

# Advances in neoadjuvant therapies for early breast cancer

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The aims of neoadjuvant systemic therapy (NST) for patients with early breast cancer are to treat occult systemic disease and downstage the tumor to allow breast-conserving surgery, optimally achieving a complete pathologic response (pCR) and prolonging survival. A substantial proportion of patients do not achieve a pCR with current established neoadjuvant therapies. Furthermore, many of the established agents are known to be susceptible to a range of multidrug resistance mechanisms. Various studies, both current and recent, have evaluated novel chemotherapy regimens and agents, as well as hormonal and targeted agents, for NST of early breast cancer. Novel agents that are not affected by resistance issues, such as the epothilone analogs, offer particular promise in this setting. Such novel therapies, together with informed treatment decisions based on biomarker information, will undoubtedly contribute substantially to long-term outcome benefits for patients with early breast cancer.

**I**n the United States, breast cancer is the most frequent cancer in women and one of the most common causes of cancer-related death in women.<sup>1</sup> Among patients initially diagnosed with early breast cancer (cancer that has not yet spread outside the breast or lymph nodes), up to 75% eventually relapse and develop metastatic disease. The likelihood of survival, however, increases with early diagnosis, giving patients diagnosed with early breast cancer the best long-term prognosis.

Appropriate local therapy remains the basis of treatment for patients with early-stage breast cancer. The majority will undergo surgery to remove cancerous tissue, followed by radiotherapy.<sup>2</sup> Standard treatment for patients who have undergone surgery and are deemed to be at high risk for breast cancer recurrence may involve adjuvant systemic chemotherapy, hormonal therapy, and anti-human epidermal growth factor receptor 2 (HER2) therapy, depending on the biologic characteristics of the tumor.<sup>2</sup>

Neoadjuvant systemic therapy (NST) given prior to surgery is also being widely used in patients with early breast cancer who are eligible for adjuvant therapy. Initially established for patients with inoperable locally advanced or inflammatory breast cancer, NST has since been shown to improve the rate of breast-conserving surgery in patients with large, and, more recently, small operable breast tumors ( $T > 2$  cm).<sup>3,4</sup>

The first wave of randomized trials comparing neoadjuvant and adjuvant therapies involving the same drug combinations showed that NST increases the proportion of women eligible for breast-conserving surgery and that achievement of pathologic complete response (pCR) predicts a favorable outcome.<sup>3,4</sup> However, data from randomized trials of NST failed to demonstrate an overall improvement in recurrence-free survival (RFS) and overall survival (OS) compared with postoperative adjuvant therapy.

The aims of NST for patients with early breast cancer are to downstage the tumor to allow breast-conserving surgery and, optimally, achieve a pCR and prolong survival. Administering preoperative therapy should theoretically help to eradicate any potential micrometastases, including those that are surgically induced. Furthermore, the efficacy of NST can be used as an *in vivo* assay of drug sensitivity and resistance and therefore can inform the choice of adjuvant therapy. NST options include chemotherapy, endocrine therapy, and, more recently, targeted therapy with agents such as trastu-

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zumab (Herceptin).

Primary tumors may harbor intrinsic resistance to current therapies such as anthracyclines and taxanes. The use of these established therapies in early disease therefore potentially compromises future treatment options. Novel agents and combinations of agents that have demonstrated anticancer activity and decreased susceptibility to multiple mechanisms of resistance are therefore needed. Currently, an intense program of research is under way to establish which agents offer the best prognosis and long-term outcomes in this setting. This article provides an overview of the range of agents, combinations, and alternative regimens that are under evaluation.

### Method of data collection

Recently completed and ongoing clinical studies of novel chemotherapy, hormonal therapy, and targeted therapies for use in NST in early breast cancer were identified through a search of the following databases: PubMed (citations added in the past 2 years), [www.clinicaltrials.gov](http://www.clinicaltrials.gov), American Society of Clinical Oncology (ASCO) abstracts (2007–2008), and San Antonio Breast Cancer Symposium (SABCS) abstracts (2007). The terms “early” and “neoadjuvant” were specified in all searches, and details in abstracts and study reports were manually reviewed to confirm their suitability for inclusion in this review. A total of 20 trials of novel chemotherapy agents or regimens were identified (Table 1; available at [www.communityoncology.net/journal/0607.html](http://www.communityoncology.net/journal/0607.html)),<sup>5–15</sup> together with 28 further trials of hormonal and/or targeted agents (Table 2; available at [www.communityoncology.net/journal/0607.html](http://www.communityoncology.net/journal/0607.html)).<sup>16–24</sup> The wide variety of NST clinical trials recently completed or ongoing in early breast cancer reflects the pressing need to identify the most effective agents and regimens to optimize both surgical and long-term

outcomes for these patients.

### Novel chemotherapy regimens

Anthracyclines and taxanes are the standard of care in the adjuvant setting, and there is also evidence to support their use in NST. The NSABP B-27 trial showed that the addition of 4 cycles of preoperative docetaxel (Taxotere) after 4 cycles of preoperative Adriamycin (doxorubicin) and cyclophosphamide (AC) for operable breast cancer resulted in significantly higher rates of clinical CR (complete response) and pCR compared with AC alone.<sup>25</sup> Both the combined and sequential uses of anthracyclines and taxanes are considered acceptable in NST, but this review of recent and ongoing studies suggests that the best schedule of administration is still an active area of investigation (Table 1). Dose-dense chemotherapy is an attractive option for NST because of the reduced treatment duration and possible increased activity. However, a recent phase II trial of weekly paclitaxel demonstrated only a modest pCR rate.<sup>6</sup> Furthermore, a recent retrospective analysis confirmed that significant neurotoxicity can be a problem for some patients treated with dose-dense paclitaxel.<sup>5</sup> Dose-dense and metronomic anthracycline schedules are also areas of interest.

The introduction of trastuzumab into neoadjuvant regimens for the management of HER2-positive early breast cancer has focused attention on anthracyclines that afford more favorable cardiotoxicity safety profiles than doxorubicin. Accordingly, a substantial proportion of studies identified in this review incorporated epirubicin. The largest of them is a study ongoing in the United Kingdom, which aims to recruit 800 patients (NCT00070278). This four-arm study is investigating the optimal sequence of administration for epirubicin/cyclophosphamide and paclitaxel, with or without gemcitabine (Gemzar). In arms I and II,

patients receive single-agent paclitaxel after (arm I) or before (arm II) epirubicin/cyclophosphamide; arms III and IV are identical to arms I and II, respectively, except that patients receive paclitaxel in combination with gemcitabine. The incorporation of additional cytotoxic agents to the established anthracycline- and taxane-based regimens is an obvious area of interest. Other agents as well as gemcitabine are being evaluated in this context, including vinorelbine and the platins.

Of the 19 trials involving chemotherapy regimens that were identified, 6 included the oral fluoropyrimidine capecitabine (Xeloda). The largest of these trials, the GeparTrio study, was conducted in 2,090 female patients who had primary breast cancer.<sup>10,11</sup> Interestingly, this study incorporated an *in vivo* chemosensitivity test. All patients were treated initially with 2 cycles of Taxotere (docetaxel) plus Adriamycin (doxorubicin) and cyclophosphamide (TAC); after assessment of response, responding patients were randomized to receive 4 or 6 further cycles of TAC, and nonresponders were randomized to receive 4 further cycles of TAC or vinorelbine plus capecitabine. Recently published mature results demonstrate that in nonresponders, the pCR rates were similar in the two treatment arms (5.3% and 6.0%, respectively), but the switch to vinorelbine/capecitabine appeared to afford marginal benefits with respect to tolerability. Similarly, in responding patients, pCR rates were similar after 6 and 8 TAC cycles (21.0% and 23.5%, respectively). However, rates of grade 3 or 4 leukopenia and edema, as well as of various milder adverse events, were higher in the patients receiving the prolonged schedule.

Of the novel chemotherapeutic agents, the epothilone analog class is of particular interest. Epothilones promote tumor cell death by stabilizing microtubules and inducing apop-

tosis. Ixabepilone (Ixempra), the first in this class, has shown promising efficacy and a manageable safety profile in a range of tumor types, including multidrug-resistant breast cancer.<sup>26</sup> Notably, ixabepilone has less susceptibility to multiple tumor resistance mechanisms, including efflux transporters multidrug resistance-associated protein 1 (MRP-1) and P-glycoprotein.<sup>27</sup> In addition to direct antitumor activity, ixabepilone enhances the effects of antiangiogenic therapy due to its ability to kill tumor-associated endothelial cells.<sup>28</sup> The high rate of acquired resistance to many current therapies, including the anthracyclines and taxanes, makes investigation of this agent for NST of primary breast cancer particularly attractive.

The full results are eagerly awaited from a clinical trial evaluating single-agent ixabepilone NST (40 mg/m<sup>2</sup>) administered as a 3-hour intravenous infusion on day 1 of a 21-day cycle for  $\leq 4$  cycles in treatment-naïve patients.<sup>15</sup> Early analyses are promising, showing an acceptable safety profile and good efficacy; the pCR rate was 18% in the breast and 11% in the breast and axillary lymph nodes. These results compare favorably with those reported for studies of single-agent taxanes, in which pCR rates range from 3% to 20%.<sup>29-33</sup> In these studies, patients received 2-6 cycles of treatment. Higher response rates were observed in patients receiving 6 cycles of treatment. Moreover, ixabepilone maintained activity in patients who were estrogen receptor negative, progesterone receptor negative, and HER2 negative (triple-negative patients); the pCR rate was 26% in the breast and 19% in the breast and lymph nodes.

Additional ongoing trials include a large global study of neoadjuvant therapy (NCT00455533) in patients with early breast cancer comparing ixabepilone and paclitaxel, both given after anthracycline therapy. A direct

comparison of ixabepilone and docetaxel (NCT00630032), both given after fluorouracil, epirubicin, and cyclophosphamide (FEC), is currently being undertaken in the adjuvant setting in node-negative or node-positive patients with triple-negative breast cancer or HER2-negative and progesterone receptor-negative breast cancer.

#### *Clinical trials of targeted therapy plus chemotherapy*

NST represents an ideal setting in which to test targeted drugs because of the availability of tumor tissue before, during, and after treatment. Targeted therapy is an active area of clinical research, as evidenced by 24 of the 48 trials identified in the current review incorporating a targeted agent (Table 2).

Trastuzumab, a humanized receptor antibody directed against HER2, has demonstrated efficacy in combination with chemotherapy in patients with HER2-positive breast cancer. A large range of phase II studies is currently under way to determine the safety and efficacy of the addition of trastuzumab to NST for patients with HER2-positive tumors. These studies generally reflect the current trends in investigative NST, with regimens incorporating dose-dense chemotherapy and/or novel regimens including capecitabine and gemcitabine. Promising preliminary results from an ongoing phase II study of trastuzumab in combination with docetaxel and capecitabine have demonstrated a pCR rate of 29%.<sup>17</sup> A large, ongoing, phase III, four-arm study, aiming to recruit 1,500 patients, is evaluating the addition of capecitabine and/or trastuzumab to epirubicin, cyclophosphamide, and docetaxel (NCT00288002).

Lapatinib (Tykerb) is an oral dual tyrosine kinase inhibitor targeting both the HER1 and HER2 receptors. This agent has demonstrated good activity in refractory metastatic

breast cancer, showing potential benefit in patients with brain metastases. A number of trials are currently evaluating lapatinib in combination with chemotherapy or trastuzumab, or both, in the neoadjuvant setting. The German Breast Group is proposing a large, phase III, six-arm neoadjuvant trial including more than 2,500 patients. One part of this study will directly compare trastuzumab and lapatinib as additions to epirubicin, cyclophosphamide, docetaxel, and capecitabine (NCT00567554).

Pertuzumab, an antibody that inhibits the dimerization domain of the HER2 molecule and thereby prevents the homodimerization of HER2 as well as the heterodimerization of HER2 with HER family receptors, is also being evaluated in NST. A large, global, randomized, phase II neoadjuvant study will evaluate the addition of pertuzumab to trastuzumab, docetaxel, and the combination of trastuzumab and docetaxel (NCT00545688).

Angiogenesis is a critical step in the growth and micrometastasis of early breast cancers. The combination of antiangiogenic agents with chemotherapy is therefore a promising therapeutic option in the neoadjuvant setting. Bevacizumab (Avastin) is a recombinant, humanized, vascular endothelial growth factor (VEGF) antibody that recognizes all isoforms of VEGF-A. A phase II pilot study in 18 patients with invasive breast cancer treated with capecitabine, docetaxel, and bevacizumab demonstrated a pCR rate of 22%; breast-conserving surgery was used in 83% of patients.<sup>24</sup> Additional phase II neoadjuvant studies are evaluating the combination of bevacizumab with capecitabine and gemcitabine, and letrozole (Femara). The large, phase III, six-arm neoadjuvant trial proposed by the German Breast Group will evaluate the addition of bevacizumab to epirubicin, cyclophosphamide, docetaxel, and capecitabine (NCT00567554). The VEGF

tyrosine kinase inhibitors sunitinib (Sutent) and sorafenib (Nexavar) are also being evaluated in combination with chemotherapy in phase II neoadjuvant studies (NCT00513695 and NCT00548899). Additionally, sunitinib is being evaluated as single-agent NST in a phase II study conducted by the National Cancer Institute of Canada (NCT00482755).

There is a considerable body of preclinical data to support the evaluation of ixabepilone combinations with targeted therapies in early breast cancer. Tumor xenograft models have demonstrated synergistic activity with a range of antiangiogenic agents, including bevacizumab and sunitinib,<sup>34,35</sup> as well as trastuzumab.<sup>36</sup> Furthermore, ixabepilone demonstrates robust synergistic antitumor efficacy when used in combination with cetuximab (Erbix) or capecitabine in human xenografts.<sup>37</sup>

#### *Clinical trials of neoadjuvant hormonal therapy*

There is also renewed interest in the potential of neoadjuvant hormonal therapy in patients with hormone receptor-positive tumors. Although the use of aromatase inhibitors is well established in the neoadjuvant endocrine treatment of postmenopausal women with hormone-responsive tumors, ongoing trials are evaluating the use of the third-generation aromatase inhibitors, such as anastrozole (Arimidex) and letrozole, in this setting. In addition, their use in combination with novel targeted agents is also being evaluated. For example, in a neoadjuvant study conducted in the United States, anastrozole is being evaluated in combination with the dual VEGF/epidermal growth factor receptor tyrosine kinase inhibitor vandetanib (Zactima; NCT00481845).

#### *Prognostic and predictive biomarkers*

Although the use of novel predictive and prognostic markers in neoadjuvant therapy is of great interest,

pCR remains an established predictor of survival in this setting.<sup>25</sup> However, review of trial designs reveals substantial variation in the criteria used for the measurement of pCR. Most of the clinical data pertaining to novel NST regimens will emerge from phase II studies, and subsequent phase III trial designs will be based on these findings. Standardization of pCR evaluation is therefore required to allow useful intrastudy comparisons of pCR rates and reliable data on which further developments in treatment protocols can be based.

The neoadjuvant setting is the ideal setting for evaluation of biomarkers because of the ready availability of tumor tissue. Together with the inherent *in vivo* test of chemosensitivity, the results of biomarker studies will help to guide decisions regarding the use of adjuvant treatment. As the review of trial designs for neoadjuvant trials in early breast cancer identified in the current analysis demonstrated, biomarker evaluation is being increasingly incorporated into trial design. Of the 48 trials identified, 19 included evaluation of biomarkers or gene signatures or both. As well as relying on the more established biomarkers in breast cancer such as hormone receptor status and HER2 status, a number of trials are investigating putative biomarkers, such as the proliferation index marker Ki67 and measures of apoptosis, as well as gene signatures.

Predictive models that use biomarkers for selecting patients most likely to benefit from a particular treatment have been described. One of the largest of such studies evaluated the validity of gene-expression signatures in 125 of 212 patients treated in a phase III neoadjuvant clinical trial comparing a nontaxane regimen (FEC) with a taxane regimen (docetaxel for 3 cycles followed by epirubicin plus docetaxel [TET]).<sup>9</sup> The regimen-specific signatures significantly predicted pCR in patients treated with the appro-

priate regimen ( $P < 0.0001$ ). The FEC predictor had a positive predictive value (PPV) of 68% and a negative predictive value (NPV) of 96%. The TET predictor had a PPV of 71% and an NPV of 92%. Selection of patients who contain these signatures would therefore increase the proportion of patients achieving pCR from 44% to around 70% in this cohort. In another study using a six-gene predictive model, Baselga et al<sup>15</sup> demonstrated PPV and NPV values of 66% and 89%, respectively, for pCR after single-agent ixabepilone NST; among patients who were marker positive versus marker negative, the pCR rate was 66% versus 11%, respectively. This type of predictive model could be used in future trials to select those patients likely to benefit from ixabepilone and to exclude those who are unlikely to respond.

#### **Conclusion**

The validity of NST for early breast cancer is now largely unquestioned. This review confirms that numerous studies evaluating novel chemotherapy regimens and agents, as well as hormonal therapies and targeted agents, are under way in this setting. Many of the regimens discussed in this review are based on anthracycline- or taxane-based combinations or both. These agents are known to be susceptible to a range of multidrug resistance mechanisms, and thus their increased use in the (neo)adjuvant setting means that fewer effective options are available to treat patients with advanced disease. This, together with the fact that a substantial proportion of patients do not achieve pCR with NST, indicates that optimal agents and regimens remain to be defined. Newer agents that are free of resistance issues, such as the epothilone analogs, will play a role in neoadjuvant treatment, as they do not compromise subsequent treatment options. Treatment decisions will be

further informed by indications from biomarker testing. Such information will contribute substantially to long-term outcome benefits for patients with early breast cancer.

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