Neoadjuvant treatment for intermediate/high-risk HER2-positive and triple-negative breast cancers: no longer an ‘option’ but an ethical obligation

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Last year, we published an editorial in this journal, advocating the use of neoadjuvant treatment (NAT) in patients with breast cancer, especially for those bearing aggressive tumours (luminal B, triple-negative and HER2-positive subtypes). With the recent publication of important practice-changing data, we argue now that the use of NAT is the only ethical strategy for around one-third of women with early breast cancer.

The first reason for using NAT is that it allows surgical de-escalation, as it increases the rates of breast-conserving surgery. It may also avoid a full axillary dissection in selected patients who ‘convert’ from cN1 to a negative sentinel lymph-node biopsy. Another very important reason is that it identifies patients at a higher risk of relapse, for whom additional ‘salvage’ options are now available. Two large meta-analyses have demonstrated that patients who do not achieve a pathological complete response (pCR) after NAT have worse long-term survival, especially in triple-negative breast cancer (TNBC) and HER2-positive disease. Yet, it has recently been shown that their outcome may be improved by escalating post-NAT.

The CREATE-X trial, conducted in Asia, included both patients with oestrogen receptor (ER)-positive/HER2-negative disease and TNBC, who were randomised to receive standard postsurgical treatment either with or without capecitabine. Among patients with TNBC, capecitabine significantly improved 5-year disease-free survival: it was 69.8% in the capecitabine group versus 56.1% in the control group (HR 0.58; 95% CI 0.39 to 0.87); it also improved overall survival (HR 0.52; 95% CI 0.30 to 0.90). In patients with ER-positive/HER2-negative disease, the HR for disease-free survival was more modest: 0.81 (95% CI 0.55 to 1.17). Despite concerns on the extrapolation of CREATE-X results to non-Asian patients, international guidelines adopted adjuvant capecitabine as a possible treatment for patients with TNBC and invasive residual disease after NAT.

More recently, the KATHERINE trial randomised 1486 patients with residual invasive HER2-positive disease following NAT to adjuvant T-DM1 or trastuzumab for 14 cycles. Results were impressive: the 3-year invasive disease-free survival rate was 88.3% in the T-DM1 group versus 77.0% in the trastuzumab group (HR 0.50; 95% CI 0.39 to 0.64), making it clear that these patients with suboptimal responses to standard chemotherapy and anti-HER2 monoclonal antibodies (trastuzumab ± pertuzumab) should receive adjuvant T-DM1 instead of continuing trastuzumab. Nonetheless, there is space for further improvement in the ER-negative/HER2-positive subgroup, as 3-year invasive disease-free survival rate was 82.1% with T-DM1. Overall survival data are still immature.

Of note, there are several ongoing phase III trials testing the postneoadjuvant use of other drugs in patients with residual invasive disease after NAT, like the PENELLOPE-B trial in ER-positive/HER2-negative patients (standard endocrine therapy with/without 1 year of palbociclib; ClinicalTrials.gov identifier: NCT01864746) or the SWOG S1418/NRG BR006 trial in TNBC (1 year of pembrolizumab or placebo; NCT02954874).

Considering the above results—and particularly those of the very robust international KATHERINE trial—we advocate that clinicians must use tumour’s response to NAT as a way to tailor adjuvant treatment of patients with intermediate to high-risk HER2-positive disease or TNBC, instead of blindly prescribing chemotherapy and/or targeted agents after surgery.
NAT becomes the ‘standard of care’ for these women and not only an ‘option’ to discuss for the purpose of increasing the probability of less aggressive surgery, as it has an impact on disease-free survival and, possibly, on overall survival as well. A number of remaining questions will need to be addressed, like which adjuvant anti-HER2 therapy to prescribe to patients who achieve pCR after neoadjuvant chemotherapy with trastuzumab and pertuzumab and whether or not biomarkers evaluated after one or two courses of NAT might reliably identify patients who will not reach a pCR and who could benefit from an earlier introduction of a ‘salvage’ treatment.

The NAT strategy could also become a standard of care for high-risk luminal B disease in the near future, if it is demonstrated that those patients who do not achieve a pCR after NAT may benefit from the addition of targeted therapy to endocrine treatment. Beyond pCR ‘yes or no’, other prognostic markers can be used to identify high-risk patients, like the residual cancer burden or the PEPI score. More recently, prognostic markers like tumour-infiltrating lymphocytes in the residual tumour or the persistence of circulating tumour DNA (ctDNA) have also been explored. These markers may also be important for patients who achieve pCR, as we know that a part of these patients still relapse afterwards and we should find ways of identifying them.

Even though the use of NAT helps tailoring adjuvant therapy, in patients who do not achieve pCR (who are still the majority), the duration of neoadjuvant plus adjuvant treatment can be very long—for example, up to 18 months in HER2-positive disease. Thus, an earlier identification of patients who are benefiting or not from NAT is necessary in order to (de)escalate therapy accordingly. One possibility is the use of imaging during the course of NAT, like MRI and/or F-FDG PET/CT, which have shown to be associated with achievement of pCR. Other possibilities are measuring the drop of Ki67 after 2–4 weeks of treatment or assessing the fall in ctDNA levels during NAT.

Today, however, there is no proven benefit of changing the type of regimen used throughout NAT according to these markers, but there are ongoing trials testing this hypothesis (ie, ALTERNATE [NCT01953588] and ADAPT HR+/HER2- [NCT01779206]).

It should also be realised that the use of NAT demands a highly organised team of pathologists, radiologists, surgeons, medical oncologists, radiation oncologists and other professionals specialised in breast cancer care. As recommended by the European Society for Medical Oncology, we are strong believers that the model of ‘breast cancer units’ should now be fully implemented in Europe and abroad, as failing to do so might compromise patients’ survival. A courageous way of accelerating its dissemination would be to restrict breast cancer treatment reimbursement to hospitals which have an accredited breast cancer unit.

In conclusion, we claim that patients with intermediate to high-risk TNBC or HER2-positive disease (≥T2 and/or lymph-node positive tumours) must receive NAT, as this strategy not only increases the chance of less aggressive surgery, but identifies patients who will benefit from ‘salvage’ adjuvant therapy with an impact on long-term outcomes.

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REFERENCES

1. Reyal F, Harzy AS, Piccart MJ. Neoadjuvant treatment: the future of patients with breast cancer. ESMO Open 2018;3:e000371.
2. Asselain B, Barrow W, Bartlett J et al. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol 2018;19:27–39.
3. Simons JM, van Nijatten TJA, van der Pol CC et al. Diagnostic accuracy of different surgical procedures for axillary staging after neoadjuvant systemic therapy in node-positive breast cancer: a systematic review and meta-analysis. Ann Surg 2019;269:432–42.
4. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. The Lancet 2014;384:164–72.
5. Spring LM, Fell G, Arfe A, et al. Abstract GS2-03: pathological complete response after neoadjuvant chemotherapy and impact on breast cancer recurrence and mortality, stratified by breast cancer subtypes and adjuvant chemotherapy usage: individual patient-level meta-analyses of over 27,000 patients. Cancer Res 2019;79.
6. Masuda N, Lee S-J, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med 2017;376:2147–59.
7. Denduluri N, Chavez-MacGregor M, Telli ML, et al. Selection of optimal adjuvant chemotherapy and targeted therapy for early breast cancer: ASCO clinical practice guideline focused update. J Clin Oncol 2018;36:2433–43.
8. Gradishar WJ, Anderson BO, Abraham J. NCCN clinical practice guidelines in oncology. Breast Cancer 2019;215.
9. von Minckwitz G, Huang C-S, Mana MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med 2019;380:617–28.
10. Symmans WF, Peintinger F, Hatzis C, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. J Clin Oncol 2007;25:4414–22.
11. Ellis MJ, Tao Y, Luo J, et al. Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. J Natl Cancer Inst 2008;100:1380–8.
12. Loi S, Drubay D, Adams S, et al. Tumor-infiltrating lymphocytes and prognosis: a pooled individual patient analysis of early-stage triple-negative breast cancers. J Clin Oncol 2019;37:559–69.
13. Garcia-Murillas I, Schiavon G, Weigel B, et al. Mutation tracking in circulating tumor DNA predicts relapse in early breast cancer. Sci Transl Med 2015;7.
14. Taourel P, Pages E, Millet I, et al. Magnetic resonance imaging in breast cancer management in the context of neo-adjuvant chemotherapy. Crit Rev Oncol Hematol 2018;132:51–65.
15. Salty X-Y-L, Pan S-M, Pan J, et al. Role of magnetic resonance imaging in detection of pathologic complete remission in breast cancer.
patients treated with neoadjuvant chemotherapy: a meta-analysis. Clin Breast Cancer 2017;17:245–55.

16. Gebhart G, Gámez C, Holmes E, et al. 18F-FDG PET/CT for early prediction of response to neoadjuvant lapatinib, trastuzumab, and their combination in HER2-positive breast cancer: results from Neo-ALITTO. J Nucl Med 2019;54:1862–8.

17. Ha S, Park S, Bang J-I, et al. Metabolic Radiomics for pretreatment 18F-FDG PET/CT to characterize locally advanced breast cancer: histopathologic characteristics, response to neoadjuvant chemotherapy, and prognosis. Sci Rep 2017;7.

18. Ma CX, Gao F, Luo J, et al. NeoPalAna: neoadjuvant Palbociclib, a cyclin-dependent kinase 4/6 inhibitor, and anastrozole for clinical stage 2 or 3 estrogen receptor-positive breast cancer. Clin Cancer Res 2017;23:4055–65.

19. Guarneri V, Dieci MV, Bisagni G, et al. De-escalated therapy for HR+/HER2+ breast cancer patients with Ki67 response after 2 weeks letrozole: results of the PerELISA neoadjuvant study. Ann Oncol 2019. doi:10.1093/annonc/mdz055. [Epub ahead of print: 18 Feb 2019].

20. Nitz UA, Gluz O, Christgen M, et al. De-escalation strategies in HER2-positive early breast cancer (EBC): final analysis of the WSG-ADAPT HER2+/HR- phase II trial: efficacy, safety, and predictive markers for 12 weeks of neoadjuvant dual blockade with trastuzumab and pertuzumab ± weekly paclitaxel. Ann Oncol 2017;28:2768–72.

21. Harbeck N, Gluz O, Christgen M, et al. De-Escalation Strategies in Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Early Breast Cancer (BC): Final Analysis of the West German Study Group Adjuvant Dynamic Marker-Adjusted Personalized Therapy Trial Optimizing Risk Assessment and Therapy Response Prediction in Early BC HER2- and Hormone Receptor-Positive Phase II Randomized Trial—Efficacy, Safety, and Predictive Markers for 12 Weeks of Neoadjuvant Trastuzumab Emtansine With or Without Endocrine Therapy (ET) Versus Trastuzumab Plus ET. J Clin Oncol 2017;35:3046–54.

22. Kim J-Y, Park D, Son D-S, et al. Circulating tumor DNA shows variable clonal response of breast cancer during neoadjuvant chemotherapy. Oncotarget 2017;8:86423–34.

23. Riva F, Bidard F-C, Houy A, et al. Patient-specific circulating tumor DNA detection during neoadjuvant chemotherapy in triple-negative breast cancer. Clin Chem 2017;63:691–9.

24. Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26(suppl 5):v8–38.

25. Kesson EM, Allardice GM, George WD, et al. Effects of multidisciplinary team working on breast cancer survival: retrospective, comparative, interventional cohort study of 13 722 women. BMJ 2012;344:e2718.