result, various studies are attempting to raise PCR rates by using more chemotherapeutic medications (Bartsch et al., 2018). Adjuvant chemotherapy (AC) is one of the most important therapies for people with breast cancer. It is often used to increase survival and minimize the chance of relapse in patients, especially those with large, estrogen receptor (ER) negative, high-grade original tumors, and lymph node involvement. It is proven to lower the risk of breast cancer death by 30% to 40% when compared to patients who do not receive chemotherapy (Zhan et al., 2018). Anthracyclines, taxanes, and cytotoxic agent carboplatin are the most efficacious chemotherapy treatments for breast cancer patients, administered via injection or taken orally. These drugs include Doxorubicin and epirubicin. On the other hand, Docetaxel and paclitaxel are used as taxanes. Furthermore, these medications are frequently used in conjunction with other treatments such as fluorouracil and cyclophosphamide (Pathak et al., 2018). On the downside of this significant treatment approach, chemoresistance remains the biggest hurdle in cancer treatment. Efflux transporters, cancer stem cells, non-coding RNAs, and signaling pathways, are all possible molecular causes of chemoresistance in breast cancer (Cao et al., 2021). Moreover, side effects such as nausea, vomiting, hair loss, mouth sores, increased vulnerability to infection, leucopenia, anemia, bruising, bone marrow suppression, bleeding along with lesser common side effects like neuropathy, hand-foot syndrome, cardiomyopathy, impaired mental functions, disturbances in the menstrual cycle and reproductive abnormalities are most likely to develop in women (Stanisławek, 2021).

5.1.3 Endocrine Therapy

Patients with invasive breast cancer who have positive immunohistochemistry for ER protein expression (ER+) are treated with endocrine treatment alone or in combination with other targeted therapies (Johnston & Cheung, 2018). ET is also employed as the principal therapy

for many patients with HR+ metastatic breast cancer since it reduces tumor remission (Berkowitz et al., 2021). For HR-positive breast cancer, selective estrogen receptor modulators like tamoxifen, aromatase inhibitors like anastrozole, letrozole, and exemestane, and selective estrogen receptor down regulators like fulvestrant are now utilized in the first or second-line treatment. Also, monotherapies are available based on the previous treatment strategy of the patient (Shen et al., 2020). Despite several positive treatment outcomes with endocrine therapy, ER/PR alternation or mutation can lead to intrinsic and acquired resistance to these therapies rendering poor therapeutic outcomes. Advanced clinical investigations have developed combinational treatment options that can help overcome endocrine resistance. For example, combining anastrozole with trastuzumab, as well as mTOR inhibitors and an endocrine therapy-like treatment regimen that comprises of everolimus and letrozole, leads to tumor size reduction and cell proliferation suppression (Koch, 2017).

Following a diagnosis, standard therapies are given to help control the disease and improve survival. The goal in the later stages is to extend life and ease symptoms. Unfortunately, standard treatments are causing patients to develop resistance, resulting in unsatisfactory therapeutic outcomes. As a result, newer methods for breast cancer treatment have emerged. Innovative targeted agents can help patients by delivering medications that overcome many of the drawbacks of current breast cancer therapy regimens.

Despite the fact that the majority of women with early-stage breast cancer are detected soon enough to be successfully treated with chemotherapy, surgery, radiotherapy, or a combination of therapies, about 30% of women with the early-stage disease develop metastatic disease subsequently which leads to patient mortality (García-Aranda & Redondo, 2019). Heterogeneity of tumor cells plays a key role in developing resistant phenotypes in cancer which is the biggest reason for the failure of treatment and cancer relapse (Pucci et al., 2019). In this scenario, biological agents targeting tumor cells, provide increased tumor selectivity

and have demonstrated to be viable options for tackling breast cancer, as opposed to traditional treatments with poor tumor selectivity and the potential to cause more side effects (García-Aranda & Redondo, 2019).

5.2 Novel Treatment Modalities: Targeted Therapy

Targeted therapy is a type of treatment modality which targets molecules or cellular pathways involved in cancer proliferation and survival. As a result of better understanding of the molecular etiology of breast cancer and efforts to overcome resistance to standard chemotherapies, several targeted treatment modalities have been developed in recent decades, which have been described in this section.

5.2.1 Biologics

Biologics are therapeutic drugs that contain active ingredients derived from living cells or creatures including humans, animals, bacteria, (Uifălean et al., 2018). These drugs offer a targeted therapy approach which involves agents that prevent cancer from spreading by interfering with the activity of specific molecules involved in tumor cell proliferation and survival (Masoud & Pagès, 2017). They include anti-HER2 monoclonal antibodies, antibody-drug conjugates (ADCs), anti-vascular endothelial growth factor (VEGF) antibodies, and immune checkpoint inhibitors.

5.2.1.1 Anti-HER2 Targeted Humanized Monoclonal Antibody (mAb)

The human epidermal growth factor receptor (HER2) is characterized as a transmembrane tyrosine kinase receptor that belongs to a category of receptor family namely the human epidermal growth factor receptor (EGFR). These are found in low levels in the tissues of the breast, kidney, central nervous system, ovary, liver, and lung. Upon binding of HER2 protein with ligand phosphorylation is initiated that leads to the activation of phosphatidylinositol 3-

kinase (PI3k) and mitogen-activated protein kinase (MAPK) pathways which stimulate further cellular growth, proliferation, and metabolism (Patel et al., 2020). Overexpression of this protein is found in 25%–30% of breast cancer cells, and abnormal HER2 activity leads to rapid metastasis and therapeutic resistance (Komarova et al., 2019). As a result of improved understanding of tumor biology and HER2 signaling, anti-HER2 treatments, such as humanized monoclonal antibodies have been developed (Soiza et al., 2018).

5.2.1.1.1 Trastuzumab

Trastuzumab (Herceptin) was approved by the FDA in 1998 as the first anti-HER2 biologic drug for metastatic HER2-positive breast cancer, and since then it has shown significant clinical efficacy and extended overall survival rate in some patients suffering from HER2-positive breast cancer, making it one of the most widely used anti-HER2 targeted therapies for breast cancer (Xu et al., 2016). Herceptin interacts with the HER2 receptor's subdomain IV to inhibit HER2 signaling and prevent overexpression. Trastuzumab has a broad range of applications and is used as a standard therapeutic method in a variety of treatment options. According to a meta-analysis published in 2012, Herceptin increased pathologic complete response rates from 23% to 40%. This medicine is also utilized as an anti-HER2 treatment in adjuvant chemotherapy and extended adjuvant situations. However, studies show that if an anthracycline-based regimen is used, HER2-directed therapy should be given sequentially due to the higher risk of cardiotoxicity, whereas if a non-anthracycline-based regimen is used, chemotherapy and anti-HER2-directed therapy should be given simultaneously. In progressive breast cancer, Herceptin is used with a taxane either docetaxel or paclitaxel, and pertuzumab in a standard regimen (Patel et al., 2020).

Another anti-HER2 targeting monoclonal antibody available in the market is pertuzumab. It was approved by FDA in 2017 and works in a similar mechanism like

trastuzumab. Pertuzumab effectively prevents HER2 homo and heterodimerization by binding to an epitope inside this region, preventing HER2 tyrosine kinase activation and downstream cell signaling (Lamond & Younis, 2014). Pertuzumab in combination with trastuzumab and a taxane is now the preferred first-line therapy for patients with HER2-positive metastatic breast cancer, and dual HER2 blockade with pertuzumab plus trastuzumab and docetaxel is recommended as a first-line treatment for HER2-positive recurrent or metastatic breast cancer due to its superiority in progression-free survival (Takahashi et al., 2021).

Despite the fact that anti-HER2 monoclonal antibodies have changed the quality of healthcare for HER2-positive breast cancer patients, resistance to these drugs still persists. Trastuzumab resistance can be caused by HER2 receptor defects, elevated tyrosine kinase receptor levels, or intracellular changes (Patel et al., 2020). Furthermore, they are typically ineffective as monotherapy and must be used in conjunction with chemotherapy, which limits their use in particular patient populations (Miller & Schwartzberg, 2019). In addition to the above-mentioned targeted therapies, some newer drugs have been approved in recent times including tucatinib, Pyrotinib, Poziotinib, Neratinib, Lapatinib, Margetuximab (MGAH22), and Trastuzumab deruxtecan-nxki (DS-8201a/Enhertu) for the targeted action against HER2 positive breast cancer (Patel et al., 2020).

5.2.1.2 Antibody-Drug Conjugate (ADC)

The concept of linking toxins to antibodies marks as the leading cause for the development of antibody-drug conjugates (Adams et al., 2021). ADCs are a novel class of protein-based therapeutic agents that incorporate the cancer-killing ability of highly potent cytotoxic substances known as payloads with the targeting capabilities, high sensitivity, and stability of monoclonal antibodies to increase precise drug delivery in cancer cells while avoiding

chemotherapeutic damage to healthy tissues (Abbas et al., 2021). ADCs work by forming an ADC-Ag complex as a result of ADC binding to the surface of the antigen-presenting cell. This results in the internalization of the complex and the release of the payload inside the tumor cell. This payload binds to the intracellular DNA, tubulin, or topoisomerase 1 and exerts its cytotoxic effect (Adams et al., 2021). The first approved ADC is Ado-trastuzumab emtansine (TDM-1) for treating HER2-positive breast cancer following the treatment with taxanes and trastuzumab. Two novel ADCs have recently been approved by FDA and thus, have entered the therapeutic scenario for advanced breast cancer. In a heavily pretreated trial, Trastuzumab deruxtecan (T- DXd) demonstrated promising results in the phase II DESTINY-Breast01 trial, and sacituzumab govitecan-hziy (SG) yielded positive clinical results in phase I/II trials for metastatic TNBC (Adams et al., 2021). The emergence and use of ADCs as a novel targeted therapeutic approach in the adjuvant setting of HER2-positive breast cancer have guided the ongoing clinical trials testing ADCs to change the quality of healthcare for both patients in an early and advanced stage of breast cancer (Barroso-Sousa & Tolaney, 2021)

5.2.1.3 Recombinant Humanized Monoclonal Anti-VEGF Antibody

Tumor cells, like other normal cell types in our bodies, require sufficient oxygen and nutrients to function. This is ensured by the angiogenesis of tumor cells. Angiogenesis is defined as the rapid development of new blood vessels, and it is one of the key long-term adaptations of the tumor microenvironments to low oxygen levels. The initiation and course of tumor angiogenesis is predominantly mediated by angiogenic growth factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (Madu et al., 2020).The vascular endothelial growth factor (VEGF) signaling through its receptor, which is made up of VEGF receptors VEGFR-1, VEGFR-2, and VEGFR-3 induces angiogenesis and is responsible for tumor growth. As a result, inhibiting the VEGFR-2 pathway is crucial to

developing a potential cancer therapy (Zhang et al., 2019). Since angiogenesis is a strong predictor of breast cancer prognosis, a lot of modern breast cancer treatment focuses on inhibiting the angiogenesis pathway (Madu et al., 2020). Bevacizumab (Avastin) was the first anti-angiogenic medication approved by the FDA in 2008 in the treatment of metastatic breast cancer. It is identified as a humanized anti-VEGF monoclonal antibody that prevents tumors from growing and spreading by inhibiting angiogenesis. It is effective in advanced breast cancer when used in conjunction with chemotherapy in adjuvant settings, although it has a low overall survival rate. The usage of Bevacizumab in breast cancer management, however, is a controversial topic (Chen et al., 2021). Ramucirumab, a humanized monoclonal antibody that targets VEGFR2, was also being studied as a therapy for advanced breast cancer. However, it has not yet been approved for the treatment of breast cancer owing to the lack of significant positive results with the combination of chemotherapeutic drugs in recent studies (Yardley et al., 2016).

5.2.1.4 Immune Checkpoint Inhibitors

Immune checkpoints are elevated when immune cells become more activated, acting as a negative regulator of the immune response to protect peripheral tissues. The immune cell's ability to elicit a cytotoxic response is prevented when the checkpoint is activated. These checkpoint proteins are essential for balancing autoimmunity and self-tolerance. Tumors, on the other hand, can take advantage of this network to improve their chances of survival. Immune checkpoint signaling can generate an immunosuppressive environment, allowing tumor cells to avoid immune-mediated death (Gaynor et al., 2020). Even though immunotherapy is a fairly newer approach, several immune checkpoint inhibitors are approved to be used in the treatment of breast cancer. Pembrolizumab and nivolumab are inhibitors of programmed death receptor PD-1 and have shown remarkable clinical efficacy

in immunotherapy trials when treated against progressive triple-negative breast cancer (Swoboda et al., 2018). Recently, in 2021, pembrolizumab (Keytruda) received its FDA approval to be treated in the early-stage and metastatic TNBC both in combination with chemotherapy and as monotherapy. Additionally, atezolizumab, which is the inhibitor of the ligand of programmed death receptor PD-1 (PDL-1) is the first FDA-approved checkpoint inhibitor in treating advanced triple-negative breast cancer with chemotherapy (Gaynor et al., 2020). Pembrolizumab and atezolizumab are the anticancer agents that have been investigated the most in breast cancer, particularly in the treatment of TNBC. Considering the latest breakthrough, immune checkpoint inhibitors are now undergoing extensive clinical trials to test their efficacy in treating various types of breast cancer, leading to the development of more immunotherapy-targeted treatments in the future (Wein et al., 2018).

The biologics available in breast cancer targeted therapy has been shown in the table below (Table 1).

Table 1: Available Targeted Therapies: Biologics (Tarantino et al., 2020)

Biologic	**Indication**	**Drugs**	**Success Rate**
Anti-HER2 Targeted Humanized Monoclonal Antibody	HER2-positive breast cancer	Trastuzumab, Pertuzumab, Margetuximab	Relative improvement in overall survival rate from 75% to 85%
Antibody-Drug Conjugate (ADC)	HER2-positive breast cancer, TNBC	Ado-Trastuzumab Emtansine (T-DM1), Trastuzumab deruxtecan,	Increased overall survival by months for patients with HER2 positive

		Sacituzumab govitecan-hziy	breast cancer
Recombinant Humanized Monoclonal Anti-VEGF Antibody	HER2-negative breast cancer	Bevacizumab	Overall response rate with monotherapy was moderate
Immune Checkpoint Inhibitors	Triple-Negative Breast Cancer (TNBC)	Pembrolizumab, Nivolumab, Atezolizumab	Overall Response rate is relatively low but the therapy is well tolerated

However, the therapeutic benefits of biological therapy are outweighed by the difficulty in accessing these drugs. Biological research has a direct impact on their accessibility because of the large cost required for their production. As a result, biosimilar product approval is becoming a more organized and balanced process, as these generic copies of drugs can provide patients with a more accessible and affordable treatment option (Santos-Neto et al., 2021).

5.2.2 Biosimilars in the Treatment of Breast Cancer

The addition of targeted biologics to the breast cancer therapy algorithm has, without a doubt, enhanced the number of effective therapeutic options available for both curable and advanced breast cancers, as well as indications for supportive care to manage treatment-related toxicities and resistances (Trapani & Curigliano, 2020). However, the high cost of biologics used in cancer treatment is a major hurdle to worldwide cancer treatment uptake, resulting in discrepancies in patient access to therapy, with low- and middle-income nations bearing the

brunt of the burden, implying significant global survival differences. With the expiration of the patents of biologics, there has also been a drive for more affordable and sustainable manufacture of drugs which has led to clinical trials and production of biosimilars by various pharmaceutical companies (Trapani & Curigliano, 2020). Biosimilars are biological drugs highly comparable and interchangeable to another already approved biological medicine known as the "reference medicine" and do not differ clinically in terms of pharmaceutical quality, efficacy, safety, and immunogenicity from the parent biologic. They are produced in different cell lines or bacteria. They are made from a DNA sequence that encodes a protein that has undergone various post-translational modifications in different cell types or microorganisms, and any unidentified alterations in posttranslational structure may raise structural variability and immunogenicity issues (Simoens et al., 2021).

5.2.2.1 Biosimilars of Trastuzumab

To date, only five biosimilar medications have been approved for use in the treatment of HER2-overexpressing breast cancer (Ogivri, Herzuma, Ontruzant, Trazimera, and Kanjinti). The reference drug for all of these biosimilars is trastuzumab. Several other trastuzumab biosimilars, as well as biosimilars of other biologics, are being evaluated, produced, and are in the approval pipeline (Miller & Schwartzberg, 2019).

Trastuzumab, the monoclonal antibody used in the first-line therapy of HER2-positive breast cancer, was added to the WHO Essential Medicines List in 2015, however, at US$20,000 for a course of treatment, it is too expensive for many health systems throughout the world (The Lancet, 2020). Furthermore, the European patent for trastuzumab expired in 2014, and the US patent expired in 2019. Following these events, numerous companies filed applications for trastuzumab biosimilars, paving the way for more anti-HER2 medicines to be used in the future (Piezzo et al., 2021). Competition among manufacturers to make trastuzumab

biosimilars could drive down pricing, which could be a benefit for breast cancer patients in low-income nations where numerous biologics will be accessible and will allegedly cost 65 percent less than the reference trastuzumab (The Lancet, 2020). Currently, there are five approved biosimilars of trastuzumab for the treatment of HER2-positive breast cancer. In December 2017, the US Food and Drug Administration (FDA) approved trastuzumab-dust (MYL-1401O), also known as Ogivri, for adjuvant and metastatic therapy of HER2-overexpressing breast cancer. One year later, in December 2018, the US FDA approved trastuzumab-part (CT-P6), marketed as Herzuma, for the adjuvant and metastatic treatment of HER2-overexpressing breast cancers. Trastuzumab-dttb (SB3), also known as Ontruzant, was approved by the US FDA in January 2019 as the third trastuzumab biosimilar with authorization for HER2-overexpressing breast cancer. In March 2019, the US FDA approved a fourth trastuzumab biosimilar, trastuzumab-qyyp (PF-05280014), sold under the brand name Trazimera, and in June 2019, the fifth biosimilar, ABP980, available under the brand name Kanjinti, was approved for HER2-positive metastatic breast cancer (Miller & Schwartzberg, 2019).

Biosimilars are often subjected to a thorough market approval process based on the complete evidence supporting the prospective drug's position as a biosimilar drug, referred to as “Totally of Evidence” (Piezzo et al., 2021). An analytical examination of the potential biosimilar's structural and functional properties is required. The molecule's amino acid sequence, structural arrangement, and target binding factors are all assessed. Additionally, evaluation of pharmacological features, nonclinical activities, safety equivalence to the reference biologic, and clinical efficacy are also considered. Biosimilar drugs have been approved for use in a vast array of applications based on a combination of evidence demonstrating similarity with the original drug in terms of structure, function, pharmacological characteristics, and efficacy (Miller & Schwartzberg, 2019). As a result,

success in Phase I, II, and III trials would lead to rapid market authorization (Piezzo et al., 2021).

Various trastuzumab biosimilars are currently being developed, and comparative clinical pharmacokinetic studies in groups of healthy volunteers have revealed similarities in pharmacologic characteristics, immunogenicity, and safety profiles, implying that they could alter the trajectory of targeted therapies in breast cancer by providing new, efficacious, and sustainable therapeutic options (Blackwell et al., 2018).

The biosimilars available in breast cancer targeted therapy has been shown in the table below (Table 2).

Table 2: Available Targeted Therapies: Biosimilars (Miller & Schwartzberg, 2019)

Biosimilar	**Reference Drug**	**Year of Approval**	**Indication**	**Manufacturer**
Ogivri	Trastuzumab (Herceptin)	2017	HER2-overexpressing breast cancer in both adjuvant and metastatic settings	Mylam-Biocon Biologics
Herzuma	Trastuzumab (Herceptin)	2018	HER2-overexpressing breast cancer in metastatic scenario	Celltrion
Ontruzant	Trastuzumab (Herceptin)	2019	Adjuvant treatment of early-stage HER2-	Samsung Biopecs

			overexpressing breast cancer	
Trazimera	Trastuzumab (Herceptin)	2019	Advanced HER2-overexpressing breast cancer	Pfizer
Kanjinti	Trastuzumab (Herceptin)	2019	Neoadjuvant and adjuvant treatment of early-stage and metastatic HER2-overexpressing breast cancer	Amgen and Allergen

5.2.3 Other Targeted Agents

CDK4/6 inhibitors, PARP inhibitors, and PI3K/Akt/mTOR signaling pathway inhibitors are other modalities for the targeted treatment of breast cancer (Ju et al., 2018).

5.2.3.1 CDK4/6 Inhibitors

Endocrine therapy is considered the cornerstone of HR-positive breast cancer treatment. Resistance to hormonal therapy, on the other hand, remains a significant challenge, as 50% of patients diagnosed with metastatic HR-positive breast cancer acquire resistance to the hormonal therapy they undergo (Preusser et al., 2018). When it comes to the mechanism of resistance, the retinoblastoma (Rb) pathway plays a key role. The tumor suppressor protein, retinoblastoma (Rb) controls early cellular division by inhibiting the G1/S transition by binding to E2F transcription factors, whereas Rb inhibition permits cell division to continue.

Various growth factors can cause cyclin D to bind to cyclin-dependent kinases (CDK4 or CDK6) during G1phase, causing Rb to be phosphorylated and E2F to be released, resulting in cell cycle progression (X. Li, 2016). Incorporating a CDK4/6 inhibitor into endocrine therapy to target this resistance pathway has recently been proven to improve clinical results and delay tumor development. A combination of endocrine therapy and a CDK4/6 inhibitor is often given to patients with advanced HR+ and HER2 negative breast cancer, according to current treatment guidelines. It is used as a first-line treatment with aromatase inhibitors like tamoxifen and letrozole, or as a second-line treatment with the ER antagonist fulvestrant in postmenopausal women. Palbociclib, Ribociclib, and Abemaciclib are currently FDA-approved CDK4/6 inhibitors that have shown efficacy in HR+, and HER2-negative metastatic breast cancer. The efficacy of these biologics in treating this specific subtype of breast cancer has prompted more clinical trials to test their potency in adjuvant and neoadjuvant treatment settings, in combination with endocrine therapy (Braal et al., 2021). Remarkably, only abemaciclib, the least selective inhibitor, provides evidence for an adjuvant effect and is the only CDK4/6 inhibitor licensed for use as monotherapy in the metastatic setting (George et al., 2021).

5.2.3.2 PARP Inhibitors

Individuals with germline DNA mutations are at a higher risk of acquiring breast cancer. The BRCA1 and BRCA2 loss-of-function mutations, which are necessary for DNA repair, are among the genetic alterations that can lead to a buildup of various genetic mutations and significantly enhance the lifetime risk of growing breast cancer (Nounou et al., 2015). These mutations are observed in at least 5% of unselected breast cancer patients and around 30% of patients with a family history of this malignancy. PARP (poly adenosine diphosphate-ribose polymerase) enzymes (PARP1 and PARP2) are integral components in the DNA repair

pathways including base excision repair, homologous recombination repair (HRR) pathway, mismatch repair, and nucleotide excision repair. PARP enzymes repair the damaged DNA by attaching to the damaged part and initiating a PARP-mediated PARlytation which as a result recruits a repair effector. At the last stage, the repair effector binds to the damaged portion of the DNA, and the PARP enzyme gets dissociated. Olaparib and talazoparib, two PARP inhibitors, are currently approved as targeted monotherapies in HER2-negative metastatic breast cancer. Both were approved by the FDA in the year 2018. These agents work by inhibiting the DNA damage response pathway (DDR) thus preventing the DNA repair of tumor cells (Cortesi et al., 2021).

5.2.3.3 PI3K/Akt/mTOR Inhibitors

The PI3K/AKT/mTOR is a complex signaling pathway of our body that is responsible for certain cellular activities like cell growth, metabolism, proliferation, apoptosis, and angiogenesis. Upon binding of a ligand with the receptors on the cell, PI3K (phosphatidylinositol (3,4,5)-trisphosphate kinase) is activated. This results in the generation of a cascade of reactions in which phosphorylation of PIP2 takes up a protein kinase B which is AKT and phosphoinositide-dependent protein kinase 1 (PDK1). The AKT is phosphorylated and activated by mTORC2 (mTOR complex 2) once it has been recruited to the cell membrane. This activated AKT phosphorylates the target proteins, causing cell survival, growth, and proliferation to be stimulated. Alterations in the PI3K pathway result in the deregulation in kinase activity and lead to tumor formation (Miricescu et al., 2021). This pathway is also a major reason for endocrine resistance in individuals receiving hormonal therapy and hence, the inhibitors of the PI3K pathway are potent agents in overcoming such resistance (Dong et al., 2021). The P13K mutation is found in 50% HR+ metastatic breast cancer, in which ER+/HER2 negative breast cancer comprises 37% of total cases (Miricescu

et al., 2021). To date, the FDA has approved several PI3K inhibitors for use in hormone receptor-positive breast cancers, including alpelisib, idelalisib, copanlisib, buparlisib, and capivasertib, with alpelisib being the first-ever approved PI3K inhibitor given in combination with fulvestrant in managing patients with HR+/HER2 metastatic breast cancer. Clinical data reveal that these targeted biologics used with other chemotherapeutic drugs like fulvestrant, paclitaxel are effective for the management of HR +/HER2 negative breast cancer as first-line or second-line treatment (Dong et al., 2021). As for mTOR inhibitors, Everolimus was the first approved mTOR inhibitor for HR+/HER2-negative breast cancer used in combination with fulvestrant. Also, it has shown efficacy in HER2-positive breast cancer when used in combination with Herceptin. Everolimus targets the complex mTORC1 which is a part of the downstream signaling of the PI3K/AKT pathway. Hence, blocking this process can lead to the prevention of tumor cell growth. Additionally, Temsirolimus is an approved PI3K inhibitor that is used in ER-positive advanced breast cancer (Dong et al., 2021; Miricescu et al., 2021).

Other biological agents available in breast cancer targeted therapy have been shown in the table below (Table 3).

Table 3: Available Targeted Therapies: Other Targeted Agents (Tarantino et al., 2020)

Targeted Agents	**Indication**	**Drugs**	**Success Rate**
CDK4/6 Inhibitors	HR-positive breast cancer	Palbociclib, Ribociclib, Abemaciclib	Overall survival was approximately 7 months after administering with

			chemotherapy
PARP Inhibitors	BRCA-mutated HER2-negative breast cancer	Olaparib, Talazoparib	Shows moderate success rate in BRCA mutation associated with breast cancer
PI3K/Akt/mTOR Inhibitors	Luminal A type breast cancer	Alpelisib, Idelalisib, Copanlisib, Buparlisib, Capivasertib, Everolimus, Temsirolimus	Overall response rate was found to be 16.4% in patients with HR+/HER2- breast cancer

Chapter 6

Challenges

Despite the development of numerous targeted therapies and biosimilars, drug resistance after a while of taking medications remains the prime obstacle in anticancer therapy. Many factors contribute to building resistance to these treatments. Trastuzumab resistance, for example, is likely to develop in patients because of HER2 receptor protein amplification, RNA overexpression, and downstream signaling pathway mutations. Recently, the use of Antibody-Drug Conjugates (ADC) has proven its efficacy as an anti-HER2 agent making it a promising candidate to tackle trastuzumab resistance (Masoud & Pagès, 2017). Adding to this, monoclonal antibodies have a limited dispersion due to their size, charge, and affinity for binding to their target. They also have non-specific binding due to the monoclonal antibodies' constant region (Fc), which limits their overall efficiency (Ju et al., 2018). Resistant mechanisms have also been discovered in targeted biologics such as anti-VEGF agents with the most notable one relating to cancer cells' versatility in producing a variety of alternative angiogenic signals restricting positive treatment outcomes (Masoud & Pagès, 2017). Moreover, even though many mechanisms have been identified that may underpin resistance to traditional cytotoxic and targeted treatments, none of them can entirely explain multidrug resistance, which is invariably acquired by all patients with all types of cancers. MDR has been linked to several causes, including higher drug efflux, genetic factors (gene mutations, amplifications, and epigenetic modifications), growth factors, greater DNA repair capacity, and increased xenobiotics. All of these mechanisms result in low efficacy and survival rates (Bukowski et al., 2020). Apart from developing resistance, it is very difficult to find an efficient agent applicable for all types of tumor cells given the diversity of biomarkers. Also, research has found that some anticancer drugs enhance the risk of primary

malignancies to an extent that is not favorable for the patient (Ju et al., 2018). Furthermore, the concern about biologics being inaccessible due to their high cost remains a problem requiring a feasible solution (Uifălean et al., 2018)

Chapter 7

Future Directions

Disease relapse, metastatic spread, and eventual drug resistance remain substantial clinical difficulties that restrict the longevity of patients with all breast cancer subtypes, particularly endocrine-therapy resistant tumors and chemotherapy-resistant TNBCs. The recognition of these clinical roadblocks has sparked substantial research into the biological mechanisms driving drug resistance characteristics, as well as the development of innovative treatment strategies to overcome them. Combination therapy regimens, nanotherapeutics, and biosimilars are promising prospects in the new era of breast cancer treatment, to prevent cancer recurrence and improve overall therapeutic efficacy (Thu et al., 2018).

In recent decades, the emergence and use of targeted biologics in breast cancer therapy are not any short of a breakthrough when it comes to overcoming the problems associated with chemotherapy and other conventional modalities of treatment. However, the challenges faced with the novel treatment options open the door for the discovery of other potential therapeutic strategies that would enhance the overall patient survival and standard of care in breast cancer malignancies worldwide. Combination therapy is a promising way forward towards overcoming the shortcomings of monotherapy, especially in the metastatic scenario. This approach refers to combining different classes of drugs in a dosage regimen for adjuvant settings. Currently, there are several drugs in the pipeline being tested for their potency in combinational settings (Fisusi & Akala, 2019). A few noteworthy potential drug regimens are- lapatinib in combination with capecitabine, and gemcitabine in HER2- positive metastatic breast cancer patients with progression after treating with a taxane is under investigation in phase II clinical trial (Fisusi & Akala, 2019), in similar ways, phase II study of anti-CSF1 monoclonal antibody lacnotuzumab (MCS110) in conjunction with

Gemcitabine and Carboplatin for advanced triple-negative breast cancer is under assessment. Also, apatinib combined with endocrine therapy in HER2-negative breast cancer involving metastasis in the chest is also under study in phase II clinical trial (H. Li et al., 2021). Additionally, a combination of siRNA targeted to EGFR mRNA with liposomal gefitinib in triple-negative breast cancer is being investigated (Shekar et al., 2020). Numerous such drug combinations are under study which has shown promising results in the clinical trials. These agents could give people a ray of hope in the battle against breast cancer.

The introduction of trastuzumab biosimilars has altered the environment for HER2 positive therapy and created opportunities for more biosimilars to enter the market. When compared to the biologic, these generic copies of biologics have the potential to provide patients with more affordable therapy options (Blackwell et al., 2018). Oncologists are currently researching the nature of the bio similarity exercise and how the clinical development of a biosimilar is adapted, indicating the possibility of more biosimilars being introduced in the market (Barbier et al., 2019).

While there are certain advantages to combination therapy, the varied pharmacokinetics and off-target toxicities that come with it limit its practical application. A multidrug delivery platform utilizing nanotherapeutics can be proposed to minimize drug toxicity, optimize pharmacokinetics, and produce pharmacological synergy between medications. Due to properties such as increased blood circulation, lesser off-target toxicity, and more drug deposition in the tumor, nanomedicine has facilitated greater drug delivery with a higher therapeutic index in cancer management (El-Sahli et al., 2021).

Chapter 8

Conclusion

Despite notable advances in the therapeutic field in recent decades, the prevalence of breast cancer in women remains a matter of concern (Godoy-Ortiz et al., 2019). A greater understanding of molecular pathways supporting tumor growth has led to the identification, development, and utilization of multiple biologic therapies and biosimilars. High selectivity, target specificity, and the capability to carry out a biological function causing minimal side effects are the features that separate targeted therapies from non-specific chemotherapeutic medications. As a result, targeted therapeutic approach has been considered as the most significant breakthrough in cancer treatment in recent decades. Moreover, numerous promising potential agents have been produced in the lab and are currently undergoing clinical trials. Anti-HER2 targeted monoclonal antibodies, CDK4/6 inhibitors, immune checkpoint inhibitors, blockers of PI3K/AKT/mTOR signaling pathways, PARP inhibitors, anti-VEGF agents, and the advent of trastuzumab (Herceptin) biosimilars have achieved new milestones in the past few years in treating numerous subtypes of breast cancer (Jin et al., 2019). These treatment approaches have proven to be a highly active area in anti-cancer therapy in tackling drug resistance associated with chemotherapy, radiation, and endocrine therapy. Even though these novel treatment approaches have proven their efficacy, they sometimes cannot escape the molecular resistance mechanisms leading to cancer relapse which remains the biggest hurdle in breast cancer therapy. However, oncologists today are focusing on targeted therapies and the utilization of these novel promising approaches that include combination therapy regimens and nanomedicine in the quest to achieve the desired therapeutic outcome and prolong survival in breast cancer patients.

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