Adjuvant systemic chemotherapy has been shown to prolong survival in all subsets of patients with breast cancer. In addition, among patients with locally advanced breast cancer, neoadjuvant or preoperative chemotherapy has compared with many other malignancies, operable breast cancer (stages I-IIIA) has a long natural history with morbidity and mortality caused primarily by local recurrence and distant metastases. Although local therapy is essential for regional control, it does not completely address the problem of future metastases. Even after aggressive surgery, women with axillary lymph node involvement at the time of diagnosis have a poor prognosis without additional therapy. In 1975, Fisher et al reported that only 25% of women with lymph node involvement at the time of surgery were alive 10 years after diagnosis.[1] In addition, 10% to 50% of patients with negative axillary lymph nodes developed distant metastases following apparently curative surgery.

For many, this low survival rate was due to distant micrometastases already present at the time of surgery. This realization led to a change in the treatment paradigm in the second half of the 20th century, with the introduction of systemic treatment modalities (chemotherapy and endocrine therapy) as “adjuvants” to surgical therapy. Systemic adjuvant therapy of breast cancer has improved survival in all subsets of patients with operable disease by helping to eradicate micrometastases. This has been proven in multiple randomized studies and confirmed in two recent meta-analyses—one evaluating the benefit of tamoxifen[2] and the other evaluating systemic chemotherapy.[3]

Although effective, adjuvant systemic therapy of breast cancer cannot completely eliminate the development of distant metastases. Thus, on the basis of hypotheses generated from preclinical studies and from the use of presurgical chemotherapy as treatment for locally advanced breast cancer, interest in using the neoadjuvant approach to treat early-stage breast cancer has grown. In animal models, removal of the primary tumor increases proliferation of cancer cells at sites of metastases.[4] It has, therefore, been hypothesized that administering systemic chemotherapy prior to tumor removal helps minimize micrometastases and prevent cancer growth that might otherwise occur after removal of the primary tumor. In fact, one study found that when cyclophosphamide (Cytoxan, Neosar) was administered to mice with implanted mammary adenocarcinomas before removal of their largest tumors, it abrogated the growth spurt of the remaining tumor deposits and provided optimal tumor control.[5]

Tamoxifen administered in the preoperative setting had similar effects. Administration of systemic chemotherapy to patients with intact primary tumors might, therefore, help decrease systemic micrometastases and improve overall survival. It has also been hypothesized that preoperative systemic treatment reaches tumors earlier than does postoperative adjuvant therapy, therefore confronting fewer micrometastases.[6] Preoperative systemic therapy would also reach the primary tumor site before any surgical destruction of vascular access to the tumor-bearing area occurs. Beyond the benefits observed in research studies evaluating tumors in vitro and in vivo, the benefits of neoadjuvant chemotherapy have been seen in its use as a treatment strategy for locally advanced breast cancer. Induction (neoadjuvant) therapy of locally advanced breast cancer produces an objective response in 60% to 80% of patients, with approximately 10% to 20% achieving a clinical complete response (CR).[7] Many tumors initially considered inoperable can be rendered operable by neoadjuvant chemotherapy or endocrine therapy, and this ability to downstage multiple patients with large tumors could also theoretically translate into improved rates of breast conservation for patients with earlier-stage disease. Some researchers have proposed this approach as a method of testing the in vivo response of cancer to a particular systemic treatment regimen.[8]

Early Studies—Promise and Problems

Most studies of preoperative systemic therapy have been conducted using chemotherapy, although
the results of a few studies of neoadjuvant endocrine therapy are available.[9] Initial nonrandomized studies evaluating the benefit of neoadjuvant chemotherapy in operable breast cancer began in the early 1980s and, over the next 2 decades, confirmed that this approach was feasible for early breast cancer (Table 1).[9-17] These studies were highly heterogeneous in many aspects and, thus, cannot be directly compared to determine the overall efficacy of any one treatment approach. While highlighting the potential of neoadjuvant chemotherapy in the treatment of early-stage breast cancer, these studies (and others) have illustrated many of the difficulties associated with evaluation of the benefits of neoadjuvant chemotherapy.

**Predicting Response to Therapy**

One theoretical benefit of neoadjuvant chemotherapy is that it provides the ability to evaluate the in vivo response of disease to a specific regimen. This is potentially useful, given that there are no reliable methods of predicting response to postoperative adjuvant chemotherapy—a procedure that is, therefore, given "blindly." Although multiple attempts have been made to predict response to chemotherapy on the basis of the baseline characteristics of the primary tumor (grade, hormone-receptor status, S-phase fraction, and HER2 or p53 status), no method has proven reliable. Response to therapy, especially pathologic CR, has been reproducibly associated with long-term survival.

During neoadjuvant treatment, a major reduction (> 50%) in tumor dimensions predicts better outcome and encourages continuation of treatment with the same regimen. Conversely, if little apparent benefit is being achieved with a particular treatment, that treatment can be stopped to avoid further risk of side effects and toxicity, and the regimen can be changed to an alternative drug or combination that may produce a superior response. As shown in Table 1, high overall response rates were associated with the various regimens used in clinical trials, despite the very heterogeneous groups of patients included in these studies.

**Breast-Conserving Therapy**

High response rates may allow more patients to be eligible for breast-conserving therapy. In the early studies presented in Table 1, the criteria used to determine eligibility for breast-conserving therapy were not uniform, and, therefore, a comparison of this end point between trials is not possible. Moreover, the results were not compared with those of a control arm of surgery followed by adjuvant chemotherapy. The rates of breast-conserving therapy in these studies varied widely, ranging from 7% to 88%. However, these rates may be misleading, because the criteria used to determine operability were not uniform between trials.

The study by Schwartz et al was apparently initiated in 1979. However, breast-conserving therapy was not routinely used until 1983.[10] Among patients receiving neoadjuvant chemotherapy after 1990, the percentage who undergo breast-conserving therapy has increased to 75% of those evaluated. In some studies, an initial tumor size > 3 cm precluded patients from breast-conserving therapy[11,12]; in others, this approach was offered more liberally, depending only on the ratio of tumor size to breast size.[18] The studies using the first, more restrictive, criteria would likely be more successful in extending the indications for breast-conserving therapy after preoperative chemotherapy than would the studies using a more liberal set of criteria. Overall, these studies illustrate that breast-conserving therapy can be offered to a large percentage of patients who receive neoadjuvant therapy.

**Clinical Response and Long-Term Outcome**

The response of an individual tumor to treatment could be used as a primary end point to predict long-term outcome. Clinical response has been correlated with survival in trials evaluating neoadjuvant chemotherapy. In the study by Schwartz et al, patients whose tumor responses were amenable to breast-conserving therapy survived longer than did patients with similarly staged disease who were receiving chemotherapy and ultimately required mastectomy, although the differences were not significant.[10] Similar findings were described by Bonadonna et al.[11,12] Other reviews, by McCready et al and Kuerer et al, found that clinical response to neoadjuvant chemotherapy is a strong predictor of disease-free survival ($P = .046$).[19,20] In the second study,[20] patients who achieved a clinical CR had a 3-year disease-free survival rate of 95%, whereas patients with a clinical partial response (PR) or minor response had a 3-year disease-free survival rate of only 66%.

**Assessing Response to Neoadjuvant Systemic Therapy**

Estimating clinical response to neoadjuvant therapy has been problematic, given the dynamic modeling of tumors and breast tissue that can occur during treatment. During therapy, a fibrous
reaction can occur at the site of the tumor, leaving a palpable abnormality (which does not necessarily correlate with the pathologic response to therapy) assessable on clinical examination. Conversely, complete disappearance of palpable abnormalities cannot guarantee the absence of viable tumor cells. Improved precision in monitoring response to therapy could provide better estimates of treatment success (or lack thereof) and help guide subsequent therapy.

**Mammography vs Clinical Examination**

In addition to being a general screening tool, mammography has historically been used to identify the presence of breast tumors in patients with palpable abnormalities. Its use in evaluating clinical response to therapy is problematic, however, due to mixed data regarding its benefit. In the evaluation of response to locally advanced breast cancer, mammography has been found to have superior sensitivity and inferior specificity in determining the presence of residual tumor, compared with clinical examination.[21] However, another study showed that the ability to determine response is directly related to the delineation of normal tissue from tumor.[22] Ill-defined masses, such as those seen with lobular carcinoma, are not visualized well by mammography, thereby limiting its ability to determine response.[22] In addition, the ability of mammography to predict response is restricted when faced with the continued presence of microcalcifications at the completion of systemic therapy. Nevertheless, for patients with a clearly detectable lesion at baseline mammography, this modality combined with physical examination can be useful during chemotherapy.

**Adding Ultrasonography**

Ultrasonography, combined with mammography, has been shown to be both complementary and beneficial in defining breast cancer at diagnosis. The combined use of mammography with ultrasonography significantly increases the sensitivity and specificity of malignancy detection, with ultrasonography adding definition when determining the pathologic stage of the axillary lymph nodes.[23,24]

As a single test, neither mammography nor ultrasonography is superior to clinical examination in determining response to chemotherapy. The combination of all three modalities, however, is superior to any single one.[24] For example, a retrospective review of patients treated with anthracycline-based chemotherapy found that, compared with any single noninvasive evaluation, the combination of physical examination and mammography is best for assessing primary tumor response, while the combination of ultrasonography and physical examination is superior for evaluating the axillary lymph nodes.[24]

**Other Imaging Techniques**

To improve upon the limitations of standard radiographic techniques in evaluating response to therapy, researchers are examining the benefits of magnetic resonance imaging (MRI),[25,26] computed tomography (CT),[27] and positron-emission tomography (PET).[28] In addition to evaluating changes in tumor size after therapy, these imaging techniques may be able to better delineate residual invasive tumor from fibrosis or scarring. These modalities are still under investigation and have not been definitively proven to accurately predict response to neoadjuvant chemotherapy. Early results of PET studies suggest that a reduction in radionuclide uptake days or weeks after the initiation of neoadjuvant chemotherapy correlates closely with response to therapy. This correlation, if confirmed, could be used to make early predictions of response and decisions regarding continuation of or change in systemic therapy.

**Pathologic Findings Predict Long-Term Outcome**

Given that clinical response predicts outcome, it can be projected that pathologic data are a more specific determinant of long-term survival. The clinical response seen with neoadjuvant chemotherapy does not always correlate with the results of pathologic examination, leading to the question of which end point is a better predictive focus. In a review of two studies in over 500 women, Bonadonna et al found that although 16% of patients had a clinical CR, only 3% had a pathologic CR. Survival was significantly higher in the subset of patients who achieved a pathologic CR than in patients with only a clinical CR ($P = .0001$).[12] As seen in Table 1, the varied overall response rates vs pathologic CR rates for different treatment approaches highlight the limited sensitivity of clinical response in determining residual disease. In many studies, pathologic response is a better predictor of future relapse and survival than is clinical response.[29,30] Unfortunately, neither the clinical nor the pathologic assessments have been uniform across studies, making interpretation and generalization of the results difficult. It is important to note that although pathologic CR rates after neoadjuvant chemotherapy or endocrine
therapy correlate with long-term outcome, that is not necessarily true for pathologic CR rates obtained after combined chemotherapy and radiotherapy.

**Lymph Node Involvement**

Multiple adjuvant studies have shown that the strongest predictor of overall survival is lymph node involvement at the time of surgery.[1-3] Many researchers have been concerned that important prognostic information gained from lymph node evaluation at the time of surgery is lost with the use of neoadjuvant chemotherapy. As in the adjuvant setting, pathologic evaluation of residual disease in the lymph nodes has been correlated with outcome in patients treated with neoadjuvant chemotherapy. In several studies, an increasing number of lymph nodes involved with metastatic disease after systemic chemotherapy has been associated with a reduced disease-free survival.[19,20,29]

Pathologic evaluation of the breast and lymph nodes after neoadjuvant chemotherapy has also proven to have significant prognostic importance. This has been seen in studies in which a strict definition of pathologic CR (no residual invasive tumor in either the breast or the lymph nodes seen with serial sectioning) was used. One study found that the disease-free and overall survival of patients who achieved a pathologic CR with neoadjuvant chemotherapy was significantly prolonged at 5 years, compared with patients who had residual disease (disease-free survival rate: 87% vs 58%; overall survival rate: 89% vs 64%; \( P < .01 \)).[30]

**Probability of Micrometastases**

There are important conceptual differences between the implications of lymph node status after surgery alone and after neoadjuvant systemic therapy followed by surgery. In the first case, the presence of an increasing number of positive lymph nodes indicates a greater probability that micrometastases are present; in the second, the probability of micrometastases is compounded by the likelihood of resistance to the regimen used for systemic neoadjuvant therapy.

In the adjuvant setting, positive lymph nodes would certainly indicate the need to institute systemic adjuvant therapy to reduce the risk of recurrence and death. In the neoadjuvant setting, one would hypothesize that the presence of positive lymph nodes after neoadjuvant chemotherapy suggests that the introduction of an alternative, non-cross-resistant systemic treatment is indicated. This hypothesis is currently being evaluated in prospective randomized trials.

**Randomized Clinical Trials**

The early nonrandomized trials that evaluated the role of neoadjuvant chemotherapy in operable breast cancer highlighted the potential of this treatment approach. However, these trials did not definitively determine the long-term impact of this approach on multiple outcomes, including survival. Several randomized trials have been reported over the past 10 years, allowing better determination of the long-term impact of these regimens and their relative benefit compared with postoperative adjuvant therapy.

Seven randomized studies have been published in which neoadjuvant chemotherapy followed by surgery was directly compared with surgical resection followed by adjuvant chemotherapy in patients with operable breast cancer (Table 2).[31-39] As in earlier phase II studies, these protocols used a variety of chemotherapy regimens and criteria for offering breast-conserving therapy, and had variable lengths of follow-up. The primary objective of these studies, in general, was to determine the impact of neoadjuvant chemotherapy on survival, thereby aiding in the determination of the long-term benefit of this treatment approach.

**Makris et al Trial**

A study published by Makris et al in 1998[31] was an update of a study conducted between 1990 and 1995 and initially reported in 1995.[40] Patients who were 70 years old and younger (median: 56 years) were randomized to receive either neoadjuvant therapy with mitoxantrone (Novantrone) and methotrexate (with or without mitomycin [Mutamycin]) combined with tamoxifen for four cycles, followed by surgery, and an additional four cycles of chemoendocrine therapy in the adjuvant setting, or initial surgery followed by eight cycles of the same regimen. Patient characteristics were similar between the two treatment arms, and approximately 50% in each arm were premenopausal. Baseline tumor characteristics (stage I-IIIA) were also similar between arms. Estrogen-receptor status, progesterone-receptor status, and data from other predictive/prognostic factors were not reported in this study.

Patients who received neoadjuvant chemotherapy had significant clinical downstaging of both the breast and the axillae, with an overall response rate of 83%. After neoadjuvant chemotherapy, a significant improvement in the ability to perform breast-conserving therapy was also seen. However,
despite impressive antitumor activity, as exhibited by the ability of these regimens to downstage primary tumors, no difference in disease-free ($P = .08$) or overall survival ($P = 1.0$) was reported between the neoadjuvant and adjuvant treatment arms. The correlation between survival and clinical response or pathologic response was not assessed in this study.

**Mauriac et al Trial**

Another study, published by Mauriac et al in 1999, evaluated the use of chemotherapy with epirubicin (Ellence), mitomycin, thiotepa (Thioplex), and vindesine administered in either the neoadjuvant or adjuvant setting.[32] Patients in this study had stage II-IIIA breast cancer, a median age of 50 to 55 years, and were evenly matched for ER status, stage, and tumor grade. In the first published report (median follow-up: 34 months), only 36.9% of patients who received neoadjuvant chemotherapy required mastectomy, compared with 100% in the adjuvant arm. An additional 33% were treated with primary irradiation of the breast. In total, 69.9% of patients had received breast-conserving therapy at this point in follow-up. The patients who had received primary irradiation achieved a clinical CR after completion of neoadjuvant chemotherapy.

With a median follow-up of 124 months, the overall rate of breast-conserving therapy decreased to 45%. This can be partly explained by the finding that 47% of patients who were initially treated with primary irradiation of the breast and axillae developed disease recurrence (local recurrence in 34% of patients treated). Despite the high rate of local recurrence seen with primary irradiation, only 15% of those initially treated with breast-conserving therapy and 14% of those initially treated with mastectomy developed a local recurrence.

The use of primary irradiation makes it difficult to assess the potential efficacy of breast-conserving therapy. However, of interest, the rate of local recurrence was similar between patients who were initially treated with breast-conserving therapy and those who underwent mastectomy. Despite a decrease in the rate of breast-conserving therapy with continued follow-up, the long-term results were not adversely affected: Disease-free and overall survival rates were equivalent for patients in the neoadjuvant and adjuvant arms.

**Ragaz et al Trial**

At the 33rd annual meeting of the American Society of Clinical Oncology (ASCO) in 1997, Ragaz et al reported a study evaluating neoadjuvant chemotherapy with one cycle of CMF (cyclophosphamide, methotrexate, fluorouracil [5-FU]) followed by eight cycles of adjuvant CMF (for high-risk patients) compared with nine cycles of adjuvant CMF.[33] Enrollment of patients with stage I/II breast cancer began in 1983, and the long-term follow-up results presented were limited to survival data. The objective of the study was to determine the effect of administering a portion of the chemotherapy regimen while waiting for surgical management of the primary tumor.

At 10 years, there were no appreciable differences in overall survival between patients. However, considering that a median of three preoperative chemotherapy cycles is, in general, needed to achieve a clinical PR, this neoadjuvant protocol was unlikely to affect outcome. Moreover, a previous study that compared one perioperative cycle of CMF followed by six cycles of postoperative CMF showed no differences in disease-free or overall survivals.[41] Therefore, the study by Ragaz et al did not adequately clarify the role of neoadjuvant chemotherapy in the management of operable breast cancer.

**Scholl et al and Broet et al Studies**

Although many randomized trials over the past 10 years have had a balanced population of premenopausal and postmenopausal patients, the study initially reported by Scholl et al in 1994 (and updated by Broet et al in 1999) investigated the role of neoadjuvant chemotherapy in only premenopausal patients.[34,35] In this study, 390 evaluable premenopausal patients with stage I-IIIA (T2/3, N0/1) breast cancer were randomized to receive either four cycles of chemotherapy with doxorubicin, cyclophosphamide, and 5-FU followed by surgery or initial local therapy (irradiation with or without surgery) followed by chemotherapy with the same regimen. All patients in the adjuvant therapy arm received primary irradiation of the breast prior to evaluation for surgery. Patients with a persisting mass after irradiation had either a segmental mastectomy or a modified radical mastectomy.

Among patients in the adjuvant arm, 46% were treated with primary irradiation of the breast as a single modality for local control; an additional 32% underwent segmental mastectomy after irradiation, providing an overall breast-conserving therapy rate of 77%. Of patients receiving neoadjuvant chemotherapy, 82% received breast-conserving therapy, 51% had primary irradiation of the breast, and 31% underwent segmental mastectomy and irradiation. There was no statistically significant difference in survival or disease-free survival between arms, demonstrating the equal ability of both approaches to allow breast-conserving therapy.
Despite the apparent equivalency of adjuvant and neoadjuvant chemotherapy for local control of disease, the initial published report of this study found that patients who received neoadjuvant systemic chemotherapy had an improved 5-year overall survival, compared with patients in the adjuvant therapy arm (86% vs 78%; \( P = .04 \)). After a longer median follow-up (105 months), this survival advantage disappeared (64.6% for neoadjuvant vs 60.2% for adjuvant; \( P = \text{NS} \)).

**Semiglazov et al Trial**

Another study, reported by Semiglazov et al in 1994, evaluated the benefit of neoadjuvant chemotherapy combined with radiation therapy vs radiation therapy alone prior to surgery. A total of 271 patients with stage IIB-IIIA breast cancer were randomized to receive either primary irradiation of the breast or chemotherapy with thiotepa, methotrexate, and 5-FU for one to two cycles in combination with radiation therapy. After completion of radiation therapy (with or without chemotherapy), all patients underwent modified radical mastectomy and then received an additional four to six cycles of the same chemotherapy regimen.

Patients receiving the combination of chemotherapy and radiation therapy had a higher clinical CR rate (12.4%) and a higher mammographic CR rate (35.0%) than did patients receiving radiation therapy as a single modality (5.9% and 27.6%, respectively; \( P < .05 \)). The pathologic CR rate was also higher in the neoadjuvant chemotherapy group (29.1%) than in the group receiving primary irradiation (19.4%). The authors did not discuss the response of the axillae to this therapy. Although patients who received the combination of chemotherapy and radiation therapy had a superior disease-free survival (\( P = .0442 \)), there was no difference in overall survival between arms at a median follow-up of 53 months.

Because of the short duration of neoadjuvant chemotherapy in this study, it is doubtful that the design fully assessed the value of neoadjuvant chemotherapy. On the other hand, patients in this trial may have benefited from the close temporal proximity of the administration of chemotherapy and radiotherapy.

**Austrian Breast and Colorectal Cancer Study Group**

A more recent study was presented by the Austrian Breast and Colorectal Cancer Study Group at the 37th annual ASCO meeting in 2001. In the neoadjuvant arm of this randomized study, patients with high-risk ER-negative tumors (node-positive or large tumor size) received three cycles of CMF followed by surgery and postoperative chemotherapy based on nodal status. Node-positive patients received three cycles of epirubicin and cyclophosphamide, and node-negative patients received an additional three cycles of CMF. Patients treated in the adjuvant setting received similar chemotherapy based on nodal status.

Neoadjuvant chemotherapy improved the rate of breast-conserving therapy from 59.5% (adjuvant arm) to 66.7% (neoadjuvant arm). The pathologic CR rate achieved after three cycles of CMF was 6%. Interestingly, patients receiving neoadjuvant chemotherapy had an inferior relapse-free survival compared with patients treated in the adjuvant setting, although the difference was not statistically significant. Patients who did not respond to neoadjuvant CMF had a significantly inferior relapse-free survival rate (48.1%) compared with patients who achieved a response (70.8%) or patients treated in the adjuvant setting (77.0%, \( P = .0001 \)). The authors reported, however, that no difference in overall survival was seen between patients in the two treatment arms.

**NSABP B-18 Trial**

The largest published randomized trial to evaluate the role of neoadjuvant chemotherapy is the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial. In this trial, patients with stage I-IIIA breast cancer were randomized to receive chemotherapy with four cycles of AC (doxorubicin [Adriamycin], cyclophosphamide) in either the neoadjuvant or adjuvant setting (Figure 1). At 5-year follow-up, there was no difference in disease-free or overall survival between the 743 patients treated in the neoadjuvant setting (disease-free survival rate: 66.7%; overall survival rate: 72.3%) and the 752 patients treated in the adjuvant setting (disease-free survival rate: 67.3%; overall survival rate: 73.2%). Patients in both arms were well matched for tumor size, age, and clinical nodal status.

In the neoadjuvant arm, the overall response rate was 79%, and the clinical CR rate was 35%. The rate of breast-conserving therapy was higher among patients treated with neoadjuvant therapy (67%) than among those receiving adjuvant therapy (60%, \( P = .002 \)). This benefit was greatest for patients whose tumors were initially larger than 5.1 cm. Only 2% of patients in the adjuvant setting who had tumors larger than 5.1 cm received breast-conserving therapy, compared with 33% of patients in the neoadjuvant setting. The local recurrence rates for patients who received breast-conserving therapy were similar between treatment arms.
When survival was analyzed on the basis of treatment response, patients who achieved a clinical CR had a superior disease-free survival ($P = .0014$) and distant disease-free survival ($P = .0001$), compared with patients who achieved a clinical PR or less. Overall survival, however, was not statistically superior for those who achieved a clinical CR ($P = .19$). Patients who achieved a pathologic CR had a superior 5-year overall survival rate (88.7%), compared with patients in all other groups ($P = .0004$).

**Conclusions From the Randomized Trials**

From these randomized studies, one can conclude that neoadjuvant chemotherapy is an effective treatment for patients with operable breast cancer. With this approach, an additional 5% to 10% of patients can undergo breast-conserving therapy. Not only does neoadjuvant chemotherapy downstage the primary tumor, but it also downstages metastatic disease in the axillae.

In the NSABP B-18 trial, 72.9% of patients with clinically abnormal lymph nodes had a clinical CR to chemotherapy, and of all patients with clinically abnormal lymph nodes, 64% achieved a pathologic CR in the axillae.[38,39] These findings are supported by Kuerer et al, who reported in 2001 that, of 57 patients with clinically positive lymph nodes treated with neoadjuvant chemotherapy, 22 (39%) had pathologically negative nodes at the time of surgery; of 39 patients with positive axillary nodes by fine-needle aspiration, 11 (28%) were pathologically lymph node-negative at surgery.[42] Neoadjuvant chemotherapy has also been shown to be a safe therapy. Both the NSABP B-18 trial[38,39] and the study by Makris et al[31,40] found no evidence of increased risk for local recurrence by delaying primary therapy of the breast. Similar findings have been reported by the European Organization for Research and Treatment of Cancer (EORTC).[43] In their study, patients with operable breast cancer were randomized to receive either neoadjuvant FEC (5-FU, epirubicin, cyclophosphamide) followed by surgery or surgery followed by adjuvant FEC. With a median follow-up of 4.5 years, there were no differences in the locoregional recurrence rates (89.7% vs 90.5%; $P = .61$) or overall survival rates.

Although no overall survival advantage has been demonstrated for neoadjuvant chemotherapy, subgroups of patients (those obtaining a pathologic CR, for example) do achieve superior long-term survival compared with other patients. This response to therapy could therefore help predict who might require alternative or additional therapy when suboptimal results are obtained; it could also be used to allow earlier incorporation of neoadjuvant regimens into clinical practice. Regimens that improve the pathologic CR are more likely to have a positive impact on survival than are protocols with less optimal results.

Another perspective is that, on the basis of multiple prospective randomized trials comparing neoadjuvant and adjuvant chemotherapy regimens, no disadvantage has been demonstrated for neoadjuvant therapy. Therefore, neoadjuvant chemotherapy is an acceptable alternative to traditional strategies for primary operable breast cancer, even in patients who do not wish to preserve the breast.

**New Approaches to Improving Pathologic CR Rates**

Since the initiation of many of the randomized trials discussed above, the use of taxanes (paclitaxel and docetaxel [Taxotere]) as treatment for locally advanced and metastatic breast cancer has increased. These agents have recently been studied in the neoadjuvant setting in an effort to improve pathologic CR rates. Taxanes offer a non-cross-resistant mechanism of cytotoxicity, ie, in conjunction with anthracyclines (doxorubicin and epirubicin), which are commonly used as components of chemotherapy regimens in the neoadjuvant or adjuvant setting (FAC, AC, FEC, EC). It is hypothesized that eradicating tumor cells through multiple pathways can improve pathologic CR rates, which hopefully will translate into improved clinical survival.

Taxanes as single agents are arguably the most effective cytotoxic agents available for metastatic breast cancer. Multiple phase II studies have examined the role of paclitaxel and docetaxel in the adjuvant and neoadjuvant setting.[44-49] For example, in a phase II study from 1997 that evaluated the use of neoadjuvant docetaxel followed by surgery and then adjuvant AC, patients with stage III breast cancer achieved an overall response rate of 83% when docetaxel (100 mg/m²) was administered every 3 weeks for four treatments.[44] Recently, several randomized phase III studies of a taxane as a component of therapy for operable breast cancer have been published or presented at international meetings (Table 3).[45-48]

**Buzdar et al Trial**

A study by Buzdar et al in 1999 was designed to prospectively compare the benefit of single-agent paclitaxel vs FAC (5-FU, doxorubicin, cyclophosphamide) in the neoadjuvant setting.[33] Patients
with stage I-IIIA breast cancer were randomized to receive either paclitaxel or FAC every 3 weeks. After completing four cycles of therapy, all patients underwent local therapy followed by an additional four cycles of FAC. Pathologic evaluation of response found no statistical evidence of superiority for either treatment in producing a pathologic CR ($P = .11$). This study completed accrual in 1998, and long-term survival data are not yet available for patients treated in the neoadjuvant setting.

Preliminary results from the adjuvant portion of this protocol (patients randomized after surgery to either FAC or paclitaxel for four treatments, followed by four additional cycles of FAC) suggest a trend toward superior survival for those receiving non-cross-resistant therapy. However, the median follow-up was short, with too few events to determine the overall impact of the treatment.

**Green et al Trial**

In a study presented by Green et al at the 37th annual meeting of ASCO in 2001, patients with stage I-IIIA breast cancer were randomized to receive either weekly paclitaxel for 12 doses or paclitaxel administered every 3 weeks for four cycles followed by standard FAC chemotherapy for four cycles.[46] This study was unique, however, in that surgery was postponed until all systemic therapy was completed. Delaying surgery enabled the investigators to evaluate pathologic responses after the completion of all therapy, possibly improving the predictive value of the pathologic CRs achieved with neoadjuvant chemotherapy.

Preliminary results among the initial 127 patients enrolled showed a statistically significant improvement in the pathologic CR rate with weekly paclitaxel. The overall pathologic CR rate for patients who received paclitaxel was 31.3%, compared to 16% for patients receiving the standard schedule of paclitaxel followed by FAC. This study recently completed accrual, but there have been too few events to determine the impact of the difference in schedule and the resulting pathologic CR rate on overall survival.

**Thomas et al Study**

The idea of using non-cross-resistant chemotherapy to enhance survival has been studied previously in patients with locally advanced breast cancer.[50-52] For example, in a study reported by Thomas et al,[52] patients with stage IIIA/IIIB breast cancer received neoadjuvant VACP (vincristine, doxorubicin, cyclophosphamide, prednisone) for three cycles, followed by surgery. Patients who initially responded to chemotherapy but had residual tumor (> 1 cm) at the time of surgery were randomized to receive either additional treatment with VACP or alternative therapy with VbMF (vinblastine, methotrexate, 5-FU). With a median follow-up of 125 months, patients treated with VbMF showed a trend toward a higher disease-free survival than did patients maintained on initial therapy (46% vs 25%; $P = .133$). Perhaps the use of more efficacious agents, such as taxanes, in a similar scenario could provide a superior outcome.

**Smith et al Studies**

In an investigation conducted by Smith et al[13] in 1999 and in several recent updates,[47,48,53] patients with stage II-IIIB breast cancer were initially treated with CVAP (cyclophosphamide, vincristine, doxorubicin, prednisolone) for four cycles (Figure 2) and were then evaluated for clinical response. Those achieving a clinical CR or PR were randomized to continue therapy with the same regimen or switch to docetaxel for an additional four cycles. Patients with stable or progressive disease at the time of initial evaluation of response were automatically switched to docetaxel for four cycles without further randomization.

Of the 145 patients initially enrolled in the study, 142 had available pathologic data. With the first four cycles of CVAP, an overall clinical response rate of 67% was seen. Patients who did not achieve a response with the initial doses of CVAP and were switched to docetaxel had a final clinical CR rate of 13%. Patients with an initial response to therapy who were maintained on CVAP had an overall clinical CR rate of 34%, and initial responders who were randomized to docetaxel had a clinical CR rate of 62%.

As in other studies, the pathologic CR rates reflected the clinical response rates: Patients with an initial response to CVAP therapy who then received docetaxel had a superior pathologic CR rate of 34%; patients who received CVAP and docetaxel without an initial response to therapy had a pathologic CR rate of only 2%; and patients with an initial response who were then maintained on CVAP for an additional four cycles had an intermediate pathologic CR rate of 16%. With a median follow-up of 104 weeks, the patients who had the best response to combination therapy had a statistically significant improvement in disease-free survival, compared with patients who did not achieve such a response ($P = .022$). This study helped to confirm that alternating non-cross-resistant chemotherapy regimens can improve the pathologic CR. Hopefully, this will translate into a prolonged survival advantage.
NSABP B-27 Trial
The study by Thomas et al[52] and the study initially reported by Smith et al[47,48,53] also confirm that we can use the response to neoadjuvant chemotherapy to design additional interventions to improve overall outcome. The NSABP recently completed accrual for protocol NSABP B-27 (Figure 3). This three-arm randomized study is evaluating patients with stage I-IIIA breast cancer. Patients in the control arm receive neoadjuvant AC followed by surgery. Those randomized to the second arm receive four cycles of AC followed by four cycles of docetaxel prior to surgery. Patients in the final arm receive four cycles of AC followed by surgery and then four cycles of postoperative docetaxel. This study will hopefully confirm, on a much larger scale, that sequential non-cross-resistant chemotherapy is an important treatment strategy that can improve overall survival.

Other Ongoing Studies
Other active agents are also being evaluated in the neoadjuvant setting in an effort to improve pathologic CR rates and, hopefully, survival rates. Multiple studies are evaluating trastuzumab (Herceptin), capecitabine (Xeloda), taxanes, and anthracyclines in a variety of combinations and schedules. The immediate pathologic information gained from these studies will hopefully allow earlier incorporation of these agents into the treatment paradigm for operable breast cancer.

New Approaches to Predicting Response to Therapy
Administration of chemotherapy to a patient with an intact primary tumor provides a unique opportunity to evaluate response on the basis of known predictive factors. The information gained by correlating predictive and prognostic factors with response to a particular regimen could assist in the development of therapy tailored to an individual patient. Multiple prognostic and predictive factors have been analyzed in randomized studies and other studies evaluating patients given neoadjuvant chemotherapy (Table 4). (A prognostic factor is a feature of the tumor or patient that is present at the time of diagnosis and can help estimate the clinical course of a disease. A predictive factor is a feature usually of the tumor itself that can be identified and used to predict response to a specific treatment.[54])

Tumor Size and Nodal Status
Many features that are considered prognostic factors for patients treated in the adjuvant setting are also applicable to patients receiving neoadjuvant chemotherapy. For example, pretreatment tumor size has been correlated with prognosis; that is, large tumors are associated with poor outcome ($P < .0001$).[55] In the NSABP B-18 trial, tumor response was inversely related to initial tumor size; only 17% of patients with tumors larger than 5 cm achieved a clinical CR, compared with 59% of patients whose tumors were 2 cm or smaller.[39]

As seen in earlier neoadjuvant trials, pathologic response and lymph node status after surgery provide prognostic information similar to that provided by pathologic stage and lymph node status prior to surgery. Patients who achieve a pathologic CR in the breast and axillae have a better survival rate than patients who do not achieve such a response. Moreover, the presence of positive lymph nodes after neoadjuvant chemotherapy is more highly correlated with an inferior outcome than is the response seen at the primary tumor site.[38]

Experience with locally advanced breast cancer at The University of Texas M. D. Anderson Cancer Center has shown that, when patients are evaluated by nodal status (number of positive lymph nodes = 0, 1-3, 4-10, and so forth), their disease-free and overall survival rates are similar to those of patients who initially undergo surgery. However, when an equal number of positive lymph nodes are present in patients initially treated with surgery and in those treated with neoadjuvant chemotherapy followed by surgery, those treated in the neoadjuvant setting have a worse prognosis.[55] Residual disease in the axillae may reflect the behavior of microscopic disease elsewhere, thus signifying tumor resistance to chemotherapy.

Biological Factors
In addition to tumor size and nodal status, multiple biological factors inherent to tumors have been examined as prognostic and predictive factors (Table 5).[56-59] Selecting chemotherapy on the basis of predictive factors could someday help tailor effective chemotherapy based on characteristics of the tumor and the patient. The role of these biological factors as predictive markers, however, is still poorly defined. Of the randomized studies that have evaluated neoadjuvant therapy as treatment for operable breast cancer, Mauriac et al conducted the only one that prospectively assessed predictive factors.[32] Several features were analyzed as prognostic factors that could determine survival and were correlated with response to therapy. Patients with estrogen- and progesterone-receptor-negative tumors had an improved response to
therapy, manifested by improved rates of breast-conserving therapy. Among patients with estrogen- and progesterone-receptor-negative tumors, 77% were able to receive breast-conserving therapy, compared with only 52% of those whose tumors expressed these hormone receptors. Ki-67, a nuclear antigen expressed in proliferating cells, was also analyzed from tissue obtained prior to therapy. An increasing percentage of Ki-67 was associated with a better tumor response. HER2/neu did not provide predictive value in this study, nor did it correlate with disease-free or overall survival rates.

Table 5 highlights the complexities associated with evaluating a feature as a prognostic or predictive factor for patients receiving neoadjuvant therapy, by presenting the mixed results of multiple studies (many of which were retrospective).[56-59] At this time, the role of biological markers as prognostic and predictive factors is under continued investigation. Only prospectively collected data from well-designed clinical trials will help define the future use of these factors.

Past Progress and Future Directions

Neoadjuvant chemotherapy as a treatment paradigm for operable breast cancer continues to be developed and explored. Initial nonrandomized phase II studies have demonstrated the following potential advantages of neoadjuvant chemotherapy: (1) in vivo assessment of response, (2) downstaging of primary tumor and lymph node metastases, (3) improved rates of breast conservation, and (4) assessment of the likelihood of future relapse and death based on clinical and pathologic response. Moreover, these randomized studies have established neoadjuvant chemotherapy as a safe and effective treatment, but they do not provide evidence that this strategy, utilizing the same chemotherapy regimen, improves overall survival. Newer trials employing more aggressive (or non-cross-resistant) therapy may help improve pathologic CR rates and, hopefully, long-term survival.

Future trials have the opportunity to further define a role for neoadjuvant chemotherapy. Ongoing studies are exploring the use of in vivo response to therapy and dynamic modeling of therapy to increase pathologic CR and survival rates. The role of the currently accepted prognostic and predictive factors used in the adjuvant setting could be redefined in terms of their value in the neoadjuvant setting. New approaches, such as evaluation of gene expression profiles before, during, and after neoadjuvant therapy, may provide more specific predictive and prognostic information than can be gained from currently used tests. New technologies, such as PET, may be more accurately used to determine response to therapy and allow alteration of chemotherapy in a more specific and timely manner.

One study, published by Schelling et al in 2000, evaluated the role of PET monitoring of fluorine-18 fluorodeoxyglucose (FDG) metabolism as a determinant of response to neoadjuvant chemotherapy.[60] Patients with locally advanced breast cancer received a PET scan with FDG administration before and after the first cycle of chemotherapy (epirubicin and cyclophosphamide or paclitaxel). The results of the PET scans were correlated with pathologic findings obtained after the completion of chemotherapy. The authors found a statistically significant difference in the patterns of FDG uptake between patients who had a major pathologic response to chemotherapy and those who did not. Histopathologic response was predicted with an accuracy of 88% using PET with FDG. Although this and similar approaches are still investigational, such studies demonstrate ways in which neoadjuvant chemotherapy might be used in the future.

Conclusions

The literature reflects increasing interest in the introduction of neoadjuvant chemotherapy to the management of operable breast cancer. Several randomized trials have demonstrated the equivalence of strategies that use chemotherapy before surgery and those in which chemotherapy follows surgery. Currently, neoadjuvant chemotherapy is a safe option for patients wishing to increase their chances of breast conservation. As experience with neoadjuvant chemotherapy increases, the role of this treatment approach in operable breast cancer will become better defined. The use of two non-cross-resistant chemotherapy regimens appears to increase the pathologic CR rate and may lead to improved long-term outcome. Ongoing clinical trials will determine the role of several new active agents in neoadjuvant chemotherapy.

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