Adjuvant Chemotherapy for Early Breast Cancer: Optimal Use of Epirubicin

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Key Words. Anthracyclines • Adjuvant treatment • Neoadjuvant treatment • Doxorubicin • Epirubicin

Learning Objectives

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

1. Discuss the value of adjuvant chemotherapy in early breast cancer.
2. Critically assess the use of anthracyclines as part of adjuvant chemotherapy.
3. Describe the delivery of anthracyclines regarding dose, dose intensity, and dose density.
4. Evaluate the use of trastuzumab in the adjuvant setting.

Abstract

Anthracyclines are central components of adjuvant combination chemotherapy regimens for early breast cancer. Epirubicin is underutilized for this indication in the United States, where it was approved by the Food and Drug Administration in 1999, compared to Europe and Canada, where it gained approval in 1980. Use of epirubicin offers advantages in specific treatment settings and patient subsets, including situations where use of dose-dense and/or dose-intense protocols may provide additional benefits and where combinations including taxanes and/or trastuzumab may provide increased efficacy. Epirubicin also has a distinct safety profile compared to doxorubicin with regard to cardiotoxicity. In order to optimize treatment benefits and safety concerns for node-positive, node-negative and HER-2–positive patients as well as patients receiving neoadjuvant therapy and elderly patients it is worthwhile to consider the potential benefits of epirubicin. The Oncologist 2005;10:780–791

Introduction

The armamentarium of chemotherapeutic agents available for the treatment of breast cancer has expanded greatly over the past several decades, and complex regimens are nearly universal today. Anthracyclines, as integral components of most regimens, are central to the accepted treatment standards. These agents interact directly with DNA, inhibiting tumor cell proliferation and gene expression, and also lead to production of free radicals that may destroy tumor cells. Anthracyclines are important factors in optimizing adjuvant and neoadjuvant treatment and are indicated for adjuvant therapy regardless of the extent of nodal involvement,

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hormone receptor status, or human epidermal growth factor receptor 2 (HER-2) expression level of the tumor.

The most commonly used anthracyclines in breast cancer treatment are doxorubicin (Adriamycin®; Bedford Laboratories, Bedford, OH, http://www.bedfordlabs.com) and epirubicin (Ellence®, Pfizer Pharmaceuticals, New York, http://www.pfizer.com). The choice of which anthracycline to use is often a factor of prior experience with the agent. Epirubicin has been used to treat breast cancer in Europe and Canada since 1980; experience with this agent in the U.S. oncology community was delayed until the U.S. Food and Drug Administration approval in 1999 of epirubicin for the adjuvant treatment of breast cancer. To optimize combination chemotherapy for early breast cancer, it is important to identify those patients who are most likely to benefit from adjuvant treatment and to understand the advantages of epirubicin over doxorubicin in specific treatment settings. Currently, the inclusion of a taxane in the regimen and the use of dose-dense schedules of chemotherapy are also important considerations in optimizing treatment benefits.

**A Brief History of Adjuvant Chemotherapy**

Tables 1–4 summarize the major chemotherapeutic advances in clinical research on early breast cancer in the past 30 years. Chemotherapy with the alkylating agent cyclophosphamide in combination with two antimetabolites, methotrexate and fluorouracil (CMF), was established as the gold standard for adjuvant therapy of early stage breast cancer in the mid-1970s [1]. During the next 20 years, the use of cyclophosphamide in combination with doxorubicin, the first anthracycline available for chemotherapy for early breast cancer, proved to have equivalent efficacy to, as well as substantial advantages over, CMF in terms of tolerability. The National Surgical Adjuvant Breast and Bowel Project (NSABP) studies B-15 and B-23 (Table 1) found that a regimen of four cycles of doxorubicin and cyclophosphamide (AC) was equivalent to six cycles of CMF with respect to event-free survival, relapse-free survival (RFS), and overall survival (OS) in breast cancer patients regardless of nodal status, age, or estrogen-receptor (ER) status, but that AC offered the advantages of a shorter treatment course with fewer side effects [2]. A 5-year follow-up by the Southeastern Cancer Study Group (SECSG) (Table 2) established that OS for node-positive patients on a six-cycle cyclophosphamide, doxorubicin, fluorouracil (CAF) regimen was similar to OS for patients receiving six cycles of CMF [3]. Similar results were obtained recently in a study by the Spanish breast cancer research group GEICAM after 4 years of follow-up [4]. In the latter study, 985 patients with lymph node–positive or high-risk lymph node–negative breast cancer received either six cycles of CMF (600/60/600 mg/m²) or six cycles of FAC (500/50/500 mg/m²). Although a small benefit in disease-free survival (DFS) was identified in patients receiving FAC, OS was similar in both the CMF and FAC treatment arms. However, the subgroup of high-risk lymph node–negative patients receiving FAC had significantly longer DFS ($p = .046$) and OS ($p = .038$), while node-positive patients in both arms had similar rates of DFS and OS [4].

The Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) performed an extended 15-year follow-up meta-analysis that included more than 14,000 patients in trials that directly compared anthracycline-containing regimens with CMF [5]. That study found that anthracycline-containing regimens were significantly more effective at preventing recurrence (hazard ratio, 0.89; $p = .001$, two-tailed test) and increasing survival (risk of breast cancer death rate ratio, 0.84; $p < .00001$, two-tailed test) than were CMF regimens. The trend toward the superiority of anthracycline-based chemotherapy regimens over those containing CMF extends to the major subsets of early breast cancer patients: premenopausal (age <50) and postmenopausal (age, 50–69) patients, ER-poor and ER-positive patients, and both node-negative and node-positive patients.

Although the EBCTCG meta-analysis included both doxorubicin-treated (60%) and epirubicin-treated (40%) patients, since the 1990s, the four-cycle doxorubicin-based regimen has been established in the U.S. as the standard adjuvant treatment of early breast cancer. In Europe, the second-generation anthracycline epirubicin (the 4′-epimer of doxorubicin) has been used in several countries preferentially as a component of chemotherapy regimens for the adjuvant treatment of early breast cancer. This trend was driven by a series of large phase III clinical trials comparing various anthracycline-containing regimens as well as CMF regimens in both node-positive and node-negative patients. For example, the International Collaborative Cancer Group (ICCG) (Table 1) conducted a large randomized trial comparing two different fluorouracil–epirubicin–cyclophosphamide (FEC) dosing regimens with two different CMF dosing regimens in node-positive premenopausal patients. That study found some evidence of longer OS (log-rank test, 5.66; $p = .02$) and RFS (log-rank test, 4.55; $p = .03$) with a six-cycle FEC regimen with a 50-mg/m² epirubicin dose compared with a six-cycle CMF regimen [6].

French oncologists formed the French Adjuvant Study Group (FASG), which beginning in the 1990s conducted a series of clinical trials, each building on the results of previous trials. The FASG 05 trial (Table 2) of combination chemotherapy in node-positive breast cancer patients with hormone receptor–negative status compared epirubicin doses of 50 mg/m² (FEC50) and 100 mg/m² (FEC100). Both the
5- and 10-year follow-up analyses have shown significant advantages for the FEC100 regimen in DFS (66.3% versus 54.8%; \( p = .03 \)) and OS (77.4% versus 65.3%; \( p = .007 \)) [7]. A 10-year follow-up revealed the superiority of six cycles of FEC100 in terms of DFS (45.3% in the FEC50 arm and 50.7% in the FEC100 arm), with a relative risk reduction of 24% (Wilcoxon \( p = .03 \)), and in terms of OS, which similarly favored FEC100 [8]. The FASG 05 trial demonstrated a dose-response effect of epirubicin, as increasing the dose from 50 mg/m² to 100 mg/m² in the FEC regimen resulted in longer DFS and OS. In contrast, the Cancer and Leukemia Group B (CALGB) study (Table 2) of doxorubicin dosing of 60 mg/m², 75 mg/m², and 90 mg/m² did not show better therapeutic efficacy with increasing doses of doxorubicin. In that randomized trial of 3,121 patients, increasing doxorubicin doses produced no significant reduction in the hazard of either cancer recurrence or death [9]. The National Cancer Institute of Canada (NCIC) also evaluated both moderate-risk (1–3 positive nodes) and high-risk (>4 positive nodes) premenopausal women receiving either cyclophosphamide, epirubicin, 5-fluorouracil (CEF) or CMF. Patients fared better on the CEF regimen than on CMF; 63% of the CEF group remained relapse-free after 5 years, compared with 53% of the CMF group \( (p = .009) \), and OS rates for CEF and CMF were 77% and 70%, respectively \( (p = .03) \) [10]. Both the FASG 05 and the NCIC MA.5 trials showed the therapeutic benefit of optimal dosing of epirubicin as part of a combination chemotherapy regimen.

Table 1. Summary of early benchmark adjuvant chemotherapy trials

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Endpoints</th>
<th>Treatment</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>FASG 05</td>
<td>537 (node-positive, operable, poor prognosis)</td>
<td>DFS, OS</td>
<td>FEC50 versus FEC100</td>
<td>DFS 54.8% versus 66.3% ( p = .03 ); OS 65.3% versus 77.4% ( p = .007 )</td>
<td>~30% RR in DFS. Confirms dose-response relationship.</td>
</tr>
<tr>
<td>INT [1]</td>
<td>386 (node-positive)</td>
<td>DFS</td>
<td>CMF</td>
<td>Progress in 24% of controls versus 5.3% receiving CMF</td>
<td>Improved DFS with CMF adjuvant treatment</td>
</tr>
<tr>
<td>NSABP B15</td>
<td>2,194 (node-positive)</td>
<td>OS</td>
<td>AC × 4, CMF × 6; AC × 4 → 6 months of rest → CMF × 3</td>
<td>62.3% DFS, 83% OS (3-year)</td>
<td>AC × 4 not superior to CMF × 6 but less toxic, less costly</td>
</tr>
<tr>
<td>NSABP B23</td>
<td>2,008 (node-negative/ER-negative)</td>
<td>RFS, EFS, S</td>
<td>AC × 4, AC × 4 + tam (5 years); CMF × 6; CMF × 6 + tam (5 years)</td>
<td>RFS: 87% in AC and CMF groups ( (p = .6) ); OS: 90% for AC; 89% for CMF (5-year)</td>
<td>No significant difference in all four groups for RFS ( (p = .96) ), EFS ( (p = .8) ), S ( (p = .8) )</td>
</tr>
<tr>
<td>SECSG [3]</td>
<td>528 (node-positive)</td>
<td>OS</td>
<td>CAF × 6 versus CMF × 6 (starting dose: CAF = 500/50/500; CMF = 600/40/600)</td>
<td>OS (5-year): 74% versus 68% ( p = .41 )</td>
<td>No significant difference in survival, similar toxicity</td>
</tr>
<tr>
<td>ICCG [6]</td>
<td>759 (node-positive)</td>
<td>RFS, OS</td>
<td>CMF1 versus FEC1; CMF2 versus FEC2</td>
<td>CMF1 versus FEC1: similar RFS, OS. CMF2 versus FEC2: OS, 73.8% versus 86.6% ( p = .02 )</td>
<td>RFS and OS same with CMF1 and FEC1 ( (p = .03) ); OS and RFS improved with FEC2 versus CMF2</td>
</tr>
</tbody>
</table>

Abbreviations: A, doxorubicin; C, cyclophosphamide; CAF, cyclophosphamide, adriamycin, 5-fluorouracil; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; CMF1, F + C (C, 100 mg/m²; F, 600 mg/m²) days 1 and 8, M (40 mg/m²) days 1 and 8 every 4 weeks × 6; CMF2, F + C (600 mg/m² each) days 1 and 8, methotrexate (40 mg/m²) days 1 and 8 every 4 weeks × 6; DFS, disease-free survival; E, epirubicin; EFS, event-free survival; ER, estrogen receptor; F, fluorouracil; FASG, French Adjuvant Study Group; FEC, fluorouracil, epirubicin, cyclophosphamide; FEC2, F + C (600 mg/m² each) days 1 and 8, E (50 mg/m²) day 1 every 4 weeks × 6; FEC50, fluorouracil, epirubicin (50 mg/m²), cyclophosphamide; FEC100, fluorouracil, epirubicin (1000 mg/m²), cyclophosphamide; ICCG, International Collaborative Cancer Group; INT, Istituto Nazionale Tumori; M, methotrexate; NSABP, National Surgical Adjuvant Breast and Bowel Project; OS, overall survival; pts, patients; RFS, relapse-free survival; RR, risk ratio; S, survival; SECSG, Southeastern Cancer Study Group; tam, tamoxifen.
to achieve superior long-term 10-year survival in node-positive breast cancer patients at high risk for relapse [8, 11, 12].

Therapeutic benefit from epirubicin-containing chemotherapy has also been demonstrated in the setting of node-negative disease. In a planned pooled efficacy analysis of the National Epirubicin Adjuvant Trial and the Scottish Cancer Trials Breast Group BR9601 trials, 28% of the 2,391 patients enrolled in the two studies were node-negative. The trials compared the classic CMF regimen with 100 mg/m² epirubicin followed by CMF (ECMF) and found that ECMF produced significantly better RFS (hazard ratio, \(0.70\); 95% confidence interval [CI], 0.58–0.85; \(p = 0.0003\)) and OS (hazard ratio, \(0.64\); 95% CI, 0.51–0.81; \(p = 0.0001\)), irrespective of nodal status [13]. Those trials demonstrated that optimal dosing of epirubicin (100 mg/m²), when added to CMF combination chemotherapy in the adjuvant breast cancer setting, is required to achieve superior DFS and OS. The Danish Breast Cancer Group earlier obtained similar results. In their trial, 93% of the node-negative patients who received CEF (with 60 mg/m² epirubicin) survived for 6 years, compared with 83% of those who received CMF (\(p < .01\)) [14]. Thus, extended follow-up has confirmed that higher-dose combination chemotherapy regimens containing epirubicin improve therapeutic efficacy for both node-positive and node-negative early breast cancer patients.

**Epirubicin in Dose-Dense and Dose-Intense Adjuvant Chemotherapy**

There is a positive correlation between delivery of the intended doses of chemotherapy on schedule and better treatment outcomes in breast cancer [15–17]. Optimal dose intensity in combination chemotherapy is a function of both the dose level and schedule. Dose-dense schedules are achieved by minimizing the interval between cycles. The concept of dose-dense scheduling stemmed from the observation that breast cancer growth follows Gompertzian kinetics and that shorter intervals between chemotherapy treatments might result in a higher log-kill, thus leading to lower relapse rates and longer survival times [18, 19]. While hematologic toxicities have historically limited dose intensity and dose density, the availability of biotechnology derived drugs has enabled further increases in dose intensity and dose density of established anthracycline-based adjuvant regimes, both in terms of improved supportive care and efficacy.

One such strategy uses the cytokine G-CSF to treat chemotherapy induced neutropenia and thereby allow for dosing to be scheduled every 2 weeks instead of every 3 weeks. The CALGB trial 9741 (Table 2) compared dose-dense four-cycle AC chemotherapy followed by four cycles of paclitaxel (Taxol®, Bristol-Myers Squibb, Princeton, NJ, http://www.

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**Table 2. Summary of second-generation adjuvant chemotherapy trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Endpoints</th>
<th>Treatment</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCIC MA.05 [10]</td>
<td>710 (node-positive)</td>
<td>RFS, OS</td>
<td>CEF 120 versus CMF epirubicin 120 days 1, 8</td>
<td>DFS (5 years), 63% versus 53% ((p = 0.009)); OS (5 years), 77% versus 70% ((p = 0.03))</td>
<td>~19% RR for death; ~29% RR for relapse. Moderate dose density is reasonable approach</td>
</tr>
<tr>
<td>CALGB 9344 [57]</td>
<td>996 (node-positive)</td>
<td>LR</td>
<td>AC versus AC→T</td>
<td>T improved local control in patients receiving breast-conserving surgery, despite longer delay from surgery to RT. No apparent benefit in patients treated with mastectomy</td>
<td></td>
</tr>
<tr>
<td>BCI RG 001 [22]</td>
<td>1,491 (node-positive and node-negative)</td>
<td>TAC versus FAC</td>
<td>DFS, 75% versus 68%; OS, 87% versus 81%</td>
<td>DFS hazard ratio, 0.72 ((p = 0.001)); OS, 0.70 ((p = 0.008)). TAC/FAC hazard ratio, 0.61 (HER-2 positive), 0.76 (HER-2–negative)</td>
<td></td>
</tr>
<tr>
<td>CALGB 9741 [58]</td>
<td>2,005 (node-positive)</td>
<td>A×4→T×4→C×4 every 3 weeks; A×4→T×4→C×4 every 2 weeks with filgrastim; AC×4→T×4 every 3 weeks; AC×4→T×4 every 2 weeks with filgrastim</td>
<td>Dose-dense DFS, 82% versus 75% for other groups</td>
<td>Dose-dense DFS RR, 0.74 ((p = 0.010)); OS RR, 0.69 ((p = 0.013)). Dose-dense superior to conventional 3-week treatment</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** A, doxorubicin; BCIRG, Breast Cancer International Research Group; C, cyclophosphamide; CALGB, Cancer and Leukemia Group B; CEF120, epirubicin 120 mg/m² every 28 days; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; DFS, disease-free survival; FAC, 5-fluourouracil, adriamycin, cyclophosphamide; HER, human epidermal growth factor receptor; LR, local recurrence; NCIC, National Cancer Institute of Canada; OS, overall survival; RFS, relapse-free survival; RR, risk ratio; RT, radiation treatment; T, paclitaxel; TAC, Taxotere®, adriamycin, cyclophosphamide.
evaluated a regimen consisting of docetaxel, doxorubicin, and cyclophosphamide (TAC) versus conventional fluorouracil, doxorubicin, and cyclophosphamide (FAC) in 1,491 women with lymph node–positive breast cancer. A second analysis at a 55-month median observation time identified a hazard ratio for TAC over FAC of 0.72 ($p = .001$) in terms of DFS and 0.70 ($p = .008$) in terms of OS, significantly favoring TAC [23]. Using a sequential schedule in the PACS 01 study of 1,999 women, French and Belgian oncologists evaluated the use of docetaxel at a dose of 100 mg/m² every 3 weeks for three cycles following three cycles of standard FEC100 in women up to the age of 65 years (median age, 50 years) with node-positive breast cancer [24]. The sequential use of FEC100 followed by docetaxel did not gain a survival benefit but experienced fewer side effects (e.g., less neutropenia, less use of G-CSF, and less cardiotoxicity) than those receiving six cycles of FEC100 [24]. Women 50–65 years of age experienced benefits both in longer survival and fewer adverse events, thus making the FEC100–docetaxel regimen the most effective and least toxic among all regimens containing anthracycline and taxane components.

Several additional studies have demonstrated survival benefits [20, 21] and good tolerability [25] in higher-risk patients receiving dose-dense and dose-intense epirubicin, either with or without a taxane. Thus, it appears that epirubicin may become the anthracycline of choice for use in combination therapy with taxanes as well as in intensive chemotherapy regimens.

**Other Patient Subsets**

In addition to node-positive and node-negative patients, other subgroups, including HER-2–positive patients, patients receiving neoadjuvant treatment, and elderly patients, have also been shown to benefit from epirubicin-containing chemotherapy. Retrospective analyses of the CALGB 8869, NSABP B11, Southwest Oncology Group (SWOG) 8814, and FASG 05 adjuvant trials have suggested that overexpression of HER-2 may correlate with greater anthracycline sensitivity [26–28]. For patients whose breast tumors overexpress the HER-2 receptor protein, treatment with the monoclonal antibody trastuzumab (Herceptin®; Genentech, Inc., South San Francisco, CA, http://www.gene.com), which inhibits signaling by the HER-2 receptor, in addition to an anthracycline-containing regimen may provide additional benefits. A phase II study of the neoadjuvant treatment of advanced breast cancer patients who received epirubicin and cyclophosphamide followed by paclitaxel, gemcitabine (Gemzar®; Eli Lilly and Company, Indianapolis, http://www.lilly.com), and (for those with HER-
2–positive tumors) trastuzumab found pathologic complete responses (pCRs) in 6 of 21 patients and low cardiac toxicity [29]. In an effort to assess toxicity in more detail, an analysis of 10 patients who received trastuzumab plus conventional AC revealed no significant cardiac biopsy findings [30].

Taken together, these results suggest that the addition of trastuzumab to epirubicin-containing chemotherapy may be both relatively safe and effective, in contrast to the initial observation that the combination of doxorubicin and trastuzumab induced up to a 29% rate of cardiotoxicity [31].

Table 3. Summary of recent and ongoing adjuvant chemotherapy trials

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>End points</th>
<th>Treatment</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCIC MA.21</td>
<td>~1,500 node-positive or high-risk node-negative; postsurgery</td>
<td>DFS, OS, toxicities, QoL</td>
<td>CEF (75/60 mg/m² [day 1, day 8]/500 mg/m² × 6) every 4 wks × 6; EC (120/830 mg/m²) + G-CSF + EPO every 2 weeks × 6 → T (175 mg/m²) every 3 weeks × 4; AC (60/600 mg/m²) × 4 → T (175 mg/m²) every 3 weeks × 4</td>
<td>Ongoing</td>
<td>?</td>
</tr>
<tr>
<td>NSABP B38</td>
<td>Goal: 4,800 (node-positive)</td>
<td>DD TAC (docetaxel/doxorubicin/cyclophosphamide); DD AC → T; DD AC → T + gemcitabine</td>
<td>DD DFS ETC, 85% versus EC 82% (p = .046)</td>
<td>Ongoing</td>
<td>?</td>
</tr>
<tr>
<td>AGO [20]</td>
<td>1,018 evaluable (4+ nodes)</td>
<td>ETC (E, 150 mg/m²; T, 225 mg/m²; C, 2,500 mg/m² every 2 weeks), with or without EPO-α; EC (90/600 mg/m²) → T (175 mg/m²) × 4, every 3 weeks; ETC, DD and DI</td>
<td>DD DFS ETC, 85% versus EC 82% (p = .046)</td>
<td>Superior ETC significantly improves DFS</td>
<td></td>
</tr>
<tr>
<td>ICCG [59]</td>
<td>604 (node-positive)</td>
<td>RFS, OS</td>
<td>tam (20/mg po) versus tam + E50 × 4 yrs</td>
<td>DFS, RR 27.9% with E plus tam (p = .023)</td>
<td>Superior DFS with tam; no difference in OS</td>
</tr>
<tr>
<td>DBCG [60]</td>
<td>1,175 (premenopausal node-negative; premenopausal node-positive, ER-negative/PR-negative or unknown; postmenopausal/PR-negative or unknown; postmenopausal node-positive, ER-negative/PR-negative)</td>
<td>RFS, OS</td>
<td>CEF (600/600/600 mg/m²) every 3 weeks × 9; CEF + pamidronate × 4 years; CMF (600/40/600) q3 every 9 weeks + pamidronate × 4 years</td>
<td>6-yr RFS: CEF 63%, CMF 58% (p = .003), OS: CEF 70%, CMF 65% (p = .009)</td>
<td>RFS RR ~27%. Superior DFS for CEF in premenopausal patients</td>
</tr>
<tr>
<td>PACS 01</td>
<td>1,999 (node-positive, &lt;65 yrs)</td>
<td>DFS, OS, safety, cost, QoL, predictive factors</td>
<td>FEC100 × 6 (A); FEC100 × 3 → docetaxel (100 mg/m²) × 3 (B)</td>
<td>DFS at 5 years: 78.3% versus 73.2% in favor of FEC–D: log-rank unadjusted p = .012, adjusted p = .014; HR, 0.83 (95% CI, 0.69–0.99), p = .041. 5-year OS, 90.7% versus 86.7% in favor of FEC100 followed by docetaxel; % log-rank unadjusted p = .013; adjusted p = 0.017; HR, 0.77 (0.59–1.0), p = .05</td>
<td>Addition of a taxane to FEC100 is feasible; no unexpected toxicities</td>
</tr>
<tr>
<td>NEAT [13]</td>
<td>2,021 (NEAT); 370 (SCTBG)</td>
<td>RFS, OS, QoL, predictive factors</td>
<td>NEAT: E (100 mg/m²) × 4 → cmf × 4 versus cmf × 8; SCTBG BR9601: E (100 mg/m²) × 4 → cmf × 4 versus cmf × 8</td>
<td>ECMF: RFS HR, 0.70 (p = .003); OS HR, 0.64 (p = .001).</td>
<td>ECMF advantage regardless of node status, age, ER status.</td>
</tr>
</tbody>
</table>

Abbreviations: A, doxorubicin; AGO, Arbeitsgemeinschaft Gastrointestinal Onkologie; C, cyclophosphamide; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; cCMF, classical CMF; CI, confidence interval; DBCG, Danish Breast Cancer Cooperative Group; DD, dose dense; DFS, disease-free survival; DI, dose intense; E, epirubicin; EPO, erythropoietin; ER, estrogen receptor; F, fluorouracil; FEC100, fluorouracil, epirubicin (100mg/m²), cyclophosphamide; HR, hazard ratio; ICCG, International Collaborative Cancer Group; LR, local recurrence; M, methotrexate; NCIC, National Cancer Institute of Canada; NEAT, National Epirubicin Adjuvant Trial; NSABP, National Surgical Adjuvant Breast and Bowel Project; OS, overall survival; PACS, picture archiving and communications system; PR, progesterone receptor; QoL, quality of life; RFS, relapse-free survival; RR, risk ratio; SCTBG, Scottish Cancer Trials Breast Group; T, paclitaxel; tam, tamoxifen.

*A treatment protocol not used in North America.*
Use of neoadjuvant chemotherapy prior to definitive surgical resection of a primary breast tumor has gained increased acceptance, especially when patients present with a large tumor. The rationale is that “downsizing” a large T2 or T3 lesion to achieve a pCR may result in better long-term survival, while it also affords the opportunity to evaluate the chemoresponsiveness of the patient to a specific regimen. HER-2–positive patients who received neoadjuvant therapy consisting of sequential epirubicin-based chemotherapy (FEC90) with paclitaxel followed by trastuzumab had significantly higher rates of pathologic complete remission than patients who did not receive trastuzumab (67% versus 25%; \( p = .02 \)) [32]. Larger numbers of patients are being enrolled in neoadjuvant clinical trials based on these early but promising results.

A benefit of epirubicin in elderly patients was shown in the 338-patient FASG-08 trial, which assessed the impact of epirubicin as part of a weekly regimen in women over 65 years of age. Those who received weekly tamoxifen alone were more likely to relapse than those who received weekly epirubicin plus tamoxifen (hazard ratio, 1.85; \( p = .02 \)) [33].

**HER-2–Targeted Therapy**

Trastuzumab, a humanized hybrid monoclonal antibody that selectively binds to the extracellular domain of HER-2, has become an important component of breast cancer therapy regimens in metastatic breast cancer and more recently in preoperative therapy [32]. Trastuzumab also produced better survival in patients who had metastatic breast cancer overexpressing HER-2 when it was administered in combination with paclitaxel or docetaxel, or combinations of doxorubicin and cyclophosphamide and other cytotoxic drugs [34, 35].

Recently, several large randomized clinical trials of high-risk patients with HER-2–positive early breast cancer have demonstrated that trastuzumab provides additional beneficial effects when used subsequent to anthracycline-based chemotherapy and a taxane (Table 4). Specifically, the NSABP B31 and North Central Cancer Treatment Group (NCCTG) N9831 adjuvant trials were designed to compare doxorubicin-based chemotherapy followed by paclitaxel (AC→T) with AC→T plus trastuzumab either in sequence or concurrent with paclitaxel. Preliminary efficacy findings from a combined analysis of those trials after a mean follow-up of 2 years showed a 36% relative reduction in the risk for recurrence [36], with significant reductions in risk both in terms of DFS (hazard ratio, 0.48; \( p = 3.0 \times 10^{-12} \), two-tailed test) and OS (hazard ratio, 0.67; \( p = .015 \), two-tailed test) with AC→T plus trastuzumab (\( n = 1,672; 134 \) events) compared with AC→T (\( n = 1,679; 621 \) events); this is the greatest reduction in risk seen since the introduction of adjuvant chemotherapy and tamoxifen. This landmark analysis was performed before either trial completed accrual, resulting in premature trial closure and a short median follow-up; if the trials were analyzed individually, results would only trend toward significance.

The ongoing Herceptin® Adjuvant (HERA) trial [37] randomly assigned patients with HER-2–positive invasive breast cancer to receive either trastuzumab for 1 or 2 years or observation, with a primary end point of DFS; patients were previously treated with surgery and adjuvant or neoadjuvant chemotherapy. Unlike the B31 and N9831 trials, most patients in the HERA trial did not receive a taxane, and about 30% of patients were node-negative. An early interim analysis of the HERA trial performed at a median follow-up of 1 year after randomization demonstrated a 46%–47% reduction in the risk for recurrence in trastuzumab–treated patients, compared with observation. Analyses of 1,694 patients treated with trastuzumab (127 events) versus 1,693 untreated patients (220 events) revealed a significantly longer DFS (hazard ratio, 0.54; \( p < .0001 \)). Although the short follow-up in the HERA trial did not demonstrate a significant difference in OS, there was a trend toward superiority in the trastuzumab–treated patients (hazard ratio, 0.76; \( p < .26 \)).

The findings of the NSABP B31, NCCTG N9831, and HERA trials are indeed remarkable in that they suggest that the addition of trastuzumab to anthracycline-based chemotherapy, either with or without a taxane, may reduce the recurrence rate by approximately 50%. The magnitude of this benefit is such that the use of trastuzumab reduces the risk for tumor recurrence in women with HER-2–positive, high-risk breast cancer to rates of recurrence typical of patients with HER-2–negative cancers. Further follow-up of these patients is of course necessary to confirm these findings. Nevertheless, in most instances, particularly in North America, medical oncologists agree that the addition of trastuzumab to chemotherapy in HER-2–overexpressing breast cancer is becoming standard therapy.

**Epirubicin’s Safety Profile**

As with any chemotherapeutic agent, toxicity is a significant concern with anthracyclines, including long-term hematologic and cardiac toxicities. A meta-analysis of 8,563 NSABP adjuvant breast cancer patients found that 43 patients (0.50%) receiving cumulative doxorubicin doses of 240 mg/m² in combination with cyclophosphamide (mean cumulative dose of cyclophosphamide, 4,500 mg/m²) developed either acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) [38]. Additional studies of adjuvant treatment with AC regimens suggest that rates of secondary leukemia range from 0.5% (95% CI, 0.1%–2.4%, \( p = .01 \)) [39] to 0.8% [40]. Fumoleau et al. also reviewed all FASG studies for leukemia.
safety and found a 0.28% (95% CI, 0.17%–0.43%) cumulative risk for acute leukemia in 2,553 patients receiving epirubicin after 7 years of follow-up [41].

A large-scale meta-analysis of 9,796 early breast cancer patients showed that, for those receiving cumulative doses of epirubicin ≥720 mg/m² and cyclophosphamide ≥6,300 mg/m², the 8-year cumulative probability of developing AML/MDS was 0.31% (95% CI, 0.14%–0.48%), and for all patients receiving epirubicin (including those receiving epirubicin >720 mg/m²) it was 0.51% (95% CI, 0.30%–0.71%) [42]. Because most of the breast cancer patients who received anthracyclines also received cyclophosphamide, an alkylating agent linked independently to secondary leukemia, it is difficult to determine the precise contribution of the anthracycline component to the development of hematologic cancer in these patients. Direct comparisons of clinical trials are usually inappropriate; however, in the context of large studies and meta-analyses, epirubicin-based regimens have no more risk than doxorubicin-based regimens in terms of producing secondary leukemia, and some studies [41] suggest a trend toward a lower risk in epirubicin-treated patients.

Cardiotoxicity is known to be associated with use of anthracyclines in cancer chemotherapy and is generally linked with higher cumulative dosages. Epirubicin, like doxorubicin, can result in cardiomyopathy and congestive heart failure (CHF) in a dose-dependent manner. However, several analyses have indicated that epirubicin may be less cardiotoxic than doxorubicin at equimolar doses [14, 43]. A recent evaluation of 1,576 patients with early breast cancer (HER-2–positive, node-negative or -positive) documented frequent reductions in left ventricular ejection fraction (LVEF) after four cycles of AC (cumulative dose of doxorubicin, 240 mg/m²) [44]. In this NCCTG trial, 359 patients (23.4%) had either grade 1 (16.8%) or grade 2 (6.6%) LVEF reductions, and 37 patients (2.5%) had a >15% decrease (LVEF) after four cycles of AC (cumulative dose of doxorubicin, 240 mg/m²) [44]. In this NCCTG trial, 359 patients (23.4%) had either grade 1 (16.8%) or grade 2 (6.6%) LVEF reductions, and 37 patients (2.5%) had a >15% decrease in LVEF [44].

High cumulative doses of anthracyclines, including epirubicin, produce significant cardiotoxicity, but epirubicin doses can generally be increased by approximately

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
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<tbody>
<tr>
<td>HERA</td>
<td>5,090</td>
<td>DFS, RFS, DDFS, OS</td>
<td>H, 8 mg → 6 mg every 3 weeks (2 years); H, 8 mg → 6 mg every 3 weeks (1 year); No T</td>
<td>T (1 year) versus no T: 2-year DFS, 85.8% versus 77.4% (p &lt; .0001); 2-year RFS, 87.2% versus 78.6% (p = .0001); 2-year DDFF, 81.8% versus 89.7% (p = .0001); 2-year OS, 95.0% versus 96.0% (p = .26)</td>
<td>At 1-year follow-up, T is an effective adjuvant treatment for patients with HER-2–positive early breast cancer; benefits independent of nodal status, HR status, and type of chemotherapy, with manageable cardiac toxicity</td>
</tr>
<tr>
<td>BCIRG 006</td>
<td>3,200</td>
<td>DFS, OS</td>
<td>Arm 1, AC × 4 → docetaxel × 4; arm 2, AC × 4 → docetaxel × 4 + H every week × 12 → H every week × 40; arm 3, docetaxel + C × 6 + H every week × 18 → H every week × 34 (no anthracycline)</td>
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Abbreviations: AC, doxorubicin and cyclophosphamide; BCIRG, Breast Cancer International Research Group; C, cisplatin or carboplatin; CHF, congestive heart failure; DDFS, distant disease-free survival; DFS, disease-free survival; H, trastuzumab; HERA, Herceptin® Adjuvant; HR, Hormone receptor; LVEF, left ventricular ejection fraction; NCCTG, North Central Cancer Treatment Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; OS, overall survival; RFS, relapse-free survival; RR, risk ratio; T, paclitaxel.
80% over doxorubicin before inducing the same probability of CHF. For instance, in patients with metastatic breast cancer, a significantly higher rate of CHF was observed with cumulative epirubicin doses >950 mg/m², whereas the same risk for doxorubicin would be observed at 550 mg/m² [45]. A 7-year follow-up meta-analysis of 3,577 patients in the FASG trials found that the risk for developing left ventricular dysfunction was 1.36% (95% CI, 1.10%–1.62%) in a total of 2,553 patients who received cumulative doses of epirubicin ranging from 300 mg/m² to 628 mg/m², compared with 0.2% (95% CI, 0.06%–0.36%) in patients on other regimens (p = .004) [41]. A long-term (>10 years) prospective follow-up study (FASG 05) assessed cardiac function in 150 disease-free patients; 65 had received cumulative doses of epirubicin of 300 mg/m² (FEC50), and 85 had received epirubicin doses of 600 mg/m² (FEC100) [46]. Two patients receiving FEC100 experienced CHF that was possibly related to epirubicin, while a total of 18 FEC100 patients developed asymptomatic left ventricular dysfunction that was possibly or probably related to the treatment. No patient experienced a de novo reduction in LVEF 5 years after completion of treatment; all patients with cardiac dysfunction observed 5 or more years after treatment had some evidence of cardiac dysfunction within the 5-year treatment period. All FASG 05 patients had received postoperative irradiation to the chest wall and lymph nodes. Of the 18 patients who developed asymptomatic left ventricular cardiac dysfunction, all had received left chest wall and nodal irradiation. Thus, the combination of FEC and postoperative irradiation resulted in an acceptable incidence of cardiac dysfunction [46]. It should be noted, however, that at equimolar doses, epirubicin and doxorubicin result in the same response rates and 1-year survival rates, as well as OS rates, in patients with metastatic breast cancer [47]. Taken together, these studies suggest that the significant survival benefits of high-dose epirubicin-containing regimens, such as FEC100 and particularly FEC100 followed by docetaxel, clearly outweigh the limited risk for CHF in node-positive and also in high-risk node-negative [13] early breast cancer patients.

Although the use of trastuzumab as a component of chemotherapy regimens provides additional benefits to many patients, its use is also associated with cardiotoxicity [48], which raises concern about its administration in combination with anthracyclines. Because the cardiac profile of epirubicin is more favorable than that seen with doxorubicin at the most effective dosages, epirubicin was chosen in the M. D. Anderson Cancer Center (Houston, TX) trial of sequential combination neoadjuvant regimens. Cardiac monitoring with LVEF and cardiac troponin T, a sensitive and specific marker of myocardial injury, was performed in all patients. There was no evidence of elevated cardiac troponin T levels, and in two patients, transient LVEF reductions returned to baseline, thus demonstrating that the sequential administration of epirubicin and trastuzumab is both feasible and well tolerated; a remarkably high pathological response rate was identified with a combination of paclitaxel followed by FEC75 in a preliminary analysis [49]. The BCIRG 006 and the NCCTG N9831 trials using trastuzumab following anthracycline-based chemotherapy recently reported cardiac safety data (Table 4). An interim analysis of cardiac events in 2,277 patients enrolled in three arms of the NCCTG N9831 trial found a higher incidence of cardiac toxicity with trastuzumab following AC and paclitaxel or following AC concurrent with paclitaxel (12 cases of CHF and one probable cardiac death) compared with the same regimen without trastuzumab (no cardiac events) [50]. This marked difference did not reach the threshold of 4%, which had been prospectively designated as the stopping point, and was therefore judged to be within the acceptable safety margin. The BCIRG study tested doxorubicin-based combinations with and without trastuzumab versus a combination of docetaxel, carboplatin (Paraplatin®), Bristol-Myers Squibb), and trastuzumab, with no anthracycline in the third arm. No cardiotoxicity has been seen to date in that trial, including in the nonanthracycline arm [51]; further results from that study are awaited. Together, these studies suggest that sequencing of the HER-2–targeted agent trastuzumab after anthracycline-based chemotherapy is a well-tolerated option with the potential to yield additional benefits.

While the data summarized above strongly support adjuvant combination regimens that include epirubicin, taxanes, and trastuzumab, recent evidence suggests that epirubicin may have particular advantages over doxorubicin in terms of cardiotoxicity and, more recently, in terms of efficacy when used in combination with docetaxel. A major mechanism by which anthracyclines cause cardiac toxicity is the formation of secondary alcohol metabolites within cardiac tissue [52]. Human myocardium obtained during cardiac bypass surgery was tested in cytosol preparations in vitro to assay cardiac conversion of epirubicin and doxorubicin into their respective secondary toxic metabolites, epirubicinol and doxorubicinol. Paclitaxel was seen to strongly stimulate the conversion of doxorubicin, but not epirubicin, into its secondary alcohol metabolite [53]. A previous study by the same groups found significantly less formation of the alcohol metabolite epirubicinol compared with doxorubicinol in human myocardium, a pattern consistent with the reportedly lower cardiotoxicity of epirubicin compared with doxorubicin [52]. This suggests that, in regimens that
involve taxanes, epirubicin may be a safer choice in terms of cardiotoxicity; this advantage allows the use of higher doses of epirubicin and thus a greater clinical benefit, as shown by many studies summarized above as well as those reviewed previously [47].

**Conclusions**

Within specific patient subsets, there are compelling reasons to choose adjuvant treatment with epirubicin, as indicated by studies that have focused on specific patient groups. Epirubicin-based polychemotherapy benefits node-positive and node-negative patients in the adjuvant setting and has demonstrated superior efficacy in HER-2-positive patients, elderly patients, and patients receiving neoadjuvant treatment. Results from more than a decade of research on anthracyclines in breast cancer treatment clearly favor epirubicin as the anthracycline of choice across the entire spectrum of patients. Epirubicin has a superior safety profile compared with doxorubicin in terms of secondary leukemia and cardiotoxicity, two key concerns in determining optimal therapy for breast cancer. Dosing and toxicity studies have identified a strong dose-response relationship for epirubicin and revealed that this compound is tolerated at higher doses than doxorubicin, resulting in significantly better efficacy. For instance, the less severe cardiotoxicity of epirubicin relative to doxorubicin permits higher dosing without adverse cardiac events; cumulative doses of epirubicin of 600 mg/m² are possible, compared with doses of doxorubicin of 360 mg/m². This allows more dose intensity using epirubicin rather than doxorubicin. When given at optimal doses, particularly with G-CSF support to permit dose-dense and dose-intense regimens, epirubicin is a key component of combination therapy regimens that improves both the safety and survival of patients with breast cancer. The ability to combine these regimens with other powerful therapies, especially the taxanes and monoclonal antibodies such as trastuzumab, further expands the treatment options available to oncologists and their patients. Specifically, the use of a taxane following epirubicin-based chemotherapy promises to provide additional survival benefits, and the use of the HER-2–targeted agent trastuzumab with or after chemotherapy has demonstrated great promise to further improve outcomes in patients with elevated expression of the HER-2 receptor.

Ongoing trials should help answer many more questions about adjuvant therapy for breast cancer. For instance, NSABP B-36 is comparing the standard four-course AC regimen with a six-course FEC100 regimen in node-negative breast cancer patients [54]. The MA.21 phase III trial compares three chemotherapy combinations involving epirubicin or doxorubicin in premenopausal and early postmenopausal women with lymph node–positive and high-risk lymph node–negative breast cancer [55].

In conclusion, the use of dose-intense epirubicin regimens (FEC100 or CEF120) in the MA.5 and FASG 05 studies demonstrates superior long-term DFS and OS, with favorable toxicity profiles compared with classic CMF and without long-term adverse events. An additional significant advantage was identified in the PACS 01 study, with the sequential use of FEC100 and docetaxel. Epirubicin-based chemotherapy with the addition of a taxane can yield superior efficacy but requires G-CSF support and close observation because of potential toxicities. Epirubicin is well tolerated in combination regimens with the HER-2–targeted monoclonal antibody trastuzumab. Epirubicin is the key component in the significant improvement in survival seen across the spectrum of patient subsets and regardless of hormone receptor status, including those who are node-negative, node-positive, HER-2–expressing, elderly, and receiving neoadjuvant treatment.

**Disclosure of Potential Conflicts of Interest**

Dr. Glück has acted as a consultant for and has received support from sanofi-aventis, Genentech, Pfizer, and Novartis.

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