Targeting Therapies in the Management of Breast Carcinoma

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Abstract

One of the oldest molecular target approaches in breast cancer is the targeting of the estrogen receptor with tamoxifen which is responsible for improvement in outcome, reduced the risk of new primary breast cancer and improves survival. Targeted therapies are now a component of treatment for many including colorectal, lung, and pancreatic cancers, as well as lymphoma, leukemia, and multiple myeloma.Recent identification of specific molecular target in cancer cells, leads to development of new targeted therapeutic approach, signal transduction, angiogenesis, and more recent approaches are induction of apoptosis or inhibition of antiapoptosis which offer the possibility of improving outcome for patient with early as well as metastatic breast cancer. This review discusses target therapies for HER family, angiogenesis and signal transduction.

Abbreviations: HER -human epidermal growth factor receptor, VEGF- vascular growth factor receptor, TKI- tyrosine kinase inhibitor, EGFR- epidermal growth factor receptor, mTOR mammalian target of rapamycin, PST- primary systemic chemotherapy, ER – oestrogen receptor, CDK- cyclin-dependent kinase,PI3K-phosphatidyl-inositol3-kinase.

INTRODUCTION

Breast cancer is the most common cancer affecting women globally. It is the leading cause of death from cancer in women and has age –standardized annual incidence and mortality rates of 37.4 and 13.2 per 100 000 women. [1]The outcome of breast cancer is predicted by the extent of spread of the tumor to locoregional lymph nodes, which, in turn, predicts distant spread. [2]Patients with advanced metastatic disease have a very poor prognosis, hence the importance of effective early diagnosis and treatment to prevent later recurrences and improve survival.[2, 3]

Multimodality approach is required for early stage breast cancer. These include surgery, radiotherapy, chemotherapy, and endocrine therapies which aim both to eradicate residual cancer and prevent recurrent disease hence increased survival. Recent improvement in outcome in patients with breast cancer appears to result largely from the use of adjuvant therapies, including chemotherapy and endocrine manipulations. [4]

The current approach to increase survival in cancer breast is targeting therapy, they act by targeting the pathways that promote, sustain growth and invasion of carcinoma cells and is critical to effective treatment of breast cancer.[5]

TARGETED THERAPY-

The targeted therapy refers to a new generation of anticancer drugs that are designed to interfere with a specific molecular target, usually a protein. This approach differs from the more empirical approach used in conventional cytotoxic chemotherapy. In contrast to conventional chemotherapy, it interferes with molecular targets that have a critical role in tumor growth or progression. Since it is directed against cancer specific molecules and signaling pathways, it has limited non-specific toxicities. The molecular targets are usually located in tumor cells; some like anti-angiogenic agents may target other cells such as endothelial cells. Targeted therapies have a high specificity toward tumor cells, providing a broader therapeutic window with less toxicity. They are also often useful in combination with cytotoxic chemotherapy or radiation to produce additive of synergistic anticancer activity because their toxicity profiles often do not overlap with traditional cytotoxic chemotherapy.

RATIONALE OF TARGETING THERAPY

The normal cell growth and division are largely under the control of a network of chemical and molecular signals that

gives instructions to cells. Genetic alterations can disrupt the signaling process so that cells no longer grow and divide normally, or no longer die when they should. Alternations in two types of genes can contribute to the cancer process. Proto-oncogenes are normal genes that are involved in cell growth and division. Changes in these genes lead to the development of oncogenes, which can promote or allow excessive and continuous cell growth and division. Tumor suppressor genes are normal genes that slow down cell growth and division. When a tumor suppressor gene does not work properly, cells may be unable to stop growing and dividing, which leads to tumor growth.

TARGET THERAPIES-

MONOCLONAL ANTIBODIES AND TYROSINE KINASE INHIBITORS FOR EGFR AND HER2, INHIBITORS OF MULTIPLE HER RECEPTORS

The HER family of transmembrane receptors consists of four closely related members, including HER1 (also known as the epidermal growth factor receptor [EGFR]), HER2, HER3, HER4. These all are members of Erb B family of receptor tyrosine kinases. In general, they consist of extracellular ligands binding domain, a transmembrane domain, and an intracellular binding domain and an intracellular tyrosine kinase (TK) domain.

Monoclonal antibodies are a relatively new type of "targeted" cancer therapy. Normally, the body creates antibodies in response to an antigen entering the body, the antibodies attach to the antigen in order to mark the antigen for destruction by the body immune system. From 15% to 30% of breast cancers have been shown to express high levels of EGFR and HER2.[6]

(A) HER1 (EGFR) INHIBITORS –

Two main classes of agents have been developed that specifically target the EGFR.

1. Tyrosine kinase inhibitors (EGFR TKIs) - also known as Small Molecules.

These agents bind intracellularly. TKI s interacts with the enzyme tyrosine, which is active in a complex signaling system that is used by some cancers as a survival mechanism to allow them to grow out of control. These agents also effective in cases of endocrine resistance, as when breast cancers become resistant to endocrine therapy, growth signals through growth factor receptors and downstream kinases become dominant pathways. Thus, inhibition of these kinases may provide a basis to restore endocrine sensitivity.[7]The examples of TKIs inhibitors are eg Gefitinib and Erlotinib etc.

Gefitinib- It is a signal Transduction inhibitor. This is an example of an orally active, selective EGFR tyrosine kinase inhibitor (EGFR-TK).[6]Gefitinib has demonstrated a dose dependant anti-proliferative effect on breast cancer cell. It has been found in experimental studies that ER- independent tumors were more sensitive to tyrosine kinase inhibition.

Since EGFR signaling appears to be up regulated in endocrine resistant breast cancers, tyrosine kinase inhibition may be effective in this clinical setting.[8]Three phase III trials have examined the use of gefitinib in patients with advanced breast cancer. Clinical benefits (combined partial response and stable disease >6 months) was observed in 18 months. Pharmcodynamic studies have confirmed the ability of gefitinib to inhibit EGFR tyrosine kinase in skin and tumor biopsies. A higher response rate was observed in ER-positive, tamoxifen resistant patients. Gefitinib was generally well tolerated and showed evidence of antitumor activity.[9, 10, 11]

Baselga et al treated 31 patients with gefitinib and reported a 13% clinical benefit rate.[12]Robertson et al reported a clinical benefit at 6 months in 5(26%) of 19 patients treated with gefitinib.[13]

Gutteridge et al. in a phase II study reported the effect of the expression of ER, EGFR, HER-2, and IGF- 1R in patients treated with gefitinib. Two groups of patients were recruited: an ER- positive tamoxifen – resistant (TAM- R) group and an ER- negative group. Pretreatment samples were taken for 35 patients, of which 13 were ER positive and 22 ER-negative. Although responders were seen in both groups, responses were more frequently observed in the ER- positive (82%) patients than the ER- negative (13%) patients. All responders expressed EGFR but a higher incidence of progressive disease, and shorter time to progression (TTP) were recorded in patients with high EGFR expression. HER-2 expression was similar in the ER – positive TAM-R patients (54.5%) and ER- negative patients (47.6%). In ER positive patients, high levels of HER-2 did not preclude a response to gefitinib and expression of IGF- IR did not predict response.[14]

(2) Monoclonal antibodies (mAbs):- binds extracellulary to the receptor so avoid the ligands to bindings to the receptor thus blocks receptor dimerization, tyrosine kinase phosphorylation, and signal transduction.

EGFR- CETUXIMAB

CETUXIMAB-

An IgG_1, chimeric monoclonal antibody, competes with ligands binding to the EGFR ectodomain, resulting in an efficient blockage of the tumor promoting downstream signaling pathways. [6]

Modi S et al in a phase I study evaluated synergistic effect of cetuximab with combination using cetuximab and paclitaxel in patients with metastatic breast cancer. Cetuximab weekly therapy and paclitaxel given 3 weekly, with dose escalation of cetuximab until the maximum tolerated dose was reached. In three cohorts twelve patients were enrolled into three treatment cohorts. Of 10 patients evaluable for response, two had stable disease and eight had progression of disease, one patient out of three patients developed grade 3 skin toxicity. [15]

HER 2 INHIBITOR-

Trastuzumab- The recombinant, humanized MAb, trastuzumab (herceptin) is the first novel targeted therapy approved for routine clinical application in advanced breast cancer, targeted against the extracellular domain of HER 2. [16]

Trastuzumab binds to HER 2 and inhibits signaling through other members of the HER family by inhibition of formation of the heterodimers important for potentiation of HER signaling, and this can result in decreased angiogenesis, increased apoptosis, and decreased proliferation. [16, 17]

Currently it is used as a standard treatment not only in the metastatic settings but also in the adjuvant setting. Furthermore, recent studies have revealed that trastuzumab plus chemotherapy in form of taxens and anthracycline dramatically increases the complete pathological response in the neoadjuvant setting, prompting the future use of this combination setting. [18]

Cobleigh et al reported results of single agent trastuzumab in 222 women with metastatic breast cancer previously treated with one or two regimens for metastatic disease. All patients received the standard dose of 4 mg/kg IV weekly thereafter. An objective response rate of 15% was seen, with a median duration of response of 9.1 months, with exception of mild infusion reactions with the first dose and cardiac dysfunction in 4.7% of patients.[19]

Pegram et al evaluating in a trial chemotherapy with combination with trastuzumab, randomized 469 women with previously untreated metastatic breast cancer to chemotherapy alone vs chemotherapy plus trastuzumab. Patients received standard doses of doxorubicin and Cyclophosphamide unless they had received an anthracycline in the adjuvant setting. These patients received paclitaxel at a dose of 175 mg/m^2 every 3 weeks with or without trastuzumab. The addition of trastuzumab to chemotherapy resulted in an increased response rate (50% vs 32%, p<.001), a longer median duration of response (9.1 months vs 6.1 months<0.01), and prolonged overall survival (median 25.1 vs 20.3, p=.046). Toxicity was similar in the two groups, with the important exception of increased cardiac toxicity). With the combination of AC plus trastuzumab, 27% of patients had cardiac dysfunction compared with 8%of patients who received AC alone. The combination of paclitaxel and trastuzumab resulted in cardiac dysfunction in 13% of patients while only 1% of patients receiving paclitaxel alone had cardiac dysfunction. As a result of this trial, all patients with HER2 overexpressing metastatic breast cancer should receive trastuzumab in addition to their palliative chemotherapy, but anthracycline/trastuzumab combinations should be avoided outside of a clinical trial.[20]

Vogel et al evaluated single agent trastuzumab in the first line setting in 114 women with metastatic breast cancer. All patient had tumors scored as 2+ or 3+ by IHC. Two different dose levels were evaluated, but no difference in outcome was observed for the higher dose compared with the standard dose. The objective response rate for the whole population was 26%, with 38% having clinical benefit (response or stable disease for 6 months). Roughly half of patients with a clinical benefit or response were free of disease progression at 1 year. Median survival was 24.5 months, which rivals the chemotherapy plus trastuzumab result from the pivotal trial with a similar population. [21]

Latest data on the adjuvant use of trastuzumab highlighted by Perez, they provided an update on the clinical efficacy from the combined analysis of NSABP B31 and NCCTGN9831. Ongoing follow up of the adjuvant trastuzumab trials, in which patients received AC followed by paclitaxel, with or without the addition of trastuzumab, shows persistent and durable benefits. The difference in DFS through 4 years of follow up is 13% in absolute terms (73% without trastuzumab, 86% with trastuzumab) reflecting a 50% relative reduction in risk of recurrence. [22]

PERTUZUMAB

It is a recombinant humanized monoclonal antibody (2C4)

that is similar to trastuzumab but blocks the interactions between HER2 and its signaling partners, HER3 and EGFR. It blocks formation of HER2 heterodimers with others members of the HER family and thus reduces signaling through the multiple pathways associated with HER activation. [23] It represents a new class of targeted therapeutics known as HER dimerization inhibitors. It is mainly indicated in trastuzumab resistant breast cancer.

A recent Phase I study in patients with advanced breast cancer has shown that it is well tolerated and is clinically active; suggesting that inhibition of dimerisation may be an effective anticancer strategy.[24]

In an ongoing phase II trial preliminary results were reported. Treatment with trastuzumab and pertuzumab in patients whose tumor had worsened while receiving trastuzumab therapy, among first 33 patients treated, 18% had a partial response. This is a potentially interesting finding, although safety and efficacy data are not yet available. [25]

Inhibitors of Multiple HER Receptors-

LAPATINIB

Lapatinib is a small molecular inhibitor of TK domain of both HER 1 and HER2. EGFR or HER2 expression through decreased phosphorylation of the TK domains of both receptors drives inhibition of growth and induction of apoptosis in breast cancer cell lines.[16] Lapatinib has a significantly longer half life than gefitinib or erlotinib.[26] In a phase I b trial of lapatinib in EGFR and / or HER2 expressing cancers, sixty six patients were treated, including 30 patients with metastatic breast cancer. Four of the patients with metastatic breast cancer (13%) were believed to have stable disease at a median duration of therapy of 5 months. All 4 had progressed through prior trastuzumab. Ten patients (33%) were believed to have stable disease at a median duration of therapy of 5 months. All 10 had EGFR expression by IHC, and 8 of these 10 overexpressed HER2.[27]

Brain metastases are a considerable cause of morbidity and mortality in patients with HER 2- positive metastatic breast cancer patients treated with trastuzumab. Lapatinib has been demonstrated to cross the blood – brain barrier, thereby offering the possibility of preventing or treating brain metastasis. [28]

Based on this hypothesis, Lin and colleagues examined the use of single agent Lapatinib in patients with HER-2 positive metastatic breast cancer who had brain metastasis that progressed on whole brain radiation and /or radiosurgery. Although the partial response rate was 5%, 42% of patients had stable disease lasting greater than 8 weeks. Using a complex volumetric assessment, 26% of patients were noted of at least 20%. Patients who had disease progression in the brain or systemically were offered enrollment in an extension study, in which they received Lapatinib and capecitabine at FDA- approved doses. Of note, 60% of patients had a reduction in brain volumetric tumor of at least 20%.[29]

A phase III trial demonstrated that lapatinib plus capecitabine is superior to capecitabine alone in women with HER2 – positive advanced breast cancer that progressed after prior therapy including trastuzumab. Time to progression has been increased by addition of lapatinib and resulted in improved overall survival. [30]

In a neoadjuvant phase II study Cristofanilli M et al with paclitaxel monotherapy in combination with lapatinib in inflammatory advanced breast cancer, observed clinical response rate of 77% and a pCR of 17% were achieved in HER2 – positive tumors. Eighty percent of EGFR- positive patients exhibited a response. [31]

It is now proved by the US Food and Drug Administration.[32]

(2) Anti-angiogenesis compounds (Angiogenesis Inhibitors): VEGR and VEGF receptors

Anti angiogenesis drugs starve the cancer cells of blood that they need to survive and grow. Tumor cells, like normal cells, need an adequate blood supply in order to perform vital cellular functions. In fact, as cells multiply and grow in number and size, access to nutrients and blood supply becomes increasingly critical for their continued survival. Actively dividing tumors secrete special proteins that signal the surrounding areas to sprout new blood vessels. This new blood vessel formation is called angiogenesis, and the proteins that trigger this process are called proangiogenic factors. The main proangiogenic factor is VEGR, which stands for vascular endothelial growth factor. In essence, by secreting VEGR and other related proteins to stimulate new blood vessel growth, tumors support and feed themselves, allowing them to grow. The concept behind angiogenesis inhibition, then, is to thwart this process and thereby fight tumor progression. (Bevacizumab, sunitinib)

BEVACIZUMAB

Bevacizumab is a recombinant human MAb that inhibits the biological activities of VEGF, a protein involved in the neovascularization of malignant tumors. Studies have shown that bevacizumab has both cytostatic and cytotoxic effects, resulting in a reduction in tumor growth and increase in median survival time and time to tumor progression. Currently number of trials are ongoing that are evaluating the use of bevacizumab with other chemotherapeutic agents.

In the ECOG 2100 trial the use of bevacizumab plus paclitaxel, prolongs progression –free survival in patients with HER2- negative metastatic breast cancer by almost 6 months vs paclitaxel alone. Specifically, bevacizumab significantly improved progression – free survival in patients with triple negative cancers and in those with hormone – refractory cancers. [33] The impressive results from the ECOG 2100 trial led to the evaluation of this combination in the first line setting.

Sledge et al have evaluated the combination of capecitabine and bevacizumab as first line therapy in patients with HER-negative metastatic breast cancer. [34]

In a randomized phase III trial bevacizumab in combination with capecitabine was assessed in heavily pretreated breast cancer. Though there was a significant increase in response rate after addition of bevacizumab (19.8% vs. 9.1%), this did not translate into improved progression-free survival and overall survival. [35]

AXITINIB

Axitinib is a small molecule that targets the tyrosine kinase domain of vascular endothelial growth factor receptor (VEGFR)-2 and is a potent and selective inhibitor of VEGERs 1, 2, and 3. Following positive phase I data, 168 patients with untreated metastatic breast cancer were enrolled in a randomized phase 2 trial comparing docetaxel in combination with axitinib in a 2 to 1 fashion. Overall RR was significantly higher in patients treated with combination than with docetaxel alone (40% vs 23%; p=.038). TTP was also improved: 8 months for the combination vs 7 months for docetaxel alone (p =.052)˙ Grade 3 and grade 4 diarrhea, fatigue, stomatitis, febrile neutropenia, and thromobembolic events observed during study and resulted in 55% of patients requiring dose reduction in docetaxel.[36]

(C) APOPTOSIS – INDUCING DRUGS

Apoptosis inducing drugs acts by inducing cancer cells to undergo apoptosis by interfering proteins involved in the process.eg are Bortezomib, Genasense (Oblimersen)

BORTEZOMIB

FDA approved drug to treat multiple myeloma that has not responded to other treatment. It is a potent inhibitor of the 26S proteasome, with broad anti-tumour activity. Although bortezomib was well tolerated, it exhibited only limited clinical activity against metastatic breast cancer when used as a single agent. [6] Engel and coworkers, conducted a single institution, phase II study of bortezomib in the treatment of patients with metastatic breast cancer. There was no observed objective responses in any of the 12 patients who received treatment with Bortezomib, all patients progressed while receiving therapy with bortezomib. The study was terminated after first stage because of lack of any objective response. [37]

The combination of trastuzumab with bortezomib could increase the efficacy of trastuzumab by nuclear accumulation of the CDK inhibitor $p27^{kip1}$, causes increases the effect of trastuzumab in HER2-positive cell lines in a synergistic way.[6] The potential clinical application of this drug combination is currently under evaluation in a phase I clinical trial.[38] A phase I/II trial conducted to evaluate the combination of capecitabine and bortezomib in anthracycline-pretreated and/or taxane-pre-treated patients with metastatic breast cancer. The treatment was generally well tolerated and associated with toxic effects that were consistent with the known side effects of the individual agents. It included 35 patients, the intent-to-treat overall response rate was 15%, and an additional 27% of patients had stable disease. Median time to progression and overall survival were 3.5 months and 7.5 months, respectively. The median duration of response was 4.4 months. Although bortezomib and capecitabine are well tolerated, the combination had only moderate anti-tumour activity in heavily pretreated patients.[39]

(D) UPIQUITIN -PROTEASOME PATHWAYS

The proteasome is a structure inside the cell which breaks down proteins that have been labeled to undergo degradation and recycling. This is important process because it removes possibly damaged on defective protein. By binding part of the proteasome, a drug can inhibit the breakdown of some of these proteins that have been marked for destruction. Thus the ubiquitin – proteasome pathway is involved in the degradation of key cell cycle regulatory proteins. Multiple ubiquitin molecules bind to the protein substrates that are subsequently degraded by the multicatalytic proteasome

complex.

PS-341 is a potent and specific inhibitor of the proteasome.[16] A phase II study of this agent as monotherapy in patients with refractory breast cancer has been reported. There was no significant activity seen in the first 12 patients enrolled, and the study was closed.[40] Parthenolide inhibits IkB kinase (IkB inhibitor of Nuclear Factor -kB) and Bortezomib inhibits proteasome .

(E) Gene therapy

Gene therapy is an experimental treatment that involves introducing genetic material (DNA or RNA) into a person's cell to fight disease.

P53 TARGET FOR GENE THERAPY

The p53 gene acts as a regulator of cell growth and DNA repair in normal cells, inactivation of the gene appears to lead to cancer. About 35% of breast cancer patients have p53 mutation, of which 88% are located within exons 5 to 8.[41] p53 mutation occur in 24.5% of the axillary node negative breast carcinomas and more frequently in cancer with HER2 amplification.[42]Intra tumoral administration of a nonreplicating adenoviral vector that contains the human wild type p53 combined with chemotherapy could increase the efficacy of primary systemic chemotherapy as measured by pathological complete response in the management of patients with locally advanced breast cancer.[6]

In a prospective clinical trial II open label, 13 patients with locally advanced breast cancer were treated with six 3-week cycles of primary systemic therapy, which consisted of intra-tumoral injections of human wild type p53 (Ad5CMV-p53) for 2 consecutive days plus docetaxel and doxorubicin followed by surgery and concluded Ad5CMV-p53 combined with PST was safe, active and associated with local immune modulatory effects. The promising clinical activity of this combination deserves further investigation in randomized studies.[43]

FUTURE TARGET THERAPIES

Phosphatidyl- inositol 3- kinase – Rapamycin , wortmannin, Fulvestrant

Mammalian Target of Rapamycin and the P13K/Akt Pathway-

The PI3K pathway is involved in regulating multiple-cellular functions important for cell survival and proliferation. Signaling through Akt regulates the serine-threonine kinase mammalian target of Rapamycin (mTOR). This (mTOR) further involved in transcriptional and translational regulation proteins important to regulation of the cell cycle.[6]

In breast cancer the P13K/Akt/mTOR pathway can be activated by the ER, IGF-1 receptor, and the HER1 family , especially HER3.

Rapamycin has immunosuppressive, fungicidal, and antitumor activity through inhibition of mTOR, targets mTOR results in cell –cycle arrest in G1. Temsirolimus CCI-779, Everolimus (RAD001) are analogue of rapamycin has been found to have activity on cases of breast cancer with estrogen dependent of overexpressed HER 2 gene.[44] Wang LH et al in a study combined Rapamycin with trastuzumab and was found increase antitumor efficacy of trastuzumab in comparison with trastuzumab alone and this combination could be developed as an improved therapeutic regimen in breast cancer. Both significantly reduced level of cyclins D_1 and D_3 and increased apoptosis.[45]

(2) Farnesyltransferase inhibitors – Tipifarnib, Lonafarnib

The enzyme farnesyltranseferase is involved in the initial posttranslational modification of Ras that allows it to become associated with the plasma membrane and become active in signal transduction. Inhibition of this enzyme is thus a logical therapeutic target for malignancies associated with activated ras.[46] Several FTIs are in preclinical and clinical development and have broad preclinical activity against breast cancer lines and xenograft.

Tipifarnib and Lonafarnib-

Production of Ras protein is induced by farnesyl transferase. The Ras protein regulates genes that are involved with transcription, translation, cell growth, cell survival and cellular interactions, as well as development of the cytoskeleton. A phase II trial is currently being examined Tipifarnib and Lonafarnib.[47]

3) Inhibitors of apoptosis protein- surviivin

4) Nuclear transcription factor-Gemcitabine

CONCLUSION

Hormonal therapy with tamoxifen is the oldest molecular target therapies. Recent studies have revealed that target therapies with or without chemotherapy could increase the outcome in breast cancer as a neoadjuvant setting, prompted

the future use of these therapies as alone or in combination.

The identification of specific molecule subtypes of breast cancer along with new chemotherapeutic and targeted agents also offers the possibility of improving outcome for patient with metastatic breast cancer. Targeted therapies are generally better tolerated than traditional chemotherapy, but they are associated with several adverse effects, such as acneiform rash, cardiac dysfunction, thrombosis, hypertension, and proteinuria. Many studies are undergoing with aim to achieve improved matching of effective drug to the molecular characteristics of the individual cancer, predicating response to targeted therapies, searching the mechanisms of resistance, successful management of side effects of these therapies. In future there is need to identification of specific molecular target and developed therapies which effectively act on molecular targets either alone or in combination with cytotoxic chemotherapy.

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