The treatment of breast cancer has progressed substantially over the past 15 years. Data from randomized adjuvant trials have shown that the risk of disease recurrence and death is significantly reduced when adjuvant chemotherapy and/or hormonal therapy is added to treatment. As new strategies are incorporated, one of the continued controversies in patient management is whether adjuvant anthracyclines should be the preferred treatment for all patients. Data from randomized and translational clinical trials have become available and are helping to elucidate the proper role of anthracyclines, as well as their acute and long-term toxicities. In most situations, an anthracycline is currently preferred, but other single and combination chemotherapies are currently under evaluation and appear promising for use in the adjuvant setting. Continued breast cancer research using molecular markers (such as topoisomerase II–alpha and gene clusters) as predictors of treatment response, could help individualize decisions regarding whether to incorporate anthracyclines into adjuvant therapy regimens.

The use of adjuvant systemic therapy represents a major advance in the treatment and cure of early-stage breast cancer. Depending on tumor characteristics, chemotherapy and/or hormonal therapy following local treatment for breast cancer is the standard of care worldwide. Data from numerous randomized adjuvant trials have shown that the risk of disease recurrence and death is significantly reduced when chemotherapy and/or hormonal therapy is added to treatment, which translates into many lives saved each year. Although substantial progress has been made, controversy over the best adjuvant regimen remains. One of the central questions has been whether anthracyclines should be part of adjuvant therapy, or whether it is appropriate to recommend the CMF regimen (cyclophosphamide [Cytoxan, Neosar], methotrexate, fluorouracil [5-FU]) or another chemotherapy-based regimen instead. As the optimal treatment continues to be debated, ongoing trials are under way to help answer the treatment questions that remain.

**Benefit of Adjuvant Chemotherapy**

One of the principal investigations that reported a benefit for adjuvant combination chemotherapy was from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). The EBCTCG meets at 5-year intervals, performing meta-analyses on all mature randomized clinical trials focusing on women with early-stage breast cancer. Trials must have at least 5 years of follow-up data to be included in the analysis, with many now reporting 10 to 15 years of follow-up. The 1995 overview analysis summarized the results of trials beginning prior to 1990 and included data from 47 randomized trials with over 18,000 patients. These trials all compared polychemotherapy with no therapy in the adjuvant setting. Compared to no therapy, adjuvant chemotherapy was associated with reductions in recurrence and mortality in both younger and older women. In women under age 50 receiving chemotherapy, improvement in the absolute 10-year survival rate increased from 71% to 78% among those with node-negative disease, and from 42% to 53% among those with node-positive disease, compared to women receiving no treatment. In women aged 50 to 69 years, the absolute 10-year overall survival rate improved from 67% to 69% for node-negative disease and from 46% to 49% for node-positive disease.

Data from the 2000 EBCTCG meeting have not yet been published, but are consistent with the above benefits published in 1998.[1] Most of these trials addressed older types of chemotherapy and did not include the taxanes. However, there are excellent long-term data that can be used to reach some conclusions regarding appropriate adjuvant drug selection that will be outlined in this article. On the basis of current data, women with lymph node metastases or with primary breast cancers larger than 1 cm, regardless of nodal status, should have a discussion about adjuvant polychemotherapy. The choice of chemotherapy should be individualized for patients who have node-negative cancers less than 1 cm in diameter, as there are no prospective data demonstrating...
survival advantages for chemotherapy in this setting. Tumor grade is increasingly recognized as an additional factor to be taken into consideration in determination of prognosis.[2] In women with small, node-negative cancers who have favorable histologic subtypes such as mucinous or tubular tumors, adjuvant chemotherapy may be avoided.

**Long-Term CMF**

Long-term follow-up is now available for patients who were treated with adjuvant oral CMF chemotherapy. Data published in 1995 by Bonadonna et al reported significantly better rates of relapse-free and overall survival at 20-year follow-up in patients who received adjuvant CMF chemotherapy compared to no therapy.[3] Overall, the benefit translated into a 34% reduction in the relative risk of relapse and a 26% reduction in the relative risk of death. With the exception of postmenopausal women, a benefit from adjuvant chemotherapy was evident in all patient subgroups. Overall survival at 20 years in the CMF group was 47% for premenopausal women and 22% for postmenopausal patients. Event-free survival at 20 years in the CMF group was 23% (18% for patients who did not receive therapy). In addition, a recent Cancer and Leukemia Group B (CALGB) study reported a natural history analysis of more than 20 years for node-positive breast cancer patients who had been treated with CMF-based adjuvant therapy.[4] This study included 814 women with node-positive disease enrolled over 6 years, with a median follow-up of 22.6 years. Of the 599 patients who were known to have died, 80% died from metastatic breast cancer. Only 8.5% died of other causes and 1.3% of treatment-related causes. In addition, the disease-free survival rate at 20 years was only 23% and the 20-year overall survival was 28%. As expected, the greater the number of positive lymph nodes, the worse the outcome. In patients with more than 10 positive lymph nodes, disease-free survival at 15 years was only 9% (compared with 0% in the above Bonadonna study).

In summary, these data suggest that CMF therapy is less than optimal for patients such as those in the above trials (ie, node-positive) due to the poor disease-free and overall survival rates. This analysis stresses the need for improved adjuvant therapies in this population. It should also be mentioned that there is evidence in the metastatic setting that classical oral CMF is more effective than intravenous (IV) CMF, possibly because of the greater dose intensity of classical CMF. This was demonstrated in a randomized phase III trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) Breast Cancer Cooperative Group (10808) from 1991 comparing "classical" oral CMF vs a 3-weekly IV CMF schedule in postmenopausal patients with advanced breast cancer.[5] The response rate with classical CMF was 48% compared with 29% for IV CMF ($P = .003$). Response duration was similar at 11 months, but survival was longer for the classical schedule (17 vs 12 months, $P = .016$). Thus, if physicians select the IV adjuvant regimen with the intention of reducing toxicity or facilitating scheduling, they may be prescribing the less optimal CMF regimen in terms of antitumor activity.

**CMF vs Anthracyclines**

Until the early 1990s, CMF chemotherapy had generally been considered the standard adjuvant therapy for many breast cancer patients. Based on the above CALGB study and other studies included in the EBCTCG meta-analysis, it has become clear that more effective regimens are needed. The EBCTCG overview analysis compared approximately 6,000 women from 11 randomized trials.[1] Anthracycline- containing regimens were associated with a modest but significant reduction in disease recurrence (40.5% vs 43.2%) and death (28.8% vs 30.5%) compared to CMF adjuvant therapy. Further follow-up indicates that the benefit favoring anthracyclines is still evident at 10 years.

In addition, the 2000 National Institutes of Health (NIH) consensus concluded, "the inclusion of anthracyclines in adjuvant chemotherapy regimens produces a small but statistically significant improvement in survival over non-anthracycline-containing regimens."[6] Several randomized studies have compared CMF to an anthracycline-based regimen as adjuvant therapy. Table 1 summarizes the key randomized trials, including number of patients, disease-free survival, and overall survival.[1, 7-17] The results of these trials demonstrate that overall survival either favors an anthracycline- based regimen over CMF, or that the two regimens are equivalent.
Doxorubicin-Based Therapy vs CMF

- **INT 0102**—One of the largest, single randomized trials comparing anthracycline-based chemotherapy with CMF was the Southwest Oncology Group (SWOG)/Intergroup trial (INT 0102) conducted by Hutchins et al and presented at the American Society of Clinical Oncology (ASCO) annual meeting in 1998.[7] In this study, 4,400 women with node-negative breast cancer were stratified into high or low-risk groups. Women whose tumors were ≥ 2 cm or hormone-receptor-negative were considered high risk. Women with estrogen-receptor-positive tumors ≤ 2 cm could be classified as high risk based on S-phase fraction. The object of the study was to determine whether the CAF regimen (cyclophosphamide, doxorubicin [Adriamycin], 5-FU) is superior to CMF for high-risk, node-negative breast cancer patients. Not only was this a large study, but the two arms were very similar in regard to the number of cycles administered and doses given. All high-risk women were randomized to receive CAF or classical oral CMF chemotherapy for six cycles, with or without tamoxifen for 5 years; low-risk patients did not receive adjuvant treatment. Recurrence rates were 15% in the CAF group and 18% in the CMF arm (13% and 15%, respectively, with the addition of tamoxifen). Estimated 5-year overall survival in CAF-treated patients was 92%, compared with 90% in the CMF group. CAF chemotherapy, however, was associated with slightly more toxicity. Grade 4 neutropenia as well as grade 2 nausea and vomiting were increased in the CAF group, and alopecia was more common in the CAF group. Two fatal toxicities occurred in the CAF group, compared with one in the CMF group. The investigators concluded that CAF is slightly superior to

<table>
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<th>Study</th>
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+ = significant improvement with anthracyclines; CMF = cyclophosphamide, methotrexate, fluorouracil; EBCTCG = Early Breast Cancer Trialists’ Collaborative Group; ECOG = Eastern Cooperative Oncology Group; ICCG = International Collaborative Cancer Group; INT = Intergroup; NCIC = National Cancer Institute of Canada; NS = not significant (no difference between anthracycline and CMF chemotherapy); NSABP = National Surgical Adjuvant Breast and Bowel Project; SEG = Southeastern Cancer Study Group.
Anthracycline vs Nonanthracycline Adjuvant Therapy for Breast Cancer
Published on Diagnostic Imaging (http://www.diagnosticimaging.com)

A significantly higher number of deaths on treatment were noted in the CMF group compared to the ECMF group. It is important to note that a difference between the two groups in the number of second primaries. It is important to note that a statistically significant difference in disease-free or overall survival. (B-15 included lymph node-positive patients, and B-23 included only lymph node-negative patients.) The NSABP B-23 trial showed a relapse-free survival of 87% at 5 years in both groups and a similar overall 5-year survival of 89% vs 90% with CMF and AC, respectively.[18] The question remains, however, whether the outcome would have been different (ie, favoring the use of AC chemotherapy) if the study had used six cycles of AC instead of four.

**Epirubicin-Based Therapy vs CMF**

Epirubicin (Ellence) is another anthracycline that has been used in combination chemotherapy for adjuvant breast cancer treatment. Several randomized trials from Canada and Europe have compared epirubicin-based chemotherapy with CMF.

**NCIC MA.5**—The National Cancer Institute of Canada (NCIC) MA.5 trial was initially published in 1998 by Levine et al,[9] and recently updated.[19] The NCIC MA.5 trial randomized 710 premenopausal women with node-positive breast cancer to receive oral CMF or CEF (cyclophosphamide, 75 mg/m² orally on days 1 to 14; epirubicin, 60 mg/m² IV on days 1 and 8; and 5-FU, 500 mg/m² IV on days 1 and 8) for six cycles or oral CMF (cyclophosphamide, 100 mg/m² orally on days 1 to 14; methotrexate, 40 mg/m² IV on days 1 and 8; and 5-FU, 600 mg/m² IV on days 1 and 8). Tamoxifen was not given after chemotherapy in this study. In evaluations of hematologic toxicity, the rate of grade 3/4 neutropenia was 94% vs 60% for CEF and CMF, respectively (growth factors were not administered). Febrile neutropenia occurred in 9% of patients in the CEF group vs 1% of patients in the CMF group. Grade 3/4 thrombocytopenia was also slightly increased in the CEF arm. Grade ≥ 2 nausea and vomiting was reported in 51% and 42% of the patients receiving CEF vs 25% and 18% of patients in the CMF group (no 5-HT3 receptor antagonists were given). Stomatitis and alopecia also occurred more frequently in the CEF group. Despite the increased toxicity in the CEF group, 97% of patients in both the CEF and CMF groups completed all six cycles of therapy. The NCIC MA.5 trial reported a significantly better 5-year disease-free survival of 63% in the CEF group vs 53% in the CMF group (relative risk reduction = 29%). Overall survival at 5 years in the CEF group was 77%, compared to 70% with CMF (relative risk reduction = 19%). An update of this trial was presented at the San Antonio Breast Cancer Symposium in 2002 (median follow-up = 106 months).[19] The update showed that patients who received CEF adjuvant chemotherapy continued to have an improved survival at 10-year followup, as well as no statistically significant difference in late toxicity between CEF and CMF recipients. Specifically, the 10-year disease-free survival rate was 52% for patients who received CEF compared to 45% for CMF patients, and the 10-year overall survival was 62% and 58% for CEF and CMF patients, respectively. The rates of acute myeloid leukemia (AML) were unchanged since the original report (1% AML incidence in the CEF group vs 0.3% in the CMF group), while the rates of congestive heart failure were 1.1% in the CEF group vs 0.3% in the CMF group. In conclusion, the MA.5 trial demonstrated a benefit for CEF over CMF adjuvant chemotherapy that is maintained with longer follow-up.[19]

**European Trials**—Anthracycline-based chemotherapy can be used concurrently or sequentially as adjuvant therapy for early-stage breast cancer. Epirubicin has recently been evaluated as sequential therapy with CMF for adjuvant treatment. The National Epirubicin Adjuvant Trial (NEAT) and BR9601 trial were a combined prospective meta-analysis of two multicenter phase III randomized trials from the United Kingdom and Scotland, the results of which were presented by C. Poole at the 2003 ASCO meeting.[20] Patients were randomized to receive ECDF (epirubicin, 100 mg/m², for four cycles, followed by classical CMF for four cycles) vs CMF for six or eight cycles (NEAT: classical day-1-and-8 CMF every 4 weeks for six cycles; BR9601: IV 3-weekly CMF for eight cycles). The two studies analyzed a total of 2,391 women with node-positive and node-negative cancers who were eligible for adjuvant therapy. Toxicities were higher in the ECMF group, including nausea, vomiting, and alopecia. Febrile neutropenia was slightly higher in the ECMF group, at 13% vs 10%. There was no difference between the two groups in the number of second primaries. It is important to note that a significantly higher number of deaths on treatment were noted in the CMF group compared to the
ECMF group (13 vs 4 patients). The relapse-free survival rate was significantly better in the ECMF group-83% vs 77%-with a 31% reduction in recurrence. Overall survival was also significantly better in the ECMF group compared to the CMF group (88% vs 82.7%). In summary, sequential ECMF significantly prolongs relapse-free survival and overall survival compared to CMF adjuvant chemotherapy, and is justified as an option for standard anthracycline-based adjuvant therapy. Thus, this is another study that prospectively established the superiority of the anthracycline-containing regimen (compared to CMF alone).

**Anthracycline Toxicity**

- **Cardiac Dysfunction**—The long-term toxicities of the anthracyclines have been evaluated in several studies.[20,21] Doxorubicin is known to cause cardiac dysfunction; the incidence of cardiomyopathy and congestive heart failure secondary to this agent is dose-dependent, increasing substantially at cumulative doses greater than 500 mg/m². One study found that congestive heart failure occurred in 4% of patients who received a cumulative dose of 500 to 550 mg/m², compared to 36% of patients who received a dose greater than 601 mg/m².[20] Among women who receive the standard cumulative adjuvant doses of doxorubicin (≤ 300 mg/m²), congestive heart failure is uncommon (up to 1%), although radiation to the chest may increase the risk of cardiac toxicity from anthracyclines. Perez and colleagues recently reported data on the effect of four cycles of AC chemotherapy (doxorubicin at 60 mg/m², cyclophosphamide at 600 mg/m²) in 1,458 patients who participated in the NCCTG N9831 Intergroup adjuvant trial. This study demonstrated that "standard" AC is associated with frequent asymptomatic decreases in left-ventricular ejection fraction (LVEF). This includes reductions ≥ 15% in 2.5% of patients, and 2.9% with decreases of ≤ 15% but which fell below the lower limit of normal, with a 6.6% rate of grade 2 LVEF toxicity by NCI-CTC criteria.[20] Of note is the finding that the acute decrease in LVEF is reversible in the majority of patients receiving anthracyclines.

- **Secondary Hematologic Disease**—There is little evidence that the risk of second cancers, including treatment-related leukemia, is increased in women who receive CMF, and there is some information regarding treatment-related leukemia for anthracycline-based adjuvant regimens. In 2003, the NCIC reported the risk of acute leukemia following CMF and anthracycline-based adjuvant chemotherapy in 1,545 women.[22] At a follow-up of 8 years, the conditional probability of secondary acute leukemia was 1.7% among the 539 patients treated with CEF, 0.4% among 678 women who received CMF, and 1.3% among 231 patients treated with AC. In addition, the NSABP recently published results from six trials evaluating the incidence of AML and myelodysplastic syndrome (MDS) after AC adjuvant chemotherapy.[23] The development of AML/MDS was elevated in patients receiving the more intense regimens. In patients receiving two or four cycles of cyclophosphamide at 2,400 mg/m² with granulocyte colony-stimulating factor (G-CSF [Neupogen]) support, the cumulative incidence of AML/MDS at 5 years was 1.01%, compared with 0.21% for patients who were given standard AC. Patients who received breast radiotherapy experienced more secondary AML/MDS than did those who did not receive radiotherapy (relative risk = 2.38, P = .006). Thus, breast cancer patients treated with standard doses of anthracyclines may have a similar or slightly higher rate of secondary acute leukemia compared to CMF, which is slightly above that of the general population for the development of leukemia. The addition of radiation therapy may increase this risk.

**Summary**

Overall, we can conclude that CMF adjuvant chemotherapy is better than no treatment for early-stage breast cancer. For low-risk patients, the above studies conclude that six cycles of oral CMF or four cycles of AC every 3 weeks are equivalent in efficacy. Clinical trials that have incorporated doxorubicin and epirubicin into polychemotherapy regimens (CAF and CEF for six cycles) show a modest but clear benefit for anthracycline-based therapy compared to six cycles of CMF in adjuvant breast cancer. Based on these results, anthracycline therapy with six cycles of CAF or CEF is recommended for higher-risk patients (ie, node-positive patients), and may be used as a benchmark for newer regimens incorporating taxanes and other novel agents. It is important to note that six cycles of CAF/CEF chemotherapy regimens have not been directly compared to four or six cycles of AC in the adjuvant setting. Also, there is no current evidence of excessive cardiac toxicity in women with normal heart function who receive anthracyclines at the cumulative doses utilized in standard adjuvant programs. The trade-off for a small survival benefit with anthracyclines is a different treatment-related toxicity profile including higher incidences of alopecia, vomiting, and cytopenias compared to CMF. With the availability of effective antiemetics (5-HT3 receptor antagonists and NK1 inhibitors) and the use of growth factor support, most of these acute toxicities...
can be fairly manageable. Data regarding the long-term toxicities of anthracyclines demonstrate a low risk of cardiomyopathy and treatment-related leukemia. Overall, we seldom recommend CMF as adjuvant therapy in our practice, and most often recommend anthracycline-based therapy, although we remain very interested in the development of nonanthracycline combinations other than CMF.

**Alternatives to CMF and Anthracyclines**

**Paclitaxel**

- **Metastatic Breast Cancer**—Paclitaxel is a newer agent whose efficacy has been evaluated in both the metastatic and adjuvant breast cancer setting.[24-26] Overall response rates of 21% to 62% have been reported in phase II and III trials evaluating paclitaxel at doses of 135 to 250 mg/m² administered via either 3- or 24-hour infusions as initial or subsequent therapy in women with metastatic breast cancer. In a large phase III study by Bishop et al, 209 patients were randomized between paclitaxel (200 mg/m² every 3 weeks for eight cycles) or CMFP (cyclophosphamide at 100 mg/m²/d orally on days 1 to 14, methotrexate at 40 mg/m² IV on days 1 and 8, 5-FU at 600 mg/m² IV on days 1 and 8, and prednisone at 40 mg/m²/d orally on days 1 to 14) for six cycles, as first-line treatment for metastatic breast cancer.[24] Paclitaxel was significantly better tolerated than CMFP in regard to myelosuppression (febrile neutropenia rates were 10% vs 27% for paclitaxel and CMFP, respectively), nausea/vomiting, and mucositis. Women who received paclitaxel, however, had an increased incidence of neuropathy compared to CMFP. Median survival was significantly better in the paclitaxel arm at 17.3 months, compared with 13.9 months for patients who received CMFP. Recent reports of the activity and the tolerability of new schedules of paclitaxel have generated ongoing clinical interest. In women with metastatic breast cancer, studies administering paclitaxel weekly by 1-hour infusion at doses ranging from 80 to 100 mg/m² have reported overall response rates of 50% to 68%. Weekly paclitaxel also appears to be at least equally effective and well tolerated in older women. A large phase II study by Perez et al, evaluating weekly paclitaxel (80 mg/m²) for previously treated metastatic breast cancer, included 73 women age 65 or older and 139 women under 65.[25] The trial was conducted to better characterize the activity and safety of this therapy in women with metastatic breast cancer. Grade 3/4 neutropenia occurred in 31 patients (15%). Grade 3 neuropathy was encountered in 9% of patients. There were no substantial differences between the two age groups in the overall toxicity incidence or the incidence of grade 3/4 toxicities. The overall response rate was 21.5%, and disease stabilization occurred in 41.8% of patients. Thus, 63.3% of the patients who received weekly paclitaxel had some benefit from therapy. The rate of response observed in the older patient subgroup was similar to that observed in patients younger than age 65 years. Specifically, in the cohort of women aged ≥ 65, there were 11 partial responses (19.6%) and 28 patients with stable disease (50%). The optimal dosing schedule of paclitaxel at every 3 weeks or every week was compared in a randomized study presented by Green at the 2002 annual meeting of ASCO [27] and by Seidman at the 2004 ASCO meeting.[28] In the study by Green and colleagues, operable breast cancer patients were randomized to receive either weekly paclitaxel for 12 weeks or paclitaxel once every 3 weeks for four cycles. After this treatment, women in both arms received FAC chemotherapy (every 3 weeks for four cycles) followed by local treatment with or without tamoxifen, depending on receptor status. In an analysis of the results by schedule of paclitaxel, the therapeutic index was significantly enhanced when paclitaxel was given on a weekly schedule. Compared to the every-3-week schedule, weekly paclitaxel increased the pathologic complete response rate from 15% to 28%. Overall, the weekly lower dose of 80 mg/m² provided increased efficacy with decreased toxicity compared to the every-3-week paclitaxel 250 mg/m² regimen. A presentation of data of weekly vs every-3-week paclitaxel (with or without trastuzumab [Herceptin]) as first-line therapy for metastatic breast cancer from the CALGB 9840 study was highlighted at the 2004 ASCO meeting by the study’s principal investigator, A. Seidman.[29] This study demonstrated a response rate of 42% for the weekly regimen (doses from 100 mg to 80 mg/m²/wk) and 28% for the 175 mg/m² every-3-week paclitaxel schedule, $P = .017$. The median time to progression was also significantly improved with the weekly regimen (9 vs 5 months, $P = .0008$). Although the difference in overall survival did not reach statistical significance, it was 2 years for weekly and 1.3 years for the every-3-week schedule. Those studies of weekly paclitaxel demonstrating an improved therapeutic ratio compared to the previously standard every-3-week schedule can also be put in perspective with the TAX311 study, which demonstrated better outcomes in terms of response, time to progression, and a 2.5-month median survival difference when docetaxel at 100 mg/m² was compared to paclitaxel at 175 mg/m², both agents given every 3 weeks. Comparative data of weekly paclitaxel vs onceevery-3-week docetaxel are not available but would be of value for patient care.[28]
**Adjuvant Treatment**—Based on multiple studies reporting the efficacy of paclitaxel and docetaxel in the metastatic setting, several recent studies have incorporated these taxanes with anthracyclines for use in adjuvant breast cancer treatment. The CALGB 9344 trial showed a significant 5-year survival benefit of 80% vs 77% in women with lymph node-positive disease who received paclitaxel (175 mg/m\(^2\) over 3 hours every 3 weeks × 4) following four cycles of AC, compared to AC alone.[30] This significant trial led to the incorporation and recommendation of paclitaxel following AC administration for adjuvant polychemotherapy in women with lymph node-positive disease. The encouraging results of using paclitaxel with AC in the adjuvant setting led to the development of the CALGB 40101 Intergroup trial, which is currently under way. This study will evaluate high-risk, node-negative women (tumor > 1 cm, estrogen or progesterone receptor-negative), who are randomized in a 2:2 design. Based on the data that had been generated from weekly paclitaxel and the previous knowledge of AC chemotherapy administered every 3 weeks, this study was originally designed to compare those regimens (AC every 3 weeks for four or six cycles; paclitaxel weekly for 12 vs 18 weeks). However, for symmetry, the trial was recently modified to follow the 2-week schedule with all agents: AC (60 mg/m\(^2\) and 600 mg/m\(^2\)) every 2 weeks for four or six cycles, compared to paclitaxel (175 mg/m\(^2\)) every 2 weeks for four or six cycles, along with G-CSF (partially based on data from the C9741 Intergroup study). The end points of the study include disease-free survival, equivalence between AC and paclitaxel, determination of whether longer therapy is superior, induction of menopause, and survival. Thus, not only will the study directly compare paclitaxel with AC, but it will also address whether six cycles of AC are more effective than four cycles. One challenging aspect of this CALGB 40101 Intergroup study is that there are no prospective data for every-2-week AC in the metastatic setting, and based on the GONO MIG1 report by Venturini and colleagues, there may not be an efficacy advantage to administering an anthracycline-based adjuvant regimen (FEC) in a so-called "dose dense" every-2-week schedule with G-CSF vs the same FEC regimen at a more standard once-every-3-week schedule.[31] Another important trial is the Breast Cancer International Research Group (BCIRG) 001 study, which demonstrated improvements in disease-free survival and overall survival with six cycles of TAC (docetaxel, doxorubicin, cyclophosphamide) vs FAC (5-FU, doxorubicin, cyclophosphamide) in patients with resected node-positive breast cancer.[28]

**Summary**—The taxanes have proven to be among the most active agents in metastatic breast cancer. As a result, several studies have explored the clinical utility of adding paclitaxel to the standard AC regimen in the adjuvant treatment of node-positive, localized breast cancer. Although a number of such trials have completed accrual and others remain in progress and appear promising, currently available data are inconclusive and do not permit definitive recommendations regarding the impact of the taxanes on either relapse-free or overall survival. Also, there is currently no evidence to recommend adjuvant taxanes in node-negative breast cancer outside the setting of a clinical trial. For patients with lymph node-positive cancer, AC followed by paclitaxel or CAF/CEF should be used. Early evidence from a single trial suggests that TAC (paclitaxel [Taxol], doxorubicin, cyclophosphamide) chemotherapy may be superior to CAF in the adjuvant treatment of node-positive disease.[32]

**Capecitabine**
Capecitabine (Xeloda), an oral fluoropyrimidine, has recently been evaluated in the adjuvant setting. The response data of single-agent capecitabine ranges from approximately 20% to 30% in patients with metastatic disease who had previously been treated with anthracyclines and taxanes. Doses of 1,500 mg/m\(^2\) and 2,000 mg/m\(^2\) have been commonly used in practice as single-agent therapy (although the approved dose by regulatory agencies is 2,500 mg/m\(^2\)/d). Encouraging results using capecitabine for metastatic disease have led to the development of phase III trials comparing capecitabine in the adjuvant setting. The CALGB 49907 Intergroup trial, which is currently accruing patients, compares capecitabine with "standard" polychemotherapy for adjuvant treatment in older women. Specifically, CALGB 49907 will randomize elderly women (≥ age 65, including patients > age 80) with either node-positive or high-risk nodenegative disease (tumor > 3 cm) to receive capecitabine, AC, or CMF for adjuvant chemotherapy. The choice of AC or CMF will be the physician/patient preference, and oral cyclophosphamide will be used. The dose of capecitabine is 2,000 mg/m\(^2\)/(on days 1 to 14) or 1,500 mg/m\(^2\) in patients with a creatinine clearance of 30 to 50 mL/min. This CALGB 49907 Intergroup trial plans to accrue 1,800 women over 6 years. This study will not only report efficacy, but it will also evaluate quality of life in terms of physical, cognitive, social, and emotional functioning. Given that patients who are older than 65 comprise 60% of all cancer patients, treatments that retain or improve quality of life are essential and in need of ongoing study.
Other Adjuvant Chemotherapy Combinations

Encouraging results with the taxanes and capecitabine have led to additional trials using nonanthracycline combinations for the treatment of breast cancer. A prospective randomized trial presented at the 2003 ASCO meeting by S. Jones, compared four cycles of standard-dose AC (60/600 mg/m²) to four cycles of TC (docetaxel [Taxotere]/cyclophosphamide, 75/600 mg/m² every 3 weeks) in 1,016 stage I-III patients as adjuvant chemotherapy.[33] At a median follow-up of 36 months, there were 49 (n = 510) relapses in the AC group compared to 34 (n = 506) among patients who received TC. In the AC group, 15 deaths from cancer were reported, and in the TC group, there were 17 deaths from cancer. Although this study may be underpowered to reach definite conclusions, a trend toward longer disease-free survival was observed with TC compared to AC (a 21% relative risk reduction of recurrence at 3 years). Longer follow-up is necessary to determine if TC is more effective than AC in the adjuvant setting. However, TC could be considered as adjuvant therapy in women with a contraindication to anthracyclines (eg, prior anthracycline use, cardiac disease). The combination of paclitaxel and carboplatin (Paraplatin) has also been evaluated and found to be a possible effective alternative for first-line metastatic treatment.[34] Every-3-week and weekly regimens have been studied with similar response rates of approximately 62%. Other reasonable considerations for combination chemotherapy that are being evaluated include docetaxel (Taxotere)/carboplatin, docetaxel/ capecitabine, and paclitaxel/gemcitabine (Gemzar).[35-37] Based on the response rates of these newer combinations in women with metastatic breast cancer, future clinical trials may involve new chemotherapy combinations to be tested in the adjuvant setting.

One of these trials is the recently activated NSABP B-38 study, which compares TAC every 3 weeks for 6 weeks vs AC and T every 2 weeks with eight total doses vs AC and GT every 2 weeks for a total of eight doses. The T in TAC is docetaxel, whereas paclitaxel is being used in the sequential AC-with-T and AC-with-GT arms. The every-2-week schedules of GT (gemcitabine plus paclitaxel) are based on excellent phase II studies demonstrating high efficacy and improved mild toxicity (with high dose intensity) when taxanes and gemcitabine are given on this biweekly schedule. Some general options for testing new adjuvant combinations are listed in Table 2.

Molecular Predictors

Although advances in the selection of anthracycline vs nonanthracycline adjuvant regimens have been made on the basis of clinical trials, much more work is needed to optimize and individualize patient treatment. A promising new direction is the exploration and identification of molecular markers as predictive factors to help individualize therapy. Using molecular markers, physicians can recognize women at high risk and better predict response to certain chemotherapy. HER2, topoisomerase II-alpha, and p53 mutations or abnormalities as well
as gene profiling, are a few of the recent molecular markers that have been identified and studied in breast cancer in relation to anthracycline- vs nonanthracycline-based therapy.

<table>
<thead>
<tr>
<th>Table 3</th>
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<tr>
<td>Clinical Trials Showing Beneficial Effect of Adjuvant Anthracyclines In HER2-Positive Patients</td>
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<tr>
<td>NSABP B-15, 2000[37]</td>
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<td>CALGB 8541, 1994[38]</td>
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<td>CALGB 8869, 1998[39]</td>
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<td>NSABP B-11, 1998[40]</td>
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<td>SWOG 8814, 1998[41]</td>
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<td>NCIC CTG MA.5, 2002[17]</td>
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- **p53 Gene**—The tumor suppressor gene p53 has an important role in the induction of cellular apoptosis. Intact p53 plays a critical role in cell death and in response to treatment with cytotoxic drugs. Laboratory studies have demonstrated that certain p53 mutations are associated with anthracycline resistance and the prevention of anthracycline-induced apoptosis. It is possible that p53 mutations could hamper the response to anthracyclines even in tumors carrying topoisomerase II-alpha gene amplifications. Clinically, there are preliminary studies reporting data that links specific mutations in the p53 gene to primary resistance to doxorubicin therapy and early relapse in breast cancer patients. A study by Aas et al published in 1996 found data linking specific mutations in the p53 gene to primary resistance to doxorubicin as well as early relapse in breast cancer patients.[38]

- **HER2/neu Expression**—The c-erbB-2 amplification and expression of its protein HER2/neu is found in approximately 20% to 30% of newly diagnosed breast cancer cases. Recent data support HER2/neu expression as a marker of increased sensitivity to anthracycline therapy. As listed in Table 3, [17,39-43] many large studies have retrospectively found a predictive effect of HER2/neu expression, with an added benefit of using adjuvant anthracyclines. Based on these results, it is recommended that doxorubicin-based therapy in general (rather than CMF-based treatment) be added in patients with HER2/neu-positive tumors eligible for adjuvant therapy. An interesting corollary to this situation is the recently reported benefit of using paclitaxel instead of cyclophosphamide, both combined with epirubicin, in the setting of HER2-positive metastatic breast cancer.[44]

- **Topoisomerase II-alpha**—It has recently been suggested that the molecular marker topoisomerase II-alpha may be the main predictor for tumor responsiveness to anthracyclines, and that the predictive value of HER2 is most likely related to the concomitant amplification of the topoisomerase II-alpha gene. Topoisomerase II-alpha is the molecular enzyme target for the action of anthracycline-based chemotherapy (Table 4). In vitro data, including a study by Jarvinen et al in 2000, have established a direct correlation between sensitivity to anthracycline drugs and intracellular topoisomerase II-alpha expression levels.[45] This and several additional studies have confirmed that aberrations (amplifications/deletions) in the topoisomerase II-alpha gene are found...
only in HER2-amplified tumors. This is thought to be due to the close physical proximity of the topoisomerase II-alpha gene to the erbB-2 oncogene on chromosome 17.

Further studies have suggested that HER2-amplified breast cancer has different degrees of sensitivity to anthracyclines according to the topoisomerase II-alpha gene aberration. The in vitro study by Jarvinen et al studied nine breast cancer cell lines and 97 clinical breast tumors.[45] The HER2/neu-amplified breast cancer cell lines and tumors with topoisomerase II-alpha gene amplification showed an increased sensitivity to doxorubicin. Specifically, topoisomerase II-alpha-amplified cells were associated with a 5.9-fold increased topoisomerase II-alpha protein expression and a 2.5-fold increased sensitivity to doxorubicin. In contrast, cell lines that expressed a normal or deleted topoisomerase II-alpha gene had a decreased sensitivity to anthracyclines (which was most pronounced in the deleted group). In vivo data published by DiLeo et al in 2002, correlated the superiority of anthracycline-based regimens over CMF in HER2-positive tumors with topoisomerase II-alpha amplification.[46] In this study, HER2 and topoisomerase II-alpha gene aberrations were analyzed by fluorescence in situ hybridization in 430 breast cancer samples from women with lymph node-positive disease who had randomly received an anthracycline- or CMF-based adjuvant regimen. Thirty-eight percent of HER2-positive samples were found to have topoisomerase II-alpha gene amplifications. Although patient numbers in the study were small, findings showed a much better response to anthracyclines in cases with topoisomerase II-alpha gene amplification compared to the CMF group (hazard ratio = 1.65). With a median 4-year follow-up, disease-free survival was improved in HER2-positive and topoisomerase II-alpha-amplified patients who received anthracyline therapy, compared to CMF chemotherapy. This benefit was not found in the nonamplified group. Similar results have been found with topoisomerase II-alpha amplification and response to epirubicin. DiLeo et al presented a study at the 2002 annual ASCO meeting, demonstrating topoisomerase II-alpha gene amplification in HER2-positive tumors, and defining a subgroup of patients with a significantly higher clinical response than HER2-positive patients without topoisomerase II-alpha gene amplification (79% vs 35%).[44] The above studies have shown that topoisomerase II-alpha aberrations are present in approximately 40% to 90% of HER2/neu-positive breast cancers. Therefore, it is estimated that amplifications of the topoisomerase II-alpha gene could comprise approximately 5% to 15% of all patients diagnosed with breast cancer. Continued findings in the field of molecular research (with gene profiling and other specific markers) will ultimately affect many women diagnosed with breast cancer and may help individualize the choice of therapy in the near future.

Conclusions
Substantial progress has been made in the treatment of breast cancer over the past 15 years. The decreasing mortality rate in breast cancer patients is in part due to adjuvant systemic therapy. Indeed, adjuvant polychemotherapy should be discussed with all women who have primary breast cancers larger than 1 cm, irrespective of age and nodal status, and may be considered in patients with even smaller tumors based on grade and other biologic characteristics. When considering treatment for early-stage breast cancer, CMF adjuvant chemotherapy is better than no treatment. For low-risk patients, six cycles of oral CMF or four cycles of AC every 3 weeks are equivalent in
efficacy. Whether four cycles of AC are "enough" is a subject currently under investigation. Patients who seem to particularly benefit from an anthracycline-based therapy are higher-risk patients and HER2/neu-positive patients. The decision of whether to use an anthracycline in adjuvant therapy should take into account the potential survival benefits vs specific concern about short-term additional toxicity, with minimal risk of treatment-related leukemia or cardiac events at the recommended doses. Specifically, anthracyclines are usually contraindicated in women with underlying heart disease, or women who have received prior anthracycline therapy for a previous breast cancer. Taxanes are now being added to anthracyclines in adjuvant treatment for women with lymph node-positive cancer, and are currently under evaluation for use in node-negative adjuvant therapy. In the future, continued research with molecular markers in breast cancer, such as topoisomerase II-alpha and genetic profiling, could help further delineate the specific patient for whom anthracyclines should (or should not) be an option. For now, anthracyclines are standard for the majority of patients, but we eagerly search for alternatives such as taxanes with other chemotherapeutic agents (eg, carboplatin, capecitabine, and gemcitabine) or to-be-determined targeted molecular therapies.

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