Neoadjuvant Therapy for Breast Cancer: Assessing Treatment Progress and Managing Poor Responders

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There is no clear consensus regarding the most effective management of poor responders to neoadjuvant chemotherapy. Intensifying or changing primary systemic treatment has not been shown to offer any benefit. There is a paucity of trials testing the utility of adjuvant chemotherapy in this setting. Adjuvant hormonal treatment significantly decreases relapse rates in patients with estrogen receptor–positive breast cancer, regardless of initial response to chemotherapy. Neoadjuvant hormonal therapy is usually reserved for patients who are not candidates for chemotherapy or surgery. In patients with HER2–overexpressing tumors who are candidates for chemotherapy, trastuzumab improves outcomes when administered in the preoperative or postoperative setting. This article examines issues related to the assessment of response to preoperative therapy and the clinical use of these assessments. It reviews important clinical evidence related to the utility of further treatment in patients with breast cancer that has responded poorly to neoadjuvant treatment.

Introduction

Preoperative therapy is most often used in patients with stage II and III disease in whom surgical resection may be difficult. This approach has been shown in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 and European Organisation for Research and Treatment of Cancer (EORTC) 10902 trials to allow more women to undergo breast conservation instead of mastectomy by successfully downstaging the tumor. In some cases, neoadjuvant chemotherapy also may help make locally extensive disease that is not initially amenable to surgery resectable [1–3].

In operable disease, available evidence suggests no difference in relapse-free and overall survival between patients treated with neoadjuvant chemotherapy and those receiving postoperative, adjuvant treatment [1–4]. A meta-analysis evaluated the results of nine randomized studies involving 3946 patients with breast cancer treated with neoadjuvant chemotherapy or an identical regimen in the adjuvant setting. It found that despite a less favorable rate of locoregional disease recurrence in patients treated with neoadjuvant chemotherapy (relative risk [RR], 1.22; 95% CI, 1.04–1.43), especially in studies using radiation therapy without surgery, there was no statistically significant difference in disease-free or overall survival and the RR of disease progression was 0.99 (95% CI, 0.91–1.07) and the RR of death was 1.0 (95% CI, 0.90–1.12). An interesting finding of the study was the heterogeneity of complete responses in the group of patients receiving neoadjuvant therapy, with clinical complete response ranging between 7% and 65% ($P < 0.001$) and pathologic complete response of 4% to 29% [5].

One unique aspect of neoadjuvant chemotherapy in breast cancer is the ability to monitor tumor response. Based on several large prospective randomized studies, such as the NSABP B-18 trial, patients with a poor response to neoadjuvant chemotherapy are known to be at increased risk for local or systemic recurrence compared with those with a good response to neoadjuvant treatment and no residual breast cancer in the definitive surgical specimen [2]. It can be argued that adding additional cycles of the same chemotherapy or changing to a regimen including non–cross-resistant agents might improve recurrence risk and survival in poor responders to initial neoadjuvant chemotherapy. However, poor responders may represent a population of patients with tumors that are less responsive to chemotherapy; therefore, intensifying or changing therapy may not translate to improved response. In addition, the risk of serious complications and toxic effects from such an aggressive approach may be

significant. As reviewed in the following sections, studies have not shown any benefit from intensifying or changing therapy in poorly responding patients treated in the neoadjuvant setting. Two exceptions are hormone therapy in estrogen-positive disease and the use of trastuzumab in HER2/neu–overexpressing breast cancers, which have been shown to improve tumor response to treatment [6].

Assessing Response to Neoadjuvant Chemotherapy

Before discussing management of patients with a poor response to neoadjuvant treatment, it is important to review what tools are available to measure it. A study of 189 breast cancer patients undergoing neoadjuvant chemotherapy assessed tumor response to treatment with physical examination, mammography, or ultrasound and compared these approaches with the gold standard, pathologic examination. The study found that false-positive rates ranged from 20% to 65% for all modalities; false-negative rates were 10% to 57% [7]. The GeparTrio trial revealed a sonographic complete response in 50% of the cases examined, whereas a pathologic complete response was seen in only 5% to 6% of patients [8•,9••]. These and many other studies demonstrate that the sensitivity and specificity of physical examination, mammography, and ultrasound are poor when these methods are used to measure response to neoadjuvant chemotherapy.

MRI, a subject of intense research lately, is gaining popularity as a potential tool for monitoring response to neoadjuvant treatment [10]. Overall, trials have shown significantly better accuracy of MRI findings in estimating response to treatment compared with more conventional methods [11]. Ongoing trials are testing MRI's ability to predict outcomes by comparing images obtained before initiation of neoadjuvant chemotherapy with those taken during treatment [12]. Nevertheless, MRI's usefulness is hindered by expense and a high false-negative rate in patients undergoing chemotherapy. Other modalities, such as dynamic contrast-enhanced MRI, MRI-spectroscopy, and positron emission tomography, are still under investigation. These methods may be useful in selected cases as they can help estimate angiogenesis, microvascular permeability, water diffusion, or choline concentration within the tumor [13]. However, outside a clinical trial, these approaches are not recommended for monitoring response of breast cancer to neoadjuvant chemotherapy. The gold standard for assessing response to neoadjuvant chemotherapy for breast cancer is still pathologic evaluation [3].

Ki-67's role in patients treated with hormone therapy

Hormone therapy has unique characteristics that make more conventional methods of assessing response to treatment less suitable, mainly because of a low rate of pathologic complete response. Modalities such as ultrasound or mammography are more prone to interobserver variability and operator dependence. In addition, recent studies demonstrated that use of MRI to monitor response to hormonal treatment was hindered by a decrease in gadolinium uptake by the tumors treated with antiestrogen agents, which may be related to the antiangiogenic effects of such treatment [14]. Pathologic complete response remains the best-known marker of response, but it is rare in patients treated with hormonal agents. Ki-67 expression, which depends on cell proliferation, emerged as an important marker of tumor response to hormonal agents in research studies. Cell cycle complete response, defined as a decrease in Ki-67 expression to ≤ 1% after treatment, has been found to correlate well with clinical and radiographic response but may be superior to these methods as it can be measured more accurately [14]. What makes this modality attractive is that it is easy to obtain, although issues related to standardization of the assay and sampling errors related to tumor heterogeneity need to be addressed.

One approach currently being studied to evaluate patients receiving hormonal therapy is use of a composite score involving clinical, radiographic, and cell cycle–dependent response in the form of Ki-67 expression rate [14]. Three large clinical trials testing neoadjuvant hormonal therapy—LET (letrozole) 024, IMPACT (Immediate Preoperative Anastrozole Tamoxifen or Combined With Tamoxifen), and PROACT (Pre-Operative Arimidex Compared to Tamoxifen)—are collecting data on Ki-67 expression as one of the markers of response [15–17].

Prognostic Factors Following Preoperative Therapy

Pathologic complete response has been shown to predict improved disease-free and overall survival [3]. Factors associated with a higher likelihood of pathologic complete response include tumor size, histology (lobular vs ductal), tumor intrinsic subtype (luminal vs basaloid or HER2 positive), hormone receptor status (estrogen receptor [ER] positive vs ER negative), and grade (low vs high) [18].

A study at M.D. Anderson Cancer Center retrospectively evaluated the outcome of 340 patients with stage II or III noninflammatory disease who were treated with neoadjuvant systemic therapy and underwent breast conservation therapy. Residual disease of more than 2 cm found on pathologic review of the postmastectomy specimen was strongly associated with locoregional recurrence. Other factors, such as clinical N2 or N3 disease, lymphovascular space invasion noted at the time of biopsy or in the surgical specimen, and a multifocal or breakup pattern of residual disease, also were found to predict a poor prognosis. In this series, the 10-year in-breast recurrence rate was 10%. However, a recurrence rate of 12% (n = 43) was found in patients who had two or more of the aforementioned factors but only 3% in patients with no

factors (n = 276) [19]. These results have been validated by other studies [20,21•].

Unfortunately, pathologic response is not uniformly defined throughout clinical trials. Researchers from the NSABP study group defined *complete pathologic response* as no evidence of invasive cancer in the breast. Other groups defined the term as no evidence of invasive cancer in the breast and axillary lymph nodes. Data have shown that the presence of disease in lymph nodes following neoadjuvant chemotherapy is associated with higher relapse rates [22–24]. Interestingly, the presence of residual ductal carcinoma in situ after neoadjuvant chemotherapy has been shown not to influence prognosis [25].

Residual cancer burden: an important predictor of outcome

Several methods of estimating residual disease have been proposed, including estimated decrease in tumor volume or cellularity and change in cytologic appearance [20,26]. These were primarily descriptive and did not account for dispersed, multifocal microscopic disease in the tumor bed. Residual cancer burden (RCB) was therefore devised to overcome these problems. A study at M.D. Anderson analyzed postmastectomy pathology specimens from 241 patients treated with neoadjuvant sequential paclitaxel followed by 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC regimen) and 141 patients treated with a neoadjuvant FAC regimen. The investigators then calculated RCB, which consisted of a continuous index combining primary tumor size and cellularity as well as number and size of nodal metastases. Using multivariate analysis, they showed that RCB correlated with prognosis, independent of factors such as age, pretreatment clinical stage, hormone receptor status, hormone therapy, and pathologic response (hazard ratio, 2.5; 95% CI, 1.7–3.69; $P < 0.01$). Patients with minimal residual disease (RCB-I) had the same prognosis as those with a pathologic complete response (RCB-0). The investigators also found that patients who had extensive residual disease (RCB-II) had the poorest prognosis, which was independent of hormone receptor status, adjuvant hormone therapy, or pathologic American Joint Committee on Cancer stage of residual disease [21•]. RCB was therefore proposed as a useful tool to estimate response to neoadjuvant chemotherapy in breast cancer because it provides a quantitative value of residual disease and has prognostic significance.

Should Residual Disease After Neoadjuvant Treatment Influence Further Systemic Therapy?

Unfortunately, there are few randomized trials evaluating the value of additional systemic therapy in patients who have completed neoadjuvant treatment (Table 1). The following sections present data and draw conclusions from trials investigating whether tailoring preoperative treatment on the basis of clinical response to treatment can result in improved therapy.

Use of additional postoperative chemotherapy

Early studies testing the addition of the same chemotherapy used in the neoadjuvant setting for poor responders showed disappointing results [27]. Moreover, there were relatively few of these trials and they had small sample sizes. There also is a paucity of phase 2 or 3 randomized studies comparing treatment of poor responders with adjuvant chemotherapy versus placebo or testing different regimens in the adjuvant setting. The few clinical trials that were done have shown no statistically significant benefit from adjuvant chemotherapy in patients who responded poorly to neoadjuvant treatment, which suggests that poor responders to neoadjuvant treatment likely have chemotherapy-resistant disease.

A study at M.D. Anderson by Thomas et al. [27] is one of the largest of such trials. It enrolled 193 subjects with T3-T4 and/or N1-N3 breast cancer, who were treated with three cycles of neoadjuvant vincristine, doxorubicin, cyclophosphamide, and prednisone (VACP). Following this treatment, all study patients underwent modified radical mastectomy with level I and II lymph node dissection. One hundred and six subjects who had residual breast cancer at the time of mastectomy, which measured at least 1 cm, were randomly assigned to one of two study groups. One group, consisting of 51 patients, received an additional five cycles of the same regimen used for neoadjuvant treatment. The other group, comprising 55 patients, received five cycles of a regimen consisting of vinblastine, methotrexate, leucovorin, and fluorouracil (VbMF). The rest of the patients, who had no residual tumor or residual tumor of less than 1 cm at the time of mastectomy, received an additional five cycles of VACP. The overall response rate before mastectomy (a composite of complete, partial, and minor responses) was 83.4%. The study found a pathologic complete response in only 12.2% of patients and showed no statistically significant difference in relapse-free and overall survival between the poor responders treated with either of the two regimens, although a nonsignificant trend favored the patients who received VbMF.

In a phase 1/2 study, Formenti et al. [24] failed to show safety and efficacy of combined preoperative chemotherapy and radiation therapy in locally advanced breast cancer. The authors examined neoadjuvant therapy with twice-weekly paclitaxel at a dosage of 30 mg/m^2 for 8 weeks with concurrent external beam radiation therapy. All study subjects subsequently underwent mastectomy at least 2 weeks after the last radiation treatment. Patients who were nonresponders to neoadjuvant treatment, as evidenced by a lack of complete or partial pathologic response, were treated with four cycles of adjuvant doxorubicin and cyclophosphamide (AC); those who

Table 1. Clinical trials assessing the utility of intensifying treatment in poor responders to neoadjuvant chemotherapy

Study	Patients, *n*	Design	Findings
Thomas et al. [27]	193	3 cycles of neoadjuvant VACP, followed by surgery/radiation. Those with residual disease > 1 cm in diameter were randomly assigned to another 5 cycles of VACP vs 5 cycles of VbMF.	Overall response before mastectomy was 83.4%; pCR was 12.3%. No significant differences in relapse-free and overall survival. Stage, pCR, and clinical response were associated with better survival.
Formenti et al. [24]	44	Neoadjuvant radiation therapy and twice-weekly paclitaxel, followed by mastectomy. Pts with lack of pCR or partial pathologic response received 4 cycles of adjuvant AC. Pts with a pCR or partial response received 4 cycles of adjuvant AT.	36% achieved pCR or partial response; median survival, 15–52 mo. No comparisons due to small sample sizes. Unacceptable skin toxicity requiring dose reduction of paclitaxel. High rate of postsurgical complications.
von Minckwitz et al. (GeparTrio) [8•,9••]	2090	Subjects were treated with 2 cycles of neoadjuvant TAC; 1390 responders were randomly assigned to 4 vs 6 more cycles; 622 poor responders received 4 additional cycles of TAC or NX	Responders: no difference in pCR or clinical response rates but higher rate of grade 3–4 leukopenia and edema in pts receiving 8 cycles Nonresponders: no statistical differences in outcomes (0.7; 95% CI, –7.1–8.5). Less hematologic toxicity but more neuropathy and hand-foot syndrome in NX group.
Smith et al. (Aberdeen) [28]	162	4 cycles of neoadjuvant CVAP. Responders received 4 more cycles of CVAP or 4 cycles of docetaxel. Nonresponders were treated with 4 cycles of docetaxel.	Responders: docetaxel group, 94% achieved clinical response or pCR; CVAP group, 66% achieved clinical response or pCR ($P = 0.01$) Nonresponders: no difference in outcomes
Bear et al. (NSABP B-27) [29]	2411	Neoadjuvant AC followed by surgery vs neoadjuvant TAC followed by surgery vs neoadjuvant AC followed by surgery and adjuvant docetaxel	Clinical complete response: 40.1% in AC groups vs 63.6% in TAC group ($P < 0.001$) pCR: 13.7% in AC groups vs 26.1% in TAC group. Patients who did not respond early did not benefit from addition of docetaxel.
von Minckwitz et al. (GeparQuattro) [30••]	1421	All subjects received EC × 2, then were randomly assigned to docetaxel × 4, docetaxel × 4 and concurrent capecitabine, or docetaxel × 4 and sequential capecitabine	Trial ongoing. No difference in pCR rates (22.1%,19.3%, and 21.7%, respectively; $P = 0.5$). Capecitabine and docetaxel required dose reductions, led to more nonhematologic toxic effects.

AC—doxorubicin and cyclophosphamide; AT—doxorubicin and paclitaxel; CVAP—cyclophosphamide, vincristine, doxorubicin, and prednisone; EC—epirubicin and cyclophosphamide; NSABP—National Surgical Adjuvant Breast and Bowel Project; NX—vinorelbine and capecitabine; pCR—complete pathologic response; Pts—patients; TAC—doxorubicin, cyclophosphamide, and docetaxel; VACP—vincristine, doxorubicin, cyclophosphamide, and prednisone; VbMF—vinblastine, methotrexate, leucovorin, and fluorouracil.

had a complete or partial response received four cycles of adjuvant doxorubicin and paclitaxel (AT). Of the 44 patients who completed neoadjuvant treatment, 64% did not achieve complete or partial pathologic response. The investigators did not compare overall or relapse-free survival in responders versus nonresponders because of the small sample size in the responder group, in which there were many dropouts related to grade 3 skin toxicity and disease progression. However, the median follow-up of all patients was 32 months after surgery (range, 15–52 months). The overall estimated probability of survival was 93.9% (SE, 4.17%). The disease-specific overall survival was 97.1% (SE, 2.9%), and the disease-free survival was 75.6% (SE, 8.3%). Another drawback of this trial is the fact that the study's protocol had to be amended from a paclitaxel dosage of 60 mg/m^2 weekly to 30 mg/m^2 twice weekly because of unacceptable skin toxicity when this agent was combined with radiation treatment; the rate of grade 3 skin toxicity was 45%. Postsurgical complications were also significant, likely as a result of inflammatory changes due to the study treatment.

Based on the aforementioned data, it is not clear whether more chemotherapy in patients with a poor response to neoadjuvant treatment translates into better outcomes. It is, however, obvious that the use of additional standard chemotherapy regimens for breast cancer leads to higher toxicity rates. Therefore, until the benefit of adjuvant chemotherapy in these patients is found in larger, well-designed randomized clinical trials, its use generally is not recommended outside research protocols.

Systemic therapy in the neoadjuvant setting in nonresponders

Several trials have examined the effectiveness of adding more chemotherapy cycles or changing treatment to non–cross-resistant agents in patients with breast cancer based on response early in the course of neoadjuvant chemotherapy. In the randomized phase 3 GeparTrio trial, 2090 patients with breast cancer were treated with two cycles of neoadjuvant doxorubicin, cyclophosphamide, and docetaxel (TAC) on a 21-day schedule. Of all study subjects, 1390 patients who had more than a 50% decrease in size of the primary tumor were defined as early responders and randomly assigned to four or six more cycles of the TAC regimen. There were no significant differences in complete pathologic or clinical response rates (based on physical examination and ultrasonography). There also was no difference in the number of subjects able to undergo breast conservation surgery. Patients who received eight cycles of preoperative chemotherapy had higher rates of grade 3 and 4 leukopenia and edema. The investigators concluded that intensifying chemotherapy in responders did not improve outcomes but was associated with increased rates of serious toxic effects [8•].

In the second part of the GeparTrio study, reported separately, 622 of the 2090 patients who had less than a 50% decrease in tumor size after two cycles of neoadjuvant TAC chemotherapy and thus were classified as nonresponders were randomly assigned to four additional cycles of the TAC regimen or vinorelbine plus capecitabine (NX), a regimen thought to have activity against breast carcinoma but to be non–cross-resistant with TAC. This study again demonstrated no clinically significant difference in outcomes as measured by pathologic or clinical means [9••]. Based on these results, changing treatment to a non–cross-resistant regimen in nonresponders does not affect outcome. The most important prognostic factor in the study remained early response to neoadjuvant chemotherapy, regardless of treatment.

In the Aberdeen trial, 162 patients received four cycles of a neoadjuvant regimen consisting of cyclophosphamide, vincristine, doxorubicin, and prednisone (CVAP). At the end of four cycles, patients who responded by clinical criteria were randomly assigned to four more cycles of CVAP or four cycles of docetaxel. Those who did not respond received four cycles of docetaxel. The results in the responding patient population (102 patients) showed that switching to four cycles of docetaxel improved clinical and pathologic responses compared with patients who received four additional cycles of CVAP (94% vs 66%). However, the results in 60 patients who showed no signs of early response after an initial four cycles of chemotherapy were far more disappointing. The study showed that switching to docetaxel in nonresponders did not produce any significant improvement in response rates, although responders did benefit from intensifying neoadjuvant chemotherapy [28].

NSABP B-27 was a large phase 3 randomized trial in which 2411 study subjects were assigned to neoadjuvant AC followed by surgery, neoadjuvant AC plus docetaxel followed by surgery, or AC followed by surgery and adjuvant docetaxel. The overall study results showed clinically significant improvements in response rates in patients who received docetaxel. However, subgroup analysis demonstrated that patients who did not respond early did not benefit from the addition of neoadjuvant docetaxel [29]. Based on these and other results, patients who do not respond to initial neoadjuvant chemotherapy early do not benefit from changing or intensifying treatment and may therefore be candidates for novel approaches.

The GeparQuattro trial is examining the role of adding capecitabine to standard chemotherapy in the neoadjuvant setting. All patients in the study received four cycles of neoadjuvant epirubicin and cyclophosphamide (EC) then were randomly assigned to receive four additional cycles of docetaxel (n = 471), four cycles of docetaxel given concurrently with capecitabine (n = 471), or four cycles of docetaxel followed by capecitabine given sequentially (n = 479). Trastuzumab was also used in patients with HER2/neu-overexpressing tumors in all three groups. Following neoadjuvant treatment, all patients underwent mastectomy and radiation therapy. The study is ongoing, but preliminary results show no differences in pathologic complete response rates among the groups (22.1%, 19.3%, and 21.7%; P = 0.5). However, the study investigators found that the addition of capecitabine required dose reductions of both docetaxel and capecitabine and led to more nonhematologic toxic effects. Prolonging neoadjuvant treatment (capecitabine given sequentially as opposed to concurrently) worsens patient compliance, leads to more early tumor progressions, and does not improve pathologic complete response rate [30••].

These studies suggest that a lack of response to neoadjuvant chemotherapy identifies a group of patients who may be more resistant to chemotherapy in general. For this reason, administering additional cytotoxic agents to such patients is not recommended outside a clinical trial.

Hormonal and Target-Specific Therapy in the Neoadjuvant Setting

Hormonal therapy and trastuzumab also have been tested in the preoperative setting, but there is a lack of studies examining the ability of such treatment to improve outcomes in patients who are poor responders to neoadjuvant chemotherapy. Here, the considerations are different, as the preoperative period represents only a fraction of the total treatment time.

Neoadjuvant hormonal treatment produced responses in several large, double-blinded, randomized clinical trials, such as the IMPACT trial, which examined responses to neoadjuvant anastrazole, tamoxifen, or both [6,31]. This trial showed no difference in response rates among the three

treatment groups. However, in the P024 trial, involving 324 patients, the overall response rate was 55% for letrozole and 36% for tamoxifen in the neoadjuvant setting ($P < 0.001$). When response was defined by Ki-67 immunohistochemistry, letrozole was significantly more effective than tamoxifen in inducing cell cycle complete response ($P = 0.0009$) [32]; however, it is not clear whether this trend will continue with longer follow-up. Other studies confirmed that aromatase inhibitors show more pronounced response rates than selective estrogen receptor modulators [16,17].

An intriguing possibility is that the response to preoperative hormonal therapy could be used to determine which patients would benefit from the addition of chemotherapy and which are adequately treated by hormonal therapy alone; this hypothesis will be investigated in future trials. Postoperative hormonal therapy generally is recommended for patients who have hormone receptor–positive tumors and have completed preoperative chemotherapy, regardless of response.

Trastuzumab has been used in neoadjuvant settings as well. In a study at M.D. Anderson, 42 patients with stage II to IIIA noninflammatory breast cancer were randomly assigned to receive four cycles of neoadjuvant paclitaxel followed by four cycles of 5-fluorouracil, epirubicin, and cyclophosphamide with or without weekly trastuzumab for 24 weeks. At a median follow-up of 36.1 months, the disease-free survival rate at 1 and 3 years was 100% in the chemotherapy and trastuzumab group, compared with 94.7% and 84.3% at 1 and 3 years ($P = 0.041$) in the group treated with chemotherapy alone. Patients who responded early had a better long-term clinical response [33]. Another phase 3 trial involving 228 patients with locally advanced HER2–positive breast cancer showed that adding trastuzumab to AT/T/CMF regimen (alternating cycles of doxorubicin-paclitaxel, paclitaxel and cyclophosphamide, methotrexate, and 5-fluorouracil) improved the overall response rate from 73% to 81% ($P = 0.18$) and significantly increased the pathologic complete response rate from 23% to 43% ($P = 0.002$). Neoadjuvant trastuzumab in combination has the potential, therefore, to improve pathologic complete remission rates in locally advanced breast cancer overexpressing HER2 [34•]. Whether alternative HER2-directed therapy should be administered to patients not responding to preoperative trastuzumab-based treatment is not yet known and needs further investigation.

Conclusions

One unique aspect of using primary systemic therapy is an improved ability to closely monitor tumor response to treatment. Pathologic examination is the gold standard in assessing response to neoadjuvant treatment, but MRI is also being tested in clinical trials. RCB is one method shown to be clinically useful in assessing response to neoadjuvant treatment and correlates well with relapse and survival rates. Ki-67 is emerging as a potentially useful marker of tumor response to hormonal therapy. Poor response to neoadjuvant chemotherapy is a powerful predictor of worse disease-free and overall survival. Unfortunately, there is no well-established paradigm for managing such patients, and more clinical trials are needed to establish the best strategy. Based on the reviewed evidence, breast cancer patients who have a poor response early during neoadjuvant chemotherapy may have tumors that generally are resistant to treatment, and intensifying chemotherapy, changing treatment to a non–cross-resistant regimen, and using additional adjuvant chemotherapy are approaches that have not been demonstrated to improve outcome. Based on data from postsurgical adjuvant trials, patients with hormone receptor–positive tumors should receive hormonal therapy postoperatively, regardless of their response to preoperative chemotherapy. Patients with HER2-positive tumors should be considered for HER2-directed therapy if they are candidates for chemotherapy.

Disclosures

Dr. Budd has served on Wyeth, Pfizer, and Amgen advisory boards and has been an uncompensated consultant for Exagen. No other potential conflicts of interest relevant to this article were reported.

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This study is ongoing, but preliminary results were presented at the 2007 San Antonio Breast Cancer Symposium. The investigators found that capecitabine given concomitantly or in sequence with four cycles of neoadjuvant docetaxel that followed EC regimen (epirubicin and cyclophosphamide) did not improve pathologic complete response rates when compared with four cycles of EC followed by docetaxel alone. Adding capecitabine to EC + docetaxel regimen required dose reduction of capecitabine and docetaxel. Prolonging the neoadjuvant treatment led to more early tumor progressions and noncompliance.

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This trial provided evidence that adding trastuzumab to neoadjuvant chemotherapy can improve disease-free survival. Patients who responded early had better long-term clinical response.