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Current approaches for neoadjuvant chemotherapy in breast cancer

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Abstract

Compared to adjuvant chemotherapy, the administration of the same regimen in the neoadjuvant setting provides women with identical improvements in disease free and overall survival. Neoadjuvant chemotherapy may offer benefits to properly selected women such as broadening surgical options and enhancing the likelihood of breast conservation. Assessment of response to neoadjuvant chemotherapy provides women with an individualized estimate of prognosis. For example, a woman who achieves a complete pathological response following neoadjuvant chemotherapy has a very low risk of recurrence compared to a woman with similar tumor characteristics and a large residual disease. In this review we will provide a historical perspective and discuss the aims of neoadjuvant chemotherapy in primary operable breast cancer; as well as appropriate patient selection, treatment strategies, response monitoring, and postoperative care. We will also discuss the attractiveness of this approach to study the mechanism of action of standard and novel agents, and the role of predictive biomarkers of response to treatment and outcomes.

Keywords

Breast cancer; neoadjuvant chemotherapy; preoperative chemotherapy; primary chemotherapy; pathological complete response; biomarkers

1 Introduction

Breast cancer-related outcomes have improved in Western societies in recent decades. These improvements are attributed in part to early detection through screening and to more optimal local and adjuvant systemic therapies (Berry *et al.*, 2005). The majority of women with early

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breast cancer will be offered both local and systemic therapies to reduce the risk of recurrence and death. The types and extent of treatment are recommended based on the tumor stage and characteristics such as grade, expression of estrogen and progesterone receptors, and human epidermal growth factor receptor 2 (HER2) status. Traditionally, most women undergo a definitive surgical procedure, which allows for accurate staging, prediction of survival outcomes, and systemic treatment recommendations. Few women present with locally-advanced, unresectable disease and require the administration of systemic treatment prior to local therapy. In these women, the administration of neoadjuvant chemotherapy, also designated primary or preoperative chemotherapy, is often associated with a reduction in tumor volume that facilitates definitive local therapy.

The success observed in the locally advanced setting, the wide implementation of adjuvant chemotherapy, as well as data from preclinical models has led to investigations of neoadjuvant chemotherapy in women with resectable yet large primary tumors. In aggregate, multiple randomized clinical trials have demonstrated that neoadjuvant chemotherapy is associated with identical disease-free and overall survival compared to the administration of the same therapy in the adjuvant setting (Mauri *et al.*, 2005). Neoadjuvant chemotherapy may provide individual women with additional benefits such as improvement of surgical options and enhancement of breast conservation. The approach has also become an attractive model for new drug investigation and for studies of predictive biomarkers of treatment response and outcome. In this review, we will discuss the aims and advantages and disadvantages of neoadjuvant chemotherapy, appropriate patient selection, the necessity for multidisciplinary care, current and investigational treatment strategies, response monitoring, and the promise this approach holds in new drug investigation.

2 Historical Perspectives and Aims of Neoadjuvant Chemotherapy

Historically, women diagnosed with breast cancer were first recommended local therapy, with emphasis on surgical removal of breast tissue and loco-regional lymph nodes. Subsequently, results of multiple randomized clinical trials have demonstrated unequivocally that adjuvant chemotherapy improves disease-free and overall survival (Peto *et al.*, 2012). Adjuvant chemotherapy is commonly recommended to women with stage 2 or 3 breast cancer and to those with high risk stage 1 disease (Carlson *et al.*, 2009). Given the improvements in survival outcomes observed with adjuvant chemotherapy, investigators from the National Surgical Adjuvant Breast and Bowel Project (NSABP) led by Dr. Bernard Fisher hypothesized that, compared to adjuvant chemotherapy, the administration of the same regimen in the neoadjuvant setting would improve survival outcomes by early elimination of micrometastatic systemic disease. Indeed, the hypothesis was supported by early animal studies demonstrating superior outcomes in mice receiving systemic therapy prior to surgical removal of a tumor (Fisher *et al.*, 1989).

One of the initial clinical trials testing the hypothesis, designated NSABP Trial B-18, was designed to determine whether the neoadjuvant combination of 4 cycles of doxorubicin and cyclophosphamide (AC) would more effectively prolong disease-free and overall survival than the same chemotherapy given in the adjuvant setting. Another objective was to determine if the neoadjuvant chemotherapy would permit a more conservative breast surgery and reduce the incidence of ipsilateral breast tumor recurrence by minimizing the tumor size (Fisher *et al.*, 1997). Survival outcomes were identical among the two groups, with hazard ratio (HR) 0.93 (95% confidence interval [CI], 0.81 to 1.06; P=0.27) for disease-free survival and 0.99 (95% CI, 0.85 to 1.16; P=0.90) for overall survival (Rastogi *et al.*, 2008). Although neoadjuvant chemotherapy did not improve disease-free and overall survival, a higher proportion of women who received neoadjuvant therapy were able to undergo breast conserving surgery compared to the adjuvant group (68% and 60%, respectively, P=0.001).

Therefore, a main goal of neoadjuvant chemotherapy is to enhance surgical options and breast conservation (Kaufmann *et al.*, 2006; Kaufmann *et al.*, 2007). Dozens of trials have demonstrated similar results and the administration of neoadjuvant chemotherapy has become an attractive approach to women with stage 2 or 3 breast cancer who are not candidates for breast conservation.

Importantly, the response to therapy is a powerful individualized prognostic factor. Women who achieve a pathological complete response in the breast following neoadjuvant chemotherapy are expected to experience excellent disease-free and overall survival compared to women with large residual disease. In B-18, women achieving a pathological complete response in the breast had superior disease-free survival (DFS) and overall survival (OS) compared to those who did not achieve a pathological complete response (DFS HR=0.47, P=0.0001; OS HR=0.32, P=0.0001) (Rastogi *et al.*, 2008).

Different groups have used varied definitions of pathological complete response which may have indicated absence of invasive disease in the breast, or both in the breast and lymph nodes (Kuerer *et al.*, 1999; Carey *et al.*, 2005). Others have proposed more continuous definitions such as a residual stage or combination of anatomical and histopathological features (Chevallier *et al.*, 1993; Sinn *et al.*, 1994; Sataloff *et al.*, 1995; Symmans *et al.*, 2007). Regardless, in each of these reports, absence of disease in both the breast and lymph nodes provides the best overall outcome.

Investigations of neoadjuvant chemotherapy over the years have produced additional value by both providing data regarding selection of agents or combinations and the appropriate identification of patient populations most likely to benefit from the approach. Women should be observed closely during treatment and if there is a concern for progressive disease they should be transitioned to an alternative regimen or to a local treatment. Finally, the neoadjuvant treatment approach has become an important vehicle for new drug and biomarker investigation. Response can be assessed clinically or with standard and functional imaging. Moreover, access to tumor tissue is relatively non-invasive and allows both for assessment of biomarker modulation following standard or novel treatment and the study of drug mechanism of action.

Women should be informed that neoadjuvant chemotherapy may be associated with potential disadvantages. Initial studies raised concern that breast conserving surgery was associated with increased locoregional recurrence risk. However, newer studies suggest that with adequate free margins, the risk of locoregional recurrence is not higher in women administered neoadjuvant chemotherapy compared to those receiving the same regimen in the adjuvant setting. Another concern is that the inability to determine an accurate pathological stage may be a disadvantage of neoadjuvant chemotherapy. However, the knowledge of residual disease may provide a more personalized prognostic value.

Since disease-free and overall survival are equivalent when the same regimen is administered in the adjuvant or neoadjuvant setting, discussions with an individual woman should focus on the potential benefits and possible disadvantages she may encounter. Once neoadjuvant chemotherapy is initiated, women should be well informed of the goals of treatment, the required preoperative assessment, monitoring response, local treatment considerations, and post-treatment evaluation.

3 Selection of Patients

Members of an International Consensus Expert Panel have suggested that neoadjuvant chemotherapy should be considered in any individual for whom adjuvant chemotherapy is indicated (Kaufmann *et al.*, 2006; Kaufmann *et al.*, 2007). Once a decision has been made to

administer chemotherapy, the entire recommended chemotherapy regimen should be ideally delivered prior to the local therapy. Therefore, a careful staging evaluation must take place prior to initiation of treatment to assess the extent of the disease within the breast and regional lymph nodes, to exclude distant metastatic sites of disease, and to characterize the tumors, as described in Section 4. Initial clinical trials of neoadjuvant chemotherapy have generally included women with stage 2 or 3 disease regardless of their tumor characteristics. More recent understanding of tumor biology has led to refinement of the criteria of women who should be considered for neoadjuvant chemotherapy based on the likelihood of achieving a pathological complete response. Improvements in disease-free survival in those achieving pathological complete response were observed in luminal B/HER2-negative, HER2-positive/non-luminal, and triple-negative breast cancer; but not in luminal A, or luminal B/HER2-positive tumors (Untch *et al.*, 2012). Importantly, pathological complete response in HER2-positive (non-luminal) and triple-negative tumors was associated with excellent overall outcome.

Women with stage 2 or 3 disease whose tumors do not express ER/PR or whose tumors are HER2-positive should be considered for neoadjuvant chemotherapy. Women whose tumors are low grade with a high expression of the hormone receptors and that are HER2-negative are less likely to respond to cytotoxic therapy and should be considered for primary surgery, especially when the nodes are clinically negative. Those women may not require chemotherapy or may be recommended a less aggressive systemic regimen. Women with a limited number of positive nodes may also be eligible for clinical trials randomly assigning them to chemotherapy versus no chemotherapy based on molecular characteristics. For example, in the S1007 trial (RxPONDER) women with hormone receptor-positive, HER2-negative breast cancer with 1–3 positive nodes and a recurrence score of 25 or less are randomly assigned to standard adjuvant endocrine therapy with or without adjuvant chemotherapy (NCT01272037). Of note, women with large hormone receptor-positive cancers may be candidates for neoadjuvant hormone therapy, an approach discussed elsewhere in this issue.

4 Preoperative Assessment

Prior to initiating neoadjuvant chemotherapy it is essential to provide an accurate clinical stage and to determine tumor characteristics. Staging should include imaging studies such as a CT scan of the chest and abdomen and a bone scan, or a Positron-Emission Tomography (PET) (Carlson *et al.*, 2009). When breast conservation is contemplated, careful baseline breast imaging should be performed to identify the tumor location and to exclude a multicentric disease. Every suspicious abnormality should be biopsied prior to commencing the systemic therapy and a marker should be placed at the center of the breast tumor(s). When possible, suspicious axillary nodes should be biopsied prior to initiation of systemic treatment.

The optimal timing of sentinel node mapping has not been established. If the axillary nodes appear benign on imaging such as with an ultrasound of the axilla, sentinel lymph node mapping should be considered. The benefit for assessment of nodal status prior to systemic therapy is to allow the radiation oncologist to determine need for and extent of radiation therapy. A disadvantage, however, is that positive nodes at baseline would usually lead to a recommendation for an axillary node dissection at the time of definitive surgery. Since sentinel node evaluation is fairly reliable following neoadjuvant chemotherapy, with the exception of women with inflammatory breast cancer, it is also reasonable to consider performing the procedure following the neoadjuvant therapy, which with down-staging may eliminate the need for a nodal dissection in many women (4). However, in women whose

nodes were positive at baseline the false negative rate of sentinel node mapping following the neoadjuvant chemotherapy may be as high as 20% (Alvarado *et al.*, 2012).

In addition to proper clinical staging of the disease, it is critical to characterize the cancer microscopically. Generally a core biopsy is preferred which allows for evaluation of the architecture of the breast. An initial core biopsy should be of adequate quality demonstrating that the majority of the specimen contains invasive disease and to perform routine marker studies including evaluation of estrogen and progesterone receptors and HER2.

5 Systemic Therapy

The optimal regimen and duration of neoadjuvant chemotherapy have not been established. Given that women who are recommended neoadjuvant chemotherapy present with a stage 2 or 3 breast cancer, the general consensus is that those with HER2-negative disease should be offered a third generation chemotherapy regimen, and those with HER2-positive disease should receive trastuzumab-based regimens. Ideally, the entire chemotherapy regimen should be administered prior to the definitive surgery.

5.1 HER2-negative

In women whose tumors are HER2-negative, the mainstay of treatment consists of cytotoxic agents. Results from several adjuvant trials have demonstrated that the use of third generation regimens that contain anthracyclines and taxanes are superior to first and second generation regimens that contain anthracycline-based regimens alone, or these that are administered in a less intensive manner. Several studies in the neoadjuvant setting have mirrored large adjuvant studies. In NSABP B-27, 2,411 women with primary operable breast cancer were randomized to one of three groups: AC followed by surgery (group I), AC followed by docetaxel, followed by surgery (group II), or AC followed by surgery and then docetaxel post-operatively (group III). The administration of neoadjuvant AC followed by docetaxel was associated with a higher clinical complete response rate compared to the administration of AC alone (63.6% and 40.1%, respectively, $P<0.001$) and a higher pathological complete response rate (26.1% and 13.7%, respectively, $P<0.001$) (Bear *et al.*, 2003).

Women enrolled in the Aberdeen Breast Group Trial (Tax 301) received neoadjuvant CVAP combination (cyclophosphamide, doxorubicin, vincristine, and prednisolone) and were assessed following 4 cycles. Those with a complete or partial response to the regimen were randomly assigned 4 additional cycles of CVAP or 4 cycles of docetaxel, while those who did not respond were transitioned to docetaxel. Of the 162 patients enrolled in the trial, 66% achieved a clinical response and were randomized to continue CVAP or to transition to docetaxel. The clinical complete and partial responses were superior in the group randomized to docetaxel compared to the group that continued CVAP (94% and 66%, respectively, $P=0.001$). Likewise, the pathological complete response rate was superior in the docetaxel arm compared to the CVAP arm (34% and 16%, respectively, $P=0.04$). In those who did not respond to CVAP, a transition to docetaxel was associated with a response rate of 55% and a low pathological complete response rate of 2% (Smith *et al.*, 2002). With a median follow up of 38 months, patients randomized to docetaxel had significantly improved disease-free and overall survival compared with patients who continued to receive CVAP; disease-free survival rates were 90% and 77%, respectively ($P=0.03$) and 3-year survival 97% and 84%, respectively ($P=0.05$) (Hutcheon *et al.*, 2003).

Data from NSABP B-27 and Aberdeen Breast Group Trial support the use of anthracycline- and taxane-based regimens in both women with initial response or with relative resistance to anthracyclines. These results coupled with data from large adjuvant studies suggest that,

outside of clinical trials, candidates for neoadjuvant chemotherapy should be offered a third generation regimen (Table 1) (Carlson *et al.*, 2009).

In several recent trials investigators have evaluated the role of new cytotoxic agents or novel therapies when added to third generation regimens. In GeparQuattro, 1,421 patients received 4 cycles of neoadjuvant epirubicin and cyclophosphamide (EC) and randomized to transition to either 4 cycles of docetaxel (T), versus 4 cycles of docetaxel and capecitabine combination (TX), or 4 cycles of docetaxel followed by capecitabine (T-X). The addition of capecitabine to the anthracycline and taxane regimen did not provide a significant improvement in pathological complete response rate (22.3%, 19.5%, and 22.3% for EC-T, EC-TX, and EC-T-X, respectively) or breast conservation rates (70.1%, 68.4%, and 65.3%, for EC-T, EC-TX, and EC-T-X, respectively) (von Minckwitz *et al.*). Concomitant (but not sequential) treatment of capecitabine with docetaxel was associated with increased toxicity including diarrhea, nail changes, and hand-foot-syndrome.

In GeparQuinto, patients with HER2 negative tumors received neoadjuvant EC with or without concomitant use of the anti-angiogenic agent bevacizumab, and responders were transitioned to docetaxel, with or without concomitant bevacizumab according to the assignment in the EC portion of the trial. Non-responders were randomly assigned to weekly paclitaxel with or without everolimus. Results from the EC and docetaxel with or without bevacizumab portion of the trial revealed that, among 948 randomized participants, pathological complete response was 14.9% in the EC followed by docetaxel arm (EC-T), compare to 18.4% with EC followed by docetaxel and bevacizumab (EC-TB) (odds ratio [OR] 1.29 95% CI, 1.02–.65, $P=0.04$) (von Minckwitz *et al.*). Among patients with triple negative tumors, pathological complete response was 27.9% and 39.3%, in the EC-T and EC-TB arms respectively ($P=0.003$). In contrast, there was no difference in pathological complete response rate among hormone receptor-positive women (7.8% and 7.7%, in the EC-T and EC-TB arms respectively $P=1.00$). Breast conservation and surgical complication rates were similar between the arms. However, the addition of bevacizumab was associated with a higher incidence of significant toxicity including febrile neutropenia, mucositis, hand-foot syndrome, infection, and hypertension, compared to chemotherapy alone.

In NSABP B-40, 1,206 patients were randomly assigned to one of 6 docetaxel-containing regimens: 1) docetaxel, 2) docetaxel/bevacizumab, 3) docetaxel/capecitabine, 4) docetaxel/capecitabine/bevacizumab, 5) docetaxel/gemcitabine, or 6) docetaxel/gemcitabine/bevacizumab. Each regimen was followed by 4 cycles of AC (arms 1, 3, 5) or 4 cycles of AC and 2 cycles of bevacizumab (arms 2, 4, 6). The addition of capecitabine or gemcitabine to docetaxel did not improve pathological complete response rate compared to single agent docetaxel (29.7%, 31.8%, 32.7%, for docetaxel, docetaxel/capecitabine, and docetaxel/gemcitabine, respectively, $P=0.69$). However, the addition of bevacizumab was associated with improved pathological complete response (28.2% without and 34.5% with bevacizumab, $P=0.02$) (Bear *et al.*, 2012). Interestingly, the benefits of bevacizumab were significant in the hormone receptor-positive group (pathological complete response 15.1% without and 23.2% with bevacizumab, $P=0.007$) but not in the hormone receptor-negative group (pathological complete response 47.1% without and 51.5% with bevacizumab, $P=0.34$). In addition, the bevacizumab-containing arms were associated with higher rates of hypertension, left ventricular systolic dysfunction, mucositis, and hand-foot syndrome.

While the addition of bevacizumab was overall associated with an increased pathological complete response rate in both NSABP B-40 and in GeparQuinto, it is not clear that the modest benefit will translate into a significant survival benefit. Importantly, results of studies in the metastatic setting failed to demonstrate overall survival benefit for the addition of bevacizumab to cytotoxic therapy compared to cytotoxic therapy alone. Results from

E5103 (NCT00433511) in which women were randomized to adjuvant AC followed by paclitaxel with or without one of 2 schedules of bevacizumab, and other studies in which biomarkers of response to the agent are evaluated, will help further assess whether bevacizumab provides survival benefits, and whether specific patient or tumor characteristics would predict benefit from this therapy. Until results from E5103 and other studies evaluating biomarkers of response to bevacizumab are available, we cannot recommend the use of this agent in the adjuvant or neoadjuvant setting.

As the incorporation of additional cytotoxic agents or bevacizumab to anthracycline and taxane-based regimens has not offered a significant additional benefit to breast conservation or pathological complete response rate, new treatments are urgently needed for women with high risk primary breast cancer. The neoadjuvant setting remains an attractive approach to test promising new combinations in women with triple negative breast cancer or those with luminal B disease. Other cytotoxic agents such as carboplatin or cisplatin are currently under study in the neoadjuvant setting, especially in triple negative disease. Novel agents under investigation include anti-angiogenic agents, agents that inhibit the mammalian target of rapamycin (mTOR) pathway, poly-ADP-ribose polymerase (PARP) inhibitors, epigenetic modulators, and many others.

5.2 HER2-positive

The addition of trastuzumab to chemotherapy has led to a considerable reduction in both recurrence and death from breast cancer in the adjuvant setting. The NSABP B-31/NCCTG-N9831 and HERA adjuvant clinical trials have demonstrated that the addition of one year of trastuzumab to adjuvant chemotherapy regimens (predominantly anthracycline and taxane-based) in a HER2-positive population resulted in an approximately 50% reduction in breast cancer recurrence and 35% reduction in mortality (Piccart-Gebhart *et al.*, 2005; Romond *et al.*, 2005). Following the success in the adjuvant setting, initial reports from phase II studies indicated impressive pathological complete response rates when trastuzumab was added to neoadjuvant anthracycline and taxane-based regimens. Concurrent paclitaxel and trastuzumab, followed by concurrent FEC (5-fluorouracil, epirubicin, cyclophosphamide) and trastuzumab yielded a pathological complete response rate of 60%, without an increase in cardiac toxicity, compared to chemotherapy alone (Buzdar *et al.*, 2007). A non-anthracycline-based approach combining carboplatin, weekly paclitaxel, and trastuzumab was associated with a pathological complete response rate of 76% (Sikov *et al.*, 2009).

These results have been confirmed in the phase III setting. In the NeOAdjuvant Herceptin (NOAH) trial, the addition of trastuzumab to three cycles of doxorubicin and paclitaxel, followed by four cycles of paclitaxel and three cycles of CMF (cyclophosphamide, methotrexate, 5-fluorouracil) was associated with an improvement in outcomes compared to chemotherapy alone, including overall response rate (81% versus 73%, $P=0.18$) and pathological complete response rate (43% versus 23%, $P=0.002$) (Gianni *et al.*, 2010). Finally, GeparQuattro trial ($n=445$) reported a pathological complete response (no invasive or in situ tumor in breast) rate of 31.7% with EC followed by docetaxel and trastuzumab versus 15.7% for those receiving chemotherapy alone (Untch *et al.*, 2010). Based on both the adjuvant and neoadjuvant results available to date, trastuzumab should be incorporated in the neoadjuvant treatment strategy for women with HER2-positive early breast cancer (Table 1).

More recently, other HER2-targeted therapies such as lapatinib (a dual HER2/EGFR tyrosine kinase inhibitor) and pertuzumab (a HER2 dimerization inhibitor) have been incorporated into neoadjuvant regimens. GeparQuinto was a phase III trial which randomized 620 patients with operable or locally advanced HER2-positive breast cancer to neoadjuvant EC followed by docetaxel, concurrent with either trastuzumab or lapatinib

(Untch *et al.*, 2012). Pathological complete response (defined as no invasive tumor in breast or axillary nodes) was 30.3% in the trastuzumab arm and 22.7% in the lapatinib arm ($p=0.04$). The authors recommended that lapatinib should not be utilized as single agent anti-HER2 therapy neoadjuvantly outside of a clinical trial.

NeoALLTO was another phase III multicenter randomized trial which investigated the efficacy of neoadjuvant paclitaxel administered with either lapatinib, trastuzumab or concomitant lapatinib and trastuzumab, in patients with HER2-positive breast cancer ($n=455$) (Baselga *et al.*, 2012a). Patients were randomized to initially receive 6 weeks of a “biological window” of either lapatinib, or trastuzumab, or both. Subsequently the same targeted therapy was continued with weekly paclitaxel for additional 12 weeks, until definitive surgery. After surgery, patients received 3 cycles of adjuvant FEC followed by the same targeted therapy as in the biological window of the neoadjuvant phase for a further 34 weeks (to complete 52 weeks of anti-HER2 therapy). Pathological complete response (no invasive tumor in the breast) was significantly higher in the combination arm (lapatinib plus trastuzumab) compared with the trastuzumab arm (51.3% and 29.5%, respectively, $P=0.0001$), indicating that dual blockade of the HER2 pathway is a valid concept. There was no significant difference in pathological complete response between the trastuzumab and lapatinib arms (29.5% vs. 24.7% respectively, $P=0.34$). No major cardiac dysfunctions or toxic deaths were observed during the neoadjuvant phase. There was increased, but manageable, toxicity (mainly diarrhea and liver enzyme alterations) in the lapatinib arms. These results were corroborated by the phase II CHER-LOB trial ($n=121$), in which women received 12 weeks of neoadjuvant paclitaxel followed by 4 cycles of FEC, all concurrent with trastuzumab, lapatinib, or trastuzumab plus lapatinib (Guarneri *et al.*, 2012). Although a formal comparison between the arms was not performed, the pathological complete response rates (no invasive tumor in breast or axillary nodes) again favored the dual anti-HER2 therapy arm (25% vs. 26.3% and 46.7%, respectively, $P=0.19$).

The addition of the novel anti-HER2 agent pertuzumab to neoadjuvant regimens has also been investigated in this patient population. Pertuzumab is a humanized monoclonal antibody and is the first of a novel class of HER2-targeted agents known as HER2 dimerization inhibitors. It has recently been approved by the Food and Drug Administration (FDA) for use in the metastatic setting based on a progression free survival benefit observed with trastuzumab/pertuzumab and docetaxel versus trastuzumab and docetaxel alone (Baselga *et al.*, 2012b). NeoSphere was a Phase II randomized trial of preoperative systemic therapy comparing trastuzumab/docetaxel, trastuzumab/pertuzumab/docetaxel, trastuzumab/pertuzumab and pertuzumab/docetaxel. The pathological complete response rates (no invasive tumor in breast) were 29%, 46%, 17% and 24%, respectively. When patients were analyzed based on estrogen receptor status, a 63% pathological complete response rate was observed in those with ER-negative disease treated with trastuzumab/pertuzumab/docetaxel and 27% in those with ER-negative disease treated with trastuzumab/pertuzumab (Gianni L *et al.*, 2010). That a large proportion of women treated with biological therapy alone can obtain a pathological complete response has caused great excitement in the breast oncology community, as these patients could potentially be spared the added toxicity of chemotherapy if properly identified upfront.

A number of studies are ongoing or have been completed evaluating dual anti-HER2 therapies alone in the neoadjuvant setting. A phase II neoadjuvant study of lapatinib and trastuzumab in patients with operable HER2-positive breast cancer has been presented (Chang JCN *et al.*). Patients received 12 weeks of anti-HER2 therapy pre-operatively, as well as letrozole with or without goserelin if they had ER-positive disease (approximately 60% of study population). The overall pathological complete response rate (no invasive tumor in breast) was 28%, with a 21% rate for patients with ER-positive tumors and 40% for

those with ER-negative disease. The treatment was well tolerated and clinical responses were observed a few weeks after starting therapy. Another study is evaluating whether longer duration (12 versus 24 weeks) of anti-HER2 therapy with lapatinib and trastuzumab prior to surgery will result in a higher rate of pathological complete response (NCT00999804). Clinical trials with other novel anti-HER2 therapies are in the planning stages, such as those incorporating the antibody-drug conjugate trastuzumab-emtansine (T-DM1).

6 Monitoring Response to Therapy

Once a patient has commenced neoadjuvant therapy, regular assessment of response to therapy clinically, and if a candidate for breast conservation also radiologically, by the multidisciplinary oncology team is essential. Those with evidence of stable disease or response to therapy should continue the outlined treatment plan. For patients with progressive disease, either a transition to a non-cross-resistant regimen or proceeding with a surgical intervention for the operable disease is necessary.

Support for transitioning poor responders to an alternate regimen can be obtained from a number of trials. As noted in section 5.1, in the Aberdeen trial, a transition to a non-cross-resistant agent (docetaxel) in those responding to an initial anthracycline-based regimen, resulted in an improvement in pathological complete response and survival compared to those who continued on the anthracycline-based regimen (Smith *et al.*, 2002). Patients not responding to therapy after two cycles of docetaxel, doxorubicin, and cyclophosphamide (TAC) in the GeparTrio trial were randomized to four further cycles of TAC or to vinorelbine and capecitabine (NX). The pathological complete response rates were low in both arms (approximately 6%) with equal rates of breast conservation (approximately 60%). In patients who responded to the first two cycles of TAC, treatment intensification to six vs four additional cycles of TAC did not improve pathological complete response rates (23.5% and 21%, respectively, $P=0.27$) and was associated with a higher degree of toxicity (von Minckwitz *et al.*, 2008b; a).

Although switching to a non-cross-resistant regimen is noted to result in a higher pathological complete response rate and is generally recommended when progression through chemotherapy is observed, there is no clear evidence that other breast cancer outcomes are improved with this approach. Further study is therefore warranted to optimize treatment decisions in this patient population.

Finally, evaluation of response to therapy as outlined above is also necessary to determine the optimal surgical interventions in each individual case. This is of particular importance where breast conservation is the desired approach.

7 Postoperative Therapy

The entire planned course of cytotoxic chemotherapy should be administered prior to surgery, other than in the setting of a clinical trial. In cases where a pathological complete response is not obtained, there is currently no clear role for adjuvant chemotherapy, even in the setting of significant residual disease. However, clinical trials of novel therapies should be considered in these individuals. An example is a phase II randomized study of adjuvant bevacizumab, metronomic chemotherapy, diet and exercise after preoperative chemotherapy for breast cancer (ABCDE) in which high-risk patients with all breast cancer subtypes to 3 years of adjuvant bevacizumab with or without a dietary intervention (NCT00925652). Other studies will target women with HER2- positive residual disease post neoadjuvant anthracycline-taxane based chemotherapy who will be randomized to adjuvant trastuzumab or T-DM1.

The administration of radiation therapy following breast conservation is recommended to all women who have received neoadjuvant therapy in order to reduce the risk of locoregional recurrence. Baseline clinical extent of disease and pathologic extent of residual disease is useful in guiding the decision to prescribe post-mastectomy radiation. For those with baseline clinical stage 3 disease or positive lymph nodes on pathological review following neoadjuvant therapy, chest wall and regional nodal radiation should be considered. The role of post-mastectomy radiation in women with clinical stage 2 disease who have negative lymph nodes following chemotherapy is under investigation (Buchholz *et al.*, 2008). A number of retrospective analyses have suggested, for example, that post-mastectomy radiation may not benefit those with clinical stage 1 or 2 disease and who obtain a pathological complete response with neoadjuvant chemotherapy. A retrospective study from MD Anderson Cancer Center investigators identified 32 patients with these characteristics and found that the 10-year rates of loco-regional recurrence was 0% in both irradiated and non-irradiated groups (n=20) (McGuire *et al.*, 2007). Larger prospective studies are warranted in order to definitively answer this question.

Other adjuvant systemic treatments may be recommended either post-operatively, or during/ following completion of adjuvant radiation. At least 5 years of an adjuvant hormonal therapy such as tamoxifen or an aromatase inhibitor is recommended for the majority of patients with hormone-responsive breast cancer (Buzdar *et al.*, 2008). Finally, based on the beneficial results observed in the adjuvant setting, maintenance trastuzumab should be continued for a total of 52 weeks (or 1 year) in patients with HER2-positive disease, and may be administered during radiation.

8 Predictive Biomarkers of Treatment Response and Outcome

The preoperative period has been accepted as an important setting for evaluation of surrogate biomarkers for both response to therapy and the prediction of clinical outcome. Neoadjuvant clinical trials can provide important information using far smaller numbers of patients and a shorter follow up interval than traditional large adjuvant therapy trials. With this model, tumor response to therapy can be assessed determination pathological response or by exploiting biochemical or radiologic changes in malignant tissue prior to, during, and following neoadjuvant therapy.

The most utilized surrogate predictor of long term outcome in neoadjuvant clinical trials is pathological complete response. Despite the varied definitions in trials completed to date, it has been consistently demonstrated that pathological complete response is associated with superior disease-free and overall survival (Wolmark *et al.*, 2001). In a recent meta-analysis which included 3,776 patients in 16 studies, pathologic response was a prognostic indicator for relapse-free survival, disease-free and overall survival, confirming that patients achieving pathological complete response after neoadjuvant chemotherapy have favorable outcomes (Kong *et al.*, 2011). Women without residual invasive and noninvasive tumor cells in the breast and axillary nodes have substantially improved outcomes compared to women with similar stage and tumor characteristics and extensive residual disease. pathological complete response has been therefore utilized as a surrogate for outcome in patients receiving neoadjuvant therapy. Indeed in a recent guidance, the FDA has proposed that the rate of pathological complete response obtained with a neoadjuvant treatment strategy may be used as a surrogate endpoint to facilitate accelerated approval (Prowell & Pazdur, 2012). An improvement in disease-free or overall survival is then required for full approval of the treatment strategy.

It is possible that combining the standard definition of pathological complete response with other pathological factors or clinical stage at diagnosis may lead to improved

prognostication in this group of patients. Residual cancer burden (RCB) calculated as a continuous index combining pathologic measurements of primary tumor (size and cellularity) and nodal metastases (number and size), can be used to define categories of near-complete response and chemotherapy resistance. In addition, it was independently found to be a significant predictor of distant relapse-free survival. For example, minimal residual disease (RCB-I) in 17% of patients carried the same prognosis as pathological complete response (RCB-0) and extensive residual (RCB-III) was associated with poor prognosis irrespective of hormone receptor status, adjuvant hormone therapy, or pathologic stage of residual disease (Symmans *et al.*, 2007). A proposed novel staging system which incorporates initial clinical stage, biologic markers from the primary tumor (estrogen receptor status and tumor grade) along with the final pathologic stage may also provide more refined information on prognosis after administration of neoadjuvant chemotherapy (Mittendorf *et al.*, 2011).

Ideally, standard and novel surrogate biomarkers can be used early in the treatment paradigm to predict response to neoadjuvant chemotherapy. An attractive biomarker is one that can separate sensitive and resistant tumors to specific agent(s) early in the course of therapy could be used to modify treatment early in the course. Such determination will reduce the risk of patients receiving toxic yet futile therapies, and direct other patients towards an aggressive or investigational approach in an effort to maximize their survival outcomes. A marker can be determined at baseline, or shortly after initiation of neoadjuvant therapy.

Standard clinicopathologic factors such as age, estrogen receptor or HER2 status, grade, and proliferation index are already used routinely in clinical practice to determine the choice of therapy for those with early breast cancer. In addition to studies of single genes or proteins, gene-expression profiling allows for the rapid assessment of multiple genes simultaneously using high-throughput techniques and may be used to predict both response to therapy and clinical outcome. Several trials have evaluated multigene assays as predictors of response to therapy in the neoadjuvant setting, and validation efforts are ongoing (Ayers *et al.*, 2004; Gianni *et al.*, 2005; Chang *et al.*, 2008). A pooled analysis of publicly available gene expression studies evaluating neoadjuvant chemotherapy aimed to identify breast cancer subtype-specific associations between pathological complete response and gene modules describing biologically relevant cancer pathways (Ignatiadis *et al.*, 2012). Chromosomal instability and PTEN loss modules were associated with an increased rate of pathological complete response with anthracycline with or without taxane-based neoadjuvant chemotherapy in ER-negative/HER2-negative and ER-positive/HER2-negative cancers. A high value of IGF1 activation module was also associated with high pathological complete response rate in the ER-positive/HER2-negative subtype and in luminal B tumors. When the immune module was combined with clinicopathologic characteristics, investigators observed a substantial increase in predictive accuracy for pathological complete response in the HER2-positive breast cancers. These initial biomarker studies are intriguing but require validation in large studies with long term outcomes.

The molecular tools developed thus far, however, offer little aid in clinical decisionmaking for women with ER-negative or HER2-positive disease, and improved prognostic and predictive tools for these patients are needed. Host genetic factors such as *BRCA1* or *BRCA2* mutation status are also under investigation as potential predictors of response to neoadjuvant chemotherapy in general or to specific agents.

Imaging techniques can also provide early information regarding tumor response. MRI correctly predicts residual tumor in 63% of cases, followed in order of sensitivity by clinical examination, ultrasound, and mammography (Balu-Maestro *et al.*, 2002). PET might allow

for early prediction of pathologic response following one or two cycles of neoadjuvant chemotherapy. A recent meta-analysis of 19 studies and 920 patients with pathological complete response aimed to predict histopathological response in primary breast lesions by PET. The pooled sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) were 84%, 66%, 50% and 91%, respectively. Subgroup analysis showed that performing a post-therapy PET early (after the 1st or 2nd cycle of chemotherapy) was significantly better than scan performed following 3 or more cycles (accuracy 76% vs. 65%, $P=0.001$). In addition, the best correlation with pathology was yielded by employing a reduction rate (RR) cutoff value of standardized uptake value between 55 and 65% (Wang *et al.*, 2011). Similar findings have been observed in a clinical trial evaluating an association with even earlier changes in SUV (after 2 weeks of commencing therapy) with response to neoadjuvant chemotherapy in patients with high grade ER-positive or triple negative breast cancer (Connolly RM *et al.*).

The NeoALLTO PET substudy is the first to prospectively evaluate changes in SUV on PET as a predictor of response to neoadjuvant anti-HER2 therapy ($n=86$, 77 evaluable) (Gamez C *et al.*, 2011). PET scans were performed at baseline, week 2 and week 6 after starting therapy. A metabolic response was defined as greater than 15% reduction in SUV at 2 weeks, or greater than 25% reduction at 6 weeks per EORTC criteria (Young *et al.*, 1999). At week 2, metabolic responders had a pathological complete response rate of 42% and non-responders 21%. At week 6, metabolic responders had a pathological complete response rate of 44% compared to 19% at non-responders. Further prospective studies are recommended to adequately position MRI and PET in treatment management for breast cancer patients.

9 Discussion

Neoadjuvant chemotherapy has traditionally been recommended to women with locally advanced breast cancer, being employed predominantly to downstage inoperable tumors and allow for definitive surgery. Current consensus opinion for use of preoperative chemotherapy recommends anthracycline- and taxane-based therapy. This recommendation is based on data from several prospective trials which suggest that neoadjuvant anthracycline- and taxane-based therapy is associated with the highest response rates (Bear *et al.*, 2003; Smith *et al.*, 2005; Sparano *et al.*, 2006). Multidisciplinary management of patients undergoing neoadjuvant therapy by an experienced team is essential in order to optimize the selection of patients, choice of systemic therapy, management of the axilla and surgical approach, as well as the decision to administer adjuvant radiation therapy.

As similar survival benefits have been demonstrated for the administration of chemotherapy before or after surgery, this approach is more frequently recommended to women with primary operable stage 2 or 3 disease. Importantly, the neoadjuvant setting has been an attractive area of research attempting to improve breast cancer outcomes by identifying new effective treatment strategies and minimizing treatment-related adverse events. New chemotherapeutic combinations and schedules as well as the addition of targeted and novel therapies have and continue to be tested in the neoadjuvant setting, including new anti-HER2 agents such as pertuzumab and TDM-1. The approach is also an important model for studying drug mechanism of action, and to develop clinically applicable prognostic and predictive biomarkers in an attempt to individualize therapy. Other investigations relating to the neoadjuvant setting attempt to determine optimal management of the axilla and more selective use of radiation therapy.

Challenges exist, however, in the conduct of neoadjuvant clinical trials, often centering around the varied definitions of pathological complete response or other longer term endpoints. A recent review published by the Breast International Group (BIG) and the

National Cancer Institute-sponsored North American Breast Cancer Group (NABCG) proposes a number of standard definitions and endpoints to be implemented in future neoadjuvant clinical trials in breast cancer, in order to standardize their conduct and reporting (Fumagalli *et al.*, 2012). The proposal recommends, for example, moving forward in future neoadjuvant clinical trials with a uniform definition of pathological complete response as the absence of residual invasive cancer within both the breast and lymph nodes. In addition, breast cancer subtypes should be defined with immunohistochemical assays which comply with the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines (Hammond *et al.*, 2010), possibly in a central laboratory, with specific definitions of each subtype being outlined in the manuscript.

As we enter an era of “personalized therapy,” the identification of surrogate predictive and prognostic biomarkers are essential in order to aid treatment decisions. Future studies should continue to take advantage of the unique opportunity that the neoadjuvant setting provides as an *in vivo* model to understand not only drug mechanism of action but also patterns of sensitivity and resistance to systemic therapy. Standardization of definitions in neoadjuvant breast cancer clinical trials is imperative in order to maximize the potential of these trials, by improving both their conduct and effectiveness.

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Table 1Recommended standard regimens (modified from (Carlson *et al.*, 2009))**HER2-negative****Preferred Regimens:**

TAC×6

Dose dense AC × 4 followed by dose dense paclitaxel × 4

AC × 4 (every 2 weeks with filgrastim support or every 3 weeks) followed by weekly paclitaxel × 12

TC×6*

Other Regimens:

FAC/CAF × 6

FEC/CEF × 6

CMF × 6

AC × 4 followed by docetaxel × 4 every 3 weeks

AC × 4 followed by paclitaxel × 4 every 3 weeks

Doxorubicin × 3 followed by paclitaxel × 3 followed by cyclophosphamide × 3 every 2 weekly regimen with filgrastim support

FEC followed by docetaxel

HER2-positive**Preferred Regimens:**

AC × 4, followed by paclitaxel (various schedules) and concurrent trastuzumab

TCH×6

Other Adjuvant Regimens:

Docetaxel and trastuzumab followed by FEC

AC followed by docetaxel and trastuzumab

Paclitaxel and trastuzumab followed by CEF and trastuzumab

AC: doxorubicin, cyclophosphamide; CAF: see FAC; CEF: see FEC; CMF: cyclophosphamide, methotrexate, fluorouracil; EC: epirubicin, cyclophosphamide; FAC/CAF: fluorouracil, doxorubicin, cyclophosphamide; FEC/CEF: fluorouracil, cyclophosphamide, epirubicin; TAC: docetaxel, doxorubicin, cyclophosphamide; TC: docetaxel, cyclophosphamide; TCH: docetaxel, carboplatin, trastuzumab.

* May be appropriate for women for whom anthracyclines are not recommended