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REVIEW ARTICLE

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Neratinib in extended adjuvant therapy for HER2-positive early breast cancer

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ABSTRACT

HER2 overexpression is found in approximately 20% of patients with breast cancer and is associated with an unfavorable prognosis. The use of chemotherapy and targeted therapies blocking HER2 function in patients with early HER2 positive breast cancer has led to significant clinical benefits. Despite this, approximately 25% of patients initially treated with trastuzumab experience recurrence of invasive disease within 5 years of completion of adjuvant treatment. Neratinib is an oral, irreversible, small molecule tyrosine kinase inhibitor blocking the intracellular domain of the HER1, HER2 and HER4 receptor, whose activity in extended anti-HER2 adjuvant treatment in HER2-positive early breast cancer patients has been confirmed in ExteNET trial. It has been shown that the use of extended therapy with neratinib after adjuvant trastuzumab treatment in patients with early HER2-positive breast cancer led to a 33% reduction in the risk of invasive disease recurring, with a greater effect observed in ER/PgR positive patients and those with involvement 4 and more lymph nodes.

Key words: neratinib, extended adjuvant treatment, HER2-positive early breast cancer

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Introduction

Positive HER2 status (overexpression of HER2 receptor or *HER2* gene amplification) is found in approximately 20% of patients with breast cancer and is associated with an unfavorable prognosis [1]. The introduction of anti-HER2 therapy, which initially consisted solely in the use of trastuzumab and supplemented standard chemotherapy or hormone therapy, led to a significant improvement in clinical outcomes. During 12-years follow up of patients with HER2-positive early breast cancer, the use of standard adjuvant chemotherapy and anti-HER2 treatment for one year leads to absolute benefits in terms of disease-free survival (DFS) and overall survival (OS) of 12% and 9%, respectively [2].

Approximately 25% of patients initially treated with trastuzumab experience a recurrence of cancer within 5 years of completing adjuvant treatment, which justifies research on new therapeutic concepts to reduce the proportion of recurrent patients. One of them was based on the extended use of trastuzumab as adjuvant therapy. The results obtained during the 11-year follow-up in the HERA study indicate that the 12-month use of trastuzumab in patients with HER2-positive breast cancer leads to a significant reduction in the risk of disease recurrence or death compared to patients under exclusive observation (hazard ratio [HR] 0.76 and 0.74, respectively). Extending the adjuvant use of trastuzumab for up to 24 months did not lead to a significant improvement in progression-free survival (PFS) compared to that observed in the group of patients receiving 12-month treatment [3]. The estimated percentage of patients included in the study who survived 10 years without disease progression was 63% in the group undergoing follow-up after chemotherapy and 69% in patients receiving trastuzumab for 12 or 24 months. Lack of effect of extended treatment on disease-free survival was independent of estrogen receptors (ER) and progesterone receptors (PgR) state, although numerically it was slightly higher in the group of patients with ER/PgR expression. The was also no demonstrated impact of trastuzumab combined with lapatinib (ALTTO study) [4] or bevacizumab (BETH study) [5] on disease-free survival. Combination of trastuzumab and pertuzumab also did not signifi-

cantly improve the percentage of patients experiencing relapse after completion of adjuvant therapy — in the APHINITY study, combined use of pertuzumab and trastuzumab in adjuvant treatment led to a reduction in the risk of relapse by 19% (HR 0.81, P = 0.045], with 3-year relapse-free survival in 94.1% of patients receiving pertuzumab in combination with trastuzumab and 93.2% of patients receiving trastuzumab in combination with placebo. Subgroup analysis showed a slightly greater benefit of combination therapy in patients with axillary lymph nodes metastases (HR 0.77) [6].

The use of trastuzumab in combination with chemotherapy and hormone therapy remains a standard for the management of patients with HER2-positive early breast cancer.

The role of neratinib in extended adjuvant therapy of early HER2-positive breast cancer

Neratinib is an oral, irreversible, small molecule tyrosine kinase inhibitor blocking the intracellular domain of HER1, HER2 and HER4 receptor, with activity confirmed in patients with metastatic HER2-positive breast cancer and benefits similar regardless of prior treatment with trastuzumab [7, 8].

The mechanism of action of the drug is based on various phenomena listed below. Inhibition of autophosphorylation of the intracellular domain of the epidermal growth factor receptor (EGFR) leads to inhibition of stimulation of signalling pathways mediated by ERK family proteins or Akt protein [9]. Inhibition of pRb protein phosphorylation prevents the release of an E2F transcription factor from complexes containing pRb protein (E2F-pRb). Interactions of E2F protein with promoter regulatory sequences are crucial for the activation of transcription of genes encoding protein products determining the progression of the cell division cycle from the G1 to the S phase. The increase in p27 inhibitor protein expression leads to a decrease in cyclin D1 expression and formation of cyclin D1-cdk 4/6 complexes essential for phosphorylation of pRb protein, resulting in inhibition of cell proliferation at the G1–S interface [10]. As a result of neratinib action, the expression of HER2 receptor protein is also reduced by its ubiquitination and subsequent degradation in proteasomes in the cell cytoplasmic space [11].

Locating the drug binding site within the HER2 intracellular domain is particularly important in patients with trastuzumab resistance or primary absence of extracellular receptor domain.

The efficacy of neratinib in HER2-positive breast cancer has been well documented in patients with locally advanced or metastatic disease. As demonstrated in phase I and II studies, the use of neratinib in patients previously treated with anthracyclines, taxoids and trastuzumab resulted in objective responses rate of 32% and the clinical benefit of treatment in 44% of patients [8, 12]. For patients receiving adjuvant treatment, the data were obtained from a randomized, multicenter, phase III trial assessing the efficacy of extended adjuvant treatment with neratinib after discontinuation of anti-HER2 therapy in patients with HER2-positive breast cancer. The primary design of the ExteNET study was addressed to patients with stage II–III HER2-positive breast cancer after perioperative treatment completed within 2 years before randomization. The results of other analyzes published during recruitment [13–16] — indicating a high cancer recurrences rate observed at the end of adjuvant treatment with trastuzumab or shortly after its completion — formed the reason for limiting the ExteNET study to patients with primary involvement of regional lymph nodes and patients who discontinued adjuvant trastuzumab within 12 months before randomization. However, the above-cited papers containing also the results of analyzes carried out in patients without lymph nodes involvement showed a lower than initially assumed the risk of recurrence after the completion of adjuvant treatment.

As the inclusion and exclusion criteria changed, the definition of intended endpoints also evolved. Ultimately, the primary endpoint was invasive disease-free survival in the whole study population. Statistical analyzes to assess the significance of the effect of 12-months neratinib therapy on the primary endpoint were performed 2 years after stopping study medication instead of 5 years, as originally planned. The secondary endpoints of the ExteNET study included: recurrence of ductal carcinoma *in situ*-free survival, time to distant recurrence, distant metastases-free survival (including central nervous system metastases), overall survival (OS) and safety. The study included 2,840 HER2-positive breast cancer patients, with a comparable median time from discontinuation of trastuzumab to neratinib or placebo initiation of 4.4 months and 4.6 months, respectively. The percentage of pre- and postmenopausal patients was also comparable in both arms. Treatment with neratinib at a dose of 240 mg daily or placebo was continued for 12 months or until disease recurrence, unacceptable toxicity or consent withdrawal. Based on the analyzes a 33% reduction in the recurrence risk was demonstrated in the group of patients receiving extended treatment with neratinib compared to placebo (HR 0.67; P = 0091). The 2-year recurrence-free survival rate was 93.9% in the neratinib arm and 91.6% in the placebo group. There were no significant differences between the two groups in terms of dissemination-free survival and time from treatment cassation to distant metastases. The 2-year dissemination-free survival rate was 95.1% in the

patients receiving neratinib and was slightly higher than that observed in the group receiving placebo (93.7%). As demonstrated in the subgroup analysis, this effect was associated with hormone receptor expression (HR 0.51; P = 0.0013). Adjuvant treatment with neratinib was also relatively well tolerated. The most common toxicity was diarrhea, which in grade 2 or 3 was found in 33% and 40% of patients, respectively (the rates were significantly higher than observed in the placebo arm — 7% and 2%, respectively). The above data refer to patients with no antidiarrheal prophylaxis during treatment. The incidence of decreased left ventricular ejection fraction (LVEF), interstitial pneumonitis and pulmonary fibrosis was comparable in both groups. In patients receiving neratinib, hepatic dysfunction was observed twice as often (14% *vs*. 7%) and consisted of increased serum level of alanine aminotransferase (9% *vs*. 3%, respectively), asparagine aminotransferase (7% *vs.* 3%, respectively) and phosphatase alkaline (2% *vs*. 1% respectively) [17]. The analysis of the toxicity profile depending on the stratification factors was consistent with the general profile. In the group of patients with HER2-positive breast cancer with hormone receptors expression, the most common grade 3 or higher complication was diarrhea (39% *vs*. 1% in the placebo arm), nausea (1% *vs*. < 1%) and weakness (2% *vs*. < 1%). The occurrence of the above symptoms constituted the basis for the reduction of the dose of neratinib in 31% of patients, withholding treatment in 42% of patients or hospitalization in 6% of patients receiving neratinib) [18].

The results of preliminary analyzes presented above were supplemented with data from 5-year observations. As presented by Martin et al. [19], the use of extended adjuvant therapy with neratinib led to a 27% reduction in the risk of relapse in whole study population (P = 0.0083); 5-year invasive disease recurrence-free survival rate was 90.2% in the neratinib arm and 87.7% in the placebo group. Other benefits of neratinib were the reduction in the proportion of patients with distant relapses (6.4% *vs*. 7.8%, respectively) and local or loco-regional relapses (0.8% *vs*. 2.5%, respectively). However, there were no significant differences between the two groups of patients in terms of metastatic disease-free survival and time to disease generalization. Lesions in the central nervous system as the first relapse site were found in 1% of patients receiving neratinib and 2% of patients receiving placebo. The study also showed a beneficial effect of extended adjuvant therapy with neratinib in patients with hormone receptor expression compared to placebo. The absolute benefit in terms of invasive disease-free survival during 2-year and 5-year follow-up was 4.5% and 5.1%, respectively. A similar relationship was observed for distant metastases-free survival (the absolute benefit in the neratinib arm compared to patients receiving placebo was 3.2% and 4.7%, respectively) [18]. A similar effect, resulting from the use of neratinib, was not observed in patients without hormone receptor expression.

The aforementioned change in study inclusion/exclusion criteria allowed a comparison of treatment effects according to the time between discontinuation of maintenance treatment with trastuzumab and initiation of treatment with neratinib. Initiation of treatment with neratinib less than 1 year after stopping anti-HER2 therapy is associated with a significant impact on invasive disease-free survival compared to deferred treatment for more than 1 year (HR 0.70 *vs*. 1.0, respectively). Analysis of safety profile during 5-year follow-up did not show significant differences compared to already known from previous analyzes.

In summary, the results of 5-year observations in the ExteNET study allowed to formulate the following conclusions:

1. the use of extended therapy with neratinib after adjuvant trastuzumab in patients with early HER2-positive breast cancer leads to a 27% reduction in the risk of invasive disease recurrence (P = 0.0083);
2. the therapeutic benefit of neratinib results from a reduction in the frequency of local, loco-regional and distant relapses;
3. the effect on overall survival in patients receiving extended therapy with neratinib remains undetermined and final results are expected;
4. the effect of extended use of neratinib is mainly observed in patients with hormone receptor expression and metastases in 4 or more lymph nodes (in patients without receptor expression the effect of using neratinib is marginal);
5. the main symptom of treatment-related toxicity is diarrhea, which, when implementing appropriate preventive measures, does not force premature termination of extended adjuvant therapy.

The occurrence of the therapeutic effect of neratinib mainly in patients with hormone receptor expression results from the overlapping of ER-initiated and EGFR signalling pathways. It has been shown that inhibition of HER2 receptor function as a result of anti-HER2 treatment (trastuzumab, pertuzumab and others) leads to activation of ER-initiated signalling pathway, which results in the development of resistance to the drugs blocking HER2 function [17, 20]. The use of hormone therapy aimed at blocking ER and indirectly PgR function in cancer cells will also lead to an increase in HER2 receptor expression and activation of signalling pathways dependent on its stimulation [20].

The results of the ExteNET study were reflected in the recommendations of leading cancer societies. According to published in 2019 the European Society of Medical Oncology recommendations on the treatment

of patients with breast cancer, the extended use of neratinib can be considered in patients with HER2-positive early breast cancer at high risk of recurrence and with ER expression, in whom in adjuvant treatment HER2 double blockade was not used. The position results from not obtaining evidence in randomized clinical trials on the effectiveness of extended adjuvant therapy with neratinib in patients receiving in adjuvant treatment HER2 blockade other than trastuzumab. The authors of the recommendations also emphasize that the observed beneficial treatment effect on recurrence-free survival often occurs at the expense of severe diarrhea [21]. The British National Institute for Health and Care Excellence (NICE) recommendations are similar [22] and recommend considering the extended adjuvant treatment with neratinib in patients with HER2-positive breast cancer with hormone receptor expression who have completed adjuvant treatment with trastuzumab or in whom despite preoperative treatment invasive residual disease is still found in the primary location or regional lymph nodes. However, it is currently difficult to determine clearly the group of patients for whom extended adjuvant treatment with neratinib will be the best therapeutic option. This is due to several reasons. Firstly, a significant portion of HER2-positive breast cancer patients receives trastuzumab and pertuzumab in perioperative treatment. In the absence of results from randomized clinical trials, it is impossible to unequivocally determine the influence of HER2 double blockade on the effect of neratinib. Extended use of neratinib seems to be an option for patients without lymph nodes involvement, who are not the candidates for a combination of trastuzumab and pertuzumab. Further doubts about the extended use of neratinib concern patients with complete pathomorphological remission (pCR) after neoadjuvant treatment (absence of invasive cancer cells in the material from the primary tumor and axillary lymph nodes as well as signs of the infiltration of blood and lymphatic vessels by cancer cells). This definition allows for the presence of residual components of non-invasive cancer in post-operative tissue (based on the Union Internationale Contre le Cancer [UICC] and the American Joint Committee on Cancer [AJCC] recommendations). According to the inclusion criteria, the ExteNET study did not involve patients with pCR after preoperative treatment, hence the role of neratinib in this population is unknown. The efficacy of neratinib in the group of HER2-positive and hormone receptor-positive breast cancer patients who did not achieve pCR after preoperative treatment were presented only as a conference poster. The use of neratinib in this group of patients was associated with an increase in the disease-free survival rate of 5% and 7%, respectively during 2- and 5-year observations [18].

The National Comprehensive Cancer Network (NCCN) recommendations are less radical, allowing the use of extended adjuvant treatment with neratinib not only in patients with HER2-positive hormone receptor-positive breast cancer who have completed adjuvant trastuzumab treatment but also in patients in whom perioperative HER2 double blockade based on trastuzumab and pertuzumab was used. The authors of this recommendation emphasize, however, the lack of evidence for this approach from multicenter randomized clinical trials.

In summary, it is currently believed that the group of patients likely to benefit most from extended adjuvant treatment with neratinib are those with early HER2-positive breast cancer with hormone receptor expression whose adjuvant trastuzumab treatment has been discontinued no later than 12 months before neratinib. The value of the use of the presented therapeutic approach in patients receiving HER2 double blockade in perioperative treatment and achieving pCR as a result of preoperative treatment is still unknown.

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