Historically, neoadjuvant chemotherapy was used in an effort to improve the disease-free survival in patients with locally advanced breast cancer that was considered inoperable at presentation. These patients’ primary tumors were large, fixed to the chest wall or skin, or had overwhelming axillary nodal disease that resulted in nodes becoming matted together and difficult or impossible to separate from axillary neurovascular structures. Neoadjuvant chemotherapy offered the hope that cancer cells in large and/or fixed primary tumors and bulky axillary lymph nodes could be downsized, if not eradicated, and facilitates a routine surgical procedure (eg, modified radical mastectomy) that in combination with radiotherapy would achieve local regional control of malignancy and enhanced survival.

The initial evidence to support neoadjuvant chemotherapy in the multimodality approach to locally advanced breast cancer is based on studies from MD Anderson, where patients with stages IIB, IIA, IIIB, and regional IV disease were treated with

KEYWORDS

- Neoadjuvant chemotherapy
- Trastuzumab
- Nodal disease
- Breast cancer

KEY POINTS

- Neoadjuvant chemotherapy is still the preferred approach for patients with locally advanced disease.
- Randomized prospective trials have demonstrated that early-stage patients with breast cancer who prefer breast conservation can benefit from neoadjuvant chemotherapy by achieving about a 25% complete and a greater than 80% partial pathologic response.
- Patients who opt for neoadjuvant chemotherapy should have a clinical and radiographic assessment of the axilla.
- If nodal disease is demonstrated at the time of diagnosis, then axillary staging requires a node dissection.
- Neoadjuvant trastuzumab seems to be an excellent option for patients with Her 2-neu–positive cancers.

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initial chemotherapy followed by mastectomy, radiotherapy, and postoperative adjuvant chemotherapy.\textsuperscript{1–4} This group was compared with a historical control group treated with surgery and radiotherapy only. At least a 50% reduction in the size of the tumor (partial response) was achieved in 67% of patients and complete responses were noted in 17% of patients. The 5-year and 10-year disease-free survival was 71% and 40% for the IIB and IIIA group and 33% and 30% for the stage IIIB and IV patients, respectively. These dramatic results for patients with historically poor prognosis for disease-free survival led to the enthusiastic development of National Surgical Adjuvant Breast and Bowel Project (NSABP) protocols to evaluate the potential benefits of neoadjuvant chemotherapy for patients with earlier stage breast cancer in comparison to postoperative adjuvant systemic treatment.

The first such protocol was the NSABP B-18 trial, which randomized patients to receive Adriamycin and cytoxan before or after definitive breast surgery (either mastectomy or breast-conservation surgery).\textsuperscript{5,6} Disappointingly, there was no impact on disease-free or overall survival between the 2 treatment arms. Despite the apparent efficacy of neoadjuvant chemotherapy in the locally advanced setting, no survival benefit was apparent in the B-18 trial. However, the patients who received preoperative chemotherapy demonstrated a statistically significant ($P = .002$) increase in the use of breast conservation over mastectomy. The 36% rate of clinical complete response and 13% rate of pathologic complete response in the patients receiving neoadjuvant chemotherapy in the B-18 trial allowed for sufficient tumor shrinkage to permit an increased use of breast conservation surgery.

In the follow-up NSABP B-27 trial, the potential beneficial role of the addition of a taxane to anthracycline-based chemotherapy was investigated.\textsuperscript{7} The trial was a 3-arm study comparing preoperative adriamycin and cytoxan followed by surgery to 2 groups that received a taxane in addition to the adriamycin and cytoxan (1 before and 1 after surgery). Once again no difference in disease-free or overall survival was demonstrated. Interestingly, in this trial the addition of a taxane increased the pathologic rate of complete response to 26%, thereby increasing the potential use of breast conservation. Although both the NSABP B-18 and the NSABP B-27 studies are used to justify the use of neoadjuvant chemotherapy to maximize the opportunity to use breast conservation, it is important to acknowledge that the preoperative determination of which patients will ultimately succeed in achieving breast conservation is inexact. Nevertheless, these trials provide the best available evidence to argue in favor of using neoadjuvant chemotherapy to downsize breast tumors that have an unfavorable tumor-to-breast size ratio to increase the use of breast conservation. Patients who achieve complete or significant partial responses can avoid mastectomy that would be recommended if surgery were to precede chemotherapy. It is important to restate that the use of neoadjuvant chemotherapy for earlier stage breast cancer (T1–2, N0–1) provides no survival advantage compared with the use of traditional postoperative adjuvant chemotherapy.

The evaluation of a response to neoadjuvant chemotherapy has 3 different components. A clinical complete response is the disappearance of all palpable malignancy from the breast and axilla based on physical examination. As expected, this is an inaccurate assessment and requires a more definitive assessment that includes imaging.\textsuperscript{8–11} A complete radiographic response would be the disappearance of all radiographic evidence of malignancy. Although mammography and ultrasound have historically provided this assessment, more recently, breast magnetic resonance imaging (MRI) has been used and demonstrated to be the most accurate radiographic predictor of complete response. Unfortunately, a complete radiographic response might still be accompanied by persistence of cancer and excision of the focal point of breast
malignancy is essential to determine definitively the extent of response. The discrepancy between a radiographic and pathologic response can be due to the persistence of intraductal cancer that is in association with the primary invasive cancer. Intraductal cancer is typically not affected by cytotoxic chemotherapy and will persist during treatment. Also, invasive cancer that is no longer apparent on radiographic assessment after chemotherapy might still persist as microscopic islands of viable cancer in a background of eradicated cancer cells affected by the chemotherapy. These microscopic islands of tumor reflect a fragmented response to neoadjuvant chemotherapy that can challenge a surgeon’s ability to achieve breast conservation. Complete excision of these persistent areas of cancer after chemotherapy are essential to maximize treatment-related outcomes. Therefore, regardless of the extent of response to neoadjuvant chemotherapy, surgical excision of a portion of the breast should be performed after the patient recovers from the last planned neoadjuvant chemotherapy dose. Surgery is typically performed about 4 weeks after treatment to allow for recovery from the myelosuppressive toxicity of neoadjuvant chemotherapy. The extent of excision does not necessarily have to include the entire area of malignancy identified before chemotherapy. Instead, the central area of malignancy that should be marked with a clip before initiating chemotherapy becomes the target for excision after a complete or near complete response. The same principles that apply to breast conservation without neoadjuvant chemotherapy still apply, in that margins of excision should be assessed and considered negative. One particularly difficult dilemma arises when scattered islands of viable tumor persist without radiographic identifiers and the entire area of preoperatively demonstrated cancer is not excised. In these situations a more extensive lumpectomy should be considered. Clearly, when a complete radiographically responded cancer is excised in part and no viable tumor is identified, then additional breast surgery is not required and radiotherapy can be added to achieve acceptable rates of local tumor control.

The importance of radiotherapy cannot be overstated for patients receiving neoadjuvant chemotherapy and opting for breast conservation. In the NSABP B-18 trial, the group of patients that was predicted to need mastectomy but was converted to breast conservation after achieving a response to neoadjuvant treatment suffered a 15.7% rate of breast recurrence, which was significantly higher than the group that was considered good breast conservation candidates before neoadjuvant treatment (9.9%). This concern regarding a higher rate of local recurrence was also demonstrated in a meta-analysis that was flawed by the inclusion of patients who did not have surgery if they were considered to have achieved a complete radiographic response. Patients with persistent tumor that was not excised after neoadjuvant chemotherapy contributed to a higher than acceptable rate of local recurrence. Perhaps the most important evaluation of local recurrence after breast conservation achieved with the aid of neoadjuvant chemotherapy comes from the MD Anderson retrospective evaluation of breast conservation after neoadjuvant chemotherapy, demonstrating a low (9%) rate of local recurrence compared with breast conservation patients treated without neoadjuvant chemotherapy. The 1 subgroup that was at particular risk of local failure was the group previously mentioned, whereby chemotherapy results in a fragmented pattern of persistent tumor. This group suffered a 20% rate of local recurrence. This fragmented pattern of tumor persistence should be considered a strong relative contraindication for breast conservation after neoadjuvant chemotherapy. The final decision as to whether to pursue breast conservation after breast conservation should be based on the ability to achieve negative margins and an esthetically satisfactory-appearing breast that can be treated with whole breast radiotherapy.

Another important consideration for patients hoping to achieve breast conservation after neoadjuvant chemotherapy is placement of a radiographic marker near the
center of the tumor before initiating chemotherapy. This marker allows for detection of the appropriate breast excision site in the event of a complete radiographic response to treatment. The evaluation for complete clinical response requires both pretreatment and posttreatment imaging studies. In addition to standard mammography and ultrasound, the value of breast MRI has been reported. Although MRI is superior to clinical examination, mammography, and ultrasound, it still lacks the accuracy to select women for breast conservation reliably. There is no substitute for excellent clinical judgment that mandates that the surgeon clinically and radiographically evaluate patients before, during, and after neoadjuvant therapy to provide women the best opportunity for breast conservation. Ultimately, unless clinical and radiographic assessments clearly demonstrate an unfavorable tumor-to-breast ratio after chemotherapy, the decision to use breast conservation will be based on the pathologic assessment of a lumpectomy specimen to determine response to treatment and the adequacy of margins.

Women who receive neoadjuvant chemotherapy that does not respond present a management challenge. One of the theoretical advantages of neoadjuvant chemotherapy is the opportunity to assess a tumor’s responsiveness to treatment and develop alternative strategies for nonresponders. In reality, resistance to the effects of a chemotherapy regimen predicts resistance to alternative drugs. In a trial of more than 600 patients who received 4 cycles of neoadjuvant anthracycline-based treatment that failed to respond, patients were randomized to 4 additional cycles versus a theoretically non-cross-resistant regimen of vinorelbine and capecitabine before surgery. Neither group of patients had any significant benefit from additional chemotherapy, suggesting a broad resistance to cytotoxic systemic therapy. This cytotoxic systemic therapy should not be confused with the benefits of adding a taxane to anthracycline-based chemotherapy in the neoadjuvant setting as demonstrated in the B-27 trial. There is a difference between achieving an improved response by the addition of chemotherapy to patients likely to respond compared with adding alternative additional systemic treatment of nonresponders. In other words, tumors that are resistant to chemotherapy are broadly resistant.

Once a decision has been made to treat a woman with neoadjuvant chemotherapy, the next priority is an evaluation of the regional nodes in the axilla. When axillary nodal disease is detected on clinical examination or suggested on radiographic study, a confirmatory percutaneous biopsy (usually by fine-needle aspiration) is recommended. For patients with involved nodes at the time of diagnosis, a node dissection (levels I and II) should be performed at the time of breast surgery, regardless of the response achieved by neoadjuvant chemotherapy. For patients without evidence of axillary disease that are planning neoadjuvant chemotherapy, a decision to stage the axilla before or after systemic treatment must be made.

The advantage of mapping before chemotherapy is that axillary status can be determined at the time of diagnosis and not confounded by the response to chemotherapy. The response to chemotherapy in the axilla could be uneven with a complete response to chemotherapy being achieved in the sentinel node and an incomplete response in nonsentinel nodes. A negative sentinel node after neoadjuvant chemotherapy could potentially be a false negative finding and axillary disease in nonsentinel nodes might be left untreated, especially if radiotherapy was not to be included (eg, mastectomy patients). Proponents of performing sentinel node biopsy before neoadjuvant chemotherapy argue that the accuracy of the technique and the important prognostic information obtained provide for superior treatment planning. This opinion was more prevalent in the 1990s and early 2000s, when reports of sentinel node accuracy after neoadjuvant chemotherapy were lower than the rates achieved for patients with breast
cancer treated with initial surgery that included sentinel node mapping. An example of
the inferior sentinel node mapping rates of accuracy after neoadjuvant chemotherapy
can be found in the NSABP B-27.18 A total of 428 patients had sentinel node mapping
attempted after neoadjuvant chemotherapy and the sentinel node was identified in
only 84% of cases. Furthermore, a total of 218 patients with negative sentinel nodes
underwent a complete axillary node dissection; a false negative sentinel node was
demonstrated in 10.7% of patients. These results were published at a time when
surgeons treating early-stage breast cancer were identifying sentinel nodes in greater
than 90% of cases and false negative sentinel nodes were found in less than 5% of
cases. Subsequently, reports were published of better rates of node identification
and fewer rates of false negative sentinel node after neoadjuvant chemotherapy.
The accuracy of sentinel node mapping after neoadjuvant chemotherapy and the
opportunity to avoid an unnecessary surgical procedure before starting breast cancer
chemotherapy made axillary staging after neoadjuvant chemotherapy more attractive.
Recently, the results from the American College of Surgeons Oncology GroupZ-11 trial
have provided even more enthusiasm to defer axillary staging until after neoadjuvant
chemotherapy.19 The Z-11 trial failed to demonstrate an impact on survival or axillary
recurrence when patients with a positive sentinel node were treated with breast
conservation and whole breast radiotherapy. It is important to point out that the
Z-11 trial excluded patients treated by mastectomy and required a clinically negative
axilla at the time of breast cancer diagnosis. Although the Z-11 trial is controversial,
patients with a clinically negative axilla that undergo neoadjuvant chemotherapy to
enhance opportunities for breast conservation, with a positive sentinel node, no longer
require a complete axillary node dissection. An argument might be made that the Z-11
trial did not include patients treated with neoadjuvant chemotherapy and therefore all
such patients should have an axillary dissection for staging. In practice, when neoad-
juvant chemotherapy is used to optimize breast conservation and if the axilla is nega-
tive at the time of initial diagnosis, the results of Z-11 should still be valid.

Women with tumors that express hormone receptors can have treatment with neoad-
juvant endocrine therapy. Both tamoxifen and aromatase inhibitors have been evaluated
as neoadjuvant agents and have rates of response that approximate neoadjuvant
chemotherapy for patients who have estrogen-positive and/or progesterone-positive
tumors.20,21 These rates of response reflect the fact that neoadjuvant chemotherapy is
less effective in estrogen receptor–positive tumors compared with estrogen
receptor–negative cancer. Rates of partial response of about 60% can be expected
for neoadjuvant endocrine therapy in receptor-positive cases. Complete response to
neoadjuvant endocrine therapy is uncommon with reported rates of 3% to 10%. Patients
with estrogen-positive or progesterone-positive tumors and unfavorable tumor-
to-breast size ratios for breast conservation who achieve a partial response to neoadju-
vant endocrine therapy can be converted from requiring mastectomy to potential breast
conservation candidate, which is similar to neoadjuvant chemotherapy.

An interesting group of patients for consideration of neoadjuvant endocrine therapy
includes women with invasive lobular cancer. Invasive lobular cancer is nearly always
estrogen receptor–positive and often these tumors are poorly visualized on mammog-
raphy and therefore present at a larger size compared with invasive ductal cancer.
These larger invasive lobular estrogen receptor–positive tumors do not respond as
favorably to neoadjuvant chemotherapy and their larger size makes breast conserva-
tion challenging to accomplish.22,23 For women who hope to achieve breast conserva-
tion, neoadjuvant endocrine therapy can provide an opportunity for tumor
shrinkage and a more favorable tumor-to-breast size ratio that will allow for a cosmet-
ically satisfactory posttreatment breast appearance.
An area of ongoing investigation that holds promise for enhanced rates of response to neoadjuvant chemotherapy is the treatment of the patient with overexpression of Her 2-neu receptors. Targeted therapy to the Her 2-neu receptor with trastuzumab has the potential to improve rates of complete response. Her 2-neu has consistently proven to be a marker of an inferior prognosis; however, like many markers that reflect an increased level of biologic aggressiveness, Her 2–rich tumors when treated with systemic therapies have an increased rate of chemosensitivity and rate of response. In 1 small trial (42 patients) that used trastuzumab in the neoadjuvant setting for Her 2–positive tumors, rates of complete response were 67% compared with 25% for the chemotherapy-only arm.24

In summary, neoadjuvant chemotherapy is still the preferred approach for patients with locally advanced disease. Randomized prospective trials have demonstrated that patients with early-stage breast cancer who prefer breast conservation can benefit from neoadjuvant chemotherapy by achieving about a 25% complete and a greater than 80% partial pathologic response. These responses do not translate into a survival advantage. For earlier stage patients, neoadjuvant chemotherapy’s primary advantage is the ability to increase the use of breast conservation. Patients who opt for neoadjuvant chemotherapy should have a clinical and radiographic assessment of the axilla. If nodal disease is demonstrated at the time of diagnosis, then axillary staging requires a node dissection. When the axilla is considered negative at the time of diagnosis, sentinel node mapping should be performed after neoadjuvant chemotherapy. Negative sentinel nodes do not require node dissection. Patients with positive nodes can avoid node dissection if breast conservation with whole breast radiotherapy is planned. Neoadjuvant endocrine therapy is an option for estrogen receptor–positive patients. Neoadjuvant trastuzumab seems to be an excellent option for patients with Her 2-neu–positive cancers. The inability to predict the extent and pattern of response to chemotherapy requires that surgeons monitor patient’s response during neoadjuvant chemotherapy to provide optimal surgical planning.

REFERENCES


