Changing frameworks in treatment sequencing of triple-negative and HER2-positive, early-stage breast cancers

Lajos Pusztai, Julia Foldi, Arjun Dhawan, Michael P DiGiovanna, Eleftherios P Mamounas

Important results are emerging from clinical trials showing that surgery followed by chemotherapy might not be the optimal strategy to maximise a patient's chance of survival from triple-negative or HER2-positive breast cancers. Administering chemotherapy before surgery provides an opportunity to directly observe the efficacy of a particular chemotherapy regimen. Patients who have extensive residual invasive cancer after neoadjuvant chemotherapy are at a high risk of recurrence for metastatic disease, which, in turn, make these patients ideal candidates for clinical trials. Two important clinical trials, CREATE-X (UMIN000000843) and KATHERINE (NCT01772472), have shown improved disease-free survival with postoperative capecitabine and ado-trastuzumab emtansine in patients with either triple-negative or HER2-positive breast cancer who had residual disease after neoadjuvant chemotherapy. The opportunity for residual-disease guided therapy, as observed in these trials, is lost when patients undergo surgery first. In this Personal View, we discuss the clinical implications of the CREATE-X and KATHERINE trials and place them into context with other developments in the adjuvant setting of early-stage breast cancer. We suggest that neoadjuvant systemic therapy should be considered as the new standard of care for HER2-positive and oestrogen receptor negative breast cancer, even for patients who present with operable (T1 or T2) disease.

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Yale Cancer Center, Yale School of Medicine, New Haven, CT, USA (Prof L Pusztai MD, J Foldi MD, A Dhawan MD, M P DiGiovanna MD); **and Orlando Health, University of Florida Health Cancer Center, Orlando, FL, USA** (Prof E P Mamounas MD)

Correspondence to:
Prof Lajos Pusztai, Breast Medical Oncology, Yale Cancer Center, Yale School of Medicine, CT 06520, USA
lajos.pusztai@yale.edu

Introduction

Preoperative (ie, neoadjuvant) chemotherapy was originally introduced for patients who presented with inoperable breast cancer with the intention of rendering their disease operable. When adjuvant chemotherapy was shown to have a benefit in patients with node-positive (and subsequently node-negative) breast cancers, the use of neoadjuvant chemotherapy was expanded to include patients who had operable disease. Several randomised clinical trials done in the 1980s and 1990s showed that when the same chemotherapy regimen was administered as either neoadjuvant or as adjuvant therapy, the survival benefit remained the same.[1–4] These trials also showed high rates of clinical tumour response, which often meant that patients who previously required a mastectomy (on the basis of the extent of their disease at presentation) were now suitable candidates for breast conserving surgery. Neoadjuvant chemotherapy has also led to smaller resection volumes in patients with operable disease, which can have cosmetic advantages. In addition, the use of neoadjuvant chemotherapy resulted in clinical and pathological downstaging of involved axillary lymph nodes. Although this observation was of little clinical significance when axillary lymph node dissection was the only surgical option for staging the axilla, the development of sentinel lymph node biopsy has provided the opportunity to also decrease the extent of axillary surgery with the use of neoadjuvant chemotherapy.[5–9] In addition to these clinical benefits,[10–12] the use of neoadjuvant chemotherapy provides the opportunity to observe tumour response in vivo. Several cohort studies,[13] clinical trials,[14,15] and meta-analyses[15] have convincingly shown a strong correlation between pathological response in the breast and axillary nodes and long-term survival. Patients who achieve a complete response (pCR; =ypT0/is ypN0) have excellent long-term disease-free survival and overall survival (OS), whereas patients with residual disease have a significantly higher risk of recurrence, which is proportional to the extent of residual cancer, particularly for patients who have triple-negative or HER2-positive breast cancers.[13–15] For patients who have oestrogen receptor-positive breast cancers, achieving a pCR continues to indicate excellent long-term outcomes. However, those patients who do not achieve a pCR do not necessarily portend poor prognosis, mainly because of the number of highly effective adjuvant endocrine therapies available.[13–15]

Maximising the proportion of patients who achieve a pCR

Recognising that patients who achieve a pCR after neoadjuvant chemotherapy have excellent distant metastasis-free survival motivates efforts to motivate efforts to develop new treatment regimens that increase pCR rate. In triple-negative breast cancer, the proportion of patients who achieve a pCR range from 20% to 60% depending on the chemotherapy regimen given. Weekly paclitaxel alone (80 mg/m^2×12 treatments) induces a pCR in approximately 20% of patients,[16] whereas sequential taxane anthracycline regimens result in proportions of between 35–48% for patients with triple-negative breast cancer.[17] Inclusion of carboplatin with a taxane component further increases the proportion of patients who achieve a pCR to approximately 45–55%.[18–22] The chemotherapy doublets nab-paclitaxel (125 mg/m^2) and carboplatin (AUC2 days 1 and 8 repeated every 3 weeks x 4) has resulted in a pCR of 46%, whilst docetaxel (75 mg/m^2) and carboplatin, (AUC6 every 3 weeks ×6) has resulted in a pCR of 55%.[21,22] Sequential dose dense doxorubicin and cyclophosphamide and paclitaxel and

carboplatin (80 mg/m² weekly×12, carboplatin AUC6 every 3 weeks ×4) also resulted in a pCR of approximately 50% for patients with triple-negative breast cancer.[20] Adding bevacizumab to sequential doxorubicin and cyclophosphamide followed by paclitaxel and carboplatin further increased response to 60%.[18] Results from the I-SPY2 trial,[23] and preliminary results from the KEYNOTE-173 trial,[24] show that the inclusion of the immune-checkpoint inhibitor, pembrolizumab, with neoadjuvant chemotherapy could also increase the proportion of patients who achieved a pCR who have triple-negative breast cancer. However, in the randomised GeparNuevo trial,[25] the inclusion of durvalumab with weekly nab-paclitaxel (125 mg/m²) and dose dense epirubicin (90 mg/m²) and cyclophosphamide (600 mg/m²) resulted in only a modest numerical increase in the proportion of patients who achieved a pCR (44% *vs* 53%) (compared to chemotherapy alone) that did not reach statistical significance (p=0·287). Two large randomised clinical trials (KEYNOTE-522 and IMpassion-031) are testing the inclusion of an immune checkpoint inhibitor with taxane and anthracyline neoadjuvant chemotherapy. These trials have completed patient accrual and will establish the clinical utility of these drugs as neoadjuvant therapy in triple-negative breast cancer.

For HER2-positive breast cancer, the proportion of patients who achieve a pCR range from 20% to 80% depending on the regimen and oestrogen receptor status of the cancer. One study[26] showed that the proportion of patients who achieved a pCR was 20% when treated with a combination of trastuzumab and pertuzumab alone without any chemotherapy In general, adding trastuzumab to chemotherapy roughly doubles the proportion of patients who achieve a pCR when compared with chemotherapy alone.[27] Targeting the HER2 pathway with two different agents (ie, trastuzumab and lapatinib or trastuzumab and pertuzumab), in combination with chemotherapy, can further improve the proportion of patients who achieve a pCR.[28–30] The proportion of patients who achieve a pCR can reach 80% when trastuzumab and pertuzumab, or trastuzumab and lapatinib, are added to multidrug chemotherapy regimens in oestrogen receptor-negative and HER2-positive cancers.[28–30] In the TRYPHAENA trial,[29] patients with oestrogen receptor-negative breast cancer achieved a pCR of 80% when treated with concurrent administration of pertuzumab and trastuzumab with sequential anthracycline and taxane neoadjuvant chemotherapy, and 45% in patients with oestrogen receptor-positive cancers.[29] Similarly high pCR percentages (roughly 80%) for oestrogen receptor-negative cancers were reported in other phase 2 and phase 3 trials of trastuzumab, or trastuzumab plus pertuzumab, when administered concurrently with sequential paclitaxel and 5-fluorouracil, epirubicin, cyclophosphamide neoadjuvant chemotherapy.[27,30] These trials also showed that HER2-targeted therapy during both the anthracycline and taxane components of the sequential regimen does not improve pCR outcomes beyond use of HER2-targeted therapy, but only during the taxane phase of treatment.[27,29,30]

pCR outcomes and survival

Achieving a pCR is an important therapeutic goal for individual patients because it is associated with more than 90% distant metastasis-free survival.[15] However, there is some uncertainty regarding the correlation between increased pCR outcomes in a clinical trial group and subsequent improvements in disease-free survival and OS. Most published randomised neoadjuvant trials were adequately powered to show increases in pCR outcomes but were generally underpowered to show improved disease-free survival or OS. Only two published trials[31,32] showed statistically significant improvements in disease-free survival in the experimental groups that had had a higher proportion of patients who had achieved a pCR. A third trial, GeparSEPTO,[33] also reported improved pCR outcomes and higher disease-free survival when nab-paclitaxel was substituted for paclitaxel. However, most neoadjuvant trials have only shown a weak trend toward improved disease-free survival and OS.[34]

Neoadjuvant therapy is an efficient and direct way to assess the cytotoxic efficacy of new therapies on the primary tumour. However, the absolute improvements in survival are always lower than improvements in pCR outcomes. Several factors contribute to this disparity. First, baseline prognosis of the patient population confines the absolute improvement in survival that can be expected (ie, patients with good initial prognosis can only have small absolute gains in survival).[35] Second, the proportion of patients who achieve a pCR might be higher for patients with a good initial prognosis (eg, patients with immune infiltration-rich cancers) who have excellent survival even in the absence of any systemic therapy. Third, effective therapies after neoadjuvant therapy (ie, adjuvant endocrine therapy) improve outcomes in the residual disease group and move the survival curves closer together, which explains why residual disease in patients with oestrogen receptor-positive cancers is associated with a less negative prognostic effect than residual disease in patients with oestrogen receptor-negative cancers. Fourth, patients with a minimal residual cancer burden after neoadjuvant chemotherapy have a similar excellent prognosis as patients who achieve a pCR; therefore, if a regimen increases the proportion of patients who achieve a pCR (primarily by moving patients from the minimal residual disease category to the pCR category), the net survival benefit from having pCR would be minimal. Finally, 3–6% of patients who achieve a pCR will experience distant recurrence, indicating different chemotherapy sensitivity between the primary tumour and micrometastases. Despite these limitations, every new generation of adjuvant chemotherapy that has improved disease-free survival and OS has also shown

increased pCR outcomes when administered as neoadjuvant therapy. Overall, more effective cytotoxic regimens are likely to improve disease-free survival and OS if tested in patient populations who remain at substantial risk of disease recurrence. Several statistical models exist that integrate clinical and pathologic variables to calculate the effect of a given improvement in pCR on disease-free survival and OS.[36,37]

Improving survival for patients with residual disease after neoadjuvant chemotherapy

One of the most important developments in the field of neoadjuvant chemotherapy are studies that have shown improved outcomes for patients with residual triple-negative and HER2-positive breast cancer when treated with postoperative adjuvant cytotoxic therapy. The CREATE-X trial[38] evaluated the efficacy of adjuvant capecitabine (1250 mg/m² twice a day on days 1–14, every 3 weeks for 6 to 8 cycles) versus observation in patients with HER2-negative breast cancers who had residual invasive disease after neoadjuvant chemotherapy containing anthracycline, taxane, or both. At 5 years follow up, disease-free survival was 83% in the capecitabine group and 74% in the control group (hazard ratio [HR]=0·7; 95% CI 0·53–0·93, p=0·005). More importantly, 5-year OS also improved with capecitabine when compared to control (89% *vs* 84%, p=0·001). A preplanned subset analysis showed that the benefit in OS at 5 years was restricted to the triple-negative breast cancer group (n=286), with a disease-free survival of 70% in the capecitabine group compared with 56% in the control group (HR=0·58, 95% CI 0·39–0·87). Similarly, OS was 79% in the capecitabine group compared to 70% in the control group (0·52, 0·30–0·90). In the oestrogen receptor-positive subset (n=601), survival differences were not statistically significant. Capecitabine, added to various adjuvant or neoadjuvant chemotherapy regimens, was tested in several smaller randomised trials.[39] Although most of the individual trials have not lead to improved outcomes, a meta-analysis[39] has shown statistically significant improvement in OS outcomes with inclusion of capecitabine in adjuvant chemotherapy regimens. An unplanned subset analysis of these trials suggested that the survival benefit is mostly restricted to oestrogen receptor negative, high risk breast cancers.[40] Two randomised trials are exploring additional treatment options for patients with residual triple-negative breast cancer after neoadjuvant chemotherapy. The EA1131 trial (NCT02445391) is randomising patients to capecitabine for 12 weeks or a platinum drug for four cycles. The SWOG S1418 trial (NCT02954874) is randomising patients with residual triple-negative breast cancer to 1 year of pembrolizumab or observation, which is also allowing the use of adjuvant capecitabine therapy as standard of care before pembrolizumab treatment. The adjuvant B-55/BIG 6-13 trial (NCT02032823) is for patients who have a germline BRCA mutation and have residual triple-negative breast cancer after neoadjuvant chemotherapy, and is randomly assigning patients to olaparib or to placebo.

For HER2-positive breast cancer, a randomised phase 3 clinical trial (KATHERINE) compared adjuvant ado-trastuzumab-emtansine (TDM1) with adjuvant trastuzumab for 14 cycles in 1486 patients with residual disease after neoadjuvant HER2-targeted therapy and chemotherapy.[41] The primary endpoint was invasive disease-free survival. The trial was reported early because it had met its primary endpoint at a pre-specified interim analysis of invasive disease-free survival. At the interim analysis, TDM1 significantly improved invasive disease-free survival when compared with trastuzumab (HR=0·50; 95% CI 0·39–0·64; p<0·0001). Invasive disease-free survival occurred in 91 patients (12·2%) in the TDM1 group and 165 patients (22·2%) in the trastuzumab group. 3-year invasive disease-free survival estimates were 88·3% in the T-DM1 group compared to 77·0% in the trastuzumab group. Distant recurrence was also significantly reduced for those treated with TDM1 (HR=0·60; 95% CI 0·45–0·79). Importantly, improvements were observed in all subsets, including for those patients with oestrogen receptor-positive cancers, and for patients who received both pertuzumab and trastuzumab as part of neoadjuvant therapy. Safety data were consistent with the known safety profile of TDM1, with expected increases in adverse events for TDM1, including, fatigue, neuropathy, and decreased blood counts.

During the KATHERINE trial, two other trials established new standards of care for adjuvant therapy for HER2-positive cancers. The APHINTY trial showed that adding pertuzumab (420 mg every 3 weeks) to adjuvant trastuzumab plus chemotherapy increased the 3-year invasive disease-free survival from 91% to 93% (HR=0·81; 95% CI 0·66–1·00; p=0·045).[42] In the higher risk, node-positive subset (n=3005), 3-year recurrence rates were 9·2% in the pertuzumab group and 12·1% in the control group (HR=0·77; 95% CI 0·62–0·96). In the lower risk, node-negative subset (n=1799), there was no statistically significant improvement in recurrence rate in the pertuzumab group. The US Food and Drug Administration (FDA) approved pertuzumab in combination with trastuzumab and chemotherapy as adjuvant or neoadjuvant treatment for patients with high-risk HER2-positive, early-stage breast cancer. The ExteNET trial showed that 1 year of neratinib (240 mg daily), after completion of 1 year of trastuzumab adjuvant therapy, can also improve invasive disease-free survival when compared to placebo.[43] After a median follow up of 5·2 years, invasive disease-free survival was 90% (95% CI 88–92) in the neratinib group and 88% (95% CI 86–89) in the placebo group (HR=0·50; 95% CI 0·57–0·92, p=0·008). This improvement was primarily driven by the efficacy of neratinib in the oestrogen receptor-positive subgroup (n=1631, HR=0·60, 95% CI

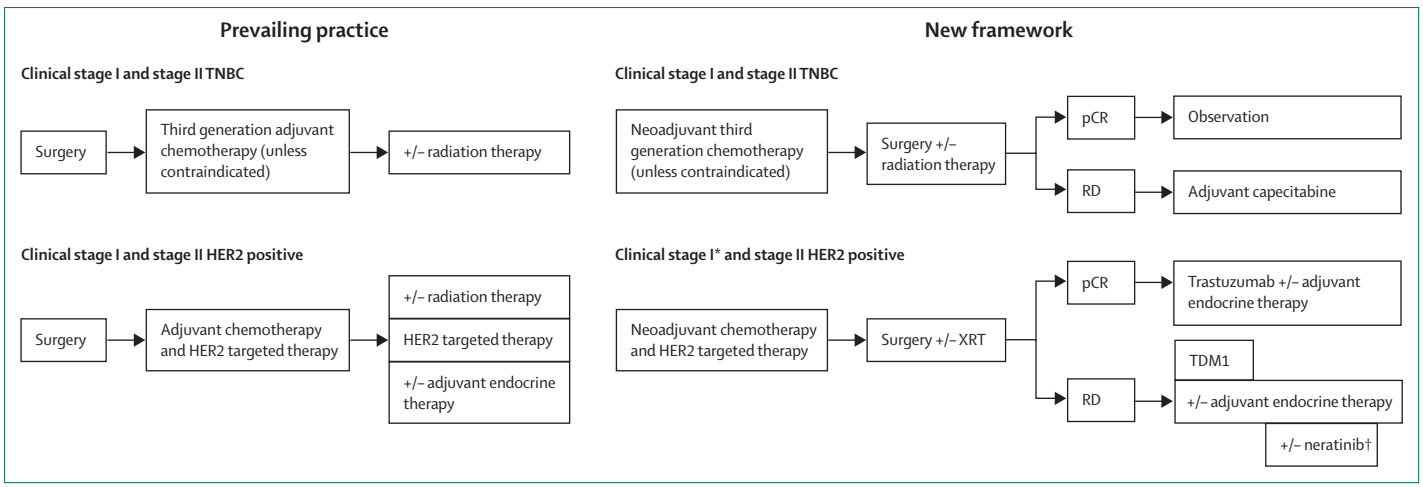

Figure: **Schematic representation of treatment strategies**

Schema focuses on clinical stage I and stage II cancers because, for stage III disease, neoadjuvant chemotherapy has long been the standard of care by causing clinical down staging and because of its beneficial impact on surgery. Most oestrogen receptor-negative stage I and stage II cancers are currently treated with surgery first. For standard of care adjuvant and neoadjuvant chemotherapy regimens and endocrine and HER2 targeted therapies, please consult NCCN, ASCO, ESMO and St Gallen guidelines. *Less than 2 cm, node-negative, oestrogen receptor-positive and HER2 positive cancers in patients >50 years can be treated with surgery first followed by weekly paclitaxel and trastuzumab adjuvant therapy, as in the APT trial. †There are no clinical trial or observational data on the efficacy of neratinib after adjuvant TDM1, since neratinib and concurrent endocrine therapy have different mechanisms of action than TDM1. Administering extended HER2 targeted adjuvant therapy (ie, neratinib) for patients with extensive residual cancer, and therefore high risk for recurrence, might be justified. pCR=pathological complete response (ypT0/ypTis/ypN0). RD=residual disease. TDM1=trastuzumab emtansine. TNBC=triple-negative breast cancer. +/-=with or without

0·43–0·83). For patients with oestrogen receptor-negative breast cancer (n=1209) the HR was 0·95 and was not significant (95% CI 0·66–1·35). The FDA approved neratinib in 2017 for the extended adjuvant treatment of HER2-positive breast cancer after adjuvant trastuzumab-based therapy. The invasive disease-free survival outcomes in the control groups of both trials underscore the importance of identifying the few patients who are at a high risk for recurrence, and therefore could benefit from the inclusion of pertuzumab or extended HER2-targeted adjuvant therapy. Extensive residual disease after neoadjuvant chemotherapy clearly defines a high-risk population and therefore the consideration of aggressive postoperative systemic therapy is reasonable for this population. Both the APHINITY[42] and ExteNET[43] trials included patients who received adjuvant, rather than neoadjuvant, chemotherapy. How to integrate these results with the KATHERINE trial remains unresolved; however, some practical extrapolations can be made. TDM1 has clinical activity in metastatic HER2-positive breast cancers that have received previous pertuzumab and trastuzumab treatments.[44] Consistent with this observation, the KATHERINE trial showed a HR of 0·54 (95% CI 0·27–1·07), suggesting benefit from TDM1 in patients who received trastuzumab and pertuzumab (or another second HER2-targeted agent) in a neoadjuvant setting. Conversely, the MARIANNE trial[45] failed to show superiority of pertuzumab plus TDM1 when compared with TDM1 alone as first-line therapy for metastatic HER2-positive breast cancer. Therefore, the most expeditious strategy might be to treat clinically high-risk, early-stage HER2-positive disease with a trastuzumab and pertuzumab and chemotherapy combination in the neoadjuvant setting, and if residual disease is found at surgery, administer adjuvant TDM1 treatment for 1 year. Patients with oestrogen receptor-positive and HER2-positive disease represent a special challenge because both treatment de-escalation and treatment escalation are supported by clinical trial evidence. The APT treatment de-escalation study (NCT00542451) is a single-arm adjuvant trial that administered weekly paclitaxel (80 mg/m²) concurrently with trastuzumab for 12 weeks, followed by trastuzumab for 1 year, with or without adjuvant endocrine therapy depending on the patient's oestrogen receptor status. This study reported 23 disease-free survival events, with only four (1·0%) distant recurrences at a median follow up of 6·5 years.[46] Of the 406 patients included in the study, 369 (91%) had cancers less than 2 cm, 402 (99%) had node-negative disease, and 272 (67%) were 50 years of age or older at diagnosis. For the 272 patients (67%) with hormone receptor-positive disease, 7-year disease-free survival was 95% (95% CI 92–98). These data show that for cancers smaller than 2 cm, are oestrogen receptor-positive or HER2-positive, are node-negative, and occur in women 50 years or older, a de-escalated chemotherapy regimen (followed by standard of care such as adjuvant endocrine therapy) carries very minimal risk (ie, approximately 1% risk of distant metastatic recurrence at 7 years after treatment). For higher-risk patients (ie, patients that do not fulfill these criteria), more aggressive regimens might be more appropriate. Residual cancer after neoadjuvant chemotherapy represents a high-risk population. In the KATHERINE trial, the HR was 0·48 (95% CI 0·35–0·67)

favouring TDM1 (3-year disease-free survival of 91%) over trastuzumab (3-year disease-free survival of 81%) in the hormone receptor-positive subset, which included 1074 patients. These results indicate that, firstly, the oestrogen receptor-positive patient population in the KATHERINE trial were higher risk than the APT study population. Secondly, TDM1 improves disease-free survival in this population; and, thirdly, some patients remain at an increased risk for recurrence despite receiving TDM1, since the 3-year disease-free survival was approximately 91% in the TDM1 group. HER2-targeted therapies have consistently shown synergy, not only with chemotherapy but with endocrine therapy as well. The ExteNET trial showed benefit from extended HER2 targeted therapy (ie, neratinib) with endocrine therapy and, therefore, it is not unreasonable to assume that neratinib concurrent with endocrine therapy in the second year after completion of TDM1 treatment might further improve therapeutic outcomes in patients with high-risk oestrogen receptor-positive and HER2-positive cancers. However, no evidence from randomised clinical trials exist to show that the addition of neratinib to endocrine therapy benefits this patient population.

Conclusion

The recognition that presence of residual disease after neoadjuvant chemotherapy can be used to guide further adjuvant treatment represents an important framework shift in treatment sequencing of early-stage triple-negative breast cancer and HER2-positive breast cancers (figure). For most patients who require adjuvant chemotherapy for these disease subtypes, preoperative (neoadjuvant) administration of planned chemotherapy has several advantages. First, neoadjuvant chemotherapy can result in a higher proportion of breast conservation and smaller resection volumes in patients with cancers more than 2 cm. Second, neoadjuvant chemotherapy downstages the disease in the axilla with reduction in the extent of axillary surgery. Third, patients who achieve a pCR can be reassured that they have an excellent distant recurrence-free survival. Lastly, and most importantly, patients with residual disease will have the option to receive further effective adjuvant systemic therapies shown to improve long-term outcomes. Adjuvant capecitabine was shown to increase disease-free survival in patients with residual triple-negative breast cancer, and adjuvant TDM1 was shown to increase disease-free survival in patients with residual HER2-positive breast cancer. Patients with HER2-negative and oestrogen receptor-positive breast cancers also have the option of extended HER2-targeted therapy with neratinib concurrent with adjuvant endocrine therapy. This opportunity for residual disease-guided therapy, which can improve survival, is lost when patients undergo surgery first. It is important to emphasise that accurate assessment of pathological complete response is crucial for residual-disease guided adjuvant therapy. Several commonly adopted, but not well studied, surgical and radiotherapy practices can interfere with the assessment of pathological complete response. For example, neoadjuvant radiotherapy to the breast in patients who have achieved a partial response, in the hope of better cosmetic outcomes after breast reconstruction, will prevent accurate assessment of response to chemotherapy. Sentinel node biopsy before surgery that yields a positive node might also prevent pCR assessment because the response of the resected node to chemotherapy can no longer be determined. When considering these interventions, the potential clinical value of sentinel node biopsy before surgery and neoadjuvant radiation therapy should be carefully weighed against the lost opportunity to accurately assess pCR.

The 2017 St Gallen guidelines[47] endorse the use of neoadjuvant therapy as initial treatment for stage II or stag III triple-negative breast cancer and HER2-positive breast cancer, but the NCCN guidelines[48] (2018, version 4) continues to state that "tailoring of therapy based on poor response to standard preoperative chemotherapy has not yet shown improved outcomes".[48] As guidelines are continually adapted documents that evolve as evidence mounts, we suggest that neoadjuvant therapy should be considered as the new standard of care for most triple-negative breast cancer and HER2-positive breast cancers that require systemic adjuvant chemotherapy.

Search strategy and selection criteria

References for this Personal View were identified through searches of Medline and Google Scholar databases and the European Society for Medical Oncology, American Society of Clinical Oncology, and San Antonio Breast cancer symposium abstracts using the search terms "neoadjuvant" and "breast cancer". Articles that were published from Jan 1, 1997, to Nov 30, 2018 were eligible for consideration. Results from papers published in English were considered when drafting the manuscript, but only the most seminal papers were selected for inclusion in the reference list.

Contributors

LP wrote the project proposal and the first draft of the paper. All authors contributed to the literature review, and manuscript discussion and revision. All authors approved the final version.

Declaration of interests

LP reports grants and personal fees from AstraZeneca, Merck, Seattle Genetics, Novartis, Genentech/Roche, Pieris, Almac, Syndax, Immunomedics, Celgene, Boehringer Ingelheim, outside the submitted work. MPD reports royalties from DAKO and NeoMarkers, consulting fees from Merck, clinical trial funding from Roche/Genentech, and prior speaking engagements with Total Health Information Services, outside of the submitted work. EPM reports personal fees from Genomic Helath, Genentech/Roche, Biotheranostics, Merck, Celquity, GRAIL, and Macrogenics, outside the submitted work. All other authors declare no competing interests.

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