Adjuvant Chemotherapy Followed by Goserelin Versus Either Modality Alone for Premenopausal Lymph Node–Negative Breast Cancer: A Randomized Trial

International Breast Cancer Study Group (IBCSG)

Background: Although chemotherapy and ovarian function suppression are both effective adjuvant therapies for patients with early-stage breast cancer, little is known of the efficacy of their sequential combination. In an International Breast Cancer Study Group (IBCSG) randomized clinical trial (Trial VIII) for pre- and perimenopausal women with lymph node–negative breast cancer, we compared sequential chemotherapy followed by the gonadotropin-releasing hormone agonist goserelin with each modality alone. Methods: From March 1990 through October 1999, 1063 patients stratified by estrogen receptor (ER) status and radiotherapy plan were randomly assigned to receive goserelin for 24 months (n = 346), six courses of “classical” CMF (cyclophosphamide, methotrexate, 5-fluorouracil) chemotherapy (n = 360), or six courses of classical CMF followed by 18 months of goserelin (CMF → goserelin; n = 357). A fourth arm (no adjuvant treatment) with 46 patients was discontinued in 1992. Tumors were classified as ER-negative (30%), ER-positive (68%), or ER status unknown (3%). Twenty percent of patients were aged 39 years or younger. The median follow-up was 7 years. The primary outcome was disease-free survival (DFS). Results: Patients with ER-negative tumors achieved better disease-free survival if they received CMF (5-year DFS for CMF = 84%, 95% confidence interval [CI] = 77% to 91%; 5-year DFS for CMF → goserelin = 88%, 95% CI = 82% to 94%) than if they received goserelin alone (5-year DFS = 73%, 95% CI = 64% to 81%). By contrast, for patients with ER-positive disease, chemotherapy alone and goserelin alone provided similar outcomes (5-year DFS for both treatment groups = 81%, 95% CI = 76% to 87%), whereas sequential therapy (5-year DFS = 86%, 95% CI = 82% to 91%) provided a statistically non-significant improvement compared with either modality alone, primarily because of the results among younger women. Conclusions: Premenopausal women with ER-negative (i.e., endocrine nonresponsive), lymph node–negative breast cancer should receive adjuvant chemotherapy. For patients with ER-positive (i.e., endocrine responsive) disease, the combination of chemotherapy with ovarian function suppression or other endocrine agents, and the use of endocrine therapy alone should be studied. [J Natl Cancer Inst 2003;95:1833–46]
involving premenopausal women. Suppressed ovarian function was achieved by surgical castration or by irradiation of the ovaries. More recently, gonadotropin-releasing hormone agonist drugs such as goserelin have been used. Suppressed ovarian function can also result from the use of cytotoxic agents. Patients who experienced amenorrhea, a consequence of suppressed ovarian function, after chemotherapy had longer disease-free survival than patients who maintained ovarian function in some studies (7–11) but not in others (12–14). Thus, a controversy exists regarding the use of agents that suppress ovarian function after chemotherapy (4). Five years of tamoxifen, the most common endocrine therapy used in the adjuvant setting, has been shown to be effective for reducing the risk of recurrent disease and death in premenopausal and perimenopausal patients with endocrine-responsive breast tumors (5).

In 1990, the International Breast Cancer Study Group (IBCSG) initiated a clinical trial (Trial VIII) for premenopausal and perimenopausal patients with lymph node–negative breast cancer to examine the role of adjuvant treatment using chemotherapy, ovarian suppression with goserelin, or the sequential combination of both modalities. Here, we provide the first report of results after a median follow-up of 7 years for women enrolled in IBCSG Trial VIII.

PATIENTS AND METHODS

Study Design

From March 1990 through October 1999, 1111 premenopausal and perimenopausal patients were randomly assigned to receive no adjuvant systemic treatment, six 28-day courses of “classical” CMF chemotherapy (in which one course consisted of oral cyclophosphamide at 100 mg/m² on days 1–14, intravenous methotrexate at 40 mg/m² on days 1 and 8, and intravenous 5-fluorouracil at 600 mg/m² on days 1 and 8), 24 monthly subcutaneous implants of goserelin (3.6 mg) every 28 days, or six 28-day courses of classical CMF followed by 18 monthly implants of goserelin. Systemic adjuvant therapy was to begin within 6 weeks of primary surgery. For the sequential treatment arm, the first goserelin implant was scheduled to be given on day 28 of the sixth course of CMF. Informed consent was required according to the criteria established within the individual countries. The protocol was reviewed and approved by institutional review boards.

In April 1992, on the basis of results from other trials (15–18), randomization to the no-adjuvant-treatment control arm was discontinued. At that time, the trial had accrued 205 patients, 46 of whom had been randomly assigned to the control arm. The results for this small initial cohort have been previously published (19). This article reports the results of comparisons between the three active adjuvant-treatment arms.

Randomization was conducted centrally (at the coordinating centers in Bern, Switzerland, and Sydney, Australia) after stratification according to estrogen receptor (ER) status (negative, positive, or unknown), whether radiotherapy was planned after breast-conserving surgery (yes or no), and by participating institution (see Appendix). The permuted blocks randomization schedule was produced by use of pseudorandom numbers generated by a congruence method.

Pre- or perimenopausal status was defined as having one of the following sets of characteristics: 1) aged older than 52 years with last normal menstrual period within 1 year, 2) aged 52 years or younger with last normal menstrual period within 3 years, 3) aged 55 years or younger with normal menstrual periods but no bilateral oophorectomy (for patients aged older than 45 years, biochemical confirmation of ovarian function was requested), or 4) biochemical evidence of continuing ovarian function (for doubtful cases).

All patients had a histologically proven unilateral breast cancer of stage T_1a , T_1b , T_1c , T_2 , T_3 , pN_0 , M_0 (according to the staging system of the Union Internationale Contre le Cancer 1987 (20)), with either ER-positive or ER-negative primary tumors. The ER-unknown status was allowed only if ER determination was not possible because of the lack of tumor material. Steroid hormone receptor concentrations in the primary tumors were determined by standard methods (21,22). ER concentrations of at least 10 fmol/mg of cytosol protein by ligand-binding assay were considered positive; lower values were considered negative. Determination of steroid hormone receptor status by immunohistochemistry was allowed later in the study. Consequently, ER status for 33% of the patients was determined by immunohistochemistry, and participating center values for positivity were used.

Surgery to remove the primary tumor was either a total mastectomy with axillary clearance or a conservative procedure (quadrantectomy or lumpectomy) with axillary lymph node dissection. Radiotherapy was recommended after breast-conserving surgery and was postponed until the end of chemotherapy, if applicable (23). Staging before randomization included chest x-ray, contralateral mammogram, bone scintogram (if clinically applicable) and was postponed until the end of chemotherapy, if applicable (23). Staging before randomization included chest x-ray, contralateral mammogram, bone scintogram (if clinically indicated), and hematologic, liver, and renal function tests.

Clinical, hematologic, and biochemical assessments were required every 3 months for the first year, every 6 months for the second year, and yearly thereafter. Modified World Health Organization toxicity grading criteria were used (24). Mammography was performed yearly. The data management and medical staff reviewed all study records (initial data, treatment, toxicity, and recurrence) and conducted regular site visit audits. In particular, the study chair (M. Castiglione-Gertsch) reviewed the records for all grade 3 or worse toxicities.

End Points and Statistical Considerations

Disease-free survival was defined as the length of time from the date of randomization to any recurrent disease (including ipsilateral breast recurrence), the appearance of a second primary cancer (including contralateral breast cancer), or death, whichever occurred first. Overall survival was defined as the length of time from the date of randomization to death from any cause.

Disease-free survival and overall survival percentages, standard errors, and treatment effect comparisons were obtained from the Kaplan–Meier method (25), Greenwood’s formula (26), and log-rank tests (27), respectively. Cox proportional hazards regression models (28) were used to control for prognostic features, to estimate relative risks (RRs) and 95% confidence intervals (CIs) for the treatment comparisons, and to test for interactions between potential predictive factors and treatment effects. To check assumptions of proportionality, curves of the log of the cumulative hazard for each value of a covariate adjusted for other covariates in the model were plotted and assessed visually to determine if the vertical shift between the
curves was constant over time. The data appeared to meet the assumptions of proportionality in all cases, with the exception of age for the goserelin alone versus CMF alone comparison in the ER-negative cohort. Adding an interaction term for age and time in the model for this treatment comparison did not change the treatment effect estimate. All probability values were obtained from two-sided tests. Results are reported at a median follow-up of 7 years.

Treatment–covariate interactions were studied by use of the nonparametric Subpopulation Treatment Effect Pattern Plot (STEEP) methodology (29,30). STEEP involves defining several overlapping subgroups of patients on the basis of a covariate of interest and studying the resulting pattern of the treatment effects estimated within each subgroup. In this article, patient age at study entry was the covariate of interest, and the treatment effects estimated within each age subgroup were measured in terms of 5-year disease-free survival percentages, both overall and for cohorts defined according to ER status.

The intention to perform separate analyses according to ER status was specified in the original protocol. After the closure of the no-adjuvant-treatment control arm in 1992, the study was redesigned to assess whether six courses of CMF followed by 18 implants of goserelin improved results relative to six courses of CMF alone (80% power to detect an improvement in 5-year DFS from 80% to 88%) and whether 24 implants of goserelin and six courses of CMF were comparable (95% chance to reject equivalence if goserelin [72% 5-year DFS] was less effective than CMF [80% 5-year DFS]). Two hundred twenty-four events were required; 228 were observed at the time of this analysis.

The Data and Safety Monitoring Committee reviewed accrual and safety data twice a year. Two predetermined interim efficacy analyses were performed (in December 1997 and June 2000), and study continuation was recommended on both occasions. In 1998, a protocol amendment restricted enrollment to patients aged 45 years or older at entry and adding approximately 30 patients with the next higher age. Each subsequent subpopulation was formed moving from left to right by dropping approximately 30 patients with the lowest age each subsequent subpopulation was formed moving from left to right by dropping approximately 30 patients with the lowest age and adding approximately 30 patients with the next higher age. The x coordinate indicates the median age for the patients in each subpopulation. The y coordinate indicates the 5-year disease-free survival percent estimated using the Kaplan–Meier method on data from patients in each subpopulation. The results for the entire study population show that, without separation of

### Patient Eligibility and Characteristics

Of the 1111 patients randomly assigned, 46 were assigned to the no-adjuvant-treatment arm and 1065 were assigned to one of the three adjuvant-treatment arms (Fig. 1). Two patients enrolled from a noncompliant participating center were excluded from all analyses. Of the remaining 1063 patients, 20 (1.9%) patients did not meet protocol eligibility criteria for the following reasons: postmenopausal status (n = 11), in situ disease only (n = 2), resection margins involved with tumor (n = 3), prior malignancy (n = 2), lymph node–positive disease (n = 1), and medical unsuitability (n = 1). However, all 20 ineligible patients are included in the intent-to-treat analyses.

The characteristics of the 1063 assessable patients who were enrolled in active treatment arms are shown in Table 1. The median age was 45 years (range = 28–58 years). Thirty percent (315) of the patients had primary tumors classified as ER-negative (11% ER absent and 19% ER low), 68% (720) were classified as ER-positive, and 3% (28) were classified as ER-unknown. The median number of axillary lymph nodes examined was 16 (range = 5–60 lymph nodes).

### RESULTS

#### Disease-Free Survival and Overall Survival

Overall, no differences were observed among the three treatment groups (CMF chemotherapy, goserelin, CMF chemotherapy followed by goserelin) in terms of disease-free survival (Fig. 2, A, and Table 2) or overall survival (Fig. 2, B). However, differences among the treatment groups were suggested for subpopulations defined according to ER status. Disease-free survival for patients with ER-negative tumors who received CMF alone (5-year DFS = 84%, 95% CI = 77% to 91%) or CMF followed by goserelin (5-year DFS = 88%, 95% CI = 82% to 94%) was greater than that for patients with ER-negative tumors who received only goserelin (5-year DFS = 73%, 95% CI = 64% to 81%) (Fig. 2, C, and Table 2). By contrast, disease-free survival estimates for patients with ER-positive tumors who received CMF alone (5-year DFS = 81%, 95% CI = 76% to 87%) or who received goserelin alone (5-year DFS = 81%, 95% CI = 76% to 87%) were equivalent, whereas there was a modest, statistically nonsignificant advantage associated with the sequential administration of CMF followed by goserelin (5-year DFS = 86%, 95% CI = 82% to 91%) (Fig. 2, D, and Table 2). Unplanned, retrospective subgroup analyses according to age suggested that, among women with ER-negative tumors, the superiority of the CMF-containing regimens compared with goserelin alone was seen for both older and younger women, whereas for women with ER-positive tumors, the advantage of CMF followed by goserelin was seen only for younger women (Fig. 2, E and F, and Table 2).

STEEP analyses were used to evaluate the differences in treatment effects in terms of 5-year disease-free survival according to age (Fig. 3). For this sliding-window STEEP analysis, each subpopulation contained approximately 165 patients, and each subsequent subpopulation was formed moving from left to right by dropping approximately 30 patients with the lowest age and adding approximately 30 patients with the next higher age. The x coordinate indicates the median age for the patients in each subpopulation. The y coordinate indicates the 5-year disease-free survival percent estimated using the Kaplan–Meier method on data from patients in each subpopulation. The results for the entire study population show that, without separation of
Table 1. Patients’ characteristics according to treatment

<table>
<thead>
<tr>
<th>Patients’ characteristics according to treatment*</th>
<th>No. of patients (%)</th>
<th>Goserelin × 6 (n = 346)</th>
<th>CMF × 6 (n = 360)</th>
<th>CMF × 6 → goserelin × 18 (n = 357)</th>
<th>Total (n = 1063)</th>
</tr>
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<tbody>
<tr>
<td>ER status†</td>
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<tr>
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<td>22 (6)</td>
<td>20 (6)</td>
<td>58 (5)</td>
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<td></td>
<td>35–39</td>
<td>51 (15)</td>
<td>46 (13)</td>
<td>54 (15)</td>
<td>151 (14)</td>
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<td></td>
<td>40–44</td>
<td>80 (23)</td>
<td>106 (29)</td>
<td>92 (26)</td>
<td>278 (26)</td>
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<td></td>
<td>≥50</td>
<td>141 (41)</td>
<td>130 (36)</td>
<td>125 (35)</td>
<td>396 (37)</td>
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<td>42 (12)</td>
<td>51 (14)</td>
<td>126 (12)</td>
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<tr>
<td></td>
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<td>172 (48)</td>
<td>174 (49)</td>
<td>527 (50)</td>
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<td>130 (38)</td>
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<td>126 (36)</td>
<td>399 (38)</td>
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<td>48 (13)</td>
<td>81 (23)</td>
<td>184 (17)</td>
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<td>128 (37)</td>
<td>143 (40)</td>
<td>125 (35)</td>
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<td>65 (62)</td>
<td>57 (55)</td>
<td>184 (58)</td>
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<td>12 (11)</td>
<td>14 (13)</td>
<td>31 (10)</td>
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<td>51 (48)</td>
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<td>41 (39)</td>
<td>126 (40)</td>
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<td>≥2.1</td>
<td>50 (47)</td>
<td>58 (55)</td>
<td>48 (46)</td>
<td>156 (50)</td>
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<td>Tumor grade</td>
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<td>97 (31)</td>
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<td>3</td>
<td>62 (58)</td>
<td>65 (62)</td>
<td>57 (55)</td>
<td>184 (58)</td>
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</table>

*CMF × 6 = cyclophosphamide at 100 mg/m² on days 1–4, orally; methotrexate at 40 mg/m² on days 1 and 8, intravenously; and 5-fluorouracil at 600 mg/m² on days 1 and 8, intravenously; repeated for six 28-day courses. Goserelin × 6 = goserelin at 3.6 mg by subcutaneous implant monthly for 24 months. For the sequential combination therapy, CMF × 6 was followed by goserelin × 18. 3 = followed by; ER = estrogen receptor; RT = radiotherapy.

†ER status was determined by a ligand-binding assay for 67% of the patients and by immunohistochemistry for the other 33% of the patients (21,22). For the ligand-binding assay, ER concentrations of at least 10 fmol/mg of cytosol protein were considered positive. For the immunohistochemistry, participating center values were used.

‡Methodologically, for tumors graded as grade 1, it is possible that the ER-negative classification might be false.
Fig. 2. Kaplan–Meier plots of disease-free survival (DFS) (panel A) and overall survival (OS) (panel B) for 1063 pre- and perimenopausal women with lymph node-negative breast cancer enrolled in the International Breast Cancer Study Group (IBCSG) Trial VIII according to randomized treatment group at a median follow-up of 7 years. Also shown are Kaplan–Meier plots of DFS for 315 patients in the estrogen receptor (ER)–negative cohort (panel C), for 720 patients in the ER-positive cohort (panel D), for 126 patients aged 39 years or younger in the ER-positive cohort (panel E), and for 594 patients aged 40 years or older in the ER-positive cohort (panel F). The number of patients, number of DFS events, 5-year DFS % and 95% confidence interval (CI) for each treatment group, and the relative risk of an event (recurrent disease, second malignancy, or death), 95% CI, and P value for each pairwise treatment comparison for DFS are shown in Table 2. For the overall survival in panel B, the 5-year OS % are 95% (95% CI = 93% to 97%; 35 deaths) for goserelin alone, 93% (95% CI = 90% to 95%; 37 deaths) for CMF alone, and 95% (95% CI = 93% to 97%; 27 deaths) for CMF followed by goserelin.
the analysis according to ER status, there was no clear pattern of treatment differences according to age (Fig. 3, A). By contrast, the CMF-containing regimens provide superior disease-free survival across all age groups for patients with ER-negative tumors (Fig. 3, B), whereas the benefit of the sequential regimen for patients with ER-positive disease increased substantially as the median age of the patient subpopulation decreased below approximately age 43 years (Fig. 3, C). Fig. 3, C, also illustrates that the equivalent outcome for CMF alone and goserelin alone was seen across all age groups.

Interactions between the magnitude of treatment differences and ER status were assessed using Cox proportional hazards models. Despite low statistical power, tests for interactions suggested that, compared with the CMF-containing regimens, goserelin alone was less effective for the ER-negative cohort than for the ER-positive cohort (interactions: \( P = .13 \) for goserelin compared with the CMF–goserelin sequence and \( P = .17 \) for goserelin compared with CMF alone).

Considering the suggestive, statistically nonsignificant differences in treatment effect and the current approach of tailoring adjuvant therapy according to the steroid hormone receptor status of the primary tumor, multiple regression analyses of disease-free survival were conducted separately for the ER-negative and ER-positive cohorts (Table 3). Factors for treatment, age, primary therapy, tumor size, and tumor grade were included in all models. Treatment differences remained statistically significant for the ER-negative cohort, even after adjustment for other factors. For the ER-positive cohort, age, primary treatment (increased risk of an event for breast-conserving surgery without radiotherapy), and tumor grade were prognostically significant (Table 3).

### Incidence of Amenorrhea

The percentage of patients who reported no menses during each month after randomization according to treatment group is shown in Fig. 4. The percentage of patients who reported no menses during each month from the no-adjuvant-therapy control group was provided as an estimate for the natural rate of cessation of menses associated with increasing age.

For patients aged 39 years or younger (Fig. 4, A), goserelin induced amenorrhea within 2 months of study entry for 90% of
Amenorrhea continued until the end of treatment (i.e., at 24 months), when menses resumed in all but a few patients. By contrast, chemotherapy-induced amenorrhea was achieved more slowly and was observed in approximately 50% of patients by the end of six courses of CMF. Among patients in whom goserelin was not given after CMF, menses resumed in approximately 15%, although amenorrhea continued in approximately 35%–40% of patients throughout the 36-month period of observation. Among patients who received goserelin after CMF, virtually all achieved amenorrhea during the 18-month goserelin treatment period. Interestingly, resumption of menses after cessation of goserelin was slower in patients who had received initial CMF chemotherapy than in those who did not receive CMF chemotherapy, although menses did return in approximately 40% of patients by the end of the 36-month follow-up period—the same percentage as among patients who had received goserelin alone.

The pattern of incidence of amenorrhea over time was different for patients aged 40 years or older at the time of study entry (Fig. 4, B). The median age at study entry for this patient cohort was 46 years. Chemotherapy-induced amenorrhea was observed sooner and in a larger percentage of patients than was observed in the younger cohort. More than 90% of patients who received six courses of CMF achieved amenorrhea by the end of chemotherapy. Although menses resumed in a few patients who did not receive goserelin after chemotherapy, a high incidence of amenorrhea was observed during the entire 36-month follow-up period, regardless of whether goserelin was used. The incidence of amenorrhea after completion of goserelin alone was the same (approximately 55%) as that observed for the no-adjuvant-therapy group during the third year of follow-up.

Sites of Treatment Failure

Of the 1063 patients, 228 (21.4%) had recurrent disease or died (Table 4). For the ER-negative cohort, the percentage of patients with visceral metastases was lower for the CMF group than for the goserelin alone group (difference = 4.6%, 95% CI = −2.3% to 11.5%), and the percentage of patients with local recurrences was lower for the CMF followed by goserelin group than for the goserelin alone group (difference = 4.6%, 95% CI = −1.4% to 10.6%). For the ER-positive cohort, the percentage of patients with local recurrences was lower for the CMF or CMF followed by goserelin groups than for the goserelin alone group (difference with CMF = 4.3%, 95% CI = 0.0% to 8.6%, and difference with CMF followed by goserelin = 3.0%, 95% CI = −1.5% to 7.5%).

CMF Treatment and Toxicity

Among the 717 patients randomly assigned to receive six courses of CMF (either alone or followed by goserelin), 646 (90%) completed all six courses, 55 (8%) received at least one but fewer than six courses, and 16 (2%) received no chemotherapy. Patient compliance was similar among treatment groups regardless of whether CMF was followed by goserelin. Grade 3 or worse toxicities (primarily leukopenia, neutropenia, and nausea/vomiting) were experienced by 18.8% of the patients during CMF, including three life-threatening toxicities (two pulmonary embolisms and one cerebrovascular accident). There were no treatment-related deaths. Of the 701 patients who received at least one course of CMF, 18.7% reported alopecia requiring them to wear a wig.
**Table 3.** Multiple regression analyses of disease-free survival for estrogen receptor (ER)-negative and ER-positive cohorts

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Relative risk (95% CI)†</th>
<th>P‡</th>
<th>Relative risk (95% CI)†</th>
<th>P‡</th>
<th>Relative risk (95% CI)†</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Rx group vs. second Rx group</td>
<td>0.77 (0.41 to 1.45)</td>
<td>.41</td>
<td>1.61 (0.93 to 2.80)</td>
<td>.09</td>
<td>0.50 (0.28 to 0.90)</td>
<td>.02</td>
</tr>
<tr>
<td>Age, y: ≤39 vs. ≥40</td>
<td>1.23 (0.57 to 2.65)</td>
<td>.60</td>
<td>0.76 (0.39 to 1.48)</td>
<td>.42</td>
<td>0.81 (0.43 to 1.54)</td>
<td>.52</td>
</tr>
<tr>
<td>Primary treatment</td>
<td></td>
<td>.36</td>
<td></td>
<td>.44</td>
<td></td>
<td>.19</td>
</tr>
<tr>
<td>BCS without RT vs. mastectomy</td>
<td>2.23 (0.78 to 6.41)</td>
<td>.61</td>
<td>1.28 (0.47 to 3.47)</td>
<td>.59</td>
<td>1.81 (0.68 to 4.78)</td>
<td>.96</td>
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<tr>
<td>Tumor size, cm</td>
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<td>.61</td>
<td></td>
<td>.59</td>
<td></td>
<td>.96</td>
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<tr>
<td>1.1–2.0 vs. ≤1.0</td>
<td>1.10 (0.34 to 3.49)</td>
<td></td>
<td>0.79 (0.29 to 2.15)</td>
<td></td>
<td>1.39 (0.39 to 4.91)</td>
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<tr>
<td>≥2.1 vs. ≤1.0</td>
<td>1.59 (0.49 to 5.20)</td>
<td></td>
<td>0.58 (0.21 to 1.58)</td>
<td></td>
<td>1.40 (0.38 to 5.23)</td>
<td></td>
</tr>
<tr>
<td>Tumor grade§</td>
<td></td>
<td>.89</td>
<td></td>
<td>.51</td>
<td></td>
<td>.28</td>
</tr>
<tr>
<td>2 vs. 1</td>
<td>0.87 (0.23 to 3.24)</td>
<td></td>
<td>1.69 (0.48 to 5.89)</td>
<td></td>
<td>2.14 (0.48 to 9.48)</td>
<td></td>
</tr>
<tr>
<td>3 vs. 1</td>
<td>1.17 (0.34 to 4.07)</td>
<td></td>
<td>2.17 (0.65 to 7.20)</td>
<td></td>
<td>2.94 (0.70 to 12.4)</td>
<td></td>
</tr>
<tr>
<td>First Rx group vs. second Rx group</td>
<td>0.80 (0.53 to 1.20)</td>
<td>.29</td>
<td>0.97 (0.66 to 1.43)</td>
<td>.90</td>
<td>0.92 (0.61 to 1.38)</td>
<td>.68</td>
</tr>
<tr>
<td>Age, y: ≤39 vs. ≥40</td>
<td>1.61 (1.01 to 2.61)</td>
<td>.04</td>
<td>2.32 (1.51 to 3.56)</td>
<td>&lt;.01</td>
<td>1.64 (0.99 to 2.72)</td>
<td>.06</td>
</tr>
<tr>
<td>Primary treatment</td>
<td></td>
<td>&lt;.01</td>
<td></td>
<td>&lt;.01</td>
<td></td>
<td>.12</td>
</tr>
<tr>
<td>BCS without RT vs. mastectomy</td>
<td>2.93 (1.46 to 5.88)</td>
<td>.58</td>
<td>2.68 (1.31 to 5.51)</td>
<td>.45</td>
<td>2.07 (0.92 to 4.66)</td>
<td>.13</td>
</tr>
<tr>
<td>BCS with RT vs. mastectomy</td>
<td>0.69 (0.45 to 1.07)</td>
<td></td>
<td>0.75 (0.48 to 1.14)</td>
<td></td>
<td>0.82 (0.53 to 1.28)</td>
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<tr>
<td>Tumor size, cm</td>
<td></td>
<td>.61</td>
<td></td>
<td>.59</td>
<td></td>
<td>.96</td>
</tr>
<tr>
<td>1.1–2.0 vs. ≤1.0</td>
<td>1.45 (0.68 to 3.06)</td>
<td></td>
<td>1.24 (0.58 to 2.65)</td>
<td></td>
<td>2.29 (0.82 to 6.43)</td>
<td></td>
</tr>
<tr>
<td>≥2.1 vs. ≤1.0</td>
<td>1.61 (0.74 to 3.48)</td>
<td></td>
<td>1.54 (0.72 to 3.35)</td>
<td></td>
<td>2.62 (0.92 to 7.47)</td>
<td></td>
</tr>
<tr>
<td>Tumor grade§</td>
<td></td>
<td>&lt;.01</td>
<td></td>
<td>&lt;.01</td>
<td></td>
<td>.01</td>
</tr>
<tr>
<td>2 vs. 1</td>
<td>2.09 (1.00 to 4.35)</td>
<td></td>
<td>1.99 (0.97 to 4.07)</td>
<td></td>
<td>2.26 (1.13 to 4.51)</td>
<td></td>
</tr>
<tr>
<td>3 vs. 1</td>
<td>4.01 (1.95 to 8.25)</td>
<td></td>
<td>2.77 (1.33 to 5.76)</td>
<td></td>
<td>2.84 (1.40 to 5.75)</td>
<td></td>
</tr>
</tbody>
</table>

*CMF × 6 = cyclophosphamide at 100 mg/m2 on days 1–14, orally; methotrexate at 40 mg/m2 on days 1 and 8, intravenously; and 5-fluorouracil at 600 mg/m2 on days 1 and 8, intravenously; repeated for six 28-day courses. Goserelin × 24 = goserelin at 3.6 mg by subcutaneous implant monthly for 24 months. For the sequential combination therapy, CMF × 6 was followed by goserelin × 18. CI = confidence interval; Rx = followed by; treatment group indicated at the top of the column; BCS = breast-conserving surgery; RT = radiotherapy.

†Relative risk for each analysis is the ratio of an event (recurrent disease, second malignancy, or death) for the treatment group indicated at the top of the column to the control group or comparison group.

‡All statistical tests (Wald test for single covariate; likelihood ratio test for multiple covariates) were two-sided. Models included indicator variables for unknown tumor size and for unknown grade.

§Methodologically, for tumors graded as grade 3 or worse, the ER-negative classification might be false.

Goserelin Treatment and Toxicity

Among the 346 patients assigned to goserelin alone, 304 (88%) received at least 22 implants, 36 (10%) received fewer implants because of recurrent disease (5%) or other reasons (5%), and six (2%) received no goserelin. Among the 357 patients assigned to goserelin following CMF, 289 (81%) received at least 17 implants, 37 (10%) received fewer implants because of recurrent disease (3%) or other reasons (7%), and 31 (9%) received no goserelin. Grade 3 or worse toxicities (primarily weight gain) were experienced by 3.9% of the 666 patients who received at least one goserelin implant (4.7% in the goserelin alone group and 3.1% in the goserelin following CMF group). One life-threatening (suicidal) depression was reported during goserelin treatment (after 6 months of CMF and four goserelin implants).

Comparisons With No Adjuvant Treatment

The median follow-up for the 205 patients who were enrolled before April 2, 1992, was 10.4 years. Disease-free survival for patients assigned to the no-adjuvant-treatment group was less than that for patients in the three treatment groups combined, but with the small number of patients, the difference was not statistically significant (P = .19). Five-year disease-free survival percentages (95% CI; sample size) were 61% (95% CI = 47% to 75%; n = 46) for no treatment, 73% (95% CI = 62% to 84%; n = 63) for goserelin alone, 79% (95% CI = 67% to 91%; n = 43) for CMF alone, and 81% (95% CI = 71% to 92%; n = 53) for CMF followed by goserelin. The corresponding values for 5-year disease-free survival percentages (95% CI; sample size) were 46% (95% CI = 19% to 73%; n = 13), 64% (95% CI = 44% to 84%; n = 22), 89% (95% CI = 74% to 98%; n = 18), 89% (95% CI = 74% to 98%; n = 18) for the ER-negative cohort and 67% (95% CI = 50% to 84%; n = 30), 73% (95% CI = 58% to 88%; n = 34), 70% (95% CI = 52% to 89%; n = 24), 81% (95% CI = 68% to 95%; n = 32) for the ER-positive cohort.

Discussion

IBCSG Trial VIII for premenopausal and perimenopausal women with lymph node–negative breast cancer began in 1990,
Ovarian function suppression was the first adjuvant systemic treatment studied for patients with early-stage breast cancer (4,32–34). Chemotherapy is effective adjuvant therapy for premenopausal women (6). For several years, the effects of cytotoxic agents on ovarian function were studied, but the interpretation of results remains controversial (7–14). The association between chemotherapy-induced amenorrhea and outcome, however, was confounded in retrospective analyses with chemotherapy dose intensity and duration. Although induction of amenorrhea was found to be an important indicator of improved outcome for chemotherapy regimens that were less dose intense and of shorter duration (7,8), the effect of amenorrhea on outcome was less evident when an intensive chemotherapy regimen was used (12). Recently, however, a randomized trial showed statistically significant increases in both the incidence of amenorrhea and disease-free survival for very young patients (i.e., aged 39 years or younger) with ER-positive tumors who received high-dose chemotherapy with peripheral blood progenitor cell support compared with standard doses of chemotherapy (35).

The incidence of amenorrhea was studied meticulously in IBCSG Trial VIII. The spontaneous amenorrhea rate in our older patients (i.e., aged 40 years or older) was approximately 50% at 3 years (Fig. 4, B, untreated group). We observed that the onset of ovarian function suppression was delayed slightly for patients who received chemotherapy relative to those who received goserelin alone. However, despite this delay, the treatment outcome was similar for all three groups of older patients with endocrine-responsive disease (Fig. 2, F), whereas the combination of the two modalities was better than the individual modalities for younger patients (i.e., those aged 39 years or younger) (Fig. 2, E). Although the underlying mechanism associated with this observation is unclear, it is possible that if chemotherapy completely suppressed ovarian function in the older patients, then subsequent treatment with goserelin may not have had the opportunity to improve outcome. This possibility might also explain the observation in the Early Breast Cancer Trialists’ Collaborative Group overview (4), which included mostly women aged 40 years or older and showed a lack of benefit of oophorectomy when administered in addition to chemotherapy. By contrast, for younger women in IBCSG Trial VIII, resumption of menses following completion of goserelin was slower and occurred less often during the 36-month follow-up for women who received initial CMF chemotherapy than for those who received no CMF chemotherapy. Consequently, prolonged amenorrhea in a higher percentage of patients treated with chemo-endocrine therapy than in those treated with endocrine therapy or chemotherapy alone may have contributed to the prolonged disease-free survival associated with the combination therapy observed in the younger cohort.

Ovarian ablation (4), tamoxifen (5), and polychemotherapy (6) have all been shown to improve disease-free survival and overall survival, and their combined use has been the subject of continuing investigation. The combination of tamoxifen and ovarian function suppression was better than either treatment individually for premenopausal patients with advanced breast cancer (36). The combination of tamoxifen plus goserelin was better than goserelin alone in the adjuvant setting following six courses of CAF (cyclophosphamide, adriamycin, fluorouracil) chemotherapy (37). Among the several studies (38–41) that have compared adjuvant chemotherapy with endocrine therapies...
that consisted of 5 years of tamoxifen and 2 or 3 years of
gonadotropin-releasing hormone (Gn-RH) agonist, the largest
has been the Austrian Breast and Colorectal Cancer Study Group
(ABCSG) Trial 5 (41), which yielded better results with com-
bination endocrine treatment than with chemotherapy alone.
Unfortunately, no trial has yet been conducted in the adjuvant
setting to compare tamoxifen plus ovarian function suppression
with tamoxifen alone, either with or without chemotherapy.
However, this question is now being addressed by the global
Suppression of Ovarian Function Trial (SOFT; coordinated by
the IBCSG on behalf of the Breast International Group and the
North American Breast Cancer Intergroup). SOFT compares
tamoxifen alone versus ovarian function suppression (by either
the Gn-RH analog triptorelin or bilateral oophorectomy or ovar-
ian irradiation) plus tamoxifen versus ovarian function suppres-
sion plus exemestane (a steroidal aromatase inhibitor) for pa-
tients with steroid hormone receptor–positive tumors who
remain premenopausal after adjuvant chemotherapy or for
whom tamoxifen alone is considered a reasonable treatment
option (42,43). The complementary Tamoxifen and Exemestane
Trial (TEXT) compares the Gn-RH analog triptorelin plus ta-
mxifen versus triptorelin plus exemestane for patients who
receive the Gn-RH analog with or without chemotherapy from
the start of their adjuvant therapy program (42,43). Thus, the
roles of ovarian function suppression and of an aromatase in-
hibitor are being prospectively studied in the adjuvant setting
for premenopausal patients with endocrine-responsive breast
cancer.

IBCSG Trial VIII was designed at a time when the Early
Breast Cancer Trialists’ Collaborative Group overview analyses
indicated that tamoxifen was not likely to be effective for
women younger than 50 years (44) and, thus, tamoxifen was not
included in the trial. Despite the absence of tamoxifen in the
study design, IBCSG Trial VIII is valuable for exploring the
relationships among hormone receptor expression, short-
duration ovarian function suppression, endocrine effects of che-
motherapy, amenorrhea, and age. Two other trials (45,46) of
adjuvant ovarian function suppression in premenopausal patients
started accrual around the same time as IBCSG Trial VIII and
also did not contain tamoxifen as a treatment option. By contrast
with IBCSG Trial VIII, both trials were conducted almost ex-
clusively in patients with lymph node–positive disease. The
results of our study are similar to those of the Zoladex Early Breast
Cancer Research Association (ZEBRA) trial, which compared go-
serelin for 2 years with CMF (intravenous, days 1 and 8, for six
courses) in 1640 patients and had more than 7 years of follow-up
(45). The second trial (46), a multicenter study conducted in
France, compared adjuvant chemotherapy (anthracycline-based
for 77% of the patients) plus ovarian suppression (either ovarian
irradiation or triptorelin for 3 years) with adjuvant chemotherapy
alone in 926 patients. After 10 years of follow-up, the results
showed similar disease-free survival and overall survival for the
two treatment groups, which led the investigators to conclude
that adjuvant chemotherapy and ovarian function suppression
have a similar mechanism of antitumor activity (46). Because
the mean age of the patients included in the French trial was 43
years and results were not provided for the youngest cohort, it is
not possible to assess the consistency of these findings with those
from IBCSG Trial VIII.

IBCSG Trial IX found that CMF followed by tamoxifen was
more effective than tamoxifen alone for postmenopausal patients
with lymph node–negative disease (47). In the present study, the
trial results confirm and extend the finding that chemotherapy is
more effective than endocrine therapy in terms of disease-free
survival for patients with ER-negative tumors. The definition of
ER-negative status on the basis of ligand-binding assay, how-
ever, represents a mixture of definitely endocrine-nonresponsive
tumors (i.e., an ER-absent cohort with no steroid hormone
receptor expression) and those with some modest responsiveness
to endocrine manipulations (i.e., an ER-low cohort with low
steroid hormone receptor expression). Thus, if the ER-absent
cohort were to be considered separately, the differences in
outcome favoring the CMF-containing regimens compared with
goserelin alone may be greater than those observed. Further-
more, disease classified as ER-negative but progesterone recep-
tor (PgR)-positive may also have some endocrine responsive-
ness, because PgR status may be the dominant indicator for
endocrine responsiveness among premenopausal women (3). A
project is underway that will assess ER and PgR expression
using quality-controlled immunohistochemical methodology in

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### Table 4. Sites of first treatment failure according to treatment

<table>
<thead>
<tr>
<th>% of total at a median follow-up of 7 years</th>
<th>All patients</th>
<th>ER-negative cohort</th>
<th>ER-positive cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Goserelin (n = 346)</td>
<td>CMF (n = 360)</td>
<td>Goserelin (n = 106)</td>
</tr>
<tr>
<td>Treatment failures</td>
<td>24.6</td>
<td>21.9</td>
<td>17.9</td>
</tr>
<tr>
<td>Deaths</td>
<td>10.1</td>
<td>10.3</td>
<td>7.6</td>
</tr>
<tr>
<td>Type of first event</td>
<td>Local</td>
<td>Regional ± local</td>
<td>Soft tissue ≤ any above</td>
</tr>
<tr>
<td></td>
<td>8.1</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>5.3</td>
<td>1.4</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>4.8</td>
<td>1.1</td>
<td>0</td>
</tr>
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<td>7.5</td>
<td>2.8</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>8.6</td>
<td>2.0</td>
<td>0.9</td>
</tr>
<tr>
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<td>1.0</td>
<td>1.0</td>
</tr>
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<td>1.2</td>
</tr>
<tr>
<td></td>
<td>4.0</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>5.3</td>
<td>1.2</td>
<td>1.2</td>
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</tbody>
</table>

*CMF = six courses of cyclophosphamide at 100 mg/m² on days 1–14, orally; methotrexate at 40 mg/m² on days 1 and 8, intravenously; and 5-fluorouracil at 600 mg/m² on days 1 and 8, intravenously. Goserelin = goserelin at 3.6 mg by subcutaneous implant monthly for 24 months. For the sequential combination therapy, six courses of CMF was followed by 18 monthly implants of goserelin. ER = estrogen receptor.
a single laboratory for patients enrolled in IBCSG Trial VIII and will assess outcomes separately for the ER- and PgR-absent and ER- or PgR-positive cohorts (48). This investigation will also clarify the relationship between steroid hormone receptor expression, response to treatment, and the degree of overexpression of c-erbB-2. The association with c-erbB-2 expression is important because the addition of ovarian ablation to tamoxifen therapy has been shown to be effective, compared with no adjuvant treatment, for patients with tumors overexpressing c-erbB-2 (49).

Very few of the premenopausal women enrolled in clinical trials that tested polychemotherapy (6) are young enough to resist the effect of cytotoxic chemotherapy on ovarian endocrine function, and thus allow the efficient testing of the role of further ovarian suppression. In fact, we observed a most intriguing finding in our subgroup of women younger than 40 years. Despite an earlier induction of ovarian function suppression with goserelin than with chemotherapy for this cohort of patients, it was the women who received chemotherapy followed by goserelin who had better disease-free survival. However, caution must be used when assessing the validity of results based on a retrospective subset analysis (50). Consequently, our observation should not alter current patient care, but rather emphasizes the relevance of current studies of chemotherapy and endocrine agents (42,43).

Premenopausal women with endocrine-responsive tumors, especially those at low risk of recurrent disease, may not require chemotherapy provided they receive adequate endocrine therapy. To investigate this issue, the IBCSG conducted a randomized clinical trial in premenopausal women with lymph node–positive disease who received combined endocrine therapy with ovarian ablation (or suppression) and tamoxifen (51). In IBCSG Trial 11–93, four cycles of adjuvant chemotherapy (AC; doxorubicin at 60 mg/m2 or epirubicin at 90 mg/m2 plus cyclophosphamide at 600 mg/m2, every 21 days) and ovarian function suppression (goserelin, bilateral oophorectomy, or ovarian irradiation) and 5 years of tamoxifen (20 mg/day) was compared with endocrine therapy (ovarian function suppression and tamoxifen) alone. The study was small, with only 174 patients randomly assigned from May 1993 through November 1998. Ninety-five percent of the patients had one to three lymph nodes involved, and 53% of the patients had only one lymph node involved. The median age was 45 years. After a median follow-up of 4.4 years, the 4-year disease-free survival ± standard error was 87% ± 4% for the group that received AC and 88% ± 4% for the endocrine therapy-alone group (RR for the addition of AC = 1.22, 95% CI = 0.53 to 2.81; P = .63), suggesting that further study of the role of chemotherapy is warranted in this setting. Today, virtually all premenopausal women with lymph node–positive, steroid hormone receptor–positive disease receive chemotherapy, despite the absence of evidence showing that it is necessary for all such women. Endocrine therapy alone with ovarian function suppression and tamoxifen or an aromatase inhibitor may be sufficient to achieve excellent outcomes without chemotherapy, especially for patients at low risk of recurrent disease. This question is being investigated in the Premenopausal Endocrine Responsive Chemotherapy (PERCHE) trial, which compares ovarian function suppression plus chemotherapy followed by tamoxifen or exemestane versus ovarian function suppression and tamoxifen or exemestane without chemotherapy for patients with steroid hor-

mone receptor–positive tumors who receive ovarian function suppression from the start of their adjuvant therapy program (42,43).

In addition to amenorrhea and ovarian function suppression, cytotoxic chemotherapy may also have direct effects on endocrine-responsive organs (52). Furthermore, the increased use of steroids as antiemetics and as supportive drugs for several old and new chemotherapy regimens (53) may provide additional antitumor effects for patients with endocrine-responsive tumors. However, disease-free survival for women younger than age 35 years with ER-positive tumors treated with either chemotherapy alone or with tamoxifen alone is statistically significantly worse than that for older premenopausal women (54–56). Thus, it is important that alternative treatment approaches such as ovarian function suppression with or without chemotherapy be studied in young patients. In addition, serum endocrine level profiles and novel technologies should be developed to investigate endocrine effects of treatments in tumor stroma and adjacent tissue, because resistance to endocrine therapies and to the endocrine effects of chemotherapy may be related to mechanisms that involve additional components of the tumor microenvironment and not just to events in the tumor cells.

Endocrine therapies are important in the adjuvant treatment of young patients with endocrine-responsive early-stage breast cancer. Because the diagnosis of breast cancer in young women is rare, widespread collaboration will be important to the successful conduct of relevant clinical trials such as the ongoing Breast International Group/North American Breast Cancer Intergroup SOFT, TEXT, and PERCHE studies (42,43).

APPENDIX

References


NOTES

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