

Neoadjuvant treatment of breast cancer

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Neoadjuvant treatment of breast cancer has become established as the safe and often effective therapeutic approach of choice for larger primary and for locally advanced breast cancer. The neoadjuvant approach offers the advantages of downstaging the disease, potentially reducing the extent of surgery and in an era of individualization of therapy, testing the efficacy of therapy administered to patients. The preoperative setting is also an effective way to study the activity of novel agents or therapeutic combinations *in vivo* against human breast cancer. For new therapies, preoperative trials avoid the issue of adaptive resistance and pretreatments that can be problematic in the advanced disease setting. For evidence of a drug targeting the cancer *in vivo*, comparisons of endocrine therapy, chemotherapy agents and/or targeted agents can provide data on activity and efficacy with a much shorter time frame and many fewer patients than for adjuvant trials; effects seen in neoadjuvant trials may even reflect what is found in the adjuvant setting. Patient benefits from the neoadjuvant approach may be greatest for those who experience complete pathologically documented response (and the consequent survival benefits) and women for whom breast conservation, rather than mastectomy, becomes possible.

Key words: biomarker, HER2, neoadjuvant, preoperative, response, targeted therapy

Introduction

The neoadjuvant (preoperative) approach to breast cancer is established as a therapeutic avenue for selected high-risk breast cancers, tumours ≥ 2 cm and for locally advanced (including initially ineligible for resection) disease. The use of neoadjuvant therapy offers several clinical advantages. In patients with large tumours, the use of neoadjuvant therapy is likely to reduce the tumour size and can make patients candidates for surgical resection or can make some patients candidates for breast-conserving surgery rather than mastectomy. Because the primary tumour remains intact during therapy, the neoadjuvant approach allows for monitoring of treatment response and discontinuation of inactive therapy in the event of disease progression, thus saving the patient exposure to potentially toxic therapy. Finally, in patients with estrogen receptor (ER)-negative tumours, it is well documented that a subset will have a complete response to therapy at the time of surgical resection (pathologic complete response, pCR) and that these patients have a notable survival advantage compared with patients who harbour residual disease [1, 2]. More recently, the preoperative setting has become recognized as an *in vivo*, human model system to explore the efficacy of therapies and can also present a short, preoperative ‘window of opportunity’ to look for evidence of tumour targeting by new agents. All three concepts have proven valuable for exploring improvements in breast cancer

treatment, but also helping us to understand breast cancer biology. Indeed, the neoadjuvant approach is no longer unique to breast cancer, but is now proving to be of utility in other tumour types.

neoadjuvant therapy

Even in countries where breast screening is established, substantial numbers of women are diagnosed with cancers greater than 2 cm in size or locally advanced disease and many such patients may be best treated by neoadjuvant endocrine therapy or neoadjuvant chemotherapy before surgery. Reassuringly, neoadjuvant chemotherapy is at least as effective as adjuvant chemotherapy in terms of survival for locally advanced breast cancer [3]. Up to half of the patients undergoing neoadjuvant treatment may become suitable for breast conservation rather than mastectomy. In one systematic review of neoadjuvant chemotherapy for operable breast cancer, patients receiving neoadjuvant chemotherapy had a lower mastectomy rate than those undergoing surgery before adjuvant chemotherapy [relative risk 0.71; 95% confidence interval (CI) 0.67–0.75] without hampering local control (hazard ratio 1.12; 95% CI 0.92–1.37) [4]. Indeed, some patients have a marked reduction in the size of their tumours with neoadjuvant therapy; thus, it is critical to mark the primary tumour at the time of pretreatment biopsy to ensure that the correct portion of breast tissue can be identified and removed. Conversely, the rare occasion where there is little response to neoadjuvant therapy, particularly chemotherapy, is a poor prognostic sign. Thus, multidisciplinary management is required to gain full benefit from the neoadjuvant approach

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involving surgeons, medical oncologists, imagers and pathologists and with due consideration given to co-morbidities and patient circumstances.

pathology

There is a recognized need for core biopsy of the primary to confirm the presence of invasive cancer (tumour fine needle aspiration is insufficient to distinguish between ductal carcinoma *in situ* and invasive cancer) and to establish the ER, progesterone receptor (PR) and HER2 status of the primary cancer, as this will determine the preferred neoadjuvant therapeutic approach. It is also important to determine the molecular features of the tumour at diagnosis since grade and receptor immunohistochemistry can alter following treatment [5]. In addition, there is an established disparity between the ER status (at least) of a core biopsy and subsequent resection specimen, even without intervening therapy, presumably due to issues of tumour fixation [6]. Thus, good-quality core biopsy specimens, preferably taken under ultrasound guidance, are key to neoadjuvant approaches in clinical practice and clinical trials.

effects on nodal disease

The degree of involvement of axillary nodes following neoadjuvant chemotherapy is the strongest predictor of subsequent relapse [7]. Hence, patients undergoing neoadjuvant therapy have, traditionally, proceeded to axillary clearance at the time of mastectomy or breast conservation. However, sentinel lymph node biopsy has become the axillary intervention of choice in breast cancer surgery and some 40% of axillae may convert from positive for disease to show a complete pathologically documented response following neoadjuvant therapy. Suspicious axillary nodes seen on diagnostic imaging should undergo biopsy by fine-needle aspiration or core-needle biopsy to confirm metastatic involvement; however, a negative biopsy or the absence of suspicious nodes on ultrasound does not exclude axillary metastasis. Sentinel lymph node biopsy should be planned at the time of definitive surgical resection of the primary tumour in patients with a 'negative' axillary work-up on the original, prechemotherapy axillary assessment. Some have advocated performing sentinel lymph node biopsy before the administration of neoadjuvant therapy; however, this approach remains controversial as clearance of involved axillary nodes with neoadjuvant therapy is a better prognostic indicator than response in the primary breast tumour alone and removal of the sentinel node does not allow for complete evaluation of pathologic response in the axilla [8]. Others, perhaps more logically, advocate sentinel node biopsy after chemotherapy, citing the reduced need for axillary lymph node dissection for node-negative patients [9]. One recent systematic review and meta-analysis has concluded that sentinel node biopsy is both feasible and accurate in patients who are clinically node-negative after the completion of neoadjuvant therapy [10].

measurement of response

Historically, clinical response to neoadjuvant therapy, preferably supported by mammographic assessment, was

considered a measure of the efficacy of the therapy, particularly in the early days of endocrine therapy for older women.

Advances in ultrasound, magnetic resonance imaging (MRI) and more recently functional imaging with MRI and positron emission tomography/computed tomography mean that in modern practice and clinical trials, ultrasound and MRI are often considered necessary to adequately assess neoadjuvant tumour responses. Nevertheless, mammography may still be used to assess the response of tumours to endocrine therapy in older women given the (usual) lucency of the surrounding normal breast tissues. However, ultrasound has the benefits of relative comfort and simplicity from the patients view point while enabling multiple visits and reproducible three-dimensional imaging for the measurement and documentation of tumour response which does not involve radiation or particularly sophisticated equipment.

During and following neoadjuvant chemotherapy, MRI may be the best currently available imaging to assess the extent of disease and the potential success of breast-conserving surgery [11]. The many subtleties of different MRI approaches and software manipulation of images, the precise timing of MRI in relation to cycles of chemotherapy and the frequency of assessment are all undergoing further research.

pathological response

Clearly, the ideal result for a patient undergoing neoadjuvant chemotherapy is eradication of the malignant disease in the breast and in the axillary lymph nodes (pCR). However, most commonly, some residual invasive and/or preinvasive disease may be identifiable by the pathologist following surgery. Thus, the assessment of the residual disease burden may be of interest. The Residual Cancer Burden (RCB) [12] combines the diameter of the residual primary cancer and the cellularity fraction of the invasive cancer with the diameter of the largest metastasis in the regional lymph nodes in a formula termed the RCB Index. Using measurements made on routine pathology material, the RCB Index identifies near pCR and subgroups of resistant cancers and has been validated as a predictor of distant relapse following anthracycline- or taxane-based neoadjuvant chemotherapy. Furthermore, for patients who receive neoadjuvant chemotherapy and go on to adjuvant endocrine therapy, the Sensitivity to Endocrine Therapy (SET) index [13] uses ER gene expression (of 165 genes) from the primary cancer to predict those patients with an intermediate or high SET who are not likely to suffer distant relapse or death. Most recently, this theme of genomic predictors for resistance or response to neoadjuvant chemotherapy (stratified according to ER status) has been further developed to identify patients with a high probability of survival following taxane and anthracycline chemotherapy [14].

endocrine therapy

Historically, primary endocrine therapy with tamoxifen was the first drug to demonstrate tumour shrinkage either obviating the need for or deferring surgery. This was particularly favoured for older, postmenopausal women with co-morbidities. Acquired tumour resistance (often in parallel with worsened co-morbidities) led to the evolution of thinking

to use neoadjuvant endocrine therapy for a period of weeks or months before surgery. The advent of aromatase inhibitors (AIs) led to comparisons of letrozole versus tamoxifen and demonstration of greater efficacy of the AI over tamoxifen [15]. Recent meta-analysis has demonstrated that neoadjuvant AIs have a better objective clinical and ultrasound response and a higher rate of breast conservation [16]. Clearly, endocrine therapy is only effective for ER-positive disease and may be most effective in the luminal A molecular subtype and lobular breast cancer.

The optimal duration of neoadjuvant AIs in postmenopausal women continues to be debated, but may be 4–6 months for most women, although 37% of patients achieve maximal response after 6–12 months letrozole [17]. While many neoadjuvant endocrine trials have been carried out using letrozole, comparison of the three AIs in common usage: exemestane, anastrozole and letrozole, suggests that all three may be of similar efficacy in the neoadjuvant setting [18].

Other endocrine approaches have included the injectable ‘pure antiestrogen’ fulvestrant for both postmenopausal and premenopausal women and, for premenopausal women, LHRH agonists as a ‘medical oophorectomy’, including in combination with AIs. Neither approaches have gained widespread use; both require injectable endocrine agents and are not likely to lead to a complete pathological response.

endocrine therapy versus chemotherapy

Direct comparisons of neoadjuvant chemotherapy against neoadjuvant endocrine therapy in ER-positive breast cancer are rare. This, in part, reflects the considerable differences in expected toxic effects between the two arms and the evidence that chemotherapies work less well in the neoadjuvant setting against ER-positive disease. A pCR to chemotherapy may be achieved in only 8% of ER-positive cancers compared with 24% in ER-negative tumours [2]. However, in postmenopausal women with ER-positive cancers, response rate and time to response may be similar between chemotherapy and hormonal therapies [19], and the results are awaited with interest for the Neoadjuvant Chemotherapy versus ENdocrine Therapy (NeoCENT) trial comparing letrozole to FEC100 for the treatment of postmenopausal women with ER-positive breast cancers.

chemotherapy

The use of neoadjuvant chemotherapy is often dependent on local preferences and emerging trial data, although reassuringly does not adversely affect survival [3]. Neoadjuvant chemotherapy regimens most commonly contain an anthracycline (adriamycin or epirubicin) in combination or sequentially administered with taxanes (paclitaxel or docetaxel). Anthracycline-based regimens also usually include cyclophosphamide with or without fluoropyrimidines, such as 5-deoxyfluorouridine, to enhance cytotoxicity.

The size of the primary cancer considered suitable for neoadjuvant chemotherapy may be as small as 1 cm in size in some practices, while others restrict the neoadjuvant approach to tumours of 4 cm or larger and locally advanced breast cancer. Emerging evidence from subgroup analyses of

neoadjuvant chemotherapy trials suggests high tumour grade and young age may identify subgroups of patients (e.g. within the luminal or triple-negative breast cancer subtypes) who have an increased benefit from neoadjuvant chemotherapy [20]. Several neoadjuvant chemotherapy trials have informed current clinical practice, combining neoadjuvant chemotherapy with novel agents, is currently achieving success.

Sequential anthracycline–taxane-based chemotherapy in combination with trastuzumab gives a pCR of 40% compared with 17% with the chemotherapy alone [21]. Higher pCR rates are also demonstrated in ER-negative cancers and may be four times as high for ER-negative compared with ER-positive cancers in some neoadjuvant trials [22]. However, higher delivered dose intensity of doxorubicin-based regimens may not result in a significantly higher pCR [23].

HER targeting

The most exciting neoadjuvant trials reporting recently have been those targeting the human epidermal growth factor receptor family, particularly HER2. While sequential anthracycline–taxane-based chemotherapy in combination with trastuzumab may be considered by many the preferred neoadjuvant therapy for HER2-positive primary breast cancer, the NOAH, NEOSPHERE and NeoALTT0 trials have all reached primary end points and ongoing neoadjuvant trials using T-DM1 are in process.

The NOAH trial compared neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone in patients with HER2-positive locally advanced breast cancer [24]. The addition of neoadjuvant and adjuvant trastuzumab to neoadjuvant chemotherapy significantly improved event-free survival in patients with HER2-positive breast cancer (hazard ratio 0.59, 95% CI 0.38–0.90; $P = 0.013$) with only 2% of the patients suffering cardiac toxicity [24]. Thus, adding anti-HER2 therapy to neoadjuvant chemotherapy was clinically advantageous. The NeoALTT0 trial of lapatanib with trastuzumab for HER2-positive early breast cancer has demonstrated synergistic inhibition of HER2 by a tyrosine kinase inhibitor and monoclonal antibody, respectively, added to paclitaxel in the neoadjuvant setting [25]. The pCR at 51% for the dual targeting of HER2 was substantially higher than for either agent alone (pCR 29.5% for trastuzumab and 24.7% for lapatanib), although there were differences in the toxicities among patient groups [25].

The NeoSphere trial investigated the combination of pertuzumab (targeting HER1 and HER2) or trastuzumab, or both, with docetaxel or without chemotherapy in the neoadjuvant setting [26]. The trial stratified women according to whether they had operable, locally advanced or inflammatory breast cancer. Patients given the combined pertuzumab, trastuzumab and docetaxel had the best pCR at 42%, ranging from 26% in those with ER-positive cancers to 63.2% in women with ER-negative cancers. Interestingly, although the pertuzumab with trastuzumab but no chemotherapy patients had a pCR of 12%, this rose to a pCR of 27.3% for the subgroup who were ER-negative [26]. Thus, dual targeting of the HER2 signalling pathway was of

demonstrable benefit in the neoadjuvant setting, confirming preclinical data.

However, despite these recent successes, at least a third of HER2-positive patients are not achieving a pCR even with combination HER2 targeted and chemotherapy combined [26], and so there is still some room for further progress.

radiotherapy

Radiotherapy is not usually considered in the context of neoadjuvant therapy for breast cancer, although dramatic effects on chest wall disease can be achieved against large, locally advanced disease. Unlike oesophageal, rectal or anal cancer, preoperative radiotherapy or chemoradiotherapy has been little studied, or used, in breast cancer.

window of opportunity trials

Window of opportunity trials present clinicians and scientists with the opportunity to study the effects of novel agents against breast cancer *in vivo* for the 2- to 4-week window between diagnosis and surgery. Key to this model is the patient consent to allow (usually additional) core biopsy material from the primary, untreated cancer to be compared with postdrug tumour material, preferably also core biopsy material rather than resected tissue [6], to seek evidence of efficacy of the agent against breast cancer *in vivo*. A clear idea of the target(s) involved is important and early-phase evidence of safety is

needed before a window of opportunity trial can proceed. Such trials may encompass new uses for established drugs (e.g. metformin) [27], molecular-targeted therapies (e.g. RAD001) [28] or novel mechanistic approaches.

The first demonstration of antitumour activity for metformin in women with breast cancer [27] was in this window of opportunity setting and established the antidiabetes drug as having both antiproliferative and insulin suppressing activities *in vivo* in women with breast cancer. Such proof-of-principle activity was predicted by epidemiological and laboratory studies and supports the current adjuvant trial (MA32) of metformin in breast cancer.

The preoperative time frame is increasingly used to examine the effects of novel agents such as the mammalian Target Of Rapamycin (mTOR) inhibitor everolimus (RAD001) [28]. This has provided evidence of the effects of RAD001 in humans substantially reducing proliferation, particularly in HER2-positive cancers. Additional biochemical changes in the tumours, as assessed by immunohistochemistry, can be identified, such as a reduction in phospho-mTOR and phospho-AKT, compatible with the expected mechanisms of action of the drug. In addition to data on (modest) side-effects, this study gained some insight into the tumours most likely to be responsive to mTOR inhibition by RAD001: those with high Ki67, high phospho-AKT and HER2-positive disease [28].

neoadjuvant versus adjuvant

Since early in the development of neoadjuvant trials, one consideration has been whether the neoadjuvant setting might provide evidence for adjuvant activity without the need for the large numbers of patients and such long-term follow-up now required for most adjuvant trials (Table 1).

For chemotherapy trials, the Neo-tAnGo and tAnGo trials of epirubicin/cyclophosphamide and paclitaxel ± gemcitabine in early breast cancer provide one exemplar of chemotherapy trials in the neoadjuvant and adjuvant setting designed to complement each other. The Neo-tAnGo trial data [29] confirmed those of the adjuvant tAnGo trial [30] in terms of the sequencing of the paclitaxel ± gemcitabine (pCR 20%; 95% CI 16–24) before the anthracycline having a significantly greater effect than administering the anthracycline first (pCR 15%; 95% CI 11–18).

The Immediate Preoperative Anastrozole, Tamoxifen or Combined with Tamoxifen (IMPACT) trial [31] tested the hypothesis that the effects of each neoadjuvant therapy in postmenopausal women with ER-positive might predict the outcome of the Anastrozole, Tamoxifen Alone or Combination (ATAC) trial [32]. Both trials demonstrated the greater efficacy of anastrozole over tamoxifen, the lack of benefit of combining tamoxifen with anastrozole and the similar adverse events profile (vaginal discharge and thromboembolic events in patients who received tamoxifen but not in those who received anastrozole). However, the IMPACT trial [31] was not able to demonstrate that short-term clinical response in the intention-to-treat population could be used as a surrogate end point to predict for the adjuvant trial setting (ATAC) [32].

Thus, on the basis of these combinations of drugs and trial designs, the neoadjuvant setting, while producing useful and

Table 1. Summary of neoadjuvant approaches

Neoadjuvant therapy	
Endocrine approaches	
Letrozole—	increase response with longer duration of therapy
Equivalence of anastrozole, exemestane and letrozole	
Chemotherapy	
Efficacy of pCR dependent on regimens used	
Other (targeted) agents—usually in combination with chemotherapy	
NOAH	
NeoSphere	Enhanced efficacy of combinations of
NeoALTTO	Chemotherapy and anti-HER2 therapy
Endocrine agent v chemotherapy	
Neoadjuvant/adjuvant link—some evidence of neoadjuvant reflecting adjuvant data	
IIMPACT/ATAC	
Neo-tAnGo/tAnGo	
Window of opportunity studies	
Biological effects	
Metformin	Evidence of <i>in vivo</i> effects of drugs
Targeted agents	Against primary breast cancer
RAD001	

compatible data for the adjuvant trial, may not completely replace the need for large adjuvant studies.

conclusions

Neoadjuvant approaches to breast cancer treatment have become widely accepted. Achieving complete pathological response after neoadjuvant chemotherapy is associated with better outcomes, with the summary odds ratio estimating the association of overall survival with pCR of 3.44 (95% CI 2.45–4.84), reflecting similar figures for disease-free survival and relapse-free survival [33]. However, it is clear that a tailored approach is required with endocrine therapies only relevant for tumours expressing ER, HER2-targeted therapies against tumours expressing HER2 and neoadjuvant chemotherapies of greater efficacy in ER-negative patients, although considerations around the duration of therapy may be important. In addition to the therapeutic benefits of neoadjuvant therapy, using the window of opportunity between diagnosis and surgical resection of breast cancer presents additional future potential for *in vivo* testing of anticancer agents.

disclosure

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