Advances in Neoadjuvant and Adjuvant Therapy for Breast Cancer
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OVERVIEW
Systemic therapy for breast cancer is evolving rapidly. The medical treatment of cancer includes chemotherapy, endocrine therapy, and therapy with targeted biologic agents. In the past, a patient’s stage, based on tumor size and nodal involvement, would determine the recommendations for medical therapy, whereas now the biologic features of the tumor direct the treatment plan. As a result of advances in the understanding of these biologic features, individualized systemic therapy is effective, less toxic, and directed at the tumor profile. Systemic treatment may influence the surgical and radiation options; thus surgeons should be involved with these medical decisions in both the neoadjuvant and adjuvant settings. In view of the many treatment options available, a multidisciplinary approach, starting at the time of diagnosis, can provide a tailored plan that results in the best outcome for patients. The adjuvant and neoadjuvant therapy for operable stages I, II, and III breast cancer are described in this chapter.

Neoadjuvant Systemic Therapy
Neoadjuvant systemic therapy has many proven benefits. Its effectiveness offers valuable prognostic information, and the rates of disease-free and overall survival are equivalent to those for adjuvant therapy. Clinicians can alter therapy if the tumor does not respond and can also distinguish a subset of patients who have an improved outcome: pathologic complete response (pCR). In addition, neoadjuvant therapy has the potential to improve surgical outcomes. For women in whom at presentation mastectomy appears to be the best option, it increases the possibility for breast-conserving surgery by approximately 16%. For women who are potential candidates for breast conservation at presentation, it limits the area of resection, and cosmesis is better. Neoadjuvant systemic therapy can be delivered either as chemotherapy, with or without biologic therapy, or as hormonal therapy.

Neoadjuvant Chemotherapy
The safety and efficacy of neoadjuvant chemotherapy have been demonstrated in several randomized controlled trials. Patients who are candidates for adjuvant therapy can also be considered for neoadjuvant therapy. Neoadjuvant chemotherapy does not increase the surgical complication rate, worsen survival by delaying surgical treatment, or decrease the accuracy of findings in the sentinel lymph node biopsy (Table 1).

There is no difference in overall survival or disease-free survival benefit between neoadjuvant and adjuvant therapy. Benefits for the patient include improved prognostic information and increased opportunities for breast conservation. Patients with a pCR after neoadjuvant therapy have an improved prognosis, and patients with no response have a considerably worse prognosis. The most immediate benefit from the neoadjuvant approach occurs in patients who are candidates for mastectomy at presentation but whose treatment can potentially be converted to breast conservation if the tumor has a favorable response to treatment; the best results occur with tumors more likely to achieve a pCR. Patients more likely to have a pCR tend to be younger (<40 years of age), have a high-grade tumor with a Ki67 protein level greater than 20%, and have tumor receptors that do not have estrogen receptor (ER), progesterone receptor (PR), or Her 2 neu (triple negative) or are ER-negative and PR-negative and Her 2 neu-positive (Table 2).

For breast cancers that are either ER+ or ER– but also Her 2 neu–negative, standard neoadjuvant chemotherapy is a doxorubicin (Adriamycin)–based regimen for 3 to 4 months before surgery. If the patient is Her 2 neu–positive, trastuzumab (Herceptin) is administered with a taxane (e.g., docetaxel) and carboplatin; doxorubicin is usually omitted because of the potential for increased cardiac toxicity. The patient should be monitored during therapy with a clinical examination after each cycle. If the tumor is not clinically responding after two to three cycles, chemotherapy should be stopped, and the patient should proceed to surgery.

Neoadjuvant Endocrine Therapy
Historically, the use of neoadjuvant endocrine therapy was limited to patients whose conditions were not suitable for chemotherapy. However, several trials demonstrated similar overall response rates in postmenopausal ER/PR-positive patients treated with neoadjuvant endocrine therapy or chemotherapy. Certain tumor characteristics are predictive of a poor response to neoadjuvant chemotherapy but could be considered for neoadjuvant endocrine therapy: low-grade tumors with high ER/PR positivity, low Ki67 protein proliferative index, and certain histologic features such as lobular, tubular, and low-grade mucinous tumors (see Table 2).

For postmenopausal patients who are candidates for neoadjuvant endocrine therapy, aromatase inhibitors are recommended over tamoxifen. Several trials have shown increased rates of response, which lead to a higher rate of breast-conserving therapy with aromatase inhibitors. The P024 trial was the first to compare neoadjuvant use of letrozole with tamoxifen in postmenopausal women with locally advanced ER/PR-positive disease. The overall response rates were 55% for letrozole and 36% for tamoxifen (P < 0.001). Significantly more letrozole-treated patients underwent breast-conserving surgery (45% vs 35%, respectively; P = 0.022). Based on the American College of Surgeons Oncology Group’s (ACOSOG’s) Z1031 trial, no particular aromatase inhibitor is preferred in the neoadjuvant setting; exemestane, letrozole and anastrozole all had equivalent outcomes.

The duration of neoadjuvant endocrine therapy must be at least 4 months to produce an optimal response; this time period varies among patients. In those who desire a lumpectomy and are showing a good clinical response, neoadjuvant endocrine therapy can safely be extended to a maximum duration of 8 months with carefully monitoring.

At this time, premenopausal women are not considered candidates for neoadjuvant endocrine therapy outside of a clinical trial. Future research will reveal whether such patients could also benefit from this treatment approach.

Surgery After Neoadjuvant Therapy
Before the initiation of systemic therapy, the tumor must be adequately marked with clips, and biopsy samples must be taken from any lesions of concern. Tumor response should be assessed with...
bimonthly clinical exams. If the clinical response is ambiguous, the breast can be imaged with ultrasonography or mammography. Evaluation of treatment response during or after neoadjuvant chemotherapy is also an accepted indication for breast magnetic resonance imaging (MRI). If the patient is receiving chemotherapy, the authors normally wait 2 to 3 weeks after the last dose of therapy or until the white blood cell count is within normal range before surgery is performed. For neoadjuvant endocrine therapy, no waiting period is necessary before surgical resection.

After the completion of systemic therapy, the surgeon and patient must decide whether a lumpectomy is feasible. Imaging with ultrasonography, mammography, or MRI, or a combination of these, can help guide this decision, but the ultimate surgical goal is to achieve negative margins, remove all malignant calcifications, and produce a cosmetically acceptable result. To achieve negative margins, a second margin excision may be necessary. In women with larger breasts, an oncoplastic approach can be used to achieve acceptable cosmesis after a larger resection. If negative margins cannot be achieved, a mastectomy with or without reconstruction should be performed.

If metastatic disease to the axilla is diagnosed before the initiation of chemotherapy, either through sentinel lymph node biopsy or through image-guided biopsy, the standard of care is to perform a lymph node dissection at the time of the tumor resection after the completion of neoadjuvant systemic therapy. The results of ACOSOG’s Z1071 study, presented in abstract form at San Antonio Breast Cancer Symposium 2012, demonstrated that with at least two nodes recovered in a sentinel lymph node biopsy after neoadjuvant chemotherapy, clinicians can accurately assess tumor response in the axilla and can reasonably assess nodal status in node-positive cases. Because neoadjuvant chemotherapy eradicated nodal disease in 40% of patients in this study, further research will dictate whether an axillary lymph node dissection can be omitted if the sentinel lymph node is negative in these patients after systemic therapy. Until that information is available, the authors recommend an axillary node dissection for most patients who had node-positive disease before neoadjuvant chemotherapy and absolutely when nodal disease persists after neoadjuvant chemotherapy.

### ADJUVANT THERAPY

#### Endocrine Therapy

Estrogen and progesterone receptor–positive tumors constitute 75% of all breast cancers. Stimulation of these receptors by estrogen is a critical step in the development of breast cancer. Three treatment options exist to target ER/PR receptors: tamoxifen, aromatase inhibitors, and ovarian suppression or ablation.
Defining ER/PR-positive breast cancers has been a controversial topic because of the heterogeneity of expression. It is now understood that any degree of positivity qualifies patients for estrogen-targeted treatment, although the greater the degree of expression of estrogen and progesterone receptors, the greater the response to treatment.

**Premenopausal Patients**

Approximately one fifth of all new cases of breast cancer occur in women younger than 50 years of age, and 60% of these cases are ER-positive. Options for these patients include tamoxifen, ovarian suppression or ablation, or a combination of ovarian suppression with tamoxifen. Tamoxifen is a selective estrogen receptor modulator, and it inhibits the growth of breast cancer cells by competitively binding to the estrogen receptor. It should be offered for at least 5 years. If it is tolerated well and the tumor is aggressive, tamoxifen can be given for up to 10 years.

The benefits of tamoxifen in the adjuvant setting were clearly demonstrated from the 2011 Early Breast Cancer Trialists Collaborative Group’s (EBCTCG’s) meta-analysis of randomized trials. In ER-positive patients, breast cancer mortality was reduced by 30% in the first 15 years of follow-up when tamoxifen was used in the adjuvant setting for 5 years. Breast cancer recurrence was reduced by 39%. This benefit was seen in both premenopausal and in postmenopausal patients. Side effects of tamoxifen are a nonsignificant increase in stroke-related deaths and an increase risk of uterine cancer (3.8% vs 1.1% in the control group). There was a trend toward a lower incidence of cardiac deaths.

Ovarian suppression in addition to tamoxifen has shown benefit in reducing rates of breast cancer recurrence and mortality. Ovarian suppression can be accomplished with the use of luteinizing hormone–releasing hormone (LHRH) agonists. For premenopausal women, the 2007 EBCTCG meta-analysis showed that LHRH agonists alone showed a trend toward reducing recurrence (28% relative reduction, $P = 0.08$) in comparison with no further systemic treatment. When LHRH agonists were administered with tamoxifen, the risk of both recurrence and death was significantly decreased.

In a more recent trial, the North American Intergroup trial INT 0101, premenopausal patients with node-positive disease were randomly assigned to receive one of three protocols: (1) chemotherapy alone: cyclophosphamide, doxorubicin, 5-fluorouracil (CAF); (2) CAF followed by 5 years of an LHRH agonist, goserelin; or (3) CAF with both goserelin and tamoxifen. With a median follow-up period of 9.6 years, addition of tamoxifen and goserelin to CAF improved disease-free survival but not overall survival. There was no benefit to the addition of LHRH agonists to chemotherapy without tamoxifen in premenopausal women. Thus the role of LHRH agonists alone or with chemotherapy but without tamoxifen requires further investigation. There is proven benefit to administering LHRH agonists over tamoxifen and chemotherapy or tamoxifen alone. In the ongoing Suppression of Ovarian Function Trial (SOFT), treatment with tamoxifen alone is being compared with ovarian suppression plus either tamoxifen or exemestane.

For adjuvant endocrine treatment in premenopausal women with ER-positive breast cancer, current guidelines recommend the use of tamoxifen alone or in combination with ovarian suppression or ablation for at least 5 years. Aromatase inhibitors are contraindicated in premenopausal women.

**Postmenopausal Patients**

Standard of care for postmenopausal women with ER/PR-positive breast cancer is at least 5 years of adjuvant therapy with an aromatase inhibitor. Aromatase inhibitors decrease plasma levels of estrogen by inhibiting the synthesis of estrogens from androgenic substrates. The benefit of aromatase inhibitors over tamoxifen in postmenopausal women was demonstrated in the 2010 EBCTCG meta-analysis, which showed a reduction in both breast cancer recurrence and mortality when aromatase inhibitors were used instead of tamoxifen. There are several aromatase inhibitors and they all have similar efficacy in the adjuvant setting; no particular agent is preferred. The optimal duration of adjuvant aromatase inhibitor therapy is at least 5 years, but this duration is still being evaluated in ongoing trials. For women who do not tolerate, have a contraindication to, or decline aromatase inhibitor therapy, tamoxifen for 5 years is recommended. Women taking an aromatase inhibitor may have difficulty with joint pain, which is the most common reason for discontinuation. They should have a dual energy x-ray absorptiometry (DEXA) scan at initiation of therapy and every 1 years to evaluate bone density because progression of osteoporosis is a known side effect. Addition of a bisphosphonate to the adjuvant regimen can decrease the osteoporosis risk, as well as decrease risk of bone metastasis.

**Adjuvant Chemotherapy**

**Molecular and Genomic Profiling**

Molecular profiling has one of the longest track records as therapy for breast cancer. With the advent of measuring the presence or absence of estrogen and progesterone receptors, medicine could be personalized with antiendocrine therapy for patients who had the appropriate tumor-based targets for response. The addition of Her 2 neu–targeting agents and the biologic agent trastuzumab (Herceptin) further refined this patient- and tumor-specific approach to adjuvant therapy.

Genomic profiling is now used for risk stratification and therapeutic decision making. For women with ER-positive breast cancer, genomic profiling may be helpful in selecting which patients should receive adjuvant chemotherapy. Genomic profiling should not be used in patients already determined to benefit from chemotherapy or in patients with multiple comorbid conditions who would be unable to tolerate chemotherapy. Patients must be cautioned that for a favorable recurrence score, chemotherapy can be omitted only if the patient commits to 5 years of antiendocrine therapy.

The best validated prognostic molecular test is the Oncotype DX (Genomic Health, Redwood City, Calif), which is used to analyze 21 genes and has been on the commercial market since 2003. One of its benefits is that paraffin-embedded fixed tissue is used, and the test can be ordered at any time in the diagnostic process. It provides a recurrence score that is predictive of responsiveness to chemotherapy and relapse rate. The activity of 16 genes and 5 control genes on breast cancer tissue is measured, and a proprietary mathematical formula is used to develop a single recurrence score to predict the risk of distant relapse despite 5 years of tamoxifen therapy. The recurrence score was validated with the use of tissue samples and the clinical database from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 study, which was a prospective randomized controlled trial in which the adjuvant treatment of tamoxifen alone was compared with tamoxifen plus chemotherapy in patients with ER-positive, node-negative early-stage breast cancer. The individual recurrence scores are further stratified into low-risk (score, <18), intermediate-risk (score, 18 to 30), or high-risk (score, >30) groups. The rates of distant recurrence at 10 years were 7%, 14%, and 31%, respectively, in these groups. Not only does the Oncotype DX test provide prognostic information, but it also demonstrated that there was no additional benefit to adding chemotherapy to the treatment regimen of a woman in the low-risk group. Other studies have shown similar scores and results when aromatase inhibitors are used instead of tamoxifen for postmenopausal women.

The true cutoff for the recurrence score number that defines who would benefit from chemotherapy is in the process of further refinement. The Trial Assigning Individualized Options for Treatment
Dose-dense chemotherapy is another schedule commonly utilized for early-stage breast cancer. This decreases the time interval between cycles of doxorubicin plus cyclophosphamide from the traditional 3 weeks to 2 weeks. This schedule has been associated with an improvement in disease-free survival rates but more on-treatment side effects. Patients with triple-negative tumors derive the greatest benefit.

The role of anthracyclines in treating early-stage breast cancer has become controversial. It is unclear whether adding a taxane to the standard regimen decreases the need for an anthracycline in certain patients. Anthracyclines have been associated with increased cardiac toxicity, especially in patients with a history of either cardiac disease or radiation therapy. Patients are now living longer as breast cancer survivors, and the seriousness of cardiac toxicity should not be minimized. In US Oncology Adjuvant Trial 9735, patients with stages I to III Her 2 neu-negative cancers were randomly assigned to receive either a regimen of docetaxel plus cyclophosphamide or a regimen of doxorubicin plus cyclophosphamide. This trial has had a median follow-up period of 7 years, and docetaxel plus cyclophosphamide improved disease-free survival (81% vs 75%) and overall survival (87% vs 82%).

**Her 2 neu-Targeted Therapy**

Approximately 20% of all breast cancers demonstrate amplification of the Her 2 neu oncogene. Women with stages I to III breast cancer and Her 2 neu overexpression should be considered for adjuvant treatment with chemotherapy and trastuzumab.

Before the use of trastuzumab, several studies had shown that patients with Her 2 neu-positive tumors smaller than 1 cm have a higher risk of recurrence than women with Her 2 neu-negative tumors of the same size. The current National Comprehensive Cancer Network guidelines recommend that trastuzumab and chemotherapy be administered for node-negative, Her 2 neu-positive tumors larger than 6 mm (stage T1b) and for all node-positive tumors.

Trastuzumab is the only Her 2 neu-directed agent to result in a survival benefit when administered with chemotherapy in the adjuvant setting. In a joint analysis of data from the North Central Cancer Treatment Group's (NCCGTG)'s N9831 trial and the NSABP's B-31 trial, treatment of Her 2 neu-positive disease with chemotherapy alone (doxorubicin plus cyclophosphamide) was compared with chemotherapy with trastuzumab; the latter produced an improvement in disease-free survival and a 39% significant reduction in death.

Trastuzumab does increase the risk of congestive heart failure and decreases left ventricular ejection fraction. The choice of which chemotherapy regimen to administer with trastuzumab depends on the patient's preexisting cardiac condition. Some regimens include anthracyclines (anthracycline, carboplatin, and taxotere [ACT]) and others do not (taxotere carboplatin: docetaxel plus cyclophosphamide). In comparison with ACT and trastuzumab, docetaxel plus cyclophosphamide with trastuzumab was found to produce a higher incidence of congestive heart failure (0.4% vs 2%) and a lower incidence of sustained loss of mean left ventricular ejection fraction (18.6% versus 9.8% [Table 3]). Because cardiac toxicity is known to be associated with trastuzumab alone and when combined with anthracyclines, there is a shift toward regimens that do not include anthracyclines, inasmuch as they appear to be equivalent in efficacy.

Trastuzumab is administered intravenously concomitantly with chemotherapy and then after the completion of the chemotherapy, for a total of 52 weeks. No data support the use of trastuzumab with endocrine therapy instead of chemotherapy for patients with triple-positive disease. Endocrine therapy should be administered with trastuzumab after the completion of chemotherapy.

Lapatinib is an oral Her 2 neu-directed agent. The current data show that there is no role for lapatinib in the adjuvant setting after chemotherapy for stages I to III breast cancer. Whether the combination of lapatinib plus trastuzumab with chemotherapy will improve survival in the adjuvant setting is currently being investigated in the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) study.
SUGGESTED READINGS


Table 3: Timing and major side effects of systemic therapy

<table>
<thead>
<tr>
<th>Systemic agent class: specific agent</th>
<th>Time of treatment</th>
<th>Side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taxanes: docetaxel, paclitaxel</td>
<td>Neoadjuvant, adjuvant</td>
<td>Cutaneous reaction Motor and sensory neuropathy Embryo-fetus toxicity Myelosuppression</td>
</tr>
<tr>
<td>Anthracyclines: doxorubicin (Adriamycin), epirubicin</td>
<td>Neoadjuvant, adjuvant</td>
<td>Cardiomyopathy, congestive heart failure Myelosuppression</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Neoadjuvant, adjuvant</td>
<td>Neurology Myelosuppression</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Neoadjuvant, adjuvant</td>
<td>With doxorubicin: cumulative risk of congestive heart failure; decreased left ventricular ejection fraction Cardiomyopathy, embryo-fetus toxicity, pulmonary toxicity</td>
</tr>
<tr>
<td>Aromatase inhibitors: anastrozole, exemestane, letrozole</td>
<td>Neoadjuvant, adjuvant</td>
<td>Arthralgias, myalgias, osteoporosis, embryo-fetus toxicity</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Adjuvant</td>
<td>Blood clots, endometrial cancer, ovarian cysts, embryo-fetus toxicity</td>
</tr>
</tbody>
</table>

SUMMARY

The array of systemic options and treatment regimens available to patients with breast cancer is progressing rapidly. These options include endocrine, cytotoxic, and targeted agents that can now be administered with improved efficacy and less toxicity. Molecular profiling has become a valuable asset in creating a treatment plan. Patients who will benefit most from chemotherapy or targeted biologic agents can be identified and treated accordingly. In contrast, patients who derive minimal benefit from chemotherapy can now avoid this toxicity and be treated instead with antiendocrine therapy. Determining the appropriateness of neoadjuvant therapy for a particular patient can improve surgical outcomes and provide prognostic information.

For surgeons, an understanding of how these therapies will affect patients’ local control options is important. The authors recommend that each patient with cancer be seen by a multidisciplinary team to allow discussion of these various options. Sometimes these teams practice in one location, but often the multidisciplinary approach requires close collaboration among colleagues who do not practice in physically adjacent spaces. Close coordination and integration of breast cancer specialists through a multidisciplinary team leads to improved outcomes for patients. A dialogue between diagnostic specialists ( imagers, pathologists) and therapeutic specialists ( breast and plastic surgeons, radiation and medical oncologists) can lead to the optimal treatment strategy. The most significant advances in breast cancer have resulted from physicians’ ability to provide an individualized treatment plan, and this can be realized only through a multidisciplinary approach.