Combination Endocrine Therapy in the Management of Breast Cancer

LAURA BOEHNKE MICHAUD, KELLIE L. JONES, AMAN U. BUZDAR

The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA

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ABSTRACT

Combination endocrine therapy has long been sought after as a means to better treat breast cancer. Agents that suppress estrogen production are given with agents that suppress estrogenic activity at the cellular level. Historically, these combinations have resulted in initial improvements in response rates, but relapse-free and overall survival were not significantly improved. Also, the increased toxicity seen with these regimens was limiting. New endocrine therapies with more potent activity and less toxicity have led to a resurgence of this idea in the management of breast cancer. Complete estrogen blockade has been compared with single-agent treatments in many different settings. The endocrine effects of this type of therapy are intriguing, but apparently do not readily predict a clinical advantage. The combination of an aromatase inhibitor and an antiestrogen, despite pharmacokinetic interactions, may prove to be beneficial. Results from ongoing trials are eagerly awaited to further address this question in postmenopausal breast cancer patients. For premenopausal breast cancer patients the options are more complex. Clinical outcomes with lutetinizing hormone releasing hormone (LHRH) agonists plus aromatase inhibitors are limited to very small phase II studies and are not clearly superior to single-agent therapy. Clinical data in the metastatic setting with premenopausal patients favor the use of an LHRH agonist with tamoxifen over the use of an LHRH agonist alone. However, a similar comparison with tamoxifen alone is lacking with only one trial including this as a treatment arm. Adjuvant therapy with this combined endocrine approach (LHRH agonist plus antiestrogen) has been more extensively studied, but lacks crucial comparisons necessary for making complex treatment decisions. Hopefully, through investigative diligence and ingenuity this issue can be adequately understood. However, many exciting new agents are on the horizon that offer hope to further advance the progress made to date although further confounding the questions already answered. The Oncologist 2001;6:538-546

INTRODUCTION

For many years, clinicians have investigated combining anticancer agents in hopes of discovering synergistic activity. This idea is fostered by the hypothesis of Goldie and Coldman in relation to chemotherapy [1]. Their hypothesis suggests that chemotherapy agents of differing mechanisms of action and nonoverlapping toxicity should be administered concurrently in hopes of maximizing cellular cytotoxicity against cancer cells. This approach to therapy is often limited by the collective toxicity experienced by the patients, but may also lack significant clinical superiority to sequential single-agent therapy in terms of efficacy. Combined endocrine therapy in breast cancer attempts to exploit this hypothesis through complete estrogen blockade. Agents that suppress estrogen production are given with agents that suppress estrogenic activity at the cellular level. Historically, these combinations have resulted in initial improvements in response rates, but relapse-free and overall survival were not significantly improved [2]. Also, the increased toxicity seen with these regimens was limiting.

New endocrine therapies with more potent activity and less toxicity have led to a resurgence of this idea in the management of breast cancer. The development of lutetinizing hormone releasing hormone (LHRH) agonists has allowed for circumvention of surgical approaches to ovarian ablation. New aromatase inhibitors are potent and specific for the enzyme and lack many of the troublesome side effects seen with arometlutethimide. These additions have allowed new combinations to be investigated with hopes of better targeting
breast cancer cells. This approach has been taken with other hormonally responsive malignancies (e.g., prostate cancer), but has not been successful at improving survival over that achieved with single-agent therapy. The focus of this manuscript is to summarize the clinical data regarding complete estrogen blockade in metastatic and early-stage breast cancer.

**Aromatase Inhibitors with Antiestrogens**

This combination approach to therapy is currently limited to the postmenopausal setting. In premenopausal women, the effects of the aromatase inhibitors alone have yet to be determined, precluding any investigation into combinations with the antiestrogens. Preclinical data regarding the combinations of an antiestrogen with an aromatase inhibitor are conflicting. Fadrozole with tamoxifen demonstrated better antitumor effects than either single agent when tested in an animal model [3]. Conversely, formestane plus tamoxifen has been shown to be less effective than formestane alone [4]. A dose-response relationship has been identified with vorozole plus tamoxifen in a rat model. A high dose of vorozole sufficient to produce similar estrogen suppression as seen with surgical castration combined with tamoxifen was less effective than either vorozole (high dose) or oophorectomy alone [5]. A marginally effective lower dose of vorozole was also combined with tamoxifen resulting in minor additional antitumor activity compared with vorozole alone, but to a lesser extent compared with oophorectomy [5].

In a similar rat tumor model, exemestane plus tamoxifen demonstrated better antitumor efficacy compared with either single agent [6]. Lu and colleagues investigated the combination of antiestrogens, tamoxifen and faslodex, with aromatase inhibitors, anastrozole and letrozole, in a nude mouse intratumoral aromatase model [7]. The antitumor effects of letrozole alone were superior to the single agents tamoxifen, faslodex, and anastrozole in this model, making it difficult to detect any additional benefits when letrozole was combined with the antiestrogens. When anastrozole was combined with tamoxifen or faslodex, efficacy was also similar to that seen with anastrozole alone. This tumor model demonstrates the ability of these agents to block local estrogen stimulation of breast tumors and may not completely represent the complex physiologic and pharmacologic interactions seen in breast cancer patients.

Pharmacokinetic interactions among agents often determine the feasibility of combination therapy. This is true for the aromatase inhibitors and antiestrogens. Historically, aminogluthethimide has decreased tamoxifen serum concentrations by approximately 50% when the two drugs were coadministered [8]. Anastrozole plus tamoxifen in breast cancer patients has demonstrated no significant effect on the pharmacokinetics of tamoxifen [9]. In this same study, the estrogen suppression seen with anastrozole was similar to that seen with the combination [9]. This is an indirect measure of anastrozole efficacy and requires clinical verification in prospective, controlled trials. Conversely, anastrozole pharmacokinetics are affected by tamoxifen, with a 27% reduction in anastrozole plasma concentrations when tamoxifen is coadministered [10]. However, in light of the previous data demonstrating similar estrogen suppression with the combination compared with anastrozole alone, this pharmacokinetic interaction may not be clinically relevant. The effects of letrozole plus tamoxifen demonstrate similar outcome as with anastrozole. Letrozole does not appear to affect the pharmacokinetics of tamoxifen [11]. The estrogen suppression seen with letrozole is not affected by the addition of tamoxifen, despite a 37% reduction in plasma levels of letrozole when tamoxifen was coadministered [12]. This information led to a recommendation of sequential therapy with letrozole and tamoxifen in ongoing clinical trials. The effects of tamoxifen on anastrozole pharmacokinetics were not available at the time combination trials were initiated. Therefore, studies with anastrozole and tamoxifen are investigating simultaneous administration in breast cancer patients. Data from ongoing prospective clinical trials investigating the efficacy of these combinations will determine the role of combination therapy in this setting.

To date, only the combination of aminogluthethimide and tamoxifen has been compared with tamoxifen alone in randomized, controlled clinical trials in metastatic postmenopausal breast cancer patients. This combination demonstrated disappointing results, with no improvement in efficacy. This may be a result of the pharmacokinetic interactions mentioned previously or may be due to the high rate of discontinuation of aminogluthethimide or both agents due to severe adverse events associated with aminogluthethimide (e.g., somnolence, rash, lethargy) [13]. New aromatase inhibitors are better tolerated, more potent, and do not affect serum concentrations of tamoxifen. All of these factors may potentially contribute to additional benefits with combination therapy. In the metastatic setting, small phase II studies are available evaluating the combination of letrozole and tamoxifen in postmenopausal breast cancer patients [11, 12]. The combination does appear to be safe and efficacious, but comparisons with either single agent have yet to be completed. As mentioned previously, ongoing trials with letrozole are examining sequential administration with tamoxifen instead of simultaneous administration due to the pharmacokinetic interactions found in early trials. Trials with letrozole and tamoxifen are being conducted only in early stage postmenopausal breast cancer patients receiving endocrine therapy in the adjuvant setting.
agents. Results from a large, multi-institutional ongoing trial with anastrozole and tamoxifen as adjuvant therapy for early-stage breast cancer are eagerly awaited and expected in late 2001 or early 2002. This trial compares anastrozole with tamoxifen as single-agent therapies versus the combination for 5 years and was designed to determine long-term safety and efficacy.

**LHRH AGONISTS WITH AROMATASE INHIBITORS**

Estrogen production in premenopausal women relies primarily on the ovaries. Production is controlled through the hypothalamic-pituitary-gonadal axis by negative-feedback mechanisms. The goal of therapy with the LHRH agonists is to inhibit ovarian estrogen production in premenopausal women, suppressing estrogen levels to that of a postmenopausal woman. If this can be accomplished, these women may then benefit from the addition of an aromatase inhibitor to further reduce estrogen levels as demonstrated in trials with aromatase inhibitors utilized in postmenopausal women. Clinical trials have accomplished such a reduction in estrogen levels with a combination of goserelin and formestane compared with goserelin alone in premenopausal, metastatic breast cancer patients [14, 15]. In these trials, the combination produced similar estrogen levels to that seen in postmenopausal women receiving formestane alone. Another investigational LHRH agonist, triptorelin, has also produced similar results. In this group of premenopausal breast cancer patients, estradiol levels were significantly lower with the combination therapy (formestane plus triptorelin) than with the single agent triptorelin (97.3% decrease versus 86.9% decrease, respectively; \( p = 0.0422 \)) [16]. Dowsett and colleagues also compared a combination regimen of goserelin plus vorozole in premenopausal patients with the single agent vorozole in postmenopausal patients with advanced breast cancer [17]. Estrogen levels in the postmenopausal patients on vorozole were lower than in the premenopausal patients on combination therapy (goserelin plus vorozole). However, in premenopausal patients, vorozole enhanced estrogen suppression beyond that achieved with goserelin alone [17]. Estrogen may or may not be an adequate marker for clinical activity in metastatic breast cancer, but may lead us to more potent alternatives for treating the disease. Until definitive clinical trials are available making similar comparisons as that presented above, the clinical utility of these combinations remains unknown.

Limited clinical data are available regarding the combination of an LHRH agonist and an aromatase inhibitor in premenopausal breast cancer patients. Dowsett and colleagues conducted a small, uncontrolled trial in patients who had progressed after initially responding to goserelin [14]. Four of the six patients treated (67%) subsequently achieved an objective response (OR) with the addition of an aromatase inhibitor, formestane. Goserelin plus anastrozole has also been evaluated in metastatic breast cancer patients who had failed the combination of goserelin and tamoxifen \((n = 13)\) [18]. At the time of publication, only nine patients had received therapy for 6 months or greater, limiting the evaluation. Objective response or stable disease (OR/SD) was obtained in all but one woman who had liver metastasis (OR/SD = 89%). Seven of the nine patients had achieved OR/SD for at least 1 year. This combination was also better tolerated than the previous regimen of goserelin plus tamoxifen [18]. These trials were small, noncomparative studies and no clear conclusions can be made from the data at this time. A larger, randomized trial is warranted to further evaluate whether combining an LHRH agonist with an aromatase inhibitor is superior to an LHRH agonist alone in the treatment of premenopausal metastatic breast cancer patients.

**LHRH AGONISTS WITH AN ANTIESTROGEN**

One of the most interesting combinations of endocrine therapies is the use of ovarian ablation in conjunction with an antiestrogen, usually tamoxifen. Tamoxifen, when administered to premenopausal women, results in an increase in serum estrogen levels [19]. Several endocrine studies have demonstrated that the coadministration of an LHRH agonist can completely suppress the stimulatory effects of tamoxifen resulting in postmenopausal levels of circulating estrogens [20-24]. Also, combining agents of differing pharmacologic mechanisms may result in additive benefit in terms of clinical activity. This approach to therapy not only seeks to suppress circulating estrogen levels through ovarian ablation, but also to block the effects of estrogen at the cellular level with an antiestrogen. By using this type of combination, a complete estrogen blockade can be achieved.

Endocrine data indicate that the level of estrogen suppression achieved with the LHRH agonist used may influence the effect of tamoxifen when administered concurrently. This is evident specifically with buserelin. The method of administration may contribute to these differences, and intranasal administration appears to be inadequate. Subcutaneous administration is more reliable, but estrogen levels should be monitored in patients on buserelin to verify that castration is achieved. Similar problems are not apparent with goserelin or leuprolide. These small nonrandomized trials exhibit many confounding factors in the use of tamoxifen plus an LHRH agonist in the treatment of breast cancer. Nonetheless, clinical trials with these combinations have been completed with interesting results.

**METASTATIC BREAST CANCER**

Premenopausal metastatic breast cancer can be effectively managed through the use of ovarian ablation plus
In order to address that issue, the European Organization for Research and Treatment of Cancer (EORTC) conducted a similar trial, enrolling 161 premenopausal patients with advanced breast cancer to receive buserelin, tamoxifen, or both agents [28]. Combined treatment was superior to either buserelin or tamoxifen alone by OR rate (48%, 34%, and 28%, respectively; odds ratio LHRH versus combined = 0.56; 95% confidence interval [CI] = 0.24-1.30); odds ratio tamoxifen versus combined = 0.42; 95% CI = 0.17-1.06, progression-free survival (hazard ratio [HR] LHRH versus combined = 1.65 (95% CI = 1.09-2.49); HR tamoxifen versus combined = 1.50 (95% CI = 1.01-2.24), and overall survival (HR LHRH versus combined = 1.95 (95% CI = 1.23-3.10); HR tamoxifen versus combined = 1.63 (95% CI = 1.03-2.59). This demonstrated a benefit of the combination over tamoxifen alone as well as the LHRH agonist alone. However, the superiority in terms of response rates could be argued based on the statistical analysis (odds ratio 95% CI cross 1) [28]. Also in question is the comparative efficacy of buserelin versus goserelin as utilized in the trials previously discussed.

A recent meta-analysis has helped to further elucidate the controversy of single-agent versus combination endocrine therapy. This analysis included the three trials discussed above in addition to a fourth unpublished trial from Japan [34]. The trials differed slightly with respect to the hormonal therapy used and their eligibility criteria. Treatment arms and response rates are listed in Tables 1 and 2. A total of 506

<table>
<thead>
<tr>
<th>References</th>
<th>Treatment arms</th>
<th>Estrogen/progestrone receptor status</th>
<th>Patient population (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jonat et al. [32]</td>
<td>A: GOS 3.6 mg s.c. implant q 4 wks</td>
<td>ER (+) = 61%</td>
<td>Locally advanced or metastatic breast cancer; pre- or perimenopausal (LMP ≤1 year ago);</td>
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<tr>
<td></td>
<td>B: GOS 3.6 mg s.c. implant q 4 wks + TAM 20 mg bid</td>
<td>ER (-) = 21%</td>
<td>no prior systemic therapy for metastases; no prior adjuvant systemic therapy during</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ER (unknown) = 18%</td>
<td>previous 6 months; crossover allowed upon progression (n = 318).</td>
</tr>
<tr>
<td>Boccardo et al. [33]</td>
<td>A: GOS 3.6 mg s.c. implant q 4 wks</td>
<td>ER (+) = 81%</td>
<td>Metastatic breast cancer; pre- or perimenopausal (LMP ≤12 months ago); age &gt;30 years;</td>
</tr>
<tr>
<td></td>
<td>B: GOS 3.6 mg s.c. implant q 4 wks + TAM 30 mg daily</td>
<td>ER (-) = 0%</td>
<td>no prior systemic therapy for metastases (n = 85).</td>
</tr>
<tr>
<td></td>
<td>C: Surgical castration (or irradiation)</td>
<td>ER (unknown) = 19%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D: Surgical castration + TAM 30 mg daily</td>
<td></td>
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<tr>
<td>Klijn et al. [28]</td>
<td>A: BUS 6.6 mg s.c. implant q 6 wks × 12 wks, then q 8 wks</td>
<td>ER (+) = 58%</td>
<td>Locally advanced or metastatic breast cancer; premenopausal (LMP &lt;3 months ago);</td>
</tr>
<tr>
<td></td>
<td>B: BUS 6.6 mg s.c. implant q 6 wks × 12 wks, then q 8 wks + TAM 20 mg bid</td>
<td>ER (-) = 11%</td>
<td>no prior systemic therapy for metastases; no prior adjuvant chemotherapy for</td>
</tr>
<tr>
<td></td>
<td>C: TAM 20 mg bid</td>
<td>ER (unknown) = 31%</td>
<td>6 months; no prior endocrine therapy for 1 year (n = 161).</td>
</tr>
<tr>
<td>Japanese trial (unpublished)</td>
<td>A: GOS 3.6 mg s.c. implant q 4 wks</td>
<td>ER (+) = 55%</td>
<td>Metastatic breast cancer; regular menstrual cycles; no prior systemic therapy for</td>
</tr>
<tr>
<td></td>
<td>B: GOS 3.6 mg s.c. implant q 4 wks + TAM 20 mg daily</td>
<td>ER (-) = 0%</td>
<td>metastases within 4 wks (n = 33).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ER (unknown) = 45%</td>
<td></td>
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</table>

Abbreviations: GOS = goserelin; BUS = buserelin; TAM = tamoxifen; ER = estrogen receptor; bid = twice daily; LMP = last menstrual period.
premenopausal, advanced breast cancer patients were evaluated. Only the LHRH agonist alone arms and the LHRH agonist plus tamoxifen arms were included in this meta-analysis. Two hundred fifty-six patients received LHRH agonists (goserelin or buserelin) alone and 250 were administered an LHRH agonist plus tamoxifen. In the combination group, there was a statistically significant benefit in median survival (2.9 years with combination versus 2.5 years with LHRH agonist alone; \( p = 0.02 \)). Median progression-free survival with combined therapy versus monotherapy was 8.7 months compared to 5.4 months (\( p = 0.0003 \)) and objective responses were observed in 38.8% and 29.7% of patients, respectively (\( p = 0.03 \)). Tolerability between the two treatment arms was not analyzed in this meta-analysis, but was discussed in the individual trials [28, 32, 33]. Tolerability did not appear to decrease with the addition of tamoxifen to the LHRH agonist when the individual trials were reviewed. Similar comparisons of tamoxifen alone and the combination of an LHRH agonist with tamoxifen have not been reported. Therefore, first-line endocrine therapy for premenopausal metastatic breast cancer patients remains tamoxifen alone or an LHRH agonist alone. However, in light of the information presented above, if an LHRH agonist is utilized, the addition of tamoxifen should be considered. Further investigations comparing tamoxifen alone with an LHRH agonist plus tamoxifen are warranted and required to demonstrate superiority with the combination.

**Early-Stage Breast Cancer**

For premenopausal patients with estrogen receptor (ER)- and/or progesterone receptor (PR)-positive tumors, the adjuvant use of endocrine therapy is often utilized sequentially after patients have completed chemotherapy. Endocrine therapy in this setting usually includes an LHRH agonist or tamoxifen. ER/PR-positive premenopausal breast cancer is less common than ER/PR-positive postmenopausal breast cancer and is not as extensively studied. Choosing between endocrine therapy and chemotherapy in the adjuvant setting has been debated for many years and is beyond the scope of this manuscript. However, the administration of chemotherapy, or lack of administration, is a confounding factor in many of the studies discussed below and will be mentioned when appropriate.

Five prospective randomized trials have been published regarding the issue of combination LHRH agonist plus tamoxifen. Some are only preliminary reports and final results may differ from what is presented here (Table 3). Rutqvist and colleagues randomized 2,631 premenopausal early-stage breast cancer patients to either tamoxifen for 2 years, goserelin for 26 months, tamoxifen plus goserelin, or no adjuvant therapy [35]. At a median follow-up of 4.3 years, a significantly lower number of first events were reported in patients receiving goserelin versus those who did not (261 versus 330 events; \( p = 0.001 \)). However, overall survival was similar between these two groups (140 versus 165 deaths; \( p = 0.12 \)). Data regarding the addition of tamoxifen to goserelin are pending. No clear conclusions can be drawn until data from all four arms are available.

Two large randomized trials have evaluated the efficacy of combination endocrine therapy compared with chemotherapy. The Italian Breast Cancer Adjuvant Study Group recently published updated data from their comparative trial with a median follow-up of 76 months [36]. Patients were randomized to receive either CMF (cyclophosphamide, methotrexate, fluorouracil) for six cycles or tamoxifen plus ovarian ablation (surgical, radiotherapeutic, or goserelin). Due to slow accrual, the trial was closed early with only 244 of 300 planned participants enrolled. In the update analysis published in 2000, no difference was observed between treatment groups with respect to overall survival or disease-free survival. Failure to detect a significant difference may have been influenced by the smaller than expected number of patients. However, one interesting finding from these data requires further discussion. Patients who achieved drug-induced amenorrhea from CMF had a lower risk of death compared with those patients who did not achieve amenor-

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>LHRH agonist alone (n = 256)</th>
<th>LHRH agonist + tamoxifen (n = 250)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (years)</td>
<td>2.5</td>
<td>2.9</td>
<td>0.02</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.78 (0.63-0.96)</td>
<td>0.70 (0.58-0.85)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>5.4</td>
<td>8.7</td>
<td>0.0003</td>
</tr>
<tr>
<td>Objective response (%)</td>
<td>29.7</td>
<td>38.8</td>
<td>0.03</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.67 (0.46-0.96)</td>
<td></td>
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</tbody>
</table>

Abbreviations: OS = overall survival; PFS = progression-free survival; HR = hazard ratio; OR = odds ratio; CI = confidence interval; \( p \) value = log-rank \( p \)-value.
rhea secondary to chemotherapy. The Austrian Breast Cancer Study Group, in a similar trial design, randomized 1,045 premenopausal patients to receive either CMF or goserelin (for 3 years) plus tamoxifen (for 5 years) [37]. Based on preliminary data, recurrence-free survival appears to favor the combination endocrine therapy arm. However, a difference in overall survival between the two groups lacks statistical significance. As was demonstrated in the Italian study discussed above, patients who developed amenorrhea after chemotherapy had a significantly improved recurrence-free survival compared with those who did not (p = 0.001 and p = 0.05, respectively) [37]. Data from these studies alone are not sufficient to warrant ovarian ablation in all premenopausal breast cancer patients who do not achieve drug-induced amenorrhea after adjuvant chemotherapy, but brings to light an important issue that requires further investigation.

The chemotherapy regimens utilized in the studies discussed thus far have not included an anthracycline. In the overview analysis updated report by the Early Breast Cancer Trialists’ Collaborative Group, anthracycline-containing adjuvant regimens have been shown to be superior to CMF-like regimens [38]. Would an anthracycline-containing regimen be superior to a combination endocrine therapy regimen? Roche and colleagues evaluated this hypothesis in a randomized trial comparing tamoxifen plus oophorectomy

### Table 3. Combination endocrine therapy for the adjuvant treatment of breast cancer

<table>
<thead>
<tr>
<th>References</th>
<th>Treatment arms</th>
<th>Disease-free survival</th>
<th>Overall survival</th>
<th>Patient population (n)</th>
</tr>
</thead>
</table>
| Ratqvist et al. [35] (abstract data) | A: GOS × 2 y  
B: TAM 20 mg/d × 2 y  
C: TAM + GOS × 2 y  
D: No treatment | GOS = 80%  
No GOS = 75%  
[HR = 0.77 (0.66 – 0.90)] (p = 0.001) | GOS = 89.3%  
No GOS = 87.6%  
[HR = 0.84 (0.67 – 1.05)] (p = 0.12) | Median follow-up = 43 years:  
premenopausal, <50 years of age, node negative or positive (stage I or II),  
treatment after surgery ± radiotherapy ± chemotherapy, benefit was less in those  
that received TAM or chemotherapy in addition to GOS (n = 2,631). |
| Boccardo et al. [36] (abstract data) | A: CMF × 6 cycles  
B: TAM 30 mg/d × 5 y + ovarian ablation (surgical, irradiation, or GOS 3.6 mg/mo × 3 y) | A = 68%  
B = 65%  
[RR = 0.94 (0.60-1.47)] (p = 0.8) | A = NA  
B = NA  
[RR = 0.69 (0.36-1.33)] (p = 0.3) | Median follow-up = 76 months:  
Pre/perimenopausal, ≥35 years of age, node positive or poorly differentiated tumors, ER+, treatment after surgery ± radiotherapy, accrual slow, study discontinued prior to reaching planned accrual (n = 244). |
| Jakesz et al. [37] (abstract data) | A: CMF × 6 cycles  
B: TAM 20 mg/d × 5 y + GOS 3.6 mg/mo × 3 y | TAM + GOS better than CMF  
(data not reported) (p < 0.02) | No statistical difference  
(data not reported) | Median follow-up = 42 months:  
Premenopausal, stage I or II, ER- and/or PR-positive, patients w/amenorrhea after CMF had better DFS and OS (n = 1,045). |
| Roche et al. [39] (abstract data) | A: FAC × 6 cycles  
B: Ovarian ablation (surgical or irradiation) + TAM 30 mg/d × 2 y | A = 55% (43%-56%)  
B = 83% (71%-90%)  
(no p-value reported) | A = 74% (63%-82%)  
B = 84% (74%-91%)  
(no p-value reported) | Median follow-up = 84 months:  
Premenopausal, node-positive, ER- and/or PR-positive, ≥10 + nodes not matched  
(A = 10 patients, B = 4 patients), small number of patients due to early study termination (n = 148). |
| Davidson et al. [40] (abstract data) | A: CAF × 6 cycles  
B: CAF + GOS 3.6 mg/mo × 5 y  
C: CAF + GOS + TAM 20 mg/d × 5 y | 5-year  
A = 67%  
B = 70%  
C = 78%  
(C versus B, p < 0.01, B versus A, p = 0.10) | 5-year  
A = 85%  
B = 86%  
C = 86%  
(no p-value reported) | Median follow-up = 6 years:  
Premenopausal, node positive, receptor positive, 6 endometrial cancers, AML, 2 MDS reported (n = 1,504). |

Abbreviations: GOS = goserelin; TAM = tamoxifen; HR = hazard ratio (95% confidence interval); RR = relative risk (95% confidence intervals); NA = not available; ER = estrogen receptor; PR = progesterone receptor; DFS = disease-free survival; OS = overall survival; AML = acute myeloid leukemia; MDS = myelodysplastic syndrome.

**CMF** = cyclophosphamide 100 mg/m²/day orally × 14 days, methotrexate 40 mg/m² i.v. days 1 and 8, fluorouracil 600 mg/m² i.v. days 1 and 8.

**CMF** = cyclophosphamide 600 mg/m² i.v. days 1 and 8, methotrexate 40 mg/m² i.v. days 1 and 8, fluorouracil 600 mg/m² i.v. days 1 and 8.

**FAC** = fluorouracil 500 mg/m² i.v. day 1, doxorubicin 50 mg/m² i.v. day 1, cyclophosphamide 500 mg/m² i.v. day 1.

**CAF** = cyclophosphamide 100 mg/m²/day orally × 14 days, doxorubicin 30 mg/m² i.v. days 1 and 8, fluorouracil 500 mg/m² i.v. days 1 and 8.


(surgical or radiotherapeutic) with standard FAC (fluorouracil, doxorubicin, and cyclophosphamide) [39]. Patients enrolled in this trial were premenopausal, node-positive, and had ER- and PR-receptor-positive breast cancer. The trial closed early due to slow patient accrual with only 153 patients fully evaluable. Disease-free survival was significantly longer in the endocrine therapy arm at a median follow-up of 7 years (82.8% [CI = 71%-90%] versus 55% [CI 43%-56%]). However, the groups were not equally matched in regard to the number of involved axillary lymph nodes, which was the most important predictive factor in terms of disease-free survival in a multifactorial analysis. When the number of positive axillary lymph nodes were taken into account, there was no difference identified between groups in regard to disease-free survival [39]. These data have only been published in abstract form and with the small number of patients enrolled, the proposed hypothesis may not be adequately answered. Until more information is available, no clear conclusions can be drawn from this trial and the use of an LHRH agonist in this setting has yet to be addressed.

The Eastern Cooperative Oncology Group/Intergroup set out to perform a similar study randomizing premenopausal early stage breast cancer patients to: A) CAF (cyclophosphamide, doxorubicin, fluorouracil) for six cycles; B) CAF for six cycles plus goserelin monthly for 5 years, or C) CAF for six cycles plus goserelin plus tamoxifen for 5 years [40]. The 5-year recurrence-free survival rates were higher in the combination endocrine therapy arm (A = 67%, B = 70%, C = 78%) at a median follow-up of 6 years. However, similar results were found with regard to overall survival among the three groups (A = 85%, B = 86%, C = 86%). This trial has only been published in abstract form, and statistical analysis was not completed. Outcomes from this study may change as more information becomes available. Several trials are ongoing investigating the adjuvant use of LHRH agonists compared with chemotherapy in premenopausal breast cancer patients. However, none of these ongoing trials include the combination endocrine therapy discussed here.

CONCLUSIONS

Complete estrogen blockade has been compared with single-agent treatments in many different settings. The endocrine effects of this type of therapy are intriguing, but apparently do not readily predict a clinical advantage. The combination of an aromatase inhibitor and an antiestrogen, despite pharmacokinetic interactions, may prove to be beneficial. Results from ongoing trials are eagerly awaited to further address this question in postmenopausal breast cancer patients.

For premenopausal breast cancer patients the options are more complex. The combination of an aromatase inhibitor with an LHRH agonist is an interesting prospect. In a sense, the endocrine goal of this therapy is similar to that seen in the postmenopausal setting with an aromatase inhibitor alone. Clinical outcomes with this combination are limited to very small phase II studies and are not clearly superior to single-agent therapy. The combination of an LHRH agonist with an antiestrogen is by far the most intriguing combination for premenopausal breast cancer patients. Clinical data in the metastatic setting favor the use of an LHRH agonist with tamoxifen over the use of an LHRH agonist alone. However, a similar comparison to tamoxifen alone is lacking with only one trial including this as a treatment arm. Hopefully, with future investigations, more distinct information will be forthcoming.

Adjuvant therapy with this combined endocrine approach (LHRH agonist plus antiestrogen) has been more extensively studied, but lacks crucial comparisons necessary for making complex treatment decisions. Indirect comparisons from the Rutqvist study indicate a potential benefit when goserelin is added to tamoxifen, but this is not clear from the preliminary data currently available [35]. More significant conclusions are found in the comparisons of chemotherapy with combined endocrine therapy. While there does not appear to be a clear advantage of chemotherapy over endocrine therapy or vice versa, the importance of chemotherapy-induced amenorrhea is demonstrated in at least two of the trials discussed. Slow accrual and early termination have plagued many of these trials. Perhaps this is indicative of the changing environment in the management of breast cancer. Chemotherapy is more commonly utilized today compared with several years ago. The questions that now need to be asked are different with regard to the issues at hand. For example, for those patients whose tumors are ER- and/or PR-positive and amenorrhea is not achieved after adjuvant chemotherapy, will inducing menopause through the use of an LHRH agonist improve outcomes? Will adding tamoxifen to the LHRH agonist further improve outcomes? The first question is being addressed in several large adjuvant trials currently ongoing, but the latter question has yet to be asked. Hopefully, through investigative diligence and ingenuity this issue can be adequately understood. However, many exciting new agents are on the horizon that offer hope to further advance the progress made to date although further confound the questions already answered.

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