Adjuvant Chemotherapy for Postmenopausal Lymph Node-Negative Breast Cancer: It Ain’t Necessarily So

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De ‘tings dat yo li’ble
To read in de Bible
It ain’t necessarily so . . .

—Ira and George Gershwin, *Porgy and Bess* (1935)

Adjuvant chemotherapy in older women diagnosed with low-risk, estrogen receptor (ER)-positive breast cancer still inspires controversy. In fact, there is very little information on polychemotherapy in women aged 70 years or older (1), a direct result of our long-standing failure as cancer investigators to recruit older women to clinical trials. In this issue of the Journal, the International Breast Cancer Study Group (IBCSG) presents the results of the IBCSG Trial IX (2). Between 1988 and 1999, 1669 postmenopausal women with lymph node-negative breast cancer were stratified by ER status and randomly assigned to receive either 5 years of tamoxifen alone or three cycles of “classical” CMF (oral cyclophosphamide on days 1–14 plus intravenous methotrexate and 5-fluorouracil on days 1 and 8, repeated every 28 days), followed by 5 years of tamoxifen. An interesting feature of this tamoxifen-based trial is that patients with ER-negative disease continued to be enrolled until the most recent publication of the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) tamoxifen overview in 1998 (3). This design *de facto* created two studies within the same trial: one study examining the role of CMF followed by tamoxifen versus tamoxifen alone in 1217 postmenopausal women with lymph node-negative, ER-positive breast cancer and a second study comparing the same regimens in 382 postmenopausal women with lymph node-negative, ER-negative breast cancer. The results indicate no benefit from the addition of chemotherapy to tamoxifen in the larger ER-positive stratum but show a statistically significant and meaningful survival benefit in the smaller ER-negative stratum.

The IBCSG findings in lymph node-negative, ER-positive patients must be viewed in the context of two other important pieces of evidence: the 1995 EBCTCG overview of polychemotherapy for early breast cancer (1) and the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-20 trial (4), which enrolled 2306 pre- and postmenopausal lymph node-negative, ER-positive breast cancer patients. These patients received 5 years of tamoxifen alone versus six cycles (rather than three cycles) of classical CMF or MF with concurrent initiation of 5 years of tamoxifen.

The 1995 overview included data from 18,000 women in 47 trials of prolonged chemotherapy versus no chemotherapy. This overview analysis showed an overall benefit from the addition of 3–6 months of polychemotherapy to tamoxifen versus tamoxifen alone with statistically significant reductions in the annual odds of recurrence (19% ± 3% [mean ± standard deviation]) and death (11% ± 4%) (1). Within each age category, the proportional risk reduction with polychemotherapy was the same with or without adjuvant tamoxifen, but the 1995 overview indicated a greater proportional risk reduction with polychemotherapy that favored younger women over older women (1). In contrast, the proportional risk reduction in the annual odds of recurrence (47% ± 3%) and death (26% ± 4%) observed with 5 years of tamoxifen was not affected by age (3). A limitation of these data is that three of the largest trials ever conducted on the role of chemotherapy when added to tamoxifen had been activated shortly before 1990 and, therefore, were not included in the 1995 overview. These trials were IBCSG IX (1669 postmenopausal patients) and NSABP B-20 (2306 pre- and postmenopausal patients) in lymph node-negative disease and Southwest Oncology Group (SWOG) 8814/Intergroup Trial (INT) 0100 (1477 postmenopausal patients) in lymph node-positive disease (5).

The IBCSG IX trial recruited 1217 patients with ER-positive disease. These patients were all likely to be postmenopausal because of a more detailed (and more precise) definition of menopause that took into account age and history of amenorrhea compared with the age criteria used by the NSABP. In fact, as noted by the IBCSG IX investigators, it is possible that some (or many) of the 358 women aged 50–54 years among the 1264 women enrolled in the aged-50-years-or-older stratum of NSABP B-20 were peri- or premenopausal at study entry. This is a group in which at least some of the benefit obtained with cytotoxic chemotherapy could be compounded by its temporary or permanent ovarian suppression effect, which could add to the antiestrogen effects of tamoxifen in premenopausal women. The accrual figures further substantiate the claim from the IBCSG IX investigators that this is the largest trial examining the role of chemotherapy followed by tamoxifen in a lymph node-negative, postmenopausal population, even if only the ER-positive stratum is considered. Its sample size allowed a statistical design with 80% power to detect a 33% relative reduction in relapse risk in the ER-positive stratum and a 50% relative reduction in the ER-negative stratum. The 5-year results are quite clear: At this time, there is no observed benefit from the addition of CMF followed by tamoxifen in the larger ER-positive stratum for either disease-free survival (DFS; relative risk [RR] = 0.99, 95%
confidence interval [CI] = 0.75 to 1.30) or overall survival (OS; RR = 0.95, 95% CI = 0.64 to 1.40). These results are not likely to change with further follow-up. However, there is a substantial benefit in the smaller ER-negative stratum for both DFS (RR = 0.52, 95% CI = 0.34 to 0.79) and OS (RR = 0.51, 95% CI = 0.30 to 0.87). An impromptu cross-stratum comparison suggests that CMF in ER-negative patients offers a 5-year DFS benefit (84%) similar to that seen with tamoxifen alone (85%) or with tamoxifen and three cycles of CMF (84%) in ER-positive patients.

NSABP B-20 (tamoxifen ± six cycles of CMF or MF) was designed to address concerns regarding the clinically significant residual risk of distant metastases (25% at 10 years) seen in so-called “good-risk” lymph node-negative, ER-positive patients treated with 5 years of tamoxifen in NSABP B-14 (6). Patient characteristics in the ER-positive stratum of the IBCSG IX trial and in the NSABP B-20 trial were quite similar. At a median follow-up of 77 months, younger patients had a more statistically significant reduction in the risk of events with the addition of chemotherapy (e.g., CMFT group RR = 0.56, 95% CI = 0.38 to 0.83), not dissimilar to the polychemotherapy findings in the overview. However, the reported benefit from chemotherapy in patients aged 50 years or older trended toward a benefit but did not reach statistical significance (MFT group, RR = 0.90, 95% CI = 0.64 to 1.25; CMFT group, RR = 0.74, 95% CI = 0.52 to 1.05) (4). An update of the results at 8 years confirms a clear-cut benefit for the whole group (DFS, 92% versus 88%, P = .018; OS, 84% versus 77%, P = .001) (7). Therefore, it is possible that a statistically significant chemotherapy benefit is seen in women aged 50 years or older might have already emerged if there had been a larger sample size (i.e., more events). The concurrent (as compared with sequential) initiation of tamoxifen with chemotherapy may also have blunted the chemotherapy benefit seen in NSABP B-20 in view of the recent update from SWOG 8814/INT 0100, which indicated an apparent disadvantage of concurrent versus sequential chemotherapy and tamoxifen with regard to survival (8).

Potential limitations of the IBCSG IX trial include the duration of CMF and the use of a nonanthracycline regimen. The 1995 overview on polychemotherapy does not permit a comparison of 6 months versus fewer months, and other studies have tried to address this issue primarily in lymph node-positive patients (9,10). Three cycles of CMF in months 1–3 added to the benefit from tamoxifen in the ER-negative patient subset (n = 470) of IBCSG VII (hazard ratio [HR] = 0.67, 95% CI = 0.50 to 0.91), a four-arm study (n = 1266) in a higher-risk postmenopausal lymph node-positive population (11). However, there was no overall survival benefit, and few patients older than 64 years were enrolled (12). Although it is not known whether chemotherapy would have added benefit to tamoxifen if six cycles had been used instead of three cycles, the statistically nonsignificant trend favoring the addition of MF or CMF in older patients noted in NSABP B-20 suggests a duration effect.

The 1995 overview showed that anthracycline-based regimens offered an additional proportional reduction in the annual odds of recurrence (12% ± 4%) and death (11% ± 5%) compared with CMF-based regimens. Results from SWOG 8814/INT 0100 demonstrate a survival advantage from the addition of CAF (oral cyclophosphamide, doxorubicin, and 5-fluorouracil) to 5 years of tamoxifen versus tamoxifen alone in postmenopausal women with lymph node-positive, receptor-positive breast cancer (5). However, there is little information on the addition of anthracycline-based regimens to tamoxifen in postmenopausal lymph node-negative patients.

What are the possible explanations for the chemotherapy benefit in IBCSG IX in lymph node-negative breast cancer to be restricted to patients with ER-negative disease? The survival benefit seen with the addition of just a few cycles of a cytotoxic regimen in the smaller ER-negative stratum of IBCSG IX might be explained by two factors. First, this group with endocrine-nonresponsive disease had a much greater risk of recurrence (DFS = 69%; OS = 81%) in the absence of any effective therapy compared with the ER-positive group treated with effective endocrine therapy (DFS = 85%; OS = 93%). Second, a more intrinsic explanation takes us back a quarter century to a report by Lippman et al. (13), suggesting a strong correlation between responsiveness to chemotherapy and ER-negative disease. Therefore, ER-negative status would indicate a tumor not amenable to endocrine manipulation but more responsive to cytotoxic chemotherapy (predictive factor) and would also serve as a surrogate marker for a more aggressive biologic behavior (prognostic factor).

Although it is often simpler to focus primarily on recurrence and survival rates, the true benefit from any therapy must take into account the impact of therapy on quality of life (QOL), especially when dealing with an older population. IBCSG IX showed a short-term (and transient) negative impact from three cycles of CMF on QOL domains, though it was not sufficient to justify withholding therapy. A reexamination of the larger database in the 1995 overview using the quality-adjusted time without symptoms of disease and toxicity of treatment (Q-TWiST) method is not pertinent, because the overview was influenced by the overrepresentation of ER-negative tumors among older patients with lymph node-negative disease, who are more likely to benefit from adjuvant chemotherapy (14).

What are the implications of IBCSG IX for our daily practice? It clearly confirms the survival benefit from a short course of CMF in older women with lymph node-negative, endocrine-unresponsive disease, with minimal long-term impact on QOL. It also reinforces the cautionary tone that already permeates the most recent clinical practice guidelines and consensus statements regarding the use of chemotherapy in similar patients with endocrine-responsive disease who will receive 5 years of adjuvant tamoxifen therapy (15–17).

Perhaps the most important legacy from these trials is a wake-up call to the research community. Breast cancer is a disease of older women, and the population of developed countries is not getting any younger. It is estimated that the projected growth and aging of the U.S. population will result in a doubling of the cancer incidence rate in the next half century (18). We must increase accrual of older women to clinical trials in general, especially to studies designed to examine survival benefits within the context of QOL domains. We agree with the IBCSG IX investigators that the development of new endocrine approaches holds the potential to further improve on the results observed with 5 years of tamoxifen in postmenopausal women with lymph node-negative, endocrine-responsive disease. However, patients with both endocrine-responsive and endocrine-nonresponsive disease will also likely benefit from the development of new and effective chemotherapy agents with a lower toxicity profile and from the development of novel molecularly targeted strategies.
that can be used more selectively and with a greater therapeutic ratio.

REFERENCES


