Anthracyclines in Early-Stage Breast Cancer: Is It the End of an Era?

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ABSTRACT

Anthracycline regimens have been the mainstay of adjuvant care in breast cancer for >20 years. A growing body of clinical experience has uncovered an unacceptable rate of significant cardiac and leukemogenic toxicities. A systematic review of the literature was performed highlighting anthracycline- and nonanthracycline-based adjuvant regimens. The published data suggest that nonanthracycline alternatives are less toxic than anthracycline-containing regimens and equally, if not more, efficacious. Molecular predictors, such as human epidermal growth factor receptor 2 and topoisomerase II α, are further refining the optimal role of anthracyclines. With these new advances, the current role of anthracycline-based chemotherapy in early-stage breast cancer demands re-examination. The Oncologist 2009;14:950–958

INTRODUCTION

The anthracycline antibiotics are among the most important anticancer agents in use today. First extracted from fungal Streptomyces species in 1958, daunorubicin [1] and subsequently doxorubicin [2] have found important roles in standard oncologic practice over the past 40 years. Biochemical modifications have produced epirubicin, idarubicin, and, more recently, liposomal preparations, further expanding their spectrum of activity and altering their toxicity profile.

In the mid 1980s, a number of clinical trials in the adjuvant breast cancer setting evaluated anthracyclines in comparison with the standard cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) regimen, thus paving the way for what might be considered the anthracycline era of early breast cancer [3–6]. However, our growing understanding of the long-term anthracycline toxicities, the increasing use of adjuvant chemotherapy in the node-negative and elderly populations, the rapidly evolving understanding of the molecular determinants of anthracycline sensitivity, and the emergence of nonanthracycline chemotherapy alternatives are calling into question the role of anthracyclines in the modern adjuvant therapy of breast cancer.

Herein, we review the literature reporting the efficacy and toxicity of adjuvant anthracycline therapy for early-stage invasive breast cancer. We limit our focus to the most common anthracyclines in clinical practice—doxorubicin and epirubicin—and summarize the progress toward molecular predictive markers of anthracycline efficacy. We
then place in context the newer nonanthracycline regimens and their relative merits.

**TOXICITIES MATERIALIZE**

**Cardiac**

Clinical experience with anthracyclines in the metastatic breast cancer setting has uncovered a significant and dose-related incidence of cardiac dysfunction [7, 8]. Anthracyclines are the most active drugs in the palliative setting of recurrent and metastatic breast cancer, with response rates higher than with nonanthracycline regimens, albeit without significant survival differences [9]. Nevertheless, because of the short survival duration of these women, the long-term risk for cardiotoxicity is less clinically important in the metastatic setting. However, in the adjuvant setting, potential life-threatening cardiac toxicities are of greater concern, given that many patients with early breast cancer can be rendered disease free following definitive surgery alone.

The reported literature on the relationship between cardiotoxicity and adjuvant anthracycline exposure must be reviewed in full awareness that studies vary widely in dose and schedule of anthracycline, methodology (including population-based, retrospective, and prospective studies), populations treated, and the intensity, duration, and nature of cardiac monitoring (Table 1) [10–16]. Furthermore, the definitions of cardiac dysfunction and congestive heart failure (CHF) have not been formally standardized, and considerable variation exists among trials. Nonetheless, there is a consensus that the risk for cardiotoxicity is related to the cumulative anthracycline dose administered, pre-existing heart disease, a history of mediastinal irradiation, and the coadministration of desrazoxane, paclitaxel, and trastuzumab [17]. Furthermore, this risk is of particular concern in the elderly. Pinder et al. [18], in their review of the Surveillance, Epidemiology, and End Results Medicare database, found a statistically and clinically significant higher risk for CHF in women aged 66–70 who received anthracycline-based chemotherapy compared with those who received nonanthracycline regimens (hazard ratio [HR], 1.26).

Among the studies examining adjuvant cardiotoxicity issues, large series have consolidated individual trial results. Valagussa et al. [19] reported a 0.8% incidence of CHF with older adjuvant regimens incorporating doxorubicin. Fumoleau et al. [20] reviewed the French Adjuvant Study Group (FASG)’s experience with adjuvant epirubicin and recorded a 1.3% incidence of clinical cardiac dysfunction. Other series have explored the influences of dose and length of follow-up. The Cancer and Leukemia Group B (CALGB) 9344 adjuvant breast cancer trial [11] found a 16% rate of cardiotoxicity (symptomatic and asymptomatic) with a doxorubicin dose of 90 mg/m² versus 11% with a dose of 60 mg/m². Zambetti et al. [21] detailed a 0.4% incidence of cardiac death in a report from a 14-year follow-up of adjuvant anthracycline regimens. Finally, the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) identified a cardiac mortality rate of 0.08% per year with anthracycline-containing adjuvant regimens [22].

Of particular interest are the emerging reports with newer adjuvant regimens incorporating trastuzumab. The recent landmark adjuvant trastuzumab trials documented substantially higher rates of cardiotoxicity: a 1.73% 1-year incidence of symptomatic CHF in the Herceptin® Adjuvant trial [23], 4.1% and 2.9% 3-year incidences of New York Heart Association (NYHA) class III/IV CHF or death from cardiac causes in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 and N9831 trials, respectively [24], and a 1.9% 3-year incidence of NYHA class III/IV CHF in the second interim analysis of the Breast Cancer International Research Group (BCIRG) 006 trial [25]. The absolute and relative risks for trastuzumab-associated cardiotoxocities are summarized in Table 2 [23–26]. Because these trials reported results at a median follow-up of...
only 3 years in women selected to have a low risk for cardiotoxicity, it is likely that the burden of cardiotoxicity will almost certainly be greater with additional follow-up and the broad use in the community of trastuzumab in women who would not necessarily have been eligible for the original adjuvant trastuzumab studies.

**Leukemogenicity**

The leukemogenic potential of alkylating agents and radiotherapy has been well established in the cancer literature [26]. The incremental risks for secondary acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) attributable to anthracyclines are apparent, in large part because of the relatively short time to onset of anthracycline-associated AML and MDS (Table 3) [10–14, 16, 22, 25]. Such topoisomerase II inhibitor triggered events are characterized by a clinically and cytogenetically defined form of treatment-related leukemia [27]. In a cohort of 3093 French women who received adjuvant anthracycline chemotherapy, Chaplain et al. [28] found a 0.41% 4-year cumulative incidence of AML/MDS, roughly 11.4 times the risk for women who did not receive adjuvant chemotherapy. The NSABP experience of adjuvant anthracycline chemotherapy, Chaplain et al. [28] found a 0.41% 4-year cumulative incidence of AML/MDS, roughly 11.4 times the risk for women who did not receive adjuvant chemotherapy. The NSABP experience of adjuvant anthracycline chemotherapy, Chaplain et al. [28] found a 0.41% 4-year cumulative incidence of AML/MDS, roughly 11.4 times the risk for women who did not receive adjuvant chemotherapy. The NSABP experience of adjuvant anthracycline chemotherapy, Chaplain et al. [28] found a 0.41% 4-year cumulative incidence of AML/MDS, roughly 11.4 times the risk for women who did not receive adjuvant chemotherapy. The NSABP experience of adjuvant anthracycline chemotherapy, Chaplain et al. [28] found a 0.41% 4-year cumulative incidence of AML/MDS, roughly 11.4 times the risk for women who did not receive adjuvant chemotherapy. The NSABP experience of adjuvant anthracycline chemotherapy, Chaplain et al. [28] found a 0.41% 4-year cumulative incidence of AML/MDS, roughly 11.4 times the risk for women who did not receive adjuvant chemotherapy. The NSABP experience of adjuvant anthracycline chemotherapy, Chaplain et al. [28] found a 0.41% 4-year cumulative incidence of AML/MDS, roughly 11.4 times the risk for women who did not receive adjuvant chemotherapy. The NSABP experience of adjuvant anthracycline chemotherapy, Chaplain et al. [28] found a 0.41% 4-year cumulative incidence of AML/MDS, roughly 11.4 times the risk for women who did not receive adjuvant chemotherapy. The NSABP experience of adjuvant anthracycline chemotherapy, Chaplain et al. [28] found a 0.41% 4-year cumulative incidence of AML/MDS, roughly 11.4 times the risk for women who did not receive adjuvant chemotherapy. The NSABP experience of adjuvant anthracycline chemotherapy, Chaplain et al. [28] found a 0.41% 4-year cumulative incidence of AML/MDS, roughly 11.4 times the risk for women who did not receive adjuvant chemotherapy. The NSABP experience of adjuvant anthracycline chemotherapy, Chaplain et al. [28] found a 0.41% 4-year cumulative incidence of AML/MDS, roughly 11.4 times the risk for women who did not receive adjuvant chemotherapy. The NSABP experience of adjuvant anthracycline chemotherapy, Chaplain et al. [28] found a 0.41% 4-year cumulative incidence of AML/MDS, roughly 11.4 times the risk for women who did not receive adjuvant chemotherapy. The NSABP experience of adjuvant anthracycline chemotherapy, Chaplain et al. [28] found a 0.41% 4-year cumulative incidence of AML/MDS, roughly 11.4 times the risk for women who did not receive adjuvant chemotherapy. The NSABP experience of adjuvant anthracycline chemotherapy, Chaplain et al. [28] found a 0.41% 4-year cumulative incidence of AML/MDS, roughly 11.4 times the risk for women who did not receive adjuvant chemotherapy. The NSABP experience of adjuvant anthracycline chemotherapy, Chaplain et al. [28] found a 0.41% 4-year cumulative incidence of AML/MDS, roughly 11.4 times the risk for women who did not receive adjuvant chemotherapy. The NSABP experience of adjuvant anthracycline chemotherapy, Chaplain et al. [28] found a 0.41% 4-year cumulative incidence of AML/MDS, roughly 11.4 times the risk for women who did not receive adjuvant chemotherapy. The NSABP experience of adjuvant anthracycline chemotherapy, Chaplain et al. [28] found a 0.41% 4-year cumulative incidence of AML/MDS,roughly 11.4 times the risk for women who did not receive adjuvant chemotherapy.

Despite the rarity of secondary hematological malignancies, newer regimens incorporating dose-intense anthracyclines may further increase the risk. An analysis of 19 adjuvant epirubicin trials, with 9,796 patients, revealed a clear relationship between epirubicin dose and the risk for AML/MDS: standard regimens carried an 8-year risk of 0.37% compared with a 4.97% risk for patients administered higher cumulative doses of both epirubicin and cyclophosphamide [30]. Although the absolute risk for leukemogenicity is overshadowed by the lower risk for death from breast cancer, the emergence of nonleukogenic alternatives mandates that these risks nonetheless be introduced in clinical discussions when making adjuvant therapy deci-

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### Table 2. Cardiotoxicity of trastuzumab regimens: Grade 3 or 4 CHF events or fatal cardiac events

<table>
<thead>
<tr>
<th>Study</th>
<th>Size</th>
<th>Follow-up (yrs)</th>
<th>CHF incidence (%)</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-31/NCCTG [24]</td>
<td>3,351</td>
<td>3</td>
<td>3.1</td>
<td>10.4</td>
</tr>
<tr>
<td>FinHER [26]</td>
<td>231</td>
<td>3</td>
<td>0.3</td>
<td>–</td>
</tr>
<tr>
<td>HERA [23]</td>
<td>3,401</td>
<td>2</td>
<td>0.6</td>
<td>10</td>
</tr>
<tr>
<td>BCIRG 006 [25]</td>
<td>3,322</td>
<td>2</td>
<td>0.6</td>
<td>10</td>
</tr>
<tr>
<td>AC-TH</td>
<td></td>
<td></td>
<td>1.9</td>
<td>5</td>
</tr>
<tr>
<td>TCH</td>
<td></td>
<td></td>
<td>0.4</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: AC-TH, doxorubicin, cyclophosphamide, paclitaxel, and trastuzumab; BCIRG, Breast Cancer International Research Group; CHF, congestive heart failure; FinHER, Finnish Herceptin®; HERA, Herceptin® Adjuvant; NCCTG, North Central Cancer Treatment Group; TCH, docetaxel, cyclophosphamide, and trastuzumab.

### Table 3. Leukemogenicity of common adjuvant regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Study</th>
<th>AML/MDS rate (%)</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAC [14]</td>
<td>BCIRG 001</td>
<td>0.27</td>
<td>5</td>
</tr>
<tr>
<td>AC-T [11]</td>
<td>CALGB 9344</td>
<td>0.39</td>
<td>5</td>
</tr>
<tr>
<td>dd AC-T [12]</td>
<td>CALGB 9741</td>
<td>0.70</td>
<td>7</td>
</tr>
<tr>
<td>CE120F [13]</td>
<td>MA-5</td>
<td>1.42</td>
<td>5</td>
</tr>
<tr>
<td>TC [16]</td>
<td>USON 9735</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>TCH [25]</td>
<td>BCIRG 006</td>
<td>0.2</td>
<td>3</td>
</tr>
<tr>
<td>AC-TH [25]</td>
<td>BCIRG 006</td>
<td>0.2</td>
<td>3</td>
</tr>
<tr>
<td>FEC-D [10]</td>
<td>PACS 01</td>
<td>0.25</td>
<td>5</td>
</tr>
<tr>
<td>CMF [22]</td>
<td>EBCTCG</td>
<td>0.02/yr</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AC-T, doxorubicin, cyclophosphamide, and paclitaxel; AC-TH, doxorubicin, cyclophosphamide, paclitaxel, and trastuzumab; AML, acute myelogenous leukemia; BCIRG, Breast Cancer International Research Group; CALGB, Cancer and Leukemia Group B; CE120F, cyclophosphamide, epirubicin (120 mg/m²), and 5-fluorouracil; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; ddAC-T, dose-dense doxorubicin, cyclophosphamide, and paclitaxel; EBCTCG, Early Breast Cancer Trials’ Collaborative Group; FEC-D, 5-fluorouracil, epirubicin, and cyclophosphamide, docetaxel; FE100C-D, 5-fluorouracil, epirubicin (100 mg/m²), cyclophosphamide, and docetaxel; MDS, myelodysplastic syndrome; TAC, docetaxel, doxorubicin, and cyclophosphamide; TC, docetaxel and cyclophosphamide; TCH, docetaxel, cyclophosphamide, and trastuzumab; USON, United States Oncology Network.
sions, particularly so if they offer any incremental survival benefit.

ADJUVANT ANTHRACYCLINE PRINCIPLES

Despite their established toxicities, anthracycline-based regimens have become the mainstay in the management of early breast cancer. First introduced as an alternative to the classic CMF cocktail, subsequent trials, cross-trial comparisons, and much debate have attempted to identify an optimal anthracycline regimen. The most comprehensive and perhaps authoritative analysis came with the EBCTCG 2000 overview [22]. A direct analysis of all registered anthracycline-containing regimens versus nonanthracycline regimens favored the former in terms of disease-free survival (DFS) and overall survival (OS), regardless of age, hormone receptor status, or nodal status, with an absolute benefit of 3% at 5 years, and 4% at 10 years.

The adjuvant anthracycline debate, however, has recently resurfaced because of a growing appreciation of long-term toxicities (discussed above), the emergence of nonanthracycline chemotherapy alternatives, and an evolving understanding of the molecular determinants of anthracycline sensitivity. With these new advances, the anthracycline status quo demands re-examination. We discuss the role of adjuvant anthracyclines in the context of three specific early-stage breast cancer subpopulations: human epidermal growth factor receptor (HER)2\(^+\), HER-2\(^-\), and hormone receptor-positive breast cancers.

HER-2\(^+\) EARLY BREAST CANCER

Invasive breast cancer is a heterogeneous disease characterized by several distinct biologic subtypes. Approximately 20% of primary breast cancers have amplification of the HER-2 gene, with resultant overexpression of the HER-2 protein. HER-2 belongs to a family of transmembrane receptor tyrosine kinases that mediate the growth, differentiation, and survival of cells. HER-2\(^+\) cancers tend to have enhanced growth and proliferation, greater invasive and metastatic capability, and stimulation of angiogenesis. Population-based studies and retrospective analyses have also shown that the HER-2 alteration is associated with poorly differentiated, high-grade tumors, lymph node involvement, and relative resistance to hormonal therapy. Until recently, breast cancer patients in whom overexpression of HER-2 occurred faced a poorer prognosis than those with HER-2\(^-\) breast cancer.

To address whether HER-2 status relates to anthracycline sensitivity, a number of adjuvant trialists have retrospectively analyzed their clinical trial outcome data and primary tumor blocks. To date, this question has been addressed in nine reported clinical trials comparing anthracycline with nonanthracycline regimens [31–39], a pooled analysis of eight of these trials [40], three studies addressing whether escalation of the anthracycline dose relates to outcomes in HER-2 dichotomized populations [41–43], and a single trial that evaluated adjuvant HER-2 therapy combined with a nonanthracycline chemotherapy regimen [25].

Nine reported trials have evaluated the predictive value of HER-2 in studies that compared anthracycline with nonanthracycline regimens (Table 4) [31–39]. In general, those trials had heterogeneous HER-2 testing methodologies, relatively small sample sizes, and, because of their retrospective nature, not all tumor blocks were available for each patient in the trials. Nonetheless, a pooled analysis of eight of those trials revealed that, for those women randomized to anthracycline versus nonanthracycline regimens, the DFS and OS HRs for women with HER-2\(^+\) primary tumors were markedly superior, at 0.71 (95% confidence interval [CI] 0.62–0.85) and 0.73 (95% CI, 0.62–0.85), respectively [40]. Because the test for treatment by HER-2 status interaction was significant, the authors concluded that the incremental benefit of adjuvant chemotherapy with anthracyclines was confined to women with HER-2\(^+\) breast cancers.

Three further trials have investigated the predictive value of HER-2 with alternative anthracycline dosing strategies and have come to disparate conclusions. Muss et al. [41] retrospectively analyzed tumor blocks for c-erbB-2 (HER-2) expression from a randomly selected cohort of women enrolled in the CALGB 8541 [43] clinical trial of varying dose cyclophosphamide, doxorubicin, and 5-fluorouracil [40]. A dose–response benefit was restricted to the 29% of women who were c-erbB-2\(^+\). A similarly designed retrospective analysis of tumor blocks from the Gono-Mig-1 study of standard dose versus dose-dense adjuvant cyclophosphamide, epirubicin (60 mg/m\(^2\)), 5-fluorouracil (FEC21 versus FEC14) was performed by Del Mastro et al. [42]. The benefit of the dose-dense regimen was again limited to the HER-2\(^+\) cohort, but it did not reach statistical significance: 5-year event-free survival rate, 62.5% versus 77.7% (p = .087) for FEC21 versus FEC14, respectively.

Finally, no survival associations were found between HER-2 status and doses of doxorubicin >60 mg/m\(^2\) in a retrospective analysis of the CALGB 9344 data [43, 11].

These results, in aggregate, raise the critical question: why would high sensitivity to anthracyclines be confined to the HER-2\(^+\) subpopulation of breast cancer patients? Recent investigations have implied a tantalizing molecular explanation. The topoisomerase II \(\alpha\) (topoIIA) gene has been mapped to chromosome 17, adjacent to the HER-2 locus [44]. Several studies using fluorescence in situ hybridiza-

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tion (FISH) analysis, albeit retrospective in nature, have revealed significant associations among HER-2/topoIIA coamplification, the use of anthracyclines, and survival outcomes (Table 5) [37, 46–48]. Three such studies revealed that topoIIA amplifications (or deletions) were predictive of a greater differential response to anthracycline-containing regimens [37, 46, 47]; however, only one of these trials suggested that topoIIA has a greater predictive value than HER-2 amplification [37]. Furthermore, one study found no differential benefit for anthracyclines in a topoIIA-expressing population of women treated with adjuvant CMF versus epirubicin plus CMF [48]. A recent meta-analysis of four anthracycline versus nonanthracycline adjuvant trials was similarly inconclusive, where topoIIA amplification provided no further predictive benefit for anthracyclines over HER-2 amplification [49]. Emerging reports regarding other putative anthracycline predictive biomarkers, such as chromosome 17 polysomy [39] or topoIIA/tissue inhibitor of metalloproteinases (TIMP) coexpression [50], remain to be validated in other retrospective analyses. It should be noted, however, that all of these studies were limited to HER-2+ patients treated without trastuzumab—the current standard of care for HER-2+ early breast cancer.

Trastuzumab (Herceptin™; F. Hoffmann-La Roche, Basel, Switzerland) is a humanized monoclonal antibody targeting the extracellular domain of the HER-2 protein. Trastuzumab activates antibody-dependent cell-mediated cytoxicity and disrupts the signal transduction process through interfering with receptor dimerization, downstream effectors, and receptor internalization and degradation. The BCIRG 006 trial reported the efficacy of adjuvant docetaxel, carboplatin, and trastuzumab (TCH) versus a standard anthracycline regimen with and without trastuzumab—doxorubicin and cyclophosphamide followed by do-
cetaxel (ACT) and doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (ACTH) [25]. Whereas both adjuvant trastuzumab arms resulted in substantially superior outcomes versus the control, there were no significant differences between the trastuzumab-containing arms concerning the 4-year DFS rate: 83% (ACTH) versus 82% (TCH). Nor were there significant 4-year OS rate differences between the two trastuzumab regimens: 92% (ACTH) versus 91% (TCH). However, the global toxicity profiles favored the nonanthracycline TCH regimen, with significantly lower incidences of grade 3 or 4 arthralgia, myalgia, hand–foot syndrome, stomatitis, vomiting, neutropenia, and leukopenia. Furthermore, the incidence of cardiotoxicity was fivefold lower with the nonanthracycline regimen: 1.9% versus 0.4% grade 3 or 4 CHF in the ACTH arm versus the TCH arm, respectively ($p = .0015$).

In summary, these data suggest that, although adjuvant anthracyclines may provide an incremental efficacy advantage in the HER-2 + population in the absence of trastuzumab, this benefit is lost when trastuzumab is introduced. Given the life-altering potential toxicities of anthracyclines, cardiotoxicity and leukemogenicity, and the substantially greater incidences of cardiotoxicity seen when trastuzumab is used in proximity to anthracyclines, the role for anthracyclines in the HER-2 + population is very much in question.

### HER-2 - Early Breast Cancer

Treatment for the HER-2 - cohort of patients with early invasive breast cancer now differs from that of their HER-2 + counterparts, in that trastuzumab is of no proven value. Given the wealth of data in the metastatic setting showing a lack of trastuzumab efficacy in breast cancers neither overexpressing HER-2 via immunohistochemistry nor possessing HER-2 amplification by FISH [51], the role of adjuvant trastuzumab in the HER-2 - adjuvant setting remains speculative [52]. Taxane-based regimens are an increasingly accepted alternative to anthracycline-based regimens, with supporting data from two major trials. Jones et al. [53] pitted adjuvant AC for four cycles against docetaxel and cyclophosphamide (TC) for four cycles in a population of early breast cancer patients unselected for HER-2 status. When presented in 2005, the data favored the nonanthracycline regimen (TC) in terms of the 5-year DFS rate, 86% versus 80%, and a trend was emerging for an OS advantage [53]. Seven-year data recently presented at the 2007 San Antonio Breast Cancer Symposium now reveal a significant OS benefit for the TC arm: an 84% (TC) versus 88% (AC) 6-year OS rate ($p = .045$) [16]. A second study examined the use of taxanes as a replacement for a standard regimen with a higher cumulative dose of anthracyclines. The PACS 01 trial compared six cycles of FEC 100 with three cycles of FEC 100 followed by three cycles of docetaxel (FEC-D) [10]. The FEC-D arm had a superior 5-year DFS rate (78.4% versus 73.2%) and OS rate (90.7% versus 86.7%). Thus, the newer taxane-based regimens are increasingly viable and accepted options because of their greater DFS and OS rates, and lower rates of anthracycline-associated toxicities.

### Estrogen Receptor-Positive Early Breast Cancer

The primacy of the anthracycline regimens has been further challenged in the estrogen receptor (ER) + domain. Elucidation of the role of estrogen in breast carcinogenesis and progression has catalyzed the development of targeted endocrine therapies, including including hormonal manipulations to cytotoxic chemotherapy. Large meta-analyses have focused on the additional benefit of hormonal manipulations to cytotoxic chemotherapy [22, 54, 55]. The EBCTCG 2005 overview explored the role of chemotherapy alone versus chemotherapy in combination with ovarian ablation or suppression. A statistically significant 3.2% 15-year benefit in breast cancer mortality (43.5% versus 40.3%) was found in the combination group. A similar benefit was seen in the analysis of tamoxifen in combination with chemotherapy: a 6.9% 10-year benefit in breast cancer mortality (29.0% versus 22.2%). Few analyses, however, have explored the possibility of hormonal manipulation as an alternative to cytotoxic chemotherapy, and even fewer have used anthracycline regimens as the comparator.

In the premenopausal population, three studies have examined combined ovarian ablation/suppression and tamoxifen versus anthracyclines in the high-risk adjuvant setting (Table 6). Roché et al. [56] randomized premenopausal, node-positive women to either ovarian ablation (surgical or radiation) with 2 years of tamoxifen or 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC). After 85 months of follow-up, there was a trend favoring the hormonal manipulation arm in terms of both the DFS rate (82.5% versus 55%) and the OS rate (84% versus 74%). Roché et al. [57] then examined a similar population in the FASG 06 trial, this time with medical oopherectomy and 3 years of tamoxifen versus FEC. Here, a statistically significant benefit in terms of the DFS rate was apparent in the hormonal arm alone versus the anthracycline regimen: 91.7% versus 80.9%, respectively. Finally, the International Breast Cancer Study Group examined a similar premenopausal, node-positive population and evaluated ovarian function suppression with 5 years of tamoxifen versus the same regimen with AC chemotherapy [58]. Although accrual was poor, there was no difference in either the DFS or OS rate with the addition of cytotoxic anthracyclines.

Hormonal manipulation has been well studied in the postmenopausal setting because of the high prevalence of...
estrogen-dependent tumors and the desire to diminish adjuvant toxicity. There is, however, a paucity of similarly designed trials comparing adjuvant endocrine therapy with anthracycline regimens, particularly in the node-negative setting because of the marginal benefit of chemotherapy in this relatively low-risk population [22]. Recent advances in molecular profiling have sought to define a cohort of low-risk women who do not appear to benefit from anthracycline-based adjuvant chemotherapy. The 21-gene recurrence score assay (Oncotype DX®; Genomic Health, Redwood City, CA) has been studied, albeit retrospectively, in both the node-negative and node-positive hormone receptor–positive populations [63, 64]. Although the results in the node-negative trial detailed a group of low-risk women who do not appear to benefit from adjuvant chemotherapy, the comparator arm, from the NSABP B-20 trial, was CMF or MF chemotherapy, and did not contain any anthracyclines [63]. The node-positive analysis was conducted with samples from the INT0100 trial, with an anthracycline-containing cyclophosphamide, doxorubicin, and 5-fluorouracil arm [64]. The results suggest that women with a low recurrence score (<18), notwithstanding their nodal positivity, can possibly be spared the toxicity of anthracycline-containing chemotherapeutics.

### CONCLUSIONS

Anthracycline regimens have been the mainstay of adjuvant chemotherapy in breast cancer for nearly 20 years. However, increasing recognition of their particular toxicities (cardiac and leukemogenic) has prompted the search for viable alternatives, and for subgroups with preferential benefit. Although the incremental efficacy advantages of anthracycline regimens now appear to be confined to the HER-2⁰ population, the arrival of trastuzumab-based nonanthracycline regimens has successfully challenged their role even in this niche. Furthermore, taxane-based adjuvant regimens have successfully reduced or eliminated the need for anthracycline exposure in the HER-2⁰ population. Finally, the incremental benefit from chemotherapy beyond that of optimal hormonal therapy is in question because of better molecular selection of hormone-sensitive populations. In aggregate, these emerging data have deeply undermined the role of adjuvant anthracyclines in modern breast cancer care.

### AUTHOR CONTRIBUTIONS

Conception/Design: Danny Robson, Sunil Verma
Collection/assembly of data: Danny Robson, Sunil Verma
Data analysis: Danny Robson, Sunil Verma
Manuscript writing: Danny Robson, Sunil Verma
Final approval of manuscript: Danny Robson, Sunil Verma

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2. Arcamone F, Cassinelli G, Fantini G et al. Adriamycin, 14-hydroxydauno-

### Table 6. Anthracycline versus hormonal manipulation trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Outcome (endocrine versus anthracycline)</th>
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</thead>
<tbody>
<tr>
<td>Premenopausal</td>
<td></td>
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<tr>
<td>Roché [56]</td>
<td>Tam + OA versus FAC</td>
<td>85-mo DFS, 82.8% (71%–90%) versus 55%</td>
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<tr>
<td>Roché [57], FACS 06</td>
<td>Tam + triptoreline versus FEC50</td>
<td>54-mo DFS, 91.7% versus 80.9%; p = .12</td>
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<tr>
<td>Thurliman [58], IBCSG 11–93</td>
<td>OA/OS versus OA/OS + AC</td>
<td>48-mo DFS, 88% versus 87%; p = .94</td>
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<tr>
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<td>Fisher et al. [59], NSABP B16</td>
<td>Tam versus AC/PAFT</td>
<td>36-mo DFS, 66% versus 84%; p = .003</td>
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<td>Albain [60], SWOG 8814</td>
<td>Tam versus CAF-Tam versus CAFTam</td>
<td>10-yr DFS, 48% versus 60% versus 53%*</td>
</tr>
<tr>
<td>Wils et al. [61], ICCG</td>
<td>Tam versus E + Tam</td>
<td>68-mo RFS, 62.1% versus 73.7%; p = .023</td>
</tr>
<tr>
<td>Namer et al. [62], FACS 02/07</td>
<td>Tam versus FEC50 + Tam</td>
<td>9-yr DFS, 72% versus 84%; p = .008</td>
</tr>
</tbody>
</table>

*a-value not reported.
Abbreviations: AC, doxorubicin and cyclophosphamide; CAF, cyclophosphamide, doxorubicin, and 5-fluorouracil; DFS, disease-free survival; E, epirubicin; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; FACS, French Adjuvant Study Group; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; IBCSG, International Breast Cancer Study Group; ICCG, International Collaborative Cancer Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; OA, ovarian ablation; OS, ovarian suppression; PAFT, phenylalanine mustard, doxorubicin, and 5-fluorouracil; RFS, relapse-free survival; SWOG, Southwest Oncology Group; Tam, tamoxifen.


Anthracyclines in Early-Stage Breast Cancer: Is It the End of an Era?

DANNY ROBSON, SUNIL VERMA


On page 955, data from the 2007 San Antonio Breast Cancer Symposium were misreported in the sixth sentence of the section entitled “HER-2’ Early Breast Cancer.” Here we print the correct text.

Seven-year data recently presented at the 2007 San Antonio Breast Cancer Symposium now reveal a significant OS benefit for the TC arm: an 88% (TC) versus 84% (AC) 6-year OS rate ($p = .045$) [16].