

REVIEW

Recent Progress in HER2 Associated Breast Cancer

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Abstract

Breast cancer is the most common cancer worldwide among women and the second most common cancer. Approximately 15-23% of breast cancers over-express human epidermal growth factor receptor2 (HER2), a 185-kDa transmembrane tyrosine kinase, which is mainly found at the cell surface of tumor cells. HER2-positive breast cancer, featuring amplification of HER2/neu and negative expression of ER and PR, has the three following characteristics: rapid tumor growth, lower survival rate, and better response to adjuvant therapies. Clinically, it is notable for its role in a pathogenesis that is associated with increased disease recurrence and acts as a worse prognosis. At the same time, it represents a good target for anti-cancer immunotherapy despite the prevalence of drug resistance. New treatments are a major topic of research, and a brighter future can be expected. This review discusses the role of HER2 in breast cancer, therapeutic modalities available and prognostic factors.

Keywords: HER2 - breast cancer - mechanism - treatment

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Introduction

Mechanism of HER2

The HER2 oncogene is located on the long arm of chromosome 17 (17q12), consisting of EGFR (HER1/ERBB1), HER3 (ERBB3), and HER4 (ERBB4) (Arcila et al., 2012; Kanthala et al., 2014; Kurata et al., 2014; Schroeder et al., 2014; Xu et al., 2014; Yan et al., 2014), it is a receptor tyrosine kinase (Morrison et al., 2014; Schroeder et al., 2014), once activated, by ways homo-dimerization or hetero-dimerization (Boulbes et al., 2014) will mediate signaling pathways including the phosphatidylinositol 3-kinase (PI3K) /protein kinase B (Akt) /mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK) pathways involved in cellular proliferation, differentiation, migration, and apoptosis (Bai et al., 2014; Dittrich et al., 2014; Lapin et al., 2014; Xu et al., 2014; Huang et al., 2015; Lanning et al., 2015).

The HER2 mono-meric protein has three major regions- the extracellular amino-terminal region comprised of four domains (domains I-IV), the hydrophobic transmembrane domain, and the carboxy-terminal kinase domain comprised of the jux-tamembrane domain, tyrosine kinase, and C-terminal tail with auto-phosphorylation sites. The intracellular portion plays a critical role in mediating optimal receptor-receptor interactions, . even though the gene-mediated protein has no known ligand (Schroeder et al., 2014). In HER2-overexpressing cells, constitutive ligand-independent dimerization with subsequent activation of the cytoplasmic kinase region can be found

which then activate the PI3K-Akt-mTOR (Ebi et al., 2013) and Ras-Raf-MEK-Erk1/2 pathways. leading to tumor growth and progression (Nahta, 2012).

Usually, HER2, as a tumor-associated antigen, is over-expressed in malignant cells (Freudenberg et al., 2009; Bilous et al., 2012; Blok et al., 2013; Boku, 2014; Victorino et al., 2014; Lanning et al., 2015), regarded as an important predictive and prognostic marker (Omenn et al., 2014; Rakha et al., 2014). Deregulation of the HER2 gene, through protein over-expression and/or gene amplification can not only promote cancers but also predict benefit from HER2-targeted therapy such as Trastuzumab.

Previously, scientists had found that the Extra Virgin Olive Oil (EVOO) could degrade the HER2 protein level and thereby inhibited HER2 activity (Menendez et al., 2008).

HER2 and breast cancer

Human epidermal growth factor receptor 2 (HER2) is over-expressed in about 20% of all breast cancers (Aksamitiene et al., 2012; Imami et al., 2012; Sclafani et al., 2013; Ballinger et al., 2014; Huynh and Jones, 2014; Iqbal and Iqbal, 2014; Kanthala et al., 2014; Kumler et al., 2014), it was proved to up-regulate the Na, HCO₃-cotransporter NBCn1/SLC4A7 in human breast cancer cells via Akt, ERK, Src, and Krüppel-like factor 4 (Gorbatenko et al., 2014). (Figure 1)

Possible signal way

The PI3K-Akt signaling; the Ras/ERK pathway ;the oxidative stress pathways.

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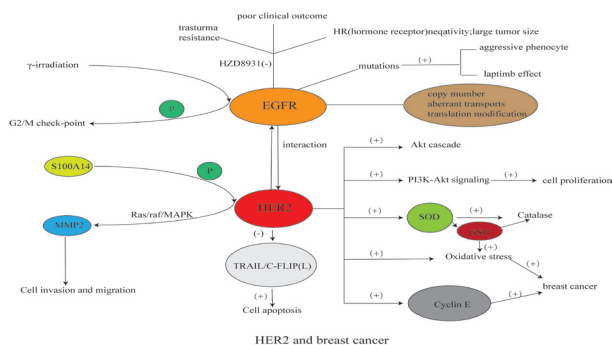


Figure 1. Overview of HER Family Signalling in HER2-Positive Breast Cancer Including the The PI3K-Akt Signaling; the Ras/ERK Pathway, and the Oxidative Stress Pathways. Also, some micromolecules such as CD24, EGFR, ER, TRAIL and C-FLIP, Centrosome amplification (CA), SGOL1 are included

Seen from many previous studies, HER2 over-expression has been linked to more aggressive disease and poorer prognosis in node-positive breast cancer. In patients with HER2-over-expressing tumors, different researches have shown cellular and/or humoral immune responses against HER2 associated with a lower tumor development at early stages of the disease (Ladjemi et al., 2010; Xia et al., 2013; Lanning et al., 2015). and for one of the mechanisms, HER2-mediated signaling effects cyclin E expression (Dong et al., 2014), which in turn deregulates the cell cycle in early high-risk breast cancer (Mittendorf et al., 2010). For another, over-expression of HER2 in breast cancer may favor tumors' proliferation by oxidative stress pathways, with the latter modulating cell fate by stimulating either cell proliferation or cell death at mild or high concentrations (Victorino et al., 2014). After HER2 activation, not only Ras/ERK and PI3K/Akt are the most relevant induced pathways, but the SOD activity, independent of catalase activity or GSH may be triggered too. Both of them leading to increased oxidative stress *in vitro* (Victorino et al., 2014), this procedure may include plasma lipid per-oxidation and MDA formation.

Not long ago, in African-American and Latina, women with breast cancer had ever been studied and an activation of the cell signaling Akt cascade via the HER2 was said to induce cell proliferation. (Wu et al., 2008; Xia et al., 2013). This is coincided with another recent study, that CD24 was just related to HER2 positive breast cancer on the consequent activation of PI3K-Akt signaling (Hosonaga et al., 2014), further, in the study, over-expressed CD24 not only supported expression of HER2, but contribute to resistance to HER2-targeted therapy.

S100A14, a recently identified member of the S100 protein family and a functional partner of HER2 whose underlying mechanisms have not been fully understood is now inducing heat discussion, it is a member of the EF-hand Calcium-binding Proteins, generally thought to contributes to cell invasion by regulating MMP2, now found over-expressed in Breast Cancer, Binding HER2 and Modulating the HER2 Signaling (Xu et al., 2014). in the experiment, Chengshan Xu et al. (2014) also noted S100A14 knockdown significantly attenuated HER2

phosphorylation, greatly affecting the activation of Ras/Raf/MAPK.

Other associated micromolecules

Recently, from a French regional cohort, HER2 over-expression is proved to be a major risk factor for recurrence in pT1a-bN0M0 breast cancer (Rouanet et al., 2014). Also, HER2 over-expression was associated with locoregional recurrence (LRR) in the pre-adjuvant trastuzumab era (Lanning et al., 2015). trastuzumab may modulate LRR risk in HER2 (+) breast cancer patients.

Particularly, like many other tumors, in (HER2)-positive primary breast cancers, we can see over-expressed of epidermal growth factor receptor (EGFR). If not in not high copy number, co-expression and interaction between HER2 and EGFR may matter much in poor clinical outcome, as well as in trastuzumab resistance (Lee et al., 2015). So concomitant inhibition of HER2 and EGFR signaling such as gefitini was a promising strategy in breast cancer therapy (Segovia-Mendoza et al., 2014). However, just not long ago, researches showed AZD8931, a novel dual tyrosine kinase inhibitor (TKI) of (EGFR)/HER2 could be more effective in blocking ligand-dependent HER signaling than the HER TKIs lapatinib or gefitini, especially in terms of the endocrine resistance which was usually mediated by HER2 (Morrison et al., 2014). But The relationship between EGFR overexpression and high EGFR copy number has not been clearly defined. And its over-expression may be induced by other mechanisms, such as mutation, aberrant transcription or translational modification.

EGFR is usually associated with hormone receptor negativity and large tumour size (Lee et al., 2015), but in other ways, breast cancer clinically also represents a heterogeneous disease that is grouped based on its hormone receptor (HR) status. In the HER2 (+) tumors, hormone exposure, saying, the pregnancy hormones, is hypothesized to disturb the HER2 signaling (Cruz et al., 2013).

In the HR filed, even estrogen, working via the non-genomic activity of estrogen receptor (ER) outside the nucleus, has been shown to activate HER2 signaling (Iqbal and Iqbal, 2014). And ER-positive/HER2-positive breast cancer appears to be exquisitely sensitive to estrogen deprivation. While, for the fact, we know, ER and HER2 can interact when co-expressed, and are critical drivers of breast cancer biology. Alqaisi et al. (2014) showed HER2 impact on ER-positive disease was reflected by younger age, higher grade and TNM stage, and increased frequency of visceral involvement (Alqaisi et al., 2014).

Then, we turn to another way, Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and C-FLIP (L)-Cellular FLICE-inhibitory protein, are two apoptosis associated factors in breast cancers with HER2 amplification, but the majority of breast cancer cell lines are highly resistant to TRAIL treatment, which poses a limitation to its use in clinic, theories show that this kind of resistance may be mediated by c-FLIP (L) which c-FLIP (L) was relatively high-expressed in HER2-positive breast cancer and played a role in inhibiting caspase-3 and caspase-8 activation in HER2-positive breast cancer

(Zang et al., 2014). While underlying mechanisms of TRAIL resistance have not been clearly characterized, this predicts c-FLIP (L) is a potential target in TRAIL treatment in HER2-positive breast cancer.

Interestingly, A novel function of HER2/Neu has come into being nowadays. In the γ -irradiation (IR)-induced DNA damage, the HER2/Neu should find its way into G2/M checkpoint (Yan et al., 2014), which is followed by certain phosphorylation., saying, the HER RTKs, but clear mechanism remain unknown. As for the G2/M checkpoint, Lapin et al. (2014) thought chemical treatment such as the prevailing trastuzumab could also exert the same function, namely inhibiting the proliferation (Lapin et al., 2014).

Finally, in the larger scale, Centrosome amplification (CA) amongst particular breast cancer subtypes (Her2+ subtype) is associated with genomic instability and aggressive tumor phenotypes., and Lee et al. (2014) concluded CA, the precursor of chromosome instability and polyploidy correlates with amplification of the Her2

receptor, which affects over 20% breast cancer patients (Lee et al., 2014). In the study, they also clarified SGOL1 (Shugoshin proteins) is an attractive target for blocking the progression., when referred to the instability, we found another interesting outcome-HER family mutations in breast cancer may matter much, but until now, Little is known about the clinical significance, In the newest study of Delphine R et al. HER2 mutants conferred an aggressive phenotype and altered effects of the TKI lapatinib (Boulbes et al., 2014), these coincided with JULIANN CHMIELECKI's declare that mutations

can also activate the ERBB2/HER2 gene in breast, while at the same time be similarly sensitive to ERBB2/HER2 inhibitors (Chmielecki et al., 2014). Joyfully, about the mutant mechanism, researchers newly reported a case that a breast cancer patient harboring an activating EGFR mutation clinically benefiting from EGFR-targeted treatment (Ali et al., 2014).

Table 1. Treatment of Breast Cancer

	name	targeting strategied	Referances
The immune way	ADCC		(Nahta, 2012)
	multiple mAbs	HER2 internalization	(Ben-Kasu et al., 2009)
	anti-HER2 vaccine	Peptide-based/DNA-based/ anti-idiotypic	(Cao et al, 2013; Tagliabue and Campiglio, 2014)
Trastuzumab		mitogenic signaling	(Schroeder et al., 2014; Kawajiri et al., 2015)
		ADCC	
	188Re-labeled HYNIC-trastuzuma	radioactivity dose-dependent fashion	(Luo et al., 2015)
	64Cu-DOTA-trastuzumab	metastatic breast cancer	(Mortimer et al., 2014)
	Trastuzumab resistance	Upregulation of HER3	(Nahta, 2012; Brady et al., 2014; Nielsen et al., 2014; Rimawi et al., 2014; Zang et al., 2014; Nam et al., 2015)
		miRNAs (miRNA-21, miR-7, miR-200c)	(Bai et al., 2014; Chen and Bourguignon, 2014; Huynh and Jones, 2014; Nielsen et al., 2014)
		HER2 copy number/ dimerization status	
		Interaction between HER2 and other ERBB	(Lee et al., 2015)
		autophagy	(Yeh et al., 2014)
Anthracyclines		HER2/TOP2A	(Fountzilias et al., 2012)
S-222611		ERBB family dimmers	(Spicer et al., 2015)
NCT		Increase pCR rates	(Shinde et al., 2015)
Flotillin		reduction of ErbB2-ErbB3	(Asp and Pust, 2014)
CC		apoptosis/ proliferation	(Khan et al., 2015)
Taspase1		Cyclins E, A, and B	(Dong et al., 2014)
Combined therapy	Trastuzumab, carboplatin, paclitaxel		(Shinde et al., 2015)
	Trastuzumab, MK-2206		(Hudis et al., 2013)
	Trastuzumab, lapatinib		(Rimawi et al., 2014; Scaltriti et al., 2014; Schroeder et al., 2014)
	lapatinib , BYL719		(Brady et al., 2014)
	AZD8931, paclitaxel		(Kurata et al., 2014)
	Hsp90, laptinib		(Huang et al., 2014; Huang et al., 2015)

Treatment of Breast Cancer

Overview of the HER2-targeted therapy

The HER2-targeted therapy which is mostly via the PI3K/Akt/mTOR pathway. (Mohd Shariel et al., 2012; Takada et al., 2013; Xia et al., 2013; Kawajiri et al., 2015; Nam et al., 2015) has shown success in preclinical models. And the HER2 gene has been established as a valid biological marker for the treatment of breast cancer. So far, Small Molecule Tyrosine Kinase Inhibitors of HER2 such as Trastuzumab, Pertuzumab, Lapatinib, Afatinib, AZD8931, AST-1306, AEE-788, CI-1033 (Canertinib), CP-724714, CUDC-101, TAK-285, AC-480 (BMS-599626), PF299804, PF299 (Dacomitinib), EKB-569 (Perlitinib) are on their way to clinical use or undergoing phase trials in aggressive breast cancer (Kumler et al., 2014; Schroeder et al., 2014), being explored for their potential to inhibit EGFR and HER2 tyrosine kinases. But we can't delay the fact that HER2 mediated resistance via multiple mechanisms is a common clinical problem (Boulbes et al., 2014; Leivonen et al., 2014). And treatment-induced toxicity, which can impair quality of life can't be ignored (Barroso-Sousa et al., 2013). Many studies are under carrying out, for the relatively newer one, Moody et al. (2014) observed elevated PRKACA expression in trastuzumab-resistant breast cancer, inactivating the pro-apoptotic protein BAD, the BCL-2-associated death promoter, but not by the usual MAPK or PI3K way. And they declare combined targeting of HER2 and the BCL-XL/BCL-2 anti-apoptotic pathway may increase responses to anti-HER2 therapy in breast cancer (Moody et al., 2014). From studies of Liqun Chen et al. (Chen and Bourguignon, 2014), we further conjecture the possible mechanism may be upregulation of survival protein (Bcl-2/IAP), which is induced by c-Jun (member of the mitogen activated protein kinase family) signaling. Fortunately, evidence have showed, for patients with HR+ disease for whom chemotherapy may not be a good option, anti-HER2 therapy with an AI (aromatase inhibitor) may be considered (Delea et al., 2013). (Table 1)

The immune way

Now, modulation of immunologic interactions in cancer tissue is a promising therapeutic strategy. Molecular alterations of HER2 and its presence on the tumor cell membrane endow this onco-protein with relevant immunological properties, making it an ideal target antigen for long-term cancer immunoprevention. Perhaps, the most significance of the vision into the HER2-specific antibodies lies in curing for breast cancer patients with HER2 therapy-resistant. Generally, HER2-specific monoclonal antibody might block phosphorylation of HER2 (Nahta, 2012), or antibody-dependent cellular cytotoxicity (ADCC), but The mechanisms underlying the anticancer activity of trastuzumab are not completely known, recently, Luca et al.(2012) revealed, exposure of cell-surface HER2 to polyclonal anti-HER2 antibody generated in mice promotes rapid receptor internalization (Luca et al., 2012). Even, there are phenomenon that, one mAb or multiple mAbs against HER2, alone or in combination, were able to induce HER2 internalization

over intervals as short as 4 hours (Ben-Kasus et al., 2009).

Clinically, different anti-HER2 vaccine strategiest are currently developed and have been or are assessed in clinical trials (Ladjemi et al., 2010; Bilous et al., 2012; Tagliabue and Campiglio, 2014). Peptide-based and DNA-based vaccines have come into clinical phase. The inhibition of PPIs (protein-protein interactions) using small molecules and peptides is challenging, mostly targeting at the EGFR-HER2 or HER2-HER3 (Kanthala et al., 2014). In other experiments, DC-targeted DNA vaccines was tested *in vivo* to be an antitumor factor (Cao et al., 2013; Tagliabue and Campiglio, 2014). Multi-peptide, Protein-based vaccines and anti-idiotypic Abs vaccines are also under clinical and preclinical use.

Trastuzumab

During these methods, trastuzumab is the first and still among the most use. Trastuzumab is a humanized mAb directed against the extracellular domain (ECD) of HER2, it functions by binding to the HER2 receptor and decreasing ligand-independent HER2-mediated mitogenic signaling, thereby reducing tumor cell proliferation and survival (Schroeder et al., 2014; Kawajiri et al., 2015). Or, it activates antibody-dependent cell-mediated cytotoxicity (ADCC) which promotes tumor cell lysis (Gennari et al., 2004).

Using of trastuzumab, in combination with chemotherapy, is playing an important role. (Mohd Shariel et al., 2012; Boku, 2014; Kumler et al., 2014; Yu et al., 2015). Even in the metastatic HER2 breast cancer, trastuzumab is recommended in the first-line setting (Iqbal and Iqbal, 2014). And as for another new filed-therapeutic radiopharmaceutical agent. Radiolabeled trastuzumab has been used to image patients with HER2-positive breast cancer. For example, 188Re-labeled HYNIC-trastuzumab can enhances cell death in a radioactivity dose-dependent fashion, while at the same time prolong the effects of apoptosis involved with the mito-chondria-dependent pathway in HER2-overexpressing breast cancer cells (Luo et al., 2015) 64Cu-DOTA-trastuzumab also visualizes HER2-positive metastatic breast cancer with high sensitivity, what's more, 64Cu-DOTA-trastuzumab PET/CT can effectively detect and quantify tumor uptake in patients with known HER2-positive disease, critical in determining treatment (Mortimer et al., 2014). Dispite the fact that improving outcomes may be associated with a risk of treatment-induced cardiotoxicity (TIC) (Barroso-Sousa et al., 2013; Zhu et al., 2013; Shinde et al., 2015; Yu et al., 2015). And in predominantly stage I HER2-positive breast cancer, treatment with adjuvant paclitaxel plus trastuzumab was associated with a risk of early recurrence of about 2% (Tolaney et al., 2015). Also, the good outcomes are limited regarding its impact on locoregional recurrence (LRR) in patients undergoing mastectomy, particularly those receiving (post-mastectomy radiation) PMRT (Lanning et al., 2015).

However, a major limit of immunotherapy with trastuzumab is the development of drug resistance (Nahta, 2012; Brady et al., 2014; Nielsen et al., 2014; Rimawi et al., 2014; Zang et al., 2014; Nam et al., 2015). Wen-Bai et al. (2014) referred, trastuzumab resistance was

characterized by enhanced invasiveness of breast cancer cells with concomitant EMT and elevated TGF- β signaling (Bai et al., 2014).

Upregulation of HER3 may be a means of escape from therapeutic suppression (Garrett et al., 2013) as recent researches shows, HER2 and HER3 are both important for HER2+ cell proliferation and required for trastuzumab effectiveness (Lapin et al., 2014). Further, ATF4, CHEK2, ENAH, ICOSLG, and RAD51 has the potential of being biomarkers of trastuzumab resistance (Nam et al., 2015), and these may be validated by their up-regulation in refractory HER2+ breast cancer cells and tumors. Leading to inhibition of DNA repair, Sueta et al. (2014) declared biomarkers such as PIK3CA mutation, and INPP4B were relevant to trastuzumab efficacy in HER2-positive breast cancer (Sueta et al., 2014).

Strangely, the resistance may have something with miRNAs, due to the capability of miRNAs to target multiple genes, up till now, this filed remains a significant clinical challenge. MiRs are a class of short non-coding single-stranded RNAs that regulate gene expression, they present an attractive strategy for targeting HER2 and its downstream signaling mediators in breast cancer. But previous reports describing the miRNA-mediated regulation of the HER family are few. Recently, miR-21 (miRNA-21) is proved highly prevalent and up-regulated in breast cancer (Chen and Bourguignon, 2014), operating in a c-Jun-dependent way, and has been linked to drug resistance in clinical and *in vitro* settings, while Boye Schnack Nielsen et al. (2014) showed elevated miR-21 expression didn't predict resistance to adjuvant trastuzumab in primary breast cancer (Nielsen et al., 2014), and Leivonen et al. (2014) only referred High-throughput of miRNAs being a cell growth promoter in HER2 positive breast cancer (Leivonen et al., 2014). Now, a new member of the miRNAs come into being in the breast cancer filed, MiR-7 was proved to inhibit HER2D16 cell migration through a mechanism involving suppression of the miR-7 target gene EGFR and sensitize refractory HER2D16 expressing cells to trastuzumab (Huynh and Jones, 2014). Also miR-200c has seen to suppress TGF- β signaling and counteract trastuzumab resistance and metastasis by targeting ZNF217 and ZEB1 in breast cancer (Bai et al., 2014).

Other Specific factors implicated in resistance include the HER2 copy number; HER2 dimerization status; presence of truncated HER2; loss of phosphatase and tensin homolog (PTEN) and p27Kip1 expression; over-expression of the EGFR protein; over-expression of insulin-like growth factor receptor 1 (IGF1R), vascular endothelial growth factor receptor, and heat shock protein 90 (HSP90); activation of the cytoplasmic tyrosine kinase SRC and so on. Specially, researchers have clarified in detail that, Interaction between HER2 and other ERBB co-receptors, such as EGFR and HER3 (ERBB3) play as a possible mechanism of resistance to trastuzumab (Lee et al., 2015), but this is not for metastatic settings. However, the significance of EGFR over-expression for trastuzumab response is still not clear in clinical settings. EGFR inhibitor gefitinib has been tried in combination with trastuzumab to treat patients with HER2-positive

metastatic breast cancer but proved to be weaker than trastuzumab alone (Luu et al., 2011).

Further, in terms of other drug resistance, another treatment drug lapatinib, also takes a large part (Schroeder et al., 2014), but this can be reversed by a p110 α -Selective PI3K inhibitor (Brady et al., 2014). if not for the resistance, high expression of HER2 have a significantly higher probability to achieve benefit from the combination of trastuzumab and lapatinib (Scaltriti et al., 2014). Several recent studies indicate that activation of autophagy, which itself is closely connected to signaling crosstalk to apoptotic pathways, and therefore influences tumor cell survival contributes to trastuzumab and lapatinib resistance. So, inhibiting autophagy makes treatment much more effective, an recently under hit-discussion kinase HUNK (upregulated by Akt), according to Elizabeth S et al., has the potential to regulate resistance to HER2 inhibitors just by the so-called autophagy mechanism (Yeh et al., 2014), they even speculated exists of an overlapping mechanism for HUNK toward Akt-specific substrates. And before this result, an heregulin-EGFR-HER3 autocrine signaling axis had been proved to mediate acquired lapatinib resistance in HER2+breastcancermodels (Xia et al., 2013).

Other treatments

Anthracyclines and taxanes which targeted on HER2/TOP2A are currently considered to be essential drugs in adjuvant chemotherapy (Fountzilias et al., 2012), which is commonly used to treat patients with locally advanced or inflammatory breast cancer (LABC); S-222611, an oral reversible, novel, selective and potent dual tyrosine kinase inhibitor of EGFR and HER2, in a dose-dependent way, providing effective blockade of all possible signaling-active ERBB family dimers (Spicer et al., 2015); NCT-Platinum-containing neoadjuvant chemotherapy, may increase Pathologic complete response (pCR) rates in HER2 (+) breast cancers (Shinde et al., 2015). largely because these tumors have defective DNA-repair pathways ; paclitaxel has demonstrated efficacy in the metastatic breast cancer (Shinde et al., 2015); Aiso, depletion of lipid raft-associated flotillin (flotillin-1 and flotillin-2) resulted in down-regulation of ErbB3 and a selective reduction of ErbB2-ErbB3 receptor complexes, with the flotillin-2 induced effect being mediated by Akt and MAPK signaling cascades (Asp et al., 2014). During the process, Asp et al. (2014) even predicted, in breast cancer cells, Hsp90 might act as an important linker between flotillins and ErbB receptors.

Further, Khan et al. (2015) recently revealed CC could further be developed as an effective drug candidate for the fact that CC-treatment at higher doses specifically induces cellular apoptosis and inhibits cellular proliferation; whereas at lower doses, it inhibits cellular migration and invasion. against metastatic breast cancer. (Khan et al., 2015), and one possible mechanism may be reversing epithelial-mesenchymal transition via downregulation of HER2/ERK1/2/MMP-9 signaling; and Afatinib, an irreversible ErbB family blocker, covalently binds to EGFR, HER2, and ErbB4, and thus irreversibly block signaling from all homo-and heterodimersformed by

the ErbB family members, differs from lapatinib and trastuzumab by its broader scope of ErbB receptor inhibition and by its covalent mode of binding resulting in potent and long-lasting activity. (Rimawi et al., 2014)

Finally, Taspase1, a highly conserved threonine protease, cleave (mixed-lineage leukemia) MLL which forms complexes with E2F transcription factors to regulate Cyclins E, A, and B expression, required for HER2/neu-induced tumor genesis (Dong et al., 2014).

Combined therapy

The concept of targeting more than 1 ErbB family member using multiple agents in the treatment of HER2-positive BC has been shown in preclinical studies (Bessadottir et al., 2014; Kumler et al., 2014), for combinations of HER2-directed agents may show additive or synergistic effect and give more hope for cure compared to the traditional sequential approach

Trastuzumab combined with carboplatin and paclitaxel improve tumor response

rates and prolong the time-to-progression (Shinde et al., 2015); trastuzumab combined with AKT investigational allosteric inhibitor MK-2206 inhibit compensatory signaling (Hudis et al., 2013). Dual HER2-targeting with lapatinib. (a dual reversible tyrosine kinase inhibitor targeting the cytoplasmic domain of EGFR and HER2) and trastuzumab (Rimawi et al., 2014; Scaltriti et al., 2014; Schroeder et al., 2014), with the former increasing HER3 expression followed HER2 inhibition, would also be superior to trastuzumab alone. while the lapatinib plus BYL719 combination can overcome acquired lapatinib resistance of breast cancer cells with simultaneous PIK3CA mutation and amplification (Brady et al., 2014). In a newly Japanese study, AZD8931 alone and in combination with paclitaxel were targeted at the EGFR, HER2 and HER3 signaling, too (Kurata et al., 2014).

while novel Hsp90 (a bis-oxazolyl macrolide compound, which is known to stabilize and potentiate HER2 activity) inhibitor FW-04-806 alone or with lapatinib inhibits cell proliferation, induces cell apoptosis and reduces the total and activated HER3 levels in these cells (Huang et al., 2014; 2015), in the research of Huang et al. (2014; 2015), treatment with FW-04-806 showed a more favorable safety profile than the traditional Hsp90 inhibitors, since it didn't affect the ATPase. Now, the new HSP90 inhibitor 17-demethoxygeldanamycin (17AAG) is undergoing clinical testing in combination with trastuzumab, too (Boulbes et al., 2014). For all these mechanism, possible methods may have something to do with PI3K/Akt and Ras/MEK/ERK pathways (Huang et al., 2015), simultaneous treatment targeting at MAPKs and BIM with gefitinib and calcitriol or EB1089 in EGFR and HER2 positive-breast cancer cells proved to be significantly better to inhibit proliferation and induce apoptosis. in a caspase 3 dependent way (Segovia-Mendoza et al., 2014).

Adding pertuzumab (a monoclonal antibody that represents the first of a new class of agents) to trastuzumab plus docetaxel significantly prolonged progression-free survival and overall survival without increasing severe adverse events (Kawajiri et al., 2015).

Totally, combination of trastuzumab plus lapatinib and trastuzumab plus pertuzumab, respectively, offered the first evidence of dual targeting being superior to single agent therapy with trastuzumab (Pazhoomand et al., 2013; Kumler et al., 2014), and more surprisingly, a recent study indicates that by using targeted therapies in a sequential order, starting with two anti-HER2 drugs, followed by treatment with an anti-HER2 drug and a PI3K/mTOR inhibitor and lastly combining all three agents can prolong survival and minimize toxic effects in mouse models bearing aggressive breast tumours (Zhang et al., 2011; Bessadottir et al., 2014).

Seen from the larger scale, two key pathways involved in breast carcinogenesis, the estrogen receptor and HER2, may be a potential co-targeting, since they have been proved to interact with each other in biological networks, invasive behavior and cell growth, for example, without a significant increase in toxicity (Mehta and Tripathy, 2014), . until now, no such trails have come into clinical treatments.

Prognosis of Breast Cancer

A newly published report shows the highest rates of breast cancer were observed at the ages of 46-55, and lowest rates were observed under the age of 25 years and above 66 years. in the HER-2 receptor-positive team, poorer prognosis was associated with younger ages (Mirmalek et al., 2014). Interestingly, there are racial differences in breast cancer outcomes (Rugo et al., 2013). A recent national registry study showed black patients had a higher likelihood of HER2-positive metastatic breast cancer (MBC), and on average had more adverse prognostic factors compared with white patients Then, as a new technology, pCR is widely accepted as a surrogate marker of survival, although it is only reliable in some subpopulations (Kumler et al., 2014).

HER2 (+) breast cancer has been envisioned as a single disease entity, but at the same time, labeled with biological heterogeneity, that is, different intrinsic subtypes predict different survival outcomes, as well as responses to hormone or lapatinib, Aleix Prat et al. (2014) observed cHER2-positivity didn't affect patient survival in the absence of HER2 targeting.

As for other gens, Pang et al. (2014) summarised the percentage of P53 positive was high in the HER2 over-expression subtype, the former is significantly associated with the latter, and coexistence of both was a strong prognostic molecular marker (Pang et al., 2014). Nair et al. (2014) proposed MYC amplification cooperated with Her2 drove a stem-like phenotype predicting diagnostic and therapeutic consequences in breast cancer, only in the context of Her2 activation did c-Myc drive the acquisition of an aggressive stem-like phenotype (Nair et al., 2014). Mesenchymal-epithelial transition factor (MET) and metastasis-associated in colon cancer-1 (MACC1) gene, especially the hMACC1 poly-morphisms had a great to do with poor clinical outcome in breast cancer, even though more studies are warranted to validate (Muendlein et al., 2014). Further, immunoglobulin constant (IGKC) gene has recently been identified as a strong prognostic marker

in HER2 (+) breast cancer, the underlying mechanisms could involve the antigen processing/presenting pathway. that is, there may be some relationship between anti-HER2 antibody responsiveness and prognosis of breast cancer (Pandey et al., 2014). Splice variants of ERBB2 (HER2/neu) in breast cancer cell lines can be a new class of protein cancer biomarker candidates, too (Omenn et al., 2014). increased expression levels of MicroRNA-21 are associated with poor prognosis both in untreated early-stage breast cancer and patients treated with chemotherapy (Nielsen et al., 2014); Accumulation of hyaluronan (HA) in breast cancer is associated with estrogen receptor negativity, HER2 positivity, high relapse rate, and short overall survival (Auvinen et al., 2014).

In HER2-positive MBC patients, circulating tumor cell (CTC) enumeration can act as a predictive factor in metastatic breast cancer (Liu et al., 2013), Duchnowska et al. (2015) found over-expression or amplification of HER2 is associated with high risk of brain metastasis (BM) (Duchnowska et al., 2015). presence of visceral metastases and the lack of trastuzumab administration in the metastatic setting was said to increase the likelihood of early BM, but molecular predictors of the BM development remain difficult to find.

In other cases, post-treatment reaction make up part of prognosis. for example, the sentinel lymph node biopsy (SLNB) acts as an effective metastatic factor, after neo-adjuvant chemo-trastuzumab therapy, the ER-poor/HER2-positive subtype of breast cancer is said to be a potential candidate for undergoing sentinel lymph node biopsy instead of regional node dissection for accurate axillary evaluation (Li et al., 2014). Similarly there are outcomes that, after the anthracycline-based neoadjuvant chemotherapy (NAC). reductions in Ki-67, Phospho-p44/42, and pAKT expression are related to the clinical response, and phospho-p44/42 expression and lymph node status after NAC could be useful for determining relapse-free survival and overall survival (Huang et al., 2013); Green et al. (2014) noted after adjuvant trastuzumab response in HER2+ breast, cancer, HER2/HER3 heterodimers and p21 expression were nice predicting factors (Green et al., 2014).

Except from metastatic cancers, EGFR protein over-expression, if not in but not high copy number (Lee et al., 2015), is an independent poor prognostic factor in HER2-positive primary breast cancer, and a predictive factor for trastuzumab response in HER2-positive primary breast cancer (Lee et al., 2015).

Conclusion

The human epithelial growth factor receptor 2 membrane tyrosine kinase growth factor receptor (HER2) is one of the main mediators of key pathways involved in breast carcinogenesis, invasive behavior and cell growth. Many important signal pathways such as the PI3K pathway, AKT and Rac1/ERK pathway, and RAF (RAF)/MEK/ERK-signaling all consists of major effectors of the HER2 activity. Novel HER2- targeted agents used in the management of breast cancer take a large part of the whole neo-adjuvant chemotherapy, but treating patients

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