New gene targets in breast cancer

Gene therapy has enabled outstanding advances in breast cancer treatment. One of the genes that play a significant role in the development of breast cancer is the human epidermal growth factor (HER) gene which is responsible for the synthesis of HER 2 receptors that are typical receptors present in breast cells (1). In normal conditions, these genes are responsible to maintain appropriate growth, division and repair of the breast cells (2). However, in 25% of breast cancer cases, these genes overexpress the HER2 receptors, causing uncontrolled division of the breast cells (1). Despite the improved survival achieved with the use of trastuzumab and chemotherapy in HER2 + breast cancer, up to 26 % of the patients may still progress or relapse (3), thus more effective other anti-HER 2 receptors are needed. Neratinib, a small oral tyrosine-kinase inhibitor, works by inhibition of the kinase in HER2 receptors, has been shown to be effective in the settings of patients who have successfully treated with trastuzumab but at high risk for disease recurrence and relapse (4).

A randomized double blind, multicentre, placebo controlled phase three clinical trial (named EXteNET), conducted in 2009 till 2012 with the primary efficacy analysis was done in 2014, the sensitivity analysis of the primary efficacy endpoint at 5 years and the analysis of the overall survival (to be done after a total of 248 events), aimed to investigate the effect of neratinib as extended adjuvant therapy post trastuzumab based regimen in patients with breast cancer. Patients were considered eligible if: Age> 18 with stage 1-3 operable breast cancer, completed their trastuzumab based therapy within 12 months of study enrollment, no signs of disease recurrence or metastasis at the study entry, high-risk of disease recurrence, left-ventricular ejection fraction >50%, normal organ function and were able to comply with oral medication. Patients with significant cardiac, gastrointestinal and psychiatric illness were excluded from the study. After receiving the institutional review board approval (IRB), eligible patients (a total of 2840 patients) were randomly divided in a 1:1 ratio to receive either 240 mg oral neratinib or matched placebo for one year. Disease recurrence, new breast cancer or intolerable adverse events were considered factors to withdraw the patient from the study. Neratinib dose was allowed to be adjusted or interrupted if significant side effect (particularly diarrhea or interstitial lung disease) develop. The primary endpoint was invasive disease-free survival (iDFS) with secondary endpoints including DFS for ductal carcinoma in situ, distant disease free survival, time to distant recurrence, cumulative incidence of CNS recurrences and safety.

The five year analysis of this study showed superior efficacy of neratinib, compared to placebo with a significantly fewer invasive disease-free survival events (116 vs 163 events; HR 0·73, p=0·0083). For the secondary endpoints; ductal carcinoma in situ (DCIS)-DFS was superior for the neratinib arm (HR of 0.63, p = 0.0017). No statistically significant different was seen in relation to the distant disease free survival, time to distant events (including brain metastasis, P value 0.333). It was also noted from this study that patients with mixed state of hormone-

receptor-positive and HER2 + were more likely to benefit from neratinib compared with those who are only HER2+ (p value 0.0013). The most reported side effect was diarrhea, forty percent of neratinib received patients develop grade 3 diarrhea. Treatment interruption, dose reduction or initiation of the anti-diarrheal agent (loperamide) was required in 31% of these patients compared to 2% of those received placebo (5).

In conclusion, a one year extended adjuvant therapy with neratinib post trastuzumab therapy, significantly improved the invasive disease free survival with no long term toxicity. Further future studies are still needed for fully understand its role in the management of this invasive disease.

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