Current Status of Adjuvant Endocrine Therapy for Breast Cancer\textsuperscript{1}

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Abstract

Adjuvant endocrine therapy is a vitally important modality for treatment of women with resected hormone-sensitive breast cancer as indicated by the presence of estrogen and/or progesterone receptors in the tumor. It is not recommended in those patients whose tumors lack these hormone receptors. Tamoxifen for 5 years has been shown to reduce the risk of recurrence and death irrespective of menopausal status or use of adjuvant chemotherapy. In postmenopausal women, the major research emphasis relates to the use of third-generation aromatase inhibitors in sequence with, instead of, and in combination with tamoxifen. In premenopausal women, ovarian ablation/suppression has demonstrated efficacy comparable with some chemotherapy regimens, but its role in women receiving chemotherapy remains to be determined.

Introduction

Endocrine therapy plays an integral role in the management of the majority of women with breast cancer. This is clearly the case in the adjuvant setting where endocrine therapy has been demonstrated to reduce the risk for recurrence and death in both premenopausal and postmenopausal women. This review will consider the current status and future directions of adjuvant endocrine therapy.

Estrogen has long been considered to play a central role in breast cancer development. Surgically induced menopause has been associated with substantial reductions in the risk of developing breast cancer (1). The two major endocrine therapy approaches in hormone-dependent breast cancer are interference with estrogen action and reduction in estrogen levels. Tamoxifen is the prime example of the former approach where its mechanism of action is considered to be primarily related to competition with estrogen for the ER,\textsuperscript{3} resulting in decreased transcription of estrogen-regulated genes (2). Reduction in estrogen levels is accomplished in premenopausal women by ovarian ablation or suppression and, in postmenopausal women, by aromatase inhibitors. At present, hormone-dependent breast cancer and potential candidacy for endocrine therapy are identified by the presence of ER and/or PgR in the tumor. The ER represents a powerful molecular predictive marker for use of endocrine therapy irrespective of the approach used. The absence of ER (and PgR) indicates essentially no potential for benefit from endocrine therapy, and confidence in the results of these assays is essential for proper decisions regarding patient management.

Tamoxifen Adjuvant Therapy. Tamoxifen has been the gold standard for adjuvant endocrine therapy for breast cancer since Food and Drug Administration approval in 1986 for postmenopausal women with resected node-positive disease and in 1990 for premenopausal and postmenopausal women with resected node-negative disease. Numerous studies have addressed the issue of duration of tamoxifen therapy. The Oxford Overview examined trials of 1, 2, and 5 years of tamoxifen and found a highly significant trend toward greater benefit with longer duration of therapy (3). The National Surgical Adjuvant Breast and Bowel Project B14 trial evaluated 5 \textit{versus} 10 years of tamoxifen in women with ER-positive, node-negative breast cancer and found a slight advantage for those who had stopped tamoxifen at 5 years. This advantage achieved significance in disease-free survival ($P = 0.03$) and approached significance in overall survival ($P = 0.07$; Ref. 4). Two notable trials addressing the duration issue are currently accruing patients, \textit{i.e.}, the ATLAS trial, Adjuvant Tamoxifen: Longer Against Shorter and the aTTom trial, adjuvant Tamoxifen Treatment, offer more? Despite these trials, the results from the National Surgical Adjuvant Breast and Bowel Project B14 are sufficiently strong such that 5 years of tamoxifen will be the standard of care for the foreseeable future.

Postmenopausal Women. Using age as a surrogate for menopausal status, the 1995 Oxford Overview data (3) revealed highly significant reductions in recurrence and death with 5 years of tamoxifen in women $\geq 50$ years of age. Considering women in the age groups 50–59, 60–69, and $\geq 70$ years, the proportional risk reductions for recurrence were $37 \text{ (SD = 6)}$, $54 \text{ (SD = 5)}$, and $54\% \text{ (SD = 13)}$, respectively, and for death were $11 \text{ (SD = 8)}$, $33 \text{ (SD = 6)}$, and $34\% \text{ (SD = 13)}$, respectively. Of particular note is that the reductions were similar, irrespective of the absence or presence of chemotherapy, with proportional risk reductions for recurrence of $46 \text{ (SD = 4)}$ and $52\% \text{ (SD = 8)}$, respectively, and for death $26 \text{ (SD = 5)}$ and $47\% \text{ (SD = 9)}$, respectively. However, in $\leq 8000$ women with low or no ER in their primary tumor, the effect of tamoxifen was small and not significant. Thus, the Overview data clearly show the strength of benefit from $\sim 5$ years of tamoxifen in reducing risk of recurrence and death in ER-positive women. This benefit remains in the 2000 Overview, which is as yet unpublished. Tamoxifen is the standard against which new endocrine agents must be tested in postmenopausal women.

 Currently, the aromatase inhibitors are the major hope for improving the effectiveness of adjuvant endocrine therapy in postmenopausal women. The enthusiasm for their study is based

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\textsuperscript{3} The abbreviations used are: ER, estrogen receptor; PgR, progesterone receptor; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; LHRH, luteinizing hormone-releasing hormone; HR, hazard ratio; CI, confidence interval; CAF, cyclophosphamide, Adriamycin, 5-fluorouracil; CRA, chemotherapy-related amenorrhea.
both on biological rationale and results of comparative trials in the metastatic disease setting. The major source of estrogen in postmenopausal or castrated women is the peripheral conversion of androstenedione, secreted by the adrenal gland, to estrone by aromatase, which is a complex of a cytochrome P450 hemoprotein and a flavoprotein. This aromatization is the rate-limiting step in the conversion of androstenedione to estrone, which can subsequently be reduced to estradiol. Although the concentration of estradiol in plasma is substantially lower in postmenopausal women than in premenopausal women, the levels of estradiol in breast cancer tissues have been found to be similar, irrespective of menopausal status (5). Preclinical studies have provided strong support for aromatization, playing a major role in tissue estrogen levels (6). The clinical data supporting the study of aromatase inhibitors as adjuvant endocrine therapy come from randomized trials of letrozole and anastrozole, each compared with tamoxifen in the first-line metastatic setting (7-10). These trials led to the Food and Drug Administration approval of both agents for this indication. Of particular note is the trial of letrozole versus tamoxifen, where the aromatase inhibitor was significantly superior in terms of time to progression, overall objective response rate, and clinical benefit rate (7). Whereas letrozole and anastrozole are nonsteroidal aromatase inhibitors, the steroidal aromatase inhibitor exemestane is currently being compared with tamoxifen in an ongoing Phase III trial in the first-line metastatic setting.

All three of the third-generation aromatase inhibitors under study, letrozole, anastrozole, and exemestane, are currently being evaluated in the adjuvant setting. These trials involve the determination of their value: (a) in sequence with tamoxifen; (b) instead of tamoxifen; and (c) in combination with tamoxifen (11) and are reviewed in the paper by Dr. Goss included in these Proceedings. The results of these studies have the potential to radically change the adjuvant endocrine therapy paradigm for postmenopausal women.

**Premenopausal Women.** Adjuvant endocrine therapy involving tamoxifen and ovarian ablation or suppression has demonstrated clear benefit in premenopausal women with ER-positive breast cancer. Again, using age as a surrogate for menopausal status, the Oxford Overview found that in women <50 years, tamoxifen produced a proportional reduction in risk of recurrence of 45% (SD = 8) and risk of death of 32% (SD = 8; Ref. 3). The risk reductions occurred, as was the case in older women, in the absence or presence of chemotherapy with proportional reductions in risk of recurrence of 47 (SD = 8) and 40% (SD = 19), respectively, and risk of death of 30 (SD = 12) and 39% (SD = 22), respectively. Thus, the data are compelling for the utilization of tamoxifen therapy for ~5 years in premenopausal women with resected ER-positive and/or PgR-positive primary breast cancer when adjuvant therapy is considered appropriate.

Ovarian ablation was the first endocrine therapy for breast cancer, having been used over a century ago by Beatson. The 1995 Oxford Overview (12) found that the impact of ovarian ablation appeared to be substantial in the absence of chemotherapy but not so when chemotherapy was used concurrently, i.e., the proportional reductions in the risk of recurrence were 25 (SD = 7) and 10% (SD = 9), respectively. Similar relationships were present in the analysis of mortality, but the number of deaths were too small to permit a reliable analysis. However, with additional follow-up, the 2000 Oxford Overview appeared to confirm this apparent difference in benefit from ovarian ablation according to the presence or absence of chemotherapy. Thus, ovarian ablation has not been demonstrated to be of value in premenopausal women who also receive adjuvant chemotherapy.

Numerous studies have been performed comparing various approaches to ovarian ablation or suppression with chemotherapy in the adjuvant setting in premenopausal women. Most, unfortunately, have been published in abstract form only, but two full manuscripts of note have been published.

The Scottish trial (13) randomized 332 premenopausal women to either ovarian ablation by surgery or radiation therapy versus CMF chemotherapy given i.v. every 3 weeks for six to eight cycles. There was an additional randomization to receive or not receive prednisolone. Neither knowledge of ER status nor ER positivity was required for entry onto this trial. With a median follow-up for living patients of 5.9 years (range of follow-up was 2-12 years), there was no significant difference in event-free or overall survival. ER assays were performed on 81% of the patients, and there was a significant interaction with ER levels with ovarian ablation being superior in patients with ER levels of ≥20 fmol/mg protein and CMF superior in patients with lower ER levels.

It has been ~20 years since it was demonstrated that LHRH analogues could produce regression in premenopausal women with metastatic breast cancer (14). The administration of LHRH analogues results in decreased gonadotropin secretion, resulting in suppression of ovarian function and a state of medical castration. Clinical trials of endocrine manipulations, including the LHRH analogues, in premenopausal metastatic breast cancer have provided evidence for relative efficacy that may be applicable in the adjuvant setting. Comparative clinical trials and meta-analyses thereof have provided the following information. Despite relatively small sample sizes and resulting wide CIs, the data suggest that tamoxifen is similar to oophorectomy (15), and the LHRH analogue goserelin is similar to oophorectomy (16). In the adjuvant setting in early breast cancer in pre or perimenopausal women, goserelin has been directly compared with CMF in the Zoladex Early Breast Cancer Association (ZEBRA) trial (17). A total of 1640 women was randomized to either goserelin administered monthly for 2 years or CMF for six cycles. A significant interaction was identified between treatment and ER status. In the ER-positive patients, who constituted ~72% of this study population, goserelin was similar to CMF in terms of disease-free survival with an HR of 0.99 (95% CI, 0.83–1.19), whereas in the ER-negative cohort (~19% of the study population), CMF was significantly superior to goserelin, as would have been expected, with an HR of 1.72 (95% CI, 1.24–2.37).

Arguably, the most interesting trial evaluating LHRH analogues in premenopausal metastatic breast cancer is from the European Organization for Research and Treatment of Cancer, which compared tamoxifen alone, the LHRH analogue buserelin alone, or the combination of these two agents (18). The combination of buserelin plus tamoxifen was significantly superior to either agent alone in terms of progression-free survival (P = 0.03) and, most importantly, overall survival (P = 0.01). There
was no difference in antitumor effect between tamoxifen and buserelin. Additional supportive dates for superiority of an LHRH analogue plus tamoxifen over LHRH analogue alone comes from a meta-analysis of four randomized trials involving 506 premenopausal women with advanced breast cancer, in which the combination was superior in terms of overall response rate \((P = 0.03; \text{odds ratio, 0.67})\), progression-free survival \((P = 0.0003, \text{HR} = 0.70)\), and overall survival \((P = 0.02, \text{HR} = 0.78; \text{Ref. 19})\).

The combination of LHRH analogue plus tamoxifen has been compared with chemotherapy alone in multiple trials in the adjuvant setting. The Italian Breast Cancer Adjuvant Study Group performed a randomized trial (GROCTA 02; Ref. 20) of six cycles of classic CMF (with oral cyclophosphamide) or tamoxifen for 5 years plus ovarian suppression with surgical oophorectomy (5% of patients receiving endocrine therapy), ovarian irradiation (26%), or goserelin (69%) given monthly for 2 years. A total of 244 patients with ER-positive disease was randomized, and with a median follow-up of 6.3 years, there was no difference between the chemotherapy or endocrine approaches in terms of either disease-free or overall survival.

Several additional trials published in abstract form only have supported the efficacy of this combined endocrine approach relative to chemotherapy alone. The Austrian Breast Cancer Study Group randomized 1045 women with ER- and/or PgR-positive breast cancer to either CMF (all i.v., days 1 and 8) for six cycles or monthly goserelin for 3 years plus tamoxifen for 5 years (21, 22). With a median follow-up of 42 months, the combination endocrine therapy was associated with a significantly improved recurrence-free survival \((P < 0.02)\) over CMF. At the time of these publications, there was no difference in overall survival.

The Eastern Cooperative Oncology Group led an American Intergroup trial evaluating CAF alone, CAF plus monthly goserelin for 5 years, or CAF plus both goserelin and tamoxifen for 5 years (23). A total of 1504 eligible patients were randomized and, with a median follow-up of 6 years, the addition of tamoxifen to CAF significantly improved time to recurrence \((P = 0.01)\), but this was not the case for the addition of goserelin to CAF \((P = 0.10)\). Clearly, further follow-up is necessary. Two French studies have compared the combined endocrine approach with anthracycline-based chemotherapy alone, FAC (5-fluorouracil, Adriamycin, cyclophosphamide) (24), and 5-fluorouracil, epirubicin, cyclophosphamide (25), with similar outcomes for the two approaches, but the sample sizes were quite small in both trials.

The evidence with respect to ovarian suppression plus tamoxifen supports the position that this combined endocrine approach is comparable with CMF as adjuvant therapy of premenopausal women with resected ER-positive breast cancer. The major issue is that CMF alone is not optimal therapy in such patients. None of these trials included tamoxifen with the chemotherapy, which, as has been noted previously, produces a further statistically and clinically significant reduction in the risk of recurrence and death even in the presence of chemotherapy. In addition, the 1995 Oxford Overview (26) revealed that, compared with CMF alone, anthracycline-containing regimens produced a significantly greater reduction in recurrence \((P = 0.006)\) and death \((P = 0.02)\). The proportional risk reductions were 12 \((SD = 4)\) and 11% \((SD = 5)\), respectively. Thus, it can be argued that CMF alone is not the optimal adjuvant therapy regimen for management of this population of patients and thus, not the proper comparator for these trials evaluating relative efficacy of endocrine therapy.

**Amenorrhea in Adjuvant Chemotherapy.** For decades, controversy has existed regarding the extent to which the efficacy of adjuvant chemotherapy is related to an endocrine or ovarian suppression effect. Retrospective analyses of adjuvant therapy trials in premenopausal women have revealed an improved outcome for those who develop amenorrhea compared with women who maintain their menstrual cycles (27, 28). The average CRA rate for CMF regimens is 68%, but this varies with age (29). Of particular note is the information relating to CRA with a regimen currently commonly used. The use of standard Adriamycin 60 mg/m² plus cyclophosphamide 600 mg/m² i.v. about every 3 weeks was found to have a CRA (with amenorrhea defined as absence of menses for 1 year after starting chemotherapy) of 43% (95% CI, 30–56%). However, this was age dependent with CRA rates of 0 in 11 patients <35 years, 14% in 14 patients 35–39 years, 39% in 18 patients 40–44 years, and 100% in 17 patients aged 45–50 years (30). The finding of a lower CRA rate in younger women is of concern, especially when one considers data from the International Breast Cancer Study Group experience. They found that in young women (<35 years) treated with chemotherapy alone, those with ER-positive tumors had a significantly worse disease-free survival than those with ER-negative disease (31). The International Breast Cancer Study Group investigators hypothesized that chemotherapy alone produced an inadequate endocrine effect in younger women with ER-positive disease and made the case for including endocrine therapy in their management. As tamoxifen would be considered indicated in addition to chemotherapy in premenopausal ER-positive women, the obvious question remains whether ovarian suppression should be added in those women who retain premenopausal after chemotherapy, and this remains an important area for future research. In those women who are rendered postmenopausal with adjuvant treatment, determination of the role of aromatase inhibitors will be an additional area of research in the future.

**The NIH Consensus Development Conference.** The NIH held a Consensus Development Conference on adjuvant therapy for breast cancer in November 2000 (32), and the resulting statement provided an assessment of the available data. The Consensus Development Panel addressed adjuvant endocrine therapy and concluded that tamoxifen for 5 years should be recommended to women whose tumors contain hormone receptor protein (ER and/or PgR). It was noted that possible exceptions to this recommendation include premenopausal women with tumors smaller than 10 mm who wish to avoid symptoms of estrogen deprivation or elderly women with similar tumors and a history of venous thromboembolic episodes. Ovarian ablation was considered to produce a benefit comparable with some chemotherapy regimens, but its addition to chemotherapy has not been demonstrated to be of value. The reader is referred to the full report for additional details (32).
Open Discussion

Dr. Matthew Ellis: I saw a young woman of about 35 who had a T1b tumor and opted to go on to tamoxifen alone, quite reasonably. She recurred with positive nodes 2½ years later. Her tumor was ER-positive, HER2/neu-positive. That’s the one situation where you might see a dramatic agonist effect on the tumor, because you’re elevating estrogen levels in a situation where the tumor is tamoxifen-resistant. I think what’s going to happen is that we’re going to have to stop thinking about breast cancer as one or as two diseases, hormone receptor-positive and hormone receptor-negative. We’re forced into adding the HER2 stages into the mix of our thinking, one, because it’s a therapeutic target; two, because it pertains to the biology of hormone dependence. As these data come on, they’ve damaged trial designs that don’t take into account these factors.

Dr. James Ingle: Let me ask you, is a postmenopausal woman the same as a premenopausal woman whose ovaries you’ve suppressed? In a perfect world you’d do the study. Premenopausal studies have been particularly hard to do. If you look at the metaanalyses for the metastatic studies, in oophorectomy versus tamoxifen, there were 200 patients in four studies.

Dr. Kent Osborne: The women may be similar, but their tumors are not. We know that there are differences in the biology of tumors diagnosed in a woman who is premenopausal compared with postmenopausal: ER distribution, HER2 frequency, ER negativity, other growth factors, and growth rate. In really young women, less than 35, the differences are magnified.

Dr. Ingle: But that’s in the tumor. As far as the hormonal implications relative to the tumor, let’s say you had an identical tumor with an identical profile in a 35-year-old woman and a 60-year-old woman.

Dr. Osborne: I would say there are differences because the postmenopausal ovaries don’t make a number of things. If you take the ovary out, they’re not making those things, such as the androgens that come from the ovary in addition to the adrenal gland, for instance.

Dr. Kathleen Pritchard: You may be actually seeing a different situation when you give an LHRH analogue. You’re suppressing estrogen production and gonadotropin production, whereas if you removed or radiated the ovaries, you’re still getting gonadotropins and whatever else they do.

Dr. Ingle: So it has to be studied. It’s just taking far too long to get the answers.

References


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