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Breast Cancer Biomarkers and their clinical utility with resistance to newer biological agent

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Abstract: In breast cancer, HER2-targeted therapy with trastuzumab has gained clinically significant attention in a subset of HER2 positive patients after results of from two National Cancer Institute-Cooperative Group trials (NSABP B31 and NCCTG N9831) were reviewed. HER2 is a transmembrane oncoprotein encoded by the HER2/neu gene and is over expressed in approximately 20 to 25% of invasive breast cancers. It can be therapeutically targeted by trastuzumab (Herceptin), a humanized monoclonal antibody. Trastuzumab therapy is important in the treatment of early, advanced and metastatic/ recurrent breast cancer. The mechanisms of action and resistance to trastuzumab are complex and crucial for the development of new therapeutic strategies therefore much effort has been spent in order to identify responders. This review summaries the current knowledge on the preclinical era and clinical era evidence about the mechanism of action of trastuzumab and mechanism of resistance and discusses their possible clinical implications.

Keywords: Trastuzumab, Monoclonal Antibody, Herceptin, Breast cancer, Biomarker, HER2 /neu

1. Introduction

Breast cancer is the leading malignancy and leading cause of cancer-related deaths in women worldwide. The incidence of female breast cancer in Iran is lower compared to low-middle-income neighboring countries. The average annual crude incidence of primary female breast cancer was 22.6 (95%CI 22.1-23.1) per 100,000 females, with an age-standardized rate 27.4 (95%CI 22.5-35.9). The mean age of the women with breast cancer was 49.6 years (95%CI 49.5-49.6). It is estimated that approximately 1 in 8 (12%) women will suffer from the disease at some point in their lifetime in US women. In the recent years, knowledge about cancer biomarker has increased. Biomarkers of breast cancer include broad range of biochemical materials, such as nucleic acids, proteins, sugars, lipids, and small metabolites, cytogenetic and cytokinetic parameters. Her2/neu, CA15.3, estrogen receptor (ER), progesterone receptor (PR), and cytokeratins are biomarkers that have been approved by the Food and Drug Administration (FDA) for disease diagnosis, prognosis, and management selection [1, 2]. The most common biomarker used in the management of breast cancer out all of these biomarkers is HER-2/neu or cerbB2, that is a component of human epidermal growth factor receptor family mapped on chromosome 17q. In addition, HER- 2/neu protein called p185HER-2/neu, as it shows substantial homology with the epidermal growth factor receptor, EGFR. The family of transmembrane receptors includes four categories: HER1/EGFR, HER2, HER3 and HER4. HER2 has been targeted to be not only a prognostic factor, but also a predictor of response to trastuzumab [3, 4]. Women with HER2-overexpressing breast cancers have an increased risk of recurrence and shortened disease-free and overall survival rates compared to HER2 negative breast malignancies. Trastuzumab is a humanized IgG1 kappa light chain recombinant mono-clonal antibody targeting is indicated for patients whose tumor demonstrates an amplified copy number for HER2 oncogene or over expressed the HER2 oncoproteins. HER2 receptor structurally include three specific domain; an extracellular domain (ECD) which is composed of four domains. A single transmebrane lipofilic region and a cytoplasmic tyrosine kinase-

converting it back to PIP2. RAF-MEK-MAPK and PAK-JNKK-JNK are two cascades of serine/ threonine kinases, which regulate the activity of various transcription factors downstream. The GTPases RAS and RAC activation of components of this pathway result in elevated levels of p27Kip1 protein as cell cycle arrest. Interactions of other signaling proteins with phosphotyrosine sites on the EGFR dimer begin downstream signaling pathways, which include the Ras/Raf/ERK kinase pathway, the PI3K/AKT/mTOR (phosphatidylinositol 3- kinase) pathway, resulting in changes in RNA transcription, cell division, apoptosis, cell migration, adhesion, and differentiation [10, 11].

3. Mechanism action of trastuzumab

Trastuzumab is a recombinant humanized monoclonal antibody directed against the extracellular domain IV of HER2 and is approved for the treatment HER2- positive breast cancer and the other cancers via over expression HER2 in combination mainly with chemotherapies such as vinorelbine, paclitaxel or docetaxel etc. or as a single agent. The studies suggest trastuzumab improved overall survival in metastatic breast cancer from 20.3 to 25.1 months. In early stage breast cancer, it reduces the risk of cancer recurrence after surgery by an absolute risk of 9.5% [12, 13]. Trastuzumab have an IgG1 subtype inducing antibody dependent cell mediated cytotoxicity (ADCC), which is triggered through the detection of fc portion of antibody by Fcã receptor on immune effectors cells, in particular natural killer cells (NK), resulting in cell lysis of HER2- positive target cells bound to trastuzumab.

Human IgG1 Fc portion binds to FcRn receptors on endothelial cells and on phagocyte cells, becomes internalized and recycled back to the blood stream to enhance its half-life within the body. Antibody-dependent cell mediated cytotoxicity (ADCC) has also been shown as a possible mechanism of action of trastuzumab in patients [14, 15]. Trastuzumab has also been shown to inhibit tumor angiogenesis, leading in decreased micro vessel density in vivo and reduced endothelial cell migration in vitro [16]. Studies have demonstrated that trastuzumab inhibits HER2 extra cellular domain (ECD) cleavage through the proposed mechanism of steric hindrance in preclinical studies; synergy with Herceptin enhanced the effects of chemotherapy [17]. Molina et al showed that trastuzumab could inhibit the shedding of the extracellular domain of HER2 by blocking metalloproteinase activity. Several clinical studies demonstrate that a decline in serum HER2 extracellular domain during target therapy with trastuzumab predicts tumor response and improves progression-free survival, which indirectly supports the hypothesis that trastuzumab may act by blocking HER2 cleavage.

4. Mechanisms of Resistance to Trastuzumab

The common mechanisms of trastuzumab resistance are: (1) blocking extra cellular domain HER2 that binds to drug; (2) HER2 downstream signaling pathways increased; (3) signaling through substitute pathways; and (4) serious problems in beginning immune mechanisms to destroy tumor cells of breast. Subsequent use of trastuzumab, other HER2-targeted agents developed for treatment of HER2 trastuzumab resistant tumors including: Lapatinib, pertuzumab, adotrastuzumab emtansine (also known as T-DM1). The pan-HER TKI CI-1033; lapatinib: is a small molecule dual TKI against EGFR; ErbB1; HER1 and HER2; Pertuzumab is a recombinant humanized monoclonal antibody that binds subdomain II of the HER2 extracellular domain and thus inhibits HER2 homo or heterodimerization between EGFR/HER2 and HER2/HER3, also pertuzumab prevents interaction between HER2 and IGF-Ir; CP-751871, an antibody against IGF-IR; T-DM1, the IGF1R kinase inhibitor NVP-AEW541; and other agents are rapamycin inhibitors RAD001, CCI-779, and AP23573 and a derivative of the antimitotic combinations [18,19,20]. P95-HER2 is a cleaved form of HER2 tyrosine kinase receptor can binds with other ERBB2 family members and binding triggers

downstream signaling pathways. These extracellular receptor domains of p95-HER2 without binding site for trastuzumab therefore studies showed that these receptors involved in the resistance to trastuzumab. Recently, studies have demonstrated that rising HER4 expression levels is associated with an elevated sensitivity towards trastuzumab. Trastuzumab resistance can be created by ligands from epidermal growth factors. Comparing tumor samples before and after of treatment with trastuzumab showed that when expression of TGF-á elevates resistance was increased. Expression of a TGF-â mutant has been illustrated to activate proteases (e.g., ADAM17), which discharges EGF ligands so the elevated expression of EGF ligands can result in Trastuzumab resistance. Other Obstructions for trastuzumab binding to HER2 ECD domain are Mucin 4 and CD44/hyaluronan polymer complex. Mucin 4 (MUC4) is large, highly O-glycosylated membrane associated glycoprotein that may interfere with trastuzumab binding to HER2 receptor also CD44 is a transmembrane receptor for hyaluronan. CD44 and hyaluronan may block the admission of trastuzumab to HER2 receptor by covering its cognate epitope [9, 21]. Two other tyrosine kinase receptors (distinct from the EGF receptors) include the IGF receptor (IGF-1R) and the HGF receptor (MET) which can influence trastuzumab sensitivity by alternate pathway. IGF-1 receptor was demonstrated to interact with HER2 in trastuzumab-resistant cell lines, inducing its phosphorylation. Breast cancer cell lines (SKBR3) with ectopic expression of IGF-1R become insensitive to trastuzumab, via a process result in degradation of p27 (G1 arrest). IGF-IR-mediated resistance to trastuzumab treatment seems to involve the PI3K pathway, leading to enhanced degradation of p27. P27 is downstream regulator of multiple converging growth factor receptor pathways including EGFR, HER2, and IGF-IR.

Also has been found which MET be overexpressed in both breast cancer cell lines and in human tumor samples. MET affected the sensitivity of the cells towards trastuzumab. In addition, used the same molecular mechanism as IGF-1R and prevented trastuzumab mediated cell cycle arrest by causing a degradation of p27 [13]. The HER2 downstream pathway PI3K/Akt, is activated by phosphorylation of the intracellular HER2 tyrosine kinase domain. PI3K/Akt pathway regulates proliferation, migration, apoptosis and angiogenesis and pro-motes carcinogenesis when unopposed. PTEN is a tumor suppressor that inhibits AKT and induce growth arrest in PI3K–Akt signaling pathway therefore in sensitive cells, trastuzumab causes a disruption of the binding of Src to HER2, allowing PTEN to inhibit AKT. Loss of PTEN function because of mutation, deletion or promoter methylation is demonstrated in up to 50% of breast cancers. Nagata et al suggested role of decreased expression of the PTEN phosphatase function in tumor cells [9,22,23]. Studies also demonstrate that specific polymorphisms in the IgG fragment C receptor or phenotype expression of valine (V) or phenyl alanine (F) at amino acid 158 on the FcãRIIIa significantly influences affinity of IgG1 to the Fcã receptor in natural killer cells. Such results demonstrate that this receptor is involved in trastuzumab mediated cytotoxicity. FcãRIII 158V/F polymorphism interferes with the ability to generate ADCC responses in vitro during target therapy with trastuzumab and significantly affect clinical outcome. Further studies required to show whether this polymorphism should be determined to identify responders [21].

5. Cardiotoxicity of trastuzumab

Trastuzumab cardiotoxicity creates by an asymptomatic abate in left ventricular ejection fraction (LVEF) and clinical heart failure is less important, including failures without symptoms (such as decreased heart function) and those with symptoms. The risks of these heart failures were highest in individuals who treated with both trastuzumab and a certain type of chemotherapy (anthracycline). Trastuzumab includes cardiac 2-7%

of cardiac dysfunctions. Trastuzumab cardiotoxicity does not seem to be related to cumulative dose however cardio-toxicity anthracycline is related to this dose. The difference between the trastuzumab and anthracyclin is that the cardiotoxicity in trastuzumab happen acute while in anthracyclin happens later. Consumption of trastuzumab has serious infusion reactions and lung problems in some individuals and can cause damage when taken by a conception woman. We need to discontinue of trastuzumab if the patient has a dangerous allergic reaction, swelling, lung failure, inflammation of the lung, or acute shortness of breath. These reactions usually create during 24 hours after of using trastuzumab. The most common problems associated with trastuzumab are fever, nausea, vomiting, swelling of the nose and throat, leucopenia, infections, infusion related reactions, diarrhea, increased cough, headache, weight loss, fatigue, lower breath, rash, alter in taste, and muscle pain. Approximately 10% of individuals cannot to consume this monoclonal antibody because of preexisting heart failure. The risk of serious cardiomyopathy is more when trastuzumab and anthracycline used simultaneously [24, 25, 26].

6. Conclusion

Trastuzumab as an monoclonal antibody having importance in the treatment of breast cancer and various cancers both in advanced and primary and advanced disease with HER2 positivity. Over expression and amplification of proto-oncogene HER/neu are crucial in a target therapy with trastuzumab. The great efforts have been accomplished to clarifying MOA, resistance, safety, side effects, and combination therapies of trastuzumab but yet researches for explaining mechanisms of resistance to trastuzumab is still question of debate.

References

1. K cole, H Junhe, L wang, Breast cancer biomarker measurements and standards, Proteomics Clin, 2013, 7, 17-29.
2. A NarayanBhatt, R Mathur, A Farooque, AVerma, B.S.Dwarakanath, Cancer biomarker Current perspective MedRes, 2010, 132,129-149.
3. S Banerjee, IE Smith .Management of small HER2 –positive breast cancers. The Lancet oncology, 2010, 12, 69-77.
4. R Singhai, A Patil, V Patil, Cancer biomarker HER2/neu in breast cancer in Indian women Breast Cancer: Targets and Therapy2011, 3, 21-26.
5. M Dokmanovic,WJ Wu, Trastuzumab–resistance and breast cancer, Breast cancer – Carcinogenesis, cell growth and signalling pathways.
6. AL A Wong, S Chin Lee, Mechanism of resistance to trastuzumab and novel therapeutic Strategies in HER2-positive breast cancer, International Journal of Breast-Cancer, 2012, 13,10-1155.
7. DJ Salmon, GM Clark, SG Wong, WJ levin, A.Ullrich, WL Mcguire, Human breast Cancer: correlation of re-lapse and survival with amplification of the Her2/neu oncogene, Science, 1987, 4785, 177-182.
8. DR Spigal, H Burstein, HER2- overexpressing meta-static breast cancer, Current Treatment Options in Oncology 2002,3,163-174.
9. R Bartsh, C Wenzel, G Steger, Trastuzumab in the man-agement of early and advanced Stage breast cancer, Biologics: Target and Terapy,2007,1,19-31.
10. MX Sliwkowski, JA Lofgren, GD Lewis, TE Hotaling, BM Fendly, JA Fox: Non clinical

Studies Addressing the mechanism of action of trastuzumab (Herceptin).Semi Oncol 1999,26, 60-70.

11. PH Tseng,Y Wang, SH Weng, JR Weng, C Chen, RW Brueggemeier, ChL Shapiro, ChY Chen,SE Dunn,MPollak,CHS Chen, Overcoming trastuzumab resistance inHER2 –overexpressing breast cancer cells by using a novel celecoxib derived Phospho-inositide-dependent kinase-1 inhibitor Molecular Pharm,2006, 70, 1534-1541.

12.J Baselga, J Albanell, MA Molina, J Arribas: Mechanism of action of trastuzumab and Scientific update. Semin On-col2001,28,4-11.

13. AM Petit, J Rak, MC hung ,et al. Neutralizing antibodies against epidermal growth Factor and ERbB-2/neu recep-tor tyrosine kinases down-regulate vascular endothelial Growth factor production by tumor cells in vitro and in vivo: angiogenic implications For signal transductions therapy of solid tumors. Am J pathol,1997,151,1523-30. Journal of Biology and today's world 513.

14. S Cooley , LJ Burns ,T Repka ,JS Miller: Natural killer-cell cytotoxicity of breast cancer targets is enhanced by twodistinct mechanisms of antibody –dependent cellu-larcytotoxicity aginst LFA-3 and Her2/neu.Exp Hematol, 1999,27,1533-1541.

15. L Arnould,M Gelly , F Penault-liorca, L Benoit, F Bonnetain,C Migeon ,V Cabaret ,V Fermeaux,,P Bertheau, J Garnier ,et al. Trastuzumab-based treatment of HER2 positive Breast cancer :an antibody –dependent cellular cytotoxicity mechanism?,Br J cancer,2006,94,259-267.

16. PR Srinivas, BS Kramer, S Srivastava .Trends in biomarker research for cancer detection, Lancet On-col.2001,2,698-704.

17. C Natoli, P Vici, ISperduti, AGrassadonia, GBisagni, N Tinari, A Michelotti, GZampa, SGori, LMoscetti, M DeTur-Tursi, M Panebianco, MMauri,IFerrarini,LPizzuti,CFIcorella, RSamaritani, LMentuccia, SIacobelli, T Gamucci, Effectiveness of neoadjuvant trastuzumab and chemotherapy in HER2-overexpressing breast cancer ,Cancer Res Cli On-col ,2013,139,1229-1240.

18. ER Wood, AT Truesdale, OB McDonaled, D Yuan , A Hassell,SH Dickerson, B Ellis, C Pennisi, E Horne ,K lacky, et al;A uinique structure for epidermal growth fac-tor receptor bound to Gw572016(lapatinib): relation-ship among protein conformation, inhibitor off rate, and receptor activity in tumor cells. Cancer Res 2004, 64:6652-6659.

19. R Nahta, LX Yung, B Zhang, R Kobayashi, FJ Esteva: Insulin-like growth factor1 –Receptor/ human epidermal growth factor receptor 2 hetrodimerization contributes to trastuzumab resistance of breast cancer cells. Cancer Res, 2005, 65, 11118-11128.

20. MF Press, MC Pike,VR Chazin, et al:Her2/neu expression in node negative breast Cancer: direct tissue quan-titation by computerized image analysis and association of Overexpression with increased risk of recurrent disease. Cancer Res, 1993,53,4960-4970.

21. PR.Pohlmann, IA.Mayer, RMernaugh, Resistance to trastuzumab in breast cancer Clinic cancer, 2009,15,7479-7491

22. R Nahta, FEsteva, Breast, Molecular mechanism of trastuzumab resistance, CancerResearch,2006,8-215.

23. Y Nagata,KH Lan,X Zhou,M Tan,FJ Esteva,AA Shahin, KS Kios, P Li, BP Monia, NT Nguyen

,et al: PTEN acti-vation contributes to tumor inhibition by trastuzumab and Loss of PTEN predicts trastuzumab resistance in patients. Cancer Cell 2004, 6,117-127.

24. DL Keefe, Trastuzumab associated cardio toxicity, Cancer 2002,95-1592.

25. EA Perez, R Rodeheffer, Clinical cardiac tolerability of trastuzumab ,J Clin Oncol,2004,22-322.

A Perez EH Romond, VJ Suman, et al. sequential versus concurrent trastuzumab in adjuvant chemotherapy for breast cancer, J Clin Oncol,2011,29-336.