



EDITORIAL

Improving the adjuvant treatment of HER2-positive breast cancer: APHINITY and ExteNET trials

Melhorando o tratamento adjuvante do câncer de mama HER2-positivo: Estudos APHINITY e ExteNET

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The natural history of HER2-positive early breast was dramatically changed in 2005 by the results of 4 randomised phase III trials evaluating the combination of chemotherapy with adjuvant trastuzumab, the first drug in the anti-HER2 class. HERA, BCIRG-006, NCCTG 9831 and NSABP-B31 established 1 year of adjuvant trastuzumab as the standard of care, and long term follow-up results of these trials (8 to 11 years) have underscored the significant and prolonged improvement in outcomes patients derive from trastuzumab use.⁽¹⁾ Toxicity, mostly cardiac in nature, has proven to be low when patients are carefully selected and followed. In addition, most cardiac events are reversible with interruption of trastuzumab and prompt cardiac treatment.⁽²⁾ Though the cost associated with adjuvant trastuzumab can be a concern, especially in developing countries, the development of biosimilar options will likely bring prices down – making trastuzumab a safe, effective and relatively affordable treatment standard.⁽³⁾ Despite these improvements, HER2-positive patients still relapse in significant numbers. The 11 year follow-up results of HERA show that approximately 30% of patients in the trastuzumab containing arms eventually experienced a relapse.⁽⁵⁾ After a new generation of anti-HER2 agents successfully improved outcomes and changed clinical practice in the advanced setting – including lapatinib, pertuzumab and T-DM1, it was only logical to hope they would be similarly effective in early disease.⁽⁶⁾ The first results of lapatinib and pertuzumab in the neoadjuvant setting showed significant improvement in pathologic complete response (pCR). NeoALTT0 tested trastuzumab + lapatinib vs trastuzumab or lapatinib alone, first alone then with paclitaxel, followed by surgery and further chemotherapy and the same anti-HER2 therapy for a year.⁽⁷⁾ Results showed the superiority of the dual blockade regimen (with an absolute improvement in pCR of approximately 20%). The NEOSPHERE study tested docetaxel + trastuzumab, docetaxel + pertuzumab or both monoclonal antibodies with or without docetaxel, also showing superior results with the dual blockade regimen (absolute improvement in pCR of approximately

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16%).⁽⁸⁾ Both trials, however, failed to show an equivalent improvement in disease-free survival (DFS)/event-free survival (EFS), though it must be said that neither trial was adequately powered to show a significant improvement in long outcomes. To change standards in the adjuvant setting, larger phase III studies were needed, leading to the design of the dual blockade ALTTO and APHINITY trials.^(10,11) Additionally, despite negative results in advanced disease, the ExteNET trial testing an alternative strategy of extending anti-HER2 therapy to 2 years with neratinib after the completion of trastuzumab was also launched.^(12,13)

The first evidence that the extent of success seen in the advanced setting would not be easily replicated were the results of the ALTTO trial, which randomised 8381 patients to 4 arms testing trastuzumab and lapatinib as single agents, in sequence (trastuzumab followed by lapatinib) or in combination (trastuzumab + lapatinib). Though the reasons for this trial proving statistically negative, despite some signal of efficacy, have been extensively debated in recent years, it brought an end to the development of lapatinib in the early setting. On the other hand, both APHINITY and ExteNET were positive trials – showing a significant improvement in invasive disease-free survival (IDFS), ultimately leading to approval by the FDA of both regimens tested in these trials.

APHINITY tested chemotherapy (either anthracycline-based or anthracycline-free) combined with trastuzumab or trastuzumab + pertuzumab for 1 year in 4805 patients. Results of the primary analysis show a statistically significant yet small absolute improvement in 3-year IDFS favouring the arm receiving dual blockade of 0.9% (hazard ratio, 0.81; 95% confidence interval [CI], 0.66 to 1.00; $p=0.045$), with absolute gains being somewhat better at 4 years (1.7%). Subgroup analysis suggests that patients with node positive disease benefitted more than node negative patients (1.8% absolute IDFs gain at 3-years), as well as a non-significant trend towards higher benefit in estrogen receptor negative (ER-negative) patients. The adverse event profile with the dual blockade regimen was overall similar to the trastuzumab single agent regimen, with the exception of a significant increase in the incidence of diarrhoea (Grade 3 or more 9.8% vs 3.7%), though it is important to note that almost all cases occurred during the chemotherapy phase.⁽¹¹⁾ Primary cardiac events were numerically increased in the combination group (17 vs 8), however the overall numbers were very low, highlighting the safety of the combination regimen in a carefully selected patient population.

The ExteNET trial randomised 2840 patients to receive standard chemotherapy and trastuzumab regimen followed either by one additional year of neratinib or placebo. 5-year IDFS results show the relative superiority of the extended regimen with an absolute benefit of 2.5% (HR 0.73, 95% CI 0.57–0.92, $p=0.0083$). Subgroup analysis suggest increased efficacy in patients with ER-positive tumours. The toxicity profile was, however, pronouncedly more intense in the extended treatment arm, notably with diarrhoea (40% vs <1%), nausea (3% vs <1%) and vomiting (2% vs <1%) grade 3 or more, which was reflected in reduced median dose intensity (82% in neratinib arm vs 98% placebo arm).⁽¹²⁾

Placing these results into the context of clinical practice, however, is likely to prove challenging for clinicians. Though both dual blockade and extended therapy proved to improve outcomes, these improvements are exceedingly small when compared to the absolute improvement in disease free survival (DFS) of 6.8% in the HERA trial. Therefore, most patients are still candidates for chemotherapy + 1 year trastuzumab and a clear example are patients falling into populations well represented in APT (T1, node negative patients with ER-positive disease) to whom paclitaxel + trastuzumab alone is a good option.⁽⁴⁾ For patients who are not candidates to this regimen, clinicians must carefully decide to either continue to use 1 year of trastuzumab alone, dual blockade with pertuzumab or extended therapy with neratinib. For high risk patients, especially those who are candidates for neoadjuvant therapy, node positive and/or ER-negative tumors, dual blockade with pertuzumab should be considered. Extended therapy with neratinib can be an option for patients at a high risk of relapse who did not receive neoadjuvant chemotherapy, especially if ER+. However, proactive management of diarrhoeas, as per the CONTROL (NCT02400476) trial, is needed to prevent low-adherence to such prolonged oral treatment.

There is no doubt that progress was achieved in the HER2-positive breast cancer population, with at least three treatment options in 2018: 1 year of trastuzumab, dual blockade with trastuzumab and pertuzumab or neratinib after trastuzumab. However, a better understanding on which population benefits the most from each of these approaches is urgently needed to better fine-tune adjuvant treatment and can only be achieved through better trial design that integrate biomarker research and selective escalation strategies.

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