Breast Cancer Biomarkers resistance to trastuzumab

Sakineh Abbasi[1], Fatemeh Shariati[2]

[1]PhD, Associate Prof, Medical Biotechnology, School of Allied Medicine, Tehran University of Medical Science, Tehran ,14177,Iran Email: sakineh4612004@yahoo.com

[2]MSC, Medical Biotechnology-Tehran University of Medical Science, Tehran, Iran

Email: shareati@yahoo.com

ABSTRACT: In breast cancer, HER2-targeted therapy with trastuzumab has gained significant attention in a subset of HER2 positive patients. HER2 is a transmembrane oncoprotein encoded by the HER2/neugene and is overexpressed in approxi-mately 20 to 25% of invasive breast cancers. It can be therapeutically targeted by trastuzumab (Herclon or Herceptin), a humanized monoclonal antibody. trastuzumab therapy is important in the treatment of both early and advanced 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 and clinical 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 one of the most common cancers among women in the United States. It is estimated that approximately 1 in 8 women will suffer from the disease at some point in their lifetime. In the recent years, knowledge about cancer biomarker has increased. Biomarkers of cancer include abroad 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 for disease diagnosis, prognosis, and therapy selection [1-4]. HER-2/neu or cerbB2 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. This family of transmembrane receptors includes four categories: HER1/EGFR, HER2, HER3, HER4. HER2 has been targeted to be not only a prognostic factor, but also a predictor of response to trastuzumab [2, 5, 6, 7, 8]. Women with HER2-overexpressing breast cancers have an increased risk of recurrence and shortened disease-free and overall survival rates .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 the HER2 oncogene and/or over expressed the HER2 oncoproteins. These 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-containing domain .Domains I these receptors, which result in activation of downstream signaling pathways, particularly the PI3K/Akt pathway. Phosphatidylinositol 3-kinase (PI3K) signaling pathway triggers with PI3K activation and PI3K phosphorylates and converts the secondary messenger phosphatidylino-sitol (4,5) bisphosphate (PIP2)

into phosphatidylinositol (3,4,5) triphosphate (PIP3), which recruits and activates phosphatidylinositol-dependent kinase 1 (PDK). PDK phosphorylates AKT, which inhibits the activities of the transcription factors (which are mediators of apoptosis and cell cycle arrest), resulting in cell survival. The PTEN which is tumor-suppressor phosphatase negatively regulates PI3K signalling by dephosphorylating PIP3, converting it back to PIP2. RAF-MEK-MAPK and PAK-JNKK-JNK are two cascades of serine/threonine kinases, which regulate the activity of a number of transcription factors downstream. The GTPases RAS and RAC Activation of components of this pathway result in elevated levels of the p27Kip1 protein as cell cycle arrest. Interactions of other signaling proteins with phosphotyrosine sites on the EGFR dimer begin the 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 [14-17].

3. Mechanism action of trastuzumab

Trastuzumab is a recombinant humanized monoclonal an-tibody 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 as a single agent, and in combination with chemotherapies such as vinorelbine, paclitaxel or docetaxel and so on. The studies on upon trastuzumab showed that it improved overall survival in metastatic stage breast cancer from 20.3 to 25.1 months. In early stage breast cancer, it reduces the risk of cancer returning after surgery by an absolute risk of 9.5% [18, 19].We consider in figure 2 that Monoclonal antibody trastuzumab is an IgG1 subtype inducing antibody dependent cell mediated cytotoxicity (ADCC), which is triggered through the detection of fc portion of antibody by the Fcγ 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 [18, 20, 21]. Trastuzumab has also been shown to inhibit tumor angiogenesis, leading in decreased microvessel density in vivo and reduced endothelial cell migration in vitro [8]. Studies have demonstrated that trastuzumab inhibits HER2 extra cellular domain (ECD) cleavage through the proposed mechanism of sterric hindrance in preclinical studies; synergy with Herceptin enhanced the effects of chemotherapy [22]. Molina et al showed that trastuzumab could inhibit the shedding of the extracellular domain of HER2 by blocking these receptors, which result in activation of downstream signaling pathways, particularly the PI3K/Akt pathway. Phosphatidylinositol 3-kinase (PI3K) signaling pathway triggers with PI3K activation and PI3K phosphorylates and converts the secondary messenger phosphatidylino-sitol (4,5) bisphosphate (PIP2) into phosphatidylinositol (3,4,5) triphosphate (PIP3), which recruits and activates phosphatidylinositol-dependent kinase 1 (PDK). PDK phosphorylates AKT, which inhibits the activities of the transcription factors (which are mediators of apoptosis and cell cycle arrest), resulting in cell survival. The PTEN which is tumor-suppressor phosphatase negatively

regulates PI3K signalling by dephosphorylating PIP3, converting it back to PIP2. RAF-MEK-MAPK and PAK-JNKK-JNK are two cascades of serine/threonine kinases, which regulate the activity of a number of transcription factors downstream. The GTPases RAS and RAC Activation of components of this pathway result in elevated levels of the p27Kip1 protein as cell cycle arrest. Interactions of other signaling proteins with phosphotyrosine sites on the EGFR dimer begin the 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 [14-17].

3. Mechanism action of trastuzumab

Trastuzumab is a recombinant humanized monoclonal an-tibody 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 as a single agent, and in combination with chemotherapies such as vinorelbine, paclitaxel or docetaxel and so on. The studies on upon trastuzumab showed that it improved overall survival in metastatic stage breast cancer from 20.3 to 25.1 months. In early stage breast cancer, it reduces the risk of cancer returning after surgery by an absolute risk of 9.5% [18, 19].We consider in figure 2 that Monoclonal antibody trastuzumab is an IgG1 subtype inducing antibody dependent cell mediated cytotoxicity (ADCC), which is triggered through the detection of fc portion of antibody by the Fcγ 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 [18, 20, 21]. Trastuzumab has also been shown to inhibit tumor angiogenesis, leading in decreased microvessel density in vivo and reduced endothelial cell migration in vitro [8]. Studies have demonstrated that trastuzumab inhibits HER2 extra cellular domain (ECD) cleavage through the proposed mechanism of sterric hindrance in preclinical studies; synergy with Herceptin enhanced the effects of chemotherapy [22]. Molina et al showed that trastuzumab could inhibit the shedding of the extracellular domain of HER2 by blocking 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 (It is explained in Figure1). 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, 27]. The HER2 downstream pathway PI3K/Akt, is activated by phosphorylation of the intracellular HER2 tyrosine kinase domain.This pathway regulates proliferation, migration, apoptosis and angiogenesis and pro-motes carcinogenesis when unopposed. The PTEN is a

tumor suppressor that inhibits AKT and induce growth arrest in the 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 an important role of decreased expression of the PTEN phosphatase func-tion in tumor cells [13, 27, 28, 29]. Data also demonstrate that specific polymorphisms in the IgG fragment C receptor or phenotype expression of valine (V) or phenylal nine (F) at amino acid 158 on the FcγRIIIa significantly influences the affinity of IgG1 to the Fcγ receptor in natural killer cells. These results demonstrate that this receptor is involved in trastuzumabmediated cytotoxicity. The FcγRIII 158V/F polymorphism interferes with the ability to generate ADCC responses in vitro during target therapy with trastuzumab and significantly impair clinical response. Further studies are required to show whether this polymorphism should be deter-mined to identify responders [27].

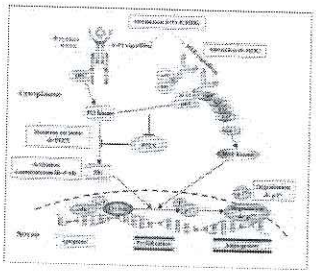

Figure1. Proposed mechanisms of trastuzumab resistance [31]

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. 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 finish consumtion 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 Herceptin are fever, nausea, vomiting, swelling of the nose and throat, infusion reactions, diarrhea, infections, increased cough, headache, weight loss, fatigue, lower breath, rash, alter in taste, decreased white and red blood cells, and muscle pain. Approximately 10% of individuals cannot to consume this monoclonal antibody because of preexisting heart failure. The danger and seriousness of cardiomyopathy is raised when trastuzumab and anthracycline use together [32, 33, 34].

6. Conclusion

trastuzumab as a monoclonal antibody is important in treatment breast cancer and the other cancers both in advanced and primary disease. Over expression and amplification protooncogene HER/neu are crucial in a target therapy with trastuzumab. The great efforts have been accompolished to clarifying the mechanisms of action, resistance, safety, side effects, and combination therapies of trastuzumab but yet researches for explaining mechanisms of resistance to trastuzumab are still not adequate.

References

[1] K cole, H Junhe, Lwang, Breast cancer biomarker measurements and standards,Proteomics Clin, 2013,7,17-29.

[2] MT Weigal, M Dowsett, Current and emerging bi-omarker in breast cancer: prognosis and prediction, En-docrine-Related Cancer, 2010, 17, R245-R246.

[3] A NarayanBhatt, R Mathur, A Farooque, AVerma, B.S.Dwarakanath, Cancer biomarker Current perspective MedRes, 2010, 132,129-149.

[4] C R James, J E Quinn, Paul B.Mullan, PG Johnston,D PHarkin,BRCA1 ,a Potential Predictive bi-omarker in the treatment of breast cancer, The Oncolo-gist, 2007,12,142-150.

[5] S Banerjee, IE Smith .Management of small HER2 –positive breast cancers.The Lancetonoclogy , 2010,12,69-77.

[6] R Singhai, A Patil, V Patil, Cancer biomarker HER2/neu in breast cancer in Indian women Breast Cancer: Targets and Therapy2011, 3, 21-26.

[7] W Dean-Colomb , FJ.Esteva, HER2-positive breast can-cer : Herceptin and beyond, European Jornal Of Cancer, 2008, 44,2806-2812.

[8] PR Srinivas, BS Kramer, S Srivastava .Trends in bi-omarker research for cancer detection ,Lancet On-col.2001,2,698-704.

[9] M Dokmanovic,WJ Wu, Trastuzumab–resistance and breast cancer, Breast cancer – Carcinogenesis, cell growth and signalling pathways.

[10] AL A Wong, S ChinLee, Mechanism of resistance to trastuzumab and novel therapeutic Strategies in HER2-positive breast cancer, International Jornal of Breast-Cancer, 2012, 13,10-1155.

[11] 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.

[12] DR Spigal, H Burstein, HER2-overexpressing meta-static breast cancer, CurrentTreatment Options in On-cology 2002,3,163-174.

[13] R Bartsh, C Wenzel, G Steger, Trastuzumab in the man-agement of early and advanced Stage breast cancer, Bio-logics :Target and Terapy,2007,1,19-31.

[14] 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.

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

[16] Z feng, H Zhang, Aj Levine,S Jin. The coordinate regula-tion of the p53 and mTOR pathway in cells. Proc Natl Acad Sci USA, 2005, 102, 8204-9.

[17] AR Tee, CG Proud .Staurosporine inhibits phosphory-lation of translational regulators linked to mTOR .Cell Death Differ .2001,8, 841-9.

[18] J Baselga, J Albanell, MA Molina, JArribas,:Mechanismof actionof trastuzumab and Scientific update.Semin On-col2001,28,4-11.

[19] AM Petit, J Rak, MC hung ,et al.Neutralising antibodies aginst 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 implicationsFor signal transductions therapy of solid tumors. Am J pathol,1997,151,1523-30. Journal of Biology and today's world 513.

[20] 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.

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

[22] C Natoli, P Vici, ISperduti, AGrassadonia, GBisagni, N Tinari, A Michelotti, GZampa, SGori, LMoscetti, M DeTur-Tur [illegible] of neoadjuvant trastuzumaband chemotherapy in HER2- overexpressing breast cancer ,Cancer Res Cli On-col ,2013,139,1229-1240.

[23] American cancer society A. Breast Cancer Facts & Fig-ures 2009-2010.

[24] 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,in hibitor off-rate,and receptor activity in tumor cells. Cancer Res 2004, 64:6652-6659.

[25] R Nahta, LX Yung, B Zhang, R Kobayashi ,FJ Esteva: Insu-lin-like growth factor1 – Receptor/human epidermal growth factor receptor 2 hetrodimerization contributes toTrastuzumab resistence of breast cancer cells. Cancer Res, 2005, 65, 11118-11128.

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

[27] R.Pohlmann,IA.Mayer,RMernaugh,Resis tence to trastuzumab in breast cancer Clinic can-cer,2009,15,7479-7491

[28] R Nahta,FEsteva,Breast,Molecular mechanism of trastuzumab resistence, CancerResearch,2006,8-215.

[30] FM Yakes, WChinrataanalab,CA Ritter,W King,S Seel-ig,CL Arteage:Herceptin-Induced inhibition of phospha-tidylinositol-3 kinase and Act is required for antibody –mediated effects on p27,cyclin D1,and antitumor ac-tion.Cancer res,2002,62,4132-4141

[31]VDieras,AVincent-salmon,ADegeorges, Pbeuzeboc, Trastuzumab(Herceptin) et cancer du sein: mechanism de resisteance, Bull-Cancer,2007,94,259-66.

[32] DL Keefe ,Trastuzumab-associated cardiotoxici-ty ,Cancer 2002,95-1592.

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

[34] EA Perez ,EH Romond ,VJ SUman, et al. sequential ver-sus concurrent trastuzumab in adjuvant chemotherapy for breast cancer ,J Clin Oncol,2011,29-3366.