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Targeted Therapy for Breast Cancer Treatment

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Abstract: The treatment of breast cancer contains numerous successes yet it persists as a leading world-wide medical problem. Molecular targeted therapy represents an essential treatment strategy because it focuses therapy on three genetic markers particularly Human Epidermal Growth Factor Receptor 2 (HER2) and Hormone Receptors (HR) along with Breast Cancer Gene (BRCA) mutations. The treatment outcomes have significantly improved by HER2 inhibitors which include trastuzumab, pertuzumab, and trastuzumab emtansine (T-DM1). The therapy of breast cancer positive for hormone receptors becomes more effective through the use of CDK4/6 inhibitors and Mechanistic Target of Rapamycin (mTOR) inhibitors which control cell growth and defeat resistance to hormone therapy. The Poly (Adenosine Diphosphate-Ribose) Polymerase (PARP) inhibitors olaparib and talazoparib prove beneficial for triple-negative breast cancer patients who have BRCA mutations. The immune checkpoint inhibitor pembrolizumab together with other immunotherapies demonstrates great benefit specifically in triple-negative breast cancer when the disease progresses rapidly. Current treatment of breast cancer faces major hurdles because patients develop drug resistance and their tumors show variation between individuals while experiencing adverse side effects. Ongoing study on combination therapeutic approaches seeks to develop treatments which increase both treatment efficacy and patient survival rates.

Keywords: *Breast Cancer; Molecular Targeted Therapy; Human Epidermal Growth Factor Receptor 2 (HER2) Inhibitors; Poly (Adenosine Diphosphate-Ribose) Polymerase (PARP) Inhibitors; Immunotherapy.*

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I. INTRODUCTION

Molecular targeted therapy stands essential in precision medicine approaches to breast cancer care management. Molecular diagnostic features enable physicians to develop targeted therapies which target specific molecular pathways critical for tumor growth that promote tumor growth and metastasis [1]. Different breast cancer characteristics demand subtype classification through specific genetic indicators such as Hormone Receptors (HR) and Human Epidermal Growth Factor Receptor 2 (HER2) together with Epidermal Growth Factor Receptor (EGFR) and Vascular Endothelial Growth Factor (VEGF) as well as Mechanistic Target of Rapamycin (mTOR) and Cyclin-Dependent Kinases 4 and 6 (CDK4/6)[2]. Treatment decisions become more effective through the identification of these markers. Breast cancer patients with HER2-positive characteristics receive treatment from trastuzumab and pertuzumab and lapatinib and trastuzumab emtansine (T-DM1) to stop the HER2 protein and halt tumor growth and improve survival rates [3]. The PI3K/AKT/mTOR signaling pathway shows frequent changes in breast cancer patients that generate unfavorable treatment results and cancer recurrence. Cancer growth of HR-positive breast cancer slows down because of drugs such as everolimus and buparlisib and ipatasertib blocks this pathway mechanism [4]. TNBC proves challenging to cure because it does not have hormone receptors nor targets HER2 receptors and this condition often develops through DNA repair mechanism alterations caused by BRCA mutations[5]. Olaparib and its counter parts talazoparib and veliparib act as PARP inhibitors to stop PARP enzymes from repairing DNA thus causing cancer cell death for patients with BRCA mutation [6]. The HR-positive breast cancer cell divide slows down under Cyclin-Dependent Kinase (CDK) 4/6 inhibitor treatment such as palbociclib, abemaciclib, and ribociclib which enhances the results of hormone therapy [7]. Bevacizumab represents a Vascular Endothelial Growth Factor (VEGF) inhibitor which hinders

Angiogenesis through VEGF blockade thereby starving the tumor of blood circulation to impede growth [8].

II. HR POSITIVE BREAST CANCER

Breast cancer that contains hormone receptors is called HR+ breast cancer and it represents a tissue type with receptors for estrogen and progesterone. These receptors propel cancer cell development by joining hormone receptors particularly estrogen or progesterone to cause cell multiplication [9].

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A. Key Characteristics of HR+ Breast Cancer:

- *Estrogen Receptor-Positive(ER+):*

Cancer cells have receptors for estrogen, meaning that estrogen promotes the growth of these cells [10].

- *Progesterone Receptor-Positive(PR+):*

Cancer cells have receptors for progesterone, another hormone that supports cancer cell growth [10].

B. Treatment of HR+ Breast Cancer:

Since HR+ breast cancer cells depend on hormones to grow, treatments aim to either block the hormone receptors or reduce hormone levels in the body [11]. Common treatments include:

C. Hormonal Therapy:

- *Tamoxifen:*

The selective estrogen receptor modulator (SERM) Tamoxifen blocks estrogen from activating cancer cell growth in ER+ breast cancer while being used for its treatment. The treatment links to receptors located on breast cancer cells which blocks estrogen signals that activate cellular growth-promoting genes. Breast cells experience Tamoxifen as an antagonist because it reduces cancer cell growth while prompting cancerous cells to die. There exist two effects of Tamoxifen on tissues: it functions as a weak estrogen agonist in bones and uterus where it helps bone density but might raise the endometrial cancer risk as well [12].

- *Aromatase Inhibitors (e.g., Letrozole, Anastrozole):*

Aromatase inhibitors function as breast cancer treatment by slowing down body estrogen production in patients with ER+ breast cancer [10]. These drugs inhibit aromatase to prevent the adrenal gland hormone conversion process into estrogen. The use of aromatase inhibitor drugs decreases body estrogen levels to halt or slow down the proliferation of breast cancer cells which need estrogen for growth. Postmenopausal women receive aromatase inhibitors for therapy because their estrogen mainly originates from the conversion process versus ovarian hormone production [13].

- *Fulvestrant:*

The selective estrogen receptor degrader drug Fulvestrant functions as a treatment option for patients who have estrogen receptor-positive breast cancer. When Fulvestrant binds to cancer cell estrogen receptors it destroys them so estrogen loses its binding target sites [2]. Fulvestrant induces estrogen receptor degradation, fully blocking signaling that hinders the development of ER+ breast cancer cells. Fulvestrant brings successful treatment results when healthcare providers use it for patients who show resistance to previous hormone therapy drugs including tamoxifen [10].

III. HER2+ BREAST CANCER

The human epidermal growth factor receptor 2 (HER2) protein shows abnormal levels of production in HER2-positive (HER2+) breast cancer cells. This protein promotes cancer cell development however excessive levels lead to cellular growth that becomes rapidly aggressive [14].

A. Key Characteristics of HER2+ Breast Cancer:

- The surface of breast cells contains HER2 receptors which function as receptor proteins. Breast cancer cells with an abnormal level of HER2 receptors show this condition because HER2 normally functions to control cell growth in healthy cells [3].
- The cellular growth rate together with aggressive nature of HER2+ breast cancers exceeds HER2-negative breast cancers [14].
- To determine HER2 status doctors use two diagnostic techniques including immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) which spot the HER2 protein in the cells [15].

B. Treatment of HER2+ Breast Cancer:

Patients with HER2+ breast cancer need treatment that blocks HER2 protein activity in combination with standard breast cancer treatments which might include chemotherapy along with surgery and radiation therapy [16].

- *Drug Examples:*

Trastuzumab (Herceptin), Pertuzumab (Perjeta), Ado-trastuzumab emtansine (Kadcyla), Lapatinib, Neratinib [14].

IV. CHEMOTHERAPY

The medical treatment of HER2-positive breast cancer requires patients to receive chemotherapy medications alongside drugs that specifically target cancer cell HER2 proteins. The chemotherapy treatment combines docetaxel and paclitaxel drugs which work together with trastuzumab and pertuzumab for targeting HER2 proteins in cancer cells [17]. The combined drugs work concurrently to eliminate cancer cells and stop their reproduction. Patients with HER2-positive breast cancer may need chemotherapy as either a preoperative treatment (neoadjuvant) or as a postoperative treatment (adjuvant) for minimizing the risk of recurrence [18]. Through HER2 protein attachment by targeted drugs cancer cells develop blocked growth signals that enable chemotherapy to work more effectively which results in better outcomes for patients with HER2-positive breast cancer[19].

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V. RADIOTHERAPY

High-energy X-rays from radiotherapy systems destroy cancer cell DNA so these cells cannot reproduce and survive. The cells of cancer undergo DNA damage during radiological treatment which results in their death or development of non-proliferative traits. Radiation treatment causes less damage to healthy cells because they have better natural recovery mechanisms which makes rapidly dividing cancer cells the most sensitive to the effects of radiation therapy. The treatment of HER2-positive breast cancer requires additional administration of trastuzumab along with other HER2-targeted radiotherapy components. HER2 receptor-targeted therapies enhance radiation treatment effectiveness because they protect cancer cells from repair pathways which would usually allow them to survive damages. The combined action produces superior treatment outcomes for these two therapies [20].

VI. SURGERY

Hospital staff commonly use surgery as a crucial treatment method for patients with HER2-positive breast cancer through mastectomy and lumpectomy procedures. A person undergoing a lumpectomy receives treatment of the tumor along with bordering tissue but a modified radical mastectomy requires removing the full breast. The treatment choice depends on tumor dimensions together with its placement and how much it has spread. Patients undergo surgery together with targeted therapy medications containing trastuzumab because this substance targets HER2 proteins to decrease recurrence risks. The evaluation of breast cancer spread requires that doctors remove nearby lymph nodes for testing. Patients undergoing breast cancer treatment can get follow-up procedures such as chemotherapy and radiation to minimize cancer recurrence [21].

VII. PI3K-AKT-mTOR PATHWAY

The PI3K-AKT-mTOR pathway inhibitors function as medication compounds which block different elements of the PI3K-AKT-mTOR signaling pathway. This vital signaling pathway controls cellular survival and growth and proliferation which makes its excessive activation a contributing factor for cancer development together with other diseases. The mechanism of specific molecule inhibition in this pathway leads to cancer cell growth reduction and death prevention [4].

A. Types of Inhibitors and Their Mechanism of Action:

➢ *PI3K Inhibitors:*

The main function of these inhibitors is to stop the activity of Phosphoinositide 3-kinase (PI3K) which generates Phosphatidylinositol (3,4,5)-trisphosphate (PIP3) from phosphatidylinositol 4,5-bisphosphate (PIP2). PI3K inhibitors block the enzyme activity that halts the recruitment and activation of downstream signaling proteins with AKT as one of these proteins. A disruption of the complete pathway results when PI3K inhibitors block the entire pathway which produces reduction of cell survival rates and cell multiplication activities [22].

- *Drug Examples:* Alpelisib

➢ *AKT Inhibitors:*

These drugs prevent both activation and operation of AKT because this kinase works to enable cell growth and survival progression. Through their inhibitory action on AKT these drugs block the phosphorylation activities which target mTOR and finally conclude in reduced cell survival and growth and resistance to programmed cell death [20].

- *Drug Examples:* Capivasertib, Ipatasertib

➢ *mTOR Inhibitors:*

The primary target of these drugs is the protein mTOR which operates in two distinct complexes named as mTORC1 and mTORC2. mTOR inhibitors mostly disrupt the mTORC1 complex to block downstream protein synthesis along with cell cycle progression and growth thus reducing cancer cell proliferation [4].

- *Drug Examples:* Temsirolimus, Everolimus

➢ *Dual PI3K/mTOR Inhibitors:*

These medication inhibitors simultaneously block the functions of PI3K and mTOR pathways. The combination treatment of both enzymes via dual inhibitors allows the complete blockade of the pathway because PI3K and mTOR maintain structural resemblances. Simultaneous multiple inhibitor therapy shows potential to defeat resistance that develops when using single inhibitors [22].

- *Drug Examples:* BEZ235 (Dactolisib)

VIII. CYCLIN-DEPENDENT KINASES 4 and 6 (CDK4/6):

Uncontrolled cell division and tumor growth occur when the Cyclin-Dependent Kinases 4 and 6 (CDK4/6) pathway becomes highly active in various cancers. This over activity results from genetic modifications, Cyclin D overexpression, Retinoblastoma (Rb) Protein dysfunction, and other regulatory defects in cell cycle control. CDK4/6 proteins play a crucial role in cell proliferation, making them important molecular targets in cancer therapy. In hormone receptor-positive (HR-positive) breast cancer, the CDK4/6 pathway drives tumor growth, so healthcare providers use CDK4/6 inhibitors to effectively block this process. These drugs inhibit CDK4/6 activity, halting cancer cell division and reducing tumor progression [7].

A. Cyclin-Dependent Kinases 4 and 6 (CDK4/6) Inhibitors:

➢ CDK4/6 inhibitors act as pharmaceutical agents that inhibit CDK4/6 protein activity, blocking Retinoblastoma (Rb) phosphorylation and preventing cancer cell cycle progression.
➢ CDK4/6 inhibitors include drug examples such as Abemaciclib, Ribociclib, and Palbociclib**.**
➢ CDK4/6 inhibitors are used in combination with hormone therapy for breast cancer treatment, effectively controlling cancer cell proliferation [23].

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IX. PARP INHIBITORS (PARP)

The Poly (Adenosine Diphosphate-Ribose) Polymerase (PARP) inhibitors use to prevent the chemical activity of the PARP1 and PARP2 enzymes. The inhibitors work best as anticancer drugs against cancer cells with broken DNA repair pathways including patients who possess BRCA1/2 mutations [6].

A. *Mechanism of Action:*

Inhibition of PARP blocks the healing process for single-strand breaks in DNA. The prolonged existence of single-strand breaks (SSBs) eventually produces lethal double-strand breaks (DSBs) after DNA replication begins. The repair of DNA double-strand breaks in normal cells requires homologous recombination which needs working BRCA1 or BRCA2 genes. Homologous recombination fails to function properly in cancer cells which possess BRCA1/2 genetic mutations. The cancer cells develop lethal DNA damage because PARP inhibition prevents their ability to repair both single-strand breaks and double-strand breaks. The cancer cells accumulate lethal DNA damage because they lack efficient capabilities to repair both SSBs and DSBs [6]. The concurrent action of PARP inhibition combined with changes in BRCA1/2 produces synthetic lethality which means the cancer cells die but regular cells survive [9]. The PARP inhibitor drugs comprise of therapeutic agents like Olaparib, Rucaparib, Niraparib, and Talazoparib [6].

X. VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF)

The drugs designed to block Vascular Endothelial Growth Factor (VEGF) inhibit protein activity that results in angiogenesis through the regulation of blood vessel formation. Tumors in cancer patients increase VEGF production to generate new blood vessels through which tumors get oxygen for expansion and dissemination. The drugs block VEGF to target the cancer by depriving the tumor of blood supply which may lead to tumor growth reduction [8].

A. *Mechanism of Action of VEGF Inhibitors in Breast Cancer:*

The VEGF pathway serves as a target for these inhibitors in breast cancer which diminishes angiogenesis processes that subsequently control tumor spreading and growth. The blockade of VEGF stops its interaction with endothelial cell receptors resulting in prevention of signaling that drives new blood vessel production [20].

- *Blocking VEGF Ligands:*

Blocking VEGF-A requires VEGF inhibitor drugs to directly bind the VEGF-A ligand so endothelial cells' receptors cannot interact with it. Bevacizumab (Avastin) functions as a monoclonal antibody which binds and interrupts VEGF-A activity because it blocks the VEGF-A from linking with its main VEGF receptors (VEGFR-1 and VEGFR-2). Signal pathways which result in new blood vessel formation cannot activate due to this prevention method [8].

- *Inhibiting VEGF Receptors (VEGFR):*

These medication blockers halt VEGF receptor function on endothelial cells which prohibits their VEGF signaling response. The tyrosine kinase activity of VEGFR-2 and sometimes other related receptors receives blockade from small molecule inhibitors such as sunitinib and sorafenib which in turn blocks the signaling pathway which promotes endothelial cell growth and migration [1].

- *Reduced Blood Supply and Tumor Starvation:*

The drugs cut off VEGF signaling to stop the formation of new blood vessels thus restricting tumor access to nutrients and oxygen. Insufficient blood circulation causes tumors either to contract in size or to grow at a diminished rate [8].

- *Example:*

VEGF inhibitors are used in combination with chemotherapy for certain types of breast cancer, such as HER2-negative metastatic breast cancer, where the cancer has spread beyond the breast and other treatments have not been effective. Bevacizumab, for example, is used alongside chemotherapy in some advanced breast cancer cases. However, the use of VEGF inhibitors in breast cancer is subject to careful consideration due to potential side effects [8].

XI. CONCLUSION

Huge strides in precision breast cancer medication development occurred during recent years specifically for patients diagnosed with HER2-positive disease. The importance of Trastuzumab as a breast cancer therapy has grown for HER2-positive patients while showing positive results in initial stages as well as later disease development. The targeted therapy utilizes HER2 protein as its main focus for cancer cell development. Tests have demonstrated that Trastuzumab improves patient survival statistics when delivered as neoadjuvant and adjuvant treatment following surgery. The advancement of targeted therapy includes utilizing dual-targeted treatment which combines trastuzumab with pertuzumab as a different HER2-targeting drug. The combination therapy provides greater effectiveness than trastuzumab stands alone because it blocks HER2 signals at stronger levels which physicians select as a preferred treatment approach for patients with HER2-positive breast cancer. The therapy T-DM1 provides a valuable treatment choice to patients who have advanced HER2-positive breast cancer and have exhausted various therapy options. The compound T-DM1 links trastuzumab with chemotherapy so the medication reaches HER2-positive cancer cells specifically. The drug has demonstrated brain barrier permeability which makes it advantageous for brain metastasized patients. The treatment outcomes for hormone receptor-positive breast cancer are supported by taking CDK4/6 inhibitors and mTOR inhibitors. The drugs assist in defeating resistance that builds up with hormonal treatments which enables more effective control of cancer

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development. The usage of PARP inhibitors delivers promising benefits to TNBC patients who possess BRCA1 or BRCA2 gene variations. The medicines exploit defects present in cancer cells to control the growth of this intense tumorous breast condition. Despite these advancements, challenges remain. The nature of breast cancer presents complex conditions that differ from patient to patient. Hospital diagnosis methods face two main challenges: biomarkers may shift throughout monitoring periods and show dissimilarities between cancer origins and spreading sites. Medical practitioners face difficulties in developing one universal therapy which can effectively treat different forms of breast cancer. The development of resistance to targeted therapies in tumors requires continuous research to create new pharmaceutical drugs which will address both primary and acquired drug resistance. Combining multiple drugs as therapy has suggested improved treatment results yet it brings about additional side effects. Certain drug mixes have the ability to block the therapeutic outcome of standard chemotherapy treatment. The distribution of targeting drugs such as monoclonal antibodies including trastuzumab remains inconsistent in patient bodies due to their structural properties. The large size of these drugs along with their specific binding targets makes them less effective in reaching every cancer cell and increases the chances of attaching to healthy cells which causes side effects. The use of targeted therapies produces substantive improvements in breast cancer therapy and extends hopeful options to cancer patients. Breast cancer treatment faces two significant difficulties regarding its intricate nature and the resistance of cancer cells against medicines.

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