Editorial Commentary

The Peony trial: adding evidence to pertuzumab use in non-metastatic breast cancer

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In the past 10 years, neoadjuvant chemotherapy (NAC) has become a common tool in our hospitals, in order to convert the unresecables tumors into resecable and to increase the rate of conservative surgeries. Having a pathological response to NAC is an independent prognostic factor o and we cannot forget that NAC allows us to carry out clinical trials with new molecules. For those reasons, nowadays a few T2 tumors receive NAC regularly, especially HER2 molecular subtypes, which globally represent 20% of the tumors that we see in our offices. HER2-positive tumors are the ones that will undergo NAC and immunotherapy because they are very sensitive to these treatments, and surgeons are doing lumpectomys with very low load of tumor at the surgical specimen.

In cancer care there are many studies showing racial disparities among different population groups, affecting main outcomes of the trials. These differences can be attributed to:

(I) Diagnostic and treatment access: social inequity in access to the best cancer treatment in different countries and in different racial groups in the same country has been extensively studied (1). An example of this is that in HER2-positive tumors, despite trastuzumab efficacy, observational studies suggest that 25–50% of European or Chinese patients do not receive it in metastatic disease (2).

(II) Differences in biology of neoplasia, with differences in tumor microenvironment (3), stem cell population (4) or other tumor characteristics.

(III) Differences in treatment efficacy (pharmacokinetic-pharmacogenomic differences) (5). It can be important in small molecules, however monoclonal antibodies (mAbs) are metabolized through proteolytic catabolism and do not interact with transporters, so ethnic differences are not expected to affect the PK of mAbs.

These differences can have a huge impact in cancer management and must be taken in account before translating results of clinical trials in populations not well represented in those trials. Regarding Asian population in clinical trials it is very important to assure their representation, because only China represents 12.2% of all newly diagnosed breast cancer and 9.6% of all deaths from breast cancer worldwide (6). Treating breast cancer in Asiatic population can have differences that cannot be well represented in global clinical trials and particularly, in western countries-based trials.

Pertuzumab has shown to increase efficacy in early breast cancer, in both neoadjuvant [Neosphere trial (7)] and adjuvant settings (Aphinity trial) (8). Both trials included an important proportion of Asian patients (23% in Neosphere, 32.3% in Aphinity) and there have not been differences in efficacy in these populations. However, Peony trial is the first one focused in this group and increases the body of evidence of pertuzumab added to trastuzumab plus chemotherapy in early breast cancer.

Peony is a multicenter, double-blind, placebo-controlled phase 3 trial enrolling patients candidates to neoadjuvant treatment and excluding T1N0 patients that have an excellent prognosis with trastuzumab and paclitaxel therapy (9). Patients received 4 cycles of docetaxel and trastuzumab

and were randomized 2:1 to pertuzumab standard dose or placebo. After surgery, patients received 3 cycles of intravenous fluorouracil, epirubicin, and cyclophosphamide followed by 13 cycles of the same intravenous anti-ERBB2 therapy received in the neoadjuvant setting for up to 1 year.

Main results of the trial show a 39.3% pathologic complete response (pCR) rate in the pertuzumab group and 21.8% in the placebo group. No data is reported regarding overall survival nor disease-free survival, due to insufficient follow-up. Regarding toxicity, as expected, there is a higher incidence of diarrhea in pertuzumab group, mostly grade 1 and 2 (38.5% *vs.* 16.4%) and a slightly higher incidence of grade ≥3 neutropenia (38.1% *vs.* 32.7%).

The other trial of neoadjuvant treatment with chemotherapy plus trastuzumab ± pertuzumab, the Neosphere trial, randomized 417 patients to 4 arms of treatment. Of those 4 arms, two (A and B) only were different to Peony treatment regarding docetaxel dose, that could be increased to 100 mg/m^2 in the Neosphere trial. Neosphere showed 29% pCR with docetaxel trastuzumab and 45.8% with the addition of pertuzumab. A slightly higher proportion of HER2-negative patients in Neosphere (53% *vs.* 47%) and more node-negative (30% *vs.* 24%) could explain a higher pCR in Neosphere, but there are other important factors not controlled at these trials that could explain these different results, as is shown in trials like OPTI-HER HEART (10) or PAMELA (11), where intrinsic subtype modifies substantially the capacity to reach a pCR.

Independently of these considerations, Peony confirms findings of Neosphere that in HER2-positive patients pertuzumab must be incorporated to the treatment schema. In the commented trial, follow-up is short and there is no data on disease-free survival, but we can expect that results found in Neosphere with 5-year follow-up (12) will be reproduced when Peony investigators present follow-up data. Neosphere showed an increase in disease-free survival from 81% in patients receiving 4 cycles of docetaxel-trastuzumab followed by FEC ×3 and trastuzumab ×1 year to 84% when pertuzumab was added to first 4 cycles, corresponding to a HR of 0.60.

In contrast, the large Aphinity adjuvant trial, randomized 4,805 patients with node-positive or high-risk node-negative disease to standard chemotherapy plus trastuzumab 1-year *vs.* the same treatment with addition of 1 year of pertuzumab. First analysis of Aphinitytrial demonstrated a 3-year rate of invasive disease-free survival of 94.1% in pertuzumab treated patients and 93.2% in non-pertuzumab group, corresponding to a HR of 0.82. In a more mature data analysis presented at San Antonio and not yet published, at 6 years of follow-up, disease-free survival was 90.6% with pertuzumab and 87.8% with placebo (HR, 0.76). Aphinity results, despite a high proportion of node-positive patients, shows an excellent prognosis in both arms, that reduces the absolute benefit shown by the trial.

In a population that is mostly treated with NAC, and with the only available neoadjuvant clinical trial showing at least non-worse results with only 4 pertuzumab administrations, there are important questions to be resolved. The first is the optimal number of cycles of pertuzumab in early breast cancer. With trastuzumab some trials were not able to demonstrate non-inferiority with less prolonged treatment in comparison with 1-year standard duration [Phare (13), Sold (14), Short-Her (15) whilst Persephone trial did show it (16)]. The two trials that compared 6 *vs.* 12 months of trastuzumab demonstrated similar results (HR, ~1.08), but differences in definition of non-inferiority explained the positivity of Persephone and negativity of Phare. With pertuzumab we do not have this comparison and we can only speculate with Neosphere and Aphinity results.

A second important question is the need of adjuvant treatment after a pCR. A frequent question in oncology forums is which patients will need to continue pertuzumab in the adjuvant setting after using it in the neoadjuvant treatment. Patients with pCR with double blockade have demonstrated high efficacy of this combination, and maybe are who benefit most of prolonged treatment? Or maybe patients who do not achieve a pCR will be those who will need more treatment?

To this second question can help to respond the Peony trial. In Neosphere, patients treated with or without pertuzumab in the neoadjuvant part, received only trastuzumab in the adjuvant setting. In Peony trial, the same treatment received in the neoadjuvant setting will be received in the adjuvant part. So, we can speculate that if prognostic of patients that obtain a pCR is the same in both arms, pertuzumab will not be necessary after a pCR obtained with its use. In contrast, if prognosis in the pCR group is better in patients receiving pertuzumab, probably we will need to assume that continuing pertuzumab during the adjuvant phase will be the best option.

We cannot know at this moment if the number of patients included in the trial will permit to respond this question, but we hope that future results of follow-up will help us to better select treatments for HER2-positive patients.

In conclusion, Peony trial confirms the benefit of adding pertuzumab in the neoadjuvant treatment of HER2-positive patients, and that pertuzumab should be given in all the patients candidates to neoadjuvant treatment (T ≥2 or N+), irrespective of their ethnic origin.

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Footnote

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