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Focus On

Modest benefits of adjuvant chemotherapy in hormone receptor-positive breast cancer

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The benefits of adjuvant chemotherapy, endocrine therapy, and trastuzumab therapy are well-established in patients with early breast cancer. Further, there are patient and tumor characteristics that can assist in predicting which patients are more likely to benefit from specific adjuvant therapies. For example, patients whose tumors express estrogen and/or progesterone receptors (ER/PR) derive significant benefit from adjuvant endocrine therapy, whereas those whose tumors do not express these receptors derive very little or no benefit from endocrine therapy [1]. Patients whose tumors overexpress HER2 experience profound benefits from treatment with adjuvant trastuzumab [2,3]. We have recently begun to understand that ER/PR-positive breast cancer also responds differently to chemotherapy than its hormone receptor-negative counterpart. This is not, however, entirely new information. As early as 1978, it was retrospectively observed that ER-positive metastatic breast cancer had lower response rates to a variety of older chemotherapy regimens than did ER-negative disease [4].

In 2001, an analysis of IBCSG, SWOG, and NSABP trial data examined disease-free survival (DFS) and relapse-free survival (RFS) for ER-positive vs. ER-negative cohorts separately for younger ($<$35 years old) and older ($\geqslant$35 years old) premenopausal women enrolled in chemotherapy-only treatment groups. This study demonstrated a consistent pattern that chemotherapy was of less benefit for young patients with ER-positive vs. ER-negative tumors when treated with chemotherapy alone [5]. In 2002, the International Breast Cancer Study Group (IBCSG) reported the results of Trial IX, which randomized postmenopausal patients with axillary lymph node-negative breast cancer to cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) followed by tamoxifen vs. tamoxifen alone [6]. The added benefit of CMF followed by tamoxifen over tamoxifen alone was dependent on ER status. For ER-negative tumors, the addition of CMF improved DFS (5-year DFS risk ratio 0.52, 95% CI = 0.34–0.79; $P = 0.003$) and overall survival (OS) (5-year OS risk ratio 0.51, 95% CI = 0.30–0.87; $P = 0.01$), but for patients with ER-positive tumors, addition of CMF provided no benefit in terms of DFS or OS (5-year DFS risk ratio 0.99, 95% CI = 0.75–1.3 and 5-year OS risk ratio 0.95, 95% CI = 0.64–1.4). Further analysis examining quantitative ER values demonstrated a strong treatment effect associated with adding chemotherapy for patients with tumors expressing no or low levels of ER compared with virtually no improvement in DFS for patients with tumors having higher values of ER.

NSABP B-20 randomized 1577 patients with ER-positive, axillary lymph node-negative tumors to tamoxifen alone vs. CMF followed by tamoxifen [7]. The study demonstrated that the overall population derived benefit from the addition of chemotherapy to tamoxifen in RFS and OS. When the same endpoints were assessed according to age, patients aged 49 years or younger had significantly better outcomes when treated with CMF followed by tamoxifen than did those who received tamoxifen alone (see Table 1). In women aged 50–59, the advantage of CMF followed by tamoxifen over tamoxifen was significant for RFS but only of borderline significance for OS, and in women 60 years of age or older, no advantage was seen in either outcome when CMF was given with tamoxifen. When patients were grouped according to

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tumor ER concentrations, there was a trend toward greater benefit in RFS from the addition of CMF in women with lower concentrations of ER, and OS benefit from the addition of CMF was greater in women with lower tumor ER concentrations than with higher tumor ER concentrations (see Table 1). The ER concentrations were significantly higher in the tumors of women who were postmenopausal or aged 60 years or older than in those of women who were premenopausal or younger. Finally, the recent update of the Early Breast Cancer Trialists' Collaborative Group overview analysis of chemohormonal therapy found that the 5-year benefits produced by chemotherapy appear to be about twice as great in ER-poor as in tamoxifen-treated ER-positive disease [1].

An evaluation of more contemporary chemotherapy regimens focused on three large CALGB and US Breast Intergroup trials of adjuvant chemotherapy [8]. This study examined the impact of adjuvant chemotherapy in patients with ER-negative breast cancer vs. ER-positive breast cancer. This analysis included CALGB 8541, CALGB 9344 (Int 0148), and CALGB 9741 (Int c9741). CALGB 8541 randomized patients to three regimens of cyclophosphamide, doxorubicin, and fluorouracil (CAF) differing in dose intensity and had a median follow-up of 14.4 years. The women treated with high or moderate dose intensity had significantly longer DFS and OS than those treated with low dose intensity. However, the difference in survival between the two groups treated with moderate or high dose intensity was not significant [9]. CALGB 9344 randomized patients to three dose levels of doxorubicin with fixed-dose cyclophosphamide followed by paclitaxel or not. At a median follow-up 7.2 years, there was no difference by dose level of doxorubicin, but the addition of paclitaxel improved DFS and OS [10]. CALGB 9741 randomized patients to sequential doxorubicin followed by paclitaxel followed by cyclophosphamide or concurrent doxorubicin and cyclophosphamide followed by paclitaxel, with each of the chemotherapy regimens given either every 2 weeks (dose-dense) with filgrastim or every 3 weeks without filgrastim [11]. At a median follow-up of 3 years, dose-dense treatment improved DFS and OS. The joint analysis of the three trials demonstrated that in all three trials, analyzed for outcomes based on ER status, there was significant benefit for patients with ER-negative disease favoring the higher dose intensity, addition of paclitaxel, or higher dose density (see Table 2). However, in the patient population with ER-positive disease treated with adjuvant tamoxifen, there was no statistically significant benefit for DFS and OS conferred by higher dose intensity, addition of paclitaxel, or higher dose density.

The results of CALGB 9741 were updated with a median follow-up of 69 months at the 2005 San Antonio Breast Cancer Symposium [12]. The every 2-week regimens significantly improved DFS with a trend toward improvement of OS over the every 3-week regimens. In an exploratory analysis, the benefits of the every 2-week regimens were most striking in the first 3 years of follow-up and in the ER-negative

Table 1. Hazard ratios (95% CI) for addition of CMF to tamoxifen by age group and ER concentration in NSABP B-20 [7].

		RFS	OS
Age	⩽49 years	0.46 (0.31–0.68)	0.61 (0.40–0.95)
	50–59 years	0.44 (0.25–0.75)	0.57 (0.32–1.01)
	⩾60 years	0.80 (0.45–1.44)	1.21 (0.79–1.85)
ER concentration	Low ER (10–49 fmol/mg)	0.38 (0.25–0.57)	0.57 (0.37–0.87)
	High ER (⩾50 fmol/mg)	0.67 (0.46–0.97)	0.97 (0.69–1.37)

Younger patients and those with low ER levels experienced the greatest reductions in risk of relapse or death.

Table 2. Incremental hazard rate reductions (95% CI) in DFS and OS for sequential CALGB and US Breast Intergroup adjuvant breast cancer trials.*

	ER	CALGB 8541 (Higher dose) (%)	Int 0148 (Addition of paclitaxel) (%)	Int c9741 (Every 2 weeks vs. every 3 weeks treatment) (%)	Total (%)
DFS	Negative	21 (7–32)	26 (12–37)	29 (7–45)	58 (41–71)
	Positive	8 (−8–21)	15 (0–28)	10 (−18–31)	32 (2–53)
OS	Negative	14 (−3–28)	25 (11–38)	32 (8–50)	56 (35–70)
	Positive	5 (−12–19)	15 (−4–30)	11 (−25–39)	27 (−15–54)

Sequential increments in risk reductions are smaller for women with ER-positive breast cancers than ER-negative breast cancers.
*Courtesy: Data from Berry *et al*. [8].

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subset with a hazard ratio for DFS of 0.75, 95% CI = 0.57–0.97, $P = 0.031$ for the ER-negative group vs. 0.86, 95% CI = 0.67–1.11, $P = 0.26$ for the ER-positive group, and a hazard ratio for OS of 0.77, 95% CI = 0.57–1.03, $P = 0.073$ for the ER-negative group, and 0.92, 95% CI = 0.67–1.26, $P = 0.61$ for the ER-positive group. Thus, it is not clear that increasing dose density as in the every 2 weekly schedules provides improvement in outcome in women with ER-positive breast cancer.

Intergroup trial INT0100 (SWOG-8814) randomized postmenopausal patients with node-positive, ER- and/or PR- positive disease to tamoxifen alone, CAF chemotherapy with tamoxifen begun concurrently, or CAF chemotherapy with sequential tamoxifen. Benefit of adding CAF chemotherapy to adjuvant tamoxifen alone was demonstrated. In an exploratory analysis, the addition of CAF to tamoxifen was particularly effective if the ER score was low or intermediate, but no CAF benefit was seen if the tumor had a high ER score [13]. In contrast, the results of BCIRG 001, which randomized patients with axillary lymph node-positive breast cancer to docetaxel, doxorubicin, and cyclophosphamide (TAC) vs. 5-fluorouracil, doxorubicin, cyclophosphamide (FAC), demonstrated an improvement is DFS and OS for TAC over FAC, and this benefit was similar in the hormone receptor-positive as well as receptor-negative subgroups [14].

Summary

The current and emerging data suggest that the benefit, if any, of adjuvant chemotherapy in women with tumors with moderate to high levels of ER expression is much smaller than that in women with ER-negative tumors. This appears to be especially true in the older population of women with ER-positive breast cancer. Current treatment guidelines, such as the NCCN Breast Cancer Treatment Guidelines and the St. Gallen International Consensus Conference recommendations acknowledge the limited benefits of chemotherapy in women with ER-positive breast cancers [15,16]. At present, the decision to add or withhold chemotherapy in combination with hormonal therapy in women with ER-positive breast cancer should be individualized, especially in those with a favorable prognosis and in women aged 60 years or older, where the incremental benefit of chemotherapy appears to be small. Further, the impact of the addition of taxanes and dose intensity appears to be of limited value in women with ER-positive disease. The design of future clinical trials should include planned subset analyses of adjuvant chemotherapy response in hormone receptor-positive vs. hormone receptor-negative disease, and should also consider including quantitative measurements of ER.

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