MOLECULAR INHIBITORS FOR INHIBITING BREAST CANCER- A PATH OTHER THAN SURGERY

NOBENDU MUKERJEE

Department of Microbiology, Ramakrishna Mission Vivekananda Centenary College, Rahara, Kolkata, India.

Abstract:

Breast cancer is one of the most lethal cancers in women when it reaches the metastatic stage. It's on the rise, both in rural and urban India. Breast cancer is a leading cause of cancer mediated death in women. This disease is diagnosed in nearly 1.4 million women and is responsible for more than 450,000 death every year. According to the WHO, there has been a 20% increase in the number of reported world wide breast cancer patients which resulted in 522,000 deaths since 2008. Breast cancer is not gender specific. A statistical report says that one woman dies of breast cancer, every 13 minutes in India. An estimated 70,218 women died of breast cancer in India, in the year 2012, the highest in the world for that year. A 2018 report of Breast Cancer statistics recorded 1,62,468 new registered cases and 87,090 reported deaths. Only 60% of women who are treated for breast cancer, survive for at least five years post-treatment in India as compared to 89% in the US. Surgical removal is not the way to irradicate breast cancer as it might reccur a few years after the surgery too so, I have listed few molecules which targets root of breast cancer.

Keywords: apoptosis, epigenetics, kinase inhibitor, melanoma, metabolomics, small-molecule, targeted therapy, tumor, mutations, Lapatinib, HER2/3, Gefitinib, Herceptin, Neratinib, Perjeta & Herceptin, Axitinib

BRCA Genes and Other Genes Involved in DNA Repair Are Implicated in Breast Cancer:

Breast cancer is triggered by both genetic and environmental impact. Some breast cancers are due to hereditary mutations, namely those involving *BRCA1* and *BRCA2*. *BRCA1* encodes breast cancer type 1 susceptibility protein which is involved in DNA repair and is considered a caretaker gene. The BRCA1 protein interacts with RNA pol. II and also with histone deacetylase complexes. BRCA1 plays key roles in transcription, repair of breaks in double stranded DNA as well as ubiquitination. The BRCA1 protein also combines with other proteins which identifies DNA damage and other cellular signals and forms a multi-subunit protein complex known as the BRCA1-associated genome surveillance complex.

BRCA2 is also involved in the repair of DNA double strand breaks. BRCA2 binds the single stranded DNA. BRAC2 interacts with the RAD51 to stimulate strand invasion which is a critical step in homologous recombination. For RAD51 to bind the DNA double-strand breaks, a complex of BRCA1/partner and localizer of BRCA2 (PALB2)/BRCA2 is required. The risk of developing breast individuals with certain cancer-associated *BRCA1/BRCA2* alleles is 60-80% for breast cancer.

PINCH-1 associate with myoferlin to promote breast cancer progression and metastasis:

PINCH-1 is a cytoplasmic component of the cell-extracellular matrix which is frequently overexpressed in cancer. The functions and mechanism of PINCH-1 in cancer, however, remain to be determined. It's seen that PINCH-1 interacts with myoferlin, which is a transmembrane protein

that is critical for cancer progression. High expression of both PINCH-1 and myoferlin correlates with poor clinical outcome in human breast cancer patients. Excision of PINCH-1 from breast cancer cells diminished myoferlin level and suppressed breast cancer cell proliferation, migration, and endothelial cell tube formation in-vitro and breast tumor growth, angiogenesis and metastasis in vivo. Mechanistically, PINCH-1 controls myoferlin level through its interaction with myoferlin and regulation of its ubiquitination and proteasome dependent degradation. Functionally, re-expression of PINCH-1, but not that of a myoferlin binding defective ΔLIM2 mutant, effectively reversed the inhibition of myoferlin expression and breast cancer progression induced by loss of PINCH-1. Finally, restoration of myoferlin expression was sufficient to reverse PINCH-1 deficiency induced inhibition on breast cancer progression. These results reveal a PINCH-1-myoferlin signaling axis that is critical for breast cancer progression and suggest a new strategy for therapeutic control of breast cancer. (Y.Ding etal. 2019)

Epigenetic Modification of ER genes in Breast Cancer :

Methylation of the promoter region of the *ER* and other genes has been associated with their decreased expression. The methylation status of the *ER*-alpha promoter region was examined t an approx 138 sporadic breast cancer cases. The *ER*-alpha promoting region was found to be methylated in 60% cases of tumors, including 57 of 69 of the tumors which did not express ER-alpha. This determines that the probability of *ER*-alpha promoter methylation was increased in those cases that were ER-alpha and PR.

In a study of 100 sporadic primary breast cancers of which 51 were ER-alpha and 49 ER-alpha+, ER methylation was observed in 98% of ER- and 65% of ER+ tumor samples. *ER*- promoter region methylation was also associated with lack of PR expression and double receptor negative expression status of the breast cancer specimens.

The methylation of the *ER*-beta promoter region was examined in 178 sporadic breast cancer patients. *ER*-beta promoter methylation was observed in 44.9% of breast tumor samples. In contrast *ER*-beta promoter hyper-methylation was detected in only 14.3% of patients with benign breast hyperplasia. 58% of the ER-beta- tumors exhibited *ER*-beta promoter region methylation whereas 36.7% of the ER-beta+-positive cases exhibited methylation at the *ER*-beta promoter region. As the levels of *ER*-beta promoter methylation increased- the levels of ER-beta protein detected decreased in the tumor samples. A strong correlation between *ER*-alpha promoter methylation and *ER*-beta promoter methylation was observed. (Zhao L etal. 2009)

Small Molecular inhibitors:

Cancer is a ‘mutation’ caused disease, initiation and further progression of cancer depends on over activation of various extrinsic and intracellular signalling pathways. Small molecule cancer drugs, because of their small size, have been successfully used to target the extracellular, cell surface ligand binding receptors as well as the intracellular proteins, including anti-apoptotic proteins that play a key role in transducing downstream signalling for cell growth and metastasis promotion. Research on molecularly targeted cancer drug discovery over the last few decades has resulted in a number of small molecule drugs being successfully introduced in the clinic for cancer treatment. Most of these drugs inhibit critical cancer targets such as serine/threonine/tyrosine kinases, matrix metallo-proteinases(MMPs), heat shock proteins (HSPs), proteosome and other proteins playing a role in signal transduction pathways. Although a number of SMIs that target a variety of cell signaling molecules have been developed and currently being utilized, the emergence of drug-resistant variants of cancers remain a significant and formidable problem that necessitates identification of additional, master signaling molecules and exploitation of this knowledge for the development of additional strategies to effectively treat resistant cancer.

Lapatinib (tykerb):

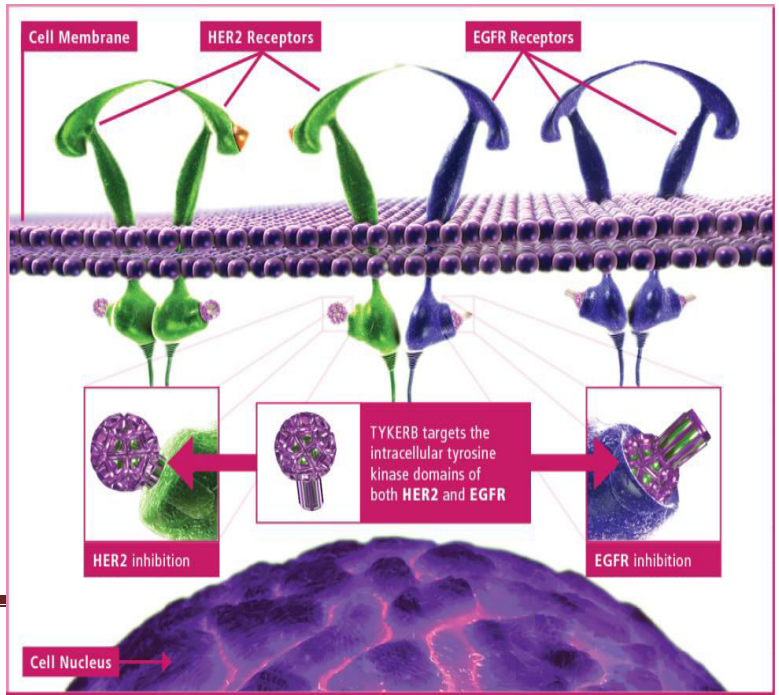
Lapatinib is a reversible dual TKI that selectively targets and inhibits HER2 and EGFR with proven effectiveness in clinical trials. Cancer cells grow in

an uncontrolled fashion. Tykerb works inside the cancer cell by interfering with certain proteins, called kinases, that can stimulate this uncontrolled growth. Lapatinib is an anti-cancer drug developed by GlaxoSmithKline (GSK) as a treatment for solid tumours such as breast and lung cancer. It wa s approved by the FDA on March 13, 2007, for use in patients with advanced metastatic breast cancer in conjunction with the chemotherapy drug Capecitabine. Lapatinib is human epidermal growth factor receptor type2 (HER2/ERBB2) and epidermal growth factor receptor (HER1/EGFR/ERBB1) tyrosine kinases inhibitor. It binds to the intracellular phosphorylation domain to prevent receptor auto-phosphorylation upon ligand binding. Lapatinib is a small molecule and a member of the 4-anilinoquinazoline class of kinase inhibitors. An anti-cancer drug, lapatinib was developed by GlaxoSmithKline (GSK) as a treatment for solid tumours such as breast and lung cancer.

Lapatinib is a 4-anilinoquinazoline kinase inhibitor of the intracellular tyrosine kinase domains of both epidermal growth factor receptor (HER1/EGFR/ERBB1) and human epidermal growth factor receptor type 2 (HER2/ERBB2)with a dissociation half-life of ≥300 minutes. Lapatinib inhibits ERBB-driven tumor cell growth in vitro and in various animal models. An additive effect was demonstrated in an in vitro study when lapatinib and 5-florouracil (the active metabolite of capecitabine) were used in combination in the 4 tumor cell lines tested. The growth inhibitory effects of lapatinib were evaluated in trastuzumab-conditioned cell lines. Lapatinib retained significant activity against breast cancer cell lines selected for long-term growth in trastuzumab-containing medium in vitro. These in vitro findings suggest non-cross-resistance between these two agents. Lapatinib undergoes extensive metabolism, primarily by CYP3A4 and CYP3A5, with minor contributions from CYP2C19 and CYP2C8 to a variety of oxidated metabolites, none of which accounts for more than 14% of the dose recovered in the feces or 10% of lapatinib concentration in plasma.

Lapatinib inhibits proliferation of several human cancer cell lines from vulva, breast, lung, and esophagus. In vitro studies showed that lapatinib inhibited the activation of the three main EGFR and HER2 downstream signaling pathways, MAPK, PI3K-AKT and PLCγ, through decreased phosphorylation of target receptors and the Raf, ERK, AKT, and PLCγ1 proteins. Additionally, this TKI increased p38 expression, a stress-induced member of the MAPK pathway that is involved in apoptosis, the subG1 phase of the cell cycle (a hallmark of apoptosis), and the cyclin-dependent kinase inhibitors p21 and p27. Lapatinib inhibited cell proliferation and migration of breast cancer cell lines expressing different levels of EGFR and HER2; however, cells overexpressing HER2 were more sensitive to this TKI. Lapatinib enhances pro-apoptotic protein BIM at the transcriptional level and reduced protein expression of survivin, an apoptosis inhibitor protein, which expresses approx 90% of all breast cancer cases and is cause of poor outcome for this pathology. Although lapatinib is a dual TKI that targets both HER2 and EGFR, it has been demonstrated that it also inhibited phosphorylation of HER3. A resume of lapatinib mechanisms is found in shown diagrammatically via a diagram.

There is a high incidence of brain metastases in patients with HER2-overexpressing breast cancer even if they were treated with trastuzumab. Interestingly, in a preclinical mouse model, lapatinib could prevent the metastatic outgrowth of HER2-overexpressing breast cancer cells in the brain. In this in vivo metastasis model, lapatinib reduced the phosphorylation of HER2 but it did not affect EGFR, contrary to in vitro studies. Moreover, EGFR small-interfering RNA (siRNA) knockdown in HER2-positive breast cancer cells did not affect the anti-proliferative activity of lapatinib, whereas



depletion of HER2 causes lapatinib resistance, indicating that lapatinib effects are mediated mainly through HER2 pathway. The stated above suggests a direct correlation between lapatinib sensitivity and HER2 expression only.

A subgroup of HER2-overexpressing tumors also express p95HER2, an amino terminally truncated receptor, that has kinase activity but lacks the epitope recognized by trastuzumab; hence, expression of this form confers resistance to trastuzumab. In addition, p95HER2 has been considered as a biomarker of an aggressive subtype of HER2 positive breast cancer. Lapatinib inhibited p95HER2, AKT, MAPK phosphorylation and the growth of cells that express the truncate receptors. Moreover, lapatinib showed antitumor activity in p95HER2 tumor xenografts.

Other study demonstrated that lapatinib inhibited insulin-like growth factor I (IGF-I) signaling in both trastuzumab -sensitive and -resistant HER2 overexpressing cells. Cross-talk between the IGF-I receptor and HER2 in trastuzumab-resistant cells increased HER2 receptor phosphorylation. Significantly, lapatinib blocked HER2 and IGF-1R crosstalk. In addition, this compound also increased fragmentation of poly ADP-ribose polymerase (PARP), a protein involved in programmed cell death, and downregulated survivin expression in trastuzumab sensitive and resistant HER2 overexpressing cells.In addition, lapatinib inhibited activation of nuclear factor κB (NF-κB) in HER2-overexpressing breast cancer cells. The TKI inactivates NF-κB through reducing phosphorylation of its inhibitor IkB-α via blocking the PI3K/AKT cascade. This fact is relevant due to co-operation between HER2 and NF-κB signaling which causes tumor resistance to radiotherapy.

Overexpression of EGFR and HER2 contributes to clinical radiation resistance and several EGFR inhibitors sensitize tumor cells to ionizing radiation. In this regard, lapatinib treatment enhanced the radiosensitization of EGFR and HER2 overexpressing breast cancer cells through inhibition of MEK/ERK signaling pathway.In the SK-BR-3 HER2-amplified breast cancer cell line prolonged exposure to lapatinib reduced the expression and activity of the enzyme topoisomerase-IIα, which renders cells resistant to the cytotoxic effects of doxorubicin, etoposide, and m-AMSA.

Lapatinib regulates many microRNAs (miR) that play an important role in the anti-tumor action in the HER2-postive breast carcinoma cells. In this regard, lapatinib treatment upregulated miR575 and miR-1225-5 expression, contributing in this manner to downregulation of the oncogenic protein phospholipase C PLCXD1 (phosphatidyl-inositol specific phospholipase-C-X-domain-containing-1), a target transcript of miR-575 and miR1225-5p. (AMJ etal. 2015)

Gefitinib:

Gefitinib is a reversible EGFR TKI that has been approved by the FDA for the treatment of advanced non-small cell lung carcinoma with activating EGFR mutations.EGFR is overexpressed in breast cancer tissue with a positivity range of 20-70%. Overexpression of this receptor is associated with aggressive metastatic breast tumors. In addition, breast tumors that cooverexpress EGFR and HER2 exhibited a worse outcome than tumors that overexpressed either receptor alone. Interruption of EGFR function with specific TKIs may disrupt EGFR-HER2 cross-talk, resulting in HER2 inactivation.

Gefitinib inhibits the growth of both breast cancer cell lines and human tumor xenografts expressing different levels of EGFR or HER2. Gefitinib effects on HER2 and EGFR co-expressing breast cancer cells are mediated by reducing basal EGFR, HER2 and HER3 phosphorylation, resulting in the blockage of downstream signaling of the AKT, MAPK and STAT3 pathways. Also, this TKI increased p27 levels and the subG1/G1 phases of the cell cycle; reduced cyclin D1 and Cdk4. In addition, gefitinib reduced the phosphorylation of glycogen synthase kinase 3 beeta (GSK-3β, a target of the AKT kinase). In EGFR-HER2 breast cancer cells, gefitinib induced cytostatic and apoptotic effects. This action of gefitinib is in part mediated by increased p38 MAPK levels, dephosphorylation of FOXO3a with a subsequent increased of p27Kip1, caspase 3 and BIM protein expression. Gefitinib has also been shown to downregulate the mTOR signaling pathway in human breast cancer cells.

In a similar manner as described above in the cell lines, gefitinib inhibited EGFR and MAPK phosphorylation in tumor biopsies. However, gefitinib had not effect on AKT phosphorylation or Ki67 levels. Moreover, the TKI did not increase p27 levels.

Gefitinib treatment disrupted the formation of the HER3/HER2 heterodimer and further association of HER3 with p85α the regulator subunit of PI3K. In addition, the TKI inhibited the activation of the EGFR/HER2 and EGFR/HER3 heterodimers mediated by EGF and heregulin, respectively.

EGFR over expression did not determine gefitinib sensitivity in the particular case of HER2 over expressing breast cancer. In this regard, gefitinib was more potent to inhibit the proliferation of breast cancer cells with high levels of HER2 and low levels EGFR compared to those cells with high levels of EGFR without HER2 expression. In contrast, gefitinib effects on AKT, MAPK, and p27 were not seen in EGFR-negative breast cancer cells. Interestingly, inhibition of MAPK phosphorylation was observed in EGFR-negative tumor biopsies, suggesting that gefitinib may be inhibiting other EGFR family members.

In the same way as observed with lapatinib, prolonged exposure to gefitinib induced resistance to doxorubicin, etoposide, and m-AMSA through downregulation of topoisomerase-IIα. (Sanchez-Martin M etal. 2016)

Neratinib:

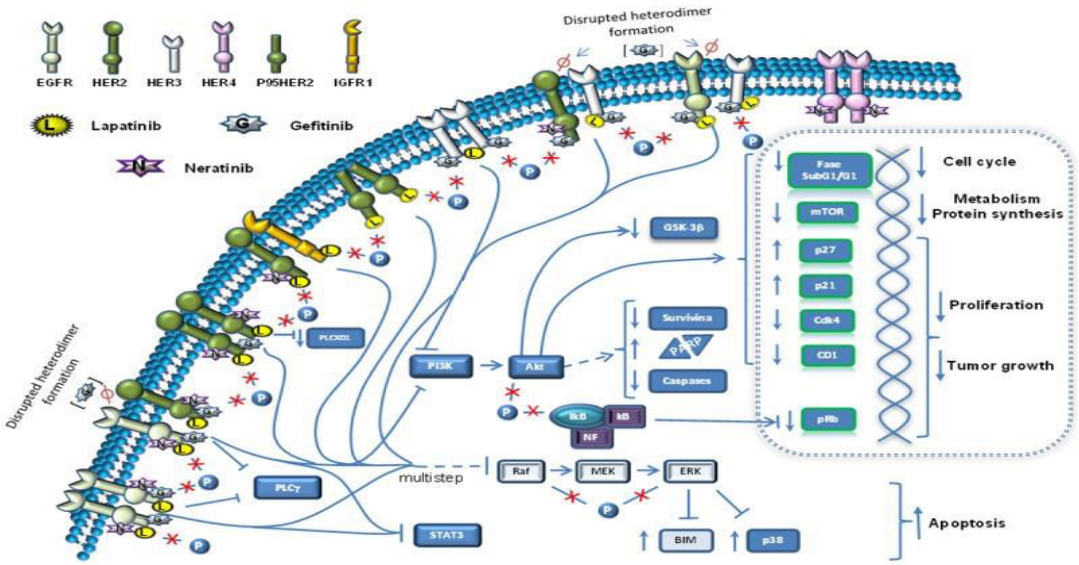
Neratinib is another oral, but irreversible TKI, known as a pan-inhibitor because interacts with the catalytic domain of several EGFR family members (EGFR, HER2 and HER4) and blocks their downstream signaling pathways. Neratinib covalently binds a specific and shared cysteine residue in the ATP-binding pocket of the receptors in the EGFR family. In particular, neratinib binds to cysteine residues Cys-773 and Cys-805 in HER1 and HER2, respectively.

Neratinib derives from structural modifications of EKB-569, another potent and irreversible EGFR inhibitor. Neratinib has significant activity in naïve and previously exposed to trastuzumab patients, making it an alternative treatment for HER2-positive breast cancer. Currently, this TKI is in clinical trials and has been used to treat solid tumors and metastatic HER2 breast cancer.

There are some reports that describe the mechanism of action of neratinib in breast cancer. A pioneering work from Rabindran showed that neratinib inhibited proliferation and EGFR, HER2, HER4, AKT and MEK phosphorylation in HER2 overexpressing breast cancer cell lines. The regulation of downstream signal transduction by neratinib leads to arrest at the G1-S phase transition resulting in increased p27 levels and decreased phosphorylated retinoblastoma protein (pRb) and cyclin D1 expression. Interestingly, neratinib showed less antiproliferative activity in cell lines that express neither HER2 nor EGFR. Moreover, HER2-positive breast cancer cell lines are more likely to respond to neratinib than EGFR-positive cells or HER2 non-amplified cell lines. Another antineoplastic mechanism for neratinib in cancer cell lines is that it can reverse membrane-bound ATP transporters-mediated multidrug resistance. The inhibition of multidrug resistance via ATP transporters by neratinib may be an alternative mechanism that could improve the response to chemotherapy agents used in HER2-positive breast cancer.

Similarly, neratinib enhanced the therapeutic response and counteracted trastuzumab resistance by decreased trastuzumab-induced HER4 nuclear translocation in HER2-positive breast cancer. (Wyeth; Pfizer etal. 2011)

THIS IS THE DIAGRAMATIC APPROACH TO THE MECHANSIM OF THE ABOVE MENTIONED MOLECULES :



Schematic representation of the action of 3 TKIs and their interaction with receptors of the EGFR family. As TKIs are homologous to ATP, they compete for ATP binding domain of protein kinases preventing their phosphorylation and subsequent activation of the signal transduction pathways, which leads to apoptosis, decreased cellular proliferation and eventually cell cycle arrest. Inhibition of phosphorylation of the receptors by TKIs (X) disrupted hetero-dimer formation by gefitinib, avoid the interaction between receptors (Φ), upregulated (↑), downregulated (↓)

Perjeta & Herceptin :

These are immuned targeted drug therapy. Cancer cells grow in an uncontrolled fashion. Perjeta works on the surface of the cancer cell by blocking the chemical signals that can stimulate this uncontrolled growth. Genes are like instruction manuals that tell each cell of our body how to grow, what kind of cell to become, and how to behave. Genes do this by ordering the cell to make special proteins that cause a certain activity — such as cell growth, rest, or repair.

Some cancer cells have abnormalities in genes that tell the cell how much and how fast to grow. Sometimes the cancer cells have too many copies of these genes with abnormalities. When there are too many copies of these genes, doctors refer to it as "overexpression." With some forms of gene overexpression, cancer cells will make too many of the proteins that control cell growth and division, causing the cancer to grow and spread. Some breast cancer cells make (overexpress) too many copies of a particular gene known as *HER2*. The *HER2* gene makes a protein known as a HER2 receptor. HER2 receptors are like ears, or antennae, on the surface of all cells. These HER2 receptors receive signals that stimulate the cell to grow and multiply. But breast cancer cells with too many HER2 receptors can pick up too many growth signals and so start growing and multiplying too much and too fast. Breast cancer cells that over express the *HER2* gene are said to be HER2-positive. Like Herceptin, Perjeta is a HER2 inhibitor targeted therapy that works by attaching itself to the HER2 receptors on the surface of breast cancer cells and blocking them from receiving growth signals. Perjeta targets a different area on the HER2 receptor than Herceptin does, so it's believed to work in a way that is complementary to Herceptin. By blocking the signals, Perjeta can slow or stop the growth of the breast cancer.

In addition to blocking HER2 receptors, Perjeta can also help fight breast cancer by alerting the immune system to destroy cancer cells onto which it is attached.

Axitinib Targeted Cancer Stemlike Cells to Enhance Efficacy of Chemotherapeutic Drugs via Inhibiting the Drug Transport Function of *ABCG2:*

Axitinib (AG013736; trade name Inlyta) is a small molecule tyrosine kinase inhibitor developed by Pfizer. It has been shown to significantly inhibit growth of breast cancer in animal (xenograft) models and has shown partial responses in clinical trials with renal cell carcinoma (RCC) and several other tumour types. Stem like cells have been isolated by their ability to efflux Hoechst 33342 dye and are called the side population (SP). We evaluated the effect of axitinib on targeting cancer stemlike cells and enhancing the efficacy of chemotherapeutical agents. We found that axitinib enhanced the cytotoxicity of topotecan and mitoxantrone in SP cells sorted from human lung cancer A549 cells and increased cell apoptosis induced by chemotherapeutical agents. Moreover, axitinib particularly inhibited the function of adenosine triphosphate (ATP)-binding cassette subfamily G member 2 (*ABCG2*) and reversed *ABCG2*-mediated multidrug resistance (MDR) *in vitro*. However, no significant reversal effect was observed in *ABCB1*-, *ABCC1*- or lung resistance–related protein (LRP)-mediated MDR. Furthermore, in both sensitive and MDR cancer cells axitinib neither altered the expression of *ABCG2* at the mRNA or protein levels nor blocked the phosphorylation of AKT and extracellular signal-regulated kinase (ERK)1/2. In nude mice bearing *ABCG2*-overexpressing S1-M1-80 xenografts, axitinib significantly enhanced the antitumor activity of topotecan without causing additional toxicity. Taken together, these data

suggest that axitinib particularly targets cancer stemlike cells and reverses *ABCG2*-mediated drug resistance by inhibiting the transporter activity of *ABCG2*.

Breast cancer resistance protein (BCRP/ABCG2): its role in multidrug resistance and regulation of its gene expression:

Breast cancer resistance protein (BCRP)/ATP-binding cassette subfamily G member 2 (ABCG2) is an ATP-binding cassette (ABC) transporter identified as a molecular cause of multidrug resistance (MDR) in diverse cancer cells. BCRP physiologically functions as a part of a self-defense mechanism for the organism; it enhances elimination of toxic xenobiotic substances and harmful agents in the gut and biliary tract, as well as through the blood-brain, placental, and possibly blood-testis barriers. BCRP recognizes and transports numerous anticancer drugs including conventional chemotherapeutic and targeted small therapeutic molecules relatively new in clinical use. Thus, BCRP expression in cancer cells directly causes MDR by active efflux of anticancer drugs. Because BCRP is also known to be a stem cell marker, its expression in cancer cells could be a manifestation of metabolic and signaling pathways that confer multiple mechanisms of drug resistance, self-renewal, and invasiveness (aggressiveness), and thereby impart a poor prognosis. Therefore, blocking BCRP-mediated active efflux may provide a therapeutic benefit for cancers. Delineating the precise molecular mechanisms for BCRP gene expression may lead to identification of a novel molecular target to modulate BCRP-mediated MDR. Current evidence suggests that BCRP gene transcription is regulated by a number of trans-acting elements including hypoxia inducible factor 1α, estrogen receptor, and peroxisome proliferator activated receptor. Furthermore, alternative promoter usage, demethylation of the BCRP promoter, and histone modification are likely associated with drug-induced BCRP over expression in cancer cells. Finally, PI3K/AKT signaling may play a critical role in modulating BCRP function under a variety of conditions. These biological events seem involved in a complicated manner. Untangling the events would be an essential first step to developing a method to modulate BCRP function to aid patients with cancer. This review will present a synopsis of the impact of BCRP-mediated MDR in cancer cells, and the molecular mechanisms of acquired MDR currently postulated in a variety of human cancers. (D.D Ross etal. 2018)

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