Mortality from breast cancer continues to decline in North America and other parts of the world (1,2). This improvement was initially attributed to widespread adoption of mammography screening recommendations. However, much of the recent ongoing decline in breast cancer mortality is most likely a result of the increased use of systemic adjuvant chemotherapy and hormonal therapy. The benefit from adjuvant treatment is observed not only in women with axillary lymph node–positive disease but also in women diagnosed with the most common presentation in North America: axillary lymph node–negative breast cancer. For patients with
hormone receptor–negative breast cancer, systemic chemotherapy improves the odds of disease-free and overall survival to the same relative degree as it does for patients with lymph node–positive disease, whereas hormonal therapy such as tamoxifen is not helpful for patients with receptor-negative disease. A meta-analysis of worldwide adjuvant clinical trials by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) demonstrated statistically significant reductions in 10-year recurrence and death as a result of chemotherapy in receptor-negative, lymph node–negative, and lymph node–positive breast cancer (3).

Three trials of the National Surgical Adjuvant Breast and Bowel Project (NSABP), updated in this issue of the Journal (4), contributed to the lymph node–negative, receptor-negative portion of the EBCTCG overview. The first chronologically was NSABP B-13 (5), which along with the North American Intergroup trial (6), was a pivotal phase III trial in receptor-negative, lymph node–negative disease. Using surgery-only control women, both trials provided the first documentation of the worth of adjuvant chemotherapy in this group of patients with early-stage breast cancer. The NSABP B-13 trial was followed by B-19 (7), which showed that the classic CMF regimen (oral cyclophosphamide, intravenous 5-fluorouracil, and intravenous methotrexate) given for six cycles was superior to the sequential MF program studied in B-13, although MF was given for 6 months in B-19, versus 12 months in B-13. Rounding out the trio of sequential NSABP phase III trials in this population was B-23 (8), a study that was disappointing for the popular four-cycle regimen AC (intravenous doxorubicin and cyclophosphamide), in that this anthracycline-containing program was not superior to CMF overall.

The report in this issue (4) is important because although no new findings pertaining to the primary objectives of each of the three trials as originally published are presented, long-term follow-up provides solid evidence regarding the role of adjuvant chemotherapy in increasing survival in lymph node–negative, receptor-negative disease. Of the 3863 women enrolled on the B-13, B-19, and B-23 studies, 3760 (97.3%) were eligible, with follow-up for 16, 13, and 8 years, respectively. The surgery-alone control arm of B-13 demonstrated that despite negative lymph nodes, only 63% of these women were free of recurrence after 16 years. This statistic again presents a challenge to clinical trialists: to define and validate prognostic profiles that will identify the 63% with lymph node–negative, receptor-negative breast cancer who are cured with surgery alone and who thus can avoid chemotherapy. These efforts are actively underway with molecular profiling of tumors, serum proteomics, and other collaborative translational efforts using banked specimens and national cooperative group trial databases.

The favorable survival impact of systemic adjuvant chemotherapy compared with surgery alone in axillary lymph node–negative, receptor-negative breast cancer is underscored in the NSABP update of long-term outcomes (4). Because these trials had nearly identical eligibility requirements and were conducted sequentially by the same group of investigators with state-of-the-art monitoring, this type of analysis presented by the authors—one in which the trials are interrelated—can be justified as useful for validation of earlier results and for hypothesis generation. The MF regimen resulted in a 9% absolute improvement in recurrence-free survival over surgery alone or a 32% relative reduction in recurrence. For overall survival the benefit was 4%, a 17% relative improvement. However, for either CMF or AC, the absolute impact on recurrence-free survival over surgery alone was 16%, a 58% relative reduction in recurrence; for overall survival the benefit was 8% (40% relative improvement). In most analyses, the major improvement was in the reduction of local-regional disease, although distant metastases were reduced as well. Thus, when these three regimens are under consideration for a given patient, CMF or AC should in general be chosen over the MF program.

Multiple subset analyses are presented by the authors, most of which were planned, although others were unplanned and thus must be considered exploratory. Those pertaining to age and treatment benefit are of greatest interest. In the planned analyses, it is clear that the benefit of chemotherapy (versus surgery alone) extends to women of all ages who fit the eligibility criteria of these trials. For CMF and MF, there were no significant age-by-treatment interactions or menopausal status-by-treatment interactions for either recurrence-free or overall survival (4). However, in B-23, the interaction term was statistically significant for recurrence-free survival in the menopausal status-by-treatment analysis. That is, AC appeared to benefit postmenopausal women, whereas for premenopausal women AC and CMF afforded similar benefit (interaction P = .022 for recurrence-free survival and P = .089 for overall survival). Regarding age, women 60 years or older had an absolute improvement in recurrence-free and overall survival from AC over CMF of 5% and 7%, respectively, which corresponded to reductions in recurrence and mortality of 34% and 42%. These data are in line with many reports of a relative lack of benefit of CMF-based regimens in postmenopausal women with positive axillary lymph nodes (compared with its benefit in premenopausal women) but are in contrast with data from other clinical trials that found definite improvements in recurrence-free and overall survival when anthracycline-based programs were used in postmenopausal women (9,10).

Given the lack of a statistically significant overall interaction between age and treatment benefit in the planned analyses, the authors’ conclusion in the abstract and discussion that the degree of benefit from chemotherapy is age related prompts further scrutiny. The basis for this conclusion was an interesting exploratory analysis that related recurrence rate to age as a continuous variable according to a statistical “smoothing method” approach (11). This analysis showed that a decrease in the degree of chemotherapy benefit on recurrence-free survival with age was primarily due to a decrease in recurrences with increasing age in the surgery-only arm of B-13. Also, although the benefit to recurrence-free survival of CMF appeared to decrease with age (counter to the lack of a statistically significant age-by-treatment interaction in the main analysis), the benefit to AC persisted in older women. As the authors state, these exploratory analyses must be viewed with caution. There are, in fact, other data that do not support the authors’ conclusions regarding lower recurrence rates by age. For example, Singh et al. (12) demonstrated that in a Cox multivariable model, age (by decade) extends to women of all ages without major comorbidities, adjuvant chemotherapy should be considered for women with higher-risk, lymph node–negative, receptor-negative breast cancer. And, as women age, perhaps the anthracycline-containing regimens provide optimal benefit.
During the late 1980s and early 1990s, adjuvant tamoxifen was often prescribed on an ad hoc basis for women with receptor-negative breast cancer and was allowed as an optional treatment in many clinical trials. A possible favorable survival impact from tamoxifen was studied in two of these trials: NSABP B-23 (8) and the intergroup trial 0100 (SWOG-8814). The authors state that the B-23 findings conflict with the conclusions of the second main objective of intergroup 0100, which in their view seem “tenuous.” These conclusions were that for postmenopausal women with receptor-positive lymph node–positive breast cancer, the disease-free and overall survival benefits of CAF (oral cyclophosphamide, intravenous doxorubicin, and intravenous 5-fluorouracil) plus tamoxifen versus tamoxifen alone were optimized when tamoxifen was given after CAF rather than concurrently with CAF (9,14). However, the design of B-23 does not directly address this question, because it neither provides randomized data on the timing of tamoxifen with chemotherapy nor studies receptor-positive disease, the very group in which an interaction of tamoxifen timing with chemotherapy would be postulated to occur. Furthermore, in intergroup 0100 there was still a benefit to CAF when given concurrently with tamoxifen, although it was not nearly as great as when CAF was given before the start of tamoxifen. Although there is no rationale today to prescribe tamoxifen for women with receptor-negative disease (for reduction in recurrences or second primaries), the B-23 trial confirms that doing so does not abrogate the benefit of chemotherapy. However, when the disease is receptor positive, there is a clear interaction between the amount of chemotherapy benefit and the timing of tamoxifen administration.

The updated results of the sequential NSABP trials in lymph node–negative, receptor-negative breast cancer add to the growing international database that confirms the lasting benefit of adjuvant chemotherapy. This report provides reassurance for those considering AC or CMF in the adjuvant setting in this cohort. However, women with higher-risk, lymph node–negative disease have survival potentials that are, at best, no better than those of many subsets of lymph node–positive disease. Given that the proportional benefits to adjuvant therapy are the same in both nodal groups (3), other regimens proven to be superior to AC or CMF in predominately lymph node–positive disease, as well as regimens actively under study as a result of their benefits in locally advanced disease, should be preferred for this group with higher-risk, lymph node–negative disease as well. These regimens include CAF, CEF (oral cyclophosphamide, intravenous epirubicin, intravenous 5-fluorouracil), AC followed by docetaxel, dose-dense AC or EC (intravenous epirubicin and cyclophosphamide) followed by paclitaxel, taxane-based triplets such as TAC (where T is docetaxel), and metronomic therapy with continuous AC followed by paclitaxel (9,13,15–20). Indeed, many current clinical trials allow entry of patients with either high-risk lymph node–negative or lymph node–positive disease. If the increase in cure rates in early breast cancer are to continue, among our highest clinical research priorities should be increased accrual to ongoing clinical trials along with research efforts dedicated to determining who should get chemotherapy and who should not and, for those who should, what regimen will best target the molecular profile and biology of an individual’s breast cancer.

REFERENCES


