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Is chemotherapy necessary for premenopausal women with lower-risk node-positive, endocrine responsive breast cancer? 10-year update of International Breast Cancer Study Group Trial 11-93

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Abstract

Introduction—International Breast Cancer Study Group (IBCSG) Trial 11-93 is the largest trial evaluating the role of the addition of chemotherapy to ovarian function suppress/ablation (OFS) and tamoxifen in premenopausal patients with endocrine-responsive early breast cancer.

Methods—IBCSG Trial 11-93 is a randomized trial comparing 4 cycles of adjuvant chemotherapy (AC: doxorubicin or epirubicin, plus cyclophosphamide) added to OFS and five years of tamoxifen versus OFS and tamoxifen without chemotherapy in premenopausal patients with node-positive, endocrine-responsive early breast cancer. 174 pts were randomized from May, 1993 to Nov, 1998. The trial was closed before the target accrual was reached due to low accrual rate.

Results—Patients randomized tended to have lower risk node-positive disease and the median age was 45. After 10 years median follow up, there remains no difference between the two randomized treatment groups for disease-free (hazard ratio=1.02 (0.57-1.83); p=0.94) or overall survival (hazard ratio=0.97 (0.44-2.16); p=0.94).

Conclusion—This trial, although small, offers no evidence that AC chemotherapy provides additional disease control for premenopausal patients with lower-risk node-positive endocrine-responsive breast cancer who receive adequate adjuvant endocrine therapy. A large trial is needed to determine whether chemotherapy adds benefit to endocrine therapy for this population.

Keywords

breast cancer; estrogen receptor; goserelin; ovarian ablation; ovarian function suppression; tamoxifen

INTRODUCTION

Estrogen deprivation remains a cornerstone of the treatment for women with hormone-sensitive breast cancer. In premenopausal patients oophorectomy has been successfully used for more than a century as first systemic treatment for advanced disease, and later in the adjuvant setting (1). Reversible ovarian function suppression can be achieved with gonadotropin hormone releasing hormone-agonist analogues (GnRH AA). These GnRH AAs have been used for more than 25 years and are an accepted method of estrogen deprivation in the adjuvant treatment of premenopausal patients (2). Tamoxifen is generally accepted as standard adjuvant treatment for patients with hormone-sensitive breast cancer irrespective of age, nodal status, and the addition of chemotherapy. The combination of ovarian function suppression by GnRH AA and tamoxifen has been shown to be superior to GnRH AA treatment alone in a meta-analysis of studies in metastatic breast cancer (3). Ovarian function suppression plus tamoxifen was endorsed as a standard treatment option for premenopausal patients with hormone-sensitive disease by 84% of the St. Gallen Consensus Conference panelists in 2007 (4). Whereas the benefit of adding combined endocrine treatment after chemotherapy in premenopausal patients has been confirmed in large trials (5), the benefit of adding chemotherapy to combined endocrine treatment with ovarian ablation / function suppression and tamoxifen remains unclear (6,7).

The International Breast Cancer Study Group (IBCSG) initiated a randomized clinical trial (IBCSG Trial 11-93) to investigate the role of chemotherapy in premenopausal patients with node positive and hormone-sensitive breast cancer, who received combined endocrine therapy with ovarian ablation or suppression and tamoxifen (8). When this trial was launched in 1993, the optimal treatment for premenopausal patients with endocrine-responsive breast cancer was still very much an open question. The IBCSG, as well as other trialists, were building on the knowledge available from studies that did not tailor treatments based on endocrine-responsiveness. Furthermore, the 1988 Early Breast Cancer Trialists' Collaborative Group overview presented evidence that patients less than 50 years age did not benefit from tamoxifen

(9). Thus most trials conducted during the 1980s and 1990s for premenopausal women included chemotherapy in all arms without tamoxifen. For example, in IBCSG Trial 13-93 (10) premenopausal women with node-positive breast cancer were randomized to tamoxifen or no tamoxifen, but all patients received chemotherapy. For women with ER-positive disease, investigators could choose between Trial 11-93 (for patients suitable for endocrine therapy alone) and Trial 13-93 (for patients not suitable for endocrine therapy alone). Trial 13-93 accrued at a much faster pace than expected while Trial 11-93 accrued very slowly and was eventually closed when it became clear that the accrual rate was not increasing.

When originally reported (8), the results of Trial 11-93 indicated no advantage for the addition of chemotherapy to ovarian function suppression and tamoxifen for premenopausal patients with node-positive, endocrine-responsive breast cancer. Here we present the results of Trial 11-93 with a median follow-up of 10 years.

PATIENTS AND METHODS

From May 1993 to November 1998, 174 premenopausal patients with estrogen receptor and/or progesterone-positive tumors and at least one involved axillary lymph node were randomized to endocrine therapy alone or endocrine therapy plus four cycles AC chemotherapy. Endocrine therapy included ovarian ablation or suppression plus tamoxifen to 5 years. Protocol requirements have been described elsewhere (8). The planned sample size was 760 patients to provide an 80 percent power to detect a 10 percent difference in 5-year disease-free survival. The protocol was closed because of the low accrual rate on November 1, 1998, before the target accrual was achieved.

All patients had a histologically proven unilateral breast cancer, classified as T_{1a,b,c}, T₂ or T₃, pN₁, M₀ (UICC 1987), with either ER-positive or PgR-positive primaries. Steroid hormone receptor concentrations in the primary tumors were determined by immunohistochemistry or by standard ligand binding methods for which ER or PgR concentrations ≥ 10 fmol per milligram of cytosol protein were considered positive.

The method of ovarian function suppression was the choice of the participating center and was either bilateral surgical oophorectomy, bilateral ovarian radiotherapy, or GnRH analogue 3.6 mg every 28 days continuing for 2 years or until the patient was 55 years old, whichever was longer. Patients who initially received either GnRH analogue or ovarian radiotherapy could change to another method during the course of the trial.

Tamoxifen was given at a dosage of 20 mg daily, until five years from randomization, or until relapse or intolerance, whichever occurred first. Patients assigned to chemotherapy received four courses of adjuvant anthracycline-cyclophosphamide (AC: doxorubicin 60 mg/m² or epirubicin 90 mg/m² plus cyclophosphamide 600 mg/m² day one intravenously for four 21-day courses).

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

DFS and OS percentages were estimated with the Kaplan-Meier method (11). Greenwood's formula was used for the calculation of standard error (12). Cox proportional risk regression models (13) were used to estimate hazard ratios, confidence intervals (CIs), and p-values for the treatment comparisons. All probability values were two sided. Results are reported at a median follow-up of 10 years.

During the course of the study, the Data and Safety Monitoring Committee (DSMC) reviewed accrual and safety data twice a year. There were never a sufficient number of events to conduct an interim efficacy review. The study was coordinated and funded by the International Breast Cancer Study Group (IBCSG). The ethics committees and required health authorities of each participating center approved the study protocol, and all patients gave written informed consent. The chairman (BT) vouches for the accuracy and completeness of the data.

RESULTS

Patient and disease characteristics

The patient and disease characteristics are shown in Table 1. The median age was 45 years, ranging from 26 to 56 years. Eighty-eight percent of the patients had primary tumors classified as both ER-positive and PgR-positive. The patients entered on this trial tended to be lower risk, with 97 percent having 1-3 positive nodes, and 55 percent with only one positive node. Fifty-eight percent had tumor size less than or equal to 2 cm and 76 percent of the tumors were grade one or two.

Treatment

Treatment details are shown in Table 2. Among the 89 patients assigned to receive AC, 88 received all four cycles and one patient refused all AC.

Most patients (109, 63%) began with GnRH analogue, while 26% (45 patients) received surgical oophorectomy, 11% (19 patients) received bilateral ovarian radiation, and one patient refused OFS. The median duration of GnRH analogue for the 109 patients who started was 2.0 years (range .07-12.6). Thirty patients (28%) switched to another form of ovarian ablation, most within one year of starting GnRH analogue; 19 received surgical oophorectomy and 11 received radiation. Six patients are still receiving GnRH analogue. One patient started ovarian radiation and switched to surgical oophorectomy.

Three patients did not start tamoxifen, and the median duration of tamoxifen was 5.0 years (range 0 to 9).

Disease-free Survival (DFS) and Overall Survival (OS)

No advantage was observed for patients who received chemotherapy in addition to OFS and tamoxifen in terms of either disease-free survival (hazard ratio=1.02, CI=0.57-1.83, p=0.94) or overall survival (hazard ratio=0.97, CI=0.44-2.16, p=0.94) (Figure1). Forty-five of the 174 patients (26 percent) have had an invasive breast cancer recurrence or second (non-breast) malignancy. Recurrences were mostly in the bone and viscera (Table 3). Five patients had second primary tumors observed (OFS+T: pancreatic, melanoma; OFS+AC+T: endometrial, colon, glioma). Twenty-four patients have died. No deaths without recurrence have occurred.

DISCUSSION

Overview results and analyses of individual trials demonstrate a highly significant benefit for chemotherapy compared to no chemotherapy, especially for women less than 50 years of age (2). Why then is the question addressed in IBCSG Trial 11-93 important or even ethical to pursue? The role of steroid hormone receptor content in the primary tumor in defining the degree of responsiveness of various therapies is becoming better understood (4). The endocrine effects of chemotherapy among young women are also well documented (6). While several thousand women have been enrolled in trials comparing chemotherapy alone versus ovarian function suppression/ablation (with or without tamoxifen) (6), a recent editorial emphasizes that the more appropriate question is comparing chemotherapy plus hormone therapy versus

hormone therapy alone (14). Among premenopausal women with endocrine responsive disease who have other features that predict for a low risk of recurrence, it is entirely possible that chemotherapy provides no additional benefit beyond that of an optimal combination of ovarian function suppression / ablation (OFS) plus tamoxifen.

Trial 11-93, with 174 patients enrolled, is the only published randomized comparison addressing the role of chemotherapy in premenopausal patients with endocrine responsive disease who receive combined endocrine therapy with ovarian function suppression / ablation and tamoxifen. The results show that these patients, 97% of whom have 1 to 3 positive axillary lymph nodes, have a surprisingly good prognosis overall. There is no indication that eliminating chemotherapy has a detrimental effect on disease control, while 20% of the patients receiving chemotherapy experienced grade 3 or worse toxicity (8). It is important to note that the side effects of chemotherapy associated with premature menopause are usually underreported and not trivial (15) and should not be underestimated when considering a course of adjuvant therapy for premenopausal women. The median age in the present trial was 45 years. It remains possible that younger patients may derive benefit from the addition of chemotherapy, as we reported for the subset of premenopausal women with node-negative disease aged <40 years in IBCSG Trial VIII (16).

Obviously, the results of IBCSG Trial 11-93 cannot definitively exclude the value of chemotherapy in patients receiving adequate endocrine therapy. It must be considered that the trial is highly underpowered. Furthermore, the AC regimen has been shown by indirect evidence to be less effective than other anthracycline-containing regimens on average in trials unselected for endocrine responsiveness and risk of recurrence (2). Nevertheless, the absence of any evidence of benefit from AC chemotherapy in Trial 11-93 motivated the IBCSG to launch the PERCHE (**P**remenopausal **E**ndocrine **R**esponsive **C**hemotherapy) trial in 2003, which compared chemotherapy with no chemotherapy, with all patients receiving optimal endocrine therapy (17). Although available to all North American Breast Intergroup and Breast International Group (BIG) institutions, the PERCHE trial closed after three years with an accrual of 29 patients.

In the target population of low-risk endocrine-responsive disease, the possibility that endocrine therapy alone might be sufficient remains an open question. The currently-active trial, **T**rial **A**ssigning **I**ndividualized **O**ptions for Treatment (**R**x), or TAILORx (18), uses the Oncotype DX Recurrence Score (ODRS) to identify patients with node-negative, estrogen-receptor positive breast cancer having a disease with an intermediate risk score, and randomizes them to chemotherapy versus no chemotherapy. Both premenopausal and postmenopausal women are eligible. The trial was launched on April 7, 2006, and a total of 292 patients under the age of 50 (total recruitment 908 of all ages) had been randomized as of May 31, 2007 (Robert Gray, personal communication). Two issues concerning TAILORx might complicate the interpretation of results. According to the St. Gallen criteria (4), the estrogen receptor-positive cohort of patients includes those whose disease is highly endocrine responsive, as well as those with disease classified as incompletely endocrine responsive. This latter cohort is very likely to obtain benefit from the use of adjuvant chemotherapy even if the disease is node-negative and endocrine therapy is used. The chemotherapy benefit is likely to emerge early because the early recurrences observed while undergoing endocrine therapy are likely to be those most susceptible to control by chemotherapy. Thus, interim analyses of TAILORx could demonstrate an advantage for chemotherapy at a follow up time that is too early to be relevant for the target population – i.e., patients with highly endocrine responsive disease. A second feature of TAILORx is that, unlike Trial 11-93 and PERCHE, the endocrine therapy is not standardized. Whether or not chemotherapy is assigned might influence the selection of type of endocrine therapy, and maximal endocrine therapy including ovarian function suppression will not be received by all premenopausal patients. Both of these features might potentially

bias the chemotherapy comparison. The question addressed in Trial 11-93 and PERCHE is likely to remain unanswered even when the results of TAILORx become available.

The other currently running large study investigating the 70 gene expression signature Microarray In Node negative Disease may Avoid Chemo Therapy (MINDACT) will also not answer this question as the study is investigating the lower risk patient population with node-negative disease and the endocrine effect of the chemotherapy in general as well as different types of regimens used will have confounding effects. Moreover the interpretation of the results will be more difficult when endocrine treatments for patients with premenopausal status at diagnosis are introduced after completion of chemotherapy. (19)

The IBCSG-coordinated study TEXT (Tamoxifen and Exemestane Trial) is evaluating OFS plus tamoxifen compared with OFS + exemestane for premenopausal patients with endocrine responsive disease (17). Patients can receive chemotherapy together with OFS either by investigator/patient choice, or by randomization to chemotherapy or no chemotherapy in PERCHE (option now closed to accrual). It is interesting to note that thirty-eight percent of the 1371 patients enrolled in TEXT as of December 31, 2006, did not receive adjuvant chemotherapy, primarily on the basis of node-negative status. It is important when making treatment decisions of combined endocrine therapy with or without chemotherapy in premenopausal patients to recognize that there is a patient population with lower to intermediate risk of recurrence having node-positive disease but favorable biological features (expression of both estrogen and progesterone receptor, lower grade and few involved nodes) that has a fairly good prognosis when receiving ovarian ablation or ovarian function suppression and tamoxifen without chemotherapy.

The 10-year results from our trial, although conducted with limited patient numbers, will remain for the foreseeable future the only trial data directly addressing whether such patients benefit from the addition of chemotherapy. Our results to date do not support the use of chemotherapy in these patients. We believe that the role of adjuvant chemotherapy for premenopausal women with lower risk node-positive endocrine-responsive disease treated with optimal endocrine therapy remains unclear and should be studied in properly designed trials.

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Appendix

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Abbreviations

OFS	ovarian function suppression/ablation
AC	doxorubicin 60 mg/m ² or epirubicin 90 mg/m ² , plus cyclophosphamide 600 mg/m ² , each 21-days for 4 cycles
T	tamoxifen to five years from randomization
HR	Hazard ratio (OFS plus AC plus T: OFS plus T)
CI	confidence interval
P	p-value

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Figure 1. Kaplan-Meier plots of disease-free survival (left) and overall survival (right) according to randomized treatment group, ovarian function suppression plus tamoxifen (gray line) and ovarian function suppression plus ACx4 plus tamoxifen (black line).

Table 1
Patient and disease characteristics according to treatment [number (%)]

	OFS plus Tamoxifen	OFS plus AC plus Tamoxifen	Total
Total patients	85 (100)	89 (100)	174 (100)
Nodes Positive			
1	45 (53)	51 (57)	96 (55)
2	22 (26)	25 (28)	47 (27)
3	14 (16)	11 (12)	25 (14)
4	1 (1)	1 (1)	2 (1)
5	0 (0)	1 (1)	1 (1)
7	2 (2)	0 (0)	2 (1)
16	1 (1)	0 (0)	1 (1)
Nodes Positive			
1-3	81 (95)	87 (98)	168 (97)
4 or more	4 (5)	2 (2)	6 (3)
Tumor Size			
≤ 2 cm	45 (54)	54 (62)	99 (58)
> 2 cm	38 (46)	33 (38)	71 (42)
Unknown/ undeterminable	2	2	4
Tumor grade			
1	20 (24)	18 (20)	38 (22)
2	44 (53)	48 (55)	92 (54)
3	19 (23)	22 (25)	41 (23)
Unknown	2	1	3
Age			
Median (Range)	46 (26-54)	45 (27-56)	45 (26-56)
ER Status (ER/PgR)			
ER+/PgR+	80 (94)	74 (83)	154 (88)
ER+/PgR-	4 (5)	8 (9)	12 (7)
ER+/PgR unk	0 (0)	2 (2)	2 (1)
ER-/PgR+	1 (1)	4 (4)	5 (3)
ER-/PgR-	0 (0)	1 (1)	1 (1)

Table 2
Trial 11-93 Treatment received according to treatment [number (%)]

	OFS plus Tamoxifen	OFS plus AC plus Tamoxifen	Total
Total patients	85 (100)	89 (100)	174 (100)
Surgery/RT			
Mx	37 (44)	40 (45)	77 (44)
Mx + RT	0 (0)	1 (1)	1 (1)
LTM	2 (2)	2 (2)	4 (2)
LTM + RT	46 (54)	46 (52)	92 (53)
Anthracycline			
Doxorubicin		55 (62)	55
Epirubicin		33 (37)	33
None	85 (100)	1 (1)	1
Ovarian Function Suppression			
Surgical oophorectomy	24 (28)	21 (24)	45 (26)
Bilateral ovarian radiation	11* (13)	8 (9)	19 (11)
GnRH analogue	50 (59)	59 (66)	109 (63)
None	0	1 (1)	1 (1)
<u>GnRH analogue</u>			
GnRH alone	37 (74)	42 (71)	79 (72)
GnRH followed by surgical ooph	9 (18)	10 (17)	19 (17)
GnRH followed by ov RT	4 (8)	7 (12)	11 (10)
<u>GnRH analogue duration (n=109)</u>			
Median (range) years	1.9 (.07-10.8)	2.0 (.09-12.6)	2.0 (.07-12.6)
<u>Tamoxifen duration</u>			
Median (range) years	5.0 (0-9)	4.9 (0-6)	5.0 (0-9)

* includes 1 patient who started on RT and switched to surgical oophorectomy

Table 3

First events and sites according to treatment [number (%)]

	OFS plus Tamoxifen	OFS plus AC plus Tamoxifen	Total
Total Patients	85 (100)	89 (100)	174 (100)
Failures	22 (25.9)	23 (25.8)	45 (25.9)
Deaths	12 (14.1)	12 (13.5)	24 (13.8)
<u>Sites</u>			
Local	2 (2.4)	3 (3.4)	5 (2.9)
Contralateral breast	2 (2.4)	2 (2.3)	4 (2.3)
Regional $\pm$ local	3 (3.5)	0	3 (1.7)
Distant $\pm$ any above	13 (15.3)	15 (16.8)	28 (16.1)
Soft Tissue	1 (1.2)	0	1 (0.6)
Bone	6 (7.1)	5 (5.6)	11 (6.3)
Viscera	6 (7.1)	10 (11.2)	16 (9.2)
Second malignancy	2 (2.4)	3 (3.4)	5 (2.9)
Death without prior cancer event	0	0	0