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Short communication

Category "viewpoints and debates" Is trastuzumab as a single agent obsolete in early breast cancer? Yes

Hervé Bonnefoi*, Camille Chakiba

Department of Medical Oncology, Institut Bergonié Unicancer, Univ. Bordeaux, INSERM U1218, INSERM CIC1401, Bordeaux, France

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ABSTRACT

In 2005, two adjuvant trials revolutionised breast cancer treatment demonstrating a 50% reduction in relapses when trastuzumab was added to adjuvant chemotherapy. In order to improve further on these results three large phase III trials were conducted. ALTTO trial evaluated lapatinib. This trial was negative and lapatinib was quite toxic. ExteNET trial evaluated neratinib in patients who already had completed adjuvant treatment with trastuzumab. Neratinib reduced the risk of relapse by 27% and the drug is FDA approved. However 40% of patients experienced grade 3 diarrhoea and this toxicity profile will be an issue in daily practice. APHINITY trial evaluated a combination of pertuzumab and trastuzumab. Pertuzumab reduced the risk of relapse by 19% with a good toxicity profile. However the absolute invasive disease-free survival (IDFS) benefit at 4 years was only 1.7%. Despite this modest absolute benefit we believe that pertuzumab should be added to trastuzumab at least in two indications: first, in patients with node positive breast cancer, in whom the absolute IDFS benefit is 3.2% and qualify for a high clinical benefit based on ESMO magnitude of clinical benefit scale; second, in patients suitable for neoadjuvant chemotherapy. In this group, the absolute IDFS benefit could be estimated as high as 7% (starting pertuzumab in the neoadjuvant setting and following it in the adjuvant setting up to a total of 18 injections). Our arguments are developed in this viewpoint. Pertuzumab is approved in these two indications by FDA and EMA.

1. Introduction

In 2005, the results of US joint analysis and HERA trial presented at ASCO revolutionised breast cancer treatment. Both studies demonstrated a 50% reduction in relapses when trastuzumab was added for one year to adjuvant chemotherapy [1,2]. This reduction translated into an absolute disease-free survival (DFS) benefit of 12% at 3 years (75.4–87.1%) in the US joint analysis [1] and 8.4% at 2 years (77.4–85.8%) in the HERA trial [2]. These large absolute DFS benefits continued (11.5% in the US joint analysis and 6.8% in the HERA trial) in long term follow-up with an absolute overall survival gains of 8.8% and 6.5%, respectively [3,4]. However, despite this dramatic improvement with trastuzumab, approximately one-third of the patients will still relapse and eventually die of their disease [3,4].

2. Phase III trials evaluating dual anti-HER2 blockade

Consequently, three phase III trials evaluating new anti-human epidermal growth factor receptor 2 (HER2) treatments were conducted in the adjuvant setting: ALTTO, ExteNET and APHINITY. In the first two trials, oral lapatinib and neratinib (anti-HER2 and anti-HER1 tyrosine kinase inhibitors, respectively) were tested. In the third trial, pertuzumab, a monoclonal antibody that inhibits HER2 heterodimerisation with other HER family receptors was combined with trastuzumab.

The ALTTO trial compared four anti-HER2 treatments over one year: trastuzumab in arm A, lapatinib in arm B, trastuzumab for 3 months followed by lapatinib in arm C and trastuzumab plus lapatinib (combined treatment) in arm D [5]. The primary endpoint was invasive disease-free survival (IDFS). Arm B was stopped early for futility to demonstrate non-inferiority. Of the two comparisons planned, the first one (arm C vs arm A) failed to demonstrate non-inferiority. The second comparison (arm D vs arm A) demonstrated a 16% reduction in the risk of relapse (HR 0.84; 95%CI: 0.70–1.02; $P = 0.048$) but was statistically not significant at the pre-specified P value ≤ 0.025. Lastly, the combined treatment was more toxic. The

* Corresponding author. Department of Medical Oncology, Institut Bergonié Unicancer, Univ. Bordeaux, INSERM U1218, INSERM CIC1401, 229 Cours de l'Argonne, F-33000 Bordeaux, France.
E-mail address: h.bonnefoi@bordeaux.unicancer.fr (H. Bonnefoi).

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most frequent grade 3–4 toxicities were diarrhoea in 15%, rash in 5% and liver toxicity in 3% of patients. Based on these data lapatinib was not approved in early breast cancer.

In ExteNET trial, 2840 patients who completed neoadjuvant or adjuvant chemotherapy plus trastuzumab were randomised to receive either neratinib or placebo for one year. The primary endpoint analysis (IDFS at 2 years) was positive [6]. A second analysis was performed with a median follow-up of 5.2 years [7]. Less invasive relapses were observed in the neratinib arm (HR 0.73; 95% CI: 0.57–0.92; p = 0.0083). This difference was mainly observed in the hormone-receptor-positive group. Grade 3 diarrhoea was observed in 40% of patients (one patient experienced a grade 4). Despite its toxicity profile, neratinib was approved by the Food and Drug Administration (FDA) both for hormone-receptor-positive or negative tumours [8] and the European Medicines Agency (EMA) expressed a positive opinion in patients with hormone-receptor-positive tumours only [9]. However, we believe that grade 3 diarrhoea will be an issue in daily practice.

In the APHINITY trial, 4805 patients were randomised after surgery to receive either one year of pertuzumab or placebo in addition to standard adjuvant chemotherapy plus one year of adjuvant trastuzumab [10]. The relative risk reduction (RRR) of invasive relapse with the addition of pertuzumab in APHINITY was 19% (HR 0.81; 95%CI: 0.66–1.00; P = 0.045) with a median follow-up of 45.4 months. Pertuzumab was very well tolerated. Grade 3 diarrhoea was observed in 9.8% of patients in the pertuzumab arm and 3.7% in the placebo arm. Cardiac toxicity did not increase. The absolute IDFS benefit at 3 years and 4 years was 0.9% and 1.7%, respectively.

3. Indications for pertuzumab in two high risk populations

Some clinicians may argue that the APHINITY results do not support the use of pertuzumab in early breast cancer. We obviously agree with these colleagues when considering patients who has had surgery for a small node negative tumour and whose prognosis is excellent with weekly paclitaxel and trastuzumab single agent as demonstrated by Tolaney and colleagues [11]. However we believe that pertuzumab should be added to trastuzumab in at least two indications: patients with node positive (N+) breast cancer and patients suitable for neoadjuvant chemotherapy.

First, we will focus on 3005 N + disease patients randomised in APHINITY trial. In the trastuzumab and pertuzumab arm, the RRR of relapse was 23% (HR 0.77; 95% CI: 0.62–0.96; P = 0.02). This RRR translated to a 3.2% absolute gain at 4 years with very little additional toxicity.

In general, when assessing the potential value of a new treatment, we use the term “clinical benefit (CB)”, a necessary balance between efficacy (more precisely, the absolute magnitude of the benefit) and toxicity. In patients with N+ disease, CB observed with the addition of pertuzumab may be interpreted by many clinicians as relevant while others may consider it as modest or futile. In order to avoid a subjective interpretation of the term CB, we should refer to the European Society of Medical Oncology (ESMO) magnitude of clinical benefit scale (MCBS) [12]. The basic principle of this scale is that the CB of a new treatment for a patient is either to live longer or to live better [12]. ESMO experts consider DFS as a good surrogate for survival in studies with curative intent but without mature survival data. In a curative setting, the scale includes three grades: A, B or C. Grades correspond to an improvement in DFS alone and are defined using HR threshold (by definition in ESMO-MCBS, this HR threshold refers to the lower limit of the 95% CI). Grade A corresponds to an improvement in DFS alone with a HR < 0.65, grade B with a HR 0.65–0.8 and grade C with a HR > 0.8. Of note, pre-planned subgroup analysis can be scored separately, which applies to the N+ subgroup in APHINITY trial. Thus based on the ESMO-MCBS, CB of APHINTY in the N+ subgroup is scaled A (as mentioned above, the lower limit of the 95% CI is 0.62) which means for ESMO experts “a high level of CB” [12].

Despite this ESMO-MCBS grade A, some clinicians still believe that a 3% absolute decrease in recurrence is very modest. However, it is very likely that the same clinicians are using taxanes as standard treatment for N+ breast cancer. It is worth reminding them that the absolute benefit of taxanes is very similar to the one observed with pertuzumab in N+ breast cancer patients. The use of taxanes in the adjuvant setting results in an absolute decrease of the recurrence rate at 5 years of only 2.9% with an RRR of 14% (HR 0.86; 95% CI: 0.82–0.91; P < 0.00001) [13]. These data are from 33000 patients (82% N+) included in trials comparing anthracycline with and without taxanes (same treatment duration in both groups).

The second indication of pertuzumab should be in the neoadjuvant setting both concomitantly with chemotherapy and after surgery in the adjuvant setting. As mentioned above, in patients with N+ breast cancer, the addition of pertuzumab translated to a 3.2% absolute gain at 4 years. In patients suitable for neoadjuvant chemotherapy the risk of relapse is higher. The absolute gain is likely to be much more prominent in this group as higher the risk, higher the gain. For a precise estimation, we use the survival data of patients treated with chemotherapy and trastuzumab only in the standard arm of NeoALTTO which were recently updated with a median follow-up of 6.7 years [14]. Of note, the population of patients included in NeoALTTO cannot be considered as particularly high risk compared to other neoadjuvant trials (for example, 60% of patients were cT2). In this trial, 33% of patients presented with an invasive relapse (29% and 37% in the hormone-receptor-positive and negative groups, respectively). If we focus on hormone-receptor-negative patients and apply the 19% RRR observed in the APHINITY trial (we will not use the 23% RRR observed in the N+ group in order not to overestimate the treatment effect), the absolute benefit at 6 years is 7%. This cannot be considered as marginal. The number to treat to avoid one relapse is 14. In practice, we recommend starting pertuzumab with trastuzumab in the neoadjuvant setting. In Neosphere trial, the pathological complete response rate almost doubled (from 21.5% to 39.3%) when pertuzumab was added to trastuzumab and docetaxel in the neoadjuvant setting [15]. We also recommend following it up with adjuvant pertuzumab plus trastuzumab, up to 18 injections (including the neoadjuvantly administered injections). Of note, the effect of a shorter duration of this dual blockade has not been evaluated in a phase III trial.

Both the abovementioned indications for pertuzumab in two high-risk of relapse populations are approved by FDA and EMA. In 2013, the FDA granted accelerated approval to pertuzumab as a neoadjuvant treatment [16]. This approval was mainly based on the results of the Neosphere trial [15]. It should be reminded that approval was conditional depending on the results of the APHINITY trial looking at difference in DFS as a primary endpoint. In 2017, the results of APHINITY demonstrated a survival gain and therefore the FDA granted a regular approval for pertuzumab both “as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory in patients with locally-advanced, inflammatory, or early stage breast cancer in combination with trastuzumab and chemotherapy and in patients with early breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer” [17]. The EMA also approved pertuzumab as neoadjuvant treatment and extended the indication recently to the adjuvant setting in patients “at high risk of recurrence” [18].

4. Issues in Europe

However, in Europe, there exist three issues. First, there is already a big heterogeneity between countries as far as access to neoadjuvant pertuzumab (in general from 3 to 4 injections) is concerned. Second, the incremental cost of delivering a total of eighteen injections of pertuzumab "as part of a complete treatment regimen for early breast cancer" (approximately 70000 euros per patient) is an issue for reimbursement by national health systems. In addition, data on cost-effectiveness are lacking. Third, the term "high risk" can be interpreted in different ways. Methods assessing the risk of recurrence in patients treated with standard treatment and trastuzumab as a single agent only may help. Composite predictors including clinicopathological parameters and tumour markers similar to the ones developed in patients with hormone-receptor-positive and HER2-negative tumours [19,20] should also be developed in HER2-positive breast cancer patients. As HER2-positive hormone-receptor-positive and negative tumours have different relapse patterns over time, different predictors need to be developed [21]. These predictors may allow assessing the risk for an individual patient and potentially to better estimate the absolute DFS benefit with dual HER2-blockade.

5. Conclusion

The results of adjuvant trials with trastuzumab in early breast cancer were a revolution. Pertuzumab is an evolution. The above-mentioned risk of recurrence predictors should help to refine the indications for pertuzumab in high-risk of relapse populations and should reduce the economic toxicity of dual anti-HER2 therapy. Until we get these predictors we have to take our responsibilities as clinicians in front of our patients based on published data.

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