Adjuvant Systemic Therapies in Breast Cancer

Leonel F. Hernandez-Aya, MDa,
Ana M. Gonzalez-Angulo, MD, MScb,c,d,*

KEYWORDS
- Adjuvant • Breast cancer • Adjuvant endocrine • Adjuvant chemotherapy
- Adjuvant HER-2-targeted therapy

KEY POINTS
- Adjuvant systemic therapy has improved survival of patients with breast cancer.
- Most guidelines have recommended systemic treatment for node-positive disease and/or tumors larger than 1 cm, irrespective of other tumor characteristics.
- Oncotype DX is a validated genomic predictor of outcome and response to adjuvant chemotherapy in node-negative, estrogen receptor–positive breast cancer.
- Taxane-containing and anthracycline-containing regimens are standard adjuvant therapies for lymph node–positive and possibly in high-risk lymph node–negative patients with BC.
- Current guidelines recommend incorporating aromatase inhibitors either as up-front therapy or as sequential treatment after tamoxifen for 5 years in all patients with endocrine-sensitive tumors.
- Anti-HER2 adjuvant therapy with trastuzumab combined with chemotherapy has shown significant improvement in clinical outcomes compared with chemotherapy alone.

INTRODUCTION

The multidisciplinary approach for the treatment of breast cancer (BC) has been fundamental for the recent advances in the management of this disease. BC is the most common malignancy in women, accounting for nearly 1 in 3 cancers diagnosed among women in the United States, and it is one of the top causes of cancer-related deaths.1 Over the past 5 decades, innovative and dedicated research has generated
major advances in the diagnosis and treatment of BC with significant survival impact. A substantial portion of the success in improving clinical outcomes of patients with BC is related to the standardized use of adjuvant therapies Table 1. Cumulative evidence has demonstrated benefits in short-term and long-term outcomes by adjuvant treatments, especially when the 10-year risk of recurrence is at least 10%. A recent meta-analysis, including randomized clinical trials conducted since adjuvant therapies became widely used in the 1990s, reported a decrease in annual relative risk of relapse and mortality of 23% and 17% respectively.

The use of adjuvant therapy in BC has evolved as meaningful basic and clinical research contributes to the understanding of the complexity of breast tumors. For many years, the treatment recommendations for adjuvant therapies were based on classic anatomic and pathologic factors, such as tumor size, tumor grade, and lymph node (LN) status. With the development of immunohistochemistry (IHC), the identification of hormonal and human epidermal growth factor receptor 2 (HER2) in breast tumors allowed the classification of BC based on the expression of these markers and the development of specific receptor-targeted therapies with major clinical benefits. Furthermore, the past decade in BC research has been influenced by the development of genomic profiling techniques and the identification of tumor subtypes based on molecular expression patterns. These recent advances have raised the idea of tailoring treatments even further, personalizing therapies for those most likely to respond and avoiding unnecessary side effects from treatment in the “nonresponders.” The latter is preponderant in the adjuvant setting, given the constant challenge of distinguishing between those patients who need adjuvant treatment and those who do not.

**RATIONAL OF ADJUVANT CHEMOTHERAPY**

Before the era of adjuvant therapies, the treatment of early BC relied only on loco-regional therapies. For almost a century, a purely anatomic and mechanistic perception governed the treatment of BC with the Halsted en bloc radical mastectomy. Although some women with early BC may be cured with loco-regional treatment alone, up to 20% of patients with early-stage BC will ultimately experience treatment

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of classical and current chemotherapy regimens studied in adjuvant breast cancer therapy</th>
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<tbody>
<tr>
<td>CMF&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6 cycles of C 100 × 14 + M 40 × 2 + 5-FU 600 × 2, given q 28 d.</td>
</tr>
<tr>
<td>AC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4 cycles of A 60 + C 600, given IV q 21 d.</td>
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<tr>
<td>EC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4 cycles of E 90 + C 600, given IV q 21 d.</td>
</tr>
<tr>
<td>FAC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6 cycles of 5-FU 500 × 2 + A 50 × 1 + C 500 IVx1, q-3 wk.</td>
</tr>
<tr>
<td>FEC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6 cycles of 5-FU 500 × 2 + E 60 × 2 + C 500 IVx1, q-4 wk.</td>
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<tr>
<td>AC → P</td>
<td>4 cycles of A 60 C 600 q-3 wk → 12 cycles of P 80 q-wk</td>
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<tr>
<td>AC → D</td>
<td>4 cycles of A 60 C 600 q-3 wk → 4 cycles of D 100 q 3-wk</td>
</tr>
<tr>
<td>FEC → D</td>
<td>3 cycles of F 500 E 100 C 500 q-3 wk → 3 cycles of D 100 q 3-wk</td>
</tr>
<tr>
<td>FEC → P</td>
<td>3 cycles of F 600 E 90 C 600 q-3 wk → 8 cycles of P 100 q-wk</td>
</tr>
<tr>
<td>Dose-dense</td>
<td>4 cycles of A 60 C 600 q-2 wk → 4 cycles of P 175 q-2 wk + filgastrim days 3-10.</td>
</tr>
<tr>
<td>AC → P</td>
<td></td>
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Data are drug dose, mg/m<sup>2</sup> x frequency per cycle: ×14 = days, 1-14 oral; ×2 = days, 1 and 8 IV; ×1 = day 1 IV; q- = every.

Abbreviations: A, doxorubicin; C, cyclophosphamide; D, docetaxel; E, epirubicin; F, fluorouracil; IV, intravenous; M, methotrexate; P, paclitaxel.

<sup>a</sup> Classical and chemotherapy regimens.
failure and recurrence. The purpose of adjuvant systemic therapy is to improve the disease-free survival (DFS) and overall survival (OS) rates associated with treatment of BC by local therapies (surgery and/or radiation) alone. The elevated rates of recurrence are likely related to the presence of micrometastatic disease in 10% to 30% of LN-negative and in 35% to 90% of LN-positive patients at the time of diagnosis. Adjuvant chemotherapy emerged as an instrument to eradicate the local or distant residual microscopic metastatic disease with potentially curative effects. In the 1970s, the understanding of BC as a systemic and biologically diverse disease grounded the development of clinical trials, the results of which changed dramatically the paradigm of BC treatment. Early trials conducted by Fisher and colleagues, at the National Surgical Adjuvant Breast and Bowel Project (NSABP), and by Bonadonna and colleagues, at the Istituto Tumori Nationale in Milan, proved benefits in recurrence-free survival (RFS) and OS of adjuvant polychemotherapy in premenopausal women with node-positive BC. Following these initial studies, there were multiple prospective clinical trials conducted around the world investigating different adjuvant regimens. The benefits of the early chemotherapy trials led to the recommendation of adjuvant chemotherapy to a wide range of population. The subgroups of patients in these early trials were classified based on anatomic/pathologic findings, mainly tumor size and LN status. The differences in treatment recommendations were dictated mainly by age and estrogen receptor (ER) status for the use of hormonal therapy, but in essence all patients with node-positive disease were considered potential candidates for cytotoxic chemotherapy.

By 2000, The National Institutes of Health’s Consensus Development Conference on adjuvant therapy for BC recommended consideration of adjuvant chemotherapy for essentially all patients with tumors of 1 cm or larger. The NSABP pooled analysis of more than 1250 cases with node-negative tumors up to 1 cm in size reported improved survival of adjuvant chemotherapy and hormone therapy in patients with node-negative tumors of 1 cm or smaller. The most recent Early Breast Cancer Clinical Trialists’ Collaborative Group (EBCTCG) overview of chemotherapy studies reported that proportional risk reduction from chemotherapy was little affected by age, nodal status, tumor diameter or differentiation, ER status, or tamoxifen use, and that information was lacking about tumor gene expression markers or quantitative IHC that might help to predict risk, chemosensitivity, or both. Most guidelines have recommended systemic treatment for node-positive disease and/or tumors larger than 1 to 2 cm, irrespective of other tumor characteristics; however, the patients in these initial trials were unselected for their tumor biologic characteristics and the meta-analyses combine heterogeneous studies providing treatment benefits in a diverse population studied. Side effects of adjuvant chemotherapy can be life-threatening in up to 1% of patients. As the threshold for giving adjuvant chemotherapy is lowered, more patients will suffer the side effects of the therapy without a meaningful clinical benefit. Over the past 2 decades, extensive research has been dedicated to investigate prognostic and predictive markers to classify patients in risk-based groups with more homogeneous features and potentially find the population with higher response rates to adjuvant treatments. The decision on whether to use adjuvant systemic therapy is based on an analysis of prognostic factors that predict the likelihood of recurrence and efficacy of the treatment, counterbalanced by the toxicities of the drugs.

PROGNOSTIC AND PREDICTIVE FACTORS

Adjuvant chemotherapy has been used in oncology practice for almost all patients except those with small, node-negative, and well-differentiated invasive primary
cancers. Tumor size and nodal status have been the classic factors influencing the decision on adjuvant chemotherapy; however, the clear-cut classic indication of chemotherapy for all node-positive patients with tumors larger than 1 cm is now controversial and a treatment recommendation should not be provided based strictly on size. In addition to axillary sentinel node biopsy to identify micrometastatic disease, histologic grading systems have been used to categorize cancers further. The Nottingham Prognostic Index (NPI) includes the evaluation of histologic grades in addition to tumor size and node involvement. Three grades of differentiation are used (low, intermediate, and high grade), based on 3 morphologic features: the percentage of tubule formation, the degree of nuclear pleomorphism, and the mitotic count. The variables noted in these indices have been generally adopted as prognostic markers and have influenced recommendations for adjuvant therapy as markers of “high” risk. In addition to the variables that constitute the NPI, lymphovascular invasion (LVI) is reported as a separate finding. Quantitative measurements of ER and progesterone receptor (PR) and identification of HER2 overexpression are recommended assays in all invasive tumors. Although there is still controversy in the minimum percentage of cells stained for the receptor that should be considered positive, most groups are considering any positivity as a “positive” value. Appropriate HER2 testing is pivotal in the management of patients with BC. Overexpression can be indirectly assessed by quantifying HER2 receptors by IHC, or by directly measuring the number of HER2 gene copies using fluorescence in situ hybridization or bright field in situ hybridization. These factors have been used as prognostic markers to classify patients in high-risk groups and influence recommendations for adjuvant treatments. Tumors with a high grade of differentiation (grade 3), HER2 overexpression, and lack of ER/PR expression are considered more aggressive. Patients with these tumors are classified as “high risk” and more likely to benefit from adjuvant chemotherapy. Other factors, such as proliferation (Ki-67), weak expression of hormone receptors, and lymphovascular invasion, may be considered, but the evidence is limited. In patients with more than 3 axillary lymph nodes positive for metastasis, the use of adjuvant chemotherapy is well accepted. ER-positive BCs are considered to have better prognosis than those with ER-negative tumors; however, some patients with ER-positive, LN-negative tumors may benefit from chemotherapy. In recent adjuvant studies, a category of “high-risk” node-negative patients has been included. This group is defined by a tumor larger than 2 cm in diameter and positive for ER or PR or as a tumor larger than 1 cm in diameter and negative for both ER and PR.

During the past several years, the development of genomic profiling techniques has identified gene expression patterns in breast tumors with distinct molecular profiles, pathologic features, and clinical outcomes. Expression patterns have defined 4 different subtypes: luminal A and B (estrogen-sensitive BC), HER2-enriched, and basal-like tumors (negative ER/PR and negative HER2). Because the genetic profiling is not widely available in a standardized method, defining surrogate subtypes using immunohistochemical determination of ER/PR, and in situ hybridization technology for detecting HER2 amplification has been used as an approximation to the intrinsic subtypes. The St Gallen Consensus Conference in 2011 considered the clinicopathologic determination of ER, PR, HER2, and Ki-67 as useful for defining subtypes and to guide therapeutic choices in the absence of an available standardized test system able to molecularly characterize these subtypes. Luminal A tumors are classified by positive ER/PR, negative HER2, and low Ki-67, whereas luminal B tumors characteristically have positive ER/PR, negative HER2, and high Ki-67. The additive prognostic value of Ki-67, a cell proliferation marker, to steroid and HER2 receptors is accepted, as many significant genes in gene expression profiles are proliferation...
related. Ki-67 marks the difference between luminal A and B tumors; however, Ki-67 is not yet routinely available and standard cutoffs are not well defined.

The molecular classification has stimulated a targeted approach for the current BC therapies, including the use of hormonal therapy for luminal A tumors, HER2-targeting therapy for HER2-enriched tumors, and chemotherapy for luminal B and basal tumors. The priority of the current studies in adjuvant therapy is to identify the responders to a particular therapy and the population that does not require treatment. At the recent St Gallen Consensus Conference, the idea of using intrinsic tumor subtype for identifying responders and nonresponders to a specific therapy was considered. The goal is to move beyond the traditional prognostic factors, such as tumor size and lymph node status, to a personalized era using predictive factors of response to therapy. The subgroup of patients with BC with luminal A tumors has a good prognosis and shows response to hormonal therapies. Conversely, these patients have a low likelihood to respond to adjuvant chemotherapy, especially in node-negative disease. In these patients, the commercially available Oncotype DX (Genomic Health Inc, Redwood City, CA) and MammaPrint (Agendia BV, Irvine, CA) have a role in the prediction of chemotherapy response. In retrospective analysis of the NSABP B-20 trial in patients with node-negative disease, there was no advantage of adding chemotherapy to tamoxifen except among those with the highest levels of recurrence score (RS) as measured by Oncotype DX.

Recent data suggest that even LN-positive luminal A tumors may derive little or no benefit from cytotoxic therapy when compared with the use of hormonal therapy alone. Analysis from the IBCSG (International Breast Cancer Study Group) IX trial and IBCSG VIII trial showed no benefit of adjuvant cytotoxic therapy in premenopausal and postmenopausal patients with high endocrine receptor expression, negative HER2, and low proliferation (low Ki-67 labeling index). These features correspond to the surrogate definition of luminal A tumors. Similarly, the Southwest Oncology Group (SWOG) 8814 showed no advantage of cyclophosphamide, doxorubicin, and fluorouracil chemotherapy over tamoxifen among postmenopausal women with node-positive disease with high ER levels, negative HER2, and low RS. Penault-Llorca and colleagues analyzed the PACS (French Adjuvant Study Group) 01 trial, suggesting an additional benefit of taxane in patients with ER-positive disease with higher Ki-67 expression. As suggested by Hayes, emerging evidence suggests that this group of women with early BC with features similar to the luminal A type, may not benefit by adding chemotherapy to highly effective endocrine therapy; however, level I evidence is needed to support this thesis. Patients with luminal B breast tumors (both ER positive and HER2 positive) appear to benefit more from adjuvant chemotherapy and less from hormonal therapy. Because genetic profiling is not yet routinely performed in a standardized system, IHC is still considered standard for evaluating risk of relapse and response to therapy.

Several validated tools to define prognosis are undergoing evaluation. Adjuvant! Online (www.adjuvantage.com) for BC is a prognostic tool that uses OS data from women diagnosed with BC between 1988 and 1992 recorded in the Surveillance, Epidemiology, and End Results (SEER) registry (www.seer.cancer.gov) and applies risk reductions from the EBCTCG, to determine prognosis and treatment benefits for hormone therapy and chemotherapy. This tool has been validated in several case cohort studies, and has been assisting oncologists and patients in the decision making of chemotherapy. Specific clinicopathologic data from a patient is entered to estimate the probability of 10-year survival with no therapy, and to calculate the patient’s risk of recurrence given hormonal therapy, chemotherapy, or combined therapy. Other prognostic tools using known clinical and pathologic factors are under
investigation. Predict+ uses mortality data from the United Kingdom and includes HER2 status and mode of detection in the clinical prognostication tool. A recent study showed that Predict+ was inferior to Adjuvant! In estimating all-cause mortality, but provided better BC-specific mortality estimates that Adjuvant. The Genomic data to predict recurrence risk in women with early BC is an active area of research. Multiple assays are currently available in the United States. The Oncotype DX RS and the MammaPrint are the most widely used and perform gene-expression profiling of node-negative cancers. Oncotype DX is a validated genomic predictor of outcome and response to adjuvant chemotherapy in ER-positive BC. The 21-gene assay quantifies risk of distant recurrence in node-negative, ER-positive, tamoxifen-treated patients. It reports a continuous risk score between 1 and 100 and stratifies recurrence risk into low (0–18), intermediate (19–30), and high (>30). Women with a low 21-gene RS have a favorable prognosis that chemotherapy will not provide a meaningful benefit over the risks of toxicity, whereas chemotherapy will benefit the high-risk group. The MammaPrint is a 70-gene signature that uses microarray technology applied to fresh-frozen tissues to classify patients into good and poor prognosis categories. The high-risk group will be candidates for adjuvant chemotherapy and the low-risk group will avoid chemotherapy. Oncotype DX and MammaPrint are both available to be performed on fixed tissue. Current guidelines support the use of these studies in cases in which the need for adjuvant chemotherapy is not clear, based on clinicopathologic variables or conflicting patient preference. These tests have no value (Oncotype DX) or very limited value (MammaPrint) in stratifying ER-negative disease.

Higher level of evidence is available supporting the prognostic value of Adjuvant! Online and Oncotype DX. Prospective studies using archived tissues conducted by the NSABP B-14 and B-20 and by the SWOG 8814 have shown the ability of the 21-gene RS to independently predict response to adjuvant chemotherapy. Using data from the randomized trials NSABP B-14 and NSABP B-20, Tang and colleagues reported that both Adjuvant! Online and the 21-gene RS independently predicted distant recurrence and chemotherapy benefit. The 21-gene RS was found to be more predictive of both distant recurrence and response to adjuvant chemotherapy. This test is widely used in the evaluation of patients with node-negative, ER-positive BC, allowing less administration of chemotherapy in these women. Multiple randomized controlled trials to add level I evidence to the use of the 21-gene signature are undergoing. During the 2011 St Gallen consensus meeting, only the multiparameter gene assay Oncotype DX was considered by most as potentially useful for decision making on adjuvant chemotherapy in cases in which other factors (eg, grade, HER2) do not help.

ADJUVANT CHEMOTHERAPY REGIMENS IN BC

For almost 2 decades, multiple randomized clinical studies were conducted worldwide to find the most effective adjuvant regimen. In 1976, Bonadonna and colleagues reported the efficacy of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) as adjuvant treatment for patients with node-positive BC. CMF was the leader in adjuvant chemotherapy, considered the standard for premenopausal women with node-positive disease. In women with node-negative and ER-positive tumors, tamoxifen was recommended, whereas in the ER-negative tumors, classical CMF for 6 cycles offered a significant advantage both on relapse-free survival (RFS) and OS. The role of tamoxifen in premenopausal ER-positive patients was not yet clearly elucidated and the benefit in younger patients was attributed to the ovarian suppression of CMF.

In the mid-1980s, anthracyclines were included in the clinical trials. The initial trials comparing CMF and anthracyclines studied 6 to 12 months of CMF compared with
6 months of anthracycline-based treatment with combinations such as FAC (fluorouracil, adriamycin, cyclophosphamide) or FEC (fluorouracil, epirubicin, cyclophosphamide). These regimens achieved reductions in annual odds of recurrence of 24% and 35%, respectively, and in odds of death of 14% and 30%, respectively. Greater benefits were seen in patients younger than 50 years old, with hormone receptor-negative and node-positive disease. Based on this evidence, during the 1990s, 6 cycles of a 3-drug anthracycline-containing combination became the standard of care in adjuvant chemotherapy. In women older than 50, the initial trials (NSABP B-16) enrolling almost 1200 patients indicated greater benefit from tamoxifen plus anthracycline-containing regimen than from tamoxifen alone in hormone-responsive patients.

The most recently published meta-analysis of the EBCTCG of outcomes in 100,000 women with early BC, including more than 100 trials of old and modern adjuvant chemotherapy, confirmed the benefit of CMF and anthracycline-based therapies with proportional reduction in BC mortality rate of 20% to 25% with absolute reductions of BC mortality of 6.2% and 6.5% respectively at 10 years. Importantly, for women with ER-positive disease, if adjuvant tamoxifen therapy is given after the anthracycline-based regimen, the average annual death rate from BC would be approximately cut in half.

The Taxane Era in Adjuvant Therapy

In the early 1990s, the taxanes (paclitaxel and docetaxel) showed a potent antitumor efficacy in advanced BC and rapidly were approved to be included in adjuvant chemotherapy trials. The Cancer and Leukemia Group B 9344 (CALGB) and the NSABP B-B28 trials compared the sequential or concurrent administration of taxanes and anthracycline-based therapies, with the standard doxorubicin and cyclophosphamide regimen. These studies reported a significant reduction of 17% in the risk of recurrence when paclitaxel was added to the standard regimens. Overall survival favored the paclitaxel combination, although without reaching statistical significance. Similar results were observed comparing docetaxel, doxorubicin, and cyclophosphamide (DAC) regimen with fluorouracil, doxorubicin, and cyclophosphamide (FAC). The Breast Cancer International Research Group (BCIRG)-001 trial reported a 7% absolute improvement in RFS and a 6% improvement in OS with DAC. The Grupo Español Para la Investigación del Cáncer de Mama (GEICAM) 9805 trial also showed higher DFS rates of DAC over FAC.

Given elevated rates of side effects observed in the concurrent studies, multiple randomized trials have been conducted evaluating sequential therapy with taxanes. The CALGB 9344 and the NSABP B-28 evaluated the use of paclitaxel after 4 cycles of AC (Doxorubicin and Cyclophosphamide) and showed significant benefit in DFS (CALGB 9344 and NSABP B-28) and OS (CALGB 9344) when paclitaxel was added to the standard AC. Subsequent trials confirmed the incremental benefit of sequential docetaxel with anthracycline-containing regimens in the adjuvant setting. The Protocole Adjuvant dans le Cancer du Sein (PACS) 01 trial randomized 1999 patients with LN-positive disease to adjuvant therapy with six 21-day cycles of FEC or three 21-day cycles of docetaxel. The addition of docetaxel to FEC resulted in a 27% reduction in the risk of death (hazard ratio [HR] 0.73, 95% confidence interval [CI] 0.56–0.94, P = .017). An update at 8 years’ median follow-up demonstrated a continued benefit of docetaxel therapy for DFS (HR 0.85, 95% CI 0.73–0.99, P = .035) and OS (HR 0.79, 95% CI 0.65–0.97, P = .024). The GEICAM 9906 trial randomized 1246 LN-positive BC patients to receive six 21-day cycles of FEC or four 21-day cycles of FEC followed by 8 weekly administrations of paclitaxel
(FEC-T). After 66 months of follow-up, 5-year DFS was superior for the FEC-T arm (HR 0.74, 95% CI 0.60–0.92, \( P = .006 \)). FEC-T reduced the risk of relapse by 23%. There was no significant improvement in 5-year OS.\(^{53}\) The addition of a taxane to AC improves DFS and reduces the risk of recurrence; however, there is a lesser impact on overall survival.

The ECOG 1199 trial was intended to solve the questions about the best taxane administration regimens. The trial included 5000 patients with node-positive or high-risk node-negative (tumor size >2 cm) BC randomized to a standard AC regimen to be followed by 1 of 4 taxane regimens: paclitaxel 175 mg/m\(^2\) every 3 weeks for 4 cycles (control), 12 weekly doses of paclitaxel 80 mg/m\(^2\), docetaxel 100 mg/m\(^2\) every 3 weeks for 4 cycles, or 12 weekly doses of docetaxel 35 mg/m\(^2\). After a median of 64 months of follow-up, 5-year DFS was significantly better in the group receiving weekly paclitaxel (HR 1.27, 95% CI 1.03–1.57) and in the group receiving docetaxel every 3 weeks (HR 1.23, 95% CI 1.00–1.52) when compared with the standard every-3-week paclitaxel group. There was no significant benefit of receiving weekly docetaxel over paclitaxel every 3 weeks. Patients with HER2-negative disease treated with weekly paclitaxel had a significant improvement in DFS and OS over standard every-3-week administration of paclitaxel; this result was not seen with docetaxel administration.\(^{54}\)

Other studies have evaluated the use of taxanes without anthracycline in the adjuvant setting. The US Oncology (USO) trial 9735 compared 3-week cycles of AC versus docetaxel-cyclophosphamide (DC) in the adjuvant setting. After 7 years of median follow up, a higher DFS and OS was reported in the patients treated with DC compared with those treated with AC. A regimen of 4 cycles of AC is an inferior comparator and no longer an appropriate standard for treating node-positive patients. Therefore, DC may be considered in treating some node-negative patients (when chemotherapy is considered) but is not appropriate adjuvant therapy for node-positive patients.\(^{55}\)

New studies are undergoing to optimize taxane delivery. The CALGB 9741 trial showed that dose-dense regimens (every 2 weeks) were significantly better than the conventionally (every 3 weeks) timed regimens, improving DFS (HR = 0.74, \( P = .0072 \)), as well as OS (RR = 0.69, \( P = .014 \)). The 4-year DFS was 82% for the dose-dense regimens and 75% for the 3-weekly regimens. There was no difference in either DFS or OS between the concurrent and sequential schedules of treatment.\(^{56}\) Updated results after a median 6.5 years of follow-up continue to show an improvement in DFS and OS in favor of dose-dense chemotherapy administration with greater benefit in ER-negative tumors. Growth factor support is needed for dose-dense paclitaxel to maintain strict every-14-day scheduling.

A meta-analysis demonstrated that taxane-based regimens provide both DFS and OS benefit with an absolute 5-year risk reduction of 5% for DFS and 3% for OS when compared with standard anthracycline regimens irrespective of ER status, LN status, and age. Additionally, the improvements in DFS and OS were similar for both paclitaxel and docetaxel. This evidence supported the adoption of taxane-containing and anthracycline-containing regimens as the new standard adjuvant treatment for patients with BC with LN-positive and possibly in high-risk LN negative tumors.\(^{55}\) Scheduling of these agents include weekly and every 2-week or 3-week regimens for periods of 2 to 6 months depending on tumor stage. Women with early-stage BC have traditionally been treated with 4 cycles of an anthracycline-based regimen, whereas patients with more advanced disease (eg, stage II or III) have been treated with anthracycline-based and taxane-based therapies for 4 to 6 months. The recently published CALGB trial 40101, including 3171 patients with node-negative and 1 to 3 positive LNs, compared 4 cycles versus 6 cycles of chemotherapy. The 4 arms of therapy included 6 cycles of AC versus 4 cycles of AC, and 4 cycles of single-agent
paclitaxel versus 6 cycles of paclitaxel. The results showed no superiority of 6 cycles over 4 cycles of therapy for either OS (HR 1.12, 95% CI 0.89–1.42) and DFS (HR 1.03, 95% CI 0.84–1.28) in this population. Hematological and cardiac toxicities from AC and neuropathy from paclitaxel were more common in the patients who received 6 cycles of therapy. The results of the comparison of single-agent paclitaxel versus AC are not yet available.

More conclusive data are needed regarding the comparison between the 2 taxanes available, docetaxel and paclitaxel, the method of administration, and identification of subgroups of patients who may greatly benefit from taxane therapy based on their hormonal status or tumor biology. Studies of concurrent versus sequential taxane administration have favored the sequential use with benefits in DFS and better safety profile; however, more studies are needed in this regard. The latest meta-analysis by the EBCTCG including the taxane trials showed a small but significant BC mortality reduction of adjuvant taxane-anthracycline–based regimen (2.8% absolute gain at 8 years). Interestingly, this difference was not significant when higher doses of nontaxane regimens were given to the control group. With the limitations of molecular heterogeneity in the groups compared, limited information about HER2, and trastuzumab effect, the results suggested that these more modern regimens compared with no chemotherapy, may reduce 10-year BC mortality by about a third independent of ER receptor status and patient age. Ongoing clinical trials are evaluating other agents in combination with anthracyclines and taxanes. The Finnish Breast Cancer Group (FinXX) investigated the benefit of the addition of capecitabine to docetaxel. After a median follow-up of 59 months, the capecitabine-containing regimen did not improve DFS compared with regimens without capecitabine. Ixabepilone, a microtubule inhibitor, is being compared with weekly paclitaxel after adjuvant AC in the TITAN III trial (available at: http://clinicaltrials.gov/NCT00789581, accessed September 2012).

ADJUVANT ENDOCRINE THERAPY IN BC

Adjuvant hormone therapy is considered standard in all patients with endocrine-sensitive tumors defined by the expression of ER and PR by IHC. Approximately 70% of BCs have positive expression of the ER and are considered hormone sensitive. Adjuvant hormone therapy in BC evolved after the discovery of the ER in the 1960s. Initial studies showed that breast tumors with expression of ER and PR correlated with hormonal sensitivity in metastatic breast tumors. Tamoxifen demonstrated activity in advanced BC and entered adjuvant trials, most prominently in Europe with the Nolvadex Adjuvant Trial Organization (NATO) trial. Tamoxifen demonstrated activity in advanced BC and entered adjuvant trials, most prominently in Europe with the Nolvadex Adjuvant Trial Organization (NATO) trial. Adjuvant studies with tamoxifen have demonstrated a significant benefit in hormone-sensitive patients. In premenopausal women, tamoxifen remains the only endocrine agent approved by the Food and Drug Administration in the adjuvant setting. Treatment with tamoxifen for 5 years reduces the risk of recurrence by 41% and BC mortality by 34%. Nevertheless, more than 30% of patients will develop a recurrent tumor in the first 15 years following diagnosis. Although an early peak of recurrence is seen in the first 2 to 3 years after surgery, late recurrence remains an important concern in adjuvant therapy. There is a persistent 2% to 3% annual recurrence risk in years 5 through 9, which has been lowered by tamoxifen (relative risk reduction, 32%). After 10 years, the annual risk of recurrence is approximately 2%, and there is no lasting risk reduction on a year-to-year basis for having received tamoxifen for the initial 5 years.

The aromatase inhibitors (AI) prevent estrogen synthesis through inhibition of the aromatase enzyme. This enzyme results in the synthesis of estrogen in peripheral tissues, but not in the ovary. Therefore, AI therapy is used only in postmenopausal
patients. Over the past decade extensive research has been conducted with AIs in postmenopausal women. Anastrozole was approved in 1996 for the treatment of metastatic endocrine-sensitive BC. Subsequently, multiple randomized phase III clinical trials using third-generation AIs (anastrozole, letrozole, exemestane) have demonstrated benefits in DFS of postmenopausal women with ER-positive BC with the use of AIs as upfront therapy or in sequence with tamoxifen.62–66

**Adjuvant Trials Using Aromatase Inhibitors**

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, is a pivotal trial in adjuvant hormone therapy.62 The ATAC trial compared the adjuvant use of anastrozole (n = 3125) with tamoxifen (n = 3116) or anastrozole plus tamoxifen (n = 3125) in postmenopausal women with early-stage BC. A recent updated report of the ATAC trial showed a continuous benefit of anastrozole over tamoxifen at 120 months of follow-up in all patients studied and more pronounced in the HR+ patients. At 10 years, anastrozole as initial therapy showed increased DFS (HR 0.86, P = .003), time to local and distant recurrence (HR 0.79, P = .0002; HR 0.85, P = .02, respectively), and reduced indices of contralateral BC (HR 0.62 P = .003) compared with tamoxifen. As in the initial results, there was no significant difference in overall mortality between the 2 groups.67 The results of the ATAC trial influenced the changes in the adjuvant endocrine therapy and outcomes in women with early-stage BC. In December 2001, the NCCN Clinical Practice Guidelines in Oncology included anastrozole as an alternative to tamoxifen in the initial adjuvant treatment of postmenopausal women.

Since the ATAC trial, other important studies have been conducted using AIs in adjuvant endocrine therapy. The 3 different AIs (anastrozole, exemestane, and letrozole) have been studied up front or sequential after 2 to 3 years of tamoxifen and as extended therapy after 5 years of tamoxifen. The Breast International Group 01–98 (BIG 1–98) included 8010 postmenopausal patients to compare letrozole to tamoxifen in the adjuvant setting in 2 monotherapy arms and 2 sequential arms.64 Letrozole as a monotherapy for 5 years significantly improved DFS (HR 0.81, P = .003), and time to distant recurrence (HR 0.73, P = .001), compared with tamoxifen. No significant differences were observed in OS (HR 0.86, P = .16). An analysis of predictors of early relapse in the BIG 1–98 trial (n = 7707) found that adjuvant letrozole therapy had a pronounced benefit in reducing the risk of distant metastases early on, at 2 years (87 vs 125 events). In the report of the sequential analysis at 71 months of follow-up, there were no significant differences in DFS or OS between sequential treatments in either order compared with letrozole monotherapy. Subgroup analyses revealed that letrozole was particularly effective in patients with more than 4 axillary lymph node metastases and in patients with highly proliferative BC.68 Based on these results, the investigators suggested that adjuvant endocrine therapy should begin with letrozole, particularly in patients at high risk for local or distant recurrence.64 Both the ATAC and the BIG trial showed reductions in DFS but no improvement in OS. The trials showed differences in the toxicity profile with tamoxifen being related to more thromboembolic events and AIs associated with more fractures and arthralgias.

In the Intergroup Exemestane Study (IES) trial, postmenopausal women with early BC who had already completed 2 to 3 years of adjuvant tamoxifen therapy were randomized to switch to exemestane or to continue on tamoxifen for a total of 5 years.65 At a median follow-up of 91 months, a significant improvement in DFS was observed in patients who had switched to exemestane (HR 0.84; P = .002). A modest but statistically significant improvement in OS was observed with an absolute difference in survival outcome at 8 years of 2.4% (HR 0.86, 95% CI 0.74–0.99; P = .04) in favor of switching to exemestane compared with those continuing treatment with tamoxifen.69 MA.17
examined the idea of extending endocrine therapy beyond 5 years of tamoxifen. This trial randomized postmenopausal women who had completed 4.5 to 6.0 years of tamoxifen to letrozole versus placebo for a planned 5-year period. In the intent-to-treat analysis at 30 months of median follow-up, the DFS was 94.4% in the letrozole arm versus 89.8% in the placebo group (\(P<.001\)). When the analyses were restricted to those with ER-positive tumors, the HR for recurrence or contralateral BC substantially favored letrozole (HR 0.58, 95% CI 0.45–0.76). No OS advantage was noted; however, a survival advantage was reported in node-positive patients (\(P = .04\)).

From the data reported and summarized in Table 2, AIs provide benefit in DFS compared with tamoxifen in postmenopausal women with early-stage BC. The benefits of anastrozole in DFS are maintained or extended with long-term follow-up. Although there has been lack of significant OS advantage in all studies reported (see Table 2), subgroup analyses of both MA.17 and BIG 1–98 demonstrated a survival benefit with AI therapy in node-positive patients. The lack of survival advantage has been attributed to the limited follow-up for a long-term disease, non-BC deaths, and the contribution of loco-regional or contralateral BC events to study end points, and late crossover from tamoxifen to AI treatments. With adjustment for that high rate of crossover, the MA.17 study and the BIG 1–98, reported a survival advantage for use of an AI instead of tamoxifen alone. These findings suggest that up-front adjuvant therapy with an AI may benefit a subgroup of patients with poor prognostic factors at the time of surgery (large and highly proliferative tumors, high number of axillary lymph node metastases).

The best treatment regimen, up front or sequential after tamoxifen, and choice of AIs, remains to be defined. Also, multiple questions regarding the optimal duration of AI, long-term adverse effects of AIs, and the predictive value of molecular markers, such as PR, are being addressed by ongoing clinical trials. At present, there are no clinical or biologic markers sufficiently reliable to determine whether duration should vary from patient to patient. The available evidence has led to major changes in oncologic practice, placing the AIs as the most commonly prescribed adjuvant endocrine therapy for postmenopausal women with early ER-positive BC. Current guidelines from the American Society of Clinical Oncology recommend incorporating AI either as up-front

<p>| Table 2 | Summary of results from adjuvant aromatase inhibitor therapy trials in postmenopausal women with hormone receptor-positive |</p>
<table>
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<tr>
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<td>Up-front AI vs TAM</td>
<td>Benefit in DFS (HR 0.87, (P = .01)) No OS benefit</td>
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<td>Letrozole</td>
<td>Up-front AI vs TAM Sequential AI after TAM</td>
<td>Up-front AI: DFS ((P = .03)) T → AI vs AI: DFS (HR 1.05, 99% CI 0.84–1.32) No OS benefit</td>
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<td>IES</td>
<td>Exemestane</td>
<td>Sequential AI after TAM vs up-front AI</td>
<td>+ Benefit in DFS ((P = .0001)) OS ((P = .05)) when restricted to ER+</td>
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<td>MA.17</td>
<td>Letrozole</td>
<td>Extended after 5 y of TAM</td>
<td>+ Benefit DFS ((P&lt;.001)) OS ((P = .04)) in LN+</td>
</tr>
<tr>
<td>TEAM</td>
<td>Exemestane</td>
<td>Up-front Exemestane vs TAM → Exemestane</td>
<td>No difference in DFS ((P = .60))</td>
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Abbreviations: AI, aromatase inhibitor; DFS, disease-free survival; ER+, estrogen receptor–positive patients; HR, hazard ratio; LN+, lymph node–positive patients; OS, overall survival; TAM, tamoxifen.
therapy or as sequential treatment after tamoxifen for 5 years and acknowledge that the “optimal timing and duration of endocrine treatment remain unresolved.” The St Gallen Consensus Conference panel in 2011 also considered appropriate to include AIs at some point in the adjuvant treatment of postmenopausal women, especially in LN-positive patients.73

ADJUVANT THERAPY IN HER2 POSITIVE BCS

Approximately 15% to 20% of all BCs present with amplification of the HER2 gene. HER2 overexpression is reported to be an independent predictor of poor prognosis.74,75 This poorer prognosis can be addressed by the incorporation of anti-HER2 therapy with trastuzumab, a monoclonal antibody targeting the extracellular domain of the HER2 protein, which in the adjuvant setting has shown significant improvement in clinical outcomes from adjuvant chemotherapy plus trastuzumab compared with chemotherapy alone. The initial trials led by the NSABP and the North Central Cancer Center Group showed benefits in DFS and OS with addition of trastuzumab, sequentially or concurrently with paclitaxel, after a regimen of doxorubicin and cyclophosphamide.76 Based on results from 5 randomized clinical trials, a trastuzumab-containing regimen for up to 1 year is now considered standard for all patients with HER2-positive tumors larger than 1 cm.77–79 Patients received either chemotherapy alone or chemotherapy with sequential treatment with trastuzumab for 12 months. One of these trials, the Herceptin Adjuvant (HERA) trial, included 5102 patients evaluating trastuzumab as adjuvant treatment for patients with HER2-positive BC. After a median follow-up of 4 years, the DFS was significantly higher in the trastuzumab group (HR 0.76, 95% CI 0.66–0.87) with no significant benefit in OS likely secondary to crossover of 52% of patients.

On the other hand, trials evaluating trastuzumab given concomitantly with chemotherapy have shown benefits in OS. The North Central Cancer Treatment Group (N9831) trial directly compared concomitant trastuzumab and paclitaxel versus sequential trastuzumab in the adjuvant setting. At a median follow-up of 6 years, the results favored the concomitant administration of trastuzumab with paclitaxel relative to sequential administration.80 The Breast Cancer International Research Group 006 (BCIRG 006) trial evaluated trastuzumab combined with either docetaxel after AC (AC–TH) or docetaxel plus carboplatin (TCarloH), with a control arm of doxorubicin/cyclophosphamide/docetaxel (ACT). The trial did not permit or facilitate crossover, and only 1.6% of patients in the control group crossed over to trastuzumab. At a median follow-up of 5.5 years, AC–TH and TCarboH were each associated with statistically significant improvements in DFS and OS compared with ACT. 79 In the combined analysis of the North Central Cancer Treatment Group trial N9831 and the NSABBP trial B-31, 20.9% of patients in the control group crossed over to trastuzumab.77 An updated efficacy analysis (median follow-up of 2.9 years) showed that combining trastuzumab with paclitaxel after doxorubicin/cyclophosphamide (AC) significantly improved DFS (HR 0.49, 95% CI 0.41–0.58, P<.0001) and OS (HR 0.63, 95% CI 0.49–0.81, P = .0004) compared with chemotherapy alone.80 These trials have led to the preferred use of trastuzumab concurrent with chemotherapy in the treatment patients with HER2-positive BC larger than 1 cm and medically fit to tolerate chemotherapy (Table 3).

The appropriate duration of anti-HER2 therapy is under investigation. Ongoing trials are evaluating 6 versus 12 months of adjuvant trastuzumab (http://www.clinicaltrials.gov/NCT00381901) and 9 weeks versus 1 year of trastuzumab in combination with chemotherapy (http://www.clinicaltrials.gov/NCT00593697). In the oncology practice, if there is easy access to the medication, 1 year of therapy is recommended. On the
other hand, in the case of limited resources, shorter duration may be an option. Given the absence of conclusive data, adjuvant trastuzumab therapy over more than 1 year is not accepted as standard treatment.

Since the eligibility criteria for the phase III adjuvant trials of trastuzumab included tumor diameter of greater than 1 cm or positive LN, the effect of trastuzumab in very small tumors (pT1a/b, N0) is still under investigation. Several studies have reported worse DFS in HER2-positive small (<1 cm) tumors.81 A subgroup analysis of the BCIRG 006 phase III trial evaluated patients with small (<1 cm), node-negative, and HER2-positive tumors. To be eligible, patients with small tumors needed to be younger than 35 years, with ER/PR negative or histologic and/or nuclear grade 2 to 3.79 The estimated 5-year rates of DFS were 86% in the trastuzumab-containing arms (AC followed by docetaxel every 3 weeks plus 52 weeks of trastuzumab [AC-TH]; docetaxel and carboplatin plus 52 weeks of trastuzumab [TCH]) and 72% in the chemotherapy-only arm (doxorubicin and cyclophosphamide followed by docetaxel every 3 weeks [AC-T]). The HR for DFS for trastuzumab with anthracycline based chemotherapy was 0.36 (P = .03), whereas for the trastuzumab and nonanthracycline-based chemotherapy, the HR was 0.45 (P = .10).79 The scarce data available, suggest benefit of trastuzumab in small HER2-positive tumors in patients with other risk factors, such as young age, high nuclear grades, or absence of HR expression. It has been proposed to consider a course of chemotherapy plus trastuzumab especially in patients with T1b or with unfavorable risk factors.82 The main concerns in this population are the side effects from trastuzumab therapy. The rates of grade III/IV congestive heart failure (CHF) reported in the adjuvant trials have been up to 3.3%. The trastuzumab-related cardiotoxicity seems to be reversible and not related to cumulative doses.83 Nonanthracycline regimens plus trastuzumab are being evaluated in early-stage BC to minimize the risk of CHF (http://www.clinicaltrials.gov/NCT00542451; accessed September 2012). In patients with HER2-enriched and ER-positive BC, MammaPrint’s “low-risk” tumors have been associated with a good prognosis; therefore, it is attractive to omit adjuvant chemotherapy and trastuzumab in these patients in favor of hormone therapy alone; however, MammaPrint has no shown predictive value.

Ongoing trials are evaluating other novel HER2-targeting agents. Pertuzumab is a recombinant humanized monoclonal antibody directed against the dimerization domain II of HER2. This agent has shown beneficial effects in the metastatic setting combined with trastuzumab and chemotherapy.84 In the adjuvant setting, phase III clinical trials are undergoing to evaluate pertuzumab combined with trastuzumab and chemotherapy in patients with operable HER2-positive BC (http://www.clinicaltrials.gov/NCT01358877; accessed September 2012).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Adjuvant regimens containing trastuzumab for HER2 overexpressed/amplified breast cancer</th>
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<tbody>
<tr>
<td>Phase III Clinical Trials</td>
<td>Regimens with Improved Outcomes</td>
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<tr>
<td>HERA78</td>
<td>Any Adjuvant therapy × 4 cycles → T (52 wk)</td>
</tr>
<tr>
<td>NSABP B-3176</td>
<td>A 60 C 600 × 4 → P 80 weekly × 12 + T (52 wk)</td>
</tr>
<tr>
<td>NCCTG N983177</td>
<td>A 60 C 600 × 4 → P 80 weekly × 12 → T (52 wk)</td>
</tr>
<tr>
<td>BCIRG-00679</td>
<td>A 60 C 600 × 4 → P 80 weekly × 12 + T (52 wk)</td>
</tr>
</tbody>
</table>

Data are drug dose in mg/m² × (per number of cycles); q- = every; → (followed by); + (in addition to).

Abbreviations: A, adriamycin; C, cyclophosphamide; D, docetaxel; P, paclitaxel; T, trastuzumab.
SUMMARY

The benefit of the adjuvant therapies in BC has been extensively proven over several decades. Polychemotherapy regimens, including taxanes and hormone-targeted and HER2-targeted medications, are part of the armamentarium of the multidisciplinary teams that care for women with operable BC. The emerging genomic data reflecting the heterogeneity of the disease with potential predictive value is currently the focus of extensive research with the purpose of evolving from a universal use of adjuvant therapy to a more personalized approach.

REFERENCES


33. Viale G, Regan MM, Maiorano E, et al. Chemoendocrine compared with endocrine adjuvant therapies for node-negative breast cancer: predictive value of


