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The role of tyrosine-kinase inhibitor in breast cancer

Summary

The article presents a brief description about the role of tyrosine-kinase inhibitor in breast cancer, tumor genesis and progression. The efficacy and safety of lapatinib, trastuzumab, capecitabine in breast cancer petients were evaluated.

Key words: tyrosine-kinase inhibitor, breast cancer, tyrosine-kinase, lapatinib, trastuzumab, capecitabine, tumor.

Breast cancer is the most common cancer type and the second largest cause of death among women. Despite the number of diseased, owing to the screening programs and expansion the treatment methods nowadays increase and the death rate sharply decreases among patients with breast cancer. Approximately in 20 % of the cases, breast cancer is observed with HER2 overexpression. Overexpression is detected either as gene amplification (by fluorescence in situ hybridization) or as protein expression (by immunohistochemistry). The existence of it results in the aggressive phenotype that is associated with high recurrence risk and decrease in overall survival.

The ErbB receptor family counts four members, ErbB1 (HER1/EGFR), ErbB2 (HER2/Neu), ErbB3 (HER3) and ErbB4 (HER4), that are ubiquitously expressed in epithelial, mesenchymal, and neuronal cells.

Tyrosine-kinase receptors are the transmembrane protein consisting of cytoplasmatic catalytical C-termial domain, transmembrane domain, and N-terminal extra cellular domain.

ErbB1, ErbB3, and ErbB4 receptors have eleven ligands, although ErbB2 receptor does not possess any ligand. ErbB2 receptor can engage in dimerisation process with other receptors without any ligands.The dimerisation process occurs after ligand binds with receptor, and as a result of it homo- and hetero-dimer forms are created. After dimerization, the tyrosine residues are phosphorylated, resulting in protein kinase activation and downstream signaling.

The role of tyrosine-kinase receptors in tumor genesis and progression created a base for its research as potential therapeutic target and therefore, it was the beginning for the creation of new target drugs which are used in treatement of breast cancer with modern techniques. The use of these target drugs changed the natural progress of HER2 positive disease, it increased overall survival both at adjuvant setting and metastatic disease. A bit later the role of tyrosine-kinase inhibitors were investigated in the case of resistance to trastuzumab

Lapatinib is an oral tyrosine-kinase inhibitor that is used in the treatment of breast cancer. Lapatinib in combination with letrozole for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor and for whom hormonal therapy is indicated and approved by FDA in 2010. The approval was based on a clinically meaningful increase in progression-free survival (PFS) observed in a single trial, known as EGF30008. The lapatinib plus letrozole combination had a median PFS of 35.4 weeks, compared to 13.0 weeks for the placebo plus letrozole arm (HR = 0.71, p = 0.019). The overall survival data are not mature at this time.

The U. S. Food and Drug Administration approved lapatinib for use in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who had received prior therapy including anthracycline, taxane, and trastuzumab .

The efficacy and safety of lapatinib in combination with capecitabine in breast cancer were evaluated in a randomized trial. Patients were randomly assigned to receive either lapatinib, or to receive capecitabine alone every 21 days. The primary endpoint was time-to-progression (TTP). The median TTP was 27.1 vs. 18.6 weeks (HR 0.57, p=0.00013) for the lapatinib / capecitabine combination and capecitabine-alone arms, respectively.

As a result of this research, lapatinib/capecitabime combination began to be used as the next line treatment of metastatic HER2 positive breast cancer progressed after first line treatment.

LANDSCAPE is the single-arm phase 2, open-label, multicentre study, eligible patients had HER2-positive metastatic breast cancer with brain metastases not previously treated with WBRT, capecitabine, or lapatinib. The trial builds on previous data from small studies indicating that the combination of capecitabine and lapatinib might be active in patients with brain metastases of HER2-positive breast, particularly in those not previously treated with radiotherapy to the brain.

Theoretically, lapatinib a small-molecule tyrosine kinase inhibitor, should penetrate the CNS, and demonstrated some promise in this trial. Treatment with capecitabine/lapatinib yielded a 67 % response rate and a median time to progression of 5.5 months, which are significantly better outcomes than seen in other studies of this combination.

One of the researches was done regarding lapatinib use is NEALTTO. The results of this research were presented in 2013 at San-Antonio Breast Cancer Symposium. In NeoALTTO trials we compared trastuzumab single agent, lapatinib single agent, and the vertical dual HER2 blockade by combination of trastuzumab plus lapatinib in neoadjuvant settings. In these studies the substitution of lapatinib

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for trastuzumab in combination with chemotherapy resulted in similarly high pCR rates (52.5 % with trastuzumab versus 53.2 % with lapatinib, p = 0.985) (Robidoux et al., 2013; Baselga et al., 2012). Furthermore, in the long follow-up of the NeoALTTO trial, neither EFS nor OS did differ between the lapatinib and trastuzumab groups (EFS: HR 1.06, p = 0.81; OS: HR 0.86, p = 0.65) However, the combination of trastuzumab and lapatinib plus chemotherapy led to a higher pCR rate compared to antiHER2 single agent treatment in theNeoALTTO trial (51.3 % with combination versus 29.5 % with single agent; p = 0.0001)

Another important research done regarding the lapatinib is ALLTO trial. The first results of it were announced in 2014 at ASCO's (American Society of Clinical Oncology). The ALTTO trial is an international, intergroup, open-label, phase III randomized trial in patients with HER2-positive early breast cancer. The trial compared four treatment groups, each of 1-year duration: intravenous T; oral L; a sequence of the two agents (T→L); and the combination of the two anti-HER2 agents (L+T)

In summary, adjuvant treatment with the combination of L+T resulted in a non-significant improvement in DFS, which was not clinically significant. One year of adjuvant T remains standard of care.

Along with lapatinib, currently the usage of new tyrosine-kinase inhibitors (afatinib, sapitinib canertinib, neratinib et al.) that included to various Phase II trials brings in positive results. While go in through the research done, we can infer that tyrosine-kinase inhibitors creates new waves of hope in treatment of HER2 positive breast cancer.

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Резюме

Роль ингибитора тирозинкиназы при раке молочной железы

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В статье представлено краткое описание роли ингибитора тирозинкиназы при раке молочной железы в генезе и прогрессировании опухоли. Оценивали эффективность и безопасность применения лапатиниба, трастузумаба, капецитабина у пациентов, больных раком молочной железы.

Ключевые слова: ингибитор, рак молочной железы, тирозинкиназа, лапатиниб, трастузумаб, капецитабин, опухоль

Резюме

Роль інгібітора тирозинкінази при раку молочної залози

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У статті подано короткий опис ролі інгібітора тирозинкінази при раку молочної залози в генезі та прогресуванні пухлини. Оцінювали ефективність і безпечність застосування лапатінібу, трастузумабу, капецитабіну у пацієнтів, хворих на рак молочної залози.

Ключові слова: інгібітор, рак молочної залози, тирозинкіназа, лапатініб, трастузумаб, капецитабін, пухлина

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