Two interesting trials from the Adjuvant Breast Cancer (ABC) Trials Collaborative Group (1,2) are reported in this issue of the Journal. Although their interpretation is impeded by the lack of estrogen receptor (ER) measurements in more than 40% of patients, these trials provide important information regarding adjuvant therapy for women with breast cancer.

The ABC Ovarian Ablation or Suppression (OAS) Trial examines women randomly allocated to receive ovarian ablation or suppression compared with no ovarian ablation or suppression, against a background of 5 years of tamoxifen treatment with or without chemotherapy. Among 2144 women who were randomly assigned between 1993 and 2000, there was no evidence of benefit for relapse-free survival (hazard ratio [HR] = 0.95, 95% confidence interval [CI] = 0.81 to 1.12; \( P = .56 \)) or overall survival (HR = 0.93, 95% CI = 0.78 to 1.13; \( P = .44 \)). In a small, unplanned analysis of 56 women younger than 40 years who did not receive chemotherapy, there was a more suggestive but not statistically significant effect (overall survival, HR = 0.55, 95% CI = 0.17 to 1.85).

Patients in the trial were not preselected by ER status, and only two-thirds of those with ER data were ER positive. Not surprisingly, there was a trend toward a greater benefit of ovarian ablation or suppression in those with ER-positive tumors but no statistically significant evidence of heterogeneity for either relapse-free survival or overall survival among the subgroups. Two other studies support this paradigm (3,4). In the study by Davidson et al. (3), 1504 node-positive premenopausal women with ER-positive breast cancer were randomly assigned to six cycles of oral (cyclophosphamide, Adriamycin, and 5-fluorouracil [CAF]) chemotherapy compared with CAF plus goserelin (Zoladex) (CAFZ) and to CAFZ plus 5 years of tamoxifen (CAFZT). Although median survival was superior for CAFZT compared with CAF, there was not sufficient power to detect a significant difference in the trend toward superiority for CAFZT over CAF alone. Hypothesis-generating subgroup analyses suggested, as in the ABC (OAS) study, that women younger than age 40 years at trial entry with premenopausal estradiol levels after chemotherapy or who retained menses after chemotherapy benefited most from goserelin. Similarly, the study by Arriagada et al. (4) showed no benefit of ovarian ablation or suppression overall in subgroups based on ER status or in women who experienced amenorrhea following chemotherapy, but it did show that women aged 39 years and younger had a statistically significant benefit from goserelin following (cyclophosphamide, methotrexate, and 5-fluorouracil [CMF]) (HR = 0.34, 95% CI = 0.14 to 0.87).

The results of the ABC (OAS) Trial are limited by methodologic issues. The fact that fewer than 60% of women had tumor ER levels determined retrospectively limits the ability to perform the subset analyses that could prove most interesting. In addition, 11% of patients refused allocated treatment. The authors have correctly analyzed their data by intent to treat, but the high percentage of refusal dilutes the possibility of seeing important treatment effects. Furthermore, the effects of concomitant tamoxifen may overlap with those of ovarian ablation or suppression, thereby reducing the ability to attribute effects to either alone.

Nonetheless, this large study (1,2) adds to available data concerning this question. In addition, subset analyses from the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) overview (5) may help in elucidating these issues. The ABC (OAS) Trial also focuses attention on the ongoing Suppression of Ovarian Function Trial, which is randomly assigning women with ER-positive tumors who are still premenopausal following chemotherapy to tamoxifen alone or to tamoxifen plus a luteinizing hormone–releasing hormone [LH-RH] agonist or the aromatase inhibitor exemestane plus an LH-RH agonist (6). The Suppression of Ovarian Function Trial should provide firm results addressing this question, particularly when added to the EBCTCG overview. The limitations of the ABC (OAS) Trial however stress the importance of measuring potential biologic prognostic and predictive factors carefully and ensuring access to archived tumor specimens because not all such factors will be known during study initiation and conduct.

The ABC Chemotherapy Trial randomly assigned 1991 women to standard chemotherapy (mainly CMF) compared with none against a background of 5 years of tamoxifen with or without ovarian ablation or suppression. Two-thirds of the women in the trial were older than 50 years and fewer than 60% had known ER status, of whom fewer than two-thirds were ER positive. Chemotherapy improved relapse-free survival (HR = 0.86, 95% CI = 0.73 to 1.01; \( P = .06 \)) and overall survival (HR = 0.83, 95% CI = 0.70 to 0.99; \( P = .03 \)). The benefits of chemotherapy were greater in younger women, particularly premenopausal women who did not receive ovarian ablation or suppression.

Again, this trial was impaired by lack of ER data. It is now hypothesized that chemotherapy is more effective in women with ER-negative than ER-positive tumors (unpublished data: Winer E, Pritchard KI, Buyse M, Piccart M, Wood W, Clarke M, et al.; 7,8). All trials should now have ER and progesterone receptor as well as...
HER-2 status available. The inability, in spite of valiant efforts of the ABC investigators to obtain these retrospectively, highlights the importance of ensuring availability of archived tumor specimens in all current and future trials of adjuvant therapy.

What this trial does not adequately address is the value of adding chemotherapy to ovarian ablation or suppression in women with ER-positive tumors. Forest plots suggest that chemotherapy has less of an effect among those who were premenopausal and had ovarian ablation or suppression than in those who were premenopausal and did not. These subset results may relate partly to the fact that chemotherapy in those without deliberate ovarian ablation or suppression produced ovarian ablation or suppression in many cases. The real question, however, is whether the subset of women with high hormone responsivity and low or intermediate risk of recurrence could be effectively treated with endocrine therapy alone. Data from this study, although they begin to answer this question, will need to be combined with other data before the question can be adequately explored. Once again, subset analyses from the EBCTCG overview may be able to address these questions.

In summary, these two studies present important data concerning the role of chemotherapy and ovarian ablation or suppression in adjuvant therapy of breast cancer. Unfortunately, the unavailability of archived tumor specimens in trials for which correlative science studies were not preplanned limits the interpretation of data. Nonetheless, these studies confirm the role of CMF or equivalent chemotherapy in women receiving 5 years of tamoxifen with or without ovarian ablation or suppression and suggest that further investigation of ovarian ablation or suppression added to tamoxifen or to chemotherapy is worthwhile, particularly in young premenopausal women who do not become amenorrheic following chemotherapy. Most of all, however, these studies stress the importance of establishing processes to ensure the availability of archived tumor specimens for all randomized adjuvant trials. The era in which such large important trials should be carried out without the availability of archived correlational tumor samples is over.

References


Notes

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