Controversies in the Therapy of Early Stage Breast Cancer

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Key Words. Drug therapy, adjuvant • Breast neoplasms • Chemotherapy, adjuvant • Antineoplastic agents, hormonal

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Select appropriate adjuvant therapies for patients with early stage breast cancer.
2. Describe the evolving role of taxanes in the adjuvant therapy of early stage breast cancer.
3. Discuss the evolving role of aromatase inhibitors in the adjuvant therapy of early stage breast cancer.
4. Discuss the controversies that remain in the treatment of early stage breast cancer.
5. Interpret the recent data supporting the use of trastuzumab in the adjuvant setting for patients with HER-2–positive, early stage breast cancer.

ABSTRACT

Breast cancer is the most common malignancy among U.S. women, with more than 200,000 new cases diagnosed annually [1]. In the U.S., mortality from breast cancer has declined in recent years as a result of more widespread screening, leading to earlier detection, as well as advances in the adjuvant treatment of early-stage disease. It is widely accepted that the appropriate use of adjuvant chemotherapy and endocrine therapy improves the disease-free and overall survival of patients with early-stage breast cancer. It is, therefore, standard clinical practice to administer adjuvant systemic therapy to patients with node-positive and high-risk, node-negative breast cancer. There remain, however, many controversies in the primary systemic therapy of breast cancer, which are discussed in this review.

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INTRODUCTION

Breast cancer is the most common malignancy among U.S. women, with more than 200,000 new cases diagnosed annually [1]. In the U.S., mortality from breast cancer has declined in recent years as a result of more widespread screening, leading to earlier detection, as well as advances in the adjuvant treatment of early-stage disease [2, 3]. It is widely accepted that the appropriate use of adjuvant chemotherapy and endocrine therapy improves the disease-free and overall survival of patients with early-stage breast cancer. It is, therefore, standard clinical practice to administer adjuvant systemic therapy to patients with node-positive and high-risk, node-negative breast cancer [4, 5]. There remain, however, many controversies in the primary systemic therapy of breast cancer, which are discussed in this review.

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ADJUVANT THERAPY

In the late 1800s, Halsted advocated the radical mastectomy based on his hypothesis that breast cancer spread in an organized or step-wise pattern, initially via regional lymphatics and then, at a later stage, hematogenously to other organs. Unfortunately, only 12% of patients treated with radical mastectomy survived 10 years [6, 7]. This disappointing outcome, as well as the observation that 20%–30% of node-negative patients ultimately develop metastatic disease, led to the currently held “micrometastatic” paradigm. This paradigm proposes that many breast cancer patients, including some with early stage disease, have distant micrometastatic disease present at the time of diagnosis, putting them at risk for the later development of overt metastatic disease. Hellman and coworkers described the tumor properties of metastagenicity, which is the ultimate likelihood of a tumor developing distant metastases, and virulence, which is the rate at which the metastatic process will occur [8–10]. He also noted that both properties increase with increasing tumor size and nodal involvement [11].

The purpose of adjuvant systemic therapy is to lower the burden of distant micrometastatic deposits. It is currently standard practice to administer systemic therapy to all patients with lymph node–positive disease. The presence of cancer in the axillary lymph nodes, however, is not the only prognostic factor used to determine the appropriateness of systemic therapy. For node-negative patients, factors such as tumor size, grade, measures of proliferation, presence of lymphovascular invasion, and human epidermal growth factor receptor 2 (HER-2)/neu overexpression are commonly used to determine the appropriateness of adjuvant therapy. Many oncologists use the computer program Adjuvant! (http://www.adjuvantonline.com) to make decisions regarding the appropriateness of adjuvant therapy. Many oncologists use the computer program Adjuvant! (http://www.adjuvantonline.com) to make decisions regarding the potential benefit of adjuvant therapy. Adjuvant! projects outcomes based on the Surveillance, Epidemiology, and End Results (SEER) database and estimates the expected efficacy of adjuvant therapy based on the Oxford Overview of Randomized Clinical Trials involving chemotherapy, endocrine therapy, and radiation therapy [12]. A similar computer program is also offered by the Mayo Clinic (Rochester, MN, http://www.mayoclinic.com/calcs).

There is increasing evidence that gene-expression profiles may provide prognostic and predictive information. Paik et al. evaluated a reverse transcriptase–polymerase chain reaction (RT-PCR) assay in node-negative, estrogen receptor (ER)–positive patients with breast cancer who were enrolled in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 and B-20 trials [13]. A 21-gene model was used to develop a recurrence score (RS) algorithm for patients treated with tamoxifen (Nolvadex®; AstraZeneca Pharmaceuticals, Wilmington, DE, http://www.astrazeneca-us.com). The risk for distant recurrence at 10 years was 6.8% for those patients with a low RS (<18), 14.3% for those with an intermediate RS (18–30), and 30.5% for those with a high RS (≥31). The RS was an independent prognostic factor on multivariate analysis. Paik et al. also evaluated the magnitude of benefit for chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) for patients in the NSABP B-20 trial as a function of this 21-gene assay and found that patients with a low or intermediate RS obtained minimal benefit from adjuvant chemotherapy [14]. For example, the 10-year relapse-free survival (RFS) rate for the low-risk group was 96% for those receiving chemotherapy, compared with 95% for those randomized to tamoxifen alone. In contrast, patients in the high-risk group received a large benefit from chemotherapy, with an 88% RFS rate, compared with a 60% RFS rate for those treated with tamoxifen alone (p = .001). This 21-gene model was also evaluated in an M.D. Anderson Cancer Center (Houston, TX) study using tumor blocks from 149 node-negative, ER-positive, and ER-negative patients who did not receive tamoxifen or chemotherapy. In this group of patients, however, RS did not predict disease-free survival (DFS) [15].

ADJUVANT CHEMOTHERAPY FACTS AND CONTROVERSIES

The first randomized adjuvant breast cancer trial was initiated in 1948 and evaluated the benefit of irradiation-induced ovarian ablation [16]. Since then, hundreds of randomized trials of adjuvant therapy have been completed, with numerous trials having decades of patient follow-up. Many of these trials, however, lack the statistical power to make definitive statements regarding the contribution of adjuvant therapy to risk reduction. In an attempt to overcome this shortcoming of individual trials, the Early Breast Cancer Trialists’ Collaborative Group (EBCTG) conducted meta-analyses of the data from all these randomized trials, with the most recent results published in 1998 [17, 18]. These analyses clearly demonstrate that adjuvant systemic therapy improves the DFS and overall survival (OS) of early stage breast cancer patients.

The most recent EBCTG update of randomized trials using adjuvant chemotherapy, published in 1998, included 18,000 women in trials of prolonged chemotherapy versus no chemotherapy, 6,000 women in trials of longer versus shorter chemotherapy, and 6,000 women in trials of anthracycline-containing regimens versus CMF or CMF-like regimens [18]. These data demonstrated that adjuvant polychemotherapy led to proportional reductions in recurrence risk of 35% for women under the age of 50 and 20% for women aged 50–69. Similarly, the proportional reductions in mortality were 27% for women under the age of...
50 and 11% for women aged 50–69. These proportional or relative reductions in mortality translated to absolute mortality reductions of 7% for women under the age 50 with node-negative disease and 11% for those with node-positive disease. For women 50–65 years of age with node-negative and node-positive disease, polychemotherapy led to absolute mortality reductions of 2% and 3%, respectively. There were too few women over the age of 70 involved in clinical trials to make any conclusions regarding that age group. These age-specific benefits were independent of menopausal status, ER status, and whether or not adjuvant tamoxifen was administered. Comparisons of longer versus shorter chemotherapy did not reveal any benefit for greater than 3–6 months of therapy. Compared with CMF, anthracycline-containing regimens produced a 12% proportional reduction in the risk for recurrence and an 11% proportional reduction in mortality, which translate into absolute benefits of 3.3% and 1.6%, respectively.

The use of adjuvant chemotherapy involves a risk for both short-term and long-term toxicities. Short-term toxicities include alopecia, bone marrow suppression, nausea/vomiting, and fatigue. The use of antiemetics and growth factors, such as G-CSF and erythropoeitin, ameliorates some of the toxicity for many patients. Long-term toxicities include premature menopause, cardiomyopathies, neuropathies, and secondary leukemias. The risks for both short and long-term toxicities must be balanced against the potential benefit of chemotherapy for each individual patient. In clinical decision making for individual patients, oncologists use the results of the overview analyses as well as the results of several important, large randomized trials investigating anthracycline-based therapy and taxane-based therapy as well as the issues of dose intensity and dose density.

Anthracyclines
Regimens containing anthracyclines—doxorubicin (Adriamycin®; Bedford Laboratories, Bedford, OH, http://www.bedfordlabs.com) and epirubicin (Ellence®; Pfizer Pharmaceuticals, New York, http://www.pfizer.com)—have been compared with CMF or CMF-like regimens, and as a result of these trials [19–22], anthracyclines are a standard element in the adjuvant treatment of breast cancer. Doxorubicin and cyclophosphamide (AC) is most commonly used in low-risk, node-negative women, whereas three-drug regimens such as 5-fluorouracil (500 mg/m²), doxorubicin (50 mg/m²), and cyclophosphamide (500 mg/m²) i.v. every 3 weeks for six cycles (FAC) or 5-fluorouracil (500 mg/m²), epirubicin (100 mg/m²), and cyclophosphamide (500 mg/m²) i.v. every 3 weeks for six cycles (FEC) are commonly used in node-positive and high-risk, node-negative patients.

Taxanes
The taxanes—paclitaxel (Taxol®; Bristol-Myers Squibb, Princeton, NJ, http://www.bms.com) and docetaxel (Taxotere®; Aventis Pharmaceuticals Inc., Bridgewater, NJ, http://www.aventispharma-us.com)—are effective agents in metastatic breast cancer therapy, leading to their evaluation in the adjuvant setting. Cancer and Leukemia Group B (CALGB) 9344 trial addressed the role of paclitaxel after four cycles of AC as well as the benefit of doxorubicin dose escalation in 3,121 node-positive breast cancer patients [23]. Patients were initially randomized to receive four cycles of cyclophosphamide (600 mg/m²) plus doxorubicin at a dose of 60, 75, or 90 mg/m² and then randomized to receive either four cycles of paclitaxel (175 mg/m²) i.v. every 3 weeks or no further chemotherapy. At 5 years of follow-up, there was no difference in DFS or OS among the three doxorubicin dosing groups. The addition of paclitaxel following four cycles of AC, however, resulted in proportional reductions in the risk for recurrence and death of 17% and 18%, respectively. Based on that trial, paclitaxel was approved by the U.S. Food and Drug Administration (FDA) for the adjuvant treatment of node-positive disease. An unplanned subgroup analysis suggested that the benefit of paclitaxel appeared to be greater in patients with hormone receptor–negative tumors [24]. The NSABP B-28 trial also evaluated the role of paclitaxel after AC chemotherapy in 3,060 node-positive patients and showed a benefit in terms of DFS (76% versus 72%; p = .008) but not OS [25]. Tamoxifen was administered concurrently with chemotherapy, and this may have affected the results of the trial, although no interaction between paclitaxel benefit and hormone receptor status or tamoxifen use was observed. Neither the CALGB 9344 nor NSABP B-28 trials controlled for the total number of cycles of chemotherapy (four versus eight cycles). Buzdar et al. reported on the M.D. Anderson Cancer Center experience, in which 524 women were randomized to receive either four cycles of paclitaxel followed by four cycles of FAC or eight cycles of FAC [26]. In this underpowered trial, there was a trend toward longer DFS for the paclitaxel group. The OS data from this trial are not yet mature.

There are also data to support the adjuvant use of docetaxel. The Breast Cancer International Research Group (BCIRG) 001 trial randomized 1,491 node-positive patients to receive either six cycles of FAC or six cycles of docetaxel, cyclophosphamide, and doxorubicin (TAC) [27]. Patients assigned to FAC received 500 mg/m² 5-fluorouracil i.v., 50 mg/m² doxorubicin i.v., and 500 mg/m² cyclophosphamide i.v. every 21 days for six cycles, while patients assigned to TAC received 75 mg/m² docetaxel i.v., 50 mg/m² doxorubicin i.v., and 500 mg/m² cyclophosphamide i.v. every 21 days for six cycles. TAC resulted in
a 28% proportional reduction in the risk for recurrence ($p = .001$) and a 30% proportional reduction in the risk for death ($p = .008$) compared with FAC. Administration of TAC resulted in a proportional reductions in the risk for recurrence of 31% in ER-negative women ($p = .0297$) and 38% in ER-positive women ($p = .0076$) in a prospectively defined subset analysis. Approximately 20% of the women were HER-2/neu–positive by fluorescence in situ hybridization (FISH). Administration of TAC, compared with FAC, resulted in relative risk reductions in terms of DFS of 34% ($p = .046$) for HER-2/neu–negative patients and 40% for HER-2/neu–positive patients ($p = .0088$).

The benefit of TAC appeared to be larger in women with one to three positive lymph nodes than in women with more than four positive nodes. Based on this trial, TAC is FDA-approved for the adjuvant treatment of node-positive breast cancer.

At present, there are no data to support the use of adjuvant taxanes in node-negative patients. The Eastern Cooperative Oncology Group (ECOG) 2197 trial randomized 2,885 women with node-negative tumors $>1$ cm or node-positive (one to three positive nodes only) tumors to receive either doxorubicin (60 mg/m$^2$) and docetaxel (60 mg/m$^2$) (AT) or AC, administered every 3 weeks for four cycles [28]. Prophylactic ciprofloxacin (Cipro®; Bayer Pharmaceuticals Corporation, West Haven, CT, http://www.bayerus.com), 500 mg orally twice a day for 10 days beginning on day 8, was administered to the AT group. At a median follow-up of 59 months, there was no difference in DFS or OS between the two groups. There was, however, more febrile neutropenia (28% versus 10%) and more treatment-related deaths (four versus two) in the AT arm.

At present, the role of taxanes in the adjuvant therapy of breast cancer is evolving. While taxanes have become standard for node-positive disease, many questions remain, including their role in node-negative disease, the proper sequencing of anthracyclines and taxanes, as well as the optimal taxane and schedule. One should be cautious in interpreting subgroup analyses, and it is currently premature to make definitive recommendations regarding the use of taxanes based on hormone or HER-2/neu status. Several trials addressing these questions have completed accrual, but the data are not mature enough to report. Table 1 lists some of these pending trials.

### Table 1. Pending adjuvant taxane trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment arms</th>
<th>Population</th>
<th>Accrual status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG 1199</td>
<td>AC×4, docetaxel every 3 wks×4 versus AC×4, docetaxel every wk×12 versus AC×4, paclitaxel every 3 wks×4 versus AC×4, paclitaxel every wk×12</td>
<td>Node-positive; high-risk node-negative</td>
<td>Closed</td>
</tr>
<tr>
<td>BCIRG 005</td>
<td>AC×4, docetaxel×4 versus TAC×6</td>
<td>Node-positive; HER-2–negative</td>
<td>Closed</td>
</tr>
<tr>
<td>NSABP B-30</td>
<td>AC×4, docetaxel×4 versus AT×4 versus TAC×4</td>
<td>Node-positive</td>
<td>Closed</td>
</tr>
<tr>
<td>US Oncology</td>
<td>AC×4, docetaxel×4 versus AT×4 versus docetaxel/capecitabine×4</td>
<td>Node-positive; high-risk node-negative</td>
<td>Open</td>
</tr>
<tr>
<td>BCIRG 006</td>
<td>AC×4, docetaxel×4 versus AC×4, docetaxel×4 + trastuzumab versus docetaxel/carboplatin + trastuzumab</td>
<td>HER-2–positive, node-negative, and high-risk node-negative</td>
<td>Closed</td>
</tr>
<tr>
<td>GEICAM 9805</td>
<td>TAC versus FAC</td>
<td>Node-negative</td>
<td>Closed</td>
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</tbody>
</table>

Abbreviations: AC, doxorubicin and cyclophosphamide; AT, doxorubicin and docetaxel; BCIRG, Breast Cancer International Research Group; ECOG, Eastern Cooperative Oncology Group; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; GEICAM, Grupo Español de Investigación de Cáncer de Mama; NSABP, National Surgical Adjuvant Breast and Bowel Project; TAC, docetaxel, doxorubicin, and cyclophosphamide.
NCCTG 9831 trial were node-negative. For the joint analysis, the trastuzumab-containing arm of the NSABP B-31 trial was combined with arm B of the NCCTG N9831 trial and compared with the combined control arms of both studies. At a median follow-up of 2 years, the use of adjuvant trastuzumab resulted in a 52% proportional reduction in the risk for recurrence (p = 3 × 10−12, two-tailed test) and a 33% proportional reduction in the risk for death (p = .015, two-tailed test) with the use of adjuvant trastuzumab. These proportional results translated into an 18% absolute reduction in the risk for recurrence and a 4% absolute reduction in the risk for death. The cardiac status of the patients in these trials was monitored closely, and the risk for a cardiac event in the NSABP B-31 trial was 4.1%. An unplanned interim analysis of NCCTG N9831 revealed a 36% relative reduction in the risk for recurrence for concurrent compared with sequential trastuzumab (p = .0114) [30]. Further follow-up is necessary to see whether this trend continues.

The Herceptin® Adjuvant (HERA) trial randomized HER-2–positive women with early stage breast cancer who had completed surgical and neoadjuvant or adjuvant chemotherapy to one of three arms: observation; 1 year of trastuzumab, administered every 3 weeks; or 2 years of trastuzumab, administered every 3 weeks. The type of adjuvant chemotherapy was not dictated. Approximately one third of the patients in the HERA trial were node-negative. A preliminary analysis of 1 year of trastuzumab versus observation in 5,081 patients revealed an 8% absolute improvement in DFS (p < 0.0001) [31]. Symptomatic congestive heart failure (CHF) occurred in 0.5% of the patients who received trastuzumab. Results regarding optimal trastuzumab duration (1 year versus 2 years) are expected to be available by 2008.

These results make the use of adjuvant trastuzumab a reasonable option for node-positive and high-risk, node-negative patients. While only a small number of node-negative patients has been included in these analyses, they appear to derive a similar proportional benefit as node-positive women.

**Dose Intensity**

Escalation of both cyclophosphamide and doxorubicin doses has been evaluated in clinical trials without any apparent improvement in outcome [23, 32, 33]. Furthermore, several randomized trials have been reported thus far examining the benefit of myeloablative therapy with stem cell support for patients at very high risk for recurrence [34–38]. These trials have failed to show a clear benefit and, therefore, at the present time there is no role for myeloablative therapy in the adjuvant setting outside of a clinical trial.

**Dose Density**

Dose density refers to a strategy of administering chemotherapy agents with a shorter intertreatment interval, based on the belief that human cancer cells grow by nonexponential Gompertzian kinetics and that chemotherapy kills a certain fraction, rather than a fixed number, of cancer cells. Since regrowth of cells between cycles of chemotherapy is rapid in Gompertzian cancer models, it has been postulated that more frequent administration of chemotherapy would be more effective in minimizing residual tumor volume [37–41]. One clinical trial that addresses this issue is CALGB 9741, which made two independent comparisons: sequential doxorubicin, paclitaxel, and cyclophosphamide (A,T,C) compared with concurrent AC followed by paclitaxel and dose-dense (every 2 weeks) compared with conventional (every 3 weeks) scheduling in node-positive breast cancer patients [42]. A total of 2,005 women was randomized to receive one of four arms: sequential doxorubicin for four cycles every 3 weeks, followed by paclitaxel for four cycles every 3 weeks and cyclophosphamide for four cycles every 3 weeks (36 weeks of therapy); sequential doxorubicin for four cycles every 2 weeks, followed by paclitaxel for four cycles every 2 weeks and cyclophosphamide for four cycles every 2 weeks (24 weeks of therapy); concurrent AC for four cycles every 3 weeks, followed by paclitaxel for four cycles every 3 weeks (24 weeks of therapy); or concurrent AC for four cycles every 2 weeks, followed by paclitaxel for four cycles every 2 weeks. All four arms received the same total amount of each chemotherapy drug. At 36 months of median follow-up, every-2-weeks therapy resulted in a 26% proportional improvement in DFS and a 31% proportional improvement in OS compared with conventional every-3-weeks scheduling. A subsequent analysis of the data, however, suggested that there was minimal benefit to every-2-weeks administration in ER-positive patients [24]. There was no difference in DFS or OS between the concurrent and sequential schedules, and there was no apparent interaction between density and sequence. At present, there does not appear to be a higher rate of myelodysplastic syndrome or leukemia in the dose-dense arms. Use of G-CSF was mandated for the every-2-weeks arms in this trial, thereby increasing the regimen’s cost. In practice, however, G-CSF may not be necessary for the paclitaxel portion of the regimen.

Mobus et al. randomized 1,284 women with at least four positive lymph nodes to receive either three cycles of epirubicin (150 mg/m²), paclitaxel (225 mg/m²), and cyclophosphamide (2,500 mg/m²) (ETC) every 2 weeks with G-CSF support or four cycles of epirubicin (90 mg/m²) and cyclophosphamide (600 mg/m²) every 3 weeks followed by four cycles of paclitaxel (175 mg/m²) every 3 weeks (EC–T) [43].
At 28 months of follow-up, there was a significant difference in the RFS rate (80% versus 70%; \( p = .0009 \)) and OS rate (90% versus 87%; \( p = .03 \)) favoring the ETC arm. This experimental design, however, is not a pure test of dose density because the individual drug doses were not kept constant, as in the CALGB 9741 trial.

The GeparDuo trial randomized women with operable breast cancer to receive either four cycles of preoperative AC followed by four cycles of preoperative docetaxel or four cycles of dose-dense, every-2-weeks doxorubicin (50 mg/m²) and docetaxel (75 mg/m²) [44]. Recruitment to the study was stopped after 913 patients because of the significant difference in pathologic complete response (pCR) rate favoring AC followed by docetaxel (22.4% versus 11%; \( p < .001 \)). Interpretation of this trial, however, is confounded by the major difference in the number of chemotherapy cycles in the two arms (eight versus four).

The ability to administer chemotherapy in a dose-dense fashion may not be possible for all drugs and regimens. Dang et al. treated 44 patients with at least four positive lymph nodes with six cycles of FEC every 2 weeks followed by 18 weeks of alternating weekly paclitaxel and docetaxel [45]. That trial was stopped because of toxicity when only 17 patients had completed treatment. Two of 17 patients (12%) developed grade 4 pericardial/grade 3 bilateral pleural effusions requiring pericardial window. Four of 44 patients (9%) developed pneumonitis attributed to the dose-dense FEC. While there were no treatment-related deaths, hospital admissions and blood transfusions were required for 27% and 7% of the patients, respectively.

Results from the CALGB 9741 trial suggest that AC followed by paclitaxel is best administered in a dose-dense fashion. It is possible that the results of this trial reflect the schedule dependency of paclitaxel, and it is unclear at the present time whether the dose-dense approach may be applied to other regimens with different agents. Subsequent trials are therefore needed to further evaluate the role of dose density in the adjuvant treatment of breast cancer.

**Preoperative Versus Postoperative Therapy**

Preoperative, or neoadjuvant, chemotherapy has been extensively evaluated in locally advanced breast cancer, including inflammatory breast cancer. Most clinical trials demonstrated a clinical response in 60%–80% of patients, with 10%–20% achieving pCRs [46–49], leading to the evaluation of neoadjuvant therapy in operable breast cancer. Two of the largest randomized phase III trials to compare neoadjuvant with adjuvant chemotherapy are the European Organisation for Research and Treatment of Cancer (EORTC) 10902 and NSABP B-18 trials. In the EORTC 10902 trial, 698 women with operable breast cancer were randomized to receive four cycles of FEC i.v. every 3 weeks either preoperatively or postoperatively [50]. Objective responses were observed in 49% of the neoadjuvant patients. pCRs were achieved by 3.7% of the neoadjuvant patients, and those patients did have a longer OS than those patients who did not achieve a pCR (\( p = .008 \)).

The NSABP B-18 trial randomized 1,523 women with T1–3, N0–1 breast cancer to receive surgery followed by four cycles of AC or AC followed by surgery [51, 52]. Among patients receiving preoperative AC chemotherapy, 80% experienced tumor reduction, with 36% achieving clinical complete responses (cCRs); however, only 26% of the patients with a cCR had a pCR, or 9% of the total population. The evaluation of pCR in that trial was limited to patients who attained cCRs. At 5 years of follow-up, there was no difference in breast recurrence, DFS, or OS between the neoadjuvant and adjuvant groups. However, patients who were candidates for lumpectomy only after downstaging by chemotherapy experienced a higher local recurrence rate than those patients who were candidates for lumpectomy before chemotherapy (14.5% versus 6.9%, respectively; \( p = .04 \)). Interestingly, a pCR at the time of surgery did appear to be predictive for DFS and OS, raising the possibility of its use as a surrogate end point in evaluating preoperative treatments.

A meta-analysis of nine randomized neoadjuvant trials was recently published, showing equivalent risks for death, disease progression, and distant disease recurrence with neoadjuvant and adjuvant therapy [53]. Neoadjuvant therapy, however, was associated with a statistically significantly higher risk for locoregional recurrence than adjuvant therapy, particularly in trials in which more patients in the neoadjuvant arm received radiation therapy without surgery. Generally, however, a slightly higher local recurrence rate is acceptable because the patients can be salvaged with a mastectomy with no impact on OS.

Many trials have evaluated the role of taxanes in the neoadjuvant or primary therapy of breast cancer. Buzdar et al. randomized 174 women with operable breast cancer to receive either four cycles of neoadjuvant chemotherapy with paclitaxel (250 mg/m²) as a 24-hour infusion or FAC. All patients received four cycles of adjuvant FAC after their local therapy [54]. Overall response rates (complete responses plus partial responses) were 79.3% for FAC and 80.2% for paclitaxel, while 16.4% of the FAC-treated patients and 8.1% of the paclitaxel-treated patients achieved a pCR. Estimated 2-year DFS rates were 89% for FAC and 94% for paclitaxel (\( p = .44 \)). The Aberdeen trial treated patients with large or locally advanced (T3, T4, N2) tumors with four cycles of neoadjuvant cyclophosphamide (1,000
mg/m²), doxorubicin (50 mg/m²), and vincristine (Oncovin®; Eli Lilly and Company, Indianapolis, http://www.lilly.com) (1.5 mg/m²) i.v. on day 1 with prednisolone (Orapred®; BioMarin Pharmaceutical Inc., Novato, CA, http://www.biomarinpharm.com), 40 mg, for 5 days (CVAP). Those patients who had clinical responses were then randomized to receive another four cycles of preoperative CVAP or four cycles of preoperative docetaxel (100 mg/m²) [55]. Patients who had not responded to the initial four cycles of CVAP were not randomized and received four cycles of preoperative docetaxel. Among the randomized patients, docetaxel resulted in a significantly greater response rate (94% versus 64%; p < .002) and pCR rate (34% versus 16%; p = .04) than CVAP. Furthermore, at a median follow-up of 5 years, docetaxel resulted in a significantly greater OS rate (93% versus 78%; p = .04) than CVAP.

In a larger trial, NSABP B-27, the role of docetaxel in the neoadjuvant or primary therapy of operable breast cancer was evaluated [56, 57]. A total of 2,411 women with operable breast cancer was randomly assigned to one of three groups: group 1 received four cycles of AC followed by surgery; group 2 received four cycles of AC followed by four cycles of docetaxel (100 mg/m²) every 3 weeks; and group 3 received four cycles of AC followed by surgery followed by four cycles of docetaxel. In that trial, preoperative AC followed by docetaxel produced a higher pCR rate (13.7% versus 26.1%; p < .001) and greater proportion of patients with negative lymph nodes (50.8% versus 58.2%; p < .001) than AC alone. Unfortunately, this higher pCR rate did not translate into longer DFS or OS. Tamoxifen was administered concurrently with chemotherapy to all the patients in the trial, and this may have influenced the results. Also, survival may not have been improved because an insufficient number of patients attained pCRs.

At the present time, the role of neoadjuvant or primary therapy in patients with operable breast cancer is unclear. The most studied regimens appear to have equal efficacy to those administered postoperatively. The neoadjuvant approach, however, may be useful in the design of future trials aimed at clinical-biological end points.

**Role of Chemotherapy in Postmenopausal Women**

Trials comparing tamoxifen alone with tamoxifen plus doxorubicin-based chemotherapy have shown a significant benefit of the addition of chemotherapy to postmenopausal women. The NSABP B-16 trial randomized 1,124 node-positive, hormone receptor–positive women aged ≥50 years to receive tamoxifen alone, tamoxifen plus AC, or tamoxifen plus melphalan (Alkeran®; GlaxoSmithKline, Philadelphia, http://www.gsk.com), doxorubicin, and 5-fluorouracil (PAF). AC plus tamoxifen resulted in significantly better DFS and OS than tamoxifen alone [58]. The NSABP B-20 trial randomized 2,306 patients with node-negative, hormone receptor–positive breast cancer to receive tamoxifen, tamoxifen plus methotrexate and 5-fluorouracil, or tamoxifen plus CMF. Approximately 55% of those women were ≥50 years old. Although the advantage of chemotherapy in this group was not as great as in younger patients, CMF and tamoxifen led to a 25% lower risk for distant failure and a 20% lower risk for death than tamoxifen alone [59]. Furthermore, a Southwest Oncology Group (SWOG) Intergroup trial compared tamoxifen alone with either concurrent or sequential CAF and tamoxifen. At 5 years of follow-up, chemotherapy led to significantly better DFS and OS than with tamoxifen alone [60, 61]. That trial also demonstrated that sequential chemotherapy followed by tamoxifen is superior to concurrent chemotherapy and tamoxifen [62]. As a result, for all hormone receptor–positive patients who warrant chemotherapy, it is standard practice to administer tamoxifen in a sequential fashion following chemotherapy.

The 1998 Oxford overview analysis confirms the benefit of chemotherapy in addition to tamoxifen in hormone receptor–positive women who are 50–65 years of age. Limited data, however, are available regarding the benefits of chemotherapy in women over the age of 70 [18].

Other data, however, question the benefit of chemotherapy in postmenopausal, hormone receptor–positive, node-negative women. The International Breast Cancer Study Group (IBCSG) IX trial randomized 1,669 postmenopausal women to tamoxifen for 60 months or CMF for 3 months followed by 57 months of tamoxifen, and at a median follow-up of 6 years, found no difference between the groups for hormone receptor–positive women over the age of 40 [63]. Similarly, the NSABP performed a retrospective analysis of six NSABP trials involving 11,669 women and found that hormone receptor–positive women over the age of 60 did not appear to benefit from CMF in addition to tamoxifen [64].

Muss et al. reported on the experience of older, node-positive women enrolled in CALGB adjuvant trials [65]. Data from 6,489 women enrolled in four CALGB trials evaluating different doses and schedules of adjuvant chemotherapy were analyzed. While older patients were greatly under-represented in these trials, they appeared to receive similar benefits from chemotherapy, in terms of lower risks for breast cancer–related recurrence and mortality, as younger women. In a multivariate analysis, age was not found to be a predictor of RFS. Older women, however, had a significantly higher overall mortality because of more non-breast cancer–related deaths.
As a result of these data, it is standard practice to administer adjuvant chemotherapy in addition to tamoxifen to women over the age of 50 with lymph node–positive disease. Lymph node–negative disease in this group must be evaluated individually using other prognostic factors to determine the patient’s baseline recurrence risk. It is particularly important in older postmenopausal women, whether they be lymph node–negative or –positive, to consider other comorbidities that may influence toxicity of treatment and overall mortality.

Adjuvant Endocrine Therapy Facts and Controversies

Tamoxifen Versus Aromatase Inhibitors

The most recent EBCTCG overview analysis of randomized trials using adjuvant tamoxifen, published in 1998, included 37,000 women [17]. That analysis demonstrated that 5 years of adjuvant tamoxifen led to proportional reductions in the risk for recurrence and mortality for hormone receptor–positive patients of 47% and 26%, respectively. The proportional reductions in mortality were similar for node-negative and node-positive patients and translated into absolute mortality reductions of 5.6% for those with node-negative disease and 10.9% for those with node-positive disease. Furthermore, adjuvant tamoxifen was beneficial regardless of menopausal status, age, or whether or not chemotherapy was administered. While 5 years of adjuvant tamoxifen led to a greater risk reduction than shorter durations of therapy, trials evaluating a longer duration of tamoxifen have failed to show a benefit with more than 5 years of therapy [66]. Five years of adjuvant tamoxifen also led to a proportional reduction of 47% in the risk for contralateral breast cancer, thereby providing the rationale for the NSABP P-1 tamoxifen prevention trial [67]. No benefit for tamoxifen in hormone receptor–negative women was observed. As a result of these data, 5 years of tamoxifen became the standard adjuvant endocrine therapy for all women with hormone receptor–positive disease who warranted adjuvant systemic therapy. Recent trials evaluating the use of aromatase inhibitors, however, have challenged this standard in postmenopausal women.

The Arimidex® versus Tamoxifen Alone or in Combination (ATAC) trial compared 5 years of therapy using anastrozole (Arimidex®; AstraZeneca Pharmaceuticals) (1 mg/day) alone with tamoxifen (20 mg/day) alone and with the combination in 9,000 postmenopausal women with hormone receptor–positive breast cancer [68]. The primary end points were DFS and safety/tolerability. The initial analysis of that trial, at a median follow-up of 33 months, revealed superior DFS for the anastrozole arm compared with the tamoxifen arm, 89.4% versus 87.4%, respectively (p = .013). Results from the combination arm were not significantly different from those with tamoxifen alone, and this arm was therefore discontinued. The incidence of contralateral breast cancer was also significantly lower with anastrozole than with tamoxifen, with an odds ratio of 0.42 (p = .007). Anastrozole was significantly better tolerated than tamoxifen with respect to cerebrovascular events, venous thromboembolic events, endometrial cancer, vaginal bleeding, and hot flashes, while tamoxifen was significantly better tolerated than anastrozole with respect to musculoskeletal disorders (primarily joint pain) and fractures. There were significantly fewer withdrawals from anastrozole treatment than from tamoxifen treatment, 21.9% versus 26%, respectively (p = .002). The ATAC trial was recently updated with 68 months of follow-up, and the benefit of anastrozole over tamoxifen was maintained [69]. With only 8% of patients remaining in the trial, DFS was significantly longer for anastrozole than for tamoxifen, with a hazard ratio of 0.74 (p = .0002) and an absolute difference of 3.7% between the two arms. At present, there is not a significant survival difference.

The IBCSG-98 trial randomized 8,028 postmenopausal women with hormone receptor–positive breast cancer to one of four arms: 5 years of tamoxifen; 5 years of letrozole (Femara®; Novartis Pharmaceuticals Corporation, East Hanover, NJ, http://www.pharma.us.novartis.com); 2 years of tamoxifen followed by 3 years of letrozole; 2 years of letrozole followed by 3 years of tamoxifen. Data presented at the 2005 St. Gallen’s Conference revealed that treatment initiated with letrozole led to a 19% proportional reduction in the risk for recurrence compared with treatment initiated with tamoxifen [70]. Although not statistically significant, there were more cardiovascular events among the women in the letrozole arm and this warrants further analysis. At present, there is no significant difference in the OS rate. Data from the sequential arms are not available at present.

Use of Aromatase Inhibitors After Tamoxifen

An alternative approach of tamoxifen followed by an aromatase inhibitor has also been evaluated in randomized trials. Boccardo et al. randomized 426 postmenopausal, ER-positive women who had already been taking tamoxifen for 2 years to either continue on tamoxifen for a total of 5 years or to switch to anastrozole (1 mg/day) for the remaining 3 years of therapy [71]. Both groups received a total of 5 years of adjuvant endocrine therapy. At a median follow-up of 24 months, switching to anastrozole resulted in a 36% proportional risk reduction (p = .006) in recurrence compared with continued tamoxifen use. There was no significant difference in OS in this underpowered trial. The Austrian Breast
and Colorectal Cancer Study Group (ABCSDG) Trial 8 and the Arimidex®–Nolvadex® (ARNO) trial also randomized a combined total of 3,224 postmenopausal, ER-positive women who had already been taking tamoxifen for 2 years to either continue on tamoxifen for a total of 5 years or to switch anastrozole (1 mg/day) for the remaining 3 years of therapy. At a median follow-up of 28 months, switching to anastrozole resulted in a 40% proportionally greater ($p = .0009$) event-free survival compared with continued tamoxifen use [72]. This translates into a 3.1% absolute benefit for switching to anastrozole. Similarly, the Inter-group Exemestene Study (IES) randomized 4,742 postmenopausal, ER-positive women who had already received 2–3 years of adjuvant tamoxifen to either complete 5 years of tamoxifen or switch to exemestane (Aromasin®; Pfizer Pharmaceuticals, New York, http://www.pfizer.com) (25 mg/day) for the remaining 2–3 years of therapy [73]. At the second interim analysis, triggered by the reporting of 358 events, the data and safety monitoring committee recommended that the efficacy data be released. After a median follow-up of 36 months, switching to exemestane resulted in 32% proportional and 4.7% absolute reductions in the risk for recurrence ($p = .00005$). There is no statistically significant difference in OS at this time. Thromboembolic events were more common in the tamoxifen group ($p = .007$), while there was a trend toward more fractures in the exemestane group.

The National Cancer Institute of Canada Clinical Trials Group MA.17 trial evaluated the benefit of 5 years of letrozole in postmenopausal, ER-positive women who had completed 5 years of tamoxifen [74]. In this double-blinded, placebo-controlled trial, 5,187 women were randomized to receive either 5 years of letrozole or placebo after completing 5 years of tamoxifen. After a median follow-up of 2.4 years, the use of letrozole resulted in a 43% proportional reduction in the risk for recurrence compared with placebo ($p = .00008$). Estimated 4-year DFS rates for the letrozole and placebo groups were 93% and 87%, respectively. Patients with both node-negative and node-positive disease had longer DFS from letrozole. Distant DFS was significantly better in the letrozole group in the overall population ($p = .002$) and in the subgroup of node-negative patients ($p = .001$), while OS was significantly better in the subgroup of node-positive patients ($p = .04$) [75]. Interpretation of this trial is limited by the fact that it was terminated early because of the efficacy results. At the time of unblinding, no patient had completed 5 years of letrozole. As a result, the optimal length of letrozole therapy is unknown. It is currently planned to re-randomize the women in this trial after completion of 5 years of letrozole to either another 5 years of letrozole or placebo.

Results of the ATAC, IES, and MA.17 trials suggest a detrimental effect of aromatase inhibitors on bone density. A subprotocol of the ATAC trial included 308 women from the ATAC trial and a control group consisting of 46 unrandomized postmenopausal patients with invasive early-stage breast cancer not receiving endocrine therapy [76]. After 1 year of therapy, anastrozole use was associated with a decrease in bone mineral density (BMD) in the spine and hip, while tamoxifen was associated with an increase in BMD. After 2 years of therapy, anastrozole continued to be associated with a decrease in BMD and tamoxifen with an increase in BMD. The rate of bone loss associated with anastrozole therapy appeared to be constant over year 1 and year 2. In the IES trial, patients treated with exemestane had a higher incidence of osteoporosis than those remaining on tamoxifen, 7.4% versus 5.7%, respectively ($p = .05$) [73]. In the MA.17 trial, letrozole treatment resulted in significantly more cases of osteoporosis than placebo, 8% versus 6% ($p = .003$) [75].

Many issues regarding the adjuvant use of aromatase inhibitors remain unsettled, such as the optimal duration of treatment, the optimal sequencing with tamoxifen, and the optimal aromatase inhibitor. The long-term side effects in a patient population expected to live many years also remain to be determined. Trials addressing these issues are shown in Table 2.

The American Society of Clinical Oncology convened a Technology Assessment Working Group in 2002, 2003, and 2004 to review the available data and make recommendations regarding the optimal use of aromatase inhibitors in the adjuvant setting [77–79]. This Working Group concluded in 2004 that optimal adjuvant endocrine therapy for a postmenopausal woman with hormone receptor–positive breast cancer should include an aromatase inhibitor either as initial therapy or after a period of treatment with tamoxifen. The panel left open the questions of the optimal aromatase inhibitor and the optimal treatment algorithm.

It should also be emphasized that the present data for aromatase inhibitors are for postmenopausal women only. Use of aromatase inhibitors in premenopausal women with functioning ovaries is contraindicated. The use of aromatase inhibitors with ovarian ablation in premenopausal women is currently under study and is not recommended outside of a clinical trial.

**Ovarian Ablation in Premenopausal Women**

The impact of ovarian ablation on the reduction in the risk for recurrent breast cancer was well established by the Oxford overview analysis [80]. At 15 years of follow-up, premenopausal women treated with ovarian ablation had statistically significantly higher RFS and OS rates (45%...
versus 39% and 52.4% versus 46.1%, respectively) than women in the control group. Trials of ovarian ablation plus chemotherapy compared with chemotherapy alone have shown no additive benefit. Unlike adjuvant tamoxifen, ovarian ablation did not result in a lower risk for contralateral breast cancer.

One of the mechanisms by which chemotherapy confers its effects in premenopausal breast cancer patients is chemically induced ovarian ablation. Several trials have, therefore, addressed the role of ovarian ablation as a substitute for cytotoxic chemotherapy. Interpretation of most of these trials is limited by many factors, including mixed populations of ER-positive and ER-negative patients, lack of tamoxifen in the chemotherapy arms and in the majority of the trials, and lack of an anthracycline. Taxanes were also not evaluated in these trials. Trials of chemotherapy versus chemotherapy plus ovarian ablation are complicated by the fact that chemotherapy results in premature menopause in many women, leading to a relatively small group of women who remain premenopausal following the completion of their chemotherapy and who could therefore benefit from the addition of ovarian ablation.

The Zoladex® Early Breast Cancer Research Association trial randomized 1,640 pre-/perimenopausal, node-positive women to receive either goserelin (Zoladex®; AstraZeneca Pharmaceuticals) at a dose of 3.6 mg s.c. every 28 days for 2 years or six cycles of CMF chemotherapy [81]. Approximately 74% of the patients were ER-positive. After a median follow-up of 7.3 years, CMF was superior to goserelin for the ER-negative patients. Among the ER-positive patients, however, DFS and OS rates were equivalent for goserelin and CMF. The ABCSG randomized 1,034 women with stage I/II, ER-positive disease to receive either goserelin (3.6 mg s.c.) every 28 days for 3 years plus 5 years of tamoxifen or six cycles of CMF with no tamoxifen [82]. RFS favored goserelin plus tamoxifen with a nonsignificant trend toward an OS benefit.

The IBCSG Trial VIII randomized 1,063 pre-/perimenopausal women with node-negative disease to receive either goserelin (3.6 mg s.c.) every 28 months or six cycles of CMF followed by goserelin (3.6 mg s.c.) every 28 days for 3 years plus 5 years of tamoxifen or six cycles of CMF with no tamoxifen [82]. RFS favored goserelin plus tamoxifen with a nonsignificant trend toward an OS benefit.

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or CAF plus 5 years of tamoxifen and monthly goserelin. With a median follow-up of 5 years, a significant benefit was seen for the addition of tamoxifen to CAF plus goserelin but not for the addition of goserelin alone to CAF. An exploratory subset analysis revealed a trend toward benefit for the addition of goserelin after CAF for women <40 years of age. Unfortunately, there was no treatment arm of CAF plus tamoxifen without goserelin [84]. At the present time, the role of ovarian ablation after chemotherapy is unclear. Several ongoing trials are addressing this question and we await their results.

In conclusion, the role of ovarian ablation in the adjuvant therapy of premenopausal women remains unclear. It does not appear to be an adequate substitute for tamoxifen. It is likely equivalent to some forms of chemotherapy; however, several issues, including the lack of tamoxifen in the chemotherapy arms as well as the lack of anthracycline- and taxane-based chemotherapy regimens, hamper the interpretation of these trials. It remains a reasonable option for premenopausal women who are candidates for, but decline, adjuvant chemotherapy. Its role in adjuvant therapy following chemotherapy is also unclear, and further data are needed before its use may be considered standard. Table 3 lists the currently open trials that address this important issue.

### CONCLUSIONS

Many advances have been made in recent years, improving the survival of early stage breast cancer patients. As a result of randomized trials in this setting:

- It has become standard to administer an anthracycline-containing regimen to lymph node–positive and high-risk, node-negative patients.
- It has become standard to integrate a taxane into chemotherapy regimens for node-positive patients.
- There is an increasing use of aromatase inhibitors in the adjuvant setting, both in sequential use with tamoxifen and as a substitute for tamoxifen.

Many questions remain, however, and these will be addressed in trials that are currently ongoing or have recently completed accrual. Some of the questions include:

- Is there a role for taxanes in high-risk, node-negative women?
- What is the optimal use of aromatase inhibitors in the adjuvant setting?
- Is there a potential benefit of ovarian ablation after chemotherapy in premenopausal patients?

We encourage enrollment in clinical trials to answer these important questions.

### DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

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