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The Effect of Adding Pertuzumab to Adjuvant Trastuzumab in Early HER2-Positive Breast Cancer

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Abstract

Objectives: In this trial, it has been investigated whether pertuzumab, when added to adjuvant trastuzumab and chemotherapy, improves outcomes among patients with HER2-positive early breast cancer in compares to patients who received only Herceptin.

Methods: After surgery and central HER2-positive confirmation, about randomly 220 patients assigned with high-risk HER2-positive, operable breast cancer to received Anthracycline based chemotherapy 3 cycles fallowed by Taxotere 3 + either pertuzumab+hercetin 3 or standard adjuvant Herceptin alone, 17 cycles in 1 year. The patients were followed up for 3 years.

Results: Results were indicated that about 50% of the patients who were randomly assigned to arm A received pertuzumab + Herceptin 3 cycles every 3 weeks (110 patients) and arm B 50% (110 patients) received Herceptin alone 17 cycles every 3 weeks. Disease recurrence occurred in 12 patients (10.9 %) in the pertuzumab group and 8 patients (7.2%) in the arm B group (hazard ratio, 0.81; 95% confidence interval [CI], 0.66 to 1.00; $P = 0.045$). The estimates of the 3-year rates of invasive-disease-free survival were 89% in the pertuzumab + herceptin group and 93% in the herceptin group. Heart failure, cardiac death, and cardiac dysfunction were infrequent in both treatment groups. Diarrhea of grade 3 or higher occurred almost exclusively during chemotherapy and it was more frequent with pertuzumab than with group B (7.9% vs. 2.8%).

Conclusions: The study showed that pertuzumab + Trastuzumab adjuvant in 3 cycles worse rates of invasive-disease-free survival among patients with HER2-positive, operable breast cancer in compares with classical trastuzumab alone in 17 cycles. Diarrhea was more common with pertuzumab than with classical Trastuzumab therapy.

Keywords: Breast neoplasms, HER2-positive, drug therapy

Introduction

Patients with HER2-positive Breast cancer who relapse despite receiving recommended adjuvant therapy still have unmet medical needs. The 10-years update of the four pivotal trials shows that, after receiving optimum chemotherapy and trastuzumab for a year, at least one patient out of every four eventually develops breast cancer again. In order to increase the long-term cure rates in high-risk patients, it is becoming more and more important to risk stratify HER2+ Breast cancer and optimize HER2-directed therapy, maybe taking treatment-escalation into consideration.[1] Pertuzumab's extensive clinical routine use in the adjuvant context is still up for conflict. One of the causes is the limited ability of pertuzumab to convert its benefits at the individual level, as was seen in the previous study.[2]

The positive results of the KATHERINE research in 2019, which amply indicated that trastuzumab cannot any longer be regarded as the sole ideal adjuvant treatment in all patients with HER2+ Breast cancer, have recently drawn attention to the possibility of a targeted escalation of the anti-HER2 treatment.[3] Additionally, the encouraging findings of the EXTEnet research, which involved women who had finished receiving standard trastuzumab-based adjuvant therapy, provide additional evidence that certain cases of HER2+ Breast cancer may improve.[4]

Combining trastuzumab, an anti–human epidermal growth factor receptor 2 (HER2) monoclonal antibody, with neo-adjuvant chemotherapy was clinically improved outcomes among cases with HER2-positive early stage of breast cancer, which might reducing the risk of disease recurrence and death.[5,6] Both chemotherapy in one year of treatment with trastuzumab adjuvant has been reported to be current standard of care for this patient population.[7]

Pertuzumab is a humanized monoclonal antibody that has mechanisms of action complementary to those of trastuzumab, binding to different domains.[8,9] Trastuzumab binds near to the trans-membrane domain, inhibiting HER2 dimerization, whereas pertuzumab binds to the dimerization domain, inhibiting HER2 heterodimerization with other types of HER family receptors. Both antibodies induce antibody-dependent cell-mediated cytotoxicity.

In case of patients with HER2-positive metastatic breast cancer, pertuzumab added to trastuzumab and docetaxel was shown to significantly prolong both progression-free survival and overall survival. Higher frequencies of grade 3 or 4 febrile neutropenia, any neutropenia, and diarrhea were associated with the addition of pertuzumab, but the rate of cardiac adverse events has been indicated to be similar to that in the control group.[9] Dual HER2 blockade with pertuzumab and trastuzumab is the standard of care as first-line therapy for patients with advanced HER2-positive disease.[7,10]

As part of a neoadjuvant regimen, pertuzumab added to trastuzumab plus docetaxel has been shown significantly increased the rate of pathological complete response, which led to its approval by health authorities.-Here we report the results of adding pertuzumab to the trastuzumab as adjuvant treatment for patients with HER2-positive early breast cancer.

Methods

A retrospective study included 220 patients in oncology center – Linkoping University Hospital in Sweden with high risk HER2- positive. Eligible patients received adjuvnat Anthracycline based cytotoxic 3 cycles fallowed by Taxotere + Pertuzumab + Trastuzumab 3 cycles (110 patients) in compare with arm B patients group (110 patients) who received Taxatere 3 cycles + Trastuzumab 17 cycle in 1-year adjuvant treatment.

Patients and Eligibility Criteria

Patients with non-metastatic, adequately excised, histologically confirmed invasive HER2-positive breast cancer were eligible for participation in the trial. "HER2 positivity had to be centrally confirmed and was defined as an immunohistochemical score of 3+ (scores range from 0 to 3+, with higher scores indicating higher staining intensity) in more than 10% of immune-reactive cells or HER2 +2 amplification of *ERBB2* (the gene encoding HER2) by in situ hybridization. Patients with synchronous bilateral invasive disease were eligible if both lesions were HER2-positive. Eligible patients had to have either node-positive disease or node-negative disease with a tumor diameter greater than 1.0 cm. Patients with node-negative tumors between 0.5 and 1.0 cm in diameter were initially eligible if at least one of the following high-risk features was present: Histologic or nuclear grade 3, negativity for estrogen and progesterone receptors, or age younger than 35 years."

The baseline left ventricular ejection fraction had to be at least 55%. Patients with any of the following conditions or previous treatments were ineligible: Previous invasive breast cancer; non breast cancer, any previous chemotherapy or radiotherapy for cancer; any previous anti-HER2 therapy, serious cardiac or cardiovascular disease or severe pulmonary conditions within 5 years before randomization.

Randomization and Treatment

A "Web-based system was used to collect patient screening information and to randomly assign eligible patients in a 1:1 ratio to one of the two treatment groups. A permuted-blocks randomization procedure was used, with patients stratified according to nodal status, adjuvant chemotherapy regimen, hormone-receptor status, and protocol version."

The patients who included in group A received chemotherapy plus pertuzumab plus Trastuzumab 3 cycles (840 mg as a loading dose administered intravenously, followed by 420 mg intravenously every 3 weeks) and trastuzumab (8 mg per kilogram of body weight intravenously as a loading dose, followed by 6 mg per kilogram intravenously every 3 weeks), while the patients in group B received similar 6 cycle chemotherapy plus classical 17 cycles Trastuzumab alone. Patients with hormone-receptor–positive tumors received standard endocrine therapy starting at the end of chemotherapy; the endocrine therapy was planned to continue for at least 5 years. Radiotherapy was given as clinically indicated at the end of chemotherapy and concomitantly with anti-HER2 treatment.

A physical examination and an assessment of safety and concomitant medications were conducted every 3 months during the first 12 months of participation in the trial and every 6 months thereafter. Cardiac monitoring, including an assessment of the left ventricular ejection fraction, was performed every 3 months during treatment, every 6 months up to month 36. Hematologic and liver-function tests were conducted every 3 months up to 36 months. Other investigations were recommended only when clinically indicated.

Statistical Analysis

The "primary end point, invasive-disease–free survival, was defined as the time from randomization until the date of the first occurrence of one of the following events: Recurrence of ipsilateral invasive breast tumor, recurrence of ipsilateral locoregional invasive disease, a distant disease recurrence, contralateral invasive breast cancer, or death from any cause. Data from patients without documented events were censored at the date the patient was last known to be disease-free. The stratified log-rank test was used to compare the rates of invasive-disease–free survival between the two treatment groups. The Kaplan–Meier approach was used to estimate 3-year percentages for each treatment group. The secondary end points included overall survival, disease-free survival"(including noninvasive breast cancers), "invasive-disease–free survival, relapse-free interval and distant-relapse–free interval, safety, and health-related quality of life. The primary cardiac end point was defined as heart failure of New York Heart Association (NYHA) class III or IV and a substantial decrease in left ventricular ejection fraction, defined as a decrease of at least 10 percentage points from baseline and to below 50%, or cardiac death. Cardiac death was identified by the cardiac advisory board for the trial in accordance with a prospective definition. A secondary cardiac end point was an asymptomatic or mildly symptomatic (NYHA class II) substantial decrease in left ventricular ejection fraction, as assessed by echocardiography, confirmed by a second left ventricular ejection fraction assessment."

Results

Retrospectively from January 2019 to December 2021, total of 220 patients were randomly assigned to receive Trastuzumab plus Pertuzumab 110 patients or Herceptin alone (110 patients). The baseline characteristics of the patients were balanced between the two groups, with 25% having node-positive disease and 15% having hormone-receptor–negative disease. Patients age between 30–65 years. All patients received Anthracycline based and Taxane based chemotherapy adjuvant. The median follow-up period in the intention-to-treat population was 36 months. One year of treatment was completed by 93.3%[11] of the patients in the Pertuzumab group A and 97.3%[7] of the patients in group B.

In the analysis of the primary end point," the addition of Pertuzumab in group A showed significantly lower rate of invasive-disease–free survival than group B. In total, invasive-disease events were reported in 9 patients (8.7%) in the Pertuzumab group and 5 patients (4.5%) in the group B. The 3-year rate of invasive-disease–free survival was 92.2% in the Pertuzumab group and 97.1% in the group B, with a hazard ratio for an invasive-disease event of 0.81 (95% confidence interval [CI], 0.66 to 1.00; $P = 0.045$) in favor of classical Herceptin alone."

Distant "recurrence occurred as the first invasive-disease event in 7 patients (6.3%) in the Pertuzumab group and 4 patients (3.6%) in the group B, whereas the numbers of patients with locoregional recurrences were 2 (1.8%) and 1 (0.9%), respectively. Central nervous system metastases occurred as the first invasive-disease event in 3 (2.7%) of the patients in the Pertuzumab group and 2 (1.9%) of the patients in group B. A visceral or central nervous system site was more common than bone as the site of first distant recurrence."

Kaplan–Meier Plot of Invasive-Disease–free Survival

Invasive-disease–free survival was defined as the time from randomization until the date of the first occurrence of one of the following invasive-disease events: Recurrence of ipsilateral invasive breast tumor, recurrence of ipsilateral locoregional invasive disease, a distant disease recurrence, contralateral invasive breast cancer, or death from any cause, results were presented in Table 1.

The tests for interaction of the treatment effect were not significant for any of the patient subgroups considered, including those based on nodal status and hormone-receptor status.

Primary cardiac events occurred in 4 patients (3.6%) in the pertuzumab group and in 2 patients (1.8%) in group B.

The "largest differences between the treatment groups for all grades of adverse events were found for diarrhea (23% with pertuzumab and 15% in group B) and rash (15% with pertuzumab and 9% in group B) Baseline functional quality-of-life scores were similar between the treatment groups and remained stable during treatment."

A substantial decrease in left ventricular ejection fraction (LVEF) is defined as a decrease of 10 or more percentage points, to a value lower than 50%.[8]

Discussion

The addition of Pertuzumab to Trastuzumab as adjuvant – short course therapy, was not improve the outcomes of patients with HER2-positive in early breast cancer moreover gave statistically less effect. There was no new safety issues noted, but diarrhea was more common in the Pertuzumab group.[11] "The median period of follow-up for this primary analysis was 36.4 months, which might be not enough for a full assessment of the effect size, especially in the follow up of patients with hormone-receptor–positive or node-negative disease. Subsequent analyses are planned in accordance with the trial protocol, with up to 10 years of minimum follow-up.

Table 1. **Site of first invasive-disease event**

Event	Pertuzumab Group (*N* = 110) *No. (%)*	Placebo Group (*N* = 110) *No. (%)*
Any invasive-disease event	7 (6.3)	4 (3.6)
Category of first invasive-disease event		
Distant recurrence	6 (4.7)	3 (2.7)
CNS metastases	3 (2.7)	2 (1.9)
Locoregional recurrence	1 (1.8)	1 (0.9)
Contralateral breast cancer	0 (0.)	0 (0)

On "December, 2017, the Food and Drug Administration granted regular approval to pertuzumab (PERJETA, Genentech, Inc.) for use in combination with trastuzumab and chemotherapy as adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence.

"Approval was based on data from APHINITY (NCT01358877), a multicenter, randomized, double-blind, placebo-controlled trial in 4804 patients with HER2-positive early breast cancer. Patients were then randomized to receive pertuzumab or placebo, in combination with adjuvant trastuzumab and chemotherapy. The main efficacy outcome was invasive disease-free survival (IDFS)."

After an appropriate follow-up of 45.4 months, the proportion of IDFS events in the intent-to-treat population was 7.1% (n = 171) in the pertuzumab arm and 8.7% (n = 210) for those receiving placebo." High-risk patients included patients such as those with hormone receptor negative or those with node positive breast cancer. The proportion of IDFS events in patients with hormone receptor negative disease was 8.2% (n = 71) and 10.6% (n = 91) in the pertuzumab and placebo arms, respectively. The proportion of IDFS events for patients with node positive disease was 9.2% (n = 139) and 12.1% (n = 181) in the pertuzumab and placebo arms, respectively. Overall survival data are not yet mature.[12,13]

Pertuzumab was associated with a higher rate of diarrhea that was generally mild (grade 1 or 2). "The rate of treatment discontinuation due to adverse events was 1.1 percentage points higher with Pertuzumab than classical Herceptin arm B."

The addition of Pertuzumab to Trastuzumab–docetaxel neoadjuvant treatment for 12 weeks in the randomized, multicenter, open-label NeoSphere trial resulted in a significant increase in the pathological complete response rate, from 29.0% to 45.8%. The NeoSphere trial showed a numerically higher 5-year rate of progression-free survival among patients receiving only 12 weeks of pertuzumab than among patients receiving trastuzumab alone. The results seen in studies of dual HER2 blockade in the neo-adjuvant context have not always been in concordance with the results seen when it is used as adjuvant therapy.[13,14]

Pertuzumab has been demonstrated to be effective for progressive growth against trastuzumab single-agent treatment for metastatic HER2-positive breast cancer. "On the other hand, pertuzumab does not appear to be beneficial in patients with node-negative, small primary tumors in adjuvant and neoadjuvant therapy for early HER2-positive breast cancer patients. [12–14]

Cost-effectiveness of pertuzumab is controversial and it is important to establish efficient methods for selecting which patients it is most suitable for, in order to improve the cost-effectiveness.

In conclusion, it has been found that pertuzumab adjuvant, when added to trastuzumab adjuvant 3 cycle short course, dose not significantly improved the rates of invasive-disease–free survival among patients with HER2-positive early breast cancer. Pertuzumab was associated with more toxic effects than placebo — mainly low-grade diarrhea.

Because "only 3 doses of pertuzumab treatment were investigated in this study, the effectiveness of other treatment durations remains unknown nevertheless we recommend to

study larger patient group, longer study period, longer and pertuzumab course."

Conclusion

It can be anticipated that the usage of adjuvant trastuzumab will continue to rise in clinical practice given the results of observational studies that support the findings from clinical research on its efficacy in early stage HER2-positive breast cancer patients. In patients at a high risk of recurrence due to node involvement of hormone receptor negativity, the addition of pertuzumab to standard trastuzumab-based adjuvant therapy has provided a clinically significant benefit in terms of invasive disease-free, event-free, distant relapse-free survival. The ideal adjuvant pertuzumab duration and whether combining trastuzumab and pertuzumab HER2 blockage with immunotherapy drugs intended to further activate the immune system would result in extra benefit in the early setting are still open concerns.

Conflict of Interest

None.

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