Anthracycline vs Nonanthracycline Adjuvant Therapy for Breast Cancer

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The authors present a comprehensive review of anthracycline-based adjuvant chemotherapy regimens, supporting the use of these regimens over CMF (cyclophosphamide [Cytoxan, Neosar], methotrexate, fluorouracil [5-FU]) in early-stage breast cancer. They conclude that the addition of taxanes to anthracycline-containing regimens in node-positive disease may confer additional benefit. Newer regimens containing taxanes and other agents that omit the use of anthracyclines show promise but are still under investigation.

Importance of Dose and Scheduling
A variety of anthracycline-containing regimens have been tested in the adjuvant setting. Dose and scheduling of anthracyclines are important factors to consider when choosing one of these anthracycline-based regimens. The number of cycles may be important, as pointed out by the authors in the setting of node-negative breast cancer, where six cycles of CAF (cyclophosphamide, doxorubicin [Adriamycin], 5-FU) are superior to CMF (INT 0102) but four cycles of AC (doxorubicin, cyclophosphamide) are only equivalent to CMF (as shown in National Surgical Adjuvant Breast and Bowel Project [NSABP] trials B-15 and B-23). Cancer and Leukemia Group B (CALGB) 40101 is addressing this issue in node-negative disease with a direct comparison of four vs six cycles of dose-dense AC. Anthracycline dose level per cycle may also influence efficacy. A doxorubicin dose of 60 mg/m^2 per cycle was superior to 30 mg/m^2 per cycle in CALGB 8541.[1] CALGB 9344 did not show that escalating the doxorubicin dose over 60 mg/m^2 per cycle was beneficial, but higher doses of epirubicin (Ellence) per cycle seem to be associated with better outcome. The superior results seen in National Cancer Institute of Canada (NCIC) MA.5 may have been due to an epirubicin dose of 120 mg/m^2 per cycle when used in a CEF regimen (cyclophosphamide, epirubicin, 5-FU) as compared to CMF, and the French Adjuvant Study Group showed that 100 mg/m^2 of epirubicin was superior to 50 mg/m^2 when used in the FEC-100 regimen.[2] In addition to dose, the cycle interval may be important. Dose-dense scheduling every 2 weeks with growth factor support may confer an additional benefit over standard scheduling every 3 weeks, as demonstrated in CALGB 9741.[3]

Addition of Taxanes
The 2000 National Institutes of Health (NIH) Consensus Conference supported the addition of taxanes to anthracycline-containing regimens, based on the results of CALGB 9344 for women with node-positive breast cancer.[4] These results have been updated and are now supported by the results of NSABP B-28, showing a benefit for ACT (doxorubicin, cyclophosphamide, paclitaxel [Taxol]) over AC for relapse-free survival at 5 years,[5] and Breast Cancer International Research Group (BCIRG) 001, showing a benefit for TAC (docetaxel [Taxotere], doxorubicin, cyclophosphamide) over FAC for both relapsefree and overall survival at 3 years.[6] All of these trials were restricted to women with node-positive disease. Taxane-containing regimens have not yet been compared with some of the higher-dose anthracycline-containing regimens such as CEF or FEC-100. The best combination and dose of agents is yet to be determined; there may well be several regimens with equivalent efficacy.

HER2 Overexpression
Several trials have demonstrated an association between HER2 (c-erbB2) overexpression and better
outcome with anthracyclines, as noted in the authors' Table 3. Some of these trials were hampered by less reliable immunochemical methods of c-erbB2 detection, so these conclusions remain somewhat controversial.[7] Current trials such as CALGB 49909, NSABP B-31, and the recently completed BCIRG 006 trial are testing the safety and efficacy of adding trastuzumab (Herceptin) to adjuvant regimens. Given that anthracycline cardiotoxicity is enhanced by trastuzumab, taxanes and/or other agents such as capecitabine (Xeloda) or gemcitabine (Gemzar) may ultimately prove to be better choices for treating HER2-positive breast cancer.

Risk Estimates
To date, most clinical trials have divided women into risk groups based on the presence or absence of nodal disease, and treatment recommendations are primarily based on this one factor. It is well established that other factors such as age, tumor size, grade, and lymphovascular invasion also influence the risk of relapse and mortality. An estimate of an individual woman's risk can readily be obtained by using one of the online risk calculators.[8,9] For example, a 45-year-old woman with a 3-cm high-grade node-negative breast cancer would have a substantially higher risk of relapse and death in 10 years than a 65-year-old woman with a 2-cm intermediate-grade tumor and one positive lymph node. These risk estimates have recently been validated by outcome data from the British Columbia Cancer Agency.[10] A comparison of the benefit of various regimens, including hormonal therapy, can be made using the principle of proportional benefit. We recommend taking into account a global estimate of a woman's risk of relapse and mortality when discussing choices for adjuvant therapy, and suggest that this type of risk estimate be incorporated into future clinical trials.

Future Investigations
The authors suggest several possible avenues for future clinical trials comparing current standard regimens to regimens incorporating newer agents and combinations that have shown promise in the metastatic setting. Although the addition of another agent to current regimens might result in a small improvement in outcome, a more innovative approach will likely need to be taken to see more substantial improvements. Incorporation of agents with novel mechanisms of action, such as those targeting the HER2 and epidermal growth factor receptor pathways may prove fruitful. Testing these new combinations in the neoadjuvant setting, using pathologic response rates as a surrogate for activity, may allow identification of promising regimens without having to wait for results from a randomized controlled phase III trial that has survival as its primary end point. The authors rightfully point out that better predictors of response are needed and present convincing early data for measurement of topoisomerase II-alpha overexpression as a predictor of anthracycline sensitivity. A recent evaluation of topoisomerase II-alpha in patients treated with different doses of anthracyclines in CALGB 8541, however, showed no relationship between topoisomerase II-alpha and outcome.[11] Measurements of expression of HER2, topoisomerase II-alpha, and other molecular markers may become increasingly important factors in recommending individualized treatment, but further data are needed.

Conclusions
We support the authors' conclusions that anthracycline-containing regimens remain the standard of care for women with early-stage breast cancer, except for those with a low risk of recurrence for whom CMF is a suitable choice. A careful assessment of risk and benefit is important for a thorough discussion of treatment options between physician and patient. Incorporation of other active chemotherapeutic agents with lower toxicity profiles (such as capecitabine and gemcitabine) into future clinical trials or the development of new treatments with novel mechanisms of action may eventually replace the anthracyclines, but for now they remain an integral part of adjuvant therapy for breast cancer.

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