EDITORIALS

Combined Endocrine Therapy for Breast Cancer—New Life for an Old Idea?

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Endocrine therapy has been a mainstay of breast cancer treatment for more than 100 years. The first interventions, oophorectomy for premenopausal women and pharmacologic doses of estrogen for postmenopausal women, have been supplanted by targeted therapy, including selective estrogen receptor modulators (SERMs) like tamoxifen, luteinizing hormone-releasing hormone (LHRH) agonists, and aromatase inhibitors. The initial attempts to combine hormonal therapies generally led to the finding of increased response rates but at the expense of higher toxicity and without an obvious survival advantage when compared with the survival with sequential monotherapy. These results have led to the current practice of serial hormonal manipulation in advanced breast cancer—i.e., the use of one endocrine therapy until disease progression, followed by a second intervention until its failure and so on. In practice, this means that a strategy of tamoxifen followed by ovarian ablation or the reverse has been the norm for premenopausal women with metastatic breast cancer who are believed to be candidates for endocrine therapy.

This practice dogma is challenged by the findings of Klijn et al. (2) reported in this issue of the Journal. In this European Organization for Research and Treatment of Cancer (EORTC) study, 161 premenopausal women with potentially hormone-responsive metastatic breast cancer were randomly assigned to tamoxifen, buserelin (an LHRH agonist that effects a chemical castration), or the combination. Not surprisingly, the effects of tamoxifen or buserelin alone on a number of clinical end points were similar. However, contrary to prevailing views, the combination of tamoxifen and buserelin led to a superior response rate and to improved median progression-free and overall survivals, as well as a doubling of 5-year survival from 15%–18% for the single agents to 34% for the combined therapy.

For comparison, a contemporaneous U.S. trial of surgical oophorectomy versus goserelin (another LHRH agonist) in premenopausal women with steroid receptor-positive metastatic breast cancer (3) gave intermediate results. A response rate of 31%, a median failure-free survival of 6 months, a median overall survival of 37 months, and an estimated 5-year survival of 25% were noted for the 69 patients assigned to goserelin.

The major strengths of the trial conducted by Klijn et al. (2) are its maturity and its design, which permits direct comparison of the three interventions, a rare opportunity in breast cancer. In addition, the definition of the premenopausal state was rigorous, and registration was limited to women with steroid receptor-positive tumor or receptor-unknown tumor with a long disease-free interval. Thus, this trial, unlike many trials of ovarian ablation, was targeted toward the population of women most likely to benefit from this approach. The results are biologically plausible because ovarian ablation and tamoxifen could potentially function in part via different pathways (those of estrogen withdrawal and estrogen receptor blockade, respectively) and might, therefore, target different cell populations. The ancillary laboratory study measuring serial estrogen levels is congruent with other studies showing that tamoxifen can increase circulating $17\beta$-estradiol, whereas LHRH agonists decrease it to a postmenopausal level. Indeed, the study by Klijn et al. (2) suggests that these divergent effects on the level of serum $17\beta$-estradiol are not clinically significant because there was no major difference in clinical outcomes for the tamoxifen or buserelin groups.

But our ability to interpret the results of the trial is undermined by three features. First, the sample size is small because the trial was stopped early as a result of poor accrual; this could possibly give anomalous results. Second, for pragmatic reasons, it was not possible to carry out the perfect clinical experiment—a crossover design where all patients received both tamoxifen and ovarian ablation and only the order of administration varied. Finally, our ability to generalize these results to current clinical practice is limited because a minority of the patients in this trial had received any form of adjuvant systemic therapy. In particular, only four patients had taken adjuvant tamoxifen. Thus, these trial results may not apply to today’s premenopausal women with advanced hormone-responsive breast cancer, most of whom will have received adjuvant tamoxifen and/or chemotherapy. For these reasons, it is difficult to draw a definitive conclusion that a combination of ovarian ablation and tamoxifen should be the standard of care for premenopausal women with metastatic endocrine-responsive breast cancer.

A key question is what these results might teach us about approaches to adjuvant therapy and chemoprevention. The Early Breast Cancer Trialists’ Collaborative Group meta-analyses of tamoxifen and ovarian ablation (4,5) demonstrate unequivocally that tamoxifen and ovarian ablation are effective adjuvant strategies for women under 50 years of age, particularly for those whose tumor expresses estrogen receptor. Indirect comparison of results from these analyses suggests comparable effects, but direct comparison is not possible. Results of randomized trials that address questions of ovarian ablation and tamoxifen in steroid receptor-positive, early-stage breast cancer in premenopausal women are beginning to emerge. Regrettably, their design in aggregate fails to shed much light on...
the important issue of combined versus single endocrine therapy. Rather, the major issue addressed in several trials is the relative efficacy of ovarian ablation (surgical or medical) plus tamoxifen versus standard adjuvant chemotherapy regimens such as the combination of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) or the combination of 5-fluorouracil, doxorubicin (i.e., Adriamycin) or epirubicin, and cyclophosphamide (FAC or FEC) in premenopausal women with receptor-positive breast cancer. Four such trials (6–9) suggest equivalence or improved outcome with the combined hormone approach; unfortunately, it is not possible to judge whether tamoxifen or ovarian ablation alone would give similar results. Indeed, two trials of oophorectomy versus CMF for premenopausal women with estrogen receptor-positive tumors (10,11) demonstrated similar or better outcome with oophorectomy, whereas a trial of tamoxifen versus CMF and epirubicin (12) favored tamoxifen in the premenopausal lymph node-positive, estrogen receptor-positive subset.

Other adjuvant trials have examined the effects of the LHRH agonist goserelin with or without tamoxifen. One trial randomly assigned premenopausal women with lymph node-negative, receptor-positive breast cancer to therapy with tamoxifen alone or with tamoxifen plus some form of ovarian ablation (radiation treatment, surgery, or LHRH agonist). Like the EORTC study (2) reported in this issue of the Journal, entry in this trial was terminated early because of poor accrual in an era of increasing use of adjuvant chemotherapy. A second study (13) compared the effects of the combination of cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF), CAF plus goserelin, and CAF plus goserelin and tamoxifen for lymph node-positive, steroid receptor-positive premenopausal women. It showed improved disease-free survival at 5 years for CAF plus goserelin and tamoxifen when compared with CAF; however, the addition of goserelin alone to CAF offered no clear advantage. A retrospective subset analysis raised the provocative finding that addition of goserelin was more effective in women under the age of 40 years (i.e., those who are less likely to become postmenopausal after chemotherapy) and that the combination of tamoxifen and goserelin was even more efficacious. Again, conclusions about the role of combined hormone therapy are difficult to draw in the absence of a CAF plus tamoxifen arm. Ideally, prospective randomized trials will further explore these issues.

In the prevention setting, results from the Breast Cancer Prevention Trial (14) comparing tamoxifen with placebo as a means of breast cancer risk reduction for women at high risk for breast cancer development have demonstrated a 50% reduction in breast cancer incidence in women of all ages in the tamoxifen group. Epidemiologic studies (15) suggest that ovarian ablation at an early age is also associated with a diminished risk of breast cancer. Thus, a strategy of combined ovarian ablation and SERM administration may be worthy of study in certain premenopausal women who are at high risk for breast cancer development.

Finally, the advent of the aromatase inhibitors has reopened the question of combined hormone therapy for postmenopausal women as well, and combinations of tamoxifen and aromatase inhibitors are under study. It is hoped that positive results from trials like these using newer selective endocrine agents will validate our renewed interest in combination hormone therapy for breast cancer.

REFERENCES

(3) Taylor CW, Green S, Dalton WS, Martino S, Rector D, Ingle JN, et al. Multicenter randomized clinical trial of goserelin versus surgical ovariec-
(7) Boccardo F, Rubagotti A, Amoroso D, Mesiti M, Minutoli N, Aldrighetti D, et al. CMF versus tamoxifen (tam) plus goserelin (gos) as adjuvant treatment of ER positive (ER+) pre-perimenopausal breast cancer (ca) pa-
(9) Roche H, Mihura I, de Lafontant B, Reme-Saumon M, Martel P, Dubois JB, et al. Castration and tamoxifen versus chemotherapy (FAC) for premeno-
pausal, node and receptor positive breast cancer patients: a randomized trial with a 7 years median follow-up [abstract]. Proc ASCO 1996;15:117.
(10) Ejertsen B, Dombernovsk N, Mouridsen HT, Kambly C, Kjaer M, Rose C, et al. Comparable effect of ovarian ablation (OA) and CMF chemo-
therapy in premenopausal hormone receptor positive breast cancer patients (PRP) [abstract]. Proc ASCO 1999;18:66a.
(11) Scottish Cancer Trials Breast Group and ICRF Breast Unit, Guy’s Hospital, London. Adjuvant ovarian ablation versus CMF chemotherapy in premeno-
date at 7 years of the 1st GROCTA (Breast Cancer Adjuvant Chemo-
(14) Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cro-

NOTE

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