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Neoadjuvant treatment: the future of patients with breast cancer

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In a recent paper published in the *British Medical Journal* by Vaidya and colleagues,[1] the authors call for reconsidering the routine use of neoadjuvant chemotherapy in patients with breast cancer. Their main arguments are (1) the increased risk of locoregional recurrence, (2) the imperfect correlation between the response to primary chemotherapy and overall survival, and (3) the complexity of surgery after neoadjuvant chemotherapy. We strongly disagree with this opinion paper.

First, great care should be applied in interpreting 15-year locoregional recurrence rates published in the recent Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis,[2] as considerable changes have occurred in the past 15 years in terms of diagnosis and staging (MRI, ultrasound, PET/CT), medical treatments (chemotherapy/targeted therapy/endocrine therapy), surgical techniques and radiation protocols. Similar hot debates on the increased risk of local relapse emerged in the transition period from radical Halstedt mastectomy to breast conservating surgery plus radiation therapy, with the latter no longer being controversial as a standard of care.

Second, in response to the inconsistent relationship between treatment response and survival, the authors advocate to limit the use of neoadjuvant chemotherapy (NAC). Contrarily, we see this theme as a great opportunity to better understand breast cancer. Since National Surgical Adjuvant Breast and Bowel Project (NSABP)-18,[3] a large body of literature has proved survival equivalence between chemotherapy administered in the neoadjuvant and in the adjuvant setting. Beyond the binary character of pathological complete response (pCR), a variety of post-NAC scores have been developed and validated, allowing to sharply refine individual prognosis. Residual cancer burden score by Symmans and colleagues[4] proved to be a robust and reproducible tool to identify a group of patients with very poor prognosis. To our knowledge, no such powerful prognostic marker has been validated so far in the adjuvant setting.

On the other hand, critical beneficial aspects of neoadjuvant treatment should be highlighted and can be grouped into three main axes: (1) patient benefits/care pathway, (2) access to innovation and (3) research and development.

Regarding patient benefits, the unequivocal increase in conservative surgery rates is associated with an improved quality of life and a reduction of the need for breast reconstruction. Primary chemotherapy also prevents from rushed oncogenetic screening and enables in case of BRCA1–2 mutation a much needed reflexion period to discuss surgical curative treatment options (total mastectomy/conservative surgery) and/or prophylactic procedures (contralateral breast/ovaries). Finally, beginning oncological treatment sequence with chemotherapy avoids delays in systemic treatment caused by surgical complications; the latter become more and more frequent as the complexity of surgical techniques increases (sentinel lymph node vs axillary dissection, lumpectomy vs oncoplasty, mastectomy vs mastectomy plus immediate breast reconstruction).

The second distinct feature of NAC is more rapid *access to innovation*. Many neoadjuvant clinical trials are currently opening due to the FDA-accelerated approval path for drugs achieving a higher rate of pathological response. Great progress has been made in identifying tumours unlikely to reach pCR, and patients can be offered 'early switch' trials. At NAC completion, patients with an excellent response can be enrolled into de-escalation trials, whereas patients with high tumour burden can be included in 'salvage therapy' trials testing new drugs. The residual tumour burden can be submitted to next-generation sequencing in order to identify actionable mutations or may be used to generate patient-derived xenograft.

Third, in terms of *research and development*, neoadjuvant therapy is a strategic opportunity. It gives access successively to intrinsic baseline tumour characteristics, in vivo analysis of the sensitivity to treatment and to final postoperative evaluation of the residual tumour, making it the optimal framework for translational research. It enables serial tumour and blood biobanking, as well as iterative imaging procedures to lead comprehensive research programmes aimed at understanding tumour dynamics and resistance to treatments. In addition, the neoadjuvant setting allows the testing of new hypotheses and the identification of new predictive biomarkers. Let us just mention a few illustrative examples: the superiority of weekly paclitaxel over a three weekly administration,[5] of aromatase inhibitors over tamoxifen[6 7] and of sequential anthracycline–taxane over anthracycline alone[8] has first been shown in neoadjuvant trials with subsequent confirmation in large adjuvant studies. The same is true for the dynamic biomarker Ki67, the drop of which after 2 weeks of endocrine therapy predicts endocrine sensitivity.[9] Finally, neoadjuvant treatment makes it possible to investigate the role various factors play in modulating the response to treatment such as the microbiota, patient comorbidities and comedications, or other extrinsic factors. Decades of adjuvant clinical trials with needs of high number of patients to observe few 'events', long follow-up times to obtain mature survival data and huge costs have led to the conclusion that this model is no longer sustainable for drug development. In contrast, the neoadjuvant modal represents a more flexible setting, with shorter treatment durations, hundreds instead of thousands of patients who enrol and reduced costs. In the era of personalised oncology, adapative trial designs such as those promoted by the I-SPY two group are remarkable templates for efficient and cost-effective drug development strategies.[10]

In conclusion, NAC is a not-to-be-missed opportunity for patients, physicians and researchers, and should in fact be the preferred approach for the majority of patients bearing aggressive forms of the disease (namely luminal B, triple negative and *HER2*-positive subtypes).

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REFERENCES

1. Vaidya JS, Massarut S, Vaidya HJ, *et al*. Rethinking neoadjuvant chemotherapy for breast cancer. *BMJ* 2018;360:j5913.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). 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. Fisher B, Bryant J, Wolmark N, *et al*. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol* 1998;16:2672–85.
4. 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.
5. Green MC, Buzdar AU, Smith T, *et al*. Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel once every 3 weeks. *J Clin Oncol* 2005;23:5983–92.
6. Eiermann W, Paepke S, Appfelstaedt J, *et al*. Preoperative treatment of postmenopausal breast cancer patients with letrozole: a randomized double-blind multicenter study. *Ann Oncol* 2001;12:1527–32.
7. Dowsett M, Ebbs SR, Dixon JM, *et al*. Biomarker changes during neoadjuvant anastrozole, tamoxifen, or the combination: influence of hormonal status and HER-2 in breast cancer—a study from the IMPACT trialists. *J Clin Oncol* 2005;23:2477–92.
8. Smith IC, Heys SD, Hutcheon AW, *et al*. Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. *J Clin Oncol* 2002;20:1456–66.
9. Dowsett M, Smith IE, Ebbs SR, *et al*. Prognostic value of Ki67 expression after short-term presurgical endocrine therapy for primary breast cancer. *J Natl Cancer Inst* 2007;99:167–70.
10. Bartsch R, de Azambuja E. I-SPY 2: optimising cancer drug development in the 21st century. *ESMO Open* 2016;1:e000113.