Chapter 12
Print ISBN: 978-93-5547-702-6, eBook ISBN: 978-93-5547-703-3

Drugs that Target Cellular Signaling Pathways for Breast Cancer Treatment

Nadeem Kizilbash [a*], Marjan Assefi [b], Naila Mahmood [c], Sohila Nankali [d], A. Nanklai [e] and Gholamreza Abdi [f]

DOI:10.9734/bpi/cpms/v6/3114B

ABSTRACT

The identification of genetic mutations and the exploration of several cellular signaling pathways has led to the development of a number of molecular targeting agents, which can be targeted in several ailments for therapeutic basis. Recently, many drugs have been introduced to treat breast cancer. These drugs are administered either orally or via an injection. These drug delivery systems minimize toxicity and improve efficiency. These new drugs and delivery mechanisms have replaced the older cumbersome strategies and have helped the patients in several ways. They offer greater benefits to patients and have reduced side effects.

Keywords: Cellular signaling; breast cancer treatment; genetic mutations.

1. INTRODUCTION

Breast cancer is a very common malignancy (Fig. 1) and is the second leading cause of cancer-related deaths for women in the US [1]. Despite the advances in local and adjuvant systemic therapies, approximately 40,000 women die from this disease each year. This is a heterogeneous disease that can be classified by microscopic appearance and molecular profiles that include the expression of estrogen receptor (ER) and the amplification of HER2 [2].

Targeted killing of cancer tumors was first introduced in 1906 when Ehrlich [3] used tissue-specific carriers to deliver toxic reagents to neoplastic tissue. In this

[a] *Department of Chemistry, Faculty of Physical Sciences, Quaid-i-Azam University, Islamabad-45320, Pakistan.*
[b] *University of North Carolina at Greensboro, Greensboro, NC 27403, USA.*
[c] *Molecular Immunology Laboratory, Atta-ur-Rehman School of Applied Biosciences, National University of Science and Technology, Islamabad, Pakistan.*
[d] *Northcentral University, San Diego, CA, USA.*
[e] *Kermanshah University of Medical Sciences, Kermanshah, Iran.*
[f] *Department of Biotechnology, Persian Gulf Research Institute, Bushehr, 75169, Iran.*
**Corresponding author: E-mail: fsd707@gmail.com;*

regard, Nanotechnology has revolutionized drug delivery by its advanced therapy systems for curing cancer [4].

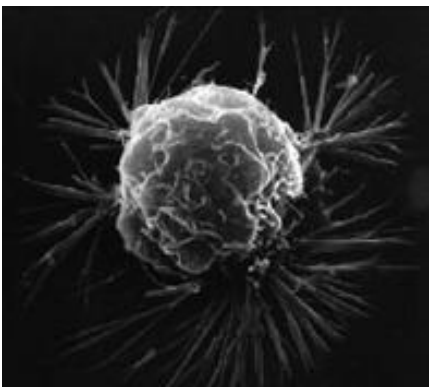

Fig. 1. A breast cancer cell up close

2. DRUGS TARGETING HER2/NEU (EGFR) SIGNALING PATHWAY

Over-expression of HER2 enables the activation of the growth factor signaling pathways and hence serves as an oncogenic driver for breast cancer [5,6]. Through both genetic and pharmacologic approaches (Fig. 2), it has been determined that HER2 is necessary for the formation of tumors in models of HER2-amplified breast cancer [7].

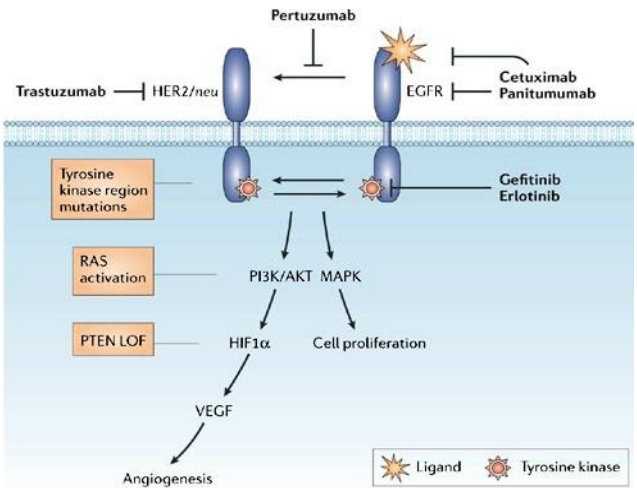

Fig. 2. Therapeutic strategies employed to block EGFR and HER2/neu (ErbB) signaling pathways

2.1 Trastuzumab (**Herceptin**)

Trastuzumab is a monoclonal antibody that binds to HER2/neureceptor. It has been shown to exhibit numerous anti-tumor properties selectively in HER2-over-expressing tumor cells [8]. Recent studies have shown that dimerization of ligand-independent HER2–HER3 is blocked by Trastuzumab selectively [9]. Trastuzumab reduces HER2 signaling pathways as well as activates immune-mediated responses against HER2-overexpressing cells [10].

2.2 Trastuzumabemtansine (T-DM1)

Trastuzumabemtansine is an antibody-drug conjugate consisting of the monoclonal antibody. Trastuzumab (Herceptin) linked to Mertansine (DM1) (Fig 3) [11-14].T-DM1 improves the therapeutic window of DM1[15,16].

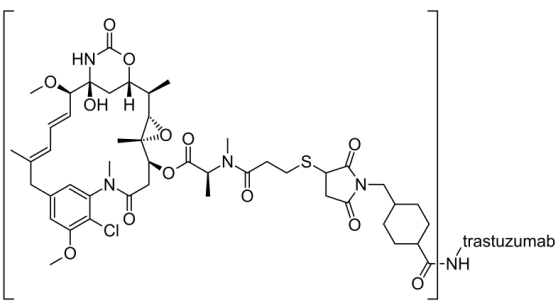

Fig. 3. Chemical structure of Trastuzumabemtansine (an antibody-drug conjugate)

2.3 Ertumaxomab (Rexomun)

Ertumaxomab is an antibody that targets both the HER-2 expressed in tumor cells and the CD3 antigen in T lymphocytes [17]. *In vitro* experiments have shown that Ertumaxomab can destroy many different HER-2 positive tumor cell lines [18].

2.4 Pertuzumab

The combination of Pertuzumab, Trastuzumab and Docetaxel has been found to benefit patients with HER2 positive metastatic breast cancer. The efficacy of Pertuzumab and Trastuzumab in conjunction with chemotherapy is currently being evaluated in the adjuvant setting 6 [19].

2.5 Lapatinib

Lapatinib is a tyrosine kinase inhibitor that is used for treatment of breast cancer and other solid tumors (Fig. 4). It interrupts the HER2/Neu and epidermal growth

factor receptor (EGFR) pathways [20,21] and is used as part of combination therapy for breast cancer [22].

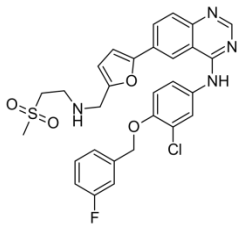

Fig. 4. Chemical structure of Lapatinib

2.6 Neratinib (HKI-272)

Neratinib (HKI-272) is an orally administered pan-ErbB receptor tyrosine kinase inhibitor that binds covalently to the intracellular tyrosine kinase domain of ErbB receptors to inhibit auto-phosphorylation and downstream signaling cascades [23,24].

3. DRUGS TARGETING ESTROGEN RECEPTOR (ER) SIGNALING PATHWAY

The majority of breast cancers (BrCa) over-express estrogen receptor (ER)α, which regulates transcription and drives estrogen-stimulated proliferation of ER+ tumor cells. ER+ patients usually receive adjuvant anti-estrogen therapy based on ER modification, down-regulation, or estrogen depletion [25,26]. Estrogen receptor antagonists bind to estrogen receptors and inhibit the action of estrogen (Fig. 5). They are useful in treating patients with estrogen sensitive breast cancers.

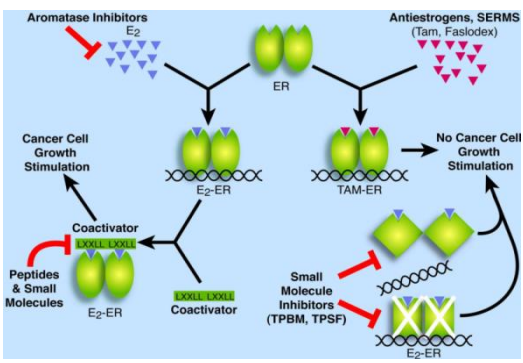

Fig. 5. Different strategies that have been used to target the Estrogen receptor (ER) during therapy for breast cancer

3.1 TPSF

TPSF (*p*-fluoro-4-(1,2,3,6,-tetrahydro-1,3-dimethyl-2-oxo-6-thionpurin-8-ylthio)) is a small-molecule inhibitor of the estrogen receptor. It does not compete with estrogen for binding to ERα. TPSF noncompetitively inhibits estrogen-dependent ERα-mediated gene expression [27].

3.2 TPBM

TPBM (theophylline, 8-[(benzylthio)methyl]) inhibits binding of ER_α to the Estrogen Response Element of the DNA. The action of TPBM is ER-specific, because progesterone and glucocorticoid receptor transcriptional activity are not significantly inhibited. TPBM inhibits 17*β*-estradiol (E2)-ER_α and 4-hydroxytamoxifen-ER_α-mediated gene expression in tamoxifen-resistant breast cancer cells that over-express ER_α [28].

3.3 Aromatase Inhibitors (AIs)

Aromatase inhibitors (AIs) have replaced Tamoxifen (TAM) as adjuvant hormonal therapy (HT) for hormone receptor-positive, postmenopausal breast cancer (BC). AIs are known for their adverse effects on bone health, yet bone health history among AI users before BC diagnosis is unknown, which may impact fracture risk after AI therapy [29,30].

3.4 Tamoxifen

Tamoxifen is used for the treatment of both early and advanced ER^+ (estrogen receptor positive) breast cancer in pre- and post-menopausal women [31] (Fig. 6). It is also the most common hormone treatment for male breast cancer.

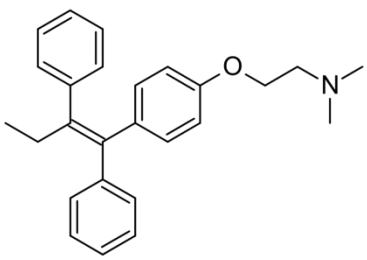

Fig. 6. Chemical structure of Tamoxifen

3.5 Fulvestrant

Fulvestrant is an estrogen receptor down-regulator (Fig. 7). It was initially approved, at a low dose of 250 mg, to treat hormone-dependant breast cancer.

However, a number ofpharmacological and pre-clinical studies have suggested that a higher dose of 500 mg may be more effective.

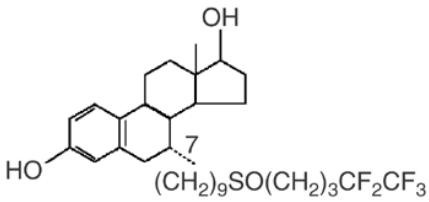

Fig. 7. Chemical structure of Fulvestrant

4. DRUGS TARGETING VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR-2 (VEGFR2) SIGNALING PATHWAY

Various defects have been reported for vascular formation and maturation in mice due to lack of various VEGF ligands or receptors [32]. Some other biological processes like lymphangiogenesis, vascular permeability and hematopoiesis are also controlled by VEGF family members [33,34]. Tumor cells are responsible for VEGF formation that induces tumor neo-vascularization (Fig. 8).

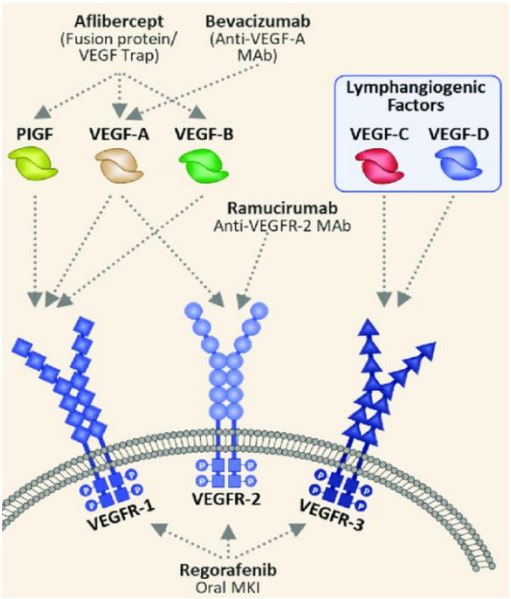

Fig. 8. Schematic showing strategies for the inhibition of tumor growth by targeting of VEGFR-2

4.1 Apatinib (YN968D1)

Formation of new blood vessels in cancer cells is blocked by Apatinib as it specifically inhibits migration and propagation of endothelial cells [35] (Fig. 9). C-Kit and c-SRC tyrosine kinases are also slightly inhibited by Apatinib. Apatinib inhibits the function of ABCB1 in certain cancers [36,37].

4.2 Bevacizumab

Bevacizumab is a monoclonal antibody and is the first FDA-approved angiogenesis inhibitor to be introduced commercially.

4.3 Salinomycin

Salinomycin is an antibacterial reagent. Studies have revealed that it kills at least 100 times more efficiently in mice than any other anti-cancer drug [38-40]. It activates an apoptosis pathway in human cancer cells that causes breakdown of apoptosis resistance.

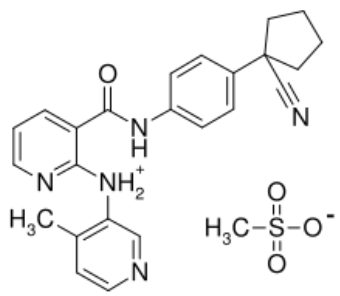

Fig. 9. Chemical Structure of Apatinib

5. CONCLUSIONS

Over the past decade, targeted therapy in combination with chemotherapy has allowed improvement in breast cancer treatment. The development of the field of molecular biology has made the treatment of different types of breast cancers more efficient. Drugs are now being designed to target molecules of signaling pathways that are important for cancer cell survival and proliferation. Estrogen receptor and HER2 signaling pathways have emerged as the most important targets for these drugs. Anti-HER2 targeted therapies have improved survival rates by 15%-23% in patients suffering from HER2 over-expressing breast cancers.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Biography of author(s)

Dr. Nadeem Kizilbash
Department of Chemistry, Faculty of Physical Sciences, Quaid-i-Azam University, Islamabad-45320, Pakistan.

Research and Academic Experience: He completed his PhD on Biophysics from Boston University (USA) and MA on Chemistry from Washington University (USA).

Research Area: His research area includes Structural Biology, Nanotechnology, Biotechnology and Molecular Biology.

Number of Published Papers: He has 50 published papers in national and International Journals.

Special Award:
He is an Editorial Board Member of following journals :

- International Clinical Case Reports Journal (October, 2021)
- Ocean Journal of Respiratory Medicine (September, 2021)
- Journal of Clinical Epidemiology and Toxicology (March, 2021)
- Acta Scientific Microbiology (February, 2021)
- Journal of Stem Cell and Therapeutics (January, 2021)
- Journal of Stem Cell and Therapeutics Research (January, 2021)
- Annals of Clinical Case Studies and Reports (December, 2020)
- Cambridge Scholars Publishing(October, 2020)
- Asian Digital Library (August, 2020)
- CPQ Medicine (August, 2020)
- AS Pharmaceutical Sciences (August, 2020)
- Stem Cell Research & Therapeutics (February, 2019)
- International Journal of Diabetes and Endocrinology (December, 2018)
- Advances in Cancer Research & Clinical Imaging (September, 2018)
- Trends in Technical & Scientific Research (September, 2018)
- Clinics of Oncology(August, 2018)
- CPQ Microbiology (March, 2018)
- International Journal of Nanoparticles & Nanotechnology(March, 2018)
- Cohesive Journal of Microbiology & Infectious Disease (February, 2018)
- Nanomedicine and Nanoscience Research(December, 2017)
- Research and Reviews on Healthcare: Open Access Journal (December, 2017)
- Nanotechnology & Medicine(September, 2017)
- Research & Development in Material Science (September, 2017)
- EC Pharmaceutical Science (January, 2015)
- European Journal of Biophysics (EJB) (December, 2013)
- MOJ Cell Science & Report (May, 2014)
- Journal of Cell Science & Report: Open Access (April, 2014)
- Journal of Teaching and Teacher Education(February, 2014)
- VRI Phytomedicine(September, 2013)
- Global Advanced Research Journal of Medicine and Medical Science (May, 2012)
- International Journal of Pharmacy and Pharmaceutical Sciences (November, 2012)

Any other remarkable point(s)
He is a Reviewer/Referee for Doctoral Theses

- Ph.D. thesis, Mansoura University (Egypt), Department of Zoology, Faculty of Science (November, 2014)
- Ph.D. thesis, Mansoura University (Egypt), Department of Zoology, Faculty of Science (February, 2013)

Ph.D. Supervisor Appointment
Appointment as Ph.D. Supervisor, Higher Education Commission, Pakistan, (November, 2004)

Dr. Marjan Assefi
University of North Carolina at Greensboro, Greensboro, NC 27403, USA.

Research and Academic Experience: She is an American biologist, researcher, and writer. She has a Ph.D. in Nanobiology, and a Doctorate in Healthcare Administration, and she is a fellow researcher, international speaker, and author.

Research Area: Her Research Area includes Nano Science, Nanoengineering, Medicine and Brain Mapping.

Number of Published papers: She has More than 80 Published papers in various National and International Journals.

Any other remarkable point(s): Editor of Gynaecology Journal, Fellowships.

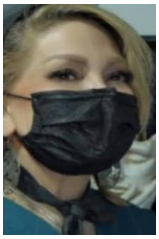
Ms. Naila Mahmood
Molecular Immunology Laboratory, Atta-ur-Rehman School of Applied Biosciences, National University of Science and Technology, Islamabad, Pakistan.

Research and Academic Experience: She is Experienced on MS Biomedical Sciences (National University of Science and Technology) and Research expertise in molecular and cell culture techniques.

Research Area: Her Research Area includes Molecular Biology and Immunology.

Number of Published papers: She has some Published papers and 2 book chapters.

Special Award: She achieve MS President's Gold Medal in Academics.



Dr. Sohila Nankali
Northcentral University, San Diego, CA, USA.

Research and Academic Experience: She is SBMT Fellow, Author, international Speaker, Editor In Chief at American Gynecology, Gynaecologist , Medical Doctor Equivalancy and accrediation Of the United States, International Health Coach.

Research Area: Her Research Area includes OBGYN, Women Health and Brain Mapping.

Number of Published papers: She has 60 published papers in National and International Journals.

Any other remarkable point(s): She is an Editor in chief of Gynaecology Journal.

Dr. A. Nanklai

Kermanshah University of Medical Sciences, Kermanshah, Iran.

Research and Academic Experience: Dr. A. Nankali is an associate professor, and practice OBGYN for more than 24 years.
Research Area: OBGYN, Medicine.
Number of Published papers: Dr. Nankali has More than 80 published papers in National and International Journals.